Vesicoureteral Reflux

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Since vesicoureteral reflux (VUR) is usually only apparent following pyelonephritis, its true incidence is difficult to assess. Those at higher risk for urinary tract infection (UTI)—females and uncircumcised males—will more often be screened and diagnosed with VUR. Anywhere from 30% to 70% of children who present with UTI will be found to have VUR. Caucasians are at higher risk for VUR compared to those of African descent. The natural history of reflux is spontaneous resolution over time so VUR is more common in younger children, particularly in those less than 1 year old.

Embryology

During normal development the ureter, which forms from the ureteral bud, meets and becomes incorporated with the urogenital sinus, the future bladder trigone. This incorporation results in an intramural portion of the ureter that travels a short distance within the detrusor muscle. The intramural ureter acts as a valve mechanism as it is compressed during bladder filling. Primary or congenital VUR occurs if budding occurs too early, resulting in lateral displacement of the ureteral orifice and shortening of the length of intramural ureter to yield an incompetent valve mechanism. An abnormality in the ureteral bud can also affect the interaction with metanephric blastema and development of the future kidney, leading to the renal dysplasia that can accompany severe VUR. Alternatively, secondary VUR occurs due to a valve mechanism overwhelmed by altered bladder dynamics. This is why VUR often coexists with conditions of high-pressure voiding, which may structurally or functionally impair the ureterovesical junction mechanism. Posterior urethral valves, ureterocele causing bladder outlet obstruction, acquired voiding dysfunction, or neurogenic bladder should be considered when VUR is diagnosed since treatment of these may correct the VUR.

Imaging

VUR is diagnosed radiographically by cystography. The most common modality is the voiding cystourethrogram (VCUG) which is performed by direct injection of iodinated contrast into the bladder and observation for reflux of urine up the ureters to the pelvicalyceal system. Alternatively, a radionuclide cystogram can be performed, which carries 1% the radiation exposure but lacks the anatomic definition afforded by the VCUG. There are 5 grades of VUR and the severity depends on the degree of blunting of the calyces and dilation of ureter (Table 100.1). It should be pointed out that this system is not always adequate in capturing the anatomy that is observed (there is no grade for a dilated ureter without calyceal blunting); thus, it is helpful to personally review the images. Other aspects of the VCUG to note are when reflux occurs (early filling, late filling, during voiding), the bladder contour (smooth or trabeculated), bladder neck anatomy, the presence of diverticula, ureterocele, and the patency of the male urethra. The bladder should be filled to capacity: in <1 year old, capacity (mL) = 38 + (2.5 × age in months); in >1 year old, capacity = (age in years + 2) × 30 and more than 1 cycle should be performed to increase the sensitivity of

Table 100.1 International classification of vesicoureteral reflux

Grade	Description
1	Reflux into a nondilated ureter
2	Reflux into the pelvis and calyces without dilation
3	Mild to moderate dilation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices
4	Moderate ureteral tortuosity and dilation of the pelvis and calyces
5	Gross dilation of the ureter, pelvis, and calyces; loss of papillary impressions; and ureteral tortuosity

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detection. If the patient has an active infection, then the study should be delayed for at least 1 week because of the risk of transmitting bacteria and potentiating pyelonephritis.

The ^{99m}Tc-labeled dimercaptosuccinic acid (DMSA) renal scan is the gold-standard imaging technique of functioning renal tissue by which relative renal function can be assessed. The presence of photopenic cortical defects indicates the absence of normal tissue due to renal dysplasia or scar. There is direct correlation between the grade of VUR and prevalence of renal abnormalities. Children with VUR have nearly 3 times higher risk of acquiring DMSA abnormalities compared to those without VUR.

Natural History

There is an expected rate of spontaneous VUR resolution as the bladder grows and the valve mechanism is allowed to mature. The likelihood of resolution is inversely correlated with VUR grade and age at VUR diagnosis such that about 80% of grade 1 or 2 VUR, 50% of grade 3 VUR, and up to 25% of grade 4 or 5 or bilateral grade 3 VUR will resolve on its own. Older children are less expected to outgrow their VUR compared to infants and the presence of voiding dysfunction can also delay spontaneous resolution. The traditional period of observation from the time of diagnosis is 5 years, but intervention may be required earlier for breakthrough infections.

Diagnosis

VUR is usually asymptomatic until pyelonephritis occurs; therefore, the circumstances of this event are important to ascertain. One should note the age, gender, fever, and severity of illness (flank pain, nausea/vomiting), and history of previous similar illnesses. If the child is toilet-trained, symptoms indicative of bladder/bowel dysfunction (BBD) should be queried, including urinary frequency and urgency, daytime incontinence, voiding postponement maneuvers (curtsy), and constipation/encopresis. The urinalysis, culture, and method of urine collection (the bagged method carries a risk of contamination and a clean catch or catheterized specimen is preferable although difficult in the uncircumcised male) should be reviewed.

On examination, indicators of renal health include height, weight, and blood pressure. The genitourinary examination should include circumcision status and hygiene. The sacral spine should be examined for signs of spinal dysraphism such as a skin tag, dimple, hair tuft, or skin discoloration.

There remains controversy over when to pursue workup for VUR, but a point of agreement is that renal US should follow a febrile UTI and if abnormal, then a VCUG should be performed.

Medical Management

With the possibility of spontaneous resolution, the mainstay treatment of reflux disease is watchful waiting, which consists of a daily low-dose antibiotic to sterilize the urine and decrease the risk of a UTI while waiting for reflux to resolve. Antibiotic prophylaxis decreases the risk of urinary tract infections by 50%. Under the age of 2 months, amoxicillin or trimethoprim is preferred; over the age of 2 months when they are able to metabolize sulfa, sulfamethoxazole-trimethoprim or nitrofurantoin is administered. Nighttime dosing allows maximum antibiotic concentration in children who are toilet trained. Follow-up is necessary to adjust the dose of antibiotics, assess compliance, and monitor for breakthrough infections, which is an indication to consider surgical intervention. The risks of breakthrough infection, acquiring antibiotic-resistant organisms, and compliance should be discussed with family. BBD in the toilet-trained child is a modifiable factor that delays VUR resolution, decreases the success of endoscopic surgery, and increases the risk of UTI despite being on antibiotics and should therefore be simultaneously addressed. Treatment options include timed voiding, anticholinergic or alpha-blocker pharmacotherapy, and biofeedback pelvic floor therapy.

Surgery

Indications to surgically address reflux include breakthrough infections while on prophylaxis, poor family compliance with medical therapy, or persistent high-grade VUR. Antireflux surgery may be performed either by either open or (robotic-assisted) laparoscopic ureteral reimplantation or endoscopic surgery using dextranomer/hyaluronic acid copolymer (Deflux®) as an injectable agent. Choice of procedure depends on a shared decision with the family who should be informed of the risks and benefits of each, in addition to surgeon experience. Both open and endoscopic surgery have been shown to reduce the risk of recurrent febrile infections.

Open ureteral reimplantation is the gold-standard surgical treatment of VUR. The success of correcting VUR is so high, about 98%, that a post-operative VCUG is often not necessary. The risks of an open ureteral reimplant include contralateral reflux (which may be initially observed because of a chance for spontaneous resolution), obstruction (US should be obtained 6–12 weeks post-operatively), and persistent reflux, in which case a workup for bladder dysfunction should be initiated. The surgical plan includes an initial diagnostic cystoscopy to look for signs of inflammation, duplication, diverticula, and ureterocele.

The option of open reimplant may be further divided into intravesical and extravesical approaches and slight variations

thereof but the underlying principle is the same, which is to construct a submucosal tunnel about 5 times the diameter of the ureter. This achieves firm detrusor support. If the ureter is very large such as is the case of megaureter, then plication or excisional tapering to decrease the ureteral diameter will fulfill this principle. Care should be taken with either approach that the path of the ureter is straight to avoid kinking and obstruction post-operatively.

The advantage of the intravesical approach is the minimal dissection involved once the bladder is accessed, especially if bilateral repair is planned. Popular intravesical techniques include the Cohen cross-trigonal, Politano-Ledbetter, and Glenn-Anderson repairs. All rely on developing the submucosal tunnel inside the bladder leaving the detrusor support intact, delivering the dissected ureters through these new, longer tunnels, and securing the ureters with absorbable suture. The disadvantage of these repairs is the post-operative gross hematuria and bladder discomfort that result from opening the bladder. On the other hand, the extravesical approach (the Lich-Gregoir repair is most popular) avoids the morbidity of open bladder surgery but requires perivesical dissection in the territory of vesical plexus, risking post-operative urinary retention especially with bilateral repair. Here lengthening of the submucosal tunnel is still accomplished but by keeping dissection outside the bladder, the detrusor is incised and detrusor flaps are developed without violating the mucosa. Keeping the bladder distended with saline helps with this dissection. The ureter is placed in the new tunnel and the detrusor flaps are closed over the ureter.

Endoscopic Surgery

The lure of endoscopic surgery to correct VUR is its outpatient basis and avoidance of major surgery. Success is 75–80% at 3 months and is grade-dependent. Long-term success remains unknown and should be discussed with the family as a disadvantage of this approach. Deflux is the most popular injectable substance used in the US. It is formed of cross-linked dextranomer microspheres suspended in a carrier gel of stabilized sodium hyaluronate. The carrier gel is reabsorbed and the dextranomer microspheres become encapsulated by fibroblast migration and collagen ingrowth. Deflux loses 20–25% of its volume after about 3 months.

Endoscopic techniques differ based on the location of the injection. The principle is to add support to the ureterovesical junction with submucosal bulk and mucosal coaptation from the injected substance. The STING (Subureteric Teflon Injection) procedure is the oldest technique described. Injection with the Deflux needle is performed at 6 o'clock in the submucosal plane just distal to the ureteral orifice. One should assess the bulking response after 0.1–0.2 mL is injected and adjust or re-puncture if necessary. The amount of substance injected is indicated when a mound or volcano appearance is achieved and the ureteral orifice acquires a crescent slit shape.

Another endoscopic technique is the double hydrodistention implantation (double HIT) method. Here fluid irrigation is opened widely through the cystoscope which is aimed at the ureteral orifice. The ureteral orifice is distended open and the injection needle is placed at mid ureteral tunnel at 6 o'clock. Enough bulking agent is injected until minimal distention is observed. A second injection with another 1–1.5 mL of Deflux at the distal intramural tunnel is done until no hydrodistention is observed.

Following Deflux injection, a VCUG is optional and should be discussed with the family who may desire to avoid further invasive testing. Alternatively, one could observe for future febrile infections which would necessitate workup with VCUG at that time for recurrent reflux. A renal ultrasound should be done routinely post-operatively to ensure the upper tracts are not disturbed by having increased resistance of the distal ureter.

Associated Anomalies

VUR occurs with several other congenital anomalies such as multicystic dysplastic kidney (MCDK), renal agenesis, VACTERL, CHARGE, and imperforate anus. VUR can occur concomitantly in 9–18% with congenital ureteropelvic junction (UPJ) obstruction. If this occurs, the UPJ obstruction should be fixed first since proximal obstruction poses risk to renal function. In duplicated systems, VUR is usually associated with the lower pole moiety and in these cases, VUR may take longer to resolve spontaneously. The presence of paraureteral diverticula does not appear to affect the rate of VUR resolving but depends on the size and location of the diverticulum; if the ureter enters within the diverticulum, the lack of any muscular support will make the resolution of VUR unlikely.

Editor's Comments

Much like gastroesophageal (GE) reflux, most VUR improves over time, especially in infants and young children, but the likelihood of spontaneous resolution depends on the severity and whether there is underlying bladder dysfunction. Although there are a number of surgical approaches, the gold standard remains ureteral implantation. Minimally invasive approaches, including laparoscopic and robotic techniques, are considered the standard of care at some centers.

VUR occurs with several other congenital anomalies such as multicystic dysplastic kidneys, renal agenesis, VACTERAL syndromes, CHARGE, and imperforate anus. In particular, the frequency with which imperforate anus and VACTERAL-

associated syndromes occur places the pediatric surgeon in a position of early diagnosis, management, and referral. Most often, the pediatric surgeon will encounter secondary VUR, which occurs when the bladder pressure is chronically or persistently elevated such that the ureter cannot empty properly. When the ureter cannot empty properly, it becomes dilated, eventually causing the valve mechanism to fail. This is a common scenario in patients with bladder dysfunction associated with neurogenic bladder and spina bifida but may also be due to anatomic abnormalities such as posterior urethral valves in boys or ureteroceles in girls. The diagnosis should also be considered in patients who present with signs and symptoms of UTI. A VCUG is the definitive test for reflux, but many use renal US as an initial noninvasive screening study. A complete workup is indicated in children under 5 with a documented UTI, in any child with a febrile UTI, girls with recurrent UTI, and boys with a UTI who are not sexually active and have no urologic history. Recurrent ascending infection can cause renal scarring, progressive nephropathy, and eventually even hypertension or renal insufficiency. Thus, children with documented reflux should be treated with low-dose antibiotic prophylaxis, usually with amoxicillin, trimethoprim-sulfamethoxazole, or nitrofurantoin, and monitored with urine cultures every 3 months.

Further Reading

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