Vesicoureteral Reflux

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1. Introduction

Vesicoureteral reflux (VUR) refers to the retrograde passage of urine from the bladder into the upper urinary tract. Although VUR was first discovered in the late 1800s, its clinical importance has only been recognized in the last five decades. Hutch's studies, reported in the 1950s, demonstrated the pathophysiologic changes with VUR in children.[1] These reports and Hodson's observations in 1959 regarding the association between VUR, urinary tract infection (UTI), and pyelonephritic scarring set the stage for the modern era of reflux management.[2]

Although most commonly diagnosed during an evaluation following a UTI, VUR may also be discovered during evaluations for hypertension, proteinuria, voiding dysfunction, or chronic renal insufficiency. In addition, VUR has been identified in asymptomatic patients with prenatally-detected hydronephrosis as well as through sibling screening.[3] More recently, the utility of aggressive diagnosis and management of all reflux has been questioned, with a more selective approach increasingly gaining favor. Once detected, therapeutic options for urinary reflux are diverse, ranging from observation with or without continuous low-dose antibiotic prophylaxis to a variety of surgical interventions.

2. Pathophysiology

Normal ureterovesical junction (UVJ) anatomy is characterized by an oblique entry of the ureter into the bladder and a length of submucosal ureter providing a high ratio of tunnel length to ureteral diameter. This anatomic configuration provides a predominantly passive valve mechanism.[4,5] As the bladder fills and the intravesical pressure rises, the resulting bladder wall tension is applied to the roof of the ureteral tunnel. This results in compression of the ureter preventing retrograde passage of urine. Intermittent increases in bladder pressure, such as during voiding, upright posture, activity, and coughing, are met with an equal and immediate increase in resistance to retrograde urine flow. This effect is supplemented by the active effects of uretero-trigonal muscle contraction and ureteral peristalsis.[4,5]

Primary VUR results from failure of the ureterovesical junction (UVJ) to function properly and is frequently associated with both a short intramural tunnel and a laterally displaced ureteral orifice. Ureters with marginal tunnels may reflux during infection due to UVJ distortion, loss of compliance of the valve roof, and intravesical hypertension. Excessively high intravesical pressure in neurogenic bladder (NGB) or bladder outlet obstruction (BOO) may also potentiate reflux as may a structurally weak detrusor floor (e.g., diverticulum or ureterocele). Spontaneous improvement or resolution of VUR occurs commonly, and is thought to be a multifactorial process related to UVJ remodeling, elongation of intravesical ureter, and stabilization of bladder voiding dynamics over time.[4,5]

Of critical importance is the concept of intrarenal reflux (IRR), which has been demonstrated clinically[7] as well as experimentally.[8] The usually oblique entry of the papillary ducts onto the surface of simple papillae inhibits IRR. In contrast, the papillary duct entrance into compound papillae facilitates IRR. The critical pressure for IRR is considered to be about 35mmHg in compound papillae.[8,9] Experimentally, this same pressure may cause scar formation in the absence of infection.[8,10] When occurring intravesically, this pressure has been associated with an increased risk of renal deterioration. Higher pressure is thought to be necessary to induce IRR in simple papillae. The combination of infection and IRR is particularly devastating. Focal scarring appears to result from the difference in susceptibility of the renal papillae to IRR. The polar distribution of compound papillae corresponds closely to the predominant occurrence of renal scarring in the upper and lower poles of the kidney.

3. Classification

Reflux has been described as low pressure (occurring during the filling phase of a voiding cystourethrogram) or high pressure (occurring only during voiding). Reflux due to a congenitally deficient UVJ is referred to as *primary* reflux, whereas that due to a bladder outlet obstruction or neurogenic bladder is defined as *secondary* reflux. Further classification includes simple versus complex reflux. Complex reflux includes reflux associated with megaureter, duplication, diverticulum or ureterocele, and the occasional refluxing ureter associated with ipsilateral ureteropelvic or ureterovesical obstruction.

The International Grading System is based on fluoroscopic voiding cystourethrogram (VCUG) findings and remains universally

accepted[11] VUR is graded from I to V and details the proximal extent of retrograde urine flow and ureteral and pelvic dilatation as well as the resultant anatomy of the calyceal fornices.

Grade I VUR refers to the visualization of a non-dilated ureter only, whereas grade II VUR refers to visualization of a non-dilated renal pelvis and calyceal system in addition to the ureter. Grade III reflux involves mild to moderate dilatation or ureteral tortuosity with mild to moderate dilatation of the renal pelvis and calyces. The fornices, however, remain sharp or only minimally blunted. Once the forniceal angle is completely blunted, grade IV reflux has developed. Papillary impressions in the majority of calyces can still be appreciated. Loss of the papillary impressions along with increased dilatation and tortuosity is referred to as grade V reflux (**Figure 2**). Intrarenal reflux is traditionally considered to be grade V reflux.

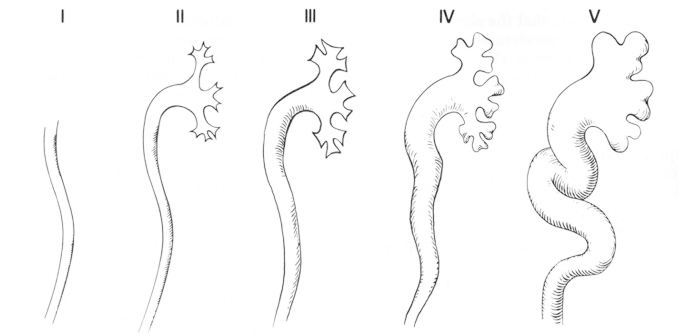

Figure 1: The international grading system for vesicoureteral reflux. See text for description. (Adapted from The International Reflux Committee: Medical versus surgical treatment of primary vesicoureteral reflux. Pediatrics 67:396, 1987.)

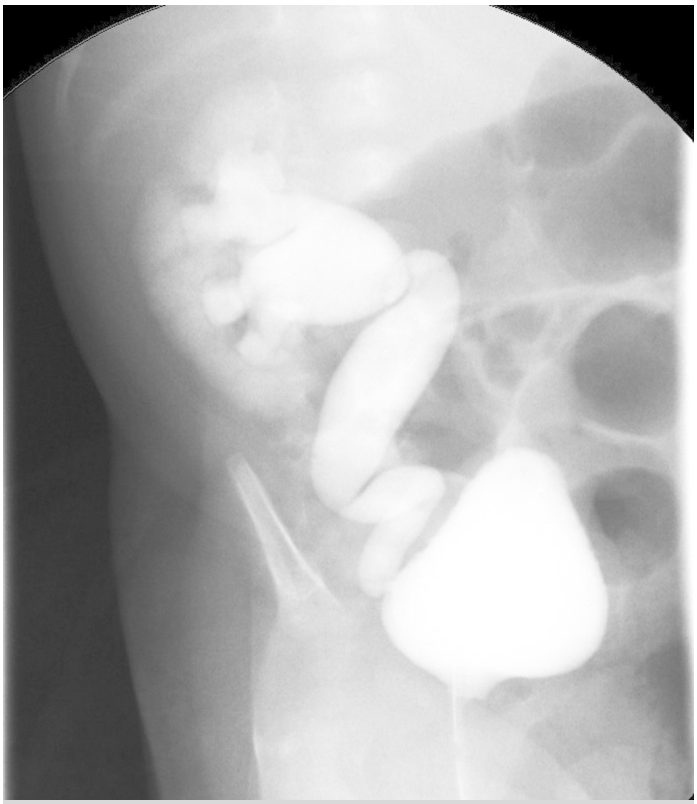

Figure 2: Grade 5 vesicoureteral reflux with ureteral dilation and tortuosity.

4. Epidemiology

The incidence of VUR in otherwise normal children is thought to be quite low.[12] A much higher incidence of VUR, between 30–40%, is reported in patients undergoing evaluation following a febrile UTI.[13,14,15,16] It is important to note that the incidence decreases as age increases.[17] Thus, an infant with a febrile UTI is more likely to be diagnosed with VUR.

Although males account for only14% of patients with VUR,[18] an increased incidence of VUR (30%) is found in those males presenting with UTI.[2] Boys with VUR tend to present at a relatively young age (25% under 3 months) and younger children tend to have the more severe degrees of reflux.[8]

Multiple studies have documented a significant risk of VUR in family members of patients with vesicoureteral reflux. The reported risk of sibling reflux ranges from 27–34%[19,20,21] while as much as 66% of offspring of women with reflux also have VUR.[19] Sibling screening is no longer routinely performed given the uncertainty of any demonstratable benefit of identifying reflux in the absence of infections or anomaly on renal-bladder ultrasound. In siblings of children with primary VUR, a VCUG is recommended if there is a history of UTI or evidence of renal abnormalities on ultrasound.[22]

A particularly important subset of VUR patients include those with secondary reflux. Most have a functional or anatomical bladder obstruction (e.g., spina bifida, posterior urethral valve) as the primary etiology. Many patients, however, have reflux not because of increased bladder pressure alone, but rather because UVJ deficiency is associated with other congenital anomalies, such as imperforate anus,[23] ureterocele,[24] or bladder exstrophy. Although many patients with posterior urethral valves (PUV) have reflux due to or exacerbated by high intravesical pressure, as demonstrated by VUR resolution after valve ablation or vesicostomy, the incidence of VUR in PUV patients is only approximately 50%. Many have congenitally abnormal ureteral insertions.[25]

In addition to these structural associations, important functional associations are found as well, including NGB, as seen in myelomeningocele,[26] and a variety of more subtle voiding disturbances.[27,28,29] A particularly important subset of VUR patients are those who have uninhibited detrusor contractions (UDCs). Three important components of maturation are found with successful toilet training: (1) growth in bladder volume; (2) development of volitional control over the striated muscle sphincter; and (3) control over bladder smooth muscle. Delay in this maturation leads to UDCs. Many children with reflux and recurrent UTI have UDCs. Such involuntary or uninhibited bladder contractions are not caused by neurologic disease. Intense voluntary constriction of the striated sphincter can occur in an attempt to ensure continence and result in excessively high intravesical pressures (i.e., detrusor-sphincter dyssynergia). This is somewhat akin to the child performing “kegel” exercises to inhibit urinary incontinence which leads to voiding dysfunction and high pressure voiding. Pressures often exceeding 150cmH2O have been observed resulting in intravesical distortions, such as diverticula, saccules, trabeculations, and abnormal ureteral orifices.[30] Reflux occurred in almost half of the children studied with UDC’s and UTI. An end-stage bladder from non-neurologic and non-obstructive voiding dysfunction is termed a Hinman bladder.[31]

Screening for symptoms indicative of bladder-bowel dysfunction (BBD) including urgency, frequency, incontinence, micturition deferral, penile or vaginal pain, constipation, and encopresis should be performed if the child is toilet-trained. Vincent's curtsy, a squatting maneuver spontaneously employed to prevent incontinence, is a common finding in voiding dysfunction.[29]

5. Diagnostic Evaluation

VUR is diagnosed with a voiding cystourethrogram (VCUG), with either radiopaque contrast medium or a nuclear radioisotope.[32,33] An advantage of fluoroscopic VCUG (**Figure 3a**) over the nuclear cystogram (**Figure 3b**) at least for the initial study is that associated abnormalities such as bladder diverticula, bladder wall trabeculation, ureteral duplication, and urethral anomalies can be diagnosed. A “spinning-top” urethra may be seen in children with incoordination of the external sphincter and bladder during voiding on VCUG. Additionally, children with overactive bladder might exhibit a “spinning-top” urethral appearance due to habitual external sphincter guarding or holding maneuvers during increased bladder pressure or urgency.[34] The scout film on VCUG can also be used to evaluate stool burden. Ultrasonography can also show impacted stool behind the bladder.

Regardless of the type of cystogram utilized, multiple cycles are preferable with voiding images to assess for reflux that only occurs at the end of filling and/or with voiding. Body temperature contrast material, which is not excessively concentrated, is instilled into the bladder through a small catheter by gravity with modest pressure in a non-anesthetized child. Given the importance of information obtained, as well as widely varying techniques and quality of VCUGs between hospitals, the American Academy of Pediatrics Sections on Urology and Radiology published a joint standardized VCUG protocol in 2016.[35] The “as low as reasonably achievable” (ALARA) and Image Gently principles should be adhered to, minimizing radiation exposure while still obtaining high quality images. During cyclic filling (at least two voiding cycles are recommended), multiple spot images are obtained, as well as urethral images during voiding. Scout and postvoid images should be obtained, and the maximum volume of contrast instilled as well as the volume at which reflux first occurs should be routinely reported. Adherence to this standardized protocol maximizes information from every VCUG.

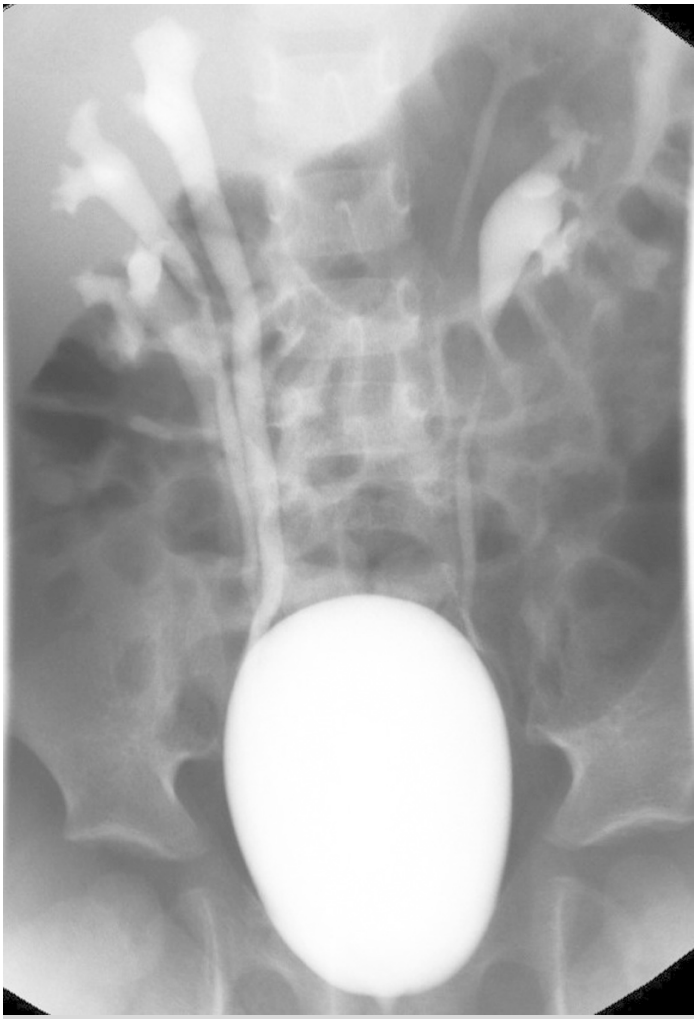

Figure 3a: Fluoroscopic VCUG showing a right triplication and left duplication anomaly and radionuclide cystogram

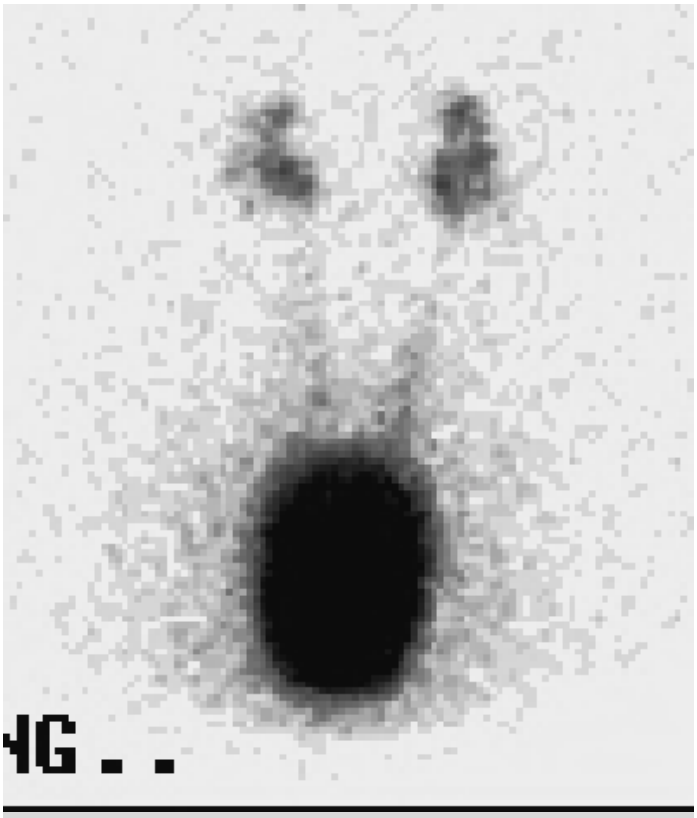

Figure 3b: Fluoroscopic VCUG showing bilateral vesicoureteral reflux comparable to grade 2.

Imaging of the upper urinary tract (kidneys and ureters) is extremely important and is typically accomplished by renal and bladder ultrasonography. This is universally available, non-invasive, and can be done in the office or hospital. Radioisotope renography is an option in some centers to detect split differential renal function and pyelonephritic scarring but requires an intravenous catheter and often sedation in young children. Both modalities may detect scarring, but isotope renography is particularly sensitive and defines the function in the case of a small or dysplastic appearing kidney. Serial ultrasound imaging is helpful in quantitating renal growth and following dilatation of the renal pelvis and/or ureters. Bladder views are important to obtain to check for bladder wall thickening, diverticula, distal ureteral dilatation, ureteroceles, and bladder emptying.

Toilet trained children with urinary frequency, urgency, incontinence, and Vincent's curtsy should also be considered for non-invasive urodynamic studies including a uroflow and perineal/abdominal electromyogram with a postvoid residual. A filling cystometrogram (formal urodynamics) is indicated in secondary VUR to follow neurovesical dysfunction or in those who have failed standard initial urotherapy.[39] The presence of UDCs or detrusor-sphincter dyssynergia should be resolved before consideration is given to an anti-reflux operation.

6. Natural History

The natural history of VUR is extremely variable, and ranges from spontaneous resolution without nephropathy to recurrent pyelonephritis to clinically silent scar formation to hypertension and end-stage renal disease (ESRD). Despite the tendency of reflux to resolve over time, a subset of children with persistent VUR remain at risk for recurrent pyelonephritis as well as potential sequela from renal injury. In general, clinicians must delineate which patients are most likely to resolve without intervention from those harboring VUR with the potential to cause to cause irreversible renal damage over time, thus placing the emphasis on the ability to predict the likelihood of recurrent febrile infections rather than resolution alone.[40] Numerous factors may contribute to resolution, including patient age, VUR grade, UVJ anatomy, length of the ureteral submucosal tunnel, and intravesical detrusor filling pressures. The American Urological Association Pediatric Vesicoureteral Reflux Guidelines Panel in 1997 (amended 2017) analyzed 26 reports comprising 1,987 patients with conservative follow-up, to estimate the probability of reflux resolution.[39] In general, a lower reflux grade correlated with a better chance of spontaneous resolution.

Younger children are thought to have a better prognosis for resolution of VUR, particularly infant males in the first year of life. This may be due to a heightened degree of trigonal growth, but the diminishing prominence of UDCs with age is also a possible explanation. Spontaneous resolution is relatively independent of grade in secondary reflux, implicating management of primary bladder dysfunction as the primary prognostic variable.[39]

Renal injury due to VUR may take the form of focal scarring, generalized scarring with atrophy, and failure of renal growth.[40] As a result, kidneys in patients with VUR should be observed not only for scarring but also for renal growth, typically with serial renal ultrasounds.[41] Reflux-induced renal injury is usually a result of the association of VUR with UTI.[17] It has been generally considered that such injury is most likely in children under the age of 2 years.17 It is now clear, however, that the risk of renal injury from VUR extends well beyond this age.[40,41,42,43] Secondary reflux can also cause renal injury in the absence of UTI due to the pressure effects from a neurogenic bladder and with either functional or anatomic bladder outlet obstruction. The ability of high intravesical pressure, when associated with VUR, to cause renal injury has been confirmed experimentally.[44]

Significant renal injury in the absence of bladder outlet obstruction, neurogenic bladder, and UTI can be found in infants.[45,46] The ureteral bud theory postulates that VUR associated with displacement of the ureteral orifice is associated with anomalies of renal differentiation.[47] Such ureters probably do not arise from the appropriate segment of the Wolffian duct and consequently make ectopic contact with the nephrogenic cord, resulting in abnormal renal development. Although this mechanism may be present in some patients, it is now clear that congenital VUR-associated renal injury (congenital dysplasia or reflux nephropathy) in the absence of outlet obstruction and infection may occur in the presence of a normally positioned ureteral orifice.[48] This finding implies that pressure from *in utero* VUR may injure the developing kidney.

In a longitudinal study of 923 children, high-pressure bladder dynamics, severity of reflux, and frequency of UTIs were the chief contributing factors in the development of new scars or the worsening of old scars.[43] Children with low-grade VUR were relatively unlikely to develop progressive renal injury when compared with those children with grades IV and V reflux. A similar relationship is seen in infants and children with secondary reflux. When monitoring these patients for progression of renal injury as an indicator of success of a therapeutic regimen, one must be cognizant of the fact that sonographic evidence of new renal injury may take several months to become apparent.

There is little consensus regarding the long-term sequelae of minor renal scars detected by high-resolution renal cortical scans. However, in a small number of patients, a spectrum of symptomatic nephropathy exists, most notably renal parenchymal hypertension and ESRD. While it is known that congenital anomalies of the kidney and urinary tract (CAKUT) can predispose children to

hypertension and cardiovascular disease, the significance and predominance of reflux nephropathy (RN) as a cause of hypertension is difficult to separate from CAKUT etiologies. Historically, RN has been a prominent urologic cause of end-stage renal disease (ESRD) in children and adults[51,52]. The 2014 annual report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) lists reflux nephropathy as being the primary diagnosis in 5% of 11186 children who received transplants since 1987. This is similar to the previously published report[53].

7. Treatment

7.1 Medical Management

Non-operative management (i.e., watchful waiting) of VUR is successful in many patients, particularly those with low grade reflux. Such management may be considered in four stages: (1) diagnostic evaluation; (2) avoidance of infection; (3) voiding dysfunction treatment; and (4) active surveillance. Diagnostic evaluation has been previously reviewed. However, it is important to stress that the exclusion and treatment of voiding dysfunction and bladder outlet obstruction is imperative. Recurrent UTI has been shown to be associated with untreated BBD, despite medical or surgical management of VUR. The CUTIE trial found that children with recurrent UTIs could be classified into three risk categories: children with VUR and BBD (at highest risk for recurrent infections), followed by BBD and no VUR, and finally those with VUR but no BBD (at lowest risk). This underscores the impact of BBD on UTI status and highlights the necessity of effectively managing underlying bladder dysfunction and constipation in children with primary reflux[54]. The cornerstone of BBD management in children remains implementation of a bowel program and timed voiding regimen, with additional treatment modalities employed depending upon prevailing symptoms[53]. Patients with problematic uninhibited detrusor contractions can be managed with low-dose anti-cholinergic medication, such as oxybutynin hydrochloride. Side effects are manageable and include constipation and facial flushing/dry mouth. Voiding dysfunction with retentive characteristics and/or dysynergia may require timed/double voiding, alpha blockers, biofeedback (pelvic floor retraining), and in severe cases, intermittent catheterization (IC). Secondary reflux from neurovesical dysfunction often requires aggressive bladder management with clean intermittent catheterization (CIC) and higher doses of anti-cholinergic medication.

Good hydration, perineal hygiene, and bowel management are crucial and apply to all patients. The use of continuous antibiotic prophylaxis (CAP) is considered a non-specific approach for prevention of recurrent UTIs. Daily low-dose antibiotics is a temporizing measure that allows for spontaneous resolution and/or optimization of bladder and bowel habits while reducing UTI risk. The maintenance of sterile urine in a patient with VUR is believed to negate the risk of the development of renal parenchymal injury and scarring due to pyelonephritis. **Table 1** lists the common anti-microbial medications/dosing used in VUR. It is important to remember that the prophylactic dose is approximately one-quarter the dose to treat an acute urinary tract infection, and knowledge of local resistance patterns is also key.

Although generally well tolerated and a common standard of care practice for decades, the long-term implications of chronic antimicrobial suppression remain incompletely investigated and are actively debated[22,54,55]. The use of CAP is under scrutiny due to adherence and anti-microbial resistance concerns. In addition to resistance, early-life antibiotic exposure has been associated increased body mass. Antibiotics affect the gut microbiota, and the link between altered gut microbiota and human metabolism is becoming increasingly apparent[56]. The 2014 NIH-funded RIVUR study has shown the efficacy of CAP in reducing recurrent UTI's in patients with VUR[57]. It is reasonable to observe an asymptomatic toilet-trained child with low-grade reflux and normal kidneys without antibiotic prophylaxis; however, the clinician must use caution in treating children with risk factors for recurrent UTI and renal scarring, including high grade VUR with bowel and bladder dysfunction. The CUTIE trial reported that children with VUR and BBD were at highest risk for recurrent UTI, and therefore antimicrobial prophylaxis could be of particular benefit in this cohort[58].

Once a non-operative regimen is selected, the patient is committed to long-term, strict surveillance. Renal imaging is performed every six to 12 months, depending on the age at diagnosis and the stability of the disease. Attention is directed at both renal growth as well as the detection of focal scarring. Voiding cystourethrography or radionuclide cystography is often performed once a year. The child's growth, renal function, and blood pressure are monitored. Urodynamics can be obtained in patients with voiding dysfunction to assess bladder/sphincter synergy. Cystoscopy is rarely necessary except at the time of anti-reflux surgery when it is performed to exclude active bladder inflammation and to confirm the position and number of ureteral orifices.

The American Urological Association (AUA) Pediatric Vesicoureteral Reflux Guidelines Panel published their recommendations for management of VUR in children in 1997 and updated their guidelines in 2010 and 2017. The AUA guideline recommends CAP for children under 1 year of age with a history of febrile UTI or dilating reflux (i.e, grades III-V) and children with VUR and BBD; CAP remains an option in other patients. There is little solid evidence or consensus about the management of VUR in older school-age patients or about the length of time that the clinician should observe a child non-operatively before recommending surgery. Treatment decisions must be carefully individualized after a thorough discussion of all the treatment options with the parents. Surgical intervention may be necessary in children with breakthrough febrile UTIs before toilet training, associated urinary tract abnormalities with decreased renal reserve/parenchymal scarring, or febrile UTIs that persist after management of bladder-bowel dysfunction.

Table 1: Common oral anti-microbial medications used in children with vesicoureteral reflux and their doses

Drug	Therapeutic Dose	Suppressive Dose	How Supplied	Comments
Trimethoprim-sulfamethoxazole	4 mg/kg trimethoprim + 20 mg/kg sulfamethoxazole twice daily	2 mg/kg trimethoprim + 10 mg/kg sulfamethoxazole once daily	Suspension: (8 mg trimethoprim + 40 mg sulfamethoxazole per mL Tablet (SS): (80 mg trimethoprim, 400 mg sulfamethoxazole)	Avoid in patients <1 month of age; Contraindicated with hyperbilirubinemia; May cause white blood cell suppression; Linked to Stevens-Johnson syndrome
Nitrofurantoin	2 mg/kg four times daily	1 mg/kg once daily	Suspension: (25 mg/5 mL) Capsule: (25, 50, 100 mg)	Avoid in patients < 1 month of age Not effective if CrCl < 40 mL/min Nausea and aversion to taste common with suspension; opening capsules and sprinkling macrocrystals into yogurt may avoid taste aversion
Trimethoprim (Primsol®)	2 months to 12 years: 4-6 mg/kg per day divided bid 13 years and older: 100 mg po bid	2 mg PO qd up to 100 mg	Oral solution: 50 mg/5 mL	Avoid in patients < 2 months of age; Can be expensive and require authorization from third party payers
Amoxicillin	Children up to 40 kg: 20-40 mg/kg/day in divided doses every 8 hours or 25-45 mg/kg/day in divided doses every 12 hours Children >40 kg: 250 - 500 mg every 8 hours or 500 - 875 mg every 12 hours	12.5 mg/kg PO qd	Suspension: 125 mg/5 ml, 200 mg/ 5 mL, 250 mg/5 ml, 400 mg/5 ml; Capsule: 250, 500 mg Tablet: 500 mg, 875 mg Chewable: 125 mg, 250 mg	Initial agent recommended for neonates < 3 months

Cephalexin	25-50 mg/kg/day in divided doses	12.5 mg/kg qd	Suspension: 125 mg/5 mL or 250 mg/5 mL Tablet: 125 mg, 250 mg, 500 mg, 750 mg	Alternative for neonates or as second agent for double antibiotic prophylaxis after a breakthrough UTI
Key	Mg: milligram; Kg: kilogram; mL: milliliter; min: minute; PO: by mouth; Bid: twice daily; qd: once daily; qid: four times daily; UTI: urinary tract infection; CrCl: creatinine clearance			
View Image.				

7.2 Surgical Management

While the decision to perform anti-reflux surgery must be carefully individualized, indications for surgical correction of VUR include (1) progressive renal injury; (2) documented failure of renal growth; (3) breakthrough pyelonephritis; and (4) intolerance or non-compliance with antibiotic suppression. Other relative indications for correction of VUR are high grade (IV–V) reflux in young children after a year of conservative follow-up, pubertal age with nephropathy at diagnosis, parental preference, and failure to spontaneously resolve after a period of watchful waiting.

7.2.1 Ureteral Reimplantation

The established principles of successful ureteral reimplantation include: (1) adequate ureteral exposure and mobilization; 2) meticulous preservation of the ureteral blood supply; and (3) creation of a valvular mechanism whose submucosal tunnel length to ureteral diameter ratio ideally exceeds 5:1. These goals can be attained by a variety of procedures, most commonly via an open Pfannenstiel approach but can also be achieved laparoscopically or robotically.

Important differences exist between these operative procedures. Variables include (1) presence or absence of a ureteral anastomosis; (2) need for detrusor closure; (3) opening of the urothelium; and (4) whether the neohiatus is fashioned by an appropriately sized detrusor incision or by the closure of the detrusor around the ureter. Performance of a ureteral anastomosis increases the risk of postoperative obstruction, whereas the need for detrusor closure increases the risk of diverticula. Three of the most commonly employed reimplantation operations for the treatment of primary VUR are the Cohen intravesical ureteral reimplantation, open extravesical detrusorraphy via the Lich-Gregoir approach (**Figure 4a-e**), and the robot-assisted laparoscopic extravesical ureteral reimplantation.

In general, excellent results are nearly uniformly attainable with a ureteral reimplantation. A meta-analysis in 1997 of 86 reports, including 6472 patients (8563 ureters), found overall success for an open ureteral reimplantation to be 96%.[58] Success was achieved in 99% with grade I, 99.1% with grade II, 98.3% with grade III, 98.5% with grade IV and 80.7% in grade V. Minimally invasive surgical techniques are increasingly employed in the pediatric population for complex reconstruction. While open surgery remains the gold standard, robotic reimplantation has gained increasing acceptance.[59,60] VUR resolution rates after extravesical robotic ureteral reimplantation reported in the literature range from 66.7 to 100% in multiple relatively small series; the overall success rate upon pooling these series is 91%.[6] A multi-institutional retrospective study reported radiographic success of 87.9%; more recently, a large prospective multi-institutional group reported a slightly higher resolution rate of 93.8%.[60,61] In comparison to open surgery, robotic surgery has been associated with decreased morbidity, less postoperative pain, lower analgesic requirements, quicker postoperative recovery, and shorter hospital stays. However, there are multiple reports of both higher costs and complication rates compared to the open approach.[62,63]

The open or robotic extravesical detrusorrhaphy approach has many advantages.[64,65,66] Because the lumen of the bladder is not entered, there is no post-operative hematuria, with minimal bladder spasms and typically a short hospitalization of one to two days. The absence of a ureterovesical anastomosis decreases the risk of postoperative obstruction. No ureteral stents, suprapubic catheters, or perivesical drains are typically needed.

The four major principles of a successful extravesical detrusorrhaphy are: (1) complete mobilization of the ureter from the peritoneal reflection to the UVJ, leaving a wide sheath of its peri-adventitial blood supply; (2) distal fixation of the ureter with long-acting absorbable sutures; (3) wide mobilization of the detrusor muscle flaps to enable firm approximation of the detrusor over the ureter; and (4) development of a sufficient tunnel length. The use of the extravesical detrusorrhaphy has been successfully expanded to include a tapered excisional megaureter repair,[66] reimplantation of the ureters associated with paraureteral Hutch diverticula,[67] as well as correction of VUR associated with duplicated collecting systems.[68]

Figure 4a-e: The ureter is mobilized outside the bladder with minimal dissection distal to the ureter.

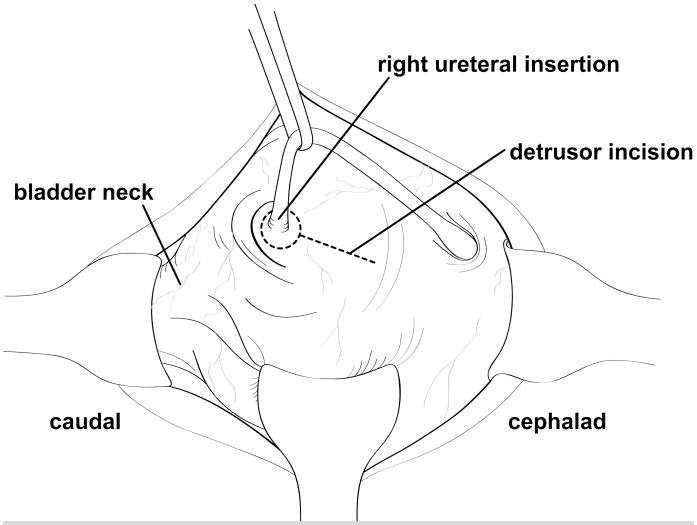

Figure 4a: The extravesical detrusorrhaphy anti-reflux surgical technique conceptually viewed from directly above the right side of the bladder.

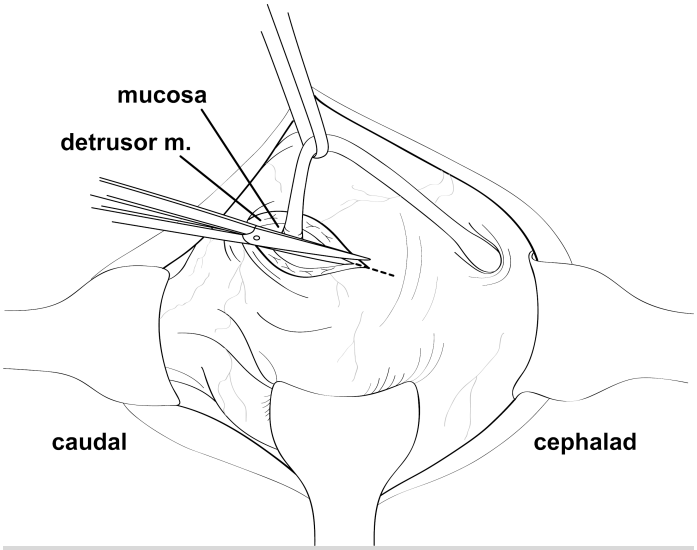

Figure 4b: The extravesical detrusorrhaphy anti-reflux surgical technique conceptually viewed from directly above the right side of the bladder.

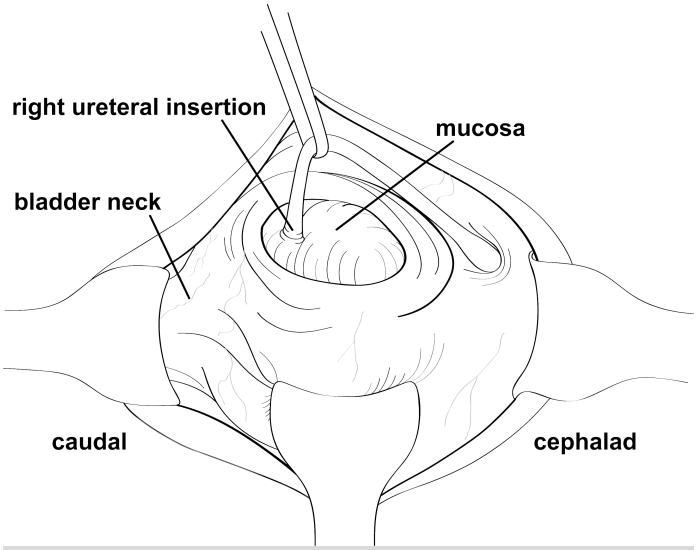

Figure 4c: The extravesical detrusorrhaphy anti-reflux

surgical technique conceptually viewed from directly above the right side of the bladder.

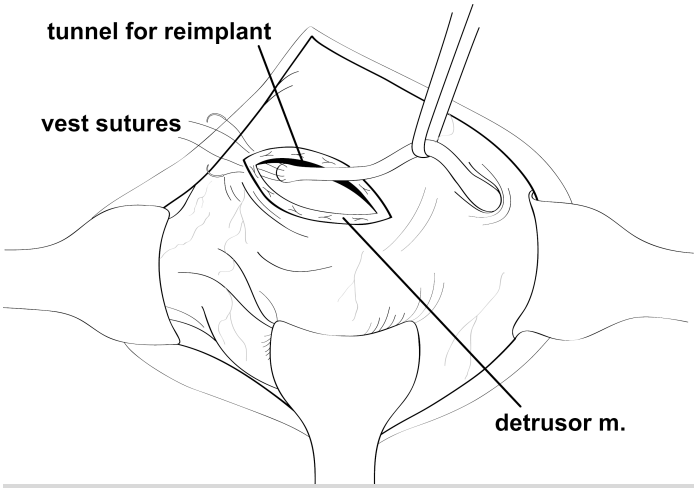

Figure 4d: The extravesical detrusorrhaphy anti-reflux surgical technique conceptually viewed from directly above the right side of the bladder.

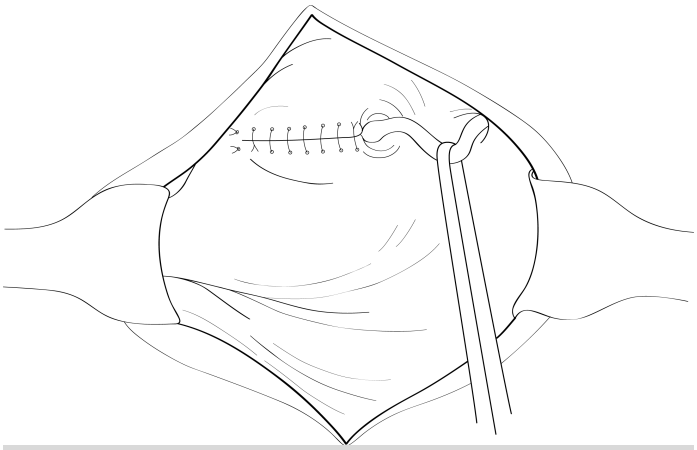

Figure 4e: The extravesical detrusorrhaphy anti-reflux surgical technique conceptually viewed from directly above the right side of the bladder.

7.2.2 Endoscopic Anti-reflux surgery

In 1984, a minimally invasive endoscopic procedure for the correction of VUR was reported (**Figure 5**). This subureteral transurethral injection (STING) utilized polytetrafluoroethylene (Teflon) and has been used successfully outside the United States for many years.[69] Many different injectable materials have subsequently been investigated and reported.[70,71,72] This ambulatory procedure performed under a brief general anesthetic has low morbidity and children may return to full activity as soon as the next day. The initial success rates were promising; however, they did not quite match those of ureteral reimplantation.[73]

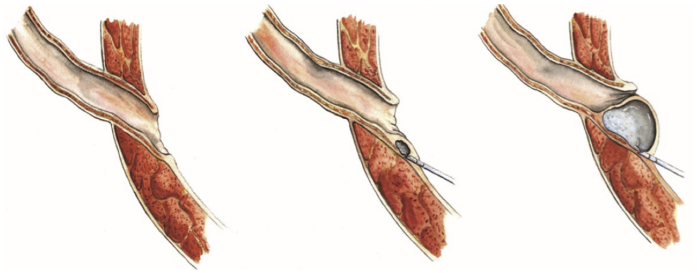

Figure 5: Technique of sub-ureteric transurethral injection of dextranomer/hyaluronic acid copolymer (STING procedure). Figure used with permission from the Salix Corporation®, Raleigh, North Carolina.

In 2001, the Food and Drug Administration approved dextranomer/hyaluronic acid (dx/HA) copolymer (Deflux®) as the first injectable substance indicated in the USA for grades I-IV vesicoureteral reflux.[74] This substance is biodegradable, has no immunogenic properties, and does not seem to have potential for malignant transformation. The injection is performed by cystoscopy under a brief general anesthetic as an outpatient procedure. Aggregate literature suggests that endoscopic therapy is relatively effective for the treatment of most primary VUR, while stressing the importance of reflux grade and structural/functional bladder anomalies on ultimate success rates.[75,76,77] In a systematic meta-analysis evaluating Dx/HA for pediatric VUR, the estimated overall reported success rate for endoscopic therapy was 72% with 89% success for grade I, 83% for grade II, 71% for grade III, 59% for IV and 62% for grade V reflux.[78] Higher success rates with larger injected volumes and multiple injection sites have been reported at some high volume centers.[79] Long-term reflux resolution rates appear to be stable, but recurrence has been found a year after the procedure.[80] Endoscopic treatment seems to be a reasonable alternative to CAP for low to mid-grades of VUR but has been advocated to “down-grade” dilating VUR with multiple repeat injections in some centers.[81]

8. Postoperative Complications

Complications of ureteral reimplantation are overall rare.[38,82] The most common complication in a unilateral repair is *de novo* contralateral reflux,[83] while the most common technical complications are ureteral obstruction, persistent reflux, and diverticula formation. Persistent reflux may be caused by an insufficient tunnel length to ureteral diameter ratio. However, the greatest risk for postoperative reflux is related to high-pressure voiding dynamics due to uninhibited bladder contraction, detrusor sphincter dyssynergia, and/or urinary retention. Ureteral obstruction may be due to ureteral kinking (at the neohiatus or obliterated umbilical artery), an excessively high placed neohiatus, construction of a tight neohiatus, ureteral twisting, anastomotic stricture, devascularization, and/or a tight submucosal tunnel.

Ureteral reimplantation remains a safe and highly successful operation. The extravesical approach for bilateral ureteral reimplantation has been questioned because of a reportedly high incidence of post-operative urinary retention.[84] In a review of a large cohort, a 4% rate of temporary incomplete bladder emptying was found which was transient with minimal morbidity.[85] Risk factors appear to be infants under age one and girls with large, thin-walled bladders and pre-existing retentive voiding dysfunction. A suprapubic tube placed at the time of surgery can be helpful to mitigate concerns for urinary retention and can be removed in the office 2-3 weeks post-operatively once complete emptying is documented.

Complications following open anti-reflux surgery are quite low but include ureterovesical obstruction and persistent vesicoureteral reflux. Acute management of an obstructed ureter in an ill-appearing child involves urgent drainage of the hydronephrotic kidney. A percutaneous nephrostomy tube can be placed without concern for finding a ureteral orifice within an edematous bladder wall to place a ureteral stent and/or potentially disrupting a fresh uretero-vesical anastomosis. Once the patient has stabilized, the nephrostomy can be used to check the patency of the UVJ with an antegrade contrast study. The nephrostomy can be subsequently exchanged for a internalized ureteral stent or removed if adequate drainage is documented.

Complications of injection therapy such as ureteral obstruction appear to be very low. The post-operative course is generally well tolerated, and patients return to normal activities almost immediately. Dysuria, gross hematuria, and urinary frequency occasionally occur, but are self-limiting. Flank pain and fever are rare. A VCUG and renal ultrasound can be obtained 3 months after the procedure while still under cover of antibiotic prophylaxis. The VCUG is not subsequently repeated if the patient remains asymptomatic off antibiotic prophylaxis. Patients having a febrile UTI after an apparently successful procedure should be re-investigated with a VCUG to assess for recurrent reflux.[86] Persistent reflux after a dextranomer-hyaluronic acid injection can be re-injected or managed with an open or robotic-assisted laparoscopic extravesical ureteral reimplantation. Sharp excision of the often migrated bleb of the implanted material can be performed concomitantly.

9. Postoperative Pathways

For ureteral reimplantation, the urethral catheter can be removed on the first or second day postoperatively dependent upon if epidural in place. Post-operative analgesia for open procedures can be maintained with either an indwelling or single-shot epidural catheter placed at the time of surgery, or infiltration of local anesthesia in the incision supplemented by intravenous narcotics as needed. Most children are discharged home simply on oral acetaminophen alone. Postoperative imaging includes a renal and bladder ultrasound at 3 months, 12 months, and 24 months after the procedure. It is not uncommon to see mild hydroureteronephrosis after a successful ureteral reimplantation in the early post-operative period and can be managed expectantly if asymptomatic. A post-operative VCUG can be safely deferred in an asymptomatic patient due to the high success rate of the procedure. If the patient has a single febrile UTI or a cluster of afebrile infections, it may be reasonable to repeat the VCUG.

For endoscopic anti-reflux surgery, it is typically performed as an outpatient procedure. A VCUG and renal ultrasound may be obtained 3 months after the procedure while still under cover of antibiotic prophylaxis. The VCUG is not subsequently repeated if the patient remains asymptomatic off antibiotic prophylaxis. Patients having a febrile UTI after an apparently successful procedure should

be re-investigated with a VCUG to assess for recurrent reflux.

10. Conclusion

Vesicoureteral reflux is a commonly encountered condition in children, particularly following evaluation for febrile urinary tract infection. The natural history varies from a benign self-limiting condition to one that can cause severe nephropathy and renal insufficiency. When surgical intervention is warranted, excellent outcomes can be achieved with a low risk of complications.

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Videos

Cohen cross trigonal ureteral reimplant

Robotic Bilateral Extravesical Reimplant

Urinary Reflux

Presentations

Vesicoureteral Reflux Presentation 1

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