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Vesico-ureteric reflux: endoscopic management

May Bisharat, Marie-Klaire Farrugia
Chelsea Children's Hospital

Learning objectives

By the end of this module the reader should be able to:

- relate the indications and contraindications of endoscopic management of vesico-ureteric reflux
- recall the availability and outcomes of the different injectable substances and injection techniques
- describe the outcomes in both simplex and duplex systems as well as in the presence of ureteral anomalies.

Introduction

Vesico-ureteric reflux (VUR) is a common condition with an incidence of 2% in the paediatric population and a prevalence of 30% in children with febrile urinary tract infections (UTIs). Vesico-ureteric reflux presents as a spectrum, and not all cases require active management (see the *BJUI Knowledge* module "Vesico-ureteric reflux: natural history, investigation and non-surgical management"). When indicated, treatment options depend on the severity of reflux, likelihood of spontaneous resolution, breakthrough UTIs and parenteral preference [1, 2]. Ureteric re-implantation remains the gold standard of surgical management, but may be associated with prolonged hospital stay and potential morbidity, driving the search for a different, less invasive treatment modality [2].

Endoscopic injection for VUR

The minimally-invasive concept of cystoscopic subureteral injection of bulking agents was introduced by Matouskek in 1981 [3]. The postulated mechanism of action of injectable bulking agents is the creation of a scaffold that decreases the diameter and relatively increases the length of the intramural ureter, thus decreasing or eliminating VUR [4].

O'Donnell and Puri popularised the technique with their description of the STING procedure (subureteric Teflon injection) in 1984 [5]. The technique involved cystoscopic visualisation of the ureteric orifice (UO) and injection of Teflon submucosally at the 6 o'clock position. A 4Fr needle was inserted 2-3mm below the UO to a depth of 4-5mm into the submucosal portion of the ureter [6]. Whilst achieving high success rates, with minimal morbidity and very short hospital stay, concerns of particle migration of the polytetrafluoroethylene (Teflon) paste to the brain and lungs of experimental animal models lead to the discontinuation of its use [7]. Cross-linked collagen was introduced with satisfactory success rates, but yet again concerns of absorption prevented wide spread use [8].

Polydimethysiloxane (Macroplastique) was created as an elastomer with larger particle size, significantly reducing the risk of migration, and the synthetic nature of it prevented absorption. The success rate reached 86.2% after a single injection [9]. A significant game-changer was evidence of the occurrence of autoimmune reaction and malignant transformation in animal studies. This diminished the use of Macroplastique and the quest for the ideal bulking agent continued [10].

In 1995, Deflux, a dextranomer/hyaluronic acid copolymer, was introduced by Stenberg and Lackgren [11]. In addition to its non-migrating non-carcinogenic property, Deflux was biodegradable and non-immunogenic [12]. A prospective trial conducted by Oswald *et al.* compared the efficacy of Macropaslique and Deflux. The difference in the success rate (86.2% vs 71.4% at three months, 80.9% vs 67.6% at 12 months follow-up) was not statistically significant. With an equal cost and ease of administration (short general anaesthetic performed as a day case) and a significantly improved safety profile, Deflux became the bulking agent of choice [9]. Deflux gained FDA approval in 2001 [1].

Table 1. Success rates of different bulking agents after one treatment [3].

Bulking agent	Resolution rate (%) after one injection
Polytetrafluoroethylene (Teflon)	66.86
Collagen	56.86
Dextranomer/hyaluronic acid (Deflux)	68.71
Polydimethysiloxane (Macroplastique)	76.46

Indications

There is no universally-accepted indication for endoscopic injection, with some authors advocating injection in all patients with VUR and others using the technique selectively in symptomatic patients [1]. Long-term outcome studies have not shown a significant difference in renal outcome between medical and surgical treatment of VUR, although surgery appears to reduce the incidence of UTIs. Hence, it seems logical to only intervene if the patient becomes symptomatic, i.e. suffers a febrile culture-positive UTI whilst on an appropriate antibiotic prophylaxis. The Swedish Reflux study suggested no difference in outcome with endoscopic injection in boys, but a reduction in the incidence of UTIs and new renal scars in girls. The evidence therefore supports endoscopic treatment as a first-line option in girls, in particular those with scarred kidneys. The VUR recurrence rate post-endoscopic injection in the Swedish Refux Trial was 26% at two years [13].

Puri *et al.* evaluated the effect of subureteral dextranomer/hyaluronic acid injection using the "STING" procedure as a first line of management in children with grade III-V VUR, also including children with grade II VUR who had evidence of renal scarring or continued breakthrough UTIs. No evidence of reflux was found in 86.5% of patients after a single injection, a further 11.8% after a second, and 1.7% after a third injection (US and MCUG performed at three months post-procedure). The highest failure rates were described in the youngest patients, in highest grades of reflux, and in children with pretreatment renal scarring [6]. The overall rate of breakthrough infection was as low as 2.6% [1].

Puri and colleagues later published the long-term outcomes of 1551 children with medium- to high-grade reflux treated with subureteral Deflux injection. The success rates were similar to these published in the 2006 paper [1], but the incidence of febrile UTI increased to 4.6%. On investigation, only a minority of patients developed recurrent reflux or neo-contralateral reflux on MCUG, this was corrected with repeat endoscopic injection. There were no incidences of obstruction in this large case series, the only reported side effect was self-limiting frank haematuria in three children [6].

The techniques: STING , HIT and double HIT

A number of endoscopic injection techniques have been described with the aim of obtaining good UO coaptation, thus improving reflux reduction rates, without increasing the risk of ureteric obstruction.

STING technique

Subureteral transurethral injection (STING) was described by Puri and O'Donnell. The cystoscopically-guided needle is inserted into the submucosa 2-3mm distal to the UO. The aim of the injection is to create a mound with a nipple-like appearance, with a narrow slit on top [6]. The published success rate for the STING procedure is 87.1% after a single injection [1, 6].

Modified STING technique (HIT procedure)

The hydrodistension implantation technique was described by Kirsch *et al.* in 2004. The modified procedure included the implantation of bulking material into the submucosal component of the intraluminal ureter, with the aim of allowing the bulking agent to surround and compress the ureter within its intramural tunnel. The success rate of the modified STING significantly increased to 92% (from 79% for the standard STING procedure) [14]. The visualisation of the UO is optimised by directing the jet of fluid directly onto the orifice, termed hydrodistention. The hydrodistention is also used to gauge treatment success (i.e. hydrodistention implies sufficient bulking agent has been injected).

Double HIT procedure

Kirsch modified the technique further by applying the same hydrodistention principle, and combining it with two injections of bulking agent. The first bolus of dextranomer/hyaluronic acid (Dx/HA) is injected at the mid-ureteral tunnel, narrowing the channel in the detrusor, the second is injected into the distal intramural tunnel , narrowing the UO [15]. The reported success rate of the double HIT procedure is as high as 92%, with only 5% requiring a second injection [16, 17]. A survey conducted amongst American paediatric urologists suggests that the double HIT procedure has gained highest popularity (used by 92%) followed by HIT and STING procedures [16].

Watters *et al.* conducted a prospective study comparing the success rate of the STING and the HIT procedure in 246 ureters. No statistical significance was found in the success rate at three months follow-up (79.75% and 80.84% rate of ureter resolution for STING and HIT respectively). It is likely that the methodology, grade of reflux and definition of success varied between the STING and HIT advocates, accounting for the discrepancy in outcome. Preoperative grade of reflux and volume of Dx/HA injected, are more accurate predictors of outcome than the technique used [18].

Description of ureteric orifice before injection (hydrodistension (HD) grading)

Kirsch *et al.* described a novel grading system for the classification of VUR (Table 2). The technique is performed using a cystoscope, with the bladder half full. Normal saline is used as the irrigation fluid with the bag hung at 80cm above the patient. The jet of saline is aimed at the UO at full flow, and the orifice and the distention of the tunnel is evaluated and noted. Kirsch's study suggested that there was minimal inter-observer variation using this grading system, and also showed a definite correlation between the grade of VUR and HD.

A further study by Arlen *et al.* established a definite relationship between grade of HD, grade of VUR on MCUG, early reflux on MCUG in addition to a correlation with the volume of bulking agent needed at the time of double HIT [19]. The main uses of this grading system are accurate documentation of the grade of reflux at time of cystoscopy and the evaluation of success of anti-reflux procedures (endoscopic injection and re-implantation) [20].

Complications

Obstruction of the UO is an infrequent complication of endoscopic management of VUR. An incidence of 1% is documented in the literature [21]. Risk factors include children with thickened abnormal bladders and abnormal ureteral anatomy [22]. Management options include stenting, open re-implantation of the ureter and excision of the implanted material [21, 22]. Several case reports of delayed obstruction (up to five years from treatment) following endoscopic management of VUR with Deflux have been reported. This is thought to be secondary to pseudo capsule formation and calcification [22]. Long-term ultrasound of the kidney, ureter and bladder (US KUB) follow-up has therefore been recommended [21-23].

Elmore *et al.* described no increase in the difficulty for a second Deflux injection following documented failure of the first [24]. A recent study by Sparks *et al.* demonstrated no significant difference between primary re-implantation and salvage procedures performed after failed Deflux. Operative difficulty, time and success rate were not significantly different between the two groups [25]. These findings were echoed by Elmore *et al.* [26].

Follow-up and usefulness of the mound

Endoscopic injection may cause a transient hyroureteronephrosis, and therefore the first follow-up ultrasound should be performed at a minimum of four weeks. It was noted on routine follow up US that the "mound" of Deflux injected was frequently visible. Ellsworth *et al.* found that a visible mound on ultrasound does not correlate with likelihood of VUR resolution [27].

The use of MCUG as a follow-up modality after endoscopic injection in the asymptomatic patient is controversial, and depends on how one defines a successful outcome: radiological or clinical. Arlen *et al.* explored this area in a study whereby patients undergoing endoscopic injection were divided into two groups. The first had a high risk of persistence of VUR/failure of endoscopic management (patients with high-grade VUR, children under the age of two and breakthrough febrile UTIs), and the second group was deemed as having low risk of recurrence. The first group was screened via a planned MCUG whilst the second group was managed expectantly. Odds ratios for clinical and radiographic success was 9.9 and 13 times higher for the "expectant management" group. However, clinically the success rate in both groups was not statistically significant (96.6 vs 91.1%, "expectant management" vs high-risk group, respectively) [28].

This study highlights the controversy with current guidelines. Whilst the MCUG will demonstrate radiographic success, there is insufficient clinical correlation with this success rate. Most importantly this procedure is unpleasant for the child and family and carries a risk for UTI. In contradistinction to the European Association of Urology (EAU) guidelines, it is the belief of the authors (and the majority of paediatric urologists in the UK) that patients should be managed expectantly with US KUB follow-up unless a clinical indication for an MCUG arises.

Definition of success and recurrence

A recent meta-analysis reported vast differences in the success rate with endoscopic management. Whilst the patient populations and the injection techniques varied between studies, so did the definition of success.

Some authors defined success as radiological (complete absence of reflux on post-intervention MCUG), with others accepting grade I VUR. Others defined success clinically as absence of breakthrough UTI, yet further groups only recognised febrile UTIs as a marker of failure. To add to the confusion, others defined success as both clinical and radiological, freedom from antibiotic prophylaxis, avoiding the need for a second set of injections or the need for open surgery. Follow-up studies revealed that a subset of patients who had radiological success on

post-intervention MCUG, developed breakthrough UTIs. Inversely, patients with persistent reflux, had no breakthough infections and did not require further intervention [1, 3, 6, 14, 15, 18].

A study by Kaye *et al.* demonstrates a vast discrepancy in outcomes within the same population, if different definitions of success are applied. This highlights the need for a universal definition and follow-up protocol.

As breakthrough febrile UTIs can cause further renal scarring, this particular clinical outcome should be considered the most important. This raises the question of whether the radiation, discomfort, anxiety and risk of infection associated with a repeat MCUG is necessary for all patients. As the documented success rate for this procedure is a high as 94% in some series, it might be possible to restrict the use of this invasive test for children who develop infections, symptoms or develop renal pelvic dilatation on follow-up [17].

Success rates in challenging cases

High-grade reflux

The success rate achieved from endoscopic management of VUR varies on a case-to-case basis. A logistic regression analysis identified grade of VUR (most significant factor) and age at endoscopic procedure (younger age carries a higher failure rate) as the only two variables predictive of success of endoscopic management. Interestingly, patient sex was not an independent predictor of success.

Both the STING and the HIT procedure have achieved high success rates in the treatment of grade IV and V VUR (75.6% and 62.4%, respectively after a the first STING procedure) [6]. The overall documented success rate for grade IV VUR is 63-71% (HIT and STING, respectively) [1, 6, 14].

Puri *et al.* describe a slight variation in the technique of the STING procedure for patients with high-grade VUR. The STING needle is not inserted below, but directly into the UO, with steady gradual withdrawal on injection, until the mound causes the ureteral coaptation and a slit-like appearance [1].

Duplex systems

The natural history of VUR resolution differs between simplex and duplex systems. Over a five year follow-up period, patients with simplex system VUR had a 50% resolution rate compared with only 20% in the duplex system group. The need for surgery was significantly higher in the duplex group (69% vs 25%) [29]. This must be considered when studying the efficacy of endoscopic management of duplex systems.

A systematic review performed by Hensle *et al.* demonstrated no significant difference in the success rate of treatment of refluxing duplex and simplex systems with Dx/HA (64% vs 68%, respectively). The review included 17 studies that included 2879 patients. The overall cure rate ranged from 15% to 100%. The follow-up period varied from a mean of 1.7-6.9 years, and the incidence of post-treatment breakthrough infections was poorly recorded. There was no clear documentation in most studies included if the ureters treated were complete or partial duplex systems, which decreases the validity of the results presented [30].

A retrospective single center study on 123 patients with complete duplex systems published by Hunziker *et al.* reported a success rate of 68.4% vs 87.1% after a single treatment (duplex vs simplex, respectively). This success rate increased by a further 25.7% after a second treatment. None of the included patients required open surgery, with only one patient suffering a complication (self-limiting haematuria). No incidences of obstruction were recorded [31]. These findings were echoed by Molitierno *et al.*, who obtained a 73% success rate after the first injection and an overall success rate of 85%. One patient in that series (of 52 patients), required open reimplantion [32].

Paraureteral diverticula

Congenital bladder diverticulae that occur at or adjacent to the UO have a high associated incidence of VUR. Classically this condition was managed surgically by open re-implantation of the ureter with or without divericulectomy. Cerwinka *et al.* documented a success rate of 81% in treating this condition endoscopically in a case series of 20 patients. Only a fifth of the patients required open re-implantation. A multivariate analysis revealed that diverticular size and volume of Deflux injected are the only two factors that predicted treatment failure. Interestingly, only the grade III VUR patients experienced a failure rate. Success rate for both grade IV and V was 100% in this study. The average volume of bulking agent used was 1.2mL (0.8-1.8mL), which is not significantly different from the volume used in primary VUR [33]. Long-term outcome studies for the use of Deflux in patients with para-ureteral diverticulae are not available; however, the high success rate achieved should make the clinician consider endoscopic management as a primary treatment option for such cases.

Contraindications

As endoscopic management of VUR is a safe, short, effective procedure, the contraindications for this procedure are very few. One of these is a refluxing obstructive megaureter, which may be difficult to diagnose at the outset. It is important to always request post-void views on an MCUG, firstly to ensure the bladder empties (and to exclude underlying bladder dysfunction) and secondly to ensure that the upper tracts are draining adequately. Poor drainage with VUR may be suggestive of an obstructing refluxing megaureter, where a diuretic MAG-3 renogram would be indicated. Endoscopic injection is contraindicated in this condition, as the risk of creating a full-blown obstruction is very high, meaning a ureteric re-implantation is the best option.

How many times is re-injection indicated?

Elder *et al.* published a success rate of only 67.1% after the first endoscopic injection. However, the success rate for the second and third injections was 68% and 34%, respectively, with an overall success rate of 85%. The rate of breakthrough infections was 6.75% (only 0.75% were febrile UTIs) [3]. The evolution of the HIT and double HIT procedures, led to success rates as high as 92% for the first treatment course and a subsequent drop in the need for a second set of injections to 5% [17].

As every treatment course requires a hospital admission, a general anaesthetic and a minimally-invasive procedure, a careful selection of the technique used and sufficient experience in performing the procedure are necessary to achieve optimal results. It is also important to be realistic regarding the likelihood of success with second and third attempts, and if appropriate UO coaptation is not being obtained, then ureteric re-implantation can be justified.

Studies of open and laparoscopic re-implantation of ureters that have been previously injected with Deflux have not shown an increase in complications caused by the presence of the bulking agent [25].

International guidelines

The EAU guidelines on VUR in children state that endoscopic management may be considered in children of both sexes with symptomatic or asymptomatic high- or medium-grade VUR. The guidelines state that the success rate of open intervention is superior to that of the endoscopic management in high-grade cases. The guidelines do not recommend this treatment modality for low-grade reflux with normal kidneys, but endorse the management modality for low-grade cases with abnormal kidneys [34].

The British Association of Paediatric Urologists (BAPU) Consensus Statement in 2012 advised endoscopic injection after the first febrile breakthrough UTI, but also supported it's use as a first-line treatment in cases of breakthrough UTI or UTIs after discontinuation of prophylaxis [35].

Summary

The outcomes of endoscopic management of VUR are comparable with those of surgical management. Recent evidence suggests that the success rates for difficult cases such as duplex systems, paraureteric diverticulae and high-grade reflux are high. Endoscopic management is therefore an attractive alternative to open re-implantation with less morbidity (pain, scar, hospital stay, postoperative bladder dysfunction and cost). Whilst antibiotic prophylaxis is effective in mild to moderate reflux, the issues of long-term compliance, cost, and bacterial resistance made endoscopic management an attractive alternative first-line management option. An internationally accepted and standardised approach to VUR management is needed.

Key learning points

- Endoscopic treatment of VUR is indicated after the first breakthrough febrile UTI; there is no conclusive evidence the technique benefits asymptomatic patients other than girls with scarred kidneys.
- Endoscopic treatment is safe and offers good success rates when the appropriate technique and bulking agent are used; be wary of the obstructing refluxing megaureter, which is a contraindication.
- Recently published success rates are up to 93% in low-grade VUR and just under 80% in high-grade VUR. The overall success rate in duplex systems is 85% (10% less success rate per grade of reflux in comparison to simplex systems).
- The main complication of the procedure is the 1% risk of obstruction which can be managed by temporary stenting or re-implantation.

Abbreviations

DMSA	dimercapto-succinic acid scan
Dx/HA	dextranomer/hyaluronic acid
FDA	Food and Drug Administration
HD	hydrodistention
MAG-3	mercaptoacetyltriglycine scan
MCUG	micturating cystourethrogram
RN	reflux nephropathy
US KUB	ultrasound of kidneys, ureters and bladder
UTI	urinary tract infection
UO	ureteric orifice
VUR	vesico-ureteric reflux

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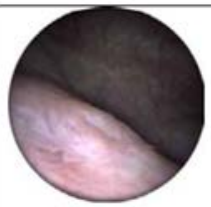
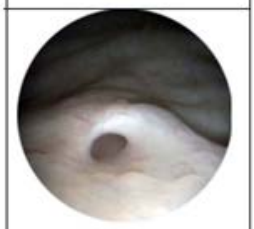
Hydrodistention Grade	Description	Cystoscopic appearance	Example
H0	No orifice distention evident		
H1	Orifice opens Intramural tunnel not evident		
H2	Orifice opens Intramural tunnel evident Extramural ureter not evident		
H3	Orifice opens Extramural ureter evident or ureter can accept cystoscope		

Table 2. Hydrodistention classification of VUR by Kirsch *et al.* (reproduced with permission from the author) [20].