Vesicoureteral Reflux

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Introduction

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder to the kidneys. This is considered an abnormal condition in human beings and has been implicated in renal injury prior to birth as well as post-natal development of urinary tract infections and further renal damage. Vesicoureteral reflux is most commonly identified in infants and children. Although much is known about the diagnosis, medical and surgical management of VUR, many questions remain regarding the potential of reflux to cause infections and renal injury. This chapter will review the current knowledge and detail the controversies that persist about VUR with a focus on the evaluation and management in children.

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Etiology

Anatomic Factors

Ureteral development in infants has been studied to understand the anatomic factors that may lead to VUR. The periureteral sheaths, intravesical ureteral muscles and trigonal muscles have been studied as potential factors for the development of VUR [1]. Based on work in 11–27 week fetuses, it has been determined that the superficial trigone is derived from the intravesical ureteral muscles and the deep trigone is derived from the deep periureteral sheath of the ureter. Fixation of the ureters in the appropriate location is very important for the development of a normal trigone and non-refluxing ureters. The intravesical submucosal length of the ureter and the oblique path of entry of the ureter into the bladder are critical factors in the prevention of VUR.

The ureterovesical junction of children with and without VUR shows no difference in scarring on microscopic evaluation. Anatomic factors in the ureterovesical junction, however, may play a role in the degree of renal injury produced by reflux, in that higher grade VUR that occurs with lower bladder pressure is associated with increased risk of nephropathy [2]. The presence of periureteral diverticula also increases the risk of renal damage and the requirement for surgical correction.

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Extra-anatomic Factors

Emrbyological development of the ureteral bud from the mesonephric duct is dependent on multiple factors. Signaling by GDNF (Glial cell line derived neurotrophic factor) has been shown in the mouse model to induce the formation of ureteral buds [3]. Misexpression of GDNF has been shown to be associated with the development of multiple ureteral buds. Additionally, GDNF is very focally expressed in the appropriate location of ureteral bud development. If GDNF is expressed in an ectopic location, the ureteral bud will develop in this ectopic location leading to lateral or medial localization of the ureter in the bladder predisposing to VUR or obstruction. Additionally, trigonal development is dependent on apoptosis induced by a Vitamin A signaling pathway [4]. Normal development of the trigone is also necessary to provide appropriate support to the distal ureter. Recent studies have shown that symmetric muscle contractions and unidirectional peristalsis also play a significant role in the competence of the ureterovesical junction [5]. Normal ureters contain greater numbers of interstitial cells of Cajal, a pacemaker cell, at the ureterovesical junction compared to those ureters with VUR.

Associated Conditions

Many anatomic and genetic conditions are associated with the presence of VUR in children. The most commonly noted anatomic conditions are Multicystic Dysplastic Kidney (MCDK), renal agenesis and renal or ureteral ectopia. VUR is also a common occurrence with many syndromic conditions.

Multicystic Dysplastic Kidney (MCDK)

Contralateral VUR is the most common abnormality noted in children with MCDK [6]. VUR has been identified in 12–28 % of contralateral kidneys in children with MCDK [7]. The impact of this contralateral VUR continues to be debated. One study has indicated that contra-lateral renal growth is compromised in the presence of VUR [8]; however, other studies have revealed that VUR into the contralateral renal unit is usually low grade and does not lead to renal compromise [9]. Study of the natural history of VUR in the presence of MCDK indicates that most boys and 40 % of girls will have spontaneous resolution.

Renal Agenesis

As with MCDK, VUR is the most common abnormality noted in the contralateral kidney in children presenting with unilateral renal agenesis. Management of VUR in the context of a solitary kidney is not different from that in patients with two kidneys [10].

Ectopia

Dilating VUR occurs in up to 26 % of children with renal ectopia and hydronephrosis [11]. VUR is the most common associated anomaly in children with renal ectopia. The presence of renal ectopia does not seem to reduce the potential for VUR to resolve spontaneously [12].

Ureteral duplication is also associated with the presence of VUR typically into the lower pole of the duplex system. The ureteral orifice is displaced proximally and laterally in children with duplex systems and plays a role in the development of VUR into the lower pole moiety. Following endoscopic management of ureteroceles associated with duplex systems, VUR may be unmasked into the lower poles unilaterally or bilaterally and may even occur into the upper pole as an iatrogenic entity. Many patients with duplex systems will require eventual surgical management for their VUR [13]. Typically surgery in these patients is indicated for the associated conditions that are present (i.e., ureteroceles, ectopic ureters, etc.).

Ureteral ectopia may also be noted into the bladder neck and urethra leading to VUR during voiding. Bilateral single system ureteral ectopia is associated with reduction in bladder growth and capacity and requires surgical management with ureteral reimplantation and possible later bladder neck reconstruction to provide continence [14]. Eventual prognosis in this condition is based on development of adequate bladder capacity.

Syndromes that have been associated with the presence of VUR include the VATER-VACTERL

syndrome, Townes-Brock Syndrome (SALLI mutation), Cat-eye Syndrome (tetrasomy, chromosome 22), Cassamasima-Morton-Nance syndrome, Renal coloboma syndrome (PAX 2 mutation), Branchio-oto-renal syndrome (EYE1 mutation) and Frasier syndrome (WT1 mutation).

Incidence and Presentation

Antenatal Diagnosis

The widespread utilization of antenatal ultrasonography has made early detection of hydronephrosis and subsequent diagnosis of VUR possible prior to the occurrence of urinary tract infections. Fetal pelvic diameter of greater than 5 mm at or beyond 28 weeks of gestation is considered hydronephrosis. About 10% of such patients diagnosed by antenatal ultrasonography have VUR [15]. Cohorts of infants with VUR diagnosed following antenatal identification of hydronephrosis have greater numbers of boys [16]. Additionally, there are more patients that have low grade VUR with greater propensity for spontaneous resolution [15, 16]. Boys with even high grades of VUR (IV–V) have a 29–37% rate of spontaneous resolution in the first year of life [17]. This potential for resolution is attributed to the presence of a mixed pattern of voiding with coordinated voiding interspersed with high pressure voiding with increased sphincteric activity.

Urinary Tract Infections

Most children continue to be diagnosed with VUR following an initial febrile urinary tract infection (UTI). VUR is diagnosed much more frequently in children than in neonates following an initial UTI. Among neonates, although urinary tract infections are diagnosed six times more frequently in males, the incidence of VUR is similar between the sexes (15–20%) [18, 19]. Additionally, the incidence of VUR is higher in those neonates who have urinary tract infections with non Escherichia Coli (E coli) bacteria than with E Coli [18]. In a cohort of 1,953 patients with urinary tract infection <2 years of age undergoing voiding noted in 30% [20]. This incidence was similar to that noted by Hoberman et al. [21].

Effect of Gender and Race

As noted above, the relationship of gender and the presence of VUR differs between the patient diagnosed following identification of hydronephrosis on antenatal ultrasonography and those diagnosed following initial urinary tract infection. The incidence of VUR in male infants diagnosed following identification of antenatal hydronephrosis is similar to that in girls [22]. It has also been noted that the incidence of dysplasia is greater in male infants with VUR. The incidence of resolution of VUR is greater in male infants [23]. Girls form a significant majority of patients presenting with VUR following a urinary tract infection.

African-american girls have a lower potential for development of VUR as compared to Caucasian girls. This difference in incidence was also noted in infants diagnosed with VUR following identification of antenatal hydronephrosis [24]. Additionally, few black girls presenting with VUR following a urinary tract infection have high grade VUR [25]. The incidence of scarring, however, is reported to be higher in African-american girls as compared to their Caucasian counterparts, although progression of scarring is less in African-american girls. Additionally, time to spontaneous resolution of VUR is shorter in African-american girls [26]. The incidence of VUR in Hispanic girls is comparable to white girls [27].

Genetics of Reflux

There is increasing evidence that primary VUR has some genetic basis, which is best indicated by its familial occurrence. The reported incidence of VUR in siblings of an affected patient varies from 27 to 45% [28]. A higher incidence of VUR has also been reported in children of parents with a history of VUR [29]. The genetics of VUR is not

clearly defined and is most certainly genetically heterogenous. Autosomal dominant inheritance with variable expression or multifactorial inheritance has been implicated for VUR and reflux nephropathy. In a study of 88 families with at least 1 person with primary VUR, the authors concluded that a single major locus was the most important causal factor in this condition [30]. Kaefer and colleagues found 100% concordance in identical twins and 50% concordance among dizygotic twins when only the youngest twins were considered [31]. One gene associated with apparent autosomal dominant VUR has been mapped to chromosome 1 [32], though two of the families studied showed negative linkage to this locus, further confirming the genetic heterogeneity of VUR.

Association of Urinary Tract Infections

VUR is believed to be the primary risk factor for pyelonephritis, although some studies dispute this association [33]. The International Reflux Study reported recurrent UTI in 28% of children with medically managed severe VUR [34]. The usual organisms that cause UTI originate from fecal flora that colonize the perineum, and the organisms that cause recurrent UTI can be found on perineal cultures prior to the onset of UTI [35]. Escherichia coli (E. Coli) is the most frequently isolated organism, being responsible for approximately 80% of UTIs, the rest being due to Klebsiella, Enterobacter, Citrobacter, Protues, Providentia, Morganella, Serratia and Salmonella species [36]. There is evidence that a variety of bacterial virulence factors increase the ability of E Coli to cause a UTI. The presence of P fimbriae allows E Coli to adhere to the epithelial cells of the urinary tract, while other virulence factors increase tissue damage and protect E Coli from serum bactericidal activity [33].

Diagnosis

VUR is identified in four groups of children – those identified during the evaluation of antenatally identified hydronephrosis, those with other congenital anomalies, following a febrile or symptomatic urinary tract infection and those evaluated following identification of a sibling or children of patients with VUR. Controversies exist in all of the scenarios as to the cohort of children that should be evaluated to maximize the potential for the identification of VUR without subjecting large groups of children to potentially invasive screening.

Ultrasonography

Ultrasound is the primary modality for evaluation of any child that is being evaluated for the potential of VUR. This permits evaluation of the upper tracts to determine the presence of anomalies (duplication, hydronephrosis, MCDK, agenesis, etc). Ultrasound should always include evaluation of the ureters and bladder prior to and following voiding to determine if there are lower tract changes that might suggest the possibility of VUR (i.e., diverticulae, ureteral dilation) or other lower tract anomalies (ureteroceles, megaureter), that may predispose to UTI.

Ultrasonography has also been used as a primary diagnostic modality for the diagnosis of VUR in an effort to reduce radiation exposure to the child [37]. This modality is not widely available and the reduction in radiation exposure with current fluoroscopic techniques and the requirement for catheterization have limited its utilization.

Voiding Cystourethrogram

The gold standard for the diagnosis of VUR is the radiographic voiding cystourethrogram (VCU) VCU requires urethral catheterization and fluoroscopy. This modality allows grading of reflux as standardized by the International Reflux Study (IRSC). Although this is the best procedure for the identification of VUR, discrepancy can be noted in the grading of VUR even among experienced readers and when multiple filling cycles are utilized [38]. The timing for the performance

of VCU has been debated. It was felt that early VCU may lead to increase in the diagnosis of VUR due to the "instability" of the vesicoureteral reflux in the child with a recent urinary tract infection. Recent studies have demonstrated that performing the VCU within a week of presenting with a UTI leads to improved compliance and does not change the potential for the identification of VUR [39].

The discomfort of catheterization has led efforts to avoid performance of the VCU. The use of sedation has been found to improve the tolerance for the procedure without changing the potential for the diagnosis of VUR [40]. Intermittent fluoroscopic evaluation has been used to reduce the exposure of radiation during the procedure, further improving the safety of the study [41].

Voiding cystourethrogram is also used for the follow-up of VUR to determine persistence or improvement. The timing of VCU follow-up also is controversial. In the past routine yearly VCU was performed, however, increasing the interval to every 2–3 years in children with dilating reflux (III–V), has permitted significant reduction in the numbers of studies performed on the individual child. With lower grades of VUR, that have no recurrence of infection, VCU can be omitted. In children on prophylactic regimens, determination of the cessation of VUR is important to determine when such regimens can be discontinued.

In an effort to reduce the radiation associated with the use of standard (conventional) VCU, radionuclide VCU has been performed. The diagnosis of VUR can be made with radionuclide VCU and there is excellent correlation to conventional VCU [42]. The major limitation of this procedure is the inability to grade VUR as recommended by the IRSC. Using this method grading is limited to mild, moderate and severe. It is an excellent modality for the follow-up of VUR and for the determination of resolution of VUR. It is also used as the modality of choice for the identification of surgical success in the correction of VUR. Since it is a very sensitive study and uses continuous data collection over the course of the test, it can be used to identify children that have low grade intermittent reflux that have had recurrent urinary tract infections and prior negative Radiographic/fluoroscopic VCU [42].

Concerns about radiation exposure in children and the need for catheterization have led to increase efforts to identify alternative imaging modalities. Magnetic resonance imaging (MRI) can be utilized for detection of VUR. This modality has been noted to have comparable accuracy with radiographic VCU [43]; however, it still requires urethral catheterization and the technique remains limited to a few centers. Also, many infants and children require sedation and even anesthesia for performance of MRI.

99 Tc Dimercapto-Succinic Acid (DMSA) Scanning

The major concern with the presence of VUR is the development of infections and subsequent renal scarring [44]. Nuclear renal scanning with 99Tc dimercaptosuccinic acid is currently the best modality to evaluate for the renal scarring in the kidneys [45]. The difficulty is to determine if the scars that are identified are the result of prenatal dysplasia or secondary to recurrent UTI [46]. Some have suggested using DMSA renal scanning as the primary test for the evaluation of children presenting with UTI. The absence of renal involvement on DMSA scanning performed during the acute phases of a febrile UTI makes higher grades of VUR unlikely [47].

Positional Instillation of Contrast (PIC) Cystogram

Children presenting with recurrent UTI who have renal scarring but do not have VUR based on standard or nuclear voiding cystourethrogram can be considered for evaluation with positional instillation of contrast (PIC) cystography to determine if there is low grade VUR [48]. The procedure requires the use of anesthesia. A cystoscope is placed into the bladder and positioned at the ureteral orifice. Contrast is injected directly at the ureteral orifice and monitored fluoroscopically [49]. When VUR is identified by this modality, correction can be accomplished in the same procedure by the use of a bulking agent.

Experience with this technique, however, remains preliminary and further studies are required to determine the role of PIC cystography in the evaluation of VUR.

Grading of VUR

Grading of VUR was standardized in 1982 [50] using the radiographic VCU, by the International Reflux Study in Children (IRSC). This system of grading divides VUR into five grades (Fig. 42.1). Grading of VUR correlates with the degree of renal scarring as well as the potential for spontaneous resolution. Lower grades of VUR have greater potential for spontaneous resolution independent of the age at diagnosis [51]. Also the grade of VUR is a consideration in the appropriate choice of management that may be considered (endoscopic vs open surgical reconstruction) [52].

Potential for Reflux Resolution

The potential for spontaneous resolution of VUR is the basis for its conservative non-operative management. All grades of VUR have the potential for resolution although the likelihood of resolution is based on the grade and presentation of VUR [53]. Overall 39 % of refluxing ureters will have spontaneous resolution. Even patients with duplex systems have the potential for spontaneous resolution [54].

Multiple studies have evaluated the rate of resolution of the various grades of VUR. According to one study, resolution of Grade I reflux was noted in 82 %, Grade II reflux was noted in 80 % and Grade II in 46 % [55]. Similar rates of resolution have been noted in other studies evaluation the medical management of VUR [56]. Resolution rates of Grade IV and V reflux were 30 % and 11 % respectively over 5 years [53]. In patients diagnosed with VUR following evaluation of

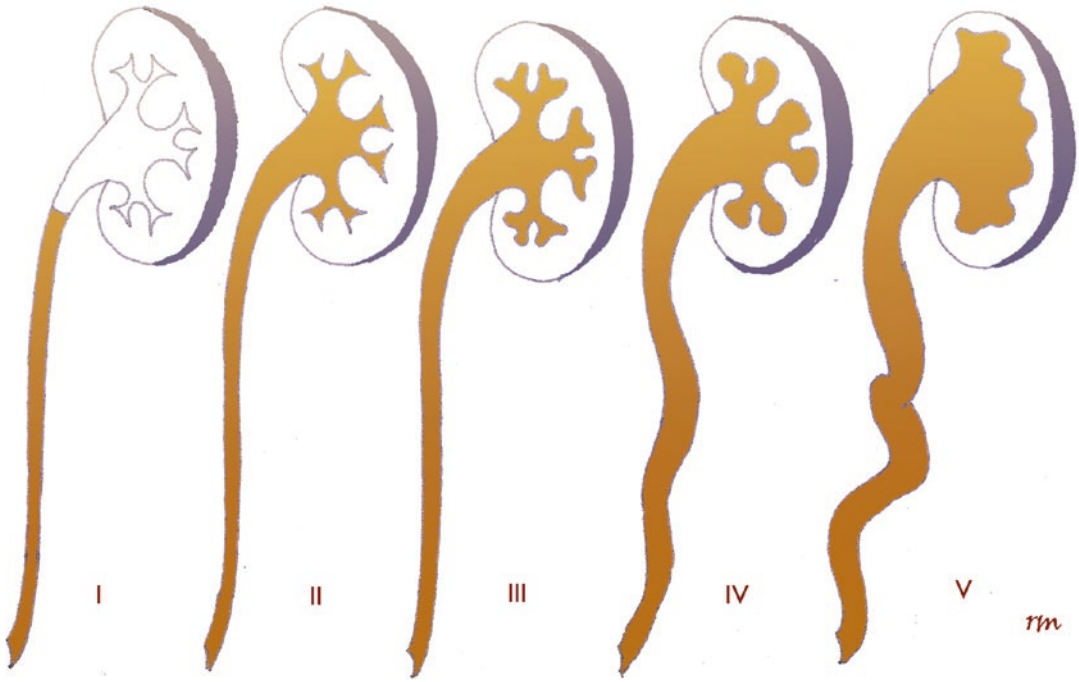

Fig. 42.1 International grading system for vesicoureteral reflux. I Grade *I* – contrast in the non-dilated ureter; Grade *II* – contrast in the non-dilated ureter and renal pelvis; Grade *III* – mild dilation of the ureter and renal pelvis with minimal blunting; Grade *IV* – moderate tortuosity of the ureter and dilation of the renal pelvis and calyces; Grade *V* – gross dilation of the renal pelvis and calyces with significant ureteral tortuosity (Grading based on International Reflux Study. *Pediatrics* 1981; 67:392–400; Figure copyrighted by Dr. Ranjiv Mathews)

antenatal hydronephrosis, there is a greater potential for resolution even in the presence of higher grades of VUR [57].

Potential for Renal Injury

A variety of factors influence the probability of scarring in children with VUR and UTI. The role of VUR in causing scarring, initially proven in piglets [58], has been shown in multiple clinical studies [59, 60]. Moreover, children with higher grades of VUR have an increased likelihood of developing renal scarring [61, 62]. Renal damage is more common in infants with UTI and VUR because of their unique renal papillary morphology [63]. Children less than 2 years of age with VUR are more likely to develop renal scarring, although some studies do not show an increased risk of renal damage in younger children after acute pyelonephritis (APN) [64]. Other factors that affect the probability of renal scarring in children with VUR and UTI include delay in the treatment of UTI, recurrent UTI and bacterial virulence [65]. Finally, there is evidence that genetic factors predispose patients with VUR to scarring as demonstrated by studies of angiotensin converting enzyme (ACE) gene polymorphisms [66], and by studies of the IL-8 receptor CXCR1 which have identified a genetic innate immune deficiency with a strong link to acute pyelonephritis and renal scarring [67, 68].

Reflux Nephropathy

Several studies have shown that scarring develops at the same site as previous infection [69]. The exact pathogenesis of renal scarring following acute pyelonephritis is not well understood. The process is an inflammatory response, with chemotaxis and phagocytosis, release of lysosomal enzymes and superoxides, production of peroxide and hydroxyl radicals, tubular ischemia and reperfusion injury [70, 71]. The fibrosis that follows is initiated mainly by macrophages [72]. Explanation for progressive parenchymal renal injury even after VUR has ceased, include autologous tubular antigens, hyperfiltration of intact nephrons, reaction to Tamm-Horsfall protein, superoxide production and persistent hypertension [73].

Besides acute complications such as sepsis, drug reaction and pyonephrosis during pyelonephritis, long-term complications and significant morbidity occur with reflux nephropathy. Reflux nephropathy is the primary diagnosis in 5.2% of children undergoing renal transplantation according to the North American registry [74]. Hypertension occurs in 10–30% of children and young adults with renal scarring [75]. Complications may occur during pregnancy and these include significant rise in blood pressure, recurrent UTI, toxemia and miscarriage [76].

Management of VUR

A close relationship between pyelonephritis and VUR was demonstrated by Hodson and Edwards in 1960 [77], VUR was believed to be detrimental to the kidneys therefore surgical procedures to stop VUR were developed during the 1960s [78]. There is, however, a high rate of resolution for VUR and therefore a more limited approach to surgical intervention has been proposed [79]. Long-term antibiotic prophylaxis with the aim of protecting children with VUR from renal damage induced by infection was introduced [80].

The potential for VUR to resolve spontaneously in many patients has changed the paradigm of management from one of immediate surgical correction to initial medical management with antibiotic prophylaxis to prevent urinary tract infections and follow-up [81]. Surgical treatment is typically reserved for those patients in whom spontaneous resolution is in doubt (i.e, those with high grade reflux), patients with recurrent urinary tract infections despite antibiotic prophylaxis and those with worsening of renal scars during follow-up.

Antibiotic Prophylaxis

The main objective of treatment in children with VUR is the prevention of recurrent UTI and renal parenchymal damage, mostly by long-term anti-

biotic prophylaxis or surgical correction of reflux. The concept of antibiotic prophylaxis was introduceds in 1975 [82]. Controlled trials demonstrated the effectiveness of low dose prophylactic trimethoprim-sulfamethoxazole (TMP-SMZ) or nitrofurantoin in preventing UTI [83]. Breakthrough infections are common in children with VUR with rates ranging from 25 to 38 % [84]. Other side effects are not uncommon and these include gastrointestinal disturbances, skin rashes, hepatotoxicity and hematological complications [85].

There is no significant outcome difference between medical and surgical management in the incidence of renal scarring. The International Reflux Study in Children (IRSC) European cohort included 300 children with VUR randomly allocated to medical or surgical groups. Follow-up with intravenous urography and DMSA scintigraphy over a period of 5 years revealed no difference in outcome in terms of the development of new renal lesions or the progression of renal scars [86]. Similar results were reported by the Birmingham Study [87].

Recently, six randomized controlled studies comparing antibiotic prophylaxis and no prophylaxis in children with symptomatic/febrile UTIs were performed [88–93]. The results of these studies were summarized in a meta-analysis published in the latest AAP clinical practice guidelines [94]. These studies were unable to show a beneficial effect of antibiotic prophylaxis; however, most children in these studies had no VUR or low grades of VUR, underlining the fact that for most patients prophylaxis is unnecessary. For children with higher grades of VUR, especially IV–V, there may be a benefit for prophylaxsis. The necessity to analyze boys and girls separately was illustrated in the Swedish Reflux Trial where a beneficial effect of prophylaxis was seen in girls with grades III–IV VUR, but not in boys [93].

Surgical Management

The major indications for surgical intervention in children with VUR include recurrent UTI in spite of appropriate antibiotic prophylaxis, worsening of renal scarring during follow-up and those patients in whom reflux resolution is unlikely – grade V VUR. There may be a greater indication for the correction of VUR in those patients that have reflux into a single renal system. Surgical management decisions, however, should be individualized based on potential risk to the renal units.

Minimally Invasive Treatment Options

Endoscopy

Multiple attempts have been made to manage VUR using minimally invasive treatments. Endoscopic techniques have typically involved the use of bulking agents to increase resistance at the ureteral orifice as a method to prevent reflux. Polytetrafluoroethylene (Polytef) has been used successfully for correction of VUR since the early 1980s [95]. Polytef had excellent surgical success that was maintained over time; however, the concern of particle migration has prevented approval in the United States (US) and has lead to the gradual decline in use worldwide. Other injectable agents were therefore developed. Polydimethylsiloxane has been utilized in Canada and has been associated with no migration and high success rates [96]. This agent has also not been approved for use in the US. Bovine cross linked collagen has been used in the US and although initial results were acceptable, long-term results have indicated that recurrence is frequent due to absorption of collagen over time [97, 98]. Other agents that have been tried include expanded chondrocytes, or placement of balloons; however, many of these techniques require multiple procedures for completion [99, 100].

Dextranomer hyaluronidase (Dx/HA, Deflux™, Salix Pharmaceuticals, Raleigh, NC, USA) has been utilized for bulking of the ureters for treatment of reflux (Fig. 42.2a, b). Initially reported by Stenberg and Lackgren in 1995 [101], worldwide experience has grown rapidly. Success rates reported with the use of Dx/HA are overall cure rates of 94 % for grade 1, 85 % for grade II, 78 % for grade III and 71 % for grade IV reflux [102]. This material has also been shown

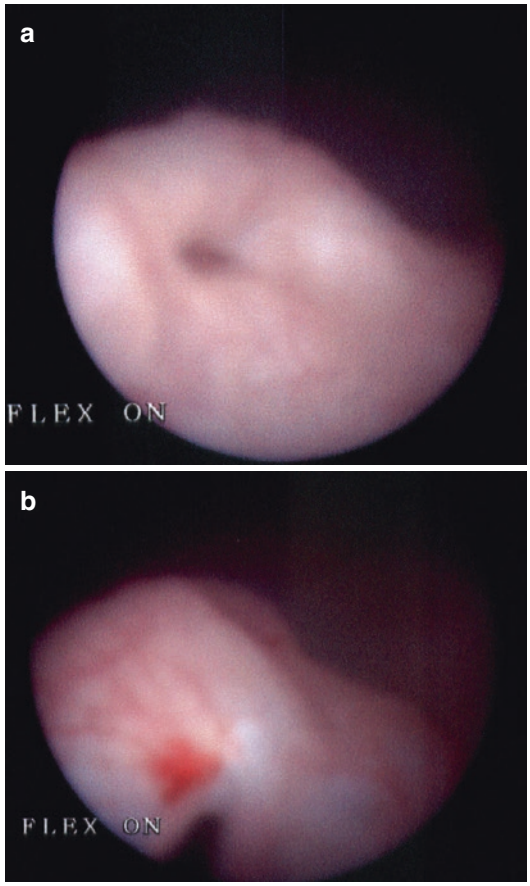

Fig. 42.2 (**a**) Endoscopic appearance of right refluxing ureter. (**b**) Injection of Dextrnomer/hyaluronidase for correction of VUR

to be of benefit in those patients that fail prior treatment and in those that have associated urologic anomalies like ureteroceles and duplex systems. Patients that fail endoscopic management are still candidates for open surgical reconstruction. Late recurrence of VUR has been noted in 20 % of patients that have had follow-up [103], with more frequent recurrence in children with higher grades of reflux.

The efficacy and relative simplicity of the use of Dx/HA for the correction of VUR has led some to question the current paradigm of VUR managment [104]. It has been suggested that Dx/HA should be used as a first line of treatment for VUR. This procedure does require the use of general anesthesia and in infants this should be a significant consideration.

Laparoscopy

Laparoscopy has been successfully utilized for the surgical correction of VUR [105]. Laparoscopic techniques allow small incisions to be used and have the potential to reduce discomfort and length of hospital stays. The technique initially involved an extravesical approach for the correction of VUR [106]. Intravesical and transvesical techniques have since been reported [107]. The presumed benefit of reduction in hospital stay and smaller incisions have been eclipsed by the advent of improved endoscopic management with Dx/HA. The recent advent of the use of robotic techniques has shortened the length of the procedure and has made laparosopic surgery for reflux more universally accepted. The results of robotic surgery are approaching those achieved with open surgery with reduction in the need for post operative narcotics [108].

Open Surgical Techniques

Open surgery remains the gold standard for the surgical correction of VUR. The technique devised by Politano-Leadbetter combined an intra and extravesical technique and has been used widely with great success [78]. This technique, however, has been supplanted by the two techniques described below. In general, open surgical techniques are associated with 90–95 % success rates and most can now be performed with a 1–3 day hospital stay. The success rates are so consistent across multiple studies that the use of routine post procedure voiding cystourethrogram has been questioned. Although high success rates for the correction of VUR have been reported along with a decrease in the incidence of pyelonephritis [109], there has been no reduction in the incidence of renal scarring noted during follow-up.

Intravesical (Cohen) Cross-Trigonal Reimplantation

Since the initial description of this technique, it has been rapidly adopted by most pediatric urologists due to the consistency of surgical outcomes and low rates of complications [110]. This tech-

nique involves the dissection of the ureters within the bladder and then the ureters are placed in submucosal tunnels created across the trigone of the bladder. Over time significant improvement in pain management have permitted reduction in hospital stays, reduction in the need for stenting and suprapubic tube placement and high patient satisfaction rates [110]. Additionally, the high rates of success have led this technique to be the most frequently performed and taught procedure for the correction of VUR. This technique is routinely used for the correction of bilateral reflux. It also allows for other bladder anomalies (ureteroceles, bladder diverticula, etc.) to be corrected at the same time. Potential complications associated with this technique are the development of contralateral reflux in those patients in whom unilateral correction is performed, ureteral obstruction and residual reflux [111].

Extravesical (Lich-Gregoir) Reimplantation

This technique allows reimplantation without entry into the bladder. The ureters are dissected prior to the entry into the bladder and reimplantation is performed by placing the ureters into troughs created in the bladder wall [112]. It has been utilized most frequently for the management of unilateral reflux as there is a concern that some patients that have had bilateral reimplantation using this technique have had secondary transient neuropathic bladder dysfunction requiring temporary intermittent catheterization [113]. This technique is also associated with high degree of success for the correction of reflux. Many patients can be managed with a 24 h hospitalization as bladder spasms are less frequently noted.

Controversies and Future Directions

Multiple questions still remain in the pathogenesis and management of vesicoureteral reflux of children and long-term consequences. The role of VUR as a cause of renal damage has not yet been clarified despite numerous studies on the subject. The advent of antenatal ultrasound has increased our knowledge on the pathogenesis of renal damage in children. In children with reflux identified during the evaluation of antenatal hydronephrosis, there is a pattern of boys with dilating VUR and renal dysplasia and girls with mild VUR and normal renal units [114]. A pattern of renal injury has also been noted in a population based cohort of children followed after a first episode of UTI [115]. However, it remains unclear if the renal damage identified is congenital or acquired. The ability to distinguish renal scarring from dysplasia on DMSA renal scan is at the center of this debate. Newer imaging modalities will potentially help to differentiate these two entities.

The evaluation of UTI in children to determine for the presence of VUR has become controversial as no clear benefit has been identified with the use of medical or surgical management in the prevention of recurrent infection or renal scarring. The Randomized Intervention for the management of Vesicoureteral Reflux (RIVUR) trial has been devised to determine if there is a benefit in the use of prophylaxis for the prevention of recurrent urinary tract infection or renal scarring in children. The study is powered appropriately to determine statistical significance and will be published soon [116]. The RIVUR study was shown to lead to reduction in the incidence of urinary tract infections in those children on prophylaxis as compared to placebo. In Europe we currently recommend prophylaxis for boys with dilating VUR during the first year of life and for girls with persisting dilating VUR until 2–3 years of age. In the US, most children identified with VUR following symptomatic UTI, continue to be managed with prophylaxis irrespective of the grade of VUR.

Endoscopic treatment of VUR has also been a source of controversy as there is an incidence of recurrence following initial surgical success. The role of endoscopic treatment remains to be clarified with the use of randomized controlled trials.

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