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New contralateral vesicoureteral reflux after unilateral reimplantation: predictive factors and clinical outcomes

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Abstract

Purpose—Although unilateral reimplantation for vesicoureteral reflux (VUR) is highly successful, a minority will develop new contralateral VUR (C-VUR). We examined predictors and clinical outcomes of C-VUR.

Materials and Methods—We reviewed patients who underwent non-tapered unilateral reimplantation for primary VUR, graded on a 3-point scale, at our institution (1/90–12/02), and identified those with C-VUR. We analyzed the association of patient/procedure characteristics with incidence and time to resolution of C-VUR and postoperative urinary tract infection (UTI). Multivariable models controlled for variables associated with incidence and time to resolution of C-VUR.

Results—395 patients (77.2% female; median age 5.3 years) had reimplantation. Preoperative VUR was grade 1 in 2.8%, 2 in 56.6%, 3 in 40.6%. Technical success was 95.4%. Postreimplantation, 39 patients (9.9%) had new C-VUR (grade 1 in 7, grade 2 in 27, grade 3 in 5). Median follow-up was 51.8 months. On multivariate analysis, younger age (≤ 6 years: odds ratio (OR) 3.7, $p=0.006$) and low observed bladder capacity (BC) as % of predicted BC ($<50\%$ predicted BC: OR 6.3, $p=0.02$) were significant predictors of C-VUR. C-VUR resolved in 21/27 (77.8%) with subsequent cystography at a median of 21.5 months. Two patients had reimplantation for persistent C-VUR. 4/39 with C-VUR (10.3%) had postoperative febrile UTI (median 26 months) with spontaneous resolution of C-VUR in all cases.

Conclusions—Younger patients and those with low observed BC (vs. predicted) may be at increased risk for postoperative C-VUR. A majority of C-VUR will resolve spontaneously, and the clinical course is typically benign.

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Keywords

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

INTRODUCTION

Although unilateral ureteral reimplantation for vesicoureteral reflux is highly successful, a small percentage of patients will develop *de novo* contralateral vesicoureteral reflux (C-VUR).[1–5] There is little data regarding risk factors for C-VUR, and its clinical significance is uncertain. Given the high success rate of bilateral reimplantation, one option is to reimplant both ureters in all patients with unilateral reflux. A less aggressive strategy, however, may be to identify preoperative risk factors for C-VUR in patients with unilateral reflux and perform selective bilateral reimplantation. The goal of this study was to examine predictors and clinical outcomes of C-VUR.

METHODS

With Institutional Review Board approval, we performed a retrospective billing and medical record review of all patients who underwent ureteral reimplantation at our institution between January 1990 and December 2002. We excluded all patients with secondary VUR (neurogenic bladder, posterior urethral valves, bladder exstrophy, renal transplant, prune belly syndrome, or ureterocele) as well as repeat, laparoscopic, or endoscopic procedures, and those requiring ureteral tapering.

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 0.9–8.9 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) into the contralateral ureter was defined as C-VUR. We evaluated patient and procedure characteristics, and clinical outcomes (VUR, UTI, and further surgery). Observed bladder capacity was determined by the bladder capacity measured on the final preoperative cystogram (RNC or VCUG). Predicted bladder capacity was calculated based on the formula proposed by Kaefer et al.[6] Correlation between final preoperative observed bladder capacity (as a % of predicted) and initial postoperative observed bladder capacity (as a % of predicted) was determined using Spearman's rank correlation coefficient.

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.[7] 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.[8]

In patients with C-VUR, the primary outcome was spontaneous resolution of C-VUR. 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” C-VUR (grade ≥ 2); in this analysis, resolution was defined as C-VUR grade 0 or 1 on subsequent cystography. Additional clinical endpoints included additional anti-reflux surgery and febrile UTI during the follow-up period. Fever was defined as a temperature of at least 38.5 C and/or flank pain and/or acute phase renal scintigraphy documenting evidence of acute infection. The number of colony-forming units required for diagnosis of a UTI was 50,000 for catheterized specimens and 100,000 for clean-catch voided specimens.

Bivariate tests of association were performed using Fisher’s exact test or Wilcoxon rank-sum test. Predictive factors of C-VUR were analyzed using multivariate logistic regression. Covariates with a p-value <0.2 on bivariate analysis were entered into the initial multivariable model. A backwards selection technique was used to identify and remove non-significant variables ($p \geq 0.05$). We also performed a survival analysis of time to resolution of C-VUR using Cox proportional hazards regression, among patients with C-VUR and ≥ 1 postoperative cystogram. In cases of additional anti-reflux procedures on the side of the contralateral 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). Graphs were created using R version 2.15.2. 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 (unilateral or bilateral) for VUR during the study period, of whom 482 (34.1%) had primary unilateral VUR. Of these, 445/482 (92.3%) had a non-tapered unilateral reimplantation. 88.8% (395/445) had a postoperative screening cystogram within 9 months of reimplantation, and represented the primary analytic cohort. There was a history of C-VUR that resolved prior to surgery in 20/395 (5.1%). The patient and procedure characteristics are presented in Table 1.

Because some patients did not undergo routine screening cystography within 9 months of reimplantation, we compared these with patients who underwent screening cystogram. Patients who had a postoperative screening cystogram were more likely to be younger (median: 5.3 vs. 7.9 years, $p=0.01$), female (77.2 vs. 50.0%, $p<0.001$) white (89.5% vs. 66.7%, $p<0.002$), have preoperative grade 3/3 VUR (40.6% vs. 24.0%, $p=0.03$) and to have presented with UTI (83.8 vs. 68.0%, $p=0.01$) than those who did not have a postoperative screening cystogram. There was no difference in surgical technique, duplex system, or history of resolved C-VUR between the two groups. Among the 50 without postoperative screening cystography within 9 months of surgery, most (66%) never had any postoperative cystography. Only one (2%) was subsequently diagnosed with C-VUR, and two (4%) had

postoperative febrile UTI. None of the 17 patients who had cystography at 9 months postoperatively had persistent ipsilateral VUR.

Post-reimplantation VUR

Of the 395 patients analyzed, 39 (9.9%) patients had VUR (grade 1) into the contralateral ureter (C-VUR). The characteristics of patients with and without C-VUR are shown in Table 1. There were no differences in gender, race, clinical presentation, preoperative VUR grade, laterality, surgical technique or type of system reimplanted. The C-VUR group was younger (median age 3.3 vs. 5.48 years, $p<0.006$) and had a lower observed bladder capacity (BC) as a percentage of predicted capacity, compared to the group with no C-VUR. Percentage of predicted BC was reasonably stable over time, at least among the 16 patients who had >1 preoperative cystogram, with moderate correlation between initial and final % predicted BC ($\rho=0.6$; $p<0.0001$). On multivariate analysis, the only significant predictors of C-VUR were younger age (age ≤ 6 years; OR 3.7 (95% CI: 1.5–9.2) and low % predicted BC ($<50\%$ predicted BC: OR 6.3 (1.3–31.5), $p=0.02$; 50–100% predicted BC: OR 1.7 (0.8–3.7), $p=0.1$). Gender, race, clinical presentation, preoperative VUR grade, surgical technique and duplication were not associated with C-VUR on multivariate analysis.

Persistent ipsilateral VUR (grade 1) occurred in 18 (4.6%) patients. 10 had subsequent cystography and 8 did not. Of the 10 who were reimaged, seven had resolution of their ipsilateral VUR and three had persistent grade 2/3 VUR. Of the 8 that did not have subsequent cystography, five were grade 1/3 and three were grade 2/3. Five of the patients with ipsilateral VUR also had C-VUR. Of these five patients, two had subsequent cystography and the remaining three did not. Of those who had subsequent cystography there was bilateral resolution of the ipsilateral VUR.

C-VUR Resolution

For 12 of the 39 patients (31%) with C-VUR, no further imaging beyond the initial postoperative screening cystogram was performed. The majority of these had low-grade C-VUR: grade 1/3 in 4 patients (33.3%), grade 2/3 in 7 patients (58.3%), and grade 3/3 in 1 patient (8.3%). These 12 patients did not differ from those with subsequent cystography in age, gender, race, presentation, preoperative VUR grade, bilaterality, surgical technique or duplication. A larger proportion of patients with no further imaging had postoperative grade 1/3 C-VUR compared to those who did have subsequent cystography (92.6 % vs. 66.7%, $p=0.06$). None of the 12 had experienced a postoperative febrile UTI at median follow-up of 42.3 months (IQR: 24.7–62.4).

Among the 27 patients (69.2%) who did have subsequent postoperative cystography, the initial postoperative C-VUR grade was grade 1/3 in 3 (11.1%) and grade 2/3 in 24 (88.9%). The relationship of preoperative ipsilateral VUR grade with postoperative C-VUR grade is shown in Table 2.

Spontaneous resolution of C-VUR (defined as grade 0/3 C-VUR) occurred in 21/27 patients (77.8%) at a median postoperative time of 22.8 months [95% CI: 18.3–40.1 months] (including all three of those with initial postoperative grade 1/3 VUR) (Figure 1). The 5-year probability of persistent C-VUR among patients with initial postoperative C-VUR was 19%.

Age, gender, laterality, surgical technique, ureteral tapering, system reimplanted, and VUR grade (preoperative or postoperative) were not associated with time to resolution.

Evaluating the secondary outcome of “clinically significant” C-VUR (grade 2), 18/24 patients (75%) had documented spontaneous resolution at a median postoperative time of 20.0 months [95% CI: 16.6–29.1] (Figure 2). The 5-year probability of persistent C-VUR in this group was 18%. Four patients had C-VUR at the final cystogram (all grade 2/3).

Only 2 patients in this series underwent additional reimplantation procedures. Both were 7-year old girls with worsening C-VUR (grade 2 progressing to grade 3) who were observed for 3 and 4 years respectively prior to contralateral reimplantation. Their final cystogram showed resolution of C-VUR.

Postoperative UTI

Of the 39 patients with initial C-VUR, 4 (10.3%) had 1 documented febrile UTI following reimplantation. None of these patients had persistent ipsilateral VUR. Median time from reimplantation to initial postoperative febrile UTI was 44.7 months (IQR 7.6–65.4). There was no difference in incidence of postoperative febrile UTI among those with C-VUR vs. those without C-VUR (10.3% vs. 7.6%, $p=0.5$).

Among the group with C-VUR and postoperative febrile UTI, the initial postoperative VUR grades were grade 1/3 in one patient (20%), grade 2/3 in two patients (40%) and grade 3/3 in two patients (40%). Four of the patients had C-VUR at the most recent check prior to the UTI (median time of cystogram 52.1 months prior to the UTI) and one patient had C-VUR on the cystogram done 1.9 months after the UTI. 4/5 had resolution of their persistent C-VUR on subsequent imaging at a median of 9.6 months post-UTI [IQR 3.9–13.2]. It is uncertain which, if any, of these four patients actually had persistent C-VUR at the time of the UTI. The remaining patient had persistent grade 2 C-VUR on final postoperative cystogram at 19.5 months post-UTI.

Age, gender, race, clinical presentation, type of collecting system, laterality, surgical technique, ureteral tapering and preoperative ipsilateral grade or postoperative C-VUR grade were not associated with postoperative febrile UTI.

Prior history of contralateral VUR

As noted above, 20 children who underwent unilateral reimplantation had a prior history of C-VUR which had resolved prior to reimplantation on 1 preoperative cystograms. Only 1 of these 20 children was among the 39 patients who developed new C-VUR (Table 2). The incidence of C-VUR was actually lower among those with a known history of resolved contralateral VUR (5.0%) compared to those with no such history (10.1%), although this difference was not statistically significant ($p=0.8$).

DISCUSSION

Although ureteral reimplantation is highly successful, patients with postoperative C-VUR represent a management challenge, and the significance of this condition is uncertain. A

number of studies describe the incidence of C-VUR, but few authors have identified factors that may influence its development. The only risk factors for C-VUR identified in this analysis were age and observed bladder capacity as a percentage of expected capacity.

Several mechanisms for the development of C-VUR have been proposed in the literature. One commonly proposed mechanism is that C-VUR develops as a consequence of elimination of the pressure “pop-off” mechanism following repair of VUR into the operated side.[9] This phenomenon may be more pronounced when the repaired side has higher-grade VUR[9], although we did not observe such an association. However, we did find that bladder capacity <50% predicted was a significant risk factor for C-VUR, and this fits conveniently into the pop-off pressure theory.

Another hypothesis is that surgical distortion of the contralateral trigone leads to the development of C-VUR.[2] If this were true, procedures with cross-trigonal dissection (e.g. Cohen) might have a higher incidence of C-VUR than procedures typically confined to one side (e.g. intravesical Glenn-Anderson, extravesical detrusorrhaphy). However, we did not find any association between surgical technique and development of C-VUR.

False-negative findings at preoperative cystography, especially in younger patients who have had only one or two studies, might also explain some cases of C-VUR. Sparr and colleagues reported that new-onset C-VUR developed in 33% of patients with unilateral disease while they were followed non-operatively.[10] This finding suggests that new C-VUR may be a manifestation of the natural history of VUR rather than an outcome associated with reimplantation. Younger age at the time of reimplantation has been reported as a risk factor for C-VUR[11], and we also observed this. It is unknown if this finding is related to developmental characteristics of the young bladder, false-negative cystography among children who simply had fewer opportunities for preoperative imaging, a combination of these, or other factors.

Notwithstanding high reported rates of C-VUR among those undergoing unilateral reimplantation despite a history of preoperatively resolved C-VUR [1, 2, 11], we did not observe this association, as only one patient (among 20 with preoperatively resolved C-VUR) developed recurrent C-VUR.

The findings of this study should be interpreted in light of its limitations, including those inherent in the methodology of a hypothesis-generating, retrospective review. Outcome assessments may be biased by missing/erroneous information, loss-to-follow-up, and recall bias. Furthermore, these single-institution findings may not be generalizable to other settings, institutions, surgeons, or to contemporary practice. As these data reflect the clinical experience of 10 surgeons trained at various institutions, the results may be more generalizable than most. Not all patients underwent identical clinical imaging regimens, resulting in differential ascertainment of outcomes. For example, only patients who had >1 postoperative cystogram were included in the survival analysis. This may introduce bias if, in fact, patients who did not get a subsequent cystogram differed systematically from those who did, and it is possible that, had all patients undergone subsequent postoperative cystography systematically, we would have observed a lower (or higher) rate of C-VUR

resolution. However, a majority of those who had no further imaging had low-grade VUR, and low-grade VUR was highly likely to resolve among those who *did* have subsequent imaging. Another limitation is the lack of cystoscopic data. Cystoscopic ascertainment of the contralateral orifice may provide predictive information regarding recurrence. However, systematic, standardized descriptions of the contralateral orifice were not consistently reported in the operative records, so this potential predictor of C-VUR was not available for analysis. Finally, while this series is large by the standards of the C-VUR literature, the small number of patients with the outcomes of interest limits our ability to detect associations or to perform large multivariate analyses.

CONCLUSIONS

Few factors reliably predict C-VUR after unilateral reimplantation. Younger patients and those with low observed BC (vs. predicted) may be at increased risk. However, a majority of C-VUR will resolve spontaneously, and the clinical course is typically benign.

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**Probability of Persistent C-VUR Among Patients with C-VUR
on Initial Postoperative Cystogram**

Figure 1.

**Probability of Persistent C-VUR($\geq$ Grade2) Among Patients with
C-VUR (Grade $\geq$ 2) on Initial Postoperative Cystogram**

Figure 2.

Table 1

Characteristics of Non-tapered Unilateral Reimplantation Patients with C-VUR versus those without C-VUR

	Total (%)	With C-VUR (n, %)	Without C-VUR (n, %)	P value*
<i>Median age at surgery (years, IQR)</i>				
	5.30 [2.2–8.0]	3.31 [1.3–5.6]	5.48 [2.3–8.3]	0.006[†]
<i>Gender</i>				
Male	90 (22.8)	8 (20.5)	82 (23.0)	0.8*
Female	305 (77.2)	31 (79.5)	274 (77.0)	
<i>Race/Ethnicity</i>				
White/Caucasian	205 (89.4)	22 (100)	183 (88.3)	0.7*
Black/African-American	2 (0.9)	0	2 (1.0)	
Asian	7 (3.1)	0	7 (3.4)	
Hispanic	13 (5.7)	0	13 (6.3)	
Other	2 (0.9)	0	2 (1.0)	
<i>Initial presentation</i>				
UTI	330 (83.7)	33 (84.6)	297 (83.7)	0.98*
Prenatal hydronephrosis	37 (9.4)	4 (10.3)	33 (9.3)	
Sibling screen/incidental diagnosis/other	27 (6.9)	2 (5.1)	25 (7.0)	
<i>Preoperative VUR grade (by patient)</i>				
Grade I	11 (2.8)	0 (0)	11 (3.1)	0.5**
Grade II	219 (56.6)	21 (56.8)	198 (56.6)	
Grade III	157 (40.6)	16 (43.2)	141 (40.3)	
<i>Observed bladder capacity (% of predicted)</i>				
<50% predicted	8 (2.4)	3 (9.7)	5 (1.6)	0.005**
>= 50% and <100%	128 (37.5)	15 (48.4)	113 (36.5)	
>=100%	205 (60.1)	13 (41.9)	192 (61.9)	
<i>Surgical technique</i>				
Extravesical	175 (44.4)	14 (35.9)	161 (45.4)	0.4*
Glenn-Anderson	6 (1.5)	1 (2.6)	5 (1.4)	
Politano-Leadbetter	109 (27.7)	14 (35.9)	95 (26.7)	
Cohen cross-trigonal	104 (26.4)	10 (25.6)	94 (26.5)	
<i>System reimplanted (by patient)</i>				
Single	321 (81.3)	32 (82.0)	289 (81.2)	1.0*
Duplex	74 (18.7)	7 (18.0)	67 (18.8)	
<i>Postoperative febrile UTI</i>				
No	364 (92.1)	35 (89.7)	329 (92.4)	0.5*
Yes	31 (7.9)	4 (10.3)	27 (7.6)	
<i>History of resolved preoperative C-VUR</i>				
No	375 (94.9)	38 (97.4)	337 (94.7)	0.8*

	Total (%)	With C-VUR (n, %)	Without C-VUR (n, %)	P value [*]
Yes	20 (5.1)	1 (2.6)	19 (5.3)	

^{*} Fisher's exact test

^{**} Chi-square trend test

[†] Wilcoxon rank-sum test

Table 2

Preoperative ipsilateral VUR grade (rows) versus postoperative C-VUR grade, among the 39 patients with C-VUR (columns)

		Postoperative C-VUR		
		Grade 1/3	Grade 2/3	Grade 3/3
Preoperative ipsilateral VUR	Grade 1/3	0	0	0
	Grade 2/3	2	17	3
	Grade 3/3	5	10	2