ABSTRACT: Vesicoureteral reflux is the retrograde passage of urine from the bladder into the ureter and kidneys during voiding. This commonly-treated entity is frequently managed by different disciplines that include Urology, Nephrology and Pediatrics. The pathophysiology of vesicoureteral reflux seems to be related to the valve mechanism of the ureterovesical junction. Abnormal location of the ureteral orifice is implicated in the short ureteral tunnel which in turn compromised the flap-valve mechanism. The grading of reflux is important since management depends on the severity according to a five grade system. At present, medical management using antibiotic prophylaxis has become well established for managing patients with low-grade reflux (grades I-III). Moderate reflux (grade III-IV) could be managed by surgery in case of breakthrough infections. Recommendations regarding the diagnosis and medical management remain complex and are continuously evolving. More frequently than not, treating pediatricians and urologists would have to make decisions by individualizing each patient and considering the likelihood that patient’s reflux will resolve.

BACKGROUND

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the urinary bladder to the upper tracts (ureter and kidneys). It is a commonly-treated and diagnosed condition; its scope covers multiple disciplines that include Urology, Nephrology and Pediatrics. Recommendations regarding the diagnosis, medical and surgical treatment of this complex condition and its associated potential complications are evolving. This manuscript may serve as a reference for the general practitioner and provide an introduction to a complex urologic topic.

INCIDENCE

VUR is characteristically a disease diagnosed in the pediatric population. Its overall incidence has been estimated to be between 1% and 10%, but is higher among younger patients. Among patients presenting with a urinary tract infection (UTI) this figure increases to 50%, highlighting the importance of screening in this population [1]. With the increased use of antenatal sonography, VUR is now diagnosed frequently among patients who initially present with prenatal hydronephrosis. In this subgroup, VUR can be expected to be the etiology in 12% to 37% of cases [2].

Gender differences may help stratify patients based on differences in the natural history of this condition. Males comprise 80% of prenatal VUR cases. These cases often are characterized by a higher grade of reflux and a higher comparative spontaneous resolution rate [3]. The majority of VUR diagnosed after presentation with a UTI occurs in females, with a yearly resolution rate of about 15%.

VUR is believed to be an autosomal dominant condition with partial penetrance, an important finding that underscores the clinician’s responsibility in familial screening. This mode of transmission explains why 66% of patients born to parents with VUR will have the condition. Among siblings, one third will have VUR, the majority of these cases being asymptomatic (no history of UTI) and less likely than index cases to have renal scarring.

PATHOPHYSIOLOGY

Reflux is related to deficiencies in the ureterovesical junction (UVJ) “flap-valve” mechanism [4]. This valve is dependent upon passive and active components that help prevent retrograde flow of urine. Passive elements include an adequate ratio of ureteral submucosal tunnel length to ureteral diameter (usually 4-5:1) and adequate bladder muscle wall backing. Active components include bladder distensibility and the trigone/bladder neck smooth muscle complex that pulls the ureteral orifice infero-medially during voiding. Defects in this mechanism may be primary or secondary to bladder or urethral pathology (see below).

Reflux is related to abnormal location of the ureteral orifice. Abnormal origination of the ureteral bud may ultimately result in a ureter that terminates too laterally and cephalad, which results in decreased length of the intramural tunnel, thus compromising the flap-valve mechanism.

Secondary VUR is seen among patients with bladder and urethral abnormalities. These include posterior urethral valves and neurogenic bladder. Dysfunctional voiding patterns seen in young boys and girls, and character-
ized by the voluntary contraction of the external urethral sphincter before or during bladder contractions, is also commonly associated with secondary reflux. These conditions share an increase in bladder pressures that, over an extended period of time, can predispose to VUR.

SIGNS AND SYMPTOMS

A complete physical examination initially performed on patients referred for evaluation of a febrile UTI or hydronephrosis is essential. VUR is associated with a multitude of genetic and developmental anomalies (i.e. Down’s syndrome) that encompass all organ systems. Of particular importance is examination of the lower back for signs of occult spinal dysraphism such as hair patch, dimples or aberrant gluteal clefts. Palpating the abdominal quadrants and flanks may reveal hydronephrotic kidneys. An over-distended bladder may be palpable on suprapubic palpation. Examination of the external genitalia is also imperative. A neurological exam focused on evaluation of the sacral spinal cord can quickly be performed by assessing sensation and motor strength in the lower extremities as well as deep tendon reflexes.

EVALUATION

The diagnostic workup of the patient referred for evaluation of a UTI begins with a sonographic evaluation of the kidneys and bladder. A child with prenatal hydronephrosis should be re-evaluated with a postnatal ultrasound. This study effectively evaluates the upper urinary tract in children referred for a febrile UTI. While a normal ultrasound is reassuring, it is important to remember that ultrasound misses 75% of reflux. Bladder assessment will screen for abnormal post-void residuals and abnormally thickened bladder walls. In addition, serial ultrasound examinations of the kidneys can demonstrate asymmetry of renal size and presence of parenchymal abnormalities and scars secondary to reflux nephropathy.

Evaluation of the lower urinary tract is accomplished through a contrast voiding cystourethrogram (VCUG), a dynamic study that evaluates the urethra and bladder while the patient voids. It provides a grade of the severity of the VUR (Fig. 1); demonstrates other abnormalities such as posterior urethral valves and bladder diverticuli and may suggest the presence of abnormal voiding patterns and bladder capacity (Fig. 2). At this time, VCUG remains the study of choice for lower urinary tract evaluation.

A radionuclear cystogram (RNC) is an alternative to the conventional cystogram (VCUG), although it provides minimal anatomic detail (Fig. 3). In addition to minimizing radiation exposure, it affords prolonged exposure under the gamma counter and this may enhance sensitivity, especially if the reflux is intermittent. RNC has become the screening study of choice due to its high sensitivity and low radiation exposure; it is also used for serial assessment of patients with VUR on prophylactic
antibiotics and is the postoperative study of choice. Renal scintigraphy using the various radio-nucleotide tracers has become integral in this diagnostic process because of its role in assessing differential renal function and presence of renal scars due to reflux. Technetium99-labeled DMSA is the best study to detect pyelonephritis and resultant renal scars (Fig. 4). Uptake is directly proportional to proximal renal tubular mass. The precise clinical indications for this study are somewhat controversial but it is helpful in cases when the initial renal ultrasound is abnormal or when there has been a history of febrile UTI. We use the DMSA renal scan as a baseline study in all children with VUR grade III or higher to assess renal parenchymal integrity.

**COMPLICATIONS RELATED TO REFLUX**

The interplay between reflux, renal development and infection is an intriguing and controversial topic. Management decisions are based on assessment of the potential effect of reflux on the kidneys. Additionally, VUR associated with chronic infection may ultimately lead to severe renal scarring, hypertension and renal failure, particularly in very young children in whom UTI may go unrecognized due to inability to describe symptoms. Clinicians must recognize that VUR does not increase the risk of urinary infection. Rather, VUR acts to convert lower urinary infection (cystitis) to upper tract infection which jeopardizes future kidney function by exposing the kidney to the deleterious effects of inflammation and subsequent renal scar formation.

Reflux damages kidneys through mechanisms thought related to the transmission of high pressure bladder urine to the renal parenchyma and by allowing infected urine to gain easy access to the kidneys during episodes of cystitis. The deleterious effect of infected urine and its association with the formation of new renal scars and blunting of renal growth have been well established [5]. The demonstration that reflux in the absence of infection or high bladder pressure is harmless to the kidneys has been the basis for medically managing the majority of patients. The developing kidney is more susceptible to the effects of reflux than the fully developed one [6]. Most urologists believe that reflux nephropathy can occur up to age 10, but the majority takes place before the patient is 5 years old.

**MANAGEMENT**

Decisions regarding the management of patients with VUR should be based on the natural history of the condition (Table I), patient age and severity of VUR and the presence of other anatomical abnormalities. Based on the finding that prevention of urinary infection in patients with reflux prevents renal injury and that reflux often resolves spontaneously, medical management with antibiotic prophylaxis has become a well established method to manage patients with low-grade reflux (grades I-III) [5]. Young patients (< 1 year old) with grades IV and V may also qualify for conservative management initially. Medically-managed patients are observed and reassessed at annual intervals for changes in the grade of the reflux, occurrence of more episodes of febrile UTI, appropriate renal growth and renal scars on ultrasound. Decisions regarding a patient should be individualized; algorithms cannot be applied uniformly. Additionally, the practitioner should assess the probable likelihood that a patient’s reflux will resolve. Although this is not absolute, factors such as initial low grade, progressive downgrading of the reflux on follow-up and absence of congenital bladder and urethral anomalies are all favorable indicators that the reflux will resolve.

**TABLE I**

<table>
<thead>
<tr>
<th>Grade of Reflux</th>
<th>Rate of spontaneous resolution (5 years)</th>
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<tbody>
<tr>
<td>Grade I</td>
<td>82-90 %</td>
</tr>
<tr>
<td>Grade II</td>
<td>63-80 %</td>
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<tr>
<td>Grade III</td>
<td>41 %</td>
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<tr>
<td>Grade IV</td>
<td>9-30 %</td>
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<tr>
<td>Grade V</td>
<td>12 %</td>
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</tbody>
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**MEDICAL MANAGEMENT**

The choice of antibiotic agent is based on the pharmacology of these agents and patient age. Infants younger than 6 weeks of age are placed on amoxicillin, which is well-tolerated and easily administered in a liquid form.
Its drawbacks include induction of fecal resistance and suboptimal bacterial coverage spectrum. With biliary system maturation occurring at 6 weeks of age, patients can be placed on sulfa-based antibiotics (trimethoprim-sulfamethoxazole), which cover most uro-pathogens [7]. Nitrofurantoin is another acceptable option in prophylaxis for patients older than 2 months. Patients are placed on half-therapeutic doses, usually administered before bedtime to insure therapeutic levels during the most susceptible period [7].

SURGICAL MANAGEMENT

Surgical intervention for VUR is indicated in situations when medical management has failed to prevent reflux nephropathy, evident by new renal scars or slowed renal growth; if patients are non-compliant with management or if the reflux is associated with congenital bladder anomalies such as bladder diverticuli that make it unlikely for the VUR to resolve spontaneously. In addition, female patients who have reached puberty without reflux resolution are eligible for surgical correction, particularly if they present with pyelonephritis.

Standard surgical correction of VUR has been highly successful, with rates of cure ranging from 92-98%. The various methods of ureteral re-implantation attempt to reconstruct a normal ratio of ureteral submucosal tunnel length to ureteral diameter (Fig. 5) [8]. They are classified broadly according to the anatomical approach to the ureter: extravesical, intravesical or combined. Generally speaking, unilateral reimplantation can be done extravesically to avoid opening the bladder and reduce postoperative problems related to hematuria and bladder spasms. Bilateral ureteral reimplantation is performed through an intravesical approach. Bilateral extravesical ureteral reimplantation has been known to cause transient urinary retention after surgery and is preferably avoided. Patients are maintained on antibiotic prophylaxis for 3 months after discharge until follow-up cystogram demonstrates reflux resolution, and an ultrasound demonstrates normal upper tracts.

Recently, attempts have been made to correct VUR endoscopically. A cystoscope is used to access the bladder and a needle placed directly beneath the refluxing ureter. A number of bulking agents can be injected in a submucosal location beneath the ureter, providing the backing necessary for the flap-valve mechanism. Procedures utilizing this technique have a 70% one-time success rate [9]. Unfortunately, there are few long-term studies demonstrating durability of the antireflux effect. This is particularly important since many of these agents are biodegradable and may persist in their intended location for short periods. Additionally, given the high long-term success rate with open ureteral re-implantation and the short-term experience with the endoscopic technique, the optimal role for endoscopic repair is yet to be defined. We recommend considering endoscopic treatment for older patients (who are often involved in the decision-making), in salvage of failed reimplantation and in children with anatomic complexity such as those with the extrophy and epispadias complex.

To summarize our surgical management philosophy...
of the patient with VUR, patients are divided based on the grade of their reflux. Grade I reflux is uniformly managed conservatively and rarely requires surgery. Grade II VUR is nonoperative unless the patient has breakthrough UTI while on prophylactic antibiotics. These low-grade VUR cases (grade I-II) have a high likelihood to resolve and should be so managed.

Grade III (moderate) VUR is often the most difficult to manage. In our experience, these patients are followed until age 7-8 years expectantly on antibiotic prophylaxis if necessary. As they approach puberty, we recommend surgical correction because post-pubertal anti-reflux surgery, if required, is made more difficult by the bladder’s natural descent into the deep pelvis and resultant ureteral inaccessibility. Endoscopic technique may have a future role in these situations.

Adolescent patients with VUR (> 12 years old) presenting late are a controversial group. In our opinion, female patients should undergo anti-reflux surgery to protect them from pyelonephritis and pregnancy-related complications. Male patients can be followed conservatively or offered endoscopic treatment.

CONCLUSION

Recent movement among medical specialists has been to downplay the importance of reflux and its complications. We believe this low rate of complications related to VUR to be a byproduct of the success of our aggressive medical and surgical management of the condition and should not be mistaken for a benign course of this condition. VUR is a complex condition that must be managed with knowledge of its ramifications. The clinician should recognize that its management is patient-based and, with careful follow-up, renal function can be preserved.

REFERENCES