# Dextranomer/hyaluronic acid injections for patients with vesicoureteral reflux

## Does the age at injection predict the outcome?

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## ABSTRACT

**INTRODUCTION:** We aimed to assess the impact of age of the initial dextranomer/hyaluronic acid (Dx/HA) injection on the subsequent outcome, including the need for repeated injections.

**METHODS:** The charts of patients who underwent Dx/HA injection from 2010–2020 were retrospectively reviewed. Two groups were created according to the number of Dx/HA injections: single vs. repeated injections. Patients who presented with antenatal hydronephrosis, neurogenic bladder, and followup less than one year after the first injection were excluded. Repeated Dx/HA injections were indicated in patients with documented vesicoureteric reflux (VUR) who experienced recurrent febrile urinary tract infection (fUTI) postoperatively.

**RESULTS:** A total of 172 patients with 189 renal units were included; 139 (73.5%) units underwent single injections, whereas 50 (26.5%) had repeated injections. Twenty-three (48.9%) patients with repeated injections presented before the age of one year vs. 24 (51.1%) after the age of one year (p=0.02). Of the repeated group, 34 (68%) units received two injections, 14 (28%) were injected three times or more, and two (4%) had other treatment modalities. Forty-four percent of units requiring repeated injections had high-grade VUR (grades 4 and 5), compared to only 22.3% of those successfully treated with a single injection (p=0.003).

**CONCLUSIONS:** In our cohort, 26.5% of renal units underwent repeated Dx/HA injections. Forty-four percent of units with repeated injections had grade 4–5 VUR. Patients with VUR who were injected or presented with fUTI before the age of one year old were at higher risk of repeated injections than those who were injected or presented later.

## INTRODUCTION

Vesicoureteral reflux (VUR) is a crucial cause of congenital hydronephrosis that affects approximately 1% of children and may increase the risk of febrile recurrent urinary tract infection (fUTI) and subsequent renal scarring, hypertension, and chronic renal failure.[1,2] The main reason for managing VUR is to prevent fUTI and subsequently preserve renal function.[3] Surgical treatment for VUR achieves a high success rate of approximately 98%, which varies depending on the procedure type performed and the reflux's severity;[4] however, ureteral reimplantation has many drawbacks, such as abdominal incisions, extended hospitalization, prolonged catheterization, and potential trigonal damage. Minimally invasive procedures have addressed many of these issues. Nevertheless, these procedures are still challenged by VUR recurrence and other less common adverse events, such as ureteral obstruction.

Endoscopic injection treatment has been widely used for VUR over the last two decades after the introduction of polytetrafluoroethylene in the early 1980s.[5] Dextranomer/hyaluronic acid (Dx/HA) is considered one of the most widely used bulking agents, with an excellent overall success rate.[4] Moreover, Dx/HA injection offers significant advantages, such as being a quick, cost-effective outpatient procedure with fewer complications. Therefore, a major shift has been observed from reimplantation toward endoscopic

injection treatments over the last few years.[6] Although surgeon experience is another important factor for successful results,[7,8] the single most important predictor for success of endoscopic injection is the preoperative grade of VUR.[9]

Endoscopic injection treatment is a convenient option for managing VUR in a single procedure; however, repeated injections may be required, depending on many factors such as the severity of reflux, ectopic location of ureters, and clinical response. We hypothesized that early Dx/HA injection may be associated with a higher failure rate and suspect that patients who present with fUTI earlier in life are more likely to require repeated Dx/HA injections when compared to those who present at an older age. The present study aimed to assess the influence of age at Dx/HA injection on the efficacy of the initial injection and to explore potential determinants that may predict procedural failure.

## METHODS

### Study design

After obtaining the local ethics review board approval, a retrospective analysis was performed for patients undergoing Dx/HA injections for VUR from January 2010 to June 2020. Inclusion criteria comprised patients who had a minimum of 24 months of post-injection followup. Patients with neurogenic bladder were excluded from this analysis. Patient demographic data included gender, side, laterality, ultrasound findings, and the grade of VUR. Initial ultrasound studies were reviewed, and hydronephrosis was graded using the Society for Fetal Urology (SFU) system and the Urinary Tract Dilation (UTD) classification systems.[10,11] Retro-vesical ureteral diameter was measured and documented as well. The severity of VUR was determined using the international classification of VUR after reviewing the voiding cystourethrography (VCUG).[12] Low-grade VUR includes grades 1, 2, and 3, whereas grades 4 and 5 were considered high-grade reflux. Urine culture reports were reviewed, and the causative pathogens were identified.

VCUG was indicated whenever a patient developed a recurrent fUTI without hydronephrosis/ hydroureter (ureteral diameter >4 mm) or a single fUTI associated with either hydronephrosis or hydroureter. Initial Dx/HA injection was performed if the patient had documented VUR complicated with fUTI, which was considered when a patient developed a fever exceeding 39 °C concurrent with the presence of pyuria and the isolation of a single pathogen at a concentration exceeding 50 000 colony-forming units/ml in a urine culture.

In most cases, antibiotic prophylaxis was initiated until the age of one year, then the Dx/HA injection procedure was performed; the antibiotic was discontinued at the next followup visit for low-grade VUR and continued for high-grade VUR. Earlier Dx/HA injection for infants younger than one year was performed if breakthrough fUTI was experienced or due to surgeon/ parent preference. Amoxicillin (2 mg/kg/day) was the antibiotic of choice in the first two months of life, then later changed to trimethoprim (2 mg/kg/day).

Dx/HA injection was performed as a day surgery procedure under general anesthesia. Hydrodistension was carried out routinely before commencing Dx/HA injection. Dx/HA was injected in a subureteral fashion (STING procedure) at the six o'clock position until obtaining the satisfying "volcano" configuration. Thereafter, hydrodistension was repeated to make sure the ureteral orifice was coapted.

Following the procedure, a followup ultrasound examination was performed within 3–4 months to exclude the possibility of obstruction attributed to the presence of a Dx/HA mound. In the absence of any subsequent fUTI, annual ultrasound evaluations were performed for a minimum duration of 4–5 years to monitor the identification of delayed obstructions and facilitate assessment of renal growth. If a patient experienced post-Dx/HA fUTI, a new VCUG was warranted to reassess the status of VUR. In the case of persistent VUR, further treatment options were discussed with the parents. Repeated Dx/HA injection was preferable to more invasive procedures.

### Study outcomes

The primary outcome of this study was to assess the influence of age at Dx/HA injection on the efficacy of the initial injection, comparing outcomes between children younger than one year and those older than one year. Data compared included post-injection VUR resolution, recurrence of fUTI, and the need for repeated interventions.

The secondary outcome was to explore potential determinants that may predict procedural failure. Patients were categorized into two groups: those who experienced successful initial injections and those who encountered a failed initial injection. A successful injection was defined as the absence of post-injection fUTI necessitating subsequent interventions, while the patient was not under antibiotic prophylaxis during this followup period. For patients with bilateral VUR who subsequently developed fUTI following injection, the absence of VUR on one side, as confirmed by a VCUG

and intraoperative hydrodistension test, were deemed indicative of a successful injection for that side.

### Data analysis

Data were analyzed using the commercially available Statistical Package for the Social Sciences, version 26. Categorical variables were conveyed in numbers and percentages, while medians and ranges were employed to portray continuous data. The assessment of categorical data was carried out using the Chi-squared test, whereas non-parametric tests (the Mann-Whitney U test) were applied for continuous data. For the evaluation of independent predictors of procedural failure, the COX regression test was used in both univariate and multivariate analyses. In the univariate analysis, any assessed factor exhibiting a significance level of $p<0.1$ was included in the multivariate model. A $p<0.05$ was established as the threshold for statistical significance.

## RESULTS

A total of 247 patients with VUR complicated by recurrent fUTI were retrospectively reviewed. We excluded 23 patients who underwent interventions other than Dx/HA injection, 37 patients with post-injection followup <2 years, 13 patients with neurogenic bladder, and two patients with high-grade VUR whose parents refused Dx/HA injection. Ultimately, 172 patients with 189 renal units were included in the data analysis.

### Presentation and initial assessment

The patient's demographics are summarized in Table 1. There were no significant differences between the groups in terms of gender, side, and laterality. Sixty patients (34.9%) underwent subureteral injection before the age of one year, whereas 112 patients (65.1%) underwent the procedure after 12 months of age. More than half of the units had a successful initial injection and almost one-third of those with failed initial injection had no hydronephrosis at initial presentation (p=0.01) (Table 2). On VCUG, two units were associated with Hutch diverticulum when Dx/HA was injected at less than 12 months old, compared to four units in the other group. Thirty-three boys underwent Dx/HA injection. All of them were offered circumcision after the initial fUTI; however, three patients (9.1%) refused. One of the three boys had failed initial injection (p=0.46).

### Initial Dx/HA injection

All enrolled patients underwent Dx/HA injections due to VUR complicated with fUTI. Nearly 88% of patients (166 units) had the initial Dx/HA injection after the age

**Table 1. Patients' demographics**

| Parameter | | Successful initial injection 139 units 125 patients | Failed initial injection 50 units 47 patients | p |
|---|---|---|---|---|
| Age at presentation median (range)* | | 25.6 (0.1–154.8) | 16.9 (1.7–154.8) | 0.41 |
| Age at presentation | ≤1 year old, n (%) | 37 (29.6) | 23 (48.9) | 0.02 |
| | >1 year old, n (%) | 88 (70.4) | 24 (51.1) | |
| Gender | Male, n (%) | 28 (22.4) | 5 (10.6) | 0.08 |
| | Female, n (%) | 97 (77.6) | 42 (89.4) | |
| Side | Right, n (%) | 65 (46.8) | 19 (38) | 0.28 |
| | Left, n (%) | 74 (53.2) | 31 (62) | |
| Laterality | Unilateral, n (%) | 111 (88.8) | 44 (93.6) | 0.35 |
| | Bilateral, n (%) | 14 (11.2) | 3 (6.4) | |
| Pathogen in first UTI | *E. coli,* n (%) | 89 (71.2) | 32 (68.1) | 0.69 |
| | Others, n (%) | 36 (28.8) | 15 (31.9) | |

*Age of presentation in months. UTI: urinary tract infection.

**Table 2. Preoperative radiologic findings**

| Parameter | | Successful initial injection | Failed initial injection | p |
|---|---|---|---|---|
| SFU | Grade 0, n (%) | 73 (52.5) | 16 (32) | 0.045 |
| | Grade 1, n (%) | 24 (17.3) | 9 (18) | |
| | Grade 2, n (%) | 27 (19.4) | 17 (34) | |
| | Grade 3, n (%) | 15 (10.8) | 7 (14) | |
| | Grade 4, n (%) | 0 | 1 (2) | |
| UTD | Normal, n (%) | 83 (59.7) | 21 (42) | 0.045 |
| | P1, n (%) | 17 (12.2) | 4 (8) | |
| | P2, n (%) | 38 (27.4) | 24 (48) | |
| | P3, n (%) | 1 (0.7) | 1 (2) | |
| Ureteric diameter median (range) | | 0 mm (0–9) | 3 mm (0–8) | 0.006 |
| Ureteral dilatation | ≤4 mm, n (%) | 111 (79.9) | 32 (64) | 0.025 |
| | >4 mm, n (%) | 28 (20.1) | 18 (36) | |
| VUR grade | Grade 1, n (%) | 27 (19.4) | 6 (12) | 0.049 |
| | Grade 2, n (%) | 42 (30.2) | 9 (18) | |
| | Grade 3, n (%) | 39 (28.1) | 13 (26) | |
| | Grade 4, n (%) | 20 (14.4) | 15 (30) | |
| | Grade 5, n (%) | 11 (7.9) | 7 (14) | |

SFU: Society for Fetal Urology; UTD: urinary tract dilation; VUR: vesicoureteric reflux.

**Table 3. Operative and followup data**

| Parameter | | Successful initial injection | Failed initial injection | p |
|---|---|---|---|---|
| **Operative data** | | | | |
| Age at 1st injection median (range)* | | 46.5 (4.9–176.9) | 37.6 (4.7–166.6) | 0.037 |
| Age at 1st injection | ≤1 year old, n (%) | 11 (7.9) | 12 (24) | 0.003 |
| | >1 year old, n (%) | 128 (92.1) | 38 (76) | |
| Amount of injected Dx/HA, median (range) | | 0.9 (0.4–2) | 1 ml (0.4–3) | 0.07 |
| Number of repeated Dx/HA injections | Single time, n (%) | 139 (100) | – | – |
| | 2 times, n (%) | – | 34 (70.8) | |
| | 3 times, n (%) | – | 9^ (18.8) | |
| | 4 times, n (%) | – | 5^ (10.4) | |
| **Followup data** | | | | |
| Followup median (range)* | | 42.2 (24–155.2) | 51.2 (29–135.5) | 0.001 |
| Last SFU | Grade 0, n (%) | 111 (79.9) | 33 (66) | 0.004 |
| | Grade 1, n (%) | 25 (18) | 10 (20) | |
| | Grade 2, n (%) | 3 (2.1) | 7 (14) | |
| | Grade 3, n (%) | 0 | 0 | |
| | Grade 4, n (%) | 0 | 0 | |
| Last UTD | Normal, n (%) | 131 (94.2) | 35 (70) | <0.001 |
| | P1, n (%) | 2 (1.4) | 5 (10) | |
| | P2, n (%) | 6 (4.4) | 10 (20) | |
| | P3, n (%) | 0 | 0 | |

*Age of presentation in months. ^1 patient had ureteric reimplantation due to recurrent UTI after the second injection and one after the third. SFU: Society for Fetal Urology; UTD: urinary tract dilation; VUR: vesicoureteric reflux.

of one year, with 116 units (61.4%) after the age of three years. Only 47.8% of units under the age of one year had successful initial Dx/HA injection compared to 77.1% of units that were injected after the age of one year (p=0.006). Interestingly, failed initial injection before the age of one was not associated with high-grade VUR, and similarly after the age of three years (p=0.54 and p=0.33, respectively) (Supplementary Figure 1; available at *cuaj.ca*).

Grade 4 and 5 reflux were predominant when injection was performed between the ages of 1–3 years (p=0.005). The amount of injected Dx/HA injection was not associated with the need for repeated injection (p=0.07).

### Subsequent Dx/HA injections/surgical interventions (Table 3)

A total of 47 patients (50 renal units) underwent subsequent Dx/HA injections. Seventy-one percent of these units had no recurrent fUTI after the second injection. Five patients (10%) underwent surgical interventions (one after the second injection, one after the third injection, and three after the fourth injection). Four units had ureteric reimplantation, and one underwent nephrectomy. Regarding the age at presentation, it is noteworthy that 38.3% of patients who presented in the first year of life subsequently required repeated injections compared to 21.4% of patients older than 12 months (p=0.02).

Regarding the age at Dx/HA injection, a subset comprising 41.7% (5/12) of patients, who experienced unsuccessful initial Dx/HA injection before one year of age, exhibited preoperative high-grade VUR compared to 44.7% (17/38) in the comparative group (p=0.85). Of six units associated with Hutch diverticulum preoperatively, five required repeated injections. Hutch diverticulum was present in two (16.7%) and three (7.9%) units when Dx/HA was injected in those younger and older than one year old, respectively (p=0.38). Of note, grade 4 reflux was predominant among patients who underwent repeated injections after reaching one year of age (13 units), while grade 3 reflux (five units) was the prevailing grade observed before the age of one.

VCUG or nuclear cystourethrogram was repeated for patients who experienced post-injection fUTI. When injection was performed before the age of one year, out of 23 units, five units (21.7%) retained the same VUR grade, while seven units (30.4%) showed downgraded grades (p=0.8). On the other hand, when injection was performed after the age of one year, 17 units showed the same grade of VUR, and the remaining had lower grades (p=0.8). The univariate analysis showed that the age at presentation, ureteric dilation, high-grade VUR, and age at injection of less than one year were significantly associated with repeated Dx/HA injection (Table 4). The multivariate model revealed that VUR grade and the age at injection were independent predictors for recurrent fUTI and the need for subsequent intervention after the initial Dx/HA injection.

## DISCUSSION

Accurate diagnosis and proper management of VUR are critical to prevent associated complications, including recurrent fUTI, hypertension, and chronic renal failure. Historically, medical treatment with prophylactic,

low-dose antibiotics was the mainstay to suppress pathogenic organisms and subsequent fUTI. Antibiotic prophylaxis requires consistent adherence and regular dose adjustment due to weight change. Furthermore, the risk of antibiotic resistance in children receiving prophylactic antibiotics should be considered when choosing management options.[13,14] In addition, prolonged antibiotic prophylaxis may have deleterious effects on the microbiome of the gut, with a significant impact on patients' overall health. Surgical intervention, specifically ureteroneocystostomy, is mainly indicated if medical therapy fails.

Cystoscopic injection of bulking agents has gained popularity due to its immediate cure with a high success rate when compared with long-term antibiotic prophylaxis. In addition, it is less invasive and associated with lower comorbidities compared with ureteric reimplantation surgery. The concept of endoscopic subureteral injection therapy has developed considerably since its introduction in the early 1980s, by forming solid support behind the intramural ureter and subsequently increasing its submucosal length.[5]

In 1995, Stenberg and Lackgren introduced the Dx/HA (Deflux®) as an injectable bulking agent, which was approved by the U.S. Food and Drug Administration in 2002.[15] Defux is a highly viscous material of dextranomer microspheres (80–250 µm in diameter) in non-animal-stabilized hyaluronic acid that acts as a carrier. Although many substances could be used for injection, including Teflon, Dx/HA, bovine collagen, and silicone/macroplastique, they have their limitations in terms of safety and efficacy in pediatric patients.[3,16] Currently, Dx/HA is a commonly used bulking agent in VUR injection in pediatrics and has a high safety profile.[1]

Early success rate of Dx/HA injection therapy has been reported in several studies, with an overall success rate of 68–92%.[17-19] Kirsch et al reported comparable early success rates of Dx/HA injection using the hydrodistension implantation technique with ureteroneocystostomy.[16] Lee et al reported a success rate of 73% in the first postoperative VCUG, a recurrence rate of 26% at one year, and an overall cumulative failure rate of 54%.[20] Kim et al reported a success rate of Dx/HA injection therapy of 79.5% at three months postoperative, 75.2% at one year, and 76.4% at three years.[21]

In our study, the overall success rate for individual renal units after the initial injection was 73.5%, 91.2% after the second injection, and 96.3% after the third injection. Five units (2.6%) of our cohort required other surgical interventions, which confirms the utility of repeated injections to avoid more invasive procedures.

**Table 4. The univariate and multivariate analysis of possible predictors of failed initial Dx/HA injection**

| Parameter | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p |
| Age at presentation >1 year | 0.552 | 0.314–0.970 | 0.039 | 1.117 | 0.532–2.345 | 0.771 |
| Gender | 2.235 | 0.690–7.246 | 0.18 | – | – | – |
| Side | 0.805 | 0.451–1.436 | 0.463 | – | – | – |
| Laterality | 1.325 | 0.702–2.494 | 0.383 | – | – | – |
| *E. coli* UTI | 1.271 | 0.708–2.282 | 0.422 | – | – | – |
| Ureteric diameter >4 mm | 1.118 | 1.012–1.234 | 0.028 | 1.725 | 0.637–4.674 | 0.283 |
| SFU grade 4 | 1 | | 0.28 | – | – | |
| SFU grade 3 | 0.533 | 0.064–4.427 | 0.533 | – | – | – |
| SFU grade 2 | 0.678 | 0.088–5.208 | 0.709 | – | – | – |
| SFU grade 1 | 0.778 | 0.095–6.346 | 0.815 | – | – | – |
| SFU grade 0 | 0.24 | 0.031–1.863 | 0.172 | – | – | – |
| UTD P3 | 1 | | 0.52 | – | – | – |
| UTD P2 | 1.192 | 0.159–8.943 | 0.864 | – | – | – |
| UTD P1 | 0.657 | 0.068–6.367 | 0.717 | – | – | – |
| UTD normal | 0.506 | 0.067–3.828 | 0.509 | – | – | – |
| VUR grade 5 | 1 | | 0.05 | 1 | | 0.045 |
| VUR grade 4 | 0.648 | 0.263–1.595 | 0.345 | – | – | – |
| VUR grade 3 | 0.709 | 0.279–1.798 | 0.469 | – | – | – |
| VUR grade 2 | 0.299 | 0.109–0.822 | 0.019 | 0.195 | 0.044–0.862 | 0.031 |
| VUR grade 1 | 0.269 | 0.089–0.81 | 0.02 | 0.169 | 0.038–0.764 | 0.021 |
| Age at injection <1 year | 3.248 | 1.68–6.280 | <0.001 | 3.379 | 1.482–7.704 | 0.004 |

CI: confidence interval; HR: hazard ratio; SFU: Society for Fetal Urology; UTD: urinary tract dilation; UTI: urinary tract infection; VUR: vesicoureteric reflux.

Kajbafzadeh et al reported the results of Dx/HA injection therapy in 372 patients, with a success rate of 86.6%.[22] In addition to the grade of preoperative VUR, they found that treatment techniques and whether to form a hyper/iso-echogenic oval protuberance around the ureterovesical junction in the postoperative ultrasound predicted the success rate in the univariate analysis. In the multivariate analysis, these factors, apart from the treatment technique, maintained their significance to the success rate.[22] An 87% success rate was described when considering the final postoperative "volcano" appearance, described by Puri et al. Indeed, post-injection morphology significantly predicted success rather than the injection technique and

the depth of needle penetration.[18] Our multivariate analysis showed that the VUR grade and age at injection would independently predict a successful initial Dx/HA injection.

To our knowledge, this is the first study to assess the impact of age at first injection on the outcome of the endoscopic procedures. Only half of the units under the age of one year had successful initial Dx/HA injection, which was significantly lower than those injected after one year (48 vs. 77%). Moreover, failed initial injection before the age of one was not associated with the grade of VUR. This may be related to technical aspects of the endoscopic intervention in this age group or the association of VUR. The grade of VUR and the Dx/HA mound were found to influence the success rate of injection therapy.[22] Furthermore, almost 40% of our infants who presented in the first year of life subsequently required surgical interventions, which was significantly higher than what was required for children who presented later. This may support the technical difficulties of endoscopic intervention in young infants.

A subgroup analysis for patients who experienced unsuccessful initial Dx/HA injection before one year of age showed more preoperative high-grade VUR than those who were injected at an older age. This may further explain the higher failure rate associated with intervention before the age of one year, as explained previously.[22]

Patients who experience failure of endoscopic treatment can be observed for spontaneous resolution of VUR unless they have fUTI or decreased renal function. A urodynamic study may help decide whether a secondary procedure is necessary in these patients.[23] A significant reduction in the severity of reflux was seen in patients with grade 2–4 VUR after a single injection. In contrast, most patients with grade 5 reflux needed more than one injection to achieve complete resolution.[24]

Endoscopic treatment has its complications, the most important of which is ureteral obstruction; however, it was reported in <1% after Defux injection, although it could possibly be higher after treatment with other materials.[25]

We believe that early Dx/HA injection, before the age of one, should not be recommended due to the relatively small size of the ureteric orifice in this age group, which poses a risk of ureteric obstruction. Moreover, the ureteral tunnel growth in patients older than one year old could explain the higher success rate. Therefore, it is better to inject Dx/HA after the age of one year, but if early injection is needed, parents should be counseled about the higher incidence of repeated injections.

### Limitations

This study is limited by its retrospective nature and the relatively small number of patients who had Dx/HA injections before one year of age. More comparative studies with larger numbers of patients who underwent initial injections before the age of one year are warranted.

VCUG was not done for all patients post-Dx/HA to confirm the resolution of VUR; however, it is our policy to reserve VCUG for symptomatic patients only to minimize unnecessary radiation exposure and procedure-related stress. Moreover, the main objective of Dx/HA therapy is to prevent fUTI, so the absence of fUTI is considered an indicator of a successful procedure.

## CONCLUSIONS

In our study, almost 27% of the included renal units underwent repeated Dx/HA injections. Forty-four percent of units with repeated injections had high-grade reflux. Patients with VUR who present with fUTI before the age of one year may have a higher risk of repeated Dx/HA injections than those who present later. VUR grade and the age at injection are independent predictors for recurrent fUTI and the need for subsequent intervention after the initial Dx/HA injection. Therefore, it is better to inject Dx/HA after the age of one year. If an early injection is considered, counseling the parents about the higher incidence of repeated injections is advised.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

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