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Long-term incidence of febrile UTI after DxHA treatment of VUR

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Abstract *Purpose:* To assess the long-term incidence of febrile urinary tract infection (fUTI) in children treated by endoscopic injection of dextranomer/hyaluronic acid (DxHA) for vesicoureteral reflux (VUR).
Materials and methods: Prospective study from January 2002 to December 2009 in children treated at our institution for VUR by endoscopic injection of DxHA. All children underwent clinical and renal/bladder ultrasound follow up at 3 months after procedure, then annually. Postoperative voiding cystourethrogram (VCUG) control was performed only for patients with recurrent fUTI.
Results: 227 children (177 female) were included. Mean patient age at inclusion was 4.7 years. The mean duration of follow-up was 51.6 months. During follow-up, 18.9% had one or several fUTIs, of whom 48.8% had VUR at VCUG. No recurrence of fUTI was observed after 4 years of follow-up. We identified three risk factors for fUTI recurrence: cystitis cystica at the time of injection ($p = 0.007$), preoperative renal scarring ($p = 0.018$), and the disappearance of the implant at 3-month follow-up ultrasound ($p = 0.037$).
Conclusions: The long-term incidence of recurrent fUTI after endoscopic treatment of VUR is low. Our data show that the clinical results of endoscopic treatment should be interpreted with a follow up of at least 4 years.

Introduction

Since the publication of the International Reflux Study in Children in 1992 [1], it is established that eliminating vesicoureteral reflux (VUR) has little impact on the prognosis of renal function, which is determined by the prior existence of renal dysplasia. However, correcting VUR significantly reduces the incidence of subsequent febrile urinary tract infection (fUTI), which represents considerable morbidity for patients and their families.

In 2010 and 2012, the American Urology Association and the European Urology Association [2,3] respectively issued

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guidelines for the management of VUR in children, aimed at reducing the risk of fUTI and renal scarring. The results of VUR treatment are evaluated according to three main criteria:

- Radiologic result, evaluated by a negative voiding cystourethrogram (VCUG)
- Renal prognosis, assessed by evolution of renal scars on dimercaptosuccinic acid (DMSA) scan
- Clinical outcome, evaluated by the cessation of recurrent fUTI (low economic cost and best quality of life for patients and their families).

Most of the published studies determine the success rate of endoscopic treatment by the disappearance of reflux on VCUG (around 70—80% at initial injection for all grades) [4]. However, the clinical outcome has not been extensively assessed in the literature.

The recurrence rate of fUTI ranges from 12% to 36% after antibiotic prophylaxis [5—7], from 4.6% to 24% after surgical reimplantation [8,9] and from 0.75% to 27% [10,11] after endoscopic treatment.

Over the past 2 decades, endoscopic treatment has become the first-line therapy for VUR. DxHA (Deflux®, Q-Med, Uppsala, Sweden), approved by the FDA in 2001, is now the most widely used bulking agent for this indication.

The purpose of this prospective study was to evaluate the long-term clinical outcome after endoscopic DxHA injection for VUR in children with a special focus on the recurrence rate of fUTI. The secondary aim was to identify possible risk factors for fUTI recurrence in this population.

Materials and methods

Patient population

This prospective cohort study was performed from January 2002 to December 2009, in a paediatric population recruited in our university hospital. Children were included after one or several episodes of fUTI. In all children, the diagnosis of VUR was confirmed by VCUG, performed after fUTIs. VUR was graded according to the international grading system established by the International Reflux Study in Children [1].

In addition to VCUG, all children underwent renal ultrasound and DMSA scan before intervention.

Exclusion criteria

We excluded patients with VUR associated with posterior urethral valve, neurogenic bladder, pyelo-ureteral duplication, and bladder diverticula. Furthermore we excluded children with a history of ureteral reimplantation, or endoscopic injection.

Technique

Endoscopic therapy consisted of a subureteral injection of DxHA according to the classical STING procedure [12]. Intervention was performed under general anaesthesia using a cystoscope (Storz®) with offset lens 9.5 Charriere and/or a direct vision 11 Charriere.

A dose of antibiotics (amoxicillin/clavulanic acid) was systematically administered at the start of the anaesthesia. After discharge, antimicrobial prophylaxis (trimethoprim—sulfamethoxazole or Cefixime) was prescribed for a limited period of 8 days.

Follow-up

All children underwent urinary tract ultrasound 3 months after the procedure.

We decided not to perform systematic postoperative VCUG, except in children with high-grade VUR.

If any anomaly was detected on pre-operative DMSA scan, repeat DMSA scan was systematically performed 3 years later. Abnormal DMSA scan was defined as the presence of scarring, single or multiple focal defects, and contribution of one kidney to total renal function $<45\%$ on DMSA Scan.

An annual visit was scheduled at our surgical unit or with the family practitioner.

The occurrence of each post injection fUTI was checked with the family doctor and/or parents by phone or regular mailing, and defined as fever above 38.5 °C, and blood C-reactive protein (CRP) level of >4 mg/L, and positive dipstick test (nitrite and leukocytes), and monomicrobial positive urine culture results at $>100\,000$ colony-forming units/mL and leukocyturia$>10\,000$/mL. Urine sample was collected with an external collector in children with uncontrolled voiding.

The exhaustiveness and accuracy of the recorded data was verified by a questionnaire sent to parents at the end of the study (December 2009). In the case of non-response despite reminders, the family physician was contacted by phone to verify the accuracy of recorded data.

Statistical analysis

Quantitative data are presented as mean $\pm$ standard deviation (SD) and categorical data as number and percentage. Categorical variables were compared using the Chi square test and quantitative variables using the Student *t* test, as appropriate.

Children were classified according to presence or absence of at least one episode of fUTI at follow up.

We evaluated the risk of recurrence of fUTI based on prognostic variables identified by bivariate analysis. Variables with a *p* value of <0.20 were retained for inclusion in the Cox regression multivariate analysis. We plotted the risk of recurrent fUTI using the Kaplan—Meier method.

All analyses were performed using SAS version 9.2. (SAS Institute, Cary, NC, USA).

Results

Patient population

From January 2002 to December 2009, 259 patients were treated in our centre for VUR by endoscopic injection of

DxHA. Among these, 32 (12.3%) were excluded due to presence of non-inclusion criteria (23 pyelo-ureteral duplication, 7 neurogenic bladder and 2 posterior urethral valves). A total of 227 patients (324 refluxing renal units) were included; 177 (78%) were girls and 50 (22%) were boys. The average age at the time of endoscopic injection was 4.7 years [range 1.4—15.5 years]. The average follow-up was 51.6 months [range 12—96 months]. The baseline characteristics of the study population are presented in Table 1. The VUR was unilateral in 130 (57.3%) and bilateral in 97 (42.7%). The VUR grading chart is shown in Fig. 1.

Pre-operative renal/bladder ultrasound (RBUS) showed dilation of the urinary tract in 8.9%, and renal cortical abnormalities in 4.9%. Pre-operative DMSA scan revealed renal scars in 56 children (24.7%). Seventy-one children (31.3%) presented dysfunctional elimination syndrome (DES) at diagnosis. During the endoscopic procedure, trabeculated bladder was found in 36.6% and bladder wall inflammation or cystitis cystica in 18.9%. The mean (±SD) volume of DxHA injected per ureter was 0.78 (±0.44) mL. The analysis of volume of DxHA injected by grade of VUR showed a mean volume of DxHA injected per ureter of 0.73 (±0.38) mL for grade I, 0.71 (±0.29) mL for grade II, 0.88 (±0.45) mL for grade III and 1.15 (±0.96) mL for grade IV.

At 3 months' follow up, the clinical status and ultrasonography were uneventful in 209 (92.1%) patients and mild upper tract dilatation was observed in 17 (7.5%). RBUS showed new renal scarring in one patient (0.4%).

Table 1 Characteristics of patients with vs. without recurrent febrile urinary tract infection.

	No recurrence $n = 184$(%)	Recurrent fUTI $n = 43$(%)	p
Age[a] *(years)*	4.75	4.40	0.53
Sex			
Female	140 (76.6)	83.7 (36)	0.4
Male	43 (23.4)	16.3 (7)	
Reflux grade			0.48
Grade I	26 (14.1)	8 (18.6)	
Grade 2	88 (47.8)	17 (39.5)	
Grade 3	59 (32.1)	17 (39.5)	
Grade 4	11 (6)	1 (2.4)	
Dysfunctional elimination syndrome			0. 36
Yes	55 (29.9)	16 (37.2)	
No	129 (70.1)	27 (62.8)	
Ultrasound findings			0.20
Renal cortical abnormalities	11 (6.1)	0 (0)	
Dilation	17 (9.4)	3 (7)	
Normal	153 (84.5)	40 (93)	
Renal scars on DMSA			0.04
Yes	40 (21.7)	27 (37.2)	
No	144 (78.3)	27 (62.8)	
Trabeculated bladder			0.48
Yes	65 (35.3)	18 (41.9)	
No	119 (64.7)	25 (58.1)	
Cystitis cystica			0.17
Yes	10 (5.4)	5 (11.6)	
No	174 (94.6)	38 (88.4)	
Position of ureteral orifice			0.90
Normal	6 (3.8)	2 (5.4)	
Laterally displaced	106 (67.5)	25 (67.6)	
Severely laterally displaced	45 (28.7)	10 (27)	
Implant visible at 3 months			0.02
Yes	59 (41)	8 (21.1)	
No	85 (59)	30 (78.9)	
Mean volume of DxHA injected (mL)	0.72	0.83	0.14

[a] Mean age.

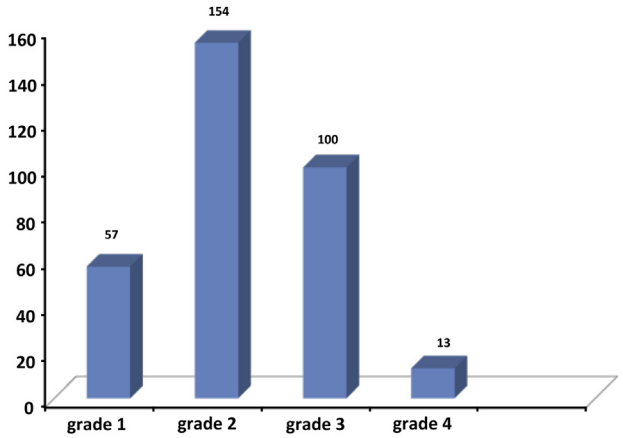

Figure 1 Distribution of refluxing ureters by grade.

Recurrence of fUTI

During post-operative follow-up, 43 children (18.9%) presented recurrent fUTI, of whom 21 (48.8%) had several episodes. Among children with recurrent fUTI, VCUG showed VUR in half (21/43).

The Kaplan—Meier estimates of the risk of recurrence of fUTI over time are shown in Fig. 2.

50% Of recurrences occurred within the first 24 months after endoscopy treatment. Beyond 4 years of follow up, the risk of recurrence was almost nil.

The factors significantly associated with recurrent fUTI by Cox multivariate regression analysis (Table 2) were renal scarring on DMSA scan, bladder wall alteration, low volume of DxHA injected, and the disappearance of the implant on 3-month ultrasound. Age, reflux grade and impaired renal function (defined as contribution of one kidney to total renal function <45% on DMSA scan) were not shown to be predictive factors of recurrent fUTI. DES did not significantly increase the risk of recurrent fUTI.

Recurrent fUTI with radiologic VUR led to a second endoscopic injection of DxHA in 8 patients, and ureteral Cohen's reimplantation in 13.

In all children with high grade of VUR (>III) ($n = 12$), postoperative VCUG was normal. Among these, only one child presented 2 recurrent fUTI. VCUG showed recurrent VUR and Cohen's reimplantation was performed.

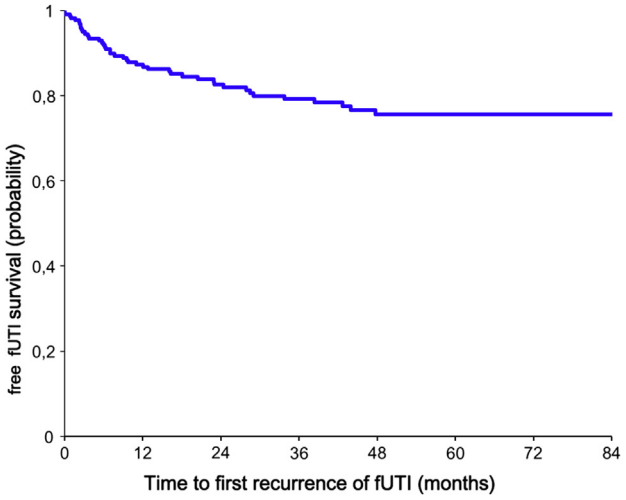

Figure 2 Kaplan—Meier curves of time to occurrence of recurrent febrile urinary tract infection (fUTI) (pyelonephritis-free survival).

Discussion

We observed a rate of recurrence of fUTI of almost 19%, which is comparable to previous reports [11,13], but higher than the average recurrence rate after endoscopic DxHA treatment, reported to be around 12% (although ranging from 0.75% to 27%) [11,13—15]. This wide variation in the rate of recurrent fUTI can be explained by the heterogeneity between reports and, often, the lack of distinction between febrile and non-febrile urinary infection. Indeed, most studies were retrospective, except the study by Brandström et al. [15], a prospective multicentre study in 203 children, randomised to three different treatment approaches. Among the 66 children in the endoscopic treatment arm, the authors observed a fUTI recurrence rate of 21% [15]. Likewise, in a monocentric study of 100 children, Wadie et al. [16] observed a recurrence rate of 13%. Puri et al. [17] reported an exceptionally low rate of recurrent UTI of only 2.6% after successful correction of VUR using DxHA, but without distinguishing between upper and lower urinary tract infection.

We decided not to perform systematic post injection VCUG, except in cases of recurring fUTI. Indeed, the aim of our study was to evaluate the clinical result of DxHA injection. This approach is debatable but preserves the minimally invasive nature of the endoscopic treatment of VUR. Harper et al. [18] also supported this option in a series of 41 patients presenting a low grade of VUR (I—III) treated by endoscopic DxHA injection. In this study, 2 children presented a postoperative recurrence of fUTI with a normal postoperative VCUG. Despite the AUA recommendation advocating postoperative VCUG, we note that post-operative follow up varies greatly between centres in the literature and in clinical practice. This post-operative management depends largely on the surgeon's experience and on the patients' clinical characteristics. In a recent study, Kalisaart [19] also questioned the need for VCUG in asymptomatic patients after endoscopic treatment of VCUG. In accordance with Harper, we feel that postoperative VCUG should be reserved for children who present recurrent fUTIs or were treated for high grade of VUR. VCUG is very unpopular among children and their families.

Thus, for children and parents, the absence of fUTI is the main criterion for successful intervention. As previously pointed out by Capozza [20], recurrent fUTI is the primary concern for parents. Indeed recurrent fUTI can cause great anxiety for the family, particularly when the patient is aged less than 3 years. In a recent study, Schwentner et al. [21] evaluated health-related quality of life in 100 children cured of VUR by endoscopic therapy using the Glasgow Children's Benefit Inventory questionnaire. With a response rate of 88%, they observed a significant and durable improvement in children's quality of life, with a significant difference ($p = 0.001$) between the score at one year post treatment (average 23.95) and at four years (average 59.72).

In our study, we assessed whether the volume of injected DxHA ureter could be a risk factor for recurrent fUTI. Our analysis confirmed this hypothesis by showing that an injected volume <0.5 mL was a risk factor for recurrent fUTI. Indeed, it has been previously reported [22] that there is a decrease in the volume of DxHA over time, particularly in the first two weeks after injection. It is possible that the residual volume is therefore insufficient,

Table 2 Risk factors for recurrent febrile urinary tract infection with odds ratios (OR) and 95% confidence interval (95%CI).

	Unadjusted OR [95% CI]	*p*	Adjusted OR [95% CI]	*p*
Male sex	0.69 [0.30; 1.56]	0.378		
Age <3 years	0.83 [0.46; 1.48]	0.543		
High reflux grade	1.26 [0.68; 2.31]	0.451		
DES	1.36 [0.73; 2.52]	0.333		
Abnormal ultrasound	2.31 [0.71; 7,47]	0.162		
Contribution of one kidney to total RF on DMSA scan <45%	1.58 [0.86; 2.91]	0.137		
Renal scars on DMSA	2.03 [1.09; 3.76]	0.026	2.22 [1.14; 4.32]	0.018
Trabeculated bladder	1.34 [0.73; 2.46]	0.343		
Cystitis cystica	1.83 [0.90; 3.73]	0.092	2.88 [1.34; 6.20]	0.007
Dx/HA volume injected <0.5 mL	2.17 [1.09; 4.32]	0.027	2.86 [1.32; 6.17]	0.007
Implant vanishing on 3 m RBUS	2.05 [0.97; 4.33]	0.060	2.42 [1.05; 5.57]	0.037

DES = dysfunctional elimination syndrome; RBUS = renal/bladder ultrasound; RF = renal function.

leading to a loss of efficacy of the initial injection over time. Other risk factors for recurrence appeared to be: renal scarring on initial DMSA scan, bladder wall alteration at endoscopy, low volume of DxHA injected, and the disappearance of the implant at 3 months. However, these factors are controversial. Particularly, while DES did not seem to increase the risk of recurrent fUTI, our systematic management of associated constipation probably explains this by the establishment of a toilet training programme. It is clear that this specific management caused a positive bias in the interpretation of the results of endoscopic treatment.

The disappearance of the implant on follow-up ultrasound at 3 months as a risk factor for recurrent fUTI can be explained by the absorption of the dextranomer, or the possible migration of the implant. Kirsch and colleagues were alerted by the risk of migration, and this prompted them to develop their modified version of the original endoscopic STING technique, which they named the HIT procedure, particularly for high-grade VUR [23].

Our study shows that minimally invasive treatment of VUR by endoscopic injection of DxHA requires at least four years of clinical follow-up to be able to draw firm conclusions regarding outcome. These results are comparable with Puri's recent retrospective series of 1551 patients over 9 years in which no fUTI was recorded beyond 3 years [14].

In our view and in accordance with Kaye et al. [24], the success of endoscopic treatment of VUR should be interpreted not only through radiologic resolution, but must importantly on clinical outcomes, especially disappearance of fUTI.

However, for long-term evaluation, the difficulties in identifying fUTI amongst other febrile affections, especially in children aged less than 3 years, are the principal weakness. Indeed, it has been reported that among children presenting an unexplained fever, only 7% of them have pyelonephritis [25].

The prospective method, long-term outcomes, and contact with parents and physicians to guarantee exhaustiveness are the strong points of our study. The small number of patients, which did not allow subgroup analysis (high or low grade of reflux), and the lack of control group may represent limitations of our study.

Conclusion

In this prospective study performed over 8 years, we observed a risk of recurrent fUTI after endoscopic treatment of 19%, of which half occurred in the first 24 months after endoscopic treatment. Our data show that the clinical results of endoscopic treatment should be interpreted with a minimum follow up of 4 years.

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Conflict of interest

None.

Ethical approval

Approved by French human protection Committee East Area II.

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