OBJECTIVES

Endoscopic injection of non–animal-stabilized hyaluronic acid/dextranomer gel is an increasingly recognized treatment option for vesicoureteral reflux. The procedure is minor compared with open surgery and, when successful, avoids the need for long-term antibiotic prophylaxis. We present data from 3 years of using non–animal-stabilized hyaluronic acid/dextranomer gel to treat children with vesicoureteral reflux.

METHODS

Pediatric patients aged 16 years with uncomplicated primary vesicoureteral reflux were recruited for endoscopic treatment with non–animal-stabilized hyaluronic acid/dextranomer gel. A follow-up voiding cystourethrogram was scheduled at 2 weeks after treatment, and vesicoureteral reflux resolution was defined as grade 0. Repeat non–animal-stabilized hyaluronic acid/dextranomer gel treatment was offered to patients with persistent vesicoureteral reflux.

RESULTS

Of 178 patients treated, 12 were lost to follow-up or yet to undergo post-treatment voiding cystourethrogram. The 166 remaining patients (efficacy population) had a mean age of 4.21 years (range: 0-16), and the median reflux grade was 3 (range: 1-5). Vesicoureteral reflux was resolved in 81.9% of patients and 86.4% of ureters after initial endoscopic treatment with non–animal-stabilized hyaluronic acid/dextranomer gel. The overall reflux resolution rate for patients increased to 89.6% after a second treatment in 19 patients, and 90.2% after a third treatment in 1 patient. No adverse events were reported. Five patients underwent open ureteral reimplantation after failed endoscopic injections.

CONCLUSIONS

Endoscopic treatment with non–animal-stabilized hyaluronic acid/dextranomer gel is effective in a high proportion of children with vesicoureteral reflux and, in our opinion, should be considered as a first-line treatment option.
cross-linked dextranomer microspheres (80-250 μm in diameter) suspended in a 1% carrier gel of non–animal-stabilized hyaluronic acid. HA/Dx gel is a biodegradable material that does not migrate to distant tissues after injection.\textsuperscript{11,12} Moreover, it does not seem to be immunogenic or carcinogenic.\textsuperscript{13} Finally, long-term series have not shown any chronic ill effects from treating children with HA/Dx gel.\textsuperscript{14,15}

Endoscopic injection is usually performed on an outpatient basis, sparing patients the trauma of major surgery and hospitalization. It is quickly performed (approximately 15 minutes), and no incision is made. Furthermore, refinements in technique have resulted in cure rates approaching those with open ureteral reimplantation.\textsuperscript{16}

We have previously described our initial experience with endoscopic injection of HA/Dx gel. However, few US urologists have reported their intermediate-term experience of endoscopically injecting HA/Dx gel for VUR. In this study, we report the efficacy and safety outcomes for all patients treated with HA/Dx gel during the past 3 years of administering this treatment after our initial 5-year experience.

**MATERIAL AND METHODS**

Children aged ≤16 years and diagnosed with uncomplicated, primary grade I-V VUR (unilateral or bilateral) were recruited for this open study. VUR was diagnosed by voiding cystourethrogram (VCUG), and all patients were presented with the following treatment choices: (1) antibiotic prophylaxis, (2) ureteral reimplantation, or (3) subureteric injection of HA/Dx gel. Parental choice determined the subsequent treatment of VUR. Exclusion criteria for subureteric injection included neuropathic bladder, Hutch diverticulum, and bladder extrophy. For patients with bilateral reflux or a history of bilateral reflux, both ureters were treated. In addition, contralateral nonrefluxing ureters with anatomic abnormalities (cephalad ectopia) or a history of previous reflux were injected, which is consistent with our indications for contralateral open reimplantation in nonrefluxing ureters.

The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of Baylor College of Medicine for retrospective review of the patients’ charts. Signed informed consent was obtained from all patients’ parents or guardians for the endoscopic treatment. Patients were treated between February 4, 2005, and March 4, 2008. Treatment was administered to each patient using both the subureteric transurethral injection (“STING”)\textsuperscript{10} and the hydrodistention-implantation technique.\textsuperscript{17} For the STING procedure, patients received general anesthesia and were placed in the lithotomy position. A 9.5F Storz cystoscope (Richard Wolf, GmbH, Knittlingen, Germany) was used to inject HA/Dx gel via a prefilled syringe (standard low-pressure type) and needle (3.7F, 21 G, with a 23-G tip) as sold by Q-Med AB. The needle was inserted tangentially to a depth of 4.5 mm, at the base of the ureteral orifice (6 o’clock position), and injection was performed until a prominent bulge was seen. Specifically, an ideal injection resulted in elevation of the distal ureter and ureteral orifice, increasing the submucosal length of the ureter. The hydrodistention-implantation technique was performed similar to the STING, but with the following differences: HA/Dx gel was injected into the distal ureteral submucosa (6 o’clock position). Pressurized irrigation (hydrodistention) of the ureter was used to facilitate correct positioning of the needle. Hydrodistention was stopped and the needle inserted to a depth of 4 mm. HA/Dx gel was then injected until complete coaptation of the ureter was achieved (a standard STING injection was performed additionally in all cases). For the first few cases in 2001, the STING injection procedure was used exclusively; however, for the duration of this review a combination treatment was almost always used, based on anatomic findings at the time of surgery and how well each procedure was progressing during initial injection.

Perioperative prophylactic cefazolin (30 mg/kg/dose) was administered at the start of each procedure. Sulfamethoxazole 200 mg and trimethoprim 40 mg per 5 mL, at 2 mg trimethoprim/kg/dose daily, or nitrofurantoin 1-2 mg/kg/d, as a single daily dose, was used for postoperative antibiotic prophylaxis, until a postoperative cystogram confirmed resolution of VUR.

To appraise treatment efficacy, children returned for a single VCUG assessment at least 2 weeks after treatment. VCUGs were carried out using a standard protocol, and resolution of reflux was defined as grade 0. In addition, patients and their parents were asked whether any adverse events had occurred after treatment. A follow-up renal ultrasound study was performed 1 year postprocedure. Another follow-up VCUG was performed for any treatment failures.

Our protocol for evaluation of infection after successful De-flux treatment is individualized to the child. Additional VCUGs are performed if patients have nongastroenteric infection–related nausea or vomiting, more than 4 nonfebrile UTI, or more than 1 postoperative febrile UTI.

Repeat treatment with HA/Dx gel injection was offered to patients with persistent postoperative reflux (grade ≥II). This second implantation was again followed by a VCUG scheduled at any time ≥2 weeks post-treatment. Patients with reflux grades 0-1 according to their last VCUG did not undergo any further treatment or assessment, unless presenting with postoperative UTIs.

Data were analyzed for all children undergoing HA/Dx gel treatment. Children without VCUG results after their last HA/Dx gel implantation were excluded from efficacy analysis. Efficacy data were stratified according to reflux grade.

**RESULTS**

**Patients and Procedures**

A total of 178 children with VUR were endoscopically treated between February 4, 2005, and March 4, 2008. The female:male ratio of these patients was 5.6:1 and their mean age was 4.21 years. One hundred seven patients had either bilateral reflux or indications in the contralateral ureter warranting HA/Dx gel injection; thus, 285 ureters were initially treated. Of these, 13 were nonrefluxing ureters meeting the criteria for contralateral open reimplantation. The mean volume of HA/Dx gel injected was 0.99 mL per ureter. No specific abnormalities were seen on postoperative ultrasonography. After the initial treatment, 12 patients were lost to follow-up or yet to undergo post-treatment VCUG. Therefore, the efficacy population consisted of 166 patients, in whom 265 ureters (252
In our present study, 13 patients were injected bilaterally although diagnosed with grade 0 reflux unilaterally by VCUG. These injections were done either due to an abnormal appearance of the ureteral orifice or a history of refluxing and 13 nonrefluxing) were treated (Table 1). The preoperative reflux grade of these ureters is shown in Table 1; the median reflux grade was 3.

Nineteen patients in the efficacy population (11.4%) underwent a second endoscopic injection because reflux did not resolve after the first treatment. At the time of repeat cystoscopy, there was either medial migration of the HA/Dx mound or no evidence of a previous injection. Three patients who had unilateral injection of Deflux, developed new contralateral reflux after endoscopic treatment (the treated side was resolved in 2 of these cases). One patient underwent a third treatment, and 5 underwent ureteral reimplantation during the study period.

### Efficacy

Reflux was resolved in 81.9% of patients and 86.4% of ureters after a single HA/Dx gel treatment (ie, bilaterally, reflux grade 0). After the second implantation, the number of patients free from reflux increased to 89.6%. After a second implantation, the cumulative reflux resolution rate by ureter was 95.6%. After a third implantation, this increased to 90.2% by patient and 96% by ureter.

The positive response rates for ureters after a single injection, stratified according to baseline reflux grade, are shown in Table 2 according to data from the first follow-up. A decrease in the resolution rate is apparent as the baseline reflux grade increases from II to V. During the study period 13 ureters were injected based on cystoscopic appearance with no evidence of VUR preoperatively. None of these 13 ureters developed new VUR postoperatively.

Of 44 children with follow-up available at 1 year, 11 (25%) suffered 1 or 2 postoperative, nonfebrile UTI episodes. No children suffered postoperative febrile UTI. Per our institution's protocol, VCUGs were not repeated in these patients.

### Safety and Tolerability

In this study, other than repeat endoscopic implantation of HA/Dx gel in select cases, there were no postoperative complications that required surgical intervention. Three patients had bladder spasms, which resolved spontaneously or with a short course of oral anticholinergic therapy (oxybutynin).

### COMMENT

This study suggests that the learning curve for endoscopic injection of HA/Dx gel in children with VUR reaches an asymptote within 5 years or less. The cumulative reflux resolution rate (reflux grade 0) for patients was 89.6% after 1-2 treatments. Likewise, the cumulative reflux resolution rate by ureter was 95.6% after 1-2 treatments. This is similar to our initial series, in which reflux was resolved in over 90% of patients and 92.6% of ureters at the time of previous VCUG, following 1-2 treatments. It is notable that consistent with our early experience, in 81.3% of children, a single endoscopic injection was sufficient. However, although none of our patients from the initial series underwent open surgery during the study period, we identified 5 patients who underwent ureteroneocystostomy. Just as we found in our early patient cohort, in patients not cured by the first endoscopic injection, repeat treatment proved viable with a resolution rate approaching two-thirds.

This study indicates that, even after the learning curve crests, there is a lower rate of reflux resolution among children with high-grade disease treated with Deflux. Our original series featured only 2 patients with grade V reflux, making it difficult to draw conclusions. In contrast, our intermediate experience included 9 patients with grade V disease, with 55.6% and 44.4% of ureters demonstrating resolution or improvement of reflux, respectively.

A relatively brief learning curve has been observed for subureteric injection, with lower cure rates in the first few cases. In our previous report we saw no such learning curve, but continued to monitor our intermediate outcomes to determine whether we would encounter another “hump” in the learning curve. Fortunately, this was not the case.

Seventy-eight ureters with grade 2 reflux were injected. The therapeutic indications were presence of contralateral reflux of higher grade or breakthrough UTIs despite prophylactic antibiotics. Surprisingly, 2.6% of the ureters with grade 2 reflux worsened after treatment. This may be because of the inherent variability of VUR interpreted by cystography.

In our present study, 13 patients were injected bilaterally although diagnosed with grade 0 reflux unilaterally by VCUG. These injections were done either due to an abnormal appearance of the ureteral orifice or a history of

### Table 1. Baseline grade of ureters included in the efficacy analysis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
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<tr>
<td>Total</td>
<td>67</td>
<td>198</td>
<td>265</td>
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Table 1. Baseline grade of ureters included in the efficacy analysis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Resolved</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worse</th>
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<td>5.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2</td>
<td>89.7%</td>
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<td>7.7%</td>
<td>2.6%</td>
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<td>3</td>
<td>89.8%</td>
<td>5.6%</td>
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<tr>
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<tr>
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<td>55.6%</td>
<td>44.4%</td>
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</table>

Table 2. Ureteral outcomes following the first HA/Dx gel treatment procedure, stratified according to baseline reflux grade

Resolved = VUR grade 0 at the last VCUG; worsened = VUR grade at the last VCUG worse than baseline.
reflux. These ureters were not included in the efficacy analysis. Contemporary reports have demonstrated a 5%-8% false-negative rate with VCUG; lending support to the concept of injecting abnormal-appearing, contralateral ureteral orifices.

Patients treated with HA/Dx gel in the present study experienced few complications, with only 5 patients with bladder spasms requiring anticholinergic therapy. In our initial cohort, 2 patients experienced mild, temporary postoperative flank pain. This finding reinforces earlier studies reporting that HA/Dx gel implantation is well tolerated.

Indeed, a histopathologic study of HA/Dx gel, done in VUR patients a mean of 3 years after surgery, showed evidence of only minor inflammatory reactions. The authors concluded that HA/Dx gel remains safe and effective for VUR in children.

A recent report has suggested that endoscopic injection of HA/Dx gel for VUR may be prone to late failures as assessed by 1-year postoperative VCUG. Because of ethical concerns, we have not repeated a VCUG on a child who has had a favorable result after a Deflux injection unless contraindicated or the patient requests repeat imaging. In our practice, if during our intermediate-term experience, have led us to continue to recommend broad usage of HA/Dx gel as first-line treatment for children with grade II-IV VUR.

CONCLUSIONS

Our intermediate-term series has shown that, after a learning curve likely much shorter than 5 years and based on a single VCUG performed shortly after surgery, VUR may be cured by endoscopic injection of HA/Dx gel in a large proportion of patients. Hence, we deem endoscopic treatment with HA/Dx gel as a valuable treatment option for children with VUR. Table 3.

Table 3. Comparison of total patients and ureters successfully treated after the first and second HA/Dx gel implantations

<table>
<thead>
<tr>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
<th>% Cured</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>Second injection</td>
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<td>11</td>
<td>64.7</td>
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<td>0</td>
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<td>0</td>
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<td>95.2</td>
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</tr>
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<td>Third injection</td>
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<td></td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Patients</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Ureters</td>
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REFERENCES