

Surgery Illustrated – Surgical Atlas

Endoscopic treatment of vesicoureteral reflux

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INTRODUCTION

Vesicoureteral reflux (VUR) affects around 1% of all children, making it the most common paediatric anomaly of the urinary tract. Around a third of infants and children with febrile UTI have VUR [1]. The urinary tract infections (UTIs) in these children with VUR are more likely to reach the upper urinary tract and develop into pyelonephritis than in those without VUR [2].

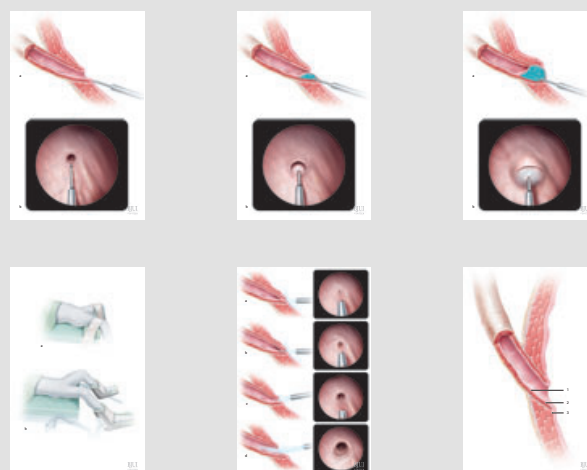
The fact that reflux may persist for a number of years provides the rationale for treating VUR. It has been shown that adults with persistent reflux and scarring may run the risk of further pyelonephritis, progressive renal disease and hypertension [3], and VUR is a likely major factor in the pathogenesis of recurrent UTI, acute pyelonephritis and renal scarring [4]. Thus, the aims of treatment are to reduce the risk of febrile UTIs affecting the upper urinary tract and possibly protect against future renal damage.

There is today general agreement that children with high grade reflux (III–V) will benefit from the treatment and cure of VUR, particularly in combination with renal scarring.

TREATMENT OF VUR

Antibiotic prophylaxis, open surgery or endoscopic treatment are today the three therapeutic options for children with VUR and UTI.

Antibiotic prophylaxis has the major disadvantage of encouraging antibiotic resistance among bacteria and there are concerns about breakthrough infections and



also about low compliance to the treatment which increases the risk of new UTI [5]. Therefore, for most patients with high grade VUR, active treatment is recommended to reduce the incidence of ascending febrile UTIs and their associated risks of renal damage. Due to its minimally invasive nature and the fact that UTI rates post endoscopic injection are as good or better than after open surgery, endoscopic injection is today generally considered preferable to ureteral reimplantation [6,7].

Endoscopic treatment of a bulking agent was pioneered by Matouschek in 1981 [8] as an alternative to conservative medical treatment and surgical reimplantation of a refluxing ureter. The technique was further developed and popularised by O'Donnell and Puri [9], who in 1984 reported results in both pigs and humans with subureteric Teflon injection (STING). Since then thousands of children

with VUR have been treated with different substances – Teflon paste, silicone paste or collagen being the most common until the introduction of NASHA/Dx gel [10] (Deflux®, Oceana Therapeutics Ltd, USA).

To ensure safety and long-term efficacy, the ideal injectable agent should be biocompatible. The risk of new renal scarring is greatest among infants and young children aged under 5 years and therefore, the bolus created, using an injectable agent should persist for a minimum of 5 years. Pre-clinical studies demonstrated the biocompatibility of NASHA/Dx gel, together with a lack of potential for migration from the injection site [11]. Both constituents of NASHA/Dx gel are biodegradable polysaccharides, ensuring that this material cannot accumulate permanently within the body. Injected NASHA/Dx gel becomes infiltrated with endogenous connective tissue, and follow-up studies (both

pre-clinical and clinical) have shown that the bolus persists for at least 3 years with no fibrosis or aggressive granulomatous reaction spreading to adjacent tissue [12–14]. Sonographic analysis [15] has shown minimal loss of injected volume for at least 3 years and long-term clinical data indicate that NASHA/Dx gel remains effective for much longer than this and that only 3% of patients experienced a febrile UTI over long term [16]. The consistency of NASHA/Dx gel is good for submucosal injection as it can be administered using finger pressure only, with no need for an injection gun. These properties represent considerable advantages compared with other substances that have been used for endoscopic injection, such as polytetrafluoroethylene (PTFE), polydimethylsiloxane (silicone) and collagen. NASHA/Dx gel is today the dominant injectable agent for endoscopic treatment of VUR.

Figure 1

THE CONVENTIONAL TECHNIQUE ('STING')

Endoscopic treatment involves submucosal injection of a bulking agent into the bladder wall below the ureteral orifice, or within the ureteral tunnel, to provide tissue augmentation. The basic principle is to provide a solid support under the refluxing ureteral orifice thereby increasing the submucosal length of the ureter and also to create a fixation point for the ureter so as to improve the valve mechanism and stop urine from refluxing into the ureter.

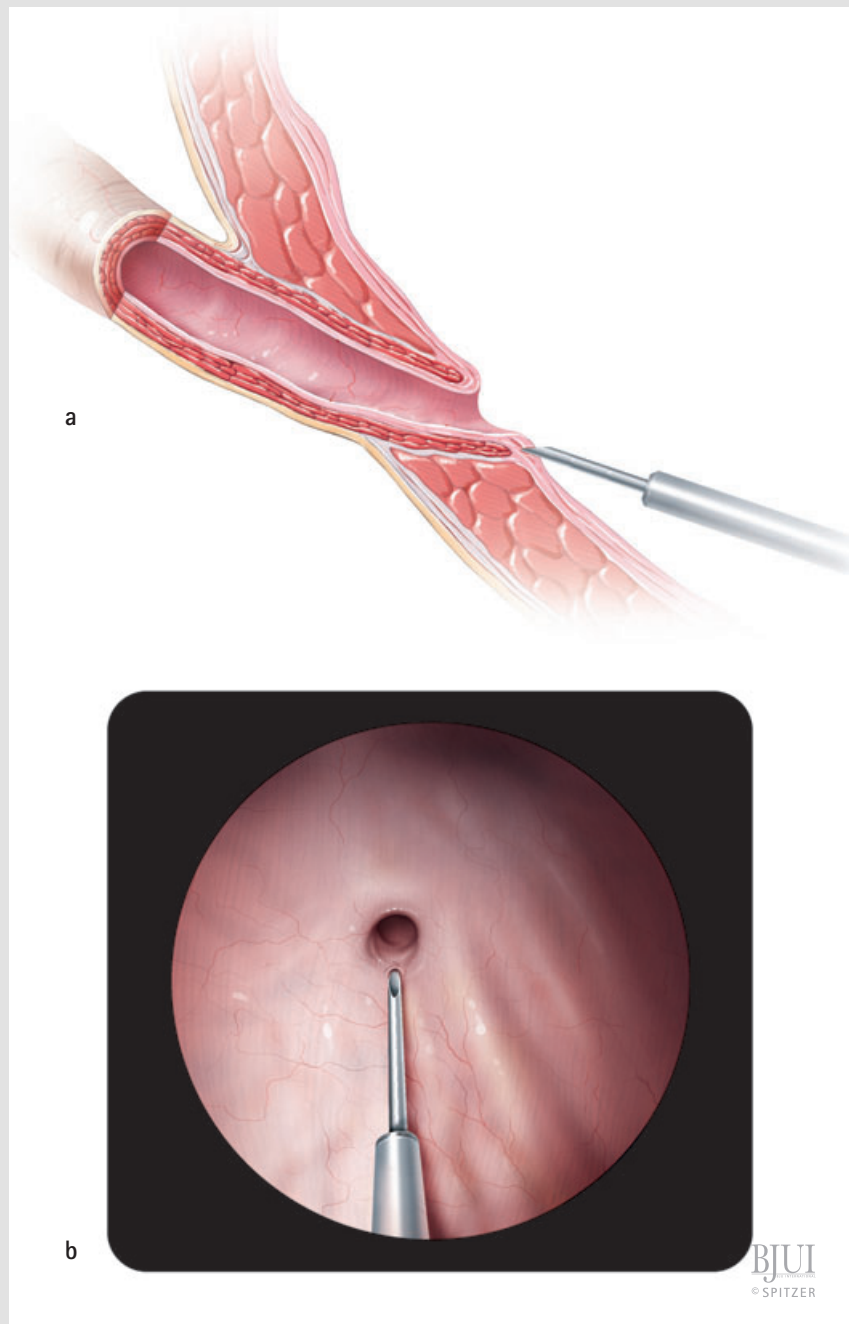


Figure 2

The traditional STING procedure [9] involves the needle being introduced under the bladder mucosa 2–3 mm below the refluxing orifice at a 6 o'clock position. The injection is continued until there is a prominent bulge and the ureteral orifice has assumed a crescent-like shape.

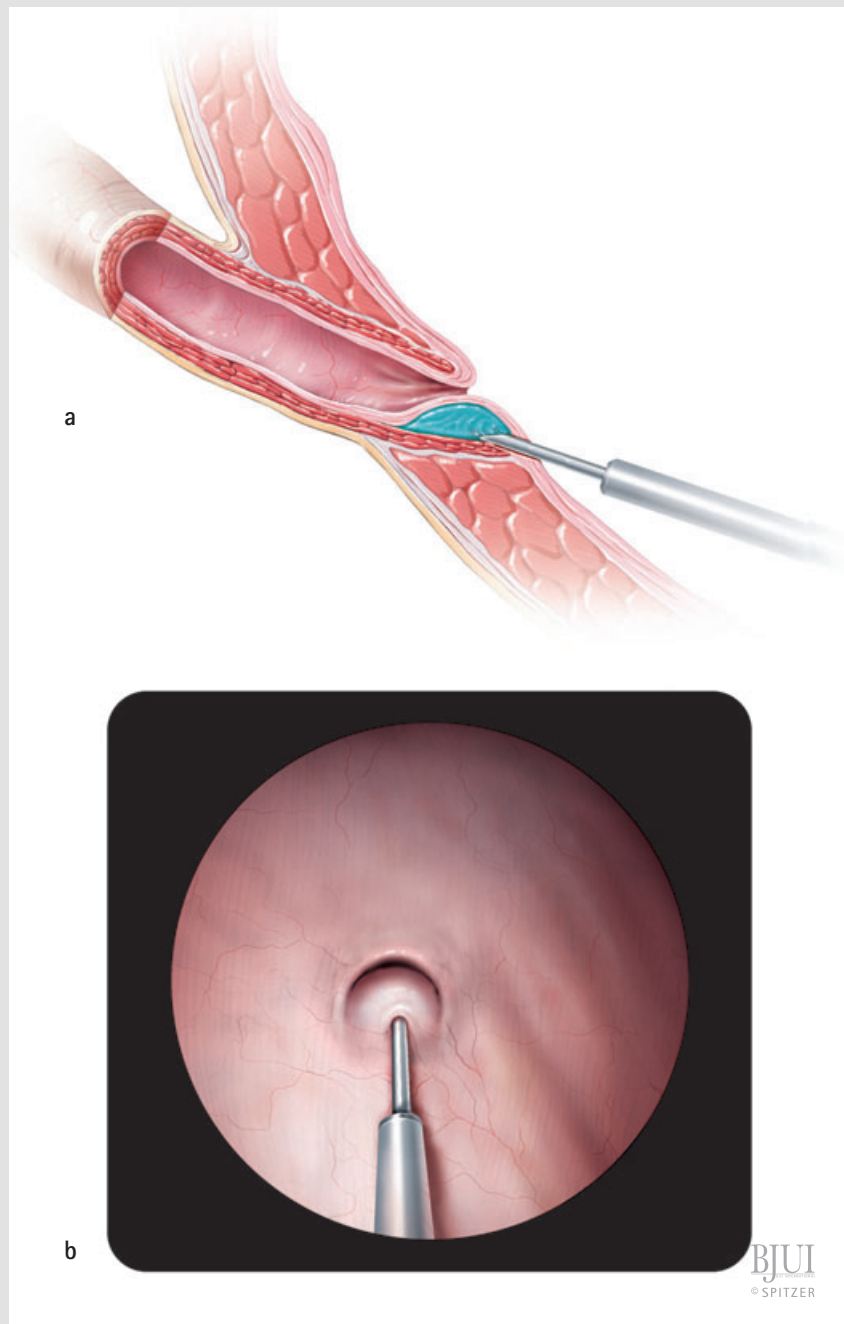
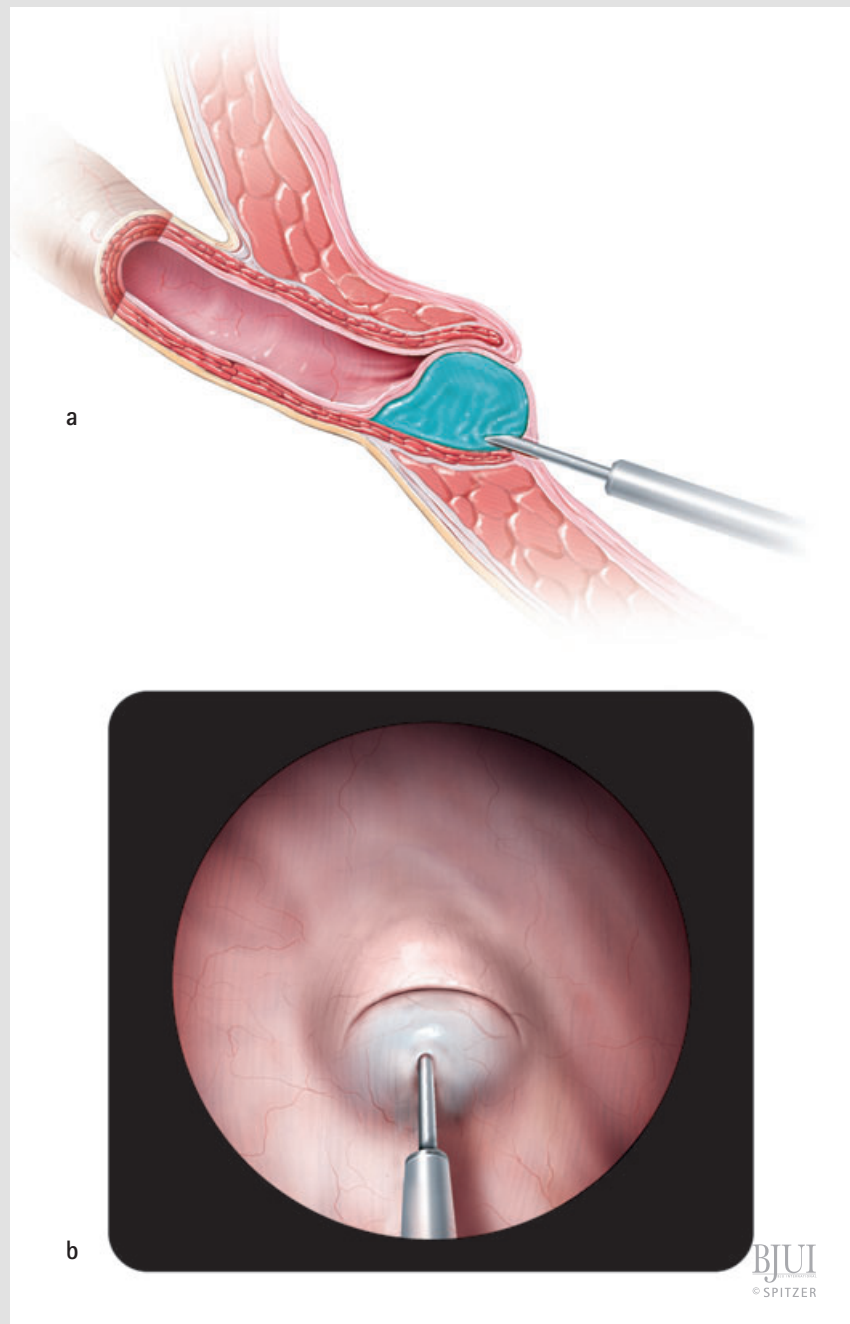


Figure 3

This technique has further been developed by Kirsch *et al.* with the introduction of intraureteral injections (HIT technique described below), which has increased the success rate significantly [17,18]. One of the reasons for this may be the increased volume injected but also that the substance is injected under the intramural ureter, which may lower the risk of bolus displacement. In most patients a combination of the intraureteric injection and the STING is used to achieve an optimal bolus.



THE EVOLUTION OF THE DOUBLE HIT METHOD

Endoscopic injection techniques have evolved from subureteric injection (e.g. STING) described above, to single intraluminal HIT (Hydrodistention Implantation Technique) to tandem proximal and distal intraluminal injection sites (Double HIT) that coapts both the ureteral tunnel and orifice [19]. A great deal of experience and skill is required to obtain results that compare favourably to open surgery. Postoperatively, failures may result from implant displacement (implant migration), disruption (mucosal breach), or dissolution (decrease in implant volume). However, it is our belief that nearly all endoscopic failures are related to unrecognised or unappreciated technical errors. These may result from improper technique, ineffective injection site(s), inadequate volume of injection, or ambiguous end points for injection. Recently, a novel needle device utilizing a Filiform wire guide and retractable needle has made the procedure more precise, easily adopted, and has improved the learning curve. New biological injectable agents are also under study.

The following information will provide a step-by-step guideline to insure a high surgical success for all grades of VUR.

CYSTOSCOPIC EQUIPMENT

Cystoscopy is performed with a pediatric cystoscope equipped with an off-set lens. An off-set lens permits direct passage of the needle in line with the ureter without bending the needle. 9.5Fr size and higher are optimal.

INJECTION NEEDLES

Several needles are available for injection. The most commonly used are the metal needle and more recently the Injekt needle.

Metal Needle (Oceana Therapeutics Ltd, USA)
Injekt™ Needle – Filiform Needle Guide (Cook Urological, Spencer, Indiana).

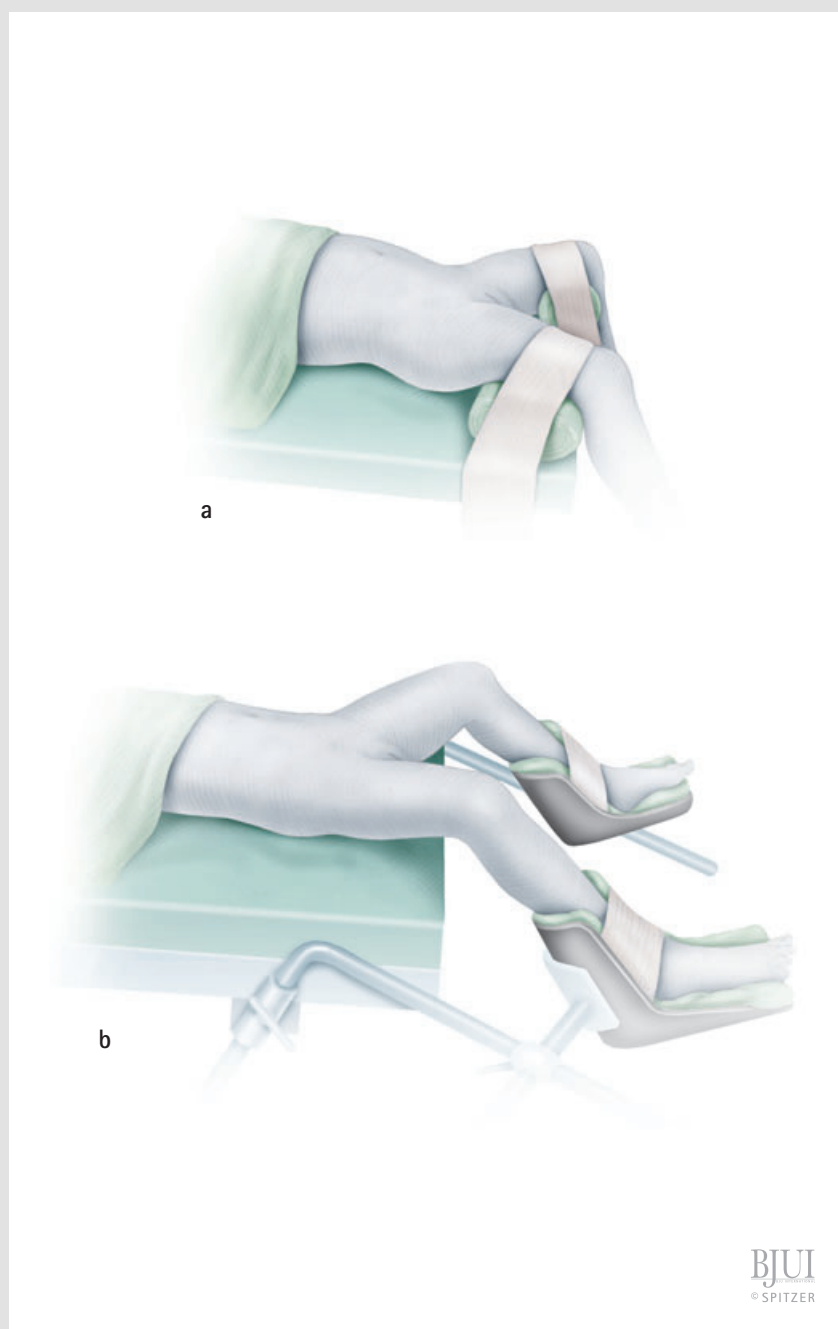


Figure 4

PATIENT POSITIONING

The child is placed in a lithotomy position and cystoscopy is performed under general anaesthesia.

It is important to be able to rotate the cystoscope over the thighs in order to inject lateral orifices. Stirrups may impede the surgeon's ability to manoeuvre and thus the use of bolsters and low stirrups are useful.

- (a) Younger child – bolsters under knees
- (b) Older child/adolescent – low stirrups

Figure 5

HYDRODISTENSION OF THE URETER

Hydrodistension (HD) is performed with the tip of the cystoscope placed at the ureteral orifice (UO), a pressured stream achieved by placing the irrigation bag approximately 1 meter above the bladder on full flow. HD is graded according to Fig. 5. HD of the distal ureter serves two purposes: It allows visualization of the intraureteral injection site and assessment of treatment progress (i.e. ureteral coaptation).

HD grade is more important than VUR grade since VUR grade is determined by the degree of dilation of the supravescical ureter and renal calyces and HD grade is determined by the distensibility of the ureteral orifice to be treated. HD grades vary considerably within each VUR grade but directly correlates with it. Refluxing ureters will show H2-H3 in the majority of cases.

(a) Hydrodistension Grade H0: No orifice, distension evident

(b) Hydrodistension Grade H1: Orifice opens, intramural tunnel not evident

(c) Hydrodistension Grade H2: Orifice opens, intramural tunnel evident, extramural ureter not evident

(d) Hydrodistension Grade H3: Orifice opens, extramural ureter evident or ureter can accept cystoscope

Higher grades of HD require more volume. Table 1 provides a guide to the appropriate injection volume for the Double HIT method based on VUR grade and HD grade. These injection volumes have been used exclusively with the Double HIT method and have resulted a cure rate of approximately 90% after 1 treatment. Injection volumes will vary with the method of injection as well as the skill of the surgeon [20].

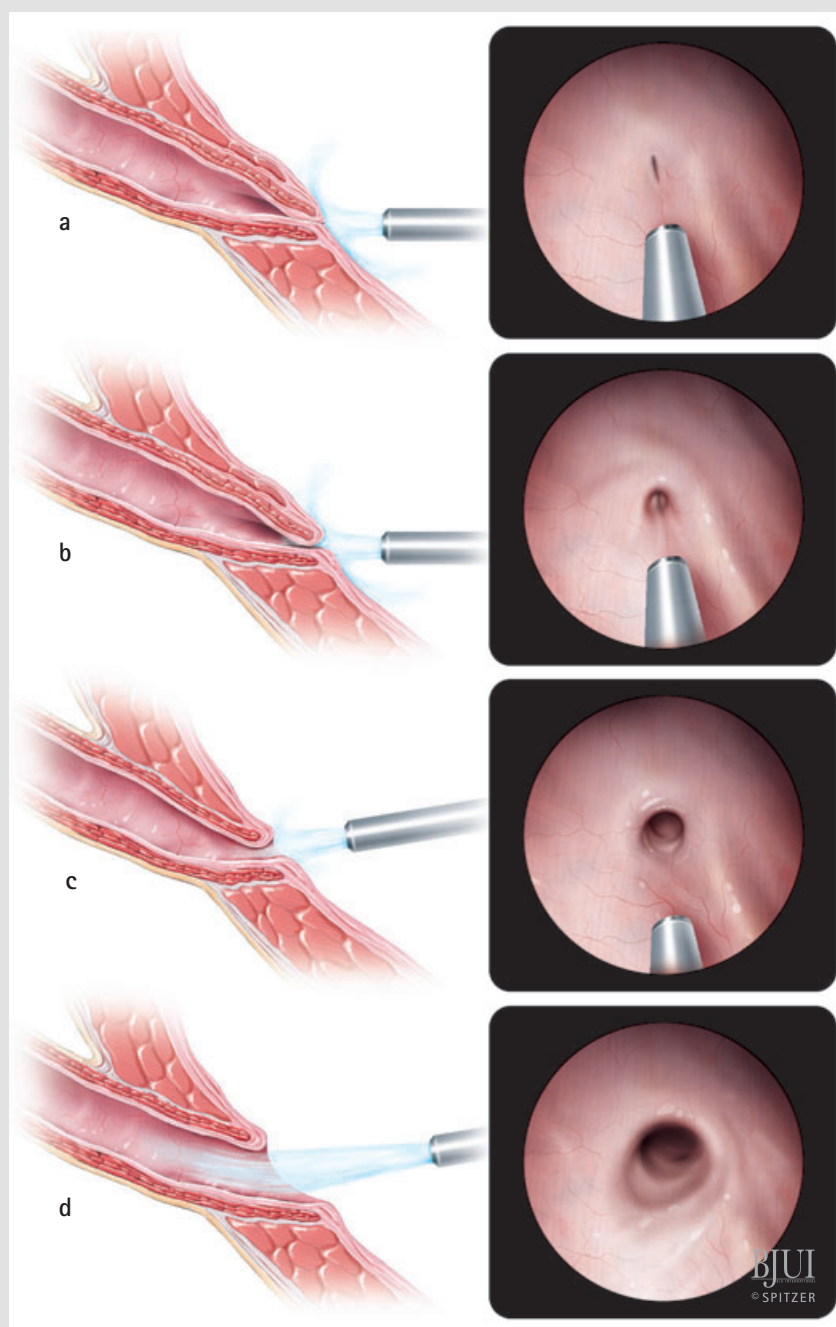


TABLE 1 Volume of injection tables based on VUR and HD grades

Volume injected (mL) by VUR grade

VUR grade	N	Mean $\pm$ SEM (mL)	95% confidence interval for mean	Range
I	40	1.21 $\pm$ 0.07	1.07–1.36	0.5–2.6
II	192	1.27 $\pm$ 0.03	1.21–1.33	0.5–2.4
III	216	1.31 $\pm$ 0.03	1.24–1.38	0.3–3.2
IV	70	1.66 $\pm$ 0.07	1.52–1.80	0.7–3.3
V	8	1.75 $\pm$ 0.21	1.25–2.25	0.8–2.4
Total	526	1.34 $\pm$ 0.02	1.30–1.38	0.3–3.3

Volume injected (mL) by HD grade

HD grade	N	Mean $\pm$ SEM (mL)	95% confidence interval for mean	Range
0	6	0.92 $\pm$ 0.15	0.522–1.31	0.5–1.5
1	53	1.02 $\pm$ 0.04	0.933–1.10	0.6–2.0
2	222	1.26 $\pm$ 0.03	1.20–1.32	0.5–3.1
3	234	1.49 $\pm$ 0.03	1.42–1.56	0.3–3.3
Total	515	1.34 $\pm$ 0.02	1.30–1.38	0.3–3.3

Volumes of injection are the same for grades I–III. A higher volume is needed for grades IV–V. A higher volume of injection is needed as the HD grades increase from H0 to H3.

Figure 6

DOUBLE HIT METHODOLOGY

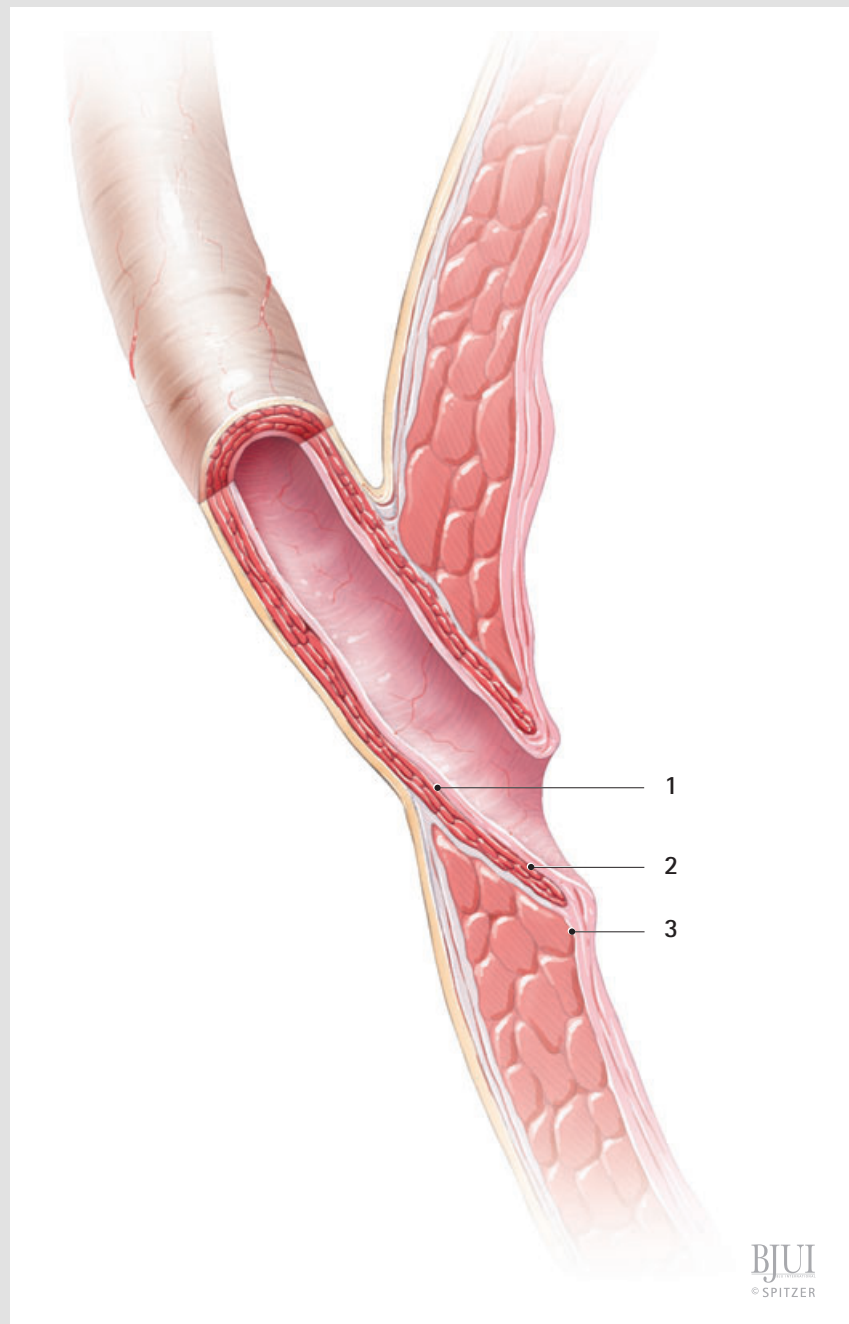
The endoscopic method currently achieving the highest success rates is the double Hydrodistention Implantation Technique (HIT). The bladder is filled to less than half capacity to permit visualization of the ureter and avoid tension within the submucosal layer of the ureter secondary to over-distention.

The needle is passed into the UO and inserted at the mid ureteral tunnel at the 6 o'clock position. Sufficient bulking agent is injected to produce a bulge, which initially coapts the detrusor tunnel, while a second implant within the most distal intramural tunnel leads to coaptation of the UO. HD is performed after each injection to monitor treatment progress; when HD ceases to dilate the UO, appropriate coaptation has been achieved.

ALGORITHM FOR NEEDLE INJECTION SITES

Needle placement algorithm for the endoscopic treatment of VUR.

Sites 1 and 2 comprise the Double HIT method, while site 3 (STING) is rarely used.



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Figures 7 & 8**FREE METAL NEEDLE TECHNIQUE**

Endoscopic treatment of vesicoureteral reflux (Double HIT technique). HD is used to expose the floor of the ureter. This is easily achieved when ureters show higher HD grade (H2-H3). The needle is passed to the 2 mm mark at the tip of the needle. A slow injection is recommended. The mucosal surface first blanches and then shows a light reflex when appropriate turgor is achieved within the tissues. Lack of HD of the ureter post-injection confirms a successful treatment.

(a,b) proximal intraureteric injection, coapted intramural ureter

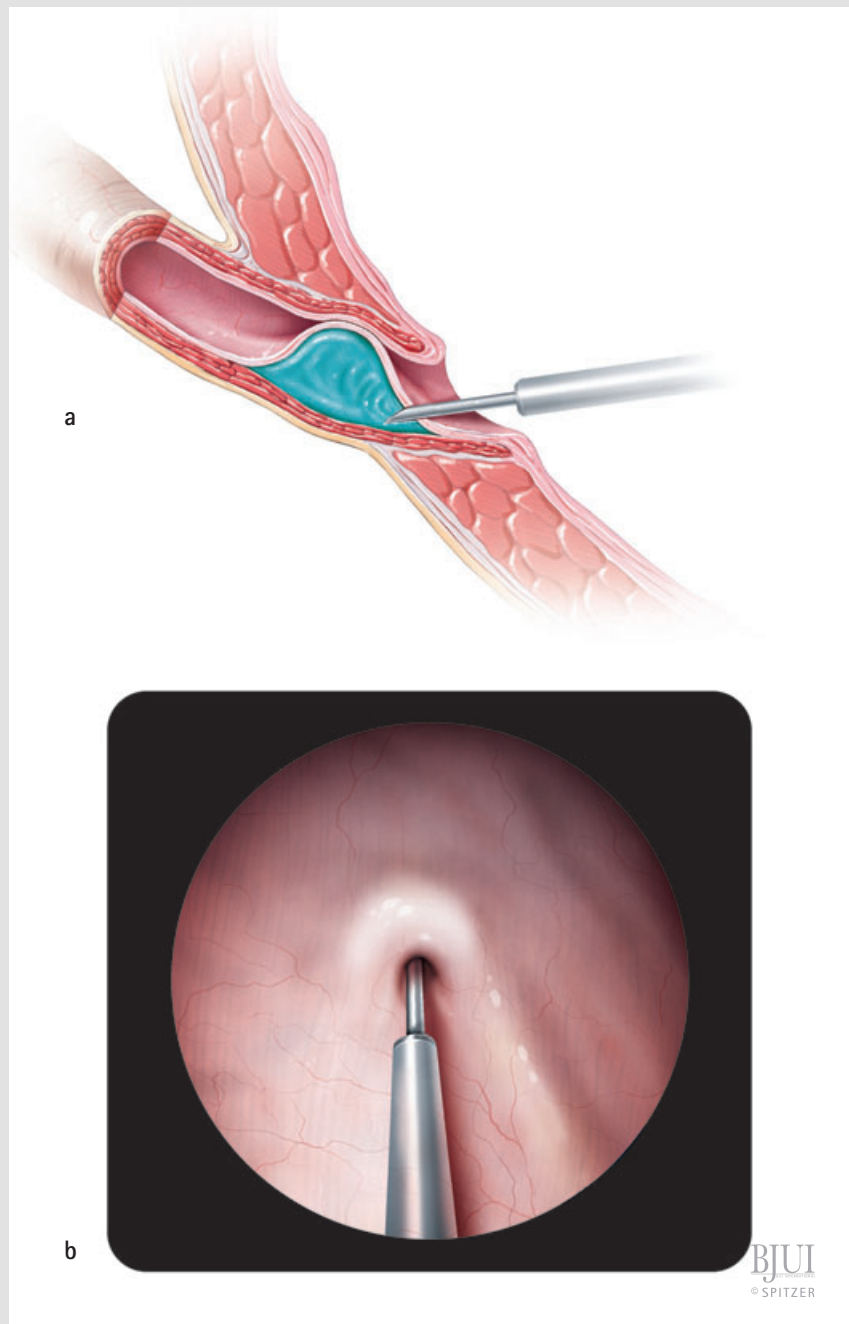


Figure 8

(a,b) distal intraureteric injection, coapted ureteral orifice

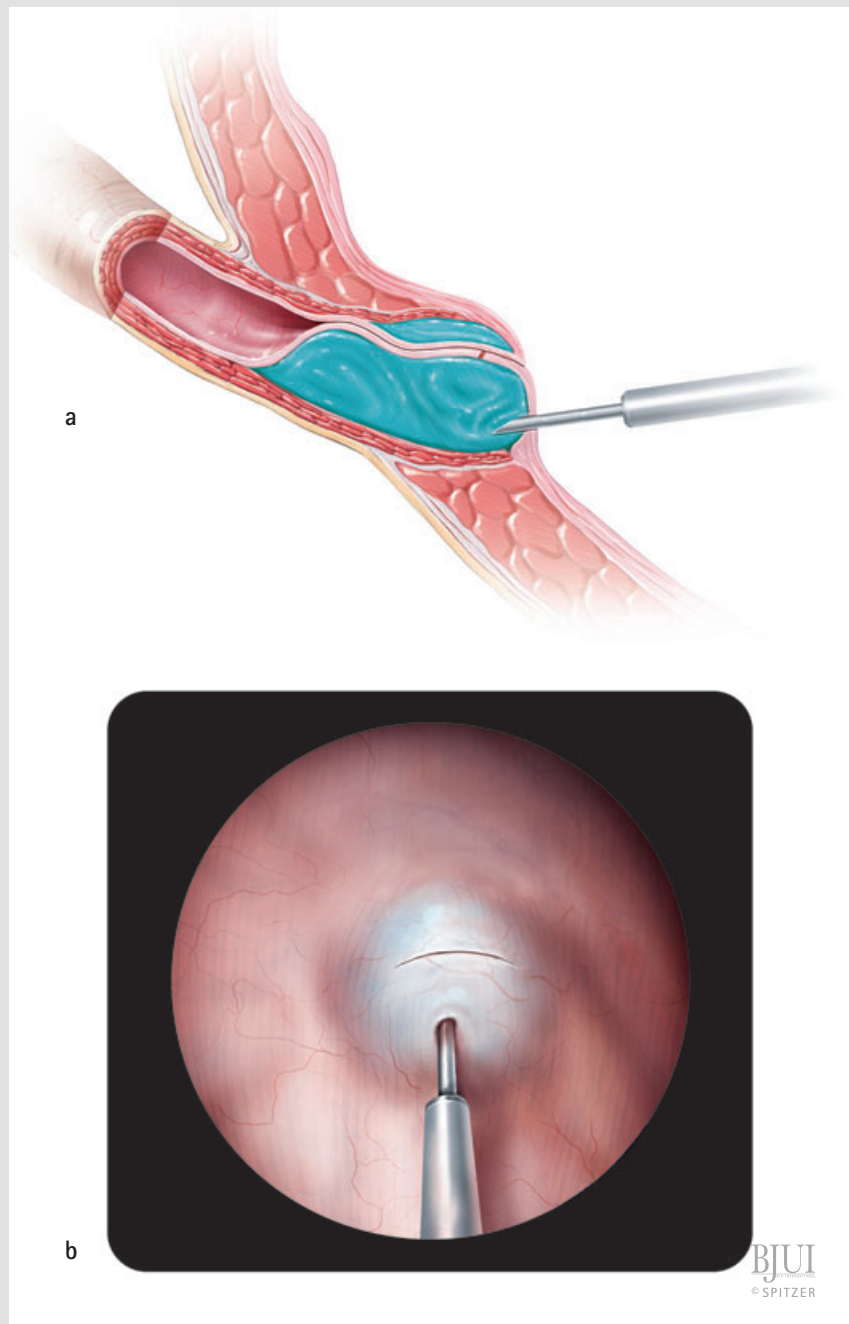


Figure 9**INJEKT NEEDLE TECHNIQUE****THE INJEKT NEEDLE GUIDE**

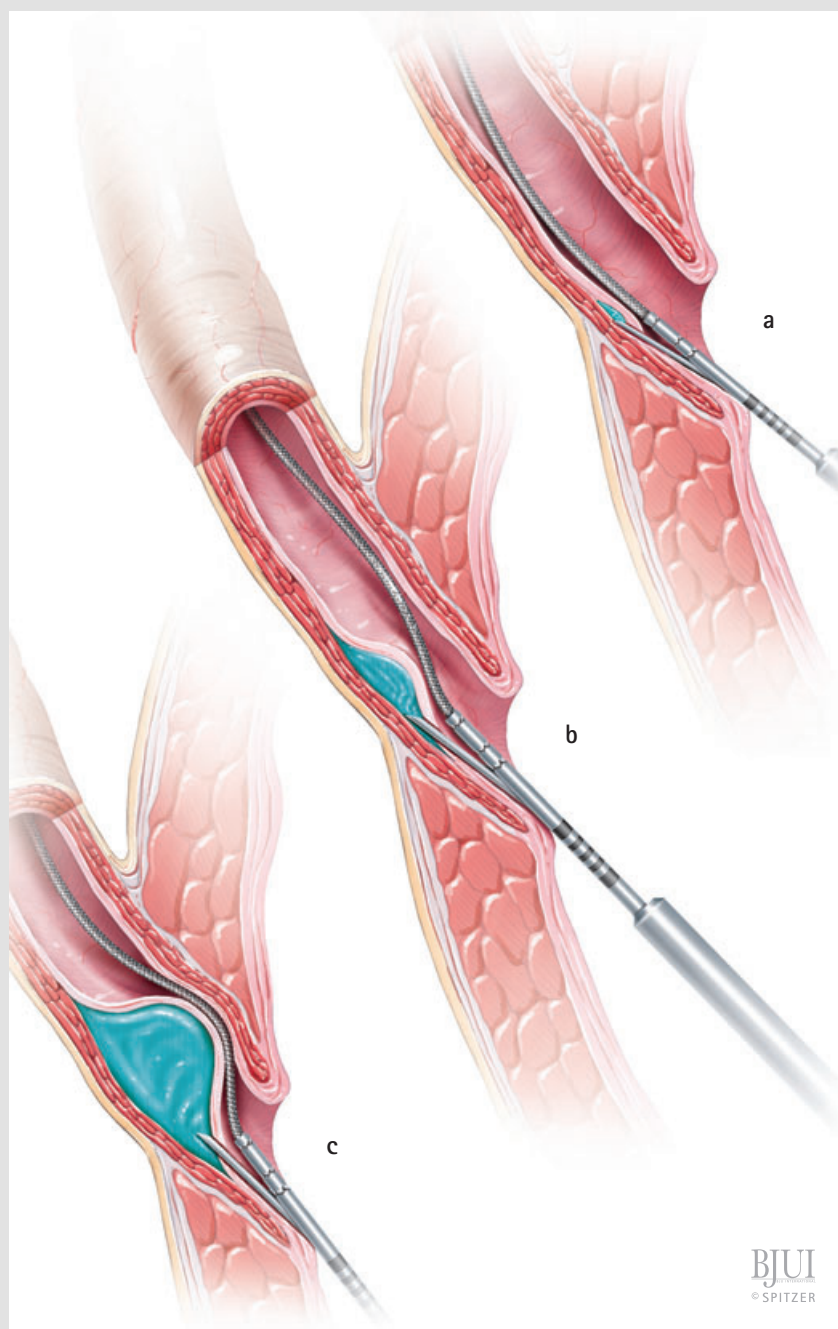
The Filiform wire easily assesses the ureteral UO. HD of the ureter is not needed for needle placement. Etch markings on the needle's sheath are used to attain precise injection location. The hub, with depth markings, provides both tactile feedback and visual markings that allows the needle to be inserted at 1 mm increments. The needle exits the side of the device at an appropriate angle via a ramp and allows more precise injection location and assures additional safety to the patient when the needle is retracted. The "V" between the extended needle and the guidewire prevents insertion of the needle deeper than the desired depth marked on the hub gauge.



Figure 10(a–c)

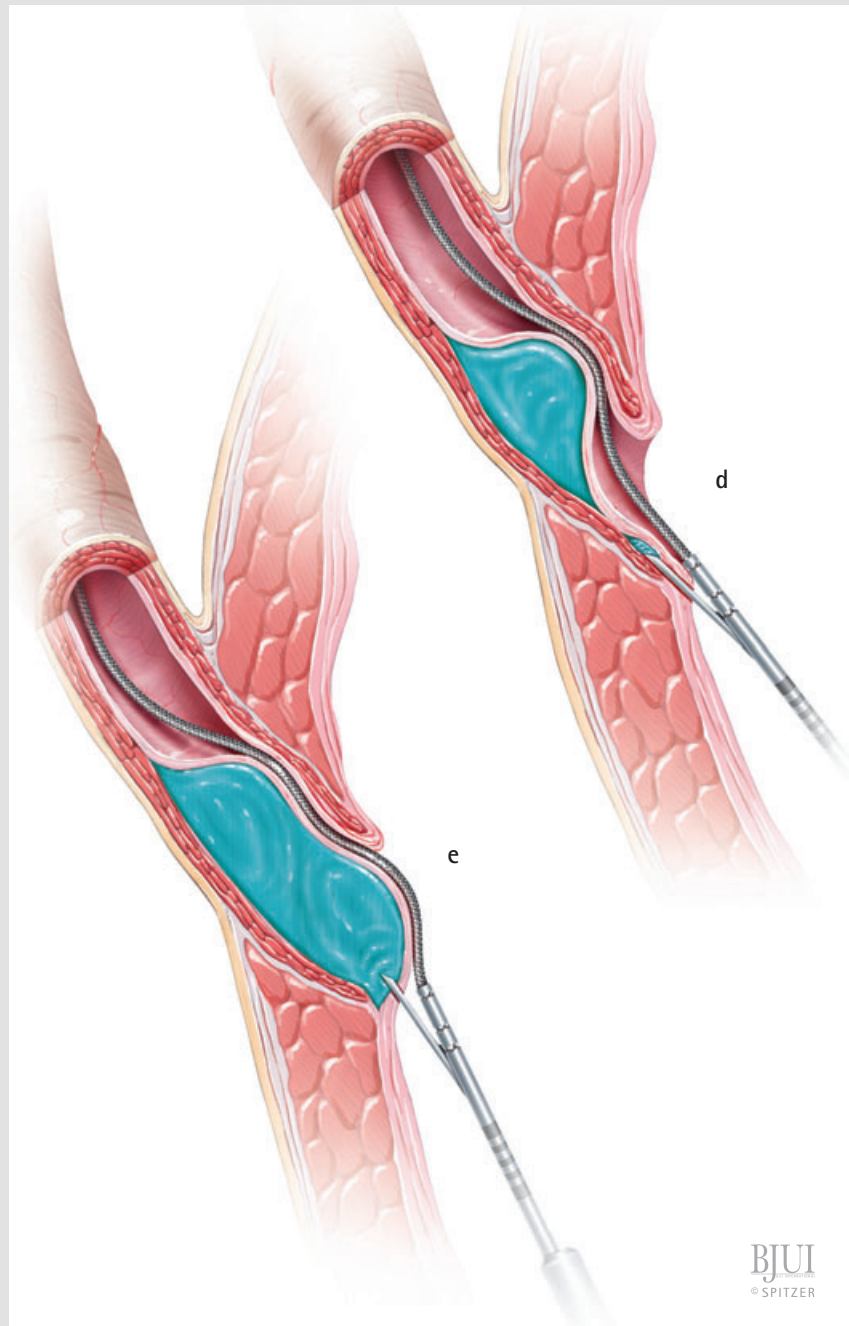
(a–e) Double HIT method using the Injekt needle guide

Lack of HD of the ureter post-injection confirms a successful treatment.

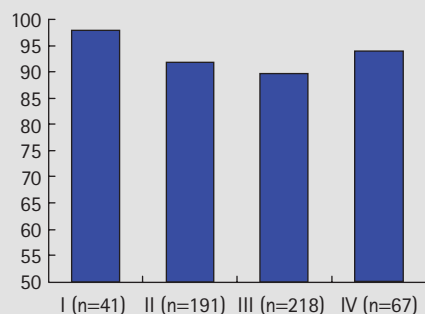


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Figure 10(d-e)

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GRAPH 1. Ureteral success rates for primary grade I–IV VUR.



POSTOPERATIVE ASSESSMENT

After endoscopic treatment, VCUG assessment is scheduled at 4–6 weeks and antibiotics are administered until that point. Provided there is a successful treatment shown at the first VCUG, the further follow-up is scheduled according to renal status and bladder function. If, however, the VUR persists at the first VCUG, a second treatment is recommended within 3 months.

It is important to minimize the number of VCUG and if the surgeon's success is high, it is reasonable not to perform any radiographic evaluation in the absence of clinical signs or symptoms. In patients with reflux and renal scarring, a DMSA scan may be the preferred follow-up and only if clinical symptoms as recurrent UTI and/or increased renal scarring is a VCUG indicated. Furthermore, ultrasound may be performed for persistent back pain and/or protracted emesis. Since the febrile UTI rate is less than 5% postoperatively, 95% of patients would be spared a VCUG.

EFFICACY (VUR RESOLUTION)

The first major study of endoscopic treatment with NASHA/Dx gel was performed on children with high grade reflux (III–V). They were treated with the conventional STING technique and at their last VCUG, 68% of patients were cured [21]. Many other studies have shown similar or better results [17,22,23]

One should bear in mind that there is an apparent learning curve with the technique, and the treatment procedure: in one study, success rates increased from 60% for the first 20 of 134 patients treated, to 80% for the last 20 cases [17].

With the development of the injection techniques described in this chapter, the success rates can be increased and more recent studies have reported much higher overall success rates by using the hydrodistention implantation technique (HIT), approaching those seen with open surgery (in the region of 90%), after up to 12 months' follow-up (Graph 1) [7,18].

The endoscopic treatment has also been shown to be effective in VUR patients with complicating factors. The cure rate is high in children with VUR and duplicated ureters following NASHA/Dx gel treatment [24,25] and also in children with a variety of different complications, including failure to respond to open surgery, neurogenic bladder and ectopic ureters [26] as well as paraureteral diverticula of small to moderate size [27], indicating that endoscopic treatment should be considered as an option in children with a wide range of complications.

Radiographic cure after 1 treatment is approximately 90%. About 5% of patients will have a febrile UTI within 4 years. Recurrent VUR was seen in only 4% of patients.

COMPLICATIONS

The most common complications following endoscopic treatment of VUR are new contralateral VUR (2.3–17.3%) and treatment failure. Less than 4% of children complain of flank pain or emesis several hours after the procedure and all respond to analgesics. Gross hematuria, urinary retention, or febrile UTIs are rarely seen. The most significant potential complication of endoscopic treatment for VUR includes a 0.6% risk of ureteral obstruction. Factors that may increase the risk of obstruction include bladder dysfunction and markedly dilated ureters. The 'primary megaureter' with VUR and a narrow distal part is a contraindication to endoscopic treatment as the risk of obstruction is significant. Patients with persistent but down-graded VUR often remain asymptomatic and without risk factors for pyelonephritis such as young age, voiding dysfunction, or significant history of UTIs may be taken off antibiotic prophylaxis and observed.

There has been concern about the risk of clinical recurrences including new febrile UTI and the risk of renal scarring. However, recent

long-term studies have shown that low rates of UTI have been observed following endoscopic treatment with NASHA/Dx gel [16,28–30]. These results compare favourably with the incidence of UTIs following ureteral reimplantation or during antibiotic prophylaxis. It has been shown that the rates of UTI and febrile UTI is significantly lower among children successfully cured of VUR by endoscopic injection of NASHA/Dx gel than those cured by open surgery [6]. Possible reasons for this apparent advantage with endoscopic treatment include the likelihood that it is effective for both VUR and bladder dysfunction [31], the fact that endoscopic treatment provides rapid cure of VUR, and the minimally invasive nature of the procedure. There is evidence that surgery may lead to long-term alteration of bladder motility patterns, and this may serve to increase the risk of UTI vs endoscopic treatment [32].

CONCLUSION

Based on today's knowledge, endoscopic treatment may be considered as first line therapy for most children with persistent high grade (III–V) reflux. Those with grade II–V with scarred kidneys or ureteral anomalies, such as double ureters, are all candidates for early endoscopic treatment as the likelihood for spontaneous resolution is very small in these patients. Open surgery may be reserved for use only in the 5–10% of patients not responding to endoscopic treatment, and in patients with severe ureteral anomalies. With the improvement of the injection techniques described in this chapter, the results of endoscopic treatment can be expected to improve significantly.

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