

Vesicoureteral Reflux

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Objectives After completing this article, readers should be able to:

1. Describe the diagnostic testing necessary to confirm the suspicion of vesicoureteral reflux (VUR).
2. Discuss the relationship among VUR, urinary tract infection, and renal scarring.
3. Describe the natural history of VUR, especially the propensity for spontaneous resolution.
4. List management protocols for mild reflux.
5. Delineate indications for surgical intervention in children who have VUR.

Introduction

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder upward toward the kidney. Reflux is due to an anatomical or functional abnormality of the normally competent ureterovesical junction. This impairment of the one-way valve mechanism at the ureterovesical junction allows retrograde flow of urine from the bladder into the upper urinary tract (ureters and kidneys). If infected bladder urine refluxes into the upper urinary tract, a renal infection (pyelonephritis) may result. VUR can be diagnosed definitively only by voiding cystography. Voiding cystograms are performed using either iodinated contrast (voiding cystourethrography [VCUG]) or a radiopharmaceutical (voiding nuclear cystography [RNC]) (Fig. 1). The study is performed by placing a catheter through the urethra into the bladder and instilling the testing agent until the bladder is full and the child voids. Unfortunately, at present there is no reliable method of diagnosing VUR without urethral catheterization.

The severity of reflux is judged on the voiding study and described by a grading system. The grading system used most commonly is that of the International Reflux Study Group, which grades reflux from I to V (Fig. 2). Grade I describes the most minimal reflux detected on the voiding study, and grade V is the most severe form of reflux. Grades IV and V often are referred to as “dilating reflux” because the VCUG reveals significant dilatation of the ureter, pelvis, and calyces.

VUR predisposes to recurrent upper urinary tract infections (UTIs), which can lead to renal parenchymal damage. The sequela of recurrent upper UTIs—renal scarring or thinning—is called reflux nephropathy. This condition once was known as chronic atrophic pyelonephritis, and it remains a frequent cause of end-stage renal disease.

The susceptibility to renal damage from a particular infection depends on several factors. A major factor in the predisposition to scarring is the age of the child. Younger children are more susceptible to infection-induced renal parenchymal injury. The likelihood of a neonate or toddler acquiring a scar as a consequence of an attack of pyelonephritis is much greater than if the child is older than 5 or 6 years of age. Another factor predisposing to scarring is delay in treatment; prompt treatment at any age reduces the likelihood of scarring. Renal scarring occurs more frequently if the patient suffers recurring infections or has high-grade reflux.

Management for children who have VUR includes surgery (most often ureteral reimplantation) or medical management with antibiotics. Antibiotics usually are administered continuously at a low dose. UTIs occurring in the child who is on a low or chemoprophylactic dose of antibiotics are referred to as breakthrough infections.

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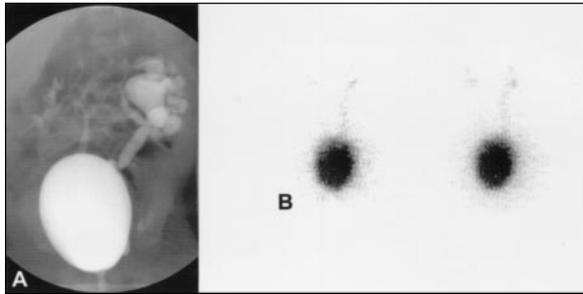


Figure 1. A. A VCUG showing bilateral reflux. On the patient's right side, contrast enters the ureter, moving into the pyelocalyceal system. The lack of significant dilation of the system indicates grade II reflux. On the patient's left side, the pyelocalyceal system shows significant dilation, indicating grade V reflux. B. Images of this radionuclide cystogram are viewed as though looking at the patient's back, making the right ureter visible on the right side and the left ureter on the left side. In the first image, reflux appears up the right ureter into the pelvis, with a very small amount of radiopharmaceutical in the left renal pelvis. In the second image, more reflux is evident on both sides. Detail on a radionuclide cystogram is not as great as on a VCUG. The right-sided reflux on the cystogram probably is grade III, and the left-sided one is grade II.

Epidemiology

The incidence of VUR in the general population is not known, but it is probably less than 1%. Almost invariably children are tested for the possibility of VUR in one of two clinical situations: during the assessment of prenatally diagnosed hydronephrosis or in the evaluation of a UTI. Approximately 10% of patients who are evaluated postnatally for antenatally diagnosed hydronephrosis have VUR. Reflux diagnosed in the evaluation of prenatally diagnosed hydronephrosis often is high grade and occurs more frequently in boys than in girls. The incidence of reflux among children evaluated because of UTIs is 25% to 40%. When VUR is diagnosed in this setting, it occurs more frequently in girls, and the diagnosis tends to be in older children.

There is a genetic predisposition to VUR. The likelihood that the sibling of a child who has VUR will prove to have reflux if evaluated with a VCUG is 30% to 50%. A girl who had reflux has a risk of having affected offspring as often as 65% of the time. VUR is much more common among Caucasian than African-American children.

Pathogenesis

Reflux is described as being "primary" if it is present when no obvious abnormality of bladder function is

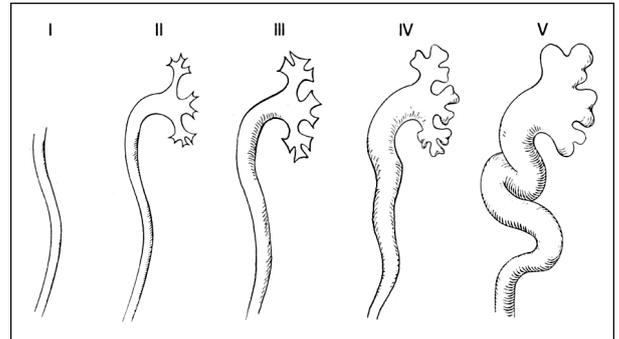


Figure 2. The International Reflux Study Grading System shows progressive filling of the upper urinary tract and dilation of the upper tracts as the grade of reflux increases beyond grade III. Grade I: Contrast only refluxes into a normal caliber ureter. Grade II: The contrast fills an undilated ureter and pyelocalyceal system, forming a cast of the normal collecting system. Grade III: Contrast shows mild dilation of ureter and pelvis. The sharp angles on the fornix of the calyx are blunted. Grade IV: There is moderate dilation of the ureter and pelvis, and the calyceal anatomy is distorted sufficiently to provide only a papillary impression. Grade V: Contrast reveals severe dilation and tortuosity of the ureter, severe dilation of the pelvis, and clubbed calyces with no papillary impression. Reprinted with permission from Lippincott Williams & Wilkins. International Reflux Study Committee. Medical versus surgical treatment of primary vesicoureteral reflux: a prospective international reflux study in children. *J Urol*. 1981;125:277-283.

perceived. Primary reflux is due to an intrinsic anatomic abnormality of the ureterovesical junction. "Secondary" reflux occurs when overt bladder or outlet pathology alters the function of the ureterovesical junction, causing reflux, such as when seen in association with a neurogenic bladder or posterior urethral valves. Urodynamic studies have revealed that high voiding pressures or high urinary storage pressures may affect the function of ureterovesical junction, resulting in reflux. Management of secondary reflux is usually directed toward the primary bladder pathology, and the reflux often improves as the bladder pressures normalize. Interestingly, the perception of primary reflux has evolved in recent years. Male neonates who have high-grade reflux had been regarded as having primary anatomic defects at their ureterovesical junctions. However, recent urodynamic studies suggest that these boys have very high voiding pressures, which represent the driving force that causes the reflux. Supportive evidence for this thesis comes from studies documenting resolution of reflux with normalization of these boys' voiding pressures.

Even minor abnormalities of bladder function may

have an impact on reflux. Dysfunctional voiding symptoms manifested by urgency, frequency, and diurnal enuresis are common among children who have VUR. A number of studies have shown that in children who have equal grades of reflux and these symptoms, the rate of reflux resolution improves if the abnormal bladder activity is treated appropriately.

Diagnosis

Evaluation of children who have prenatally diagnosed hydronephrosis consists of postnatal renal ultrasonography (RUS) and VCUG. If these evaluations reveal reflux, it is often high grade and tends to occur frequently in boys. These patients initially are managed nonoperatively because even though the reflux is high grade, a significant number of children will stop refluxing within the first 2 years of life.

The key to diagnosing VUR is to maintain an adequate index of suspicion for a UTI. The symptoms of a UTI in the infant and neonate are often occult. Pediatricians must assess many children who are ill with viral infections, and differentiating those whose symptoms may be due to UTI is challenging. The infant or toddler who is febrile or who has a persistent fever should be considered to have a UTI, and that possibility should be ruled out. The diagnosis of UTI is predicated on the collection of a properly obtained urine specimen for culture. A specimen obtained by urethral catheterization in the infant or toddler is generally the most practical and best quality for culture.

The radiologic evaluation of the child who has had a febrile UTI must include a voiding study and upper urinary tract imaging. The radiologic evaluation should be performed after diagnosing the first UTI. Renal ultrasonography is the most widely used modality for assessing the upper urinary tracts. Ultrasonography is painless, radiation-free, and noninvasive, making it ideal for the evaluation of infants and children. If the child who has a UTI is toxic and has been hospitalized, it seems reasonable to obtain the renal ultrasonography shortly after admission to rule out obstructive abnormalities of the upper urinary tract that may require surgical intervention. As noted previously, reflux can be diagnosed definitively only by a voiding study. We prefer a VCUG as the initial study in both boys and girls because of the anatomic detail it provides, but RNC may be used as the initial study in girls. RNC is employed routinely for the follow-up of reflux in both genders. Although it once was taught that performing the VCUG 6 weeks after an infection was appropriate, there seems to be no rationale for delaying the study. The VCUG can be performed

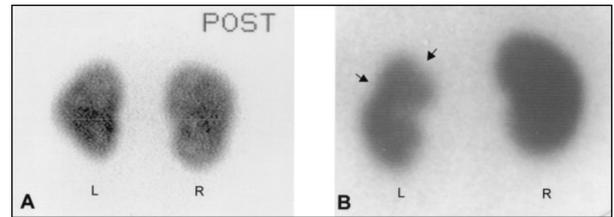


Figure 3. A. A DMSA scan showing a posterior projection over the kidneys and a slight dromedary hump on the lateral aspect of the left kidney. This is a normal variant. There are no significant photopenic areas on either kidney. B. A DMSA scan demonstrating a normal posterior projection of the right kidney, but defects in the left kidney (marked by arrows) on the lateral aspect of the cortex and at the upper pole. These represent areas of renal scarring.

safely as soon as the urine is sterile, and some reports suggest a greater likelihood of completing the study when the time from diagnosis of the infection to performance of the study is shorter.

Renal scarring frequently is present at the initial diagnosis of VUR. As many as 50% of children who have grade III and IV reflux have evidence of scarring at the time of diagnosis. If the patient is evaluated after his or her first apparent infection, there are several possible explanations for this finding. The child could have had prior undetected infections that injured the kidneys, the initial infection may have damaged the kidneys, or the refluxing kidney may have been intrinsically abnormal at birth in the absence of infections. We now understand from the evaluation of reflux discovered as a consequence of prenatally diagnosed hydronephrosis that some refluxing kidneys are functionally and morphologically impaired even though they never have been infected.

The renal scan is an adjunctive study that can be helpful in the diagnosis and management of patients who have VUR. Technetium 99 dimercaptosuccinic acid (DMSA) is the radiopharmaceutical of choice for renal imaging in affected patients. The DMSA scan allows quantification of the differential function of the kidneys, assessment for cortical defects diagnostic of scarring, and visualization of photon-deficient areas suggestive of acute infection (Fig. 3).

Management

The cornerstone of managing the child who has VUR is antibiotic prophylaxis. Prophylactic antibiotics are intended to prevent recurring infections whether the patient is being scheduled for surgery or managed nonoperatively. The antibiotics used most commonly for prophylaxis are amoxicillin in the neonate and trimethoprim-sulfamethoxazole or nitrofurantoin in older children.

There are few absolute indications for surgery. Most authorities suggest surgery for older children who have grade V reflux, and most agree that a febrile breakthrough UTI mandates surgery. Noncompliance with antibiotic prophylaxis is an indication for surgery. Relative indications for surgery include the persistence of reflux of stable moderate grade over years and reflux that persists into puberty.

The rationale for nonoperative or medical management is predicated on two principles: sterile reflux does not damage the kidney, and spontaneous resolution of reflux is expected in most children. Conceptually, if the urine can be maintained in a sterile state while waiting for spontaneous resolution of the reflux, the kidney will experience no new damage, and the child will not require an operative procedure.

Sterile reflux has not been shown to cause renal damage in either clinical or experimental series involving patients who have normal bladder function. It has been demonstrated that continuous antibiotic prophylaxis is the best method of administering antibiotics to prevent new renal injury in patients being managed nonoperatively. The safety of low-dose continuous antibiotic prophylaxis has been established over the past few decades. Although many parents are justifiably concerned about the possibility of adverse effects from long-term antibiotic prophylaxis, the risk of a breakthrough infection and subsequent renal scarring seems to far outweigh any potential deleterious antibiotic adverse effects. Years ago it was demonstrated that the use of continuous low-dose prophylactic antibiotics to prevent new renal injury was a superior approach to intermittent administration of antibiotics at the first sign of infection.

Reflux resolves spontaneously in many children. The likelihood of reflux resolution is greater if the reflux is of lower grade (Table), if it is unilateral rather than bilateral, and if the child's bladder function is normal.

Appropriate follow-up of the child receiving a medical regime includes serial imaging studies to follow the progress of the reflux. We generally obtain annual radionuclide cystography. Upper urinary tract imaging by renal ultrasonography or a DMSA renal scan may be performed at less frequent intervals, depending on the clinical situation. Annual upper urinary tract imaging may not be required for the older child whose reflux was discovered after a single febrile infection and whose kidneys appeared normal on initial ultrasonography. On the other hand, most authorities suggest annual evaluation of the upper urinary tract for younger children to follow renal growth and detect any evidence of evolving renal scars. It is important to recognize that a renal scar

resulting from a UTI may take many months or even years to evolve and that the most sensitive technique for detecting renal scars is the DMSA renal scan.

A variety of approaches are used to evaluate whether a child's urine remains sterile while receiving low-dose prophylaxis. Some physicians order urine cultures monthly; others obtain cultures three or four times a year. If the child develops a febrile illness for which there is no obvious focus, a specimen of urine must be obtained for culture and sensitivity. Published data suggest that new scars almost invariably are predated by a febrile UTI. For this reason, we obtain a urine culture to rule out the possibility of a breakthrough infection if the child has an unaccounted-for febrile illness. We do not routinely obtain cultures when the child is asymptomatic.

Management of grade I and II VUR is straightforward. Patients are followed on low-dose antibiotic chemoprophylaxis. The reflux resolves in most children over a variable length of time. Virtually all patients who have grade V reflux, except neonates, are offered surgery at diagnosis because this grade of reflux, especially if bilateral, has a very low likelihood of spontaneous resolution. Grades III and IV reflux generally are managed nonoperatively initially.

The International Reflux Study group randomized patients who had grades III and IV VUR to operative or nonoperative management. The European arm randomized patients after a second VCUG obtained at 3 months after entry confirmed persistent grade III or grade IV reflux. The rate of reflux resolution in the European arm after 5 years of follow-up was 54% among patients who had unilateral reflux and 12% among those who had bilateral reflux. There was no difference in the rate of resolution between grades III and IV reflux. The conclusion of the international study after 5 years of follow-up was that there was no difference between the outcomes

Table. Frequency of Resolution Relative to Reflux Grade

Authors	Length of Follow-up (months)	Grade (% resolution)			
		I	II	III	IV
Bellinger (1984)	30	87	63	53	33
Arant (1992)	60	82	80	46	—
Greenfield (1997)	38	69	56	49	—

— Information not available.
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of the two treatment arms. There were, however, some interesting differences in the outcomes of patients undergoing surgery in Europe and North America. The incidence of postoperative ureteral obstruction complicating the reimplantation surgery was 4.2% in Europe. Postoperative ureteral obstruction often is complicated by infection, and the coexistence of obstruction and infection frequently leads to renal parenchymal injury. No cases of ureteral obstruction occurred among patients undergoing surgery in North America, and the incidence of pyelonephritis was significantly lower among American children treated surgically compared with those placed on medical management.

Summary

VUR is diagnosed commonly following a UTI. The key to diagnosis is to maintain an adequate index of suspicion for a UTI. A VCUG or RNC is required to confirm the diagnosis. The goal of management is to prevent renal parenchymal injury, although many patients have renal scarring at the time of diagnosis. Continuous antibiotic chemoprophylaxis is the cornerstone of VUR management. Many patients who have low- or moderate-grade

reflux experience spontaneous resolution with antibiotic chemoprophylaxis. Surgery may be required in patients who have grade V reflux, persistent high-grade reflux, or febrile breakthrough infections or who are not compliant with medications.

Suggested Reading

- American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Urinary Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics*. 1999;103:843–852
- Duckett JW, Walker RD, Weis R. Surgical results: International Reflux Study in Children—United States Branch. *J Urol*. 1992;148(5 Pt 2):1674–1675
- Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol*. 1997;157:1846–1851
- Hjalmas K, Lohr G, Tamminen-Mobius T, Seppanen J, Olbing H, Wikstrom S (on behalf of the International Reflux Study in Children). Surgical results in the International Reflux Study in Children (Europe). *J Urol*. 1992;148(5 Pt 2):1657–1661
- Smellie JM. Commentary. Management of children with severe vesicoureteral reflux. *J Urol*. 1992;148(5 Pt 2):1676–1678

PIR Quiz

Quiz also available online at www.pedsinreview.org.

16. A newborn male had bilateral hydronephrosis diagnosed prenatally by ultrasonography. The kidneys are otherwise normal. Voiding cystourethrography (VCUG) demonstrates bilateral grade V reflux without bladder outlet or urethral obstruction. The urine is sterile. The *most* appropriate next step is:
 - A. Initiation of antibiotic prophylaxis.
 - B. Intermittent catheterization.
 - C. Placement of bilateral nephrostomies.
 - D. Reimplantation of both ureters.

17. A previously healthy 2-year-old girl was hospitalized recently for an initial attack of pyelonephritis. DMSA scan revealed scarring of the upper pole of the left kidney. VCUG demonstrated grade III reflux on the left. She has an allergy to sulfonamides. At this time, she would be managed *best* by:
 - A. Continuous nitrofurantoin prophylaxis.
 - B. Left nephrectomy.
 - C. Prompt treatment of each symptomatic urinary tract infection.
 - D. Reimplantation of the left ureter.

18. You are following an otherwise healthy 3-year-old girl who has a recent history of pyelonephritis. Results of renal ultrasonography were normal. VCUG demonstrated grade III reflux on the left. You have placed her on low-dose antibiotic prophylaxis. Of the following, your follow-up must include:
 - A. Monthly routine urine cultures.
 - B. Semiannual DMSA scan.
 - C. Semiannual radionuclide cystogram.
 - D. Urine culture for fever without localizing findings.

19. A 4-year-old boy who is new to your practice has a history of slow weight gain and treatment for kidney infections. No evaluation ever was performed. His height is in the 25th percentile, and his body mass index is 14.5. Results of his examination are otherwise unremarkable. Laboratory studies reveal normal renal function. Renal ultrasonography shows mild bilateral hydronephrosis, and a VCUG demonstrates bilateral grade V reflux without obstruction or postvoid residual. The urine is sterile. He has an allergy to sulfonamides. The patient's outcome is *most* likely to be positively influenced by:
 - A. Bilateral ureteral reimplantation.
 - B. Continuous nitrofurantoin prophylaxis.
 - C. Intermittent catheterization.
 - D. Prompt treatment of each symptomatic urinary tract infection.