Chapter 22
Endoscopic Injection Techniques for Vesicoureteral Reflux

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Abstract Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder to the upper urinary tract and is one of the most prevalent urologic diagnoses in children. Management options include observation with or without continuous antibiotic prophylaxis and surgical correction via endoscopic, open, or laparoscopic/robotic approaches. Surgical intervention may be necessary in children with persistent reflux, renal scarring, and recurrent febrile urinary tract infections or in cases of parental choice. Endoscopic treatment of VUR is an outpatient procedure and is associated with decreased morbidity compared to ureteral reimplantation. The classic subureteral Teflon injection (STING) technique is the most commonly described method and is now frequently referred to as subureteral transurethral injection. It involves injecting a bulking material below the ureteral orifice, providing tissue

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augmentation under the refluxing orifice thereby increasing the submucosal length of the ureter and creating a fixation point to enhance the valve mechanism. The concept of ureteral hydrodistention and intraluminal submucosal injection (hydrodistention implantation technique or HIT) has led to improved success rates in eliminating reflux. Modifications of the double HIT technique now include proximal and distal intraluminal injections that result in coaptation of both the ureteral tunnel and orifice.

Keywords Vesicoureteral reflux (VUR) • Endoscopic injection • Subureteral transurethral injection (STING) • Hydrodistention implantation technique (HIT)

Introduction

Vesicoureteral reflux (VUR) is one of the most common urologic diagnoses affecting children, with an estimated prevalence of 0.4–1.8 % in the general pediatric population and 30 % in those with a history of febrile urinary tract infection (UTI) [1, 2]. Optimal management remains controversial, and options include observation with or without continuous antibiotic prophylaxis and surgical repair. An individualized risk-based approach that takes into consideration a multitude of demographic, radiographic, and clinical factors should guide management [3]. Endoscopic repairs correct VUR by injection of a bulking substance that allows elevation and coaptation of the ureteral orifice and detrusor tunnel [4]. This chapter will focus on the endoscopic correction of VUR, as well as patient selection and potential complications.

Endoscopic Techniques

Matouschek first described endoscopic correction of VUR using a bulking agent in 1981 as an alternative to continuous antibiotic prophylaxis or ureteral reimplantation [5]. In 1984, O'Donnell and Puri further advanced this concept by performing subureteric injections using Teflon paste═coining the term "STING" (subureteric Teflon injection)[6]. In 2004, Kirsch and co-workers further modified the injection procedure by injecting *within* the intraluminal ureteral mucosa to achieve total ureteral tunnel coaptation using the hydrodistention implantation technique (HIT) followed by the double HIT, which involves proximal tunnel and distal orifice intramural injections [7, 8]. The ideal injectable material should be durable, effective, safe, and should not extrude or migrate. Currently, the only FDA-approved bulking agent is dextranomer hyaluronic acid copolymer [Deflux®]. Endoscopic injection has become the most common worldwide means of correcting VUR because of its minimal invasiveness and high success rates (Video 22.1).

Patient Selection

Spontaneous resolution of primary reflux is common secondary to remodeling of the ureterovesical junction (UVJ), elongation of the intravesical ureter, and stabilization of bladder dynamics. Resolution depends on initial grade of reflux, gender, age, voiding dysfunction, presence of renal scarring, and timing of VUR on a voiding cystourethrogram [3, 9]. Management is therefore individualized and based on patient age, health, VUR grade, clinical course, renal scarring, and parental preference. Indications for correction of VUR include moderate-to-high-grade reflux (grades III–V), low probability of spontaneous resolution, renal scarring, recurrent pyelonephritis, breakthrough febrile UTI while on continuous antibiotic prophylaxis, and parental preference [10, 11].

Endoscopic Injection Techniques

Patient Positioning and Equipment

The child is placed in the dorsal lithotomy position after induction of general anesthesia. The ability to rotate the cystoscope over the child's thighs is important, in order to adequately visualize and inject laterally displaced orifices. An offset lens should be utilized to permit direct passage of the needle in line with ureter without damaging the needle. Several needles are available for injection, including a straight metal needle as well as a filiform needle guide (Injekt® needle). The bladder should be filled to less than half its capacity during injection in order to prevent high tension within the detrusor muscle.

STING Technique

In the traditional STING procedure, the needle is introduced *under* the bladder mucosa 2–3 mm below the refluxing orifice at the 6 o'clock position, and the injection is continued until there is a prominent bulge within the orifice assuming a crescent-like shape [4, 6]. The injected material augments the tissue below the ureteral orifice, providing a solid support under the refluxing ureteral orifice. This is thought to increase the submucosal ureteral length and create a fixation point whereby the valve mechanism may be enhanced preventing retrograde reflux of urine. One concern regarding the STING method is potential caudal migration of material, particularly of low injected volume, which may result in longer-term failure despite initial coaptation. The relatively low success of the STING method compared to open ureteral reimplantation has led our group to develop the HIT and double HIT methods described below.

Table 22.1 Classification of the ureteral orifice using hydrodistention (HD) grade

Ureteral HD grade	Endoscopic findings
H0	No orifice distension evident
H1	Orifice opens, intramural tunnel not evident
H2	Intramural tunnel evident, extramural tunnel not evident
H3	Extramural tunnel evident or ureter can accept the cystoscope

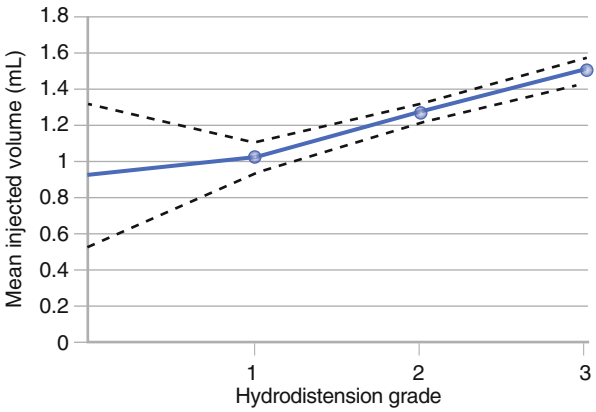

Fig. 22.1 Injection volume based on HD grade. The injected volume increases significantly with each increase in HD grade from H1 to H3. The bold line represents the average injected volume. *Dashed lines* represent the 95 % confidence intervals for the mean

HIT and Double HIT Methods

Endoscopic injection techniques have evolved from subureteric injections (STING) described above to intraluminal injections (HIT and Double HIT) [8]. Hydrodistention is performed with the tip of the cystoscope placed at the ureteral orifice; a pressure stream is achieved by placing the irrigation bag approximately 1 m above the pubic symphysis on full flow. Hydrodistention is graded according to the distensibility of the orifice (Table 22.1) and allows visualization of the intraluminal injection site as well as assessment of injection progress. Ureteral hydrodistention (HD) causes the orifice to open before treatment. Following proper implantation, the ureter should remain closed with an H0 grade. Hydrodistention grading correlates with VUR grade, with higher HD grades requiring more injected volume [8, 12]. By virtue of the technique, larger volumes are used when applying the double HIT method. In a series of 516 treated ureters from our institution, volume of injection was similar for VUR grades I–III, while a significantly higher volume was needed for VUR grades IV–V [4]. However, a progressively higher volume of injection was required as the HD grade increased from H0 to H3, as shown in Fig. 22.1. Although HD grade clearly plays a significant role determining injection volume, surgeon experience, tissue plains, and redo operations also contribute to the volume necessary to achieve an H0 ureter.

When employing the double HIT methodology, the needle is placed into the ureteral orifice and inserted in the mid-ureteral tunnel at the 6 o'clock position after performing ureteral hydrodistention. This differs from the STING technique, where the needle is inserted 2–3 mm *below* the refluxing orifice. Bulking agent is injected until a sufficient bulge is produced, which coapts the detrusor tunnel. A second injection at the distal most aspect of the intraureteral tunnel results in coaptation of the orifice (Fig. 22.2). Hydrodistention with the bladder nearly empty is performed following each injection to monitor progress. Additional injection(s) may be needed to achieve an H0 ureter during hydrodistention.

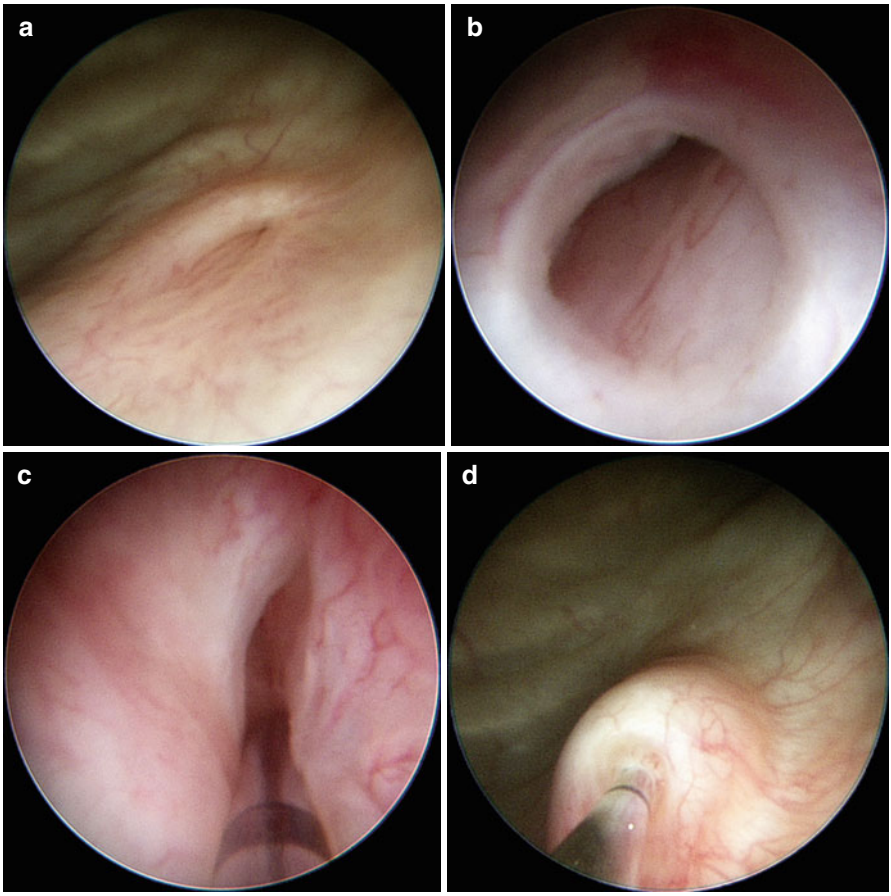

Fig. 22.2 Double HIT method. The bladder is emptied and the ureteral orifice visualized (**a**), followed by hydrodistention (**b**). The proximal HIT is performed with the needle inserted into the mid-ureteral tunnel at the 6 o'clock position (**c**), and sufficient bulking agent is injected to produce a bulge which coapts the detrusor tunnel (**d**). The distal HIT (**e**) leads to coaptation of the ureteral orifice (**f**). The double HIT coapts both the detrusor tunnel and the ureteral orifice and results in non-distensibility of the ureteral orifice (H0)

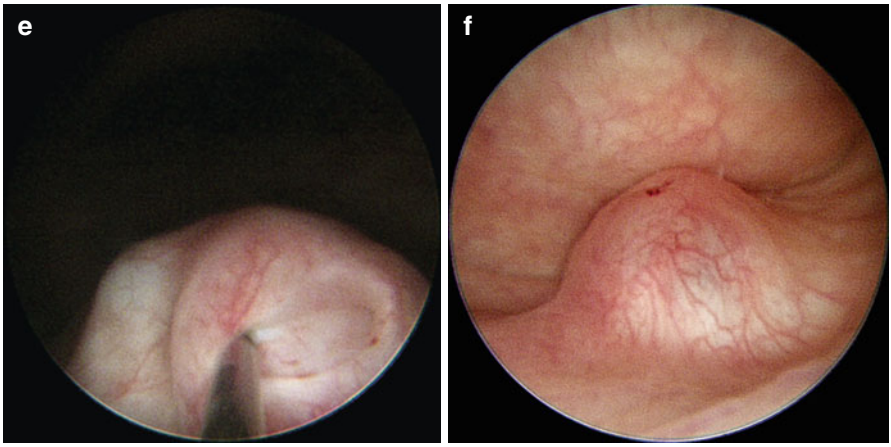

Fig. 22.2 (continued)

Clinical and Radiographic Outcomes Following Endoscopic Injection

The clinical success of any type of anti-reflux surgery can be measured radiographically (absence or downgrading of VUR) and clinically (absence or decrease in frequency of febrile urinary tract infections). In the medical literature, there is considerable variability as to how success is measured; therefore, true surgical outcomes are difficult to ascertain [13]. The average resolution of VUR following a single endoscopic injection is 83 % based on aggregate data, though success rates have ranged from 70 to 95 % [11]. In our long-term experience with the double HIT method, both radiographic and clinical successes at 1-year follow-up were 93 % [14]. Importantly, 95 % of patients avoided open surgery during a 4-year follow-up [13].

Preventative Measures to Avoid Complications

Families should be thoroughly counseled regarding the various VUR management options, and all children should undergo screening for and treatment of bowel/bladder dysfunction. In addition to proper patient selection, there are a number of technical principles that can help to ensure a successful outcome. Proper injection technique, selection of correct injection site(s), adequate injected volume, and recognizing the endpoints of the injection are all important components of the injection procedure necessary to follow in order to avert failure. Volume of injection varies depending on the injection method(s). As stated above, the HD grade of the ureter should directly correlate with the volume used when the double HIT method is employed. It is important to note that although higher grades of VUR are associated with higher HD grades, even lower grades of VUR may have high HD grades and require increased

volumes of injection [12]. After injection, the bladder should be emptied and hydrodistention repeated to confirm the absence of ureteral distensibility (i.e., H0 ureter).

Complications

Complications can be categorized into those that occur in the immediate postoperative period and those that manifest as long as several years from the time of surgical intervention. Early complications typically occur within the first 48 h following injection and are often transient. Less than 4 % of children undergoing endoscopic VUR therapy complain of flank pain or nausea postoperatively and nearly all resolve with analgesics. Ureteral obstruction following endoscopic injection occurs in approximately 0.6 % of patients and is frequently associated with voiding dysfunction, secondary VUR, or with larger ureters when a large volume of bulking agent is injected [4, 11]. If anuria or oliguria persists beyond 24 h, a renal bladder ultrasound and serum creatinine level should be obtained to exclude obstruction. Complete obstruction requires placement of either ureteral stents or nephrostomy tubes to allow upper tract drainage. The latter might be preferable because the obstruction may be transient, and resolution can be anticipated when the hyaluronic acid component dissipates within 2 weeks of the injection. Hematuria and bladder spasms are frequent complications of ureteral reimplantation, but these complications are rare following endoscopic treatment.

It is not uncommon for patients to develop a febrile urinary tract infection after endoscopic injection. Checking the urine preoperatively and beginning appropriate antibiotics if indicated can usually avoid this. In patients with a symptomatic UTI, surgery should be postponed.

Postoperative reflux may be the result of uncorrected, ipsilateral, or new onset contralateral reflux. Although persistent reflux may be the result of the aforementioned reasons for failure of the procedure, it often is the result of overt bladder pathology (neurogenic bladder or anatomical anomalies) or failure to recognize underlying bladder dysfunction. Voiding dysfunction or dysfunctional elimination accounts for treatment failures after open or endoscopic correction of VUR. These patients typically have urinary tract infections, incontinence, urgency, frequency, and constipation. Aggressive bathroom management, including strict adherence to voiding and bowel regimens, will often result in resolution of reflux as well as associated lower urinary tract infections. The 2010 AUA Reflux Guidelines recommend management of any suspected bladder/bowel dysfunction, preferably prior to any surgical intervention for VUR [2]. Patients with a previous history of voiding dysfunction must be encouraged to continue their bathroom program preoperatively.

Treatment failure following endoscopic therapy ranges from 7 to 50 % and is dependent upon the technique, VUR grade, and surgeon experience [15]. Success rates for the HIT and double HIT technique approach those following ureteral reimplantation [14] and are currently the most common procedures performed in the USA (Salix Pharmaceuticals, unpublished data).

Though perhaps not a true surgical complication, the development of contralateral VUR after unilateral endoscopic injection may require continued medical or surgical treatment. This finding has been explained on the basis of either occult reflux or even the possibility that high-grade VUR may be a pop-off mechanism for high bladder pressure, which when corrected, may destabilize the contralateral ureter. While many experts in the field consider reflux to be a bilateral process and will correct abnormally appearing contralateral orifices to prevent new reflux from occurring, the true risk benefit has not been determined [16]. In our experience, nearly 15 % of children with unilateral VUR developed contralateral VUR after treatment. By injecting all H2–H3 non-refluxing contralateral ureters, the new VUR rate dropped to 0 % [16].

Finally, previously injected dextranomer/hyaluronic acid copolymer implants may be encountered on computerized tomography as low- or high-density lesions and can be mistaken for calculi. History of vesicoureteral reflux and absence of hydronephrosis as well as hematuria should provide reassurance and prevent inappropriate intervention for misdiagnosed ureteral stones [17] or even bladder tumors [18].

Suggested Follow-Up

Patients should be kept on prophylactic antibiotics until appropriate postoperative studies have been obtained, particularly if there is a history of clinically significant urinary tract infections preoperatively. Renal ultrasound should be obtained 4–6 weeks postoperatively to assess for asymptomatic hydronephrosis. A bladder sonogram will assess the integrity of the implants, and while not directly correlating with the precise position of these implants, retained volume of injection may correlate with success after treatment using the HIT method [19]. The most recent AUA Reflux Guidelines [11] also recommend a postoperative voiding cystourethrogram, but there is wide variability in postoperative imaging dependent upon the individual patient and the surgeon's clinical experience and success rate [13].

Inasmuch as the long-term impact of VUR and renal injury in individual patients is unknown, screening for late-occurring complications of VUR can be performed yearly. Monitoring includes measurement of blood pressure, selective renal sonography, and a urinalysis to access proteinuria, renal growth, hydronephrosis, and infection. Patients with recurrent febrile urinary tract infection after successful endoscopic treatment of VUR should be evaluated for elimination dysfunction and recurrent reflux.

Summary

Endoscopic injection of bulking agents is now recognized as a safe and highly successful minimally invasive alternative to ureteroneocystostomy. The method currently achieving the highest radiographic success rates is the double HIT method,

with results approaching that of ureteral reimplantation. The postoperative febrile UTI rate is at least as low as that following open surgery, making it an excellent alternative to ureteral reimplantation [20]. Progressive ureteral obstruction is a serious complication, and although it occurs in less than 1 % of children, it requires intervention either by ureteral stenting or placement of a nephrostomy tube to achieve renal drainage. Persistent reflux is often managed conservatively, and bowel/bladder dysfunction should be addressed prior to repeating endoscopic injection.

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