11. Vesico-ureteric reflux

Anastasia Dimopoulou¹ and George Sakellaris²

¹SpR in Pediatric Surgery, Department of Pediatric Surgery, University Hospital, Heraklio, Greece
²Consultant Pediatric Surgeon, Department of Pediatric Surgery, University Hospital of Heraklion Greece

Definition incidence

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder into the ureter. A normally functioning ureteral vesical junction (UVJ) allows for the smooth expulsion of urine from the ureter into the bladder without regurgitation of urine back up the ureter, either during bladder filling or upon voiding. If this valvular mechanism fails, from whatever etiology, urine flowing backward from the bladder into the ureter and/or kidney. The competence of the UVJ valvular mechanism depends on the length of the submucosal tunnel, which tends to increase with age and is the basis for expectant management of reflux (1).

Vesicoureteral reflux is considered to be the most common urological anomaly in children. It occurs in approximately 1-3% of children and is associated with 7-17% of children diagnosed with end-stage renal disease worldwide (2, 3, 4). An estimated 30-40% of children under the age of 5 years who develop a urinary tract infection (UTI) have VUR (2, 4).

Treatment of VUR is aimed at preventing the sequelae of pyelonephritis, renal parenchymal injury, hypertension and chronic renal insufficiency. A period
of 30-40 years can pass between the first renal-scarring pyelonephritis and the development of hypertension or end-stage renal disease (2).

**Classification-etiolo**

Vesicoureteral reflux can be categorized as either primary or secondary. Primary VUR in children is frequently attributed to an abnormally congenitally short intravesical tunnel at the UVJ. A short submucosal tunnel permits reflux as the section of ureter in the bladder wall is not long enough to be compressed by rising pressure in the filling bladder. The reflux begins at the fifth month of life in utero when urine production starts. Secondary VUR occurs when reflux is induced by abnormally increased bladder pressures, such as those seen with urethral obstruction (posterior urethra valves) or neurogenic bladder dysfunction (1, 2). The severity of VUR has been most commonly reported using the classification of the International Reflux Study (5). This classification defines grade I as reflux into the ureter only, and grade II as reflux into a non-dilated pyelocalyceal system. Grade III VUR demonstration dilation of the collecting system. Grade IV involves more extensive dilation with blunting of the calyces and tortuosity of the ureter, and grade V VUR is associated with massive dilation of collecting system and severe turtuosity of the ureter.

In general, the severity of grade of VUR has been used as the main factor to determine the likelihood of spontaneous reflux resolution and risk of renal injury. Higher grades of reflux are associated with decreased resolution rates and increased prevalence of renal scars (6). In addition to grade, other factors have been shown to be predictive of reflux resolution and the risk of renal injury. These factors include age, sex, laterality, bladder volume and pressure at the onset of reflux, presence of renal scars, presence of voiding dysfunction and a history of urinary tract infection (2, 7).

**Risk of VUR**

There are four warning signs for the presence of VUR:

First, prenatal suspicion for fetal dilation of the ureter, pelvis, or both, and diagnosis of abnormal findings pontentially associated with contralateral VUR, such as multicystic dysplasia and renal agenesis (8).

Second, familial VUR, because the chance of a sibling of a child with VUR also having reflux is about 25% and the offspring of affected individuals have a 27-51% increased risk of having reflux (2,9).

Third, bladder dysfunction, which is related to VUR in children presenting with UTI and so-called daytime-voiding syndrome (as well as constipation and soiling) (10).
Vesico-ureteric reflux

Forth, UTIs, a single pyelonephritis or recurrent cystitis (most caused by Escherichia coli in infants). Urinary tract infections are the most important clinical marker of VUR (3).

VUR complications

One third of patients with VUR have renal scars. The presence of scars implies regions of renal damage, and increases the risk of long-term complications, such as renal scarring, hypertension, chronic kidney disease or end-stage renal disease. In the newborn with VUR, however, scars associated with high-grade reflux have been detected before the occurrence of infection. These congenital scars are thought to be regions of focal dysplasia or hypoplasia resulting from abnormal nephrogenesis as opposed to damaged normal tissue following pyelonephritis. Children with pre-existing renal scars are more likely to develop additional scars. Children with severe bilateral renal scars are significantly more likely to develop proteinuria, chronic renal insufficiency and failure than those with unilateral scars or unscarred kidneys (11).

Also, children with VUR and concomitant UTIs are at an increased risk of developing renal scarring compared to children without VUR suffering with UTIs and has been demonstrated that there is a direct correlation between increased prevalence of renal scarring and higher grades of VUR (12).

Diagnosis

The only tests that routinely and reliably detect reflux are voiding cystourethrography (VCUG) and nuclear cystography, because they show reflux of urine from the bladder into the ureters and kidneys either upon filling or voiding. They also assist in assessing the bladder outlet for the possibility of intravesical obstruction. An initial VCUG entails bladder catheterization and ionizing radiation and provides better anatomic details regarding reflux including the presence or absence of periureteral diverticuly, ureteral duplication and abnormality of the bladder, such as trabeculations or urethral obstruction. The VCUG also allows more precise grading of reflux. Despite concern regarding exposure of the pelvic organs to ionizing radiation during cystography in children, there is little or no reported evidence suggesting any future effect on gonadal function or an increased risk of pelvic malignancies (2).

Nuclear cystography detects all grades of VUR. At the university of Iowa, bladder pressures are routinely monitored through a dual-lumen catheter during the filling phase of a nuclear cystogram providing a nuclear
cystometrogram one; however, this technique is not widely used (13). This technique permits the measurement of the intravesical pressure at the onset of reflux, which was demonstrated as a predictor of spontaneous VUR resolution independent of the grade of VUR.

Catheterization can be a traumatic experience for a young child that often disturbs the parents and carries iatrogenic risks, although it reduces radiation exposure. Efforts to decrease the traumatic nature of the procedure include the use of lubricants containing local anaesthetics and conscious sedation. Typically, cystography is repeated on a yearly basis; however it has been suggested that, for children in whom VUR is less likely to resolve, the interval between cystograms should be longer in order to reduce exposure to radiation, the number of traumatic studies and the associated cost (2).

Dimercaptosuccinic acid scintigraphy (DMSA) and Mercaptoacetyltriglycine imaging (MAG3) are used to access renal scars associated with VUR. DMSA scintigraphy has been found to be a more sensitive study than intravenous pyelography (IVP) for the detection of reflux nephrography. In addition, the scan can detect changes of acute pyelonephritis with greater sensitivity and specificity than CT, MRI, or ultrasonography. MAG3 has also been used for renal imaging and has an improved capability in the detection of renal scarring compared to IVP. The DMSA scan is considered by many as the most sensitive test for detection of renal scars. The advantages of MAG3 imaging compared to DMSA scintigraphy include reduced radiation exposure, lower cost, and shorter time requirements, as well as improved visualization of the collecting system, which might improves specificity compared to DMSA scintigraphy in children with marked dilation of the collecting system (14). The association of renal scars with higher grades of reflux and risk for subsequent scars, as well as decreased resolution of VUR led some investigators to conclude that the standard initial evaluation of a child with a febrile UTI should begin with a renal scan rather than VCUG. Only in those children with an abnormal scan should VCUG should be performed.

Vesicoureteral reflux is unlikely to be a single nosological entity and we can distinguish two main clinical types diagnosed prenatally or postnatally (after a UTI). In children with a prenatal suspicion of VUR (mainly boys), as much as 30% already have renal lesions on a radionuclide scan, even though they have never had a UTI. In Vesicoureteral reflux diagnosed after recurrent UTIs (mainly in girls), the kidney damage is acquired, although with good health-care, significant acquired renal damage is rare in children with non-obstructive VUR (15, 16). ACE gene polymorphism might be associated with a higher incidence of congenital hypodysplastic kidneys and may be a genetic susceptibility factor contributing to scar formation in VUR (17).
Management of VUR

Prevention of urinary tract infections

The primary reason for the use of antibiotic prophylaxis has been to reduce the rate of UTIs in children with VUR and therefore bring about a reduction in renal scarring (18). The administration of prophylactic antibiotics is almost universal in children with VUR, although there is little evidence-based information. Antibiotic prophylaxis is indicated for the first year for any grade of VUR. Vesicoureteral reflux can resolve during long-term antibiotic prophylaxis, although some call this spontaneous resolution. Persistence is more frequent in high-grade VUR, in bilateral VUR, in children with pre-existing renal damage (especially in grade V or bilateral grade IV), and when the ureter is dilated (3).

The traditional paradigm of aggressive management with surgical intervention for grade I-IV VUR has been called into question in light of compelling data, demonstrating that surgical correction is not significantly better than antibiotic prophylaxis in preventing long-term complications, such as renal scarring, hypertension, CKD or end-stage renal disease, as well as the diminished risk of renal scarring following breakthrough UTI.

Long-term antibiotic prophylaxis does not fully prevent UTI or scarring, and antibiotic-related adverse events are well known. Antibiotic must be used cautiously in children with underlying VUR, with associated congenital (dysplasia) and acquired renal damage due to infection. Antibiotic-induced nephrotoxicity must be avoided, especially in newborn babies and infants, whose kidneys are immature (19). Also, one of the biggest concerns of the widespread use of antibiotics is the growing prevalence of antibiotic-resistant pathogens. Studies published worldwide have shown increasing rates of resistance of pathogens involved in UTI, such as *Escherichia coli* to commonly used antibiotics, such as trimethoprim, sulfamethazole, ampicillin and ciprofloxacin (20).

Endoscopic treatment of VUR

Since the introduction of STING (subureteric Teflon injection) two decades ago, and since the approval by the food and Drug Administration (FDA) of the dextranomer/hyaluronic acid (DX/HA) copolymer (Deflux) for the treatment of VUR, over the last years, endoscopic management has emerged as a first-line treatment for all grades of reflux in some centers. The dextranomer particle size is larger than that of polytetrafluoroethylene particles, which should prevent the complication of lymphatic migration previously demonstrated with polytetrafluoroethylene (21). Endoscopic correction of VUR offers a minimal invasive, outpatient procedure with a low risk of complications. Complications following this procedure are infrequent
and relate mainly to obstruction of the UVJ and the development of new contralateral reflux following treatment of unilateral VUR (22).

DX/HA has been proven to be effective in complex cases, that were previously considered as contraindications for endoscopic treatment. Children with voiding dysfunction, duplex ureters, high-grade VUR, paraureteral diverticuli and other complex anomalies should be offered DX/HA as a potential treatment. Additionally, it should be strongly considered for those children with persistent VUR following open ureteral reimplantation. It is recommended that open reimplantation should be reserved for those children with ectopic ureters, megaureters that require tapering or secondary grade V VUR, and those who have failed two endoscopic injections (23, 24).

The mechanism for DX/HA failure is unclear and may be multifactorial. It has been demonstrated that most failures are due to technical errors that can be avoided intraoperatively. The technique for injection (intra-ureteric, submucosal) and a means of determining the endpoint of injection may be the most important of these factors. Postoperatively, failure may result from displacement (most often caudally), disruption (bleb loss of material through a mucosal breach) and dissolution (decrease in percentage of the volume retained post injection measured sonographically). While technical failure can be avoided, the latter three mechanisms may be inescapable (22).

The treatment of failed DX/HA injection has evoked much debate. In many of the initial studies utilizing endoscopic injection of DX/HA, a high percentage of patients underwent multiple treatments (up to three) in order to achieve success. However, repeat injections are costly and initially were less successful than initial injection. Based on the current evidence it appears that open surgical treatment should be strongly considered for those who have had a second DX/HA failure (22, 25).

**Ureteral re-implantation**

The surgical treatment of VUR has evolved over the past 50 years. A lower abdominal transverse incision is now typically used, leaving a small scar in the skin crease that frequently becomes inconspicuous. While multiple different techniques for ureteral re-implantation have been performed, most fall under one of two main categories: intravesical surgery, in which the bladder is opened and the ureters are dissected intravesically and extravesical re-implantation, where the ureters are dissected away from the bladder wall without opening the bladder and are left attached to the bladder mucosa and re-implanted under flaps of bladder muscle. Improvement in analgesia, surgical techniques and the understanding that children undergoing ureteral reimplantation for primary VUR rarely need ureteral stents or prolonged
catheterization has reduced the length of hospital stay and decreased morbidity associated with the procedure (26,27). Recent studies have documented the use of laparoscopic and robotic ureteroneocystostomy in attempts to further reduce perioperative morbidity. Results of multiple series document success rates with open ureteral re-implantation of 95%, and close to 100% for lower grades of reflux (28). The surgical procedures, however, carry the risks associated with anesthesia and potential complications, including ureteral obstruction, persistent reflux, infection and bleeding.

References