Downgrading of high-grade vesicoureteral reflux is a reliable option in the treatment of children with grade IV–V reflux accompanied by breakthrough infections

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KEYWORDS
High-grade VUR; Endoscopic treatment; Downgrade VUR, long-term follow-up; Renal scarring; UTI

Abstract Purpose: To evaluate incidence of urinary tract infection (UTI) and natural history of downgraded vesicoureteral reflux (VUR) in children with high-grade VUR following endoscopic correction. Materials and methods: We retrospectively studied 54 children (13 males and 41 females) with a mean age of 1.8 years who underwent endoscopic correction of Grade IV–V VUR due to breakthrough infections while on antibiotic prophylaxis. Reflux was Grade IV in 40 (74%) and V in 14 (26%) patients comprising 95 renal refluxing units (RRU). Reflux was corrected in 72 (76%) RRU. 18 (34%) patients/23 (24%) RRU demonstrated downgrading of VUR. 21 of the 23 RRU showed Grade II and 2 Grade III VUR, and were taken off antibiotic prophylaxis and allocated to observation. Patients were followed for 2–22 years (median 14 years). Results: Technetium 99m dimercaptosuccinic acid renal scan demonstrated preoperative renal scarring in 21 (78%) of the 23 RRU with downgraded VUR. None of the children developed febrile UTI after surgery. 1 RRU showed renal function deterioration. 8 (44%) of the 18 patients underwent follow-up voiding cystourethrogram, and in 7 (88%) there was either spontaneous resolution of VUR or downgrade to Grade I VUR.

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Conclusions: Downgrading of VUR is a reasonable option in patients with high-grade VUR suffering from breakthrough infections while on antibiotic prophylaxis. It leads to the cessation of febrile UTIs, further spontaneous resolution of VUR and may potentially avoid renal damage. © 2012 Journal of Pediatric Urology Company. Published by Elsevier Ltd. All rights reserved.

Introduction

The concept of the endoscopic correction of vesicoureteral reflux (VUR) offers a minimally invasive treatment in the management of urinary tract infection (UTI) or renal parenchymal damage associated with reflux [1−3]. Recently published American Urological Association (AUA) guidelines on the treatment of VUR clearly state that there is an association between high-grade VUR, febrile UTIs and renal parenchymal damage [4]. Furthermore, the AUA guidelines demonstrate that successful correction of VUR leads to a decrease in febrile UTIs and may avoid renal scarring as a result of that. Since the introduction of endoscopic correction of VUR 2 decades ago, and over the last 7 years since the approval of dextranomer hyaluronic acid (Dx/HA) copolymer (Deflux, Q-Med Scandinavia, Uppsala, Sweden) for the treatment of VUR by the Food and Drug Administration (FDA), the endoscopic management of VUR has emerged as a first-line treatment for all grades of reflux in some centers [1−3,5,6]. The overall success rates reported by the different groups of authors range between 68% and 92%, depending mainly on the VUR grade [1−3]. Moreover, the results of endoscopic correction of high-grade VUR are inferior to those of open surgery, as reported by the majority of the researchers [3]. In spite of the large number of published reports on the different aspects of the endoscopic treatment of VUR, there are still scant data available on the natural history of patients with high-grade VUR who demonstrated downgrading of VUR after endoscopic correction and were spared an additional surgical intervention. We aimed to evaluate the incidence of UTI and natural history of downgrading VUR in children with high-grade VUR who underwent endoscopic correction due to breakthrough infection while on antibiotic prophylaxis.

Materials and methods

Over the last 2 decades more than 1000 patients underwent endoscopic correction of primary VUR in our department. Of those, we have retrospectively reviewed patients with grade IV and V VUR who required reflux correction due to breakthrough UTIs while on antibiotic prophylaxis. Following institutional review board approval we have extracted from the charts demographic data, material used for endoscopic correction, radionuclide study data before and after surgery, and post-surgery UTI occurrence.

Only patients with primary VUR were included. In order to perform a homogenous analysis children with duplex system and bladder diverticula were excluded from the study. The reflux grade was based on voiding cystourethrogram (VCUG) only, before and after the surgery, or during conservative treatment according to the International Classification System (International Reflux Study Committee) [7]. Reflux was Grade IV in 40 (74%) and Grade V in 14 (26%) patients comprising 95 renal refluxing units (RRU). Technetium-99m dimercaptosuccinic acid (DMSA) scan and renal ultrasound were performed in all patients preoperatively. DMSA renal scans were taken to assess relative renal function using background corrected regions of interest of each kidney in the posterior view and calculating the resultant percentage uptake. DMSA scan was performed at least 6 months after the last febrile UTI. Renal scintigraphy was taken 2 h after injection of DMSA. The fractional left and right renal activity was calculated for each kidney. A kidney uptake of 45%−55% of the total renal activity was considered normal. Renal damage was classified into mild−focal defects on uptake. Relative renal function of 20%−45% was considered as moderate and below 20% was considered as poor [5].

The only indication for endoscopic correction in the group of patients studied here was high-grade VUR accompanied by breakthrough infections while on antibiotic prophylaxis.

Since none of the children in this group were toilet trained we cannot assess the presence of dysfunctional voiding. However, those children who were constipated were allocated to treatment prior to the endoscopic correction until full resolution of their bowel dysfunction. The technique used for endoscopic correction of high-grade VUR was similar to that described in the literature and reported by us previously [5,8]. The injection was performed inside the ureteral orifice until full coaptation of the orifice was seen.

As we have already published, according to our standard protocol, ultrasound was performed 1 month after injection in order to identify hydronephrosis, and a VCUG was performed 3−6 months after endoscopic correction [5]. VUR was considered downgraded when VCUG showed Grade II VUR, or in those patients with Grade V VUR Grade III was demonstrated. All patients received antibiotic prophylaxis until VCUG showed either VCUR resolution or downgrading of VUR, and allocation to observation only. In patients with downgraded VUR an annual ultrasound scan was performed in the long-term follow-up. In order to follow-up renal function, all these children underwent a repeated DMSA scan at the beginning of the adolescence period and after the completion of puberty, and in the case of any signs of deterioration of the kidney appearance on ultrasound (such as worsening of hydronephrosis, thinning of parenchyma or arrest of kidney growth) being noticed. Some patients had a repeat VCUG from personal choice of their primary physician or upon enlisting in the army. The urinary samples were obtained either by urethral catheter or utilizing suprapubic bladder aspiration as a part of routine protocol in Israel. In older children a midstream voided specimen
was examined. Since almost all male children in Israel are circumcised, the possibility of contamination in these children is very low. A finding of more than 100,000 colony-forming units per milliliter was defined as a clinically significant UTI. In those who had at least two episodes of recurrent afebrile UTI, VCUG was performed in order to exclude a high-grade VUR recurrence. All patients were followed up for periods ranging from 2 to 22 years with a median follow-up period of 14 years.

Results

Demographic data of the studied population and material used for endoscopic correction are presented in Table 1. In brief, 54 children (13 males and 41 females) with a mean age of 1.8 years (range 8–34 months) underwent endoscopic correction of Grade IV–V VUR. The distribution of renal scarring in the studied patients is presented in Table 2.

In 43 (45.3%) RRU endoscopic correction was initially performed utilizing polytetrafluoroethylene (PTFE) as a tissue-augmenting substance, D4/HA copolymer was used in 50 (52.6%) RRU, and polycarbonate polialcohol bulking copolymer (Vantris) was utilized in the remaining 2 (2.1%) RRU.

Reflex was corrected in 72 (76%) of the 95 RRU. In 18 (34%) patients, 23 (24%) RRU demonstrated downgrading of VUR. Of these patients, 10 (55%) underwent endoscopic correction with PTFE, 6 (33%) Deflux, and in the remaining 2 (11%) Vantris was utilized. Of the 23 RRU, 21 showed Grade II VUR and 2 Grade III VUR, and the patients were taken off antibiotic prophylaxis and allocated to observation. DMSA renal scan demonstrated preoperative renal scarring in 21 (78%) of the 23 RRU with downgrading of VUR. None of the children developed febrile UTI after surgery. Three (16%) female patients suffered from afebrile UTI. One girl was from the PTFE group and two were from the Deflux group. In two, afebrile UTI occurred during the adolescent period and one was diagnosed with dysfunctional voiding. She noticed cessation of UTIs with improvement in the voiding pattern. Only 1 RRU showed further renal function deterioration. This patient had initial severe renal scarring (uptake on DMSA less than 20%). Eight (44%) of the 18 patients underwent follow-up VCUG. Of these, 2 had VCUG as a result of recurrent afebrile UTIs and 5 upon enlisting in the army. Seven (88%) of these patients demonstrated either spontaneous resolution of VUR or Grade I VUR.

Discussion

It has been demonstrated that every episode of pyelonephritis increases the likelihood of a subsequent episode and may lead to renal parenchymal damage [9]. Therefore, the prevention of febrile UTI is a major goal of the treatment of VUR [10–12]. The recently published AJA guidelines on the treatment of VUR clearly state that surgical correction of VUR leads to a decrease in the number of episodes of febrile UTI and in turn may avoid renal scarring [4]. VUR is a heterogeneous entity and requires a differential treatment strategy according to the existence of UTI, gender, the presence of renal scarring, and finally VUR grade. It is the general consensus that presentation with breakthrough UTIs in spite of prophylactic antibiotic treatment is an indication for surgical intervention [13–15]. Nowadays, endoscopic management of VUR is the first-line treatment for Grades II–IV of reflux in the majority of centers [16]. Regarding Grade V VUR, some researchers have presented a significantly low resolution rate compared with open surgery. However, the AJA report points out that even open surgery may achieve only 80% resolution in Grade V VUR [8]. We and others have reported a reasonable success rate in high-grade VUR utilizing a different tissue-augmenting substance [1,5,13]. Recently, the Dublin group reported their experience with Deflux injection in patients with Grade V VUR [8]. They performed endoscopic correction in 56 children with primary Grade V VUR. They cured the reflux in 89% of cases, although 6.3% of RRU required three injections. In 11% of RRU, reflux downgraded to I and those patients required no treatment. It is important to stress that in this series none of the patients underwent open surgery. Also in the series presented here we were able to achieve a success rate of 76% of all treated RRU. Although, we do not discuss here the application of the endoscopic concept to high grades of VUR, our results may serve as additional evidence of the benefit of endoscopic correction in all grades of VUR.

As aforementioned, the prevention of renal parenchymal damage is a main goal of VUR treatment. Early diagnosis of VUR, prevention of febrile UTI and immediate commencement of antibiotic therapy in those children with acute pyelonephritis may lead to the prevention of parenchymal damage. Therefore, the cessation of VUR should be considered as a means to reduce the risk of damage and UTI.

### Table 1

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Sex</th>
<th>Cause of VUR diagnosis</th>
<th>Indications for surgery</th>
<th>Bulking agent (RRU%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>13</td>
<td>41</td>
<td>10</td>
<td>43 (45.3%)</td>
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<tr>
<td></td>
<td>41</td>
<td>10</td>
<td>41</td>
<td>50 (52.6%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>41 (5.5%)</td>
<td>2 (2.1%)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>VUR grade</th>
<th>RRU</th>
<th>RRU scarring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>IV</td>
<td>73</td>
<td>34 (46.6%)</td>
</tr>
<tr>
<td>V</td>
<td>22</td>
<td>3 (13.6%)</td>
</tr>
</tbody>
</table>
recurrence, although not a goal in itself. Our study further supports this. All children were operated due to breakthrough UTIs, while on antibiotic prophylaxis. This may explain the relatively young age of the studied children. All children were from families with good compliance who followed strict recommendations regarding the antibiotic treatment. None of the children who demonstrated downgrading of VUR to Grade II and III presented with febrile UTI. New renal damage may occur also after endoscopic correction. Recently published results on the Swedish reflux trail in children with dilating VUR show that out of 65 analyzed patients allocated to endoscopic treatment and 68 who were on surveillance 5 and 6 respectively developed new renal damage\textsuperscript{14}. New renal damage was more common in children with febrile UTI recurrence and in those with a higher VUR grade. Recently also the Atlanta group stressed that clinical success is more important in the long term [13]. They studied patients with radiological failure after endoscopic correction who were considered to have residual VUR Grade I and II after correction of reflux graded from II to IV. These patients, 18% of all radiological failures, were taken off antibiotics and did not require any further treatment.

Three (16%) children in the present series had febrile UTI. In one, dysfunctional voiding was to blame, and in the remaining two teenagers sexual activity caused mild UTI. The occurrence of febrile UTI following cessation of VUR in patients after VUR surgery is well known and mostly related to the number of episodes of acute pyelonephritis which they experienced before surgical correction. Since the majority of our patients presented with three febrile UTIs prior to endoscopic correction, the relatively high incidence of febrile UTI in this small group of patients is not surprising.

VUR can resolve spontaneously and an annual resolution rate of up to 28% has been reported [17]. In our series, eight patients underwent VCUG examination during the follow-up period. In seven patients, VCUG showed either further downgrading of VUR to Grade I or full resolution, supporting the theory that downgrading of Grade IV-V and natural elongation of the intravesical part of the ureter may lead to complete reflux resolution.

The present study has limitations that warrant mention. First, its retrospective nature subjects it to all the flaws inherent to any such study. As some of the data presented here did ultimately depend upon family recall, we may have missed some incidences of febrile UTI. We have reported here a relatively small number of patients with downgrading of VUR. However, all patients have had a meticulous follow-up with delayed VCUG and DMSA showing renal parenchyma over the long term. We have not performed a VCUG for all studied patients in the long term, and therefore may have missed some with VUR recurrence to their initial grades without clinical presentation. However, all the patients underwent surgical intervention only because of recurrent febrile UTI, and since they were free of infection their current reflux grade seems irrelevant. Finally, since this is not a randomized study we are not able to compare the patients presented here with a non-treatment group with regard to the incidence of UTI and acquired scarring.

**Conclusion**

Our data show that downgrading of VUR is a reasonable option in patients with high-grade VUR suffering from breakthrough infections while on antibiotic prophylaxis. It leads to the cessation of febrile UTIs, further spontaneous resolution of VUR, and may potentially avoid renal damage.

**Conflict of interest**

None.

**Funding**

None.

**References**


