



Reflux Timing Is a Predictor of Successful Endoscopic Treatment of Vesicoureteral Reflux

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OBJECTIVE	To determine whether vesicoureteral reflux (VUR) that occurs during either the filling or voiding phase on voiding cystourethrogram (VCUG) has prognostic significance on successful endoscopic treatment.
MATERIALS AND METHODS	A retrospective review was performed of 299 patients (438 ureters) with VUR who underwent endoscopic treatment with dextranomer/hyaluronic acid copolymer (Deflux) at a single institution from 2010 to 2013. Success was defined as absence of VUR on 3-month follow-up VCUG. Preoperative VCUGs were analyzed to determine whether the onset of VUR occurred during the filling or voiding phase. Predictor variables to determine success were analyzed, with a specific focus on VUR timing.
RESULTS	Success rate was 319/438 (72.8%) by ureter and 202/299 (67.6%) by patient. Reflux was seen during the filling and voiding phases in 290 and 148 ureters, respectively. Success rate was 203/290 (78%) for filling VUR and 116/148 (70%) for voiding VUR. Univariable analysis revealed voiding VUR had significantly increased odds of success (odds ratio [OR] 3.2, $P = .049$), while high-grade reflux (OR 0.53, $P = .005$) had significantly decreased odds of success. Multivariable analysis showed that voiding VUR (OR 3.2, $P = .005$) had significantly higher odds of success while those with high grade reflux (OR 0.42, $P = .017$) had significantly decreased odds of success.
CONCLUSION	The timing of VUR on preoperative VCUG appears to be an important independent predictor of successful endoscopic treatment of VUR. This has important clinical considerations when selecting VUR patients who would be best candidates for endoscopic treatment. UROLOGY 124: 237–240, 2019. © 2018 Elsevier Inc.

The use of endoscopic injection therapy in the treatment of vesicoureteral reflux (VUR) has been widely used as a first-line treatment. While the grade of vesicoureteral reflux has historically predicted the success of endoscopic injection therapy, other factors such as physician experience, VUR grade, renal scarring, and number of prior injections have shown to contribute to overall outcomes.¹⁻³ Another study analyzed timing of reflux as a predictor of successful endoscopy therapy and showed that those with reflux during the voiding phase had higher rates of success compared to those with reflux during the filling phase.⁴ Indeed, other studies have shown that patients with voiding reflux have higher odds of spontaneous resolution of reflux.⁵

The aim of this study was to retrospectively review our cohort of patients who underwent subureteric injection of

Deflux for VUR with a specific focus on timing of reflux seen on preoperative VCUG—namely, whether the onset of reflux begins during the filling or voiding phase. Our hypothesis was that reflux that begins during the voiding phase would be predictive of an increased success rate.

MATERIALS AND METHODS

After institutional review board approval, a retrospective review was performed of all patients with VUR who underwent endoscopic injection of dextranomer/hyaluronic acid copolymer (Deflux) from 2010 to 2013 at our institution. All children underwent a voiding cystourethrogram (VCUG) as well as a renal/bladder ultrasound as part of the workup. In children where there were concerns for renal scarring, a dimercaptosuccinic acid (DMSA) nuclear medicine scan was performed. Indications for endoscopic injection included breakthrough urinary tract infection despite antibiotic prophylaxis, poor patient compliance to antibiotics, persistent vesicoureteral reflux on ≥ 2 VCUGs, and as primary treatment for VUR in cases where there were parental concerns over long-term antibiotic prophylaxis.

The injection technique was the same for all children and included both the hydrodistension implantation technique and subureteral transurethral injection. Success was defined as the absence of vesicoureteral reflux on repeat VCUG at 3-month follow-up. Exclusion criteria included children who only underwent radionuclide cystogram due to difficulty in standardizing

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Table 1. Ureter success by grade.

Grade 1	43/55	78.2%
Grade 2	121/151	80.1%
Grade 3	134/192	69.8%
Grade 4	17/31	54.8%
Grade 5	4/9	44.4%

Table 2. Characteristics by ureter.

Characteristic	Resolved	Unresolved
Number of ureters	319	119
Gender		
Male	72	28
Female	247	91
VUR grade		
1-2	164	42
3-5	155	77
Mean age (mo)	51.9	48.3
Side of VUR		
Left	94	127
Right	112	105
Reflux timing		
Filling	203	87
Voiding	116	32
Scarring on DMSA		
Yes	42	22
No	106	39
Mean DMSA/Mag3 differential function	50.2%	47.7%

DMSA, dimercaptosuccinic acid; VUR, vesicoureteral reflux.

and reporting grades compared to a VCUG, and inability to determine filling vs voiding VUR. Children who did not follow-up postinjection were also excluded.

The preoperative radiography films were reviewed to determine whether the onset of VUR occurred during the filling or voiding phases. The filling phase was defined as the period from catheter placement until the time that contrast material entered the proximal urethra. The voiding phase was defined as the period after the appearance of contrast within the proximal urethra until the completion of the study. Of note, the distinction of voiding vs filling VUR was ureter-specific rather than patient-specific; thus, a given patient with bilateral VUR may have

1 ureter that refluxed during voiding and the other that refluxed during filling.

The primary outcome of this study was successful resolution of VUR defined as absence of VUR on follow-up VCUG. For patients who underwent multiple Deflux injections, only the initial injection was analyzed for the purposes of our study. Predictor variables to determine success within the analysis included patient age at surgery, gender, indication for treatment, presence of scarring on DMSA, differential function on DMSA or Mag-3, amount of deflux, reflux present on the filling or voiding phase, and grade of reflux. As the outcome is measured by ureter and repeated measures are present within subjects, the generalized estimating equations framework with an exchangeable working correlation structure was used. Variables with *P* values less than .15 in each univariable logistic regression were included in a multivariable logistic regression. Variables in these univariable and multivariable regressions with *P* values less than .05 were considered statistically significant.

RESULTS

A total of 299 patients met inclusion criteria for a total of 438 ureters (females 76.6%, average age 53.4 months). There were 55 ureters with grade 1 VUR, 151 ureters with grade 2, 192 ureters with grade 3, 31 ureters with grade 4, and 9 ureters with grade 5 VUR. Overall success rate after 1 injection was 72.8% by ureter and 202/299 (67.6%) by patient. [Table 1](#) lists overall success rate by ureter according to grade. On VCUG, reflux was seen during the filling and voiding phases in 290 and 148 ureters, respectively. [Table 2](#) details characteristics by those with resolved vs unresolved VUR according to ureter. Between the filling and voiding VUR groups, 290 total ureters had VUR during filling and 148 ureters had voiding VUR. The success rate by the 2 groups was 203/290 (78%) for filling VUR and 116/148 (70%) for voiding VUR. Supplementary Table 1 details the indications for treatment of VUR by grade.

When analyzing the entire cohort by ureters, univariable analysis ([Table 3](#)) revealed high-grade reflux (odds ratio [OR] 0.53, *P* = .005) had significantly decreased odds of Deflux success. Additionally, reflux seen on voiding was significant with an OR of 1.6 for Deflux success with a *P* value of .049. Multivariable analysis ([Table 4](#)) showed reflux during the voiding phase (OR 3.2, *P* = .005) had significantly higher odds of success while high grade reflux (OR 0.42, *P* = .017) had significantly decreased

Table 3. Univariable analysis for resolved VUR.

Characteristic	Odds Ratio	95% Confidence Interval		<i>P</i> Value
Male gender	1.0	0.60	1.77	.91
Age	1.0	0.99	1.01	.28
Reflux 3-5	0.53	0.34	0.82	.005
Voiding reflux	1.6	1.002	2.60	.049
Scarring on DMSA	0.73	0.35	1.51	.39
Differential function	1.0	0.99	1.07	.14
Indication:				
Breakthrough UTI	0.78	0.45	1.37	.39
Renal scarring	0.98	0.49	1.99	.96
Persistent VUR	1.5	0.79	2.85	.22
Anesthesia for different procedure	1.8	0.36	9.34	.47
Parent preference	1.1	0.56	2.21	.76
Solitary kidney	0.29	0.05	1.88	.20

The bolded values were statistically significant since the *p*-values were less than 0.05.

Table 4. Multivariable analysis for resolved VUR.

Characteristic	Odds Ratio	95% Confidence Interval		P Value
Reflux grade 3-5	0.456	0.22	0.92	.035
Voiding reflux	3.128	1.37	7.14	.007
Differential function	1.033	0.99	1.08	.134

The bolded values were statistically significant since the p-values were less than 0.05.

odds of success. Supplementary Tables 2 and 3 are subgroup univariable analyses looking at the significance of voiding vs filling VUR broken down separately for the low grade and high grade cohorts. Neither model showed significance, largely due to significantly decreased sample size within each group.

DISCUSSION

It is well established that VUR is linked to an increased risk of recurrent febrile urinary tract infections (UTIs) and thereby renal scarring, which can ultimately lead to sequelae such as renal dysfunction and hypertension.⁶ The 2010 AUA guidelines for VUR indicate the 3 main goals of management are: prevention of recurrent febrile UTIs, prevention of renal injury, and to minimize morbidity of treatment and follow-up.⁷ Any decision regarding mode of surgical intervention involves analyzing treatment efficacy with relative morbidity. Endoscopic treatment is inherently less morbid than open antireflux surgery but also less effective.⁷ Thus, it is crucial to identify patients who would most benefit from Deflux treatment.

Our study shows that patients with VUR during the voiding phase on preoperative VCUG have increased rates of successful endoscopic therapy. Namely, on multivariable analysis, ureters that refluxed during the voiding phase had an approximately 3-fold independent odds of successful endoscopic treatment compared to those that refluxed during bladder filling. These results corroborate with the results of the study performed by Lee et al⁴ which also showed increased rates of Deflux success in patients with voiding reflux. They found for their cohort of 136 ureters that those with voiding reflux had 88.6% success compared to a 56.4% success rate for filling reflux ($P = .011$). Of note, it is important to note that their group's definition of successful treatment was Grade 1 VUR or less on post-treatment VCUG, while our group's definition was complete absence of VUR. Hinman et al described how reflux that occurs during bladder filling occurs at a low volume and pressure, which may indicate an open ureterovesical valve in this period.⁸ This suggests an inherent anatomic defect which would be less likely to spontaneously resolve and thus may require surgical correction. Conversely, reflux that occurs during voiding at a high pressure and high volume may indicate an immature ureterovesical valve that may be more likely to improve with time and lead to VUR resolution. Indeed, other studies have examined filling VUR compared to voiding VUR with respect to spontaneous resolution rates. Arsanjani et al⁵ found that in a population of consecutive patients diagnosed with primary VUR, reflux identified during the

filling phase was less likely to resolve spontaneously and more likely to require surgical intervention.

Other studies have looked at a similar concept of bladder volume and pressure at the onset of VUR. McMillan et al showed that patients who had VUR at a bladder volume greater than 75% of predicted bladder capacity were significantly more likely to have resolution.⁹ Additionally, their group also found that bladder volume at onset of VUR was independently associated with breakthrough febrile urinary tract infections.¹⁰ Papachristou et al showed that patients with VUR occurring at a filling volume less than 45% of bladder capacity with a concomitant bladder pressure less than 20 cm H₂O had a lower probability of VUR resolution over 36 months.¹¹ Finally, Van Arendonk et al showed that VUR occurring at higher pressures (as measured by nuclear cystometrogram) had higher odds of spontaneous VUR resolution.¹² These findings support the principle that VUR that occurs at low-volume and low-pressure is different from high-volume and high-pressure reflux. Our hospital does not routinely measure or document bladder volumes or pressures during VCUG. Perhaps in institutions that do not routinely measure these values during VCUGs, the identification of voiding vs filling reflux may be a more accessible parameter to categorize which patients have a higher probability of VUR resolution.

Our study's results must be interpreted in light of its limitations. First, our study is retrospective in nature with its inherent biases and confounding. Patient selection for injection therapy was not standardized and often based on parental and surgeon preference. Furthermore, we also did not have information regarding intraoperative findings such as ureteral or mound morphology, which studies have shown may be associated with increased success.^{3,13} Second, our comparison was performed by ureter rather than by patient, which can be a confounder due to repeated measures within subjects. However, we used statistical modeling via the generalized estimating equations framework with an exchangeable working correlation structure to correct for this. Third, filling and voiding VUR may also be influenced by intravesical pressure during VCUG but as noted above, this is currently not measured at our institution.

CONCLUSION

Our study shows that the timing of reflux appears to be an important predictor of the success of endoscopic treatment for VUR. On multivariable analysis, patients with reflux in the voiding phase on VCUG have an

approximately 3-fold increased odds of success compared to those with VUR in the filling phase. This has important clinical considerations when selecting patients who would be best candidates for Deflux treatment.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.09.034>.

References

1. Lorenzo AJ, Pippi Salle JL, Barroso U, et al. What are the most powerful determinants of endoscopic vesicoureteral reflux correction? Multivariate analysis of a single institution experience during 6 years. *J Urol*. 2006;176:1851–1855.
2. Puri P, Kutasy B, Colhoun E, Hunziker M. Single center experience with endoscopic subureteral dextranomer/hyaluronic acid injection as first line treatment in 1,551 children with intermediate and high grade vesicoureteral reflux. *J Urol*. 2012;188:1485–1489.
3. Yucel S, Gupta A, Snodgrass W. Multivariate analysis of factors predicting success with dextranomer/hyaluronic acid injection for vesicoureteral reflux. *J Urol*. 2007;177:1505–1509.
4. Lee JN, Lee SM, Ha YS, et al. VUR timing on VCUG as a predictive factor of VUR resolution after endoscopic therapy. *J Pediatr Urol*. 2016;12:255.e251–256.
5. Arsanjani A, Alagiri M. Identification of filling versus voiding reflux as predictor of clinical outcome. *Urology*. 2007;70:351–354.
6. Mathews R, Carpenter M, Chesney R, et al. Controversies in the management of vesicoureteral reflux: the rationale for the RIVUR study. *J Pediatr Urol*. 2009;5:336–341.
7. Management and screening of primary vesicoureteral reflux in children: AUA guideline. 2010.
8. Hinman F, Miller ER, Hutch JA, et al. Low pressure reflux: relation of vesicoureteral reflux to intravesical pressure. *J Urol*. 1962;88:758–765.
9. McMillan ZM, Austin JC, Knudson MJ, Hawtrey CE, Cooper CS. Bladder volume at onset of reflux on initial cystogram predicts spontaneous resolution. *J Urol*. 2006;176:1838–1841.
10. Alexander SE, Arlen AM, Storm DW, Kieran K, Cooper CS. Bladder volume at onset of vesicoureteral reflux is an independent risk factor for breakthrough febrile urinary tract infection. *J Urol*. 2015;193:1342–1346.
11. Papachristou F, Printza N, Doulas A, Koliakos G. Urinary bladder volume and pressure at reflux as prognostic factors of vesicoureteral reflux outcome. *Pediatr Radiol*. 2004;34:556–559.
12. Van Arendonk KJ, Madsen MT, Austin JC, Hawtrey CE, Graham MM, Cooper CS. Nuclear cystometrogram-determined bladder pressure at onset of vesicoureteral reflux predicts spontaneous resolution. *Urology*. 2007;69:767–770.
13. Lavelle MT, Conlin MJ, Skoog SJ. Subureteral injection of Deflux for correction of reflux: analysis of factors predicting success. *Urology*. 2005;65:564–567.