

The Deflux Procedure Reduces the Incidence of Urinary Tract Infections in Patients with Vesicoureteral Reflux

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ABSTRACT

Purpose: The aim of this study was to review the experience of a single institution with the Deflux (Q-Med Scandinavia; Uppsala, Sweden) procedure and assess its effectiveness in reducing the incidence of urinary tract infections (UTIs) in children with vesicoureteric reflux (VUR).

Materials and Methods: After institutional review board approval, the charts of 100 patients with VUR, who presented between June 2003 and June 2005, were prospectively reviewed. Data collected included: demographics, the number of preoperative and postoperative UTIs, a radiologic grade of VUR on a voiding cystourethrogram (VCUG) and the presence of VUR on a radionuclide VCUG 3 months after the procedure. Patients were continued on oral antibiotics until urine culture at 3 months was negative and no reflux was demonstrated on VCUG. The student's *t* test was used for data analysis.

Results: The mean age was 3.8 ± 0.3 years, and 76% were girls. From 155 ureters treated, 10 had Grade I reflux, 42 Grade II, 76 Grade III, 25 Grade IV, and 2 Grade V. A second injection was required in 22 ureters (14.2%). The overall success rate of the procedure (Grade 0 reflux at 3 months) was 77.4% after the first injection and 83.9% after a second injection. The success rate per grade was: 100% for Grade I, 88.1% for Grade II, 86.8% for Grade III, 64% for Grade IV, and 50% for Grade V. The mean follow-up was 446 ± 20 days. The mean volume injected/ureter was 0.6 ± 0.03 mL. Thirteen (13) patients had UTIs after the procedure, compared to 75 before. There was a 5-fold reduction in the incidence of UTIs/year, from a mean of 0.68 ± 0.09 pre- to 0.12 ± 0.04 postinjection ($P = 0.001$). The majority of UTIs were caused by *Escherichia coli* (74% pre- and 82% postinjection).

Conclusions: We conclude that the Deflux procedure is effective not only in eliminating VUR on radiologic studies, but also in reducing the incidence of UTIs and antibiotic use in children with VUR.

INTRODUCTION

VESICoureteral reflux (VUR) is the most common pediatric urologic anomaly affecting children.^{1,2} In the majority of cases, the diagnosis is made after the first febrile urinary tract infection (UTI).³ Recurrent UTIs oc-

cur in 30%–40% of children with VUR and may eventually lead to renal scarring, hypertension, and end-stage renal disease.⁴

Treatment options for VUR include observation, antibiotic prophylaxis, and/or surgical intervention.^{2,4} Surgery is usually recommended for children with break-

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through UTIs, despite antibiotic prophylaxis.² Ureteroneocystostomy has been the gold standard of surgical therapy, and the success rate is greater than 95%–98%.^{1,5}

The technique of endoscopic subureteral injection for treating VUR was first described by Matouscheck in 1981⁶ and further developed by O'Donnell and Puri in 1984.⁷ In September 2001, the Food and Drug Administration approved Dextranomer/Hyaluronic acid copolymer (Deflux; Q-Med Scandinavia, Uppsala, Sweden) for subureteral injection to treat Grades II–IV VUR in children.^{8,9} There have been several series from various centers worldwide attesting to its simplicity, safety, quickness, and effectiveness with 70%–90% success rates,^{10,11} making it a promising alternative to open surgery.

Infection rather than VUR is the most common cause of kidney damage in children.¹² With the increasing acceptance of endoscopic techniques for the correction of VUR, it should be emphasized that the primary goal of diagnosing and treating VUR should be preventing a UTI. We present our experience with the use of Deflux for the endoscopic management of VUR and assess its effectiveness in preventing UTIs.

MATERIALS AND METHODS

After institutional review board approval was obtained, a prospective study was performed on all patients who presented to our hospital for the endoscopic treatment of VUR between June 2003 and June 2005. The study included 100 patients (76 females and 24 males) between 1 and 17 years of age (mean, 3.8 ± 0.3). A total of 155 ureteric units were treated. VUR was unilateral in 48 patients (left in 36 and right in 12) and bilateral in 52. Thirteen (13) duplex systems were included in the analysis and 3 patients had bilateral duplex systems (Table 1).

Inclusion criteria included: patients with Grades II–IV VUR (according to the International Reflux Study [IRS]

classification of VUR)¹³ on a voiding cystourethrogram (VCUG) with breakthrough UTIs despite prophylactic antibiotics, persistent VUR after a period of observation, poor compliance with prophylactic antibiotics, or with evidence of new renal scarring on a ^{99m}technetium dimer-capto-succinic acid (DMSA) renal scan. Patients with Grade I VUR were only treated if they had associated contralateral higher grade reflux. One (1) patient with bilateral Grade V VUR was treated based on family preference. The preoperative work-up included a detailed history and physical examination, a VCUG, and a urinalysis and culture.

The frequency of UTIs in the treated population was recorded before and after injection, as well as the causative organism. A UTI was defined as $\geq 100,000$ colony-forming units (CFUs) per milliliter (mL) of a single organism on a clean-catch specimen.¹⁴

Success was defined as the resolution of reflux on a 3-month postoperative radionuclide VCUG. All patients were kept on prophylactic antibiotics for 3 months after injection. A urinalysis and culture were obtained at the time of the radionuclide VCUG. Antibiotics were continued only if the patient had persistent VUR or a positive urine culture. As many as 2 repeat Deflux treatments were offered to patients who did not respond to initial treatment. All patients were seen at least once a year thereafter.

Technique

All procedures were performed under general anesthesia, which was administered with the use of a laryngeal mask airway. The procedure was done with the patient in the cystolithotomy position. An 11.5 Fr Wolf pediatric cystoscope with an offset lens (Richard Wolf Medical Instruments Corporation, Vernon Hills, IL) was used. The technique for the dextranomer/hyaluronic acid (Dx/HA) implant injection was similar to that described

TABLE 1. PATIENT CHARACTERISTICS

<i>Patient characteristics</i>	<i>Number of patients (ureters)</i>
Duplex systems	10 (13)
Bilateral duplex systems	3 (6)
Lateral ureteral orifices	7 (8)
Ureteral orifices close/at bladder neck	6 (7)
Renal scars	4 (4)
Associated anomalies	
Hypospadias	2
Hutch Diverticulum	2
Extrophy/Epispadias	1
Obstructed nonfunctioning duplex system	2
Previous urologic surgery	
Ureteral implantation	1
Hypospadias	2
Bilateral pyeloplasties	1

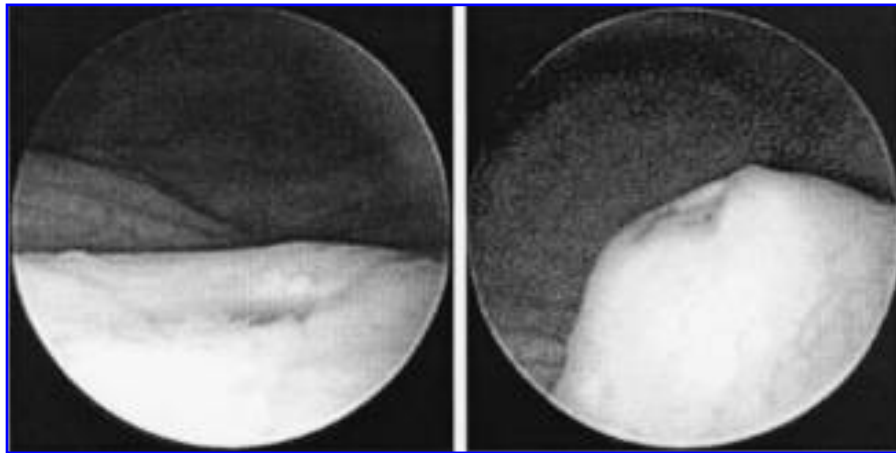


FIG. 1. The characteristic “volcanic bulge.”

previously in the literature.^{7,8} A 3.7 Fr Deflux[®] metal needle (Q-Med AB; Uppsala, Sweden) was introduced into the bladder and inserted submucosally 2–3 mm below the affected ureteral orifice at the 6 o’clock position. The needle was advanced to approximately 8 mm, which is marked on the needle. Deflux was then injected slowly with mild hydrodistension. The needle was then slowly withdrawn while the injection continued until the characteristic “volcanic bulge” was seen with the ureteral slit-like orifice sitting on top of the tight and white mound (Fig. 1). A 3 Fr Ureteral catheter (Cook Urological Inc., Spencer, IN) was used in a few cases to identify the affected ureter with a duplex system. All procedures were photographically documented. All patients were discharged home after the procedure per the day-stay protocol.

A statistical analysis was performed using an unpaired Student’s *t* test, with *P* < 0.05 being considered significant. Mean values and standard deviations were calculated for each variable.

RESULTS

One hundred and fifty-five (155) ureters were treated: 10 had Grade I reflux (6.5%), 42 Grade II (27.1%), 76 Grade III (49%), 25 Grade IV (16.1%), and 2 Grade V (1.3%). The time of mean follow-up was 446 ± 20 days (range, 118–839). The mean volume injected per ureter was 0.6 ± 0.03 mL. A second injection was required in 22 ureters (18 patients, 14.2% of the treated ureters). A third reinjection was done in 6 ureters (4 patients, 3.9% of the ureters). The overall success rate of the procedure by ureter (Grade 0 reflux at 3 months) was 77.4% after the first injection and 83.9% after a second injection. An additional 4.5% of ureters (7 ureters) had an amelioration of their reflux to Grade I with a single injection. The cumulative success rate by grade was: 100% for Grade

I, 88.1% for Grade II, 86.8% for Grade III, 64% for Grade IV, and 50% for Grade V (Fig. 2). New onset contralateral reflux developed in 6 patients (6%), 3 of whom had an injection of the new refluxing ureter during the time of this study.

There were no major intraoperative or postoperative complications. Retrograde tracking of Deflux occurred in 1 patient (1%) and intravesical extravasation of Deflux occurred in another (1%). One (1) patient had postoperative urinary retention that responded well to catheterization. One (1) patient (2 ureters) underwent open surgery to correct VUR 2 years after the Deflux injection for non-resolving bilateral Grade IV VUR.

Seventy-five (75) patients (75%) presented with recurrent UTIs prior to the Deflux injection, with a mean of 0.68 ± 0.09 UTIs per year (range, 0–4). After the procedure, only 13 patients (13%) had recurrent UTIs (12 females and 1 male), with a 5-fold reduction in the incidence of infections per year to 0.12 ± 0.04 (range, 1–3) (*P* = 0.001). The mean time to UTI after Deflux was 178 ± 36 days (range, 13–393). Eight (8) patients had

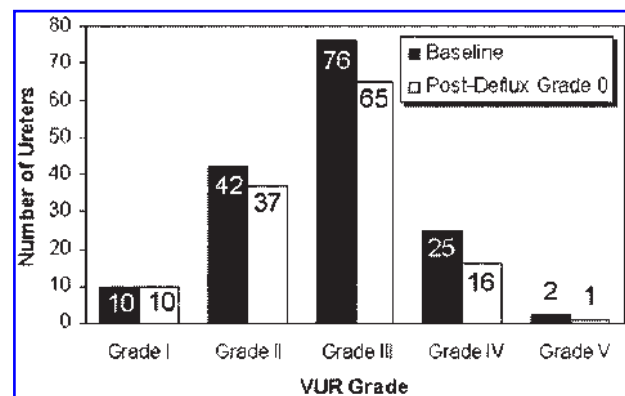


FIG. 2. Cumulative success per grade after a single injection.

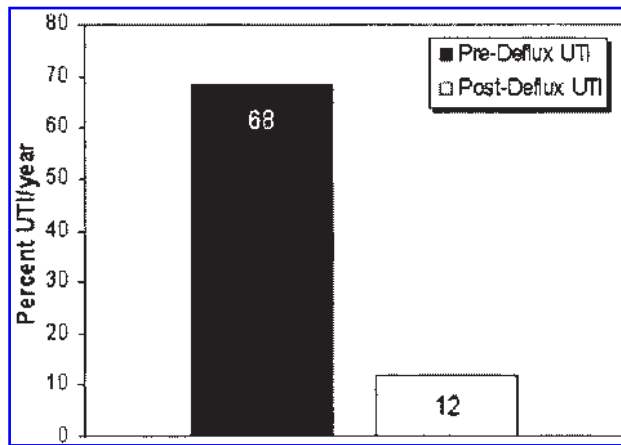


FIG. 3. Reduction of frequency of urinary tract infections.

UTIs off antibiotics, whereas the remaining 5 had UTIs within the first 3 months after the Deflux injection while still on prophylactic antibiotics. Two (2) patients who had no UTIs prior to the procedure developed new onset infections; one of these had dysfunctional voiding (Fig. 3).

Recurrent infection developed in 7 patients, with no residual VUR on follow-up radionuclide VCUG. Two (2) patients with recurrent UTIs had residual Grade I VUR on a follow-up radionuclide VCUG, 2 had residual Grade II, and 2 had residual Grade III. When patients who suffered from recurrent infections were compared with those who did not, the statistically significant differences were that baseline bilateral reflux and female gender were more evident in the recurrent infections group ($P < 0.05$). Nine (9) of the 10 patients with baseline bilateral reflux had at least Grade III VUR on one side. None of the patients with baseline Grade I VUR had recurrent infections. This procedure eliminated the need for prophylactic antibiotics in 87% of our population. The majority of UTIs were caused by *Escherichia coli* (74% of the infections preinjection and 82% postinjection). Other organisms involved are depicted in Figure 4.

DISCUSSION

VUR is a heterogeneous disease and remains one of the most controversial problems in pediatrics. VUR is di-

agnosed in one third of children who present with a UTI. There is no general agreement as to what constitutes the optimum management of children with VUR.⁹ Observation therapy does carry an ongoing risk of renal scarring.¹⁵ The overall spontaneous resolution rate is approximately 15% and the median time to resolution is 5 years.¹⁶ This may take up to 8 years for Grades III–V VUR.¹⁷ For Grades I and II VUR, long-term antibiotic prophylaxis to prevent UTIs is generally recommended as initial therapy while awaiting spontaneous resolution, a practice that may require several years of antibiotic use.¹ Pyelonephritis tends to be more common in the medically treated groups, compared with the surgical groups.¹⁸ Antibiotic prophylaxis does not fully prevent UTIs or renal scarring and antibiotic-related adverse events are well known.² Antibiotic prophylaxis has also resulted in a 24-fold increased risk of resistant *E. coli* to trimethoprim/sulfamethoxazole.¹⁹ In addition, antibiotic prophylaxis requires annual imaging that is both expensive, invasive, and may in itself cause a UTI.²⁰

Traditional indications for operative management include breakthrough UTIs, noncompliance with medical treatment, new renal scars/failure of renal growth, high grade dilating VUR (IV to V), persistent VUR (more than 3–4 years), worsening reflux, and VUR associated with fixed urinary tract defects.^{2,4} Nonetheless, surgery is not free of complications; obstruction occurs in 0.3%–9.1% of cases and reflux persists in up to 20% of those with Grade V VUR.¹⁶

Endoscopic treatment of VUR began more than 22 years ago.⁷ Different bulking agents have been used, including polytetrafluoroethylene (PTFE), silicone, autogenous blood, cross-linked bovine collagen, chondrocytes, and polydimethylsiloxane (Macroplastique). These substances, however, did not become widely accepted because of either a lack of durability, the potential for migration, a risk of secondary malignancy,^{21,22} immunogenicity, or local inflammation with granuloma formation.^{23,24}

Dextranomer/hyaluronic acid copolymer has been extensively evaluated in Europe, with up to 7 years of follow-up.¹⁰ The material consists of 80–250- μ m dextranomer microspheres mixed in a 1% high-molecular-weight sodium hyaluronan solution. Each milliliter of the system contains 0.5 mL of sodium hyaluronan and 0.5

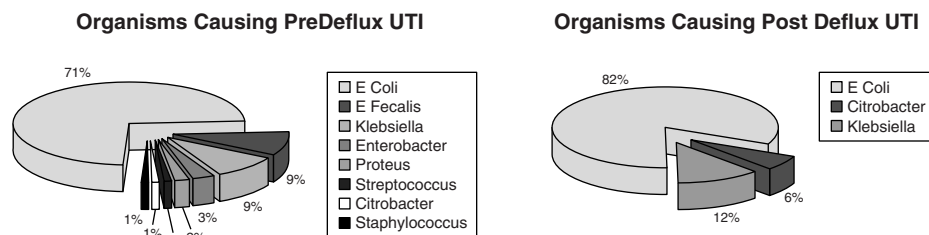


FIG. 4. Causative organisms.

mL of microspheres.⁹ It is biodegradable, nonimmunogenic, does not migrate,²⁵ has no potential to cause malignant transformation,²⁶ does not initiate a local inflammatory response, and is durable.²⁰ Reported success rates vary between 70% and 90%.^{10,11,27} Our success rate of 77.4% with a single injection was comparable, despite the fact that our definition of cure was more rigorous than that used in most European studies, where amelioration of VUR to Grade I was considered a success. If those with residual Grade I reflux were included, the efficacy of Deflux injection will rise to 82% in our population after a single injection and 88.4% after a second injection. Only 18% of our patients required a second injection, a result superior to that cited elsewhere.¹⁰

The annual incidence of UTIs is 0.9%–1.4% in healthy girls 1–6 years of age without VUR and 0.1%–0.2% in boys of the same age.²⁸ The cumulative incidence of UTIs during childhood is approximately 5%–10%.²⁹ There is no sufficient data in the literature that address the impact of the treatment modality of VUR on the incidence of UTIs. The rate of UTIs in patients treated with antibiotics only ranges between 11% and 25%.^{30,31} and withholding antibiotics does not seem to change this figure, as shown by Georgaki-Angelaki et al. Hence, these authors recommend a discontinuation of prophylactic antibiotics after 2 years in children with no evidence of new UTIs and no renal or voiding defects. These findings were confirmed by Thompson et al., who found that the reinfection rate was 0.29 and 0.24 per patient per year while on and off antibiotic prophylaxis, respectively.³² These figures are higher than our 13% incidence of UTIs in the studied population.

The IRS showed clearly that only 10% of children had febrile UTIs after antireflux surgery, compared to 21% of those who were kept on antibiotic prophylaxis at 5 years of follow-up ($P < 0.01$).³³ This group published their 10-year follow-up data and found a higher incidence of febrile UTIs with medical treatment at 10 years (25.2% with antibiotics versus 13.6% with surgery; $P < 0.03$).³⁴ In the study by Lackgren et al., 8 % of children developed relapsing infection after a Deflux injection.¹⁰ The risk of post-treatment UTI's in one study, where Deflux was used for management of complex reflux cases, was 13% overall.³⁵ These data compare favorably with our results, as only 13% of our patients had a recurrent infection. The annual rate of infection was reduced 5-fold from a mean of 0.68 ± 0.09 UTIs per year to 0.12 ± 0.04 UTI's per year. Because our time of mean follow-up was only 14 months, this figure should improve with a longer follow-up, as the highest recurrence rate is evident during the first postoperative year.^{36,37} This was true in our population, as the mean time to UTI after Deflux was 178 ± 36 days (range, 13–393). Recurrent infections were more common in females (92%) and in those with bilateral reflux (77%). The female predominance was re-

ported by other investigators³⁴ and may be attributable to the shortness of the female urethra and to host factors that weaken the antibacterial bladder defense mechanism.^{10,30,36}

Nonetheless, some reports disagree with the fact that antireflux surgery significantly reduces the risk of recurrent infections. In a meta-analysis of seven randomized, controlled trials by Wheeler et al. with 833 evaluable patients comparing antibiotics alone with a combination of antireflux procedure and antibiotics,²⁹ the frequency of all forms of recurrent UTIs and the risk of UTIs were not different between the 2 groups by 2 and 5 years of follow-up. The only statistically significant difference was that the incidence of febrile UTIs was reduced by 60% in the combined treatment group at 5 years.²⁹ Beetz et al. studied the ongoing risk of UTIs in 158 young adults who were surgically treated for VUR in childhood.³⁶ In their series, 65% of patients had recurrent UTIs during a follow-up period of 20 years after surgery. They concluded that surgery reduces the proportion of ascending febrile UTIs (pyelonephritis) but not recurrent afebrile infections. In another study, patients undergoing open surgery were subject to an approximately 25% risk of UTIs.³⁸ It is noticeable that the main antireflux modality in these studies was open surgery. Wheeler's meta-analysis included only one study where an endoscopic Deflux injection was the modality used.³⁹ The discrepancy in results between the subureteral injection series and the open surgery series may be explained by the fact that bladder function is less affected by endoscopic treatment, whereas open surgery can impair bladder function and cause bladder distortion, with a resultant increase in the incidence of infections.³⁵ This makes subureteral Deflux injection superior to surgery in this respect as it is more effective in reducing recurrent infections, the main ailment that can result in renal damage and end-stage renal disease in patients with reflux.

The main weakness of our study was the short follow-up period. Breakthrough infections can occur even after a long infection-free interval, particularly in certain periods of life as with the commencement of sexual activity or pregnancy.⁴⁰ A study with a longer follow-up is needed to assess the durability of Deflux in reducing the incidence of urinary tract infections. No studies are yet available with adequate follow-up that can compare to the open surgical series.

CONCLUSIONS

We conclude that the Deflux procedure is effective not only in eliminating VUR on radiologic studies, but also in reducing the incidence of UTIs and antibiotic use in children with VUR. Female patients with baseline bilateral reflux are at a greater risk for post-Deflux infections and should be followed at closer intervals.

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