Original Article

Recurrence of vesico-ureteral reflux in children: is still the endoscopic injection the best option?

Francesca Nascimben[1,2], Isabelle Talon[1], Consuelo Maldonado[1], Rossella Angotti[2], Francesco Molinaro[2], Raphael Moog[1], Francois Becmeur[1]

[1]Department of Pediatric Surgery, University Hospital of Hautepierre, Strasbourg, France; [2]Division of Pediatric Surgery, Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy

Contributions: (I) Conception and design: R Moog, F Nascimben, F Becmeur; (II) Administrative support: None; (III) Provision of study materials or patients: F Nascimben, F Becmeur, R Moog; (IV) Collection and assembly of data: F Nascimben, C Maldonado; (V) Data analysis and interpretation: F Nascimben, I Talon; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Francesca Nascimben, MD. Department of Pediatric Surgery, University Hospital of Hautepierre, Strasbourg, France; Division of Pediatric Surgery, Department of Medical, Surgical and Neurological Sciences, University of Siena, Viale Bracci 14, 53100 Siena, Italy. Email: francescanascimben@gmail.com.

Background: Endoscopic injection (EI) is a safe treatment for vesico-ureteral reflux (VUR) in children, but recurrences are not insignificant. This study aims to show if multiple EI is still the best first line management even if in case of recurrences.

Methods: All patients affected by primary VUR, treated with at least one EI and with at least 5 years follow up were included. All general data were analyzed. Recurrence rate after one, two and three EIs were calculated.

Results: One hundred and sixty-one patients (total number =210) were healed after 1 injection, 28 after 2 and 4 after 3 with a global success rate of 91.90%. Recurrence rate is higher in patients older than 3 years old and with IV and V reflux grade. Even if 67.7% of recurrent VUR after one injection was symptomatic, diagnosis of recurrences after multiple EI was mainly radiological. Only 8% of the patients underwent EI need an anti-reflux surgery.

Conclusions: Thanks to its low costs and the acceptable recurrence rate, Deflux EI should be proposed as the first therapeutic approach for children affected by VUR, especially in those with low and moderate grades of VUR. Multiple injections could be contraindicated only in older children thank 1 year with high-grade VUR (IV symptomatic and V grade).

Keywords: Vesico-ureteral reflux (VUR); Deflux; endoscopic injection (EI); children; recurrence

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Introduction

Vesico-ureteral reflux (VUR) is the most common urological anomaly in pediatric population with an incidence of 1–3% of asymptomatic patients (1) which increases in case of recurrent urinary tract infections (UTIs) (2). Depending on VUR grade and clinical presentation, the best therapeutic management has to be chosen among continuous antibiotic prophylaxis (CAP), minimally invasive endoscopic injection (EI) and traditional surgery (3,4). Even if traditionally, if low-dose antibiotic prophylaxis failed, the only available alternative was the anti-reflux surgery (5), in the last decades EI has become the first line therapy for children with VUR (6). Different techniques of EI such as subureteral transurethral injection or subureteric Teflon injection (STING) (7) or hydrodistension implantation technique (HIT) have developed (8) and different biocompatible materials like dextranomer/hyaluronic acid copolymer

(Deflux) and polyacrylate polyalcohol copolymer (Vantris) have been approved (9). It is a cheap, minimally invasive day hospital procedure, with a success rate of about 85% depending on the VUR grade (10-12).

EI-associated recurrence rate (defined as recurrence of VUR at imaging exams and/or relapse of symptoms) has already been described (13-16), but no studies have analyzed the real causes, the principal factors involved and the therapeutic strategies to adopt in case of failure.

This retrospective study aims to identify the best diagnostic and therapeutic management of recurrent VUR after EI failure and to show if multiple EIs is still the best option through the analysis of the results of a single center endoscopic Deflux injection in children with a diagnosis of primary VUR during a 5-year long-term follow-up. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-76/rc).

Methods

Patients

All pediatric patients younger than 16 years old affected by primary VUR who underwent sub-ureteral injection of Deflux between January 2012 and December 2017 at Department of Pediatric Surgery in Strasbourg were included in this retrospective study. All included patients benefited from a diagnosis of primary VUR, as determined by voiding cystourethrogram (VCUG).

Patients with secondary VUR because of posterior urethral valves (PUV), neurologic bladder or primary obstructive megaureter (POM), patients with a follow-up shorter than 5 years, patients who were not treated with Deflux injection or who underwent to a primary Deflux injection at other hospitals and/or before 2012 were excluded from the study.

Demographic data, clinical presentation and imaging

The case records of all patients were retrospectively analyzed and all the following data were evaluated: gender (female/male), median age at diagnosis, grade of reflux defined according to the International Reflux Classification, laterality (unilateral/bilateral), prenatal diagnosis, familiarity, associated urinary anomalies (double canal system, small kidney syndrome), comorbidities, clinical presentation at diagnosis [symptoms at onset, number of UTIs/pyelonephritis (PNPs)] and preoperative imaging workup (VCUG, dimercaptosuccinic acid (DMSA)/mercaptoacetyltriglycine (MAG3) renal scan, uro-magnetic resonance imaging (Uro-MRI).

EI

Indications for EI included breakthrough UTIs, progressive renal scarring, and failure of CAP. For all patients median age at surgery, bulking agent and number of EIs were evaluated. All patients underwent hyaluronic acid and dextran copolymer (Deflux) sub-urethral EI (STING) under general anesthesia as a day hospital procedure. Specifically they were all placed in the lithotomy position. A 9.5-Fr pediatric cystoscope was used and through a 3.7-Fr metallic needle Deflux was injected submucosally at the 6 o'clock position to create a bulge. In most patients, only 1 puncture at 6 o'clock was sufficient, but in rare cases of inadequate sub-ureteral another puncture was performed at a different location. In cases of duplication, injection was done under the refluxing ureter. The mean amount of each substance injected into the ureter was defined according to the direct visualization of the shape of the ureteral orifice before and after the injection (the bulking agent was injected until a well coapted orifice was obtained).

Outcome and follow-up

All patients underwent ultrasonography (US) 6 months

Highlight box

Key findings

- Endoscopic injection (EI) failure can be treated with a second EI in case of low and intermediate grade of reflux in children younger than 1 year old.

What is known and what is new?

- EI of Deflux is a safe and effective alternative to the traditional anti-reflux surgery for children affected by primary vesico-ureteral reflux (VUR). Deflux EI is a cheap day surgery procedure with an acceptable recurrence rate. Only 8% of patients with failed EI need anti-reflux surgery.
- Deflux injection should be proposed as the first line therapy for children affected by primary VUR and in case of failed injection in children younger than 1 year old and affected by low and intermediate VUR grade.

What is the implication, and what should change now?

- Based on our results, in case of recurrence rate, repeated EI could be done in all those patients younger than 1 year old with low and intermediate grade of reflux, instead anti-reflux surgery has to be considered in all the other cases of failure.

after discharge, DMSA renal scan both 1 and 5 years after treatment. VCUG was performed in case of symptoms or urological morbidities or pejorative radiological evolution (US or DMSA). Successful reflux treatment was defined as absence of PNPs and/or as absence of reflux or lower reflux grade at VCUG when performed and/or stable renal function at DMSA renal scans. In most of cases of primary injection failure, a second injection was performed and some of those children for whom a second injection failed received a third injection, depending on the clinical presentation and the renal function. Indications for anti-reflux surgery were: local causes of VUR such as Hutch diverticulum, persistent VUR after multiple EIs and ureteral junction obstruction secondary to the endoscopic procedure.

Ethical considerations

All parents or the caregivers of the patients included in the study have been asked to fill and sign a written consent about the surgical procedure and about the possibility to use anonymously their data for scientific research studies. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of the Clinical Research and Innovation Department approved this study (n° 20/2023).

Statistical analysis

All statistical analyses were performed using *graph-pad* and *r*. Continuous variables are presented as mean and median; they have been analysed using *t*-test. Categorical variables are presented as frequency and percentage and they have been compared by Chi-square or Fisher's exact test. Univariate and multivariate logistic regression analysis was performed to identify predictors of reflux resolution post injection. A P value <0.05 was considered statistically significant.

Results

General data

Between 2012 and 2017, 238 children received diagnosis of VUR. Twenty-eight patients were excluded from the study: 18 because of secondary VUR (specifically 3 cases of posterior urethral valves, 11 neurologic bladder and 4 primary obstructive mega-ureter), 9 patients did not undergo EI and 1 had previously treated at another center. Finally, 210 patients (339 ureters), 149 girls (71%) and 61 boys (29%) with a mean age of 41.83 months (0 to 178 months) with primary VUR were treated with sub-ureteral EI of Deflux. The median volume of injected Deflux depended on the morphological aspect of the meatus (3 to 9 mL). The mean overall follow-up period was 96.24 months (60 to 132 months). General data are shown in *Table 1*.

Descriptive data of recurrence

Among 210 patients, 161 were cured with a single Deflux injection with a success rate of 76.66%. Recurrence was found in 49/210 patients (23.33%) and in 70/339 ureters (20.64%), only 39/49 (79.59%) patients who recurred after the first injection needed a second one. Of these 39 patients, 11 patients (28.2%) who received a second injection recurred and 6/11 (54.54%) needed a third Deflux injection. Recurrence after the third injection occured in 2/6 patients (33.3%). All data about the recurrence rate after first, second and third injection based on the demographic data are summarized in *Table 2*. Recurrence rates are higher and higher as the number of injections increases. In our series, only 17/210 patients (8.1%) needed surgery, specifically 12/210 (5.71%) underwent ureteral reimplantation with a mean age at surgery of 49.86 months (10.43 to 82.57 months), while 5/210 (2.38%) were treated with ureteronephrectomy with a mean age at surgery of 38.73 months (21.7 to 70.76 months). All patients underwent anti-reflux surgery after Deflux injection failure had already a deficient renal function at DMSA renal scan. All general data of patients treated with traditional surgery are described in *Table 3*.

Relationship between recurrence and analyzed variables

All data about the recurrence rate after first, second and third injections are respectively shown in *Figure 1*. Recurrence rates are higher and higher as the VUR grade increases both after the first, the second and the third EI with a P value <0.001) (*Figure 2*). If we compare the role of PNPs, VCUG and DMSA renal scan in detecting VUR recurrence after first, second and third injection, we can see that, while after the first injection, most of recurrences were detected as symptomatic PNPs, after the second and the third one DMSA renal scan plays a fundamental role in identifying the recurrences (*Figure 3*). Comparison is shown in *Figure 4*.

Table 1 Demographic data of all patients included in the study treated with at least 1 Deflux endoscopic injection

Parameter	Number of patients, n (%)
Total	210
Sex	
Female	149 (70.95)
Male	61 (29.05)
Prenatal diagnosis	
Yes	27 (12.85)
No	183 (87.15)
Familiarity	
Yes	14 (6.66)
No	196 (93.34)
Laterality	
Unilateral	81 (38.57)
Bilateral	129 (61.42)
VUR grade	
I	7 (3.3)
II	73 (34.7)
III	112 (53.3)
IV	16 (7.7)
V	2 (1.0)
Age at diagnosis	
<1 year	55 (26.2)
1–3 years	67 (31.9)
>3 years	88 (41.9)
Clinical presentation	
0 PNP	17 (8.1)
1 PNP	76 (36.2)
2 PNP	86 (41.0)
>3 PNP	31 (14.8)
US	
Normal	124 (59.0)
Pathological	86 (41.0)
DMSA	
Normal	119 (56.6)
Pathological	91 (43.4)

VUR, vesico-ureteral reflux; PNP, pyelonephritis; US, ultrasounds; DMSA, dimercaptosuccinic acid.

Outcomes

One hundred and sixty-one patients (total number =210) were healed after 1 injection with a success rate of 76.66%. Among the 49 patients for whom the first injection failed, 39 needed a second injection. Among those who received a second injection, resolution of symptoms was obtained in 28/39 patients with a success rate of 71.79%. When the second injection failed, 6/11 needed a third Deflux injection. Four of six patients who received a third injection were healed with a success rate of 66.6%. If we add to the 161 patients who were healed after 1 injection, 28 patients who got resolution of symptoms after 2 injections and 4 after 3 injections, we obtain a global success rate of 91.90% (193/210). Only 12/210 patients (5.7%) needed anti-reflux surgery: 8/12 (66.6%) patients needed ureteral reimplantation after 1 single injection, 2/12 (16.66%) after 2 and 2/12 (16.6%) after 3. Nephrectomy was proposed to 5/210 (2.38%) patients: 2 (1 with diagnosis of obstructive mega-ureter and 1 with a double system and an ureterocele at the ureter of the superior pole)/5 (40%) after 1 single injection, 3 (1 with dysplastic inferior pole underwent)/5 (60%) after 2. The success rate after both ureteral reimplantation and nephrectomy was 100%: none of them had post-operative recurrent symptoms and follow-up DMSA renal scans were satisfying.

Discussion

VUR is the most frequent congenital anomaly of kidneys and urinary tract (CAKUT) (17-19). VUR could be complicated by a reflux-related nephropathy that cause end-stage renal failure in 3–25% of children affected by VUR (20). For decades, long-term administration of antibiotics for UTIs has been considered the best treatment for VUR in children, even if prolonged use of antibiotics started to be more and more associated with bacterial resistance (21). For many years, the only alternative management to CAP has been open surgery, but with the advance in endoscopic surgery, endoscopic treatment of VUR has become popular among pediatric surgeons (3). EI of biocompatible bulking agents as Deflux has become the first line treatment for the management of VUR in pediatric patients, especially for low and intermediate grade of VUR (22-24). Many retrospective case series studies analyzed the efficacy and the safety of EI to treat VUR in pediatric population with different results in term of success rates (25,26). The success rate of our cohort (76.66%) is included in the range

Table 2 Recurrence rate after first, second and third endoscopic injection based on demographic general variables

Parameter	First injection			Second injection			Third injection		
	Recurrence, n (%)	No recurrence, n (%)	P value (P<0.05)	Recurrence, n (%)	No recurrence, n (%)	P value (P<0.05)	Recurrence, n (%)	No recurrence, n (%)	P value (P<0.05)
Total	49 (23.3)	161 (76.7)		11 (28.2)	28 (71.8)		2 (33.3)	4 (66.7)	
Sex			>0.99			0.22			0.09
Female	38 (27.0)	103 (73.0)		7 (24.1)	22 (75.9)		1 (25.0)	3 (75.0)	
Male	11 (18.0)	50 (82.0)		4 (40.0)	6 (60.0)		1 (50.0)	1 (50.0)	
Age at surgery			<0.01			0.0001			<0.001
<1 year	2 (3.6)	53 (96.4)		0 (0)	1 (100.0)		0 (0)	0 (0)	
1–3 years	18 (26.9)	49 (73.1)		3 (17.6)	14 (82.4)		1 (20.0)	4 (80.0)	
>3 years	29 (33.0)	59 (67.0)		8 (38.1)	13 (61.9)		1 (100.0)	0 (0)	
General data			0.003			0.02			<0.001
AUA	11 (35.5)	20 (64.5)		2 (33.3)	4 (66.6)		1 (100.0)	0 (0)	

AUA, associated urological anomalies.

(6% and 87%) described in Literature. In our cohort, 49/210 patients and 70/339 ureters recurred with a recurrence rate respectively of 23.33% and 20.64% in accordance with Literature data (19.5%) (27). Among the analyzed general data of the patients included in the study, no significant difference was found in term of recurrence depending on gender, clinical presentation, prenatal diagnosis, familiarity and associated urological comorbidities, but it depends on age at diagnosis and on the grade of VUR, in fact, recurrence rate is higher in patients treated after the first year of life (P value <0.05) and it is higher and higher as VUR grade increases after both first second and third injection (P value <0.001). This is probably due to the higher alteration of the ureteral meatus in higher VUR grade making difficult and difficult the stabilization of the injected polymer placement. According to these results, it could be reasonable to propose an EI to all patients with primary VUR. In cases of recurrence, the therapeutic option should depend on age at recurrence and VUR grade: for patients with IV and V grade VUR, a traditional surgery should be considered, for patients younger than 3 years old with a I, II and III VUR grade, a second EI could be proposed, for patients older than 3 years old with a I, II or III grade VUR, the chose of the best option could depend on the results of DMSA renal scan. In our study, most of patients with recurrent VUR after the first injection were symptomatic. Many studies had already developed the major theme of association between persistent treated VUR and PNPs or UTIs (28,29). On the other hand, especially after second and third injection most of recurrences were identifies thanks to the imaging exams, which become more and more useful as the number of EIs increases. Higher VUR grade is associated to reflux-related nephropaties detected as renal failure at DMSA renal scan meaning that Deflux does not have good results for high grade VUR because of ureteral meatus malformations. Use of control imaging exams especially of DMSA renal scan should be standardized in the follow up of these patients, in particular in those patients treated with more than one injection. Only 8.09% patients needed surgery in our cohort; 5.71% underwent ureteral reimplantation and 2.38% nephrectomy. 1 out of 3 patients needed ureteral-nephrectomy after 1 injection and 2 out of 3 after 2 injection. Literature presents controversial results: in Esposito *et al.* study the success rate of EI was significantly lower than that of open and laparoscopic treatment (30); in the multicenter study of Tessier *et al.* which compared open, laparoscopic and endoscopic treatment of VUR in children, recurrent PNPs and redo-surgery are more frequent after endoscopic and laparoscopic procedures than after the open ones with the advantages of lower associated morbidities (15). In our center, multiple injections were proposed before anti-reflux surgery which was never proposed as first therapeutic option for VUR treatment in children and our results can justify this management.

Table 3 General data of patients treated with ureteral reimplantation and uretero-nephrectomy

Parameter	Ureteral reimplantation (N=12)	Uretero-nephrectomy (N=5)
Sex		
Female	10 (83.33)	3 (60.0)
Male	2 (16.7)	2 (40.0)
Prenatal diagnosis		
Yes	3 (25.0)	0 (0)
No	9 (75.0)	5 (100)
Familiarity		
Yes	0 (0)	0 (0)
No	12 (100.0)	5 (100.0)
Associated urological anomalies		
Yes	3 (25.0)	3 (60.0)
No	9 (75.0)	2 (40.0)
Laterality		
Unilateral	5 (41.7)	5 (100.0)
Bilateral	7 (58.3)	0 (0)
Type of surgery		
Lich Gregoir	4 (33.3)	–
Leadbetter Politano	8 (66.7)	–
VUR grade		
I	0 (0)	0 (0)
II	0 (0)	2 (40.0)
III	8 (66.7)	3 (60.0)
IV	4 (33.3)	0 (0)
V	0 (0)	0 (0)
Age at treatment		
<1 year	1 (8.3)	0 (0)
1–3 years	3 (25.0)	3 (60.0)
>3 years	8 (66.7)	2 (40.0)

VUR, vesico-ureteral reflux.

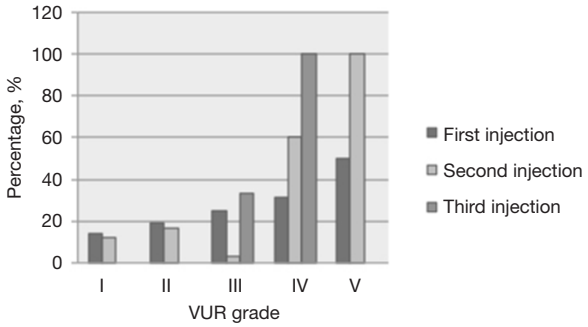

Figure 1 RR (%) according to the VUR grade after first, second and third injection. One of seven patients (14.28%) with grade I, 14/73 patients (19.1%) with grade II, 28/112 (25%) with grade III, 5/16 (31.25%) with grade IV and 1/2 (50%) with grade V failed after the first injection. One of eight patients (12.25%) with grade I, 3/18 (16.7%) with grade II, 2/6 (33.33%) with grade III, 3/5 (60%) with grade IV and 2/2 (100%) with grade V failed after the second injection. One of three patients (33.33%) with grade III and 1/1 (100%) with grade IV failed after third injection. RR is higher and higher as grade of VUR increases after first, second and third endoscopic injection (P value <0.001). RR, recurrence rate; VUR, vesico-ureteral reflux.

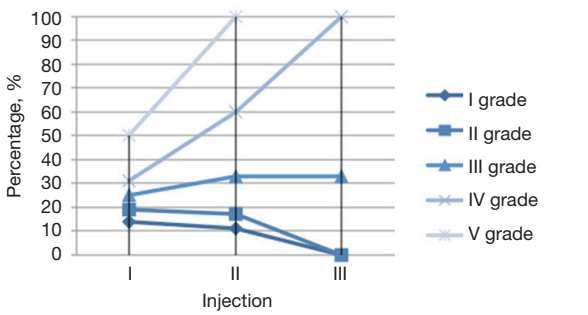

Figure 2 Comparison among RR (%) after first, second and third endoscopic injection based on VUR grade. RR is higher for higher VUR grade after both first, second and third injection. RR, recurrence rate; VUR, vesico-ureteral reflux.

Conclusions

Based on our retrospective review, EI of Deflux is a safe and effective alternative to the traditional anti-reflux surgery for children affected by primary VUR with excellent result, especially in children younger than 1 year old and affected by low and intermediate VUR grade. Deflux EI is a cheap day surgery procedure with an acceptable recurrence rate. Only 8% of patients with failed EI need anti-reflux surgery. For all these reasons, Deflux injection should be proposed as the first line therapy for children affected by primary VUR and in case of failed injection, repeated injections should be considered especially in low grade of VUR; but anti-reflux surgery probably should be considered as the gold standard for high grade VUR (IV symptomatic and V) especially of

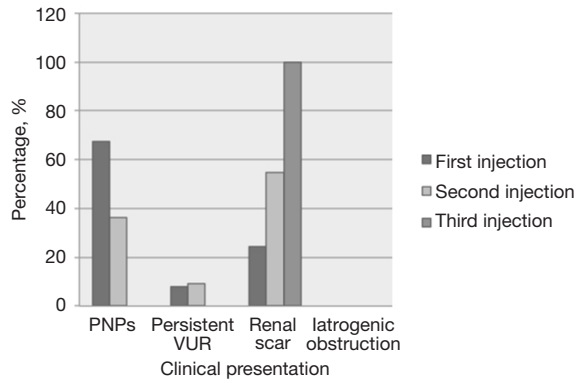

Figure 3 Different presentation types of recurrences after first, second and third injection. Among all 49 patients for whom first endoscopic injection failed, 33 (67.34%) patients had 1 or more episodes of PNPs after the first injection, in 4 (8.16%) cases persistent VUR was identified at VCUG and in 12 (24.48%) cases decreased renal function was detected at DMSA renal scan. Failure of second injection was associated to recurrence of symptoms in 4 (36.36%) cases, persistent VUR at VCUG in 1 (9.09%) case and renal failure at DMSA renal scan in the other 6 (54.54%) cases. In both 2 cases, 1 (50%) male and 1 (50%) female, failure of the third injection was detected as renal failure at DMSA renal scan. PNP, pyelonephritis; VUR, vesico-ureteral reflux; VCUG, voiding cystourethrogram; DMSA, dimercaptosuccinic acid.

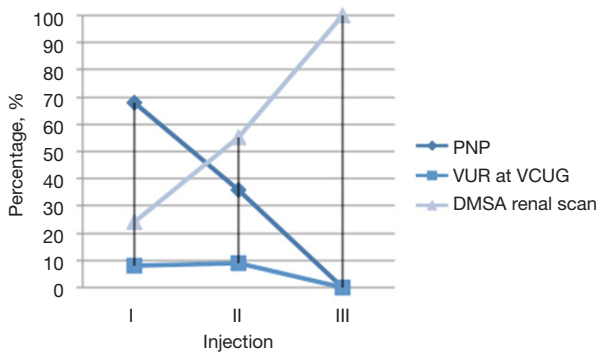

Figure 4 Role of PNP, VCUG and DMSA renal scan in detecting VUR recurrence after first, second and third injection. PNP, pyelonephritis; VCUG, voiding cysto-urethrogram; DMSA, dimercaptosuccinic acid; VUR, vesico-ureteral reflux.

associated to recurrent PNFs and urinary anomalies.

A few limitations of our study should be acknowledged. First of all, this is a retrospective study and there should be selection bias because the decision of the treatment (injection technique, volume and type of bulking agent) was dependent on surgeons and on the internal protocol of the center. On the other hand, the EIs included in the study were performed by different surgeons eve if they were all experts surgeons and the technique and amount of volume injected depended on the direct visualization of the ureteric orifice configuration at cystoscopy and on surgeon preference. Despite of these limits, we agree in considering this study able to provide prognostic and risk factors to identify a valuable stratification in the treatment of primary VUR and to decide who and when an endoscopic treatment has to be proposed to. In the future, a large-scale prospective study will be necessary to validate and standardize a successful treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-76/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-76/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-76/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All parents or the caregivers of the patients included in the study have been asked to fill and sign a written consent about the surgical procedure and about the possibility to use anonymously their data for scientific research studies. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of the Clinical Research and Innovation Department approved this study (n° 20/2023).

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