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Vesicoureteral Reflux: Current Management in Children

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Abstract Vesicoureteral reflux (VUR) is a disorder that has been studied since the early days of pediatric urology. From 1893, when it was first documented in humans by Pozzi, the research and clinical management of VUR has been marked by pendulum swings through the decades. Initially, the vesicoureteral junction was the main subject of study, whereas current practice takes into account the bladder and bowel dynamics. The primary objective, however, is unchanged: preservation of the kidney and its function. Management of the condition has included open surgery, minimally invasive surgery, endoscopic treatment, antibiotic prophylaxis, and watchful waiting. In this article, we will attempt to cover every angle of this complex pathology and its current management in children.

Keywords Index · Vesicoureteral reflux · Children · Management · Review · Pediatric urology

Introduction

Vesicoureteral reflux (VUR) is the abnormal flow of urine from the bladder to the upper urinary tract, which is caused by an abnormality of the ureterovesical junction. The incidence of VUR is estimated at 0.4–1.8 % of the pediatric population who have not presented with urinary tract infection (UTI), and 10–40 % in patients who have presented with UTI [1]. In infants under 12 months of age, it is most common in boys, a situation that is reversed after the first year of life. VUR is more common in white populations. In addition, in asymptomatic screening studies, approximately 30–35 % of siblings were found to have VUR, and the incidence of VUR in offspring of parents with the condition was 35.7 % [2•].

The primary goal in the treatment of pediatric VUR is to preserve renal function by preventing pyelonephritis and renal scarring. However, there may be renal scaring in the context of VUR in the absence of UTI, adding to the challenges of treating the disease.

Although the etiology of VUR can be classified as primary or secondary to a concomitant disease, in clinical practice, the most widely used is the VUR international classification (Fig. 1).

Vesicoureteral reflux (VUR) is a disorder that has been studied since the early days of pediatric urology. There are now many management options available for pediatric VUR, including watchful waiting, medical treatment with continuous prophylaxis antibiotics (CAS), and various surgical alternatives, highlighted by the rapid growth in the use of endoscopic treatment within the last decade.

Pathophysiology

Primary vesicoureteral reflux is caused by an anatomical defect of the vesicoureteric junction, where the relationship between the length of the intramural ureter in the bladder and its diameter is altered from the normal 4–5:1 ratio. This may occur at the stage of embryonic development of the ureter at six weeks gestation. Despite this anatomical abnormality,

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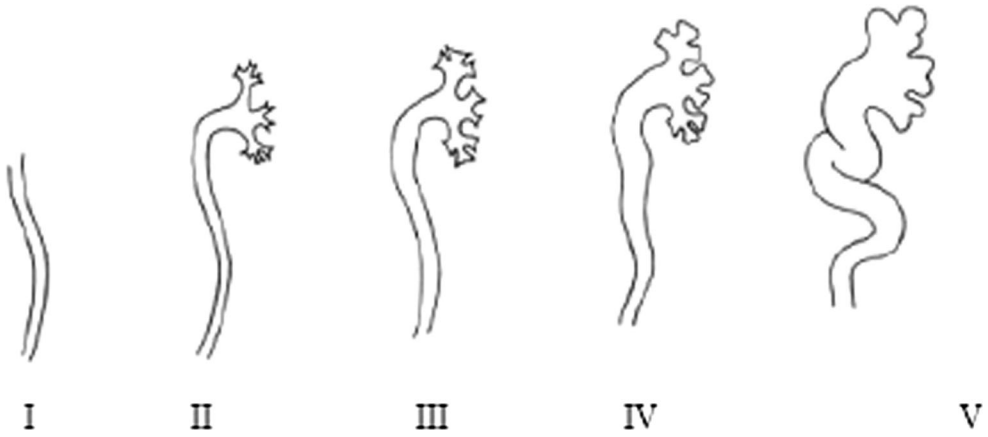

Fig. 1 International Classification of VUR. Grade I: Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation. Grade II: Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices. Grade III: Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices. Grade IV: Moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible. Grade V: Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

spontaneous resolution of vesicoureteral reflux occurs in nearly 30 % of cases [3].

Secondary reflux occurs when there is an anatomical defect and/or an imbalance in pressure on either side of vesicoureteric junction, such as that seen in voiding dysfunction, posterior urethral valves, ureteral diverticulum, and neurogenic bladder.

The relationship between acute pyelonephritis, VUR, and kidney damage has been well-established for more than 60 years. VUR increases the risk of pyelonephritis when a bladder/lower urinary tract infection occurs, with a higher rate of febrile infection in the affected population and increased risk of renal scarring and upper tract damage.

Diagnosis

The diagnosis of VUR is most common among infants with urinary tract infection (UTI) (10–40 %). In cases where prenatal hydronephrosis is identified by ultrasonography, the prevalence is 16 % (7–35 %) [2•].

Diagnosis of VUR requires a thorough medical history, including familial history, assessment of bladder and bowel dysfunction (BBD), blood pressure measurement, urinalysis and urine culture, and measurement of serum creatinine level in patients with bilateral renal parenchymal abnormalities [4•].

The standard imaging tests include renal and bladder ultrasonography, voiding cystourethrography (VCUG), and nuclear renal scanning. It is worth mentioning that the optimal diagnostic imaging approach following a first UTI is controversial. The classic "bottom-up" approach includes VCUG and renal ultrasound as initial studies, followed by dimercaptosuccinic acid (DMSA) renal scintigraphy in the event of abnormal results or in the case of febrile UTI. The current "top-down" approach begins with a renal/bladder ultrasound (RBUS) and nuclear renal scintigraphy to evaluate for renal involvement, and then a VCUG is performed only if renal involvement is identified [5]. This approach is based upon the fact that abnormal DMSA findings frequently indicate the presence of VUR, whereas normal results exclude the possibility of VUR or it is of a lower grade. This approach also provides the benefits of decreased urethral catheterizations and radiation exposure.

Recommendations of the European Association of Urology (EAU) state that VCUG should be performed in the event that cortical abnormalities, bilateral high-grade hydronephrosis, ureterocele, ureteral dilatation, or abnormal bladder are identified on ultrasonography [6].

The American Academy of Pediatrics (AAP) recommends performing VCUG under the following circumstances: renal ultrasonography revealing hydroureteronephrosis, renal scars, or other findings that suggest high-grade reflux or obstructive uropathy, and in other atypical or complex clinical circumstances; as well as with recurrence of febrile UTI [7•].

The most useful criterion for the diagnosis of VUR is detection on VCUG, which remains the gold standard, as the test allows better determination of the grade of VUR (in both single and duplex kidney) (Fig. 1) and provides better anatomical detail for the assessment of bladder and urethral configuration.

Radionuclide studies for the detection of reflux offer the benefit of lower radiation exposure compared to VCUG, but the anatomic detail depicted is inferior. Isotopic cystography

has greater sensitivity, however, and is the preferred test for monitoring and follow-up [8, 9].

Another imaging test that has been used to diagnose VUR is voiding urosonography (VUS), which entails the intravesical administration of US contrast agents. VUS may be useful for follow-up examinations and for screening high-risk patients, but its more widespread use will be made possible by the development of new US contrast agents [10].

The detection of renal scars is at least as important as VUR diagnosis. Renal scars increase the risk for developing long-term health problems such as hypertension, chronic renal insufficiency, proteinuria, growth retardation, and pregnancy complications [6].

In addition to its role as the best agent for visualizing cortical tissue and differential function between the kidneys, dimercaptosuccinic acid (DMSA) is used to detect and monitor renal scarring, and is the test of choice for detection of renal involvement in UTI. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans during follow-up [6, 11, 12].

Renal and bladder ultrasonography (RBUS) is the initial imaging test used in children with UTI, and US findings may identify renal scarring, with a focal thinning of the renal cortex, with or without indentation of the renal contour. The sensitivity of US compared to DMSA for renal scarring ranges from 37 % to 100 %, with specificity from 65 % to 99 % [13]. While these data suggest that this is an excellent modality for detecting structural renal abnormalities, the use of US in this setting nonetheless remains controversial.

Magnetic resonance urography has been proposed as a test that is at least as good as, if not superior to DMSA for detecting renal scars, with the advantage of providing a full anatomical description of the urinary tract. It also can be substituted for DMSA scintigraphy, particularly in patients requiring follow-up scanning – and, consequently, considerable radiation exposure – and can be used for the differentiation of subtle pyelonephritic foci or scar lesions [14, 15]. However, it may need to be performed under anesthesia.

Siblings of an index case have a 20–30 % likelihood of presenting with VUR. As such, RBUS is the recommended initial diagnostic method for an asymptomatic relative, and proceeding from there according to the findings [2•].

Bladder dysfunction must be considered from the beginning in a diagnosis of VUR , as it may be a critical factor. In addition to clinical history, US may show a thick bladder wall, and VCUG may show incomplete sphincter opening.

While there are various algorithms for the diagnosis of VUR, either after UTI or antenatal diagnosis of hydronephrosis, there is consensus among the medical guidelines that RBUS is always performed as the first imaging test. The decision to perform DMSA or VCUG will depend upon the age of the patient and the guidelines utilized at each center, always with the knowledge that the goal is the detection and prevention of renal scarring.

Treatment

The primary goal in the treatment of pediatric VUR is to preserve renal function by preventing pyelonephritis and to minimize the morbidity of treatment and follow-up. There are three primary approaches for treating patients with VUR: conservative (nonsurgical), endoscopic, and conventional surgery.

Conservative Approach

Conservative therapy is based on the understanding that VUR may resolve spontaneously, and includes watchful waiting, intermittent antibiotic prophylaxis or continuous antibiotic prophylaxis (CAP), and bladder rehabilitation and bowel management in patients with bladder and bowel dysfunction (BBD).

The spontaneous resolution of VUR is dependent upon age at presentation, gender, grade, laterality, mode of clinical presentation, and ureteral anatomy [3]. Faster resolution of VUR is more likely in children who are under the age of one year at presentation, have a lower grade of reflux (grades I–III), and have an asymptomatic presentation and are diagnosed on postnatal evaluation for prenatal hydronephrosis or sibling screening. Even in congenital high-grade VUR, the rate of resolution is higher during the first years of life [3].

The rates of resolution have been historically understood as approximately 80 % in VUR grades I–II and 30–50 % in VUR grades III–V within five years of follow-up. The percentage of spontaneous resolution for bilateral high-grade reflux is lower [16].

In Scandinavian studies, the rate of complete resolution for high-grade VUR in boys during the infant years was reported to be greater than 25 %, which was higher than the resolution rates of high-grade VUR for both boys and girls after the infant years [17]. The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs have been determined to be negative predictive factors for reflux resolution [18].

The use of CAP is currently controversial, as several large prospective randomized controlled trials have shown little to no benefit for CAP in the reduction in incidence of febrile UTI or renal scarring, particularly with low-grade VUR [19–21]. Furthermore, guidelines published by the European Association of Urology state that antibiotic prophylaxis is indicated only in cases of UTI with specific risk factors such as young age, high-grade reflux, lower urinary

tract dysfunction, circumcision status, female gender, and status of toilet-training [6].

These data appear to indicate that treatment without CAP (watchful waiting) for a child with VUR may be an acceptable and safe approach in the proper clinical setting, although the specific criteria for which this may be appropriate have not been definitively determined [4•]. Other trials, however, have demonstrated the usefulness of CAP in preventing renal damage, most notably in patients with grades III and IV reflux and in the presence of BBD [21, 22].

As such, a safe approach may be to use CAP only in children with high-grade VUR (IV–V) and/or dilated ureters until after children have been toilet-trained in order to ensure that there is no BBD [22].

The association between VUR and bladder/bowel dysfunction is well-established, principally in older girls who present with febrile UTIs after toilet-training. Higher frequency of UTIs has been reported in children with VUR and BBD while on antibiotic prophylaxis, as well as lower rates of spontaneous resolution of VUR and lower cure rates following endoscopic treatment.

Several studies have shown resolution of VUR after treatment for BBD, which underscores the important correlation between the treatment of BBD and higher success rates of surgical VUR treatments, as well as medical therapy, biofeedback, and behavioral treatment [23–26].

Circumcision can also be considered as a conservative approach, as this procedure has been shown to be effective in reducing the risk of infection in normal children. Circumcision decreases colonization of periurethral bacterial pathogenic flora, which is subsequently replaced by non-uropathogenic species [27, 28].

Two systematic reviews have been published that have shown the benefits of circumcision with regard to UTI. Singh-Grewal concluded that circumcision should be considered in boys with a past history of recurrent UTI or high-grade (grade III and above) vesicoureteral reflux [29], while Morris found a greater benefit in infants (relative risk [RR] of UTI, 9.91 in uncircumcised boys younger than 1 year), with a global number needed to treat of 4.29 [30•].

Both the American Urological Association (AUA) and EAU guidelines in VUR recommend circumcision in infants to prevent UTIs. Parents should be made aware of this association in order to permit informed decision-making [6, 31••].

Lastly, with regard to conservative methodologies, cranberries have been widely used for several decades for the prevention and treatment of urinary tract infections. A recent systematic review, however, concluded that cranberry products compared to placebo provided no benefit in most population groups, including children, and that cranberry juice cannot currently be recommended for the prevention of UTIs [32].

To summarize, in view of the high rates of spontaneous resolution of VUR in the first year of life, a conservative approach is recommend for children under one year of age, and "traditional" bladder surgery should be avoided during the first 12 months of life.

Endoscopic Approach

Since its first clinical application in VUR in 1984 by O'Donnell and Puri, endoscopic treatment has gained great popularity among pediatric urologists, particularly after its approval by the U.S. Food and Drug Administration (FDA) in 2001. While numerous bulking agents have been used for endoscopic treatment (Table 1), only dextranomer/hyaluronic acid copolymer (Dx/HA) has been approved by the FDA for the treatment of VUR [33].

Several endoscopic techniques have been described for treating VUR. The first was the subureteric Teflon injection (STING) by Puri and O'Donnell in 1984 [34], and this was supplanted by the hydrodistention-implantation technique (HIT) by Kirsch et al. in 2004 [35], which has recently been modified to include two intraluminal ureteric tunnel injections (double HIT) [36]. However, studies have found no differences in ureter or patient resolution among endoscopic injection techniques [37].

The success rates for endoscopic treatment described in one meta-analysis [38•] were:

- Success rate following one treatment was 78.5 % for grades I and II reflux,, 72 % for grade III, 63 % for grade IV, and 51 % for grade V.
- The second treatment following previous failure had a success rate of 68 %.
- The third treatment was successful in 34 % of cases.
- The aggregate success rate with one or more injections was 85 %.

Another recently published review of the literature reported an overall success rate of nearly 84 %, suggesting that matching the right patient with the right bulking agent may increase the chance of success [39].

Indications for injection of bulking agents have changed over time, and have included other conditions. A literature review comparing the probability of success for duplex versus single systems showed similar results (64 % vs. 68 %) between the two [40]. was Another study found considerably lower rates for neurogenic bladders (62 %) compared with normal bladders (74 %) [38•].

Endoscopic treatment of VUR has seen rapid growth, and has replaced some aspects of antibiotic treatment and open surgery, due primarily to the fact that it is minimally invasive,

Table 1 Bulking agents used for endoscopic treatment

Polytetrafluoroethylene (PTFE; Teflon, DuPont Co., Wilmington, DE, USA)
Bovine collagen
Polyacrylate-polyalcohol copolymer (Vantris, Promedon, Cordoba, Argentina)
Polydimethylsiloxane (Macroplastique, Uroplasty Inc., Geleen, The Netherlands)
Calcium hydroxyapatite (Coaptite, BioForm Medical Inc., Franksville, WI, USA)
Dextranomer/hyaluronic acid (Dx/HA; Deflux, Oceana Therapeutics Inc., Edison, NJ, USA)

quick, painless, and performed on an outpatient basis. Although its efficacy in high-grade VUR has been inconsistent, endoscopic treatment is currently considered a valuable treatment option and a viable alternative to long-term antibiotic prophylaxis.

Endoscopic treatment is well-established as a safe procedure, with very low reported complication rates . Large series have revealed obstruction rates of 0.7–0,1 % [41, 42], although a recent series reported an obstruction rate of 1.5–5 % [43–45]. Obstructions can develop immediately, several months later, or as many as five years after injection [46], and can be managed with ureteral stents, nephrostomy, balloon dilatation, and even ureteric neo-implantation. And while the associated risk is low and few cases have been reported, long-term follow-up is highly recommended.

Consideration should also be given to certain anatomical variants that many authors have attributed to a predisposition to obstruction after endoscopic treatment. These include dysfunctional voiding, myelomeningocele with neurogenic bladder, ureteral duplications, transplanted kidneys, and dilated obstructive ureters in the absence of diagnosis [42].

Last but not least is parental preference. Capozza and Caione reported that 80 % of parents preferred endoscopic treatment. In a study of newly diagnosed patients by Krill et al. parental preference for initial treatment was 36 % for antibiotic prophylaxis and 26 % for endoscopic surgery; after consultation with the urologist, final treatment choices were antibiotic prophylaxis in 68 % and endoscopic surgery in 18 % [47, 48]. After four years, given persistent VUR, preferences shifted away from antibiotic prophylaxis, and the majority (67 %) preferred the endoscopic approach [48].

Our experience has shown 92 % parent preference for endoscopic treatment, and has also reflected a high degree of parental satisfaction after endoscopic treatment (86 %).

In conclusion, endoscopic treatment is currently the method of choice among most urologists and parents for children over the age of one year, where the only accepted contraindications are obstructive refluxing megaureter, bladder diverticulum greater than 10–15 mm, and in some cases, high-grade VUR with poor kidney function (<40 %).

Surgical Approach

While various intravesical and extravesical techniques have been described for the surgical correction of VUR, all are based upon the basic principle of lengthening the intramural part of the ureter by submucosal implantation of the ureter to create a 4–5:1 ratio of submucosal tunnel length to ureteral width. The two most widely used techniques are the intravesical Cohen cross-trigonal reimplantation and the extravesical Lich-Gregoir procedures.

Success rates currently range between 95 % and 98 % for both open ureteral reimplantation procedures [49]. The extravesical ureteral reimplantation technique (Lich, 1961, Gregoir 1964) has been associated with reduced incidence of hematuria, bladder spasms, and convalescence [50], and also allows for reimplantation of massively dilated megaureters without tailoring [51].

Some groups have cautioned against simultaneous bilateral extravesical repair, as this has been associated with transient urinary retention requiring bladder catheter placement. However, with improvements of the technique studies have shown a minimal percentage of urinary retention, and use of the procedure has been reported in ambulatory surgery [50, 52–54].

The laparoscopic approach to reflux repair was first described 20 years ago [54]. Both intravesical and extravesical techniques have been utilized, with the latter being more common. The advantages include shorter hospital stay, decreased postoperative pain and analgesic requirement, better cosmesis, and faster recovery, especially in older children Laparoscopic ureteral reimplantation and robotic-assisted surgery have similar efficacy as open procedures, with success rates of 88–100 %, but do have technical challenges and longer operative times [55, 56].

While further studies and greater surgical experience are needed to analyze the cost/benefit profiles of both of these approaches over conventional open techniques, the technical advances and improved results achieved using minimally invasive techniques are gradually generating more enthusiasm. Indeed, there is a trend toward reducing the volume of surgical repair procedures for VUR. This may be explained by the increase in endoscopically treated patients as well as the movement toward a less invasive approach of watchful waiting, along with reinforcement in managing BBD. The "traditional" surgical approach, however, is still reserved for cases such as obstructive/refluxing megaureter, bladder diverticulum greater than 10–15 mm, high-grade VUR where kidney function is affected (<40 %), and in cases where endoscopic treatment has failed.

Conclusions

Management strategies and clinical treatment of VUR has evolved over the past three decades, and is still in flux. Early treatments of VUR almost always involved surgical correction, while today there are treatment paradigms for the disorder that do not even utilize antibiotic prophylaxis. The overriding theme in all treatment modalities, however, is that "it is all about the kidney."

VUR is a fascinating disease, and should be managed by pediatric urologists along with pediatric nephrologists. It is also important to bear in mind that there are myriad factors in play that influence the treatment and outcome of each individual patient with VUR.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Pedro-Jose Lopez, Dr. Soledad Celis, Dr. Francisco Reed, and Dr. Ricardo Zubieta each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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