CHAPTER 91
Vesicoureteric Reflux

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Introduction

Vesicoureteric reflux (VUR) is a common childhood condition that can be defined as the retrograde passage of urine from the bladder to the upper urinary tract due to the failure of the vesicoureteric junction (VUJ) to act as a one-way valve. This retrograde flow of urine predisposes sufferers to acute pyelonephritis by allowing bacteria to travel from the bladder to the usually sterile upper tracts. Pyelonephritis can lead to renal scarring (reflux nephropathy), which can progress to cause hypertension and renal impairment. In some cases, end-stage renal failure may ensue.

Demographics

Although VUR is common, its overall prevalence is difficult to quantify because many sufferers are asymptomatic, and invasive investigation leading to diagnosis is carried out only when clinically indicated. Studies carried out from the 1950s to the 1970s on healthy children suggest that up to 1.8% of newborns suffer from VUR.[1] More recently, it is has been shown that approximately one-third of children with urinary tract infection (UTI) will suffer from this condition.[2]

VUR has a well-recognised genetic component, although the mode of inheritance remains unclear. If a child suffers from VUR, there is a 34% chance that infant siblings will also have this condition. In addition, VUR has been shown to be present in 20–66% of the offspring of affected parents.[3]

VUR demonstrates important gender differences, with girls being more likely to suffer than boys. However, girls tend to present later than boys (2–7 years versus 0–2 years) with lower-grade reflux, often of a functional aetiology. Anatomical factors are more important in the aetiology of male disease.[4]

A study from the United States investigating the incidence of VUR in children with specific reference to age, gender, and race found that younger children are more likely to suffer from VUR than older children, that girls are twice as likely to be affected as boys, and that white children are three times more likely to have VUR than black children.[5]

Aetiologies

Vesicoureteric Reflux

VUR can be classified as being either primary or secondary in nature. Primary VUR is the product of an anatomical abnormality at the VUJ, and secondary VUR is due to abnormally high pressures within the bladder, causing an incompetent VUJ during voiding.

Note, however, that this traditional distinction between primary and secondary VUR may be an oversimplification. A proportion of patients will have a "borderline" incompetent VUJ with a degree of voiding dysfunction (such as detrusor-sphincter dyssynergia), and these two factors will act together to cause VUR. Additionally, in the first two years of life, intravesical voiding pressures are much higher than they are when the urinary system matures. These falling pressures will also contribute to the natural resolution of VUR that is seen in some cases.

Primary VUR

In the normal urinary system, a passive flap-valve mechanism prevents retrograde passage of urine from the bladder into the upper urinary tract, even at the increased pressures experienced during voiding. This valve mechanism is created by the terminal ureter travelling obliquely from the bladder wall to the trigone in an intramural and then submucosal tunnel. This enables the pressure of urine within the bladder to compress the distal ureter against the detrusor muscle and close the distal ureter as the bladder fills and then empties. The compliance of this valve depends on the length and angle of the intramural tunnel, the bladder wall thickness and tone and the site of the ureteric orifice.

In primary VUR, this valve mechanism fails with a ureter that is characteristically sited laterally and opens on the base of the bladder rather than the trigone. This shortens the intramural and submucosal portion of the distal ureter and alters the position of the ureteric orifice, resulting in reflux. Anatomical measurements suggest that the ratio of tunnel length to ureteral diameter must be at least 5:1 to prevent reflux. This observation is fundamental to almost all surgical procedures to correct the disorder. As a child grows, both the absolute and relative lengths of the submucosal tunnel increase, explaining the spontaneous resolution of VUR that is seen in some cases.

An inadequacy or absence of muscle support of the tunnel due to a local or generalised detrusor weakness, or an abnormal configuration of the ureteral orifice, can also cause primary VUR.

Secondary VUR

Secondary VUR is associated with such conditions as neuropathic bladder or posterior urethral valves, in which an elevated intravesical pressure causes retrograde passage of urine from the bladder to the upper urinary tract. Therefore, the initial management of VUR in these cases should always be to correct the underlying associated abnormality, for example, bladder augmentation to reduce pressures in the neuropathic bladder. If VUR still persists, specific surgical intervention to reduce VUR can then be carried out.

Reflux Nephropathy

Reflux nephropathy can be the result of (1) upper tract infections or (2) abnormal renal development associated with VUR. These two forms of renal injury are not mutually exclusive, however—for example, acquired renal scarring can be superimposed on congenital renal dysplasia. If a critical amount of renal parenchyma is affected, hypertension, renal insufficiency, and renal failure can result. Reflux nephropathy accounts for 5–12% of the cases of end-stage renal failure (ESRF) in North America, New Zealand, and Europe.[6] There are limited data regarding the causes of ESRF in the African setting.

Infection

In the presence of VUR, infective organisms from the lower urinary tract can be transported to the renal collecting system and parenchyma. This can lead to pyelonephritis and scarring, especially in the presence of intrarenal reflux—a phenomenon by which the anatomy of renal papillae allows backflow of urine into the collecting ducts. The cascade

of inflammation resulting from this infective process can result in local tissue ischaemia and fibrosis. The kidneys of children younger than 3 years of age seem to be particularly susceptible to damage in this way, which may be the result of reduced levels of such antioxidants as renal superoxide dismutase.

Congenital

Many children with VUR are found to suffer from renal damage at presentation. This was previously thought to be due to a single episode of pyelonephritis causing significant renal scarring—a theory named the "big bang" effect by Ransley and Risdon.[7] It has since become clear, however, that much of this damage is due to abnormal renal development in association with VUR. This renal dysplasia can be severe and may be due to defective interactions between the ureteric bud and metanephric blastema. These abnormal interactions may also result in the failure of the ureteric bud to migrate to its normal position, causing an ectopic ureter or incompetent ureteric orifice. In congenital renal dysplasia, a global reduction in functioning renal tissue tends to be seen in contrast to the focal, polar scarring seen due to infection.

Classification

The severity of VUR historically has been classified by the International Reflux Grading System on the basis of the degree of retrograde filling and dilatation of the renal collecting system seen on a voiding cystogram. This classification is as follows:

- *Grade I:* Reflux fills the ureter only without dilatation.
- *Grade II:* Reflux fills the ureter and collecting system without dilatation.
- *Grade III:* Reflux fills and mildly dilates the ureter and collecting system. There is mild blunting of the calyces.
- *Grade IV:* Reflux fills and moderately dilates the ureter and collecting system. There is mild blunting of the calyces.
- *Grade V:* Reflux fills and grossly dilates the ureter and collecting system. The ureter appears tortuous and there is severe blunting of the calyces.

More recently, there has been a trend to describe VUR as either dilating or nondilating, with or without cortical scarring or dysplasia. This newer classification enables description of VUR from high-resolution ultrasound (US) images and also fits better with the natural history of the disease.

Presentation

Prenatal Presentation

Antenatal ultrasound will detect dilatation of the upper urinary tract. Antenatal US is undertaken routinely in the West, and primary VUR accounts for at least 12% of the prenatal uropathies that are detected.[8] Male children are much more likely to suffer from prenatally diagnosed VUR, with a male-to-female ratio of 3:1.[9] Children diagnosed prenatally will often progress through evaluation and treatment without clinically significant illness.

Postnatal Presentation

The most common presentation of VUR remains symptomatic UTI, with girls being twice as likely as boys to present in this way. Unfortunately, UTI can be difficult to diagnose in children because the signs and symptoms are often nonspecific. It is important to maintain a high index of suspicion and consider UTI in any child with an unexplained fever. Other possible features include vomiting, diarrhoea, anorexia, lethargy, failure to thrive in infants, voiding symptoms in the older child, and abdominal pain (particularly loin pain in pyelonephritis).

Occasionally, advanced nephropathy leading to renal failure may be the presenting feature, especially in the African setting. This nephropathy can be the result of recurrent untreated upper UTI or secondary to congenital nephropathy. Renal failure may manifest with the symptoms of uraemia such as lethargy, itching, or nausea, or those of untreated hypertension such as congestive cardiac failure or headaches.

A family history may be suggestive of VUR, but a definitive diagnosis is impossible in the absence of imaging investigations.

Investigation

Imaging studies form the basis of diagnosis of VUR. In the United Kingdom, it is recommended that all children who suffer from a proven UTI go on to have renal tract ultrasonography and those with severe or recurrent UTIs are evaluated for VUR with micturating cystourethrogram (MCUG) and dimercaptosuccinic acid (DMSA) scintigraphy. In Africa, the decision to investigate may be modified in UTI associated with kwashiorkor. Kala has shown the prevalence of UTI in kwashiorkor to be 42% and in these patients US scans did not reveal renal tract pathology.[10]

Ultrasound

US is a commonly used, noninvasive, and relatively inexpensive investigation. Renal US allows assessment of renal tract dilatation, renal size, renal parenchyma, and visualisation of the bladder (Figure 91.1).

It is important, however, to appreciate that renal US has a high false-negative rate when used to investigate VUR. Many children with a renal tract that appears normal on ultrasound can be shown to suffer from reflux with the use of an MCUG, but even an MCUG will miss VUR in 3–9% of the cases.

Hydronephrosis in the presence of a dilated ureter is consistent with VUR, whereas hydronephrosis with a nondilated ureter would imply ureteropelvic junction obstruction. Observation of changes in hydronephrosis and hydroureter during and after voiding can be used to identify VUR noninvasively.

Renal size can be measured and followed over time to assess growth. Abnormal or dysplastic kidneys will tend to be smaller and appear brighter. Measurements of bladder wall thickness can be taken; incomplete bladder emptying may be observed in bladder dysfunction.

High-resolution US allows accurate assessment of the renal cortex and cortical loss, and split renal function can be estimated from a three-dimensional calculation of total cortical volume.

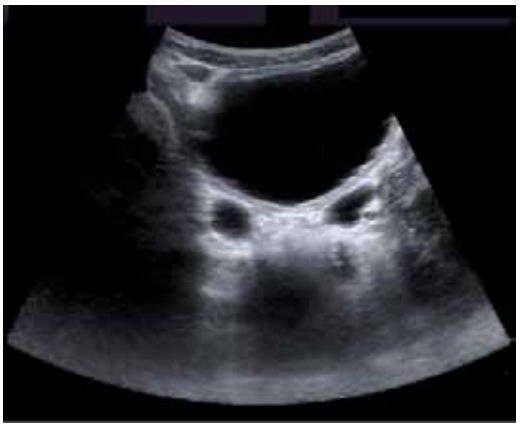

Figure 91.1: Transverse bladder view US scan showing thick-walled bladder with bilateral ureteric dilatation.

Micturating Cystourethrography

To perform an MCUG, the bladder is filled with contrast either urethrally or via suprapubic catheter. This allows the appearance of the ureters and urethra to be observed during voiding. This test also provides information regarding bladder capacity and emptying as well as revealing bladder trabeculation or diverticula, indicative of bladder outlet obstruction. Particular attention should be paid to the posterior urethra in boys to look for posterior urethral valves.

MCUG is the gold-standard investigation for the diagnosis of VUR and allows grading of the severity of disease (Figure 91.2). It is an

invasive test, however, and should be performed only if the findings are likely to alter management. Additionally MCUG should be avoided during active UTI.

Dynamic Renography

A less invasive alternative to MCUG is dynamic renography using intravenous radioactive mercaptoactyletrigylcerine (MAG3) or diethylene triamine pentaacetic acid (DTPA). However, to diagnose VUR, the child must be potty trained, and its use is therefore limited in the younger child, which is the age group most at risk of infective scarring. Dynamic renography is also less sensitive in diagnosing low-grade VUR and is therefore mainly used as a follow-up of VUR in the older child.

Dimercaptosuccinic Acid Scan

DMSA scintography is considered the best modality for assessing renal scarring and evaluating differential renal function (Figure 91.3). Persistent photopenic deficits, representing impaired tubular uptake of radionuclide isotope, correspond to renal scarring and irreversible renal damage. Diffuse decreased renal uptake may indicate renal dysplasia. This scan, however, does not provide any information regarding VUR itself.

Intravenous Urography

If DMSA is not available, intravenous urography (IVU) is an alternative method for assessing renal function, with a poorly functioning kidney showing reduced excretion of contrast.

Management

Medical Management

Many children with VUR are managed nonsurgically. The rationale for this is that in the absence of a UTI, there will be no further renal damage, and 50–85% of cases of mild to moderate VUR will spontaneously resolve.[11]

The initial treatment of UTI is discussed in all general paediatric care texts, such as the Nelson Textbook of Pediatrics,[12] but it should be noted that timely initiation of antibiotic therapy is crucial. Animal studies have suggested that permanent renal damage can occur in less than 72 hours.[13] Once this initial treatment has been completed, prophylactic antibiotics, such as trimethoprim (1–2 mg/kg per day), should be considered. Although prophylaxis is useful in some individual children, however, there is little evidence that it is effective in reducing infections or renal scarring, and prophylaxis is avoided in many countries.

Strategies to improve bladder dysfunction can also reduce VUR. Regular, timed voiding should be instituted and, in the presence of incomplete bladder emptying, double voiding should be encouraged. Anticholinergics may be a useful adjunct in bladder instability, but care should be taken not to compound problems of incomplete bladder emptying or constipation, which often coexists with bladder dysfunction.

Commitment from the medical team, child, and family are essential to the success of medical management. Arrangements need to be made to allow early treatment of breakthrough infections, and the family and child need to be motivated to correct voiding dysfunction. If the health care system does not allow for early and reliable treatment of breakthrough infection, there may be a role for primary surgical intervention.

Surgical Management

Indications for surgery are relative rather than absolute, and would include failure of medical management and reflux that is unlikely to spontaneously resolve. Dilating reflux with dysplasia or reflux associated with anatomical abnormalities, such as ureteric duplication, are unlikely to resolve spontaneously. Endoscopic treatment can be considered from the neonatal period onwards if a suitable cystoscope is available, but ureteric reimplantation will normally be delayed until the patient is older than 18 months of age unless UTIs are particularly severe.

Endoscopic intervention

The endoscopic subureteric injection of a bulking agent to prevent reflux was first popularised by O'Donnell and Puri in the 1980s.[14] The bulking agent elevates the ureteral orifice to narrow the ureteral lumen, still allowing antegrade flow but preventing retrograde flow. A variety of inert bulking agents have been used, including Teflon®, a suspension of polytetrafluoroethylene (PTFE) in glycerine, dextranomer-hyaluronic acid copolymer (Deflux®), and polydimethylsiloxane (Macroplastique®). Teflon was the first substance used for this purpose, but it has recently fallen from favour because it has been shown to migrate to other organs, such as the lungs and brain. It is from this "subureteric Teflon injection" that the acronym STING was coined. Deflux is now the most commonly used bulking agent in Europe.

To allow endoscopic injection, a cystoscope with a working channel is introduced into the bladder under general anaesthetic. Through the working channel, a rigid or flexible needle is used to inject the bulking agent, bevel up, at the 6 o'clock position at the ureteric orifice. The needle should be withdrawn after the injection of 0.5–2.0 ml of material, at which point a mound should be seen. The ureteric orifice will now be elevated so that there is a slit-like opening at the top of the mound.

An alternative to this classic method is the hydrodistention-implantation technique (HIT). In this case, a pressurised stream of fluid is used to open the ureteric orifice so that a bulking agent can be injected directly into the submucosa within the ureteric tunnel. This procedure is useful when dealing with larger ureteric orifices.

Endoscopic correction is most useful for the correction of reflux that is complicated by breakthrough UTI. Injection may need to be repeated, particularly in higher grade reflux, where the HIT technique

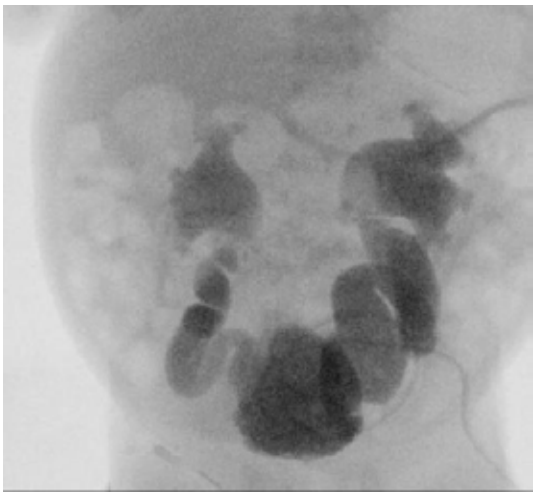

Figure 91.2: MCUG showing bilateral reflux with tortuous ureters. There is dilatation of the pelvicalyceal system with mild blunting of the calyces.

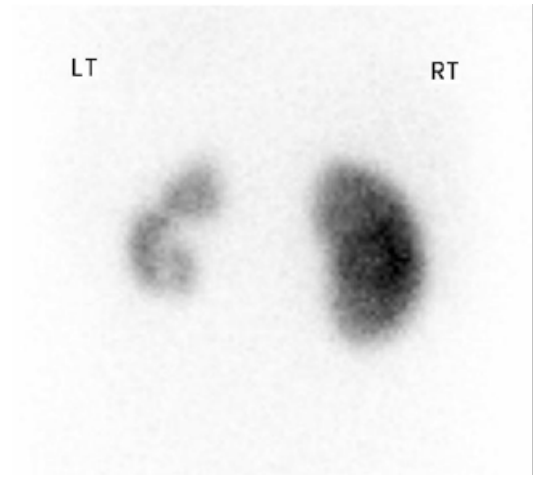

Figure 91.3: DMSA scan showing a small left kidney with cortical thinning and upper and lower pole scar. The right kidney is normal.

has improved success rates. However, in "golf hole" or abnormal ureteric orifices, it is less likely to be successful, and open surgery may need to be considered.

Ureteric reimplantation

Ureteric reimplantation is the definitive method for correcting primary VUR. A successful procedure relies on creating a submucosal channel for the affected ureter with a length-to-diameter ratio of 5:1 as well as on providing good detrusor muscle backing.

Cohen pioneered a technique that is now the favoured technique of most paediatric urologists, as it has a success rate of more than 95% and a low rate of postoperative complications.[15] In this technique, the bladder is opened, and the ureter is cannulated with a feeding tube and mobilised intravesically. A submucosal tunnel is made across the width of the trigone through which the ureter is then reimplanted. If the bladder is small and the ureter dilated, it can be difficult to achieve the required length-to-diameter ratio; in this case, the diameter of the distal ureter can be reduced by plication.

Postoperatively, the bladder should be drained for a short period either suprapubically or urethrally. The feeding tube used to cannulate the ureter may be left in place as a stent and brought out through the abdomen or the urethra in females. A current trend, however, is to leave no stent in situ unless transient obstruction is a concern.

An alternative operation is the approach of Lich and Gregoir, in which the ureter is mobilised extravesically. The detrusor, but not the mucosa, is opened and undermined to create a trough into which the ureter is placed. The detrusor can then be closed over the ureter. This technique has the benefits of reduced haematuria and discomfort postoperatively, but it is unsuitable for dilated ureters and is associated with postoperative voiding dysfunction.

Complications of reimplantation procedures include ongoing VUR, ureteric obstruction, haematuria, and infection:

- Persistent ipsilateral VUR will usually be the result of a technical problem, such as inadequate length of the submucosal tunnel, inappropriate placement of the ureteric orifice, or insufficient ureteral mobilisation, but may represent missed secondary reflux with underlying untreated bladder abnormality.
- Contralateral reflux may become apparent once the index side has been treated because it no longer acts as a pressure-relieving valve. The majority of these cases can be managed conservatively or with STING.
- Postoperative ureteric obstruction will often be secondary to oedema, blood or mucous clots, submucosal haematomas, or bladder spasm. Alternatively, ureteral angulation, ischaemia, or incorrect tunnel placement can cause chronic obstruction. Revision reimplantation can be undertaken if required, but the ureter should be transected outside the bladder before being reimplanted.
- Haematuria will usually be self-limiting.
- Infection should be treated with appropriate antibiotics.

Alternative operative procedures

Cutaneous vesicostomy or loop ureterostomy can be used to decompress the systems of young infants whose VUR is complicated by sepsis or impaired renal function. Vesicostomy will often fail to decompress the upper tracts of an infant with a particularly thick-walled bladder; in this situation, a loop ureterostomy may be more successful. Vesicostomies or ureterostomies can be reversed in the second or third year of life, when voiding pressures have fallen, and the bladder can be enlarged either as an isolated procedure or in combination with ureteric reimplantation.

Transuretoureterostomy can be used to manage recurrent VUR or ureteric obstruction complicating a reimplantation procedure.

Nephroureterectomy may need to be considered in the context of recurrent UTI and a poorly functioning kidney. Leaving the grossly scarred kidney in situ exposes the patient to the risk of hypertension and resultant systemic damage. If the differential function of the affected kidney is less than 10% and the contralateral kidney is normal, nephroureterectomy is reasonable. When removing the kidney, the ureter should also be resected in its entirety to prevent infection associated with a refluxing stump.

Prognosis and Outcomes

The outlook for children younger than 5 years of age with reflux of grades I–III is good, with more than 50% spontaneously resolving.[11] Even those with higher-grade reflux may resolve with time, but the rates are significantly lower.[16]

For those patients who do not improve with age, endoscopic subureteric injection with Deflux will cure 70% of patients with grade III reflux after only one injection.[17] For those patients who are not suitable for, or fail, endoscopic treatment, open reimplantation will definitively treat more than 95% of patients.[15,18]

Prevention

Although VUR itself cannot be prevented, once it is detected, steps can be taken to prevent renal damage. It is essential that UTI be treated quickly and effectively. Bladder function should be assessed, urolithiasis excluded, and factors such as constipation, poor voiding, and drinking patterns improved.

Evidence-Based Research

At present, there are no randomised control trials based in Africa regarding treatment of VUR. Therefore, decisions must be guided by studies carried out in the West. Table 9.1 presents the results of a clinical trial in New York that assesses whether surgical or medical management is better in preventing recurrent UTI.

Table 91.1: Evidence-based research.

Title	Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux.
Authors	Weiss R, Duckett J, Spitzer A
Institution	Albert Einstein College of Medicine, New York, New York, USA (coordinating centre)
Reference	J Urol 1992; 148:1667–1673
Problem	To determine, in children with primary VUR of grades III and IV, whether surgical management is better than medical management in preventing recurrent UTI and its complications.
Intervention	Ureteric reimplantation.
Comparison/ control (quality of evidence)	This study monitored 135 patients for new renal damage, kidney growth, changes in estimated glomerular filtration rate (eGFR), appearance of hypertension, and disappearance of VUR. These variables were assessed with urine cultures, blood pressure measurements, serum creatinine measurements, voiding cystogram, and intravenous pyelogram. Follow-up was for five years.
Outcome/ effect	Progression in renal scarring was found in a proportion of the patients, but there was no significant difference between the two groups (medical versus surgical). Similar rates of bacteriuria were found in both groups but medical patients were three times as likely to suffer from acute pyelonephritis. There were no significant differences between renal growth and eGFR between the two groups, and no new cases of hypertension. Grade IV reflux spontaneously resolved at a rate of 8% per year.
Historical significance/ comments	Rates of acute pyelonephritis are higher amongst patients managed with antibiotic prophylaxis than those undergoing surgical reimplantation. Despite this, both surgical correction and medical therapy are equally, but only partially, effective at protecting the kidney from new renal injury. Grade IV reflux will take 9 years to resolve in more than 50% of patients; therefore, prolonged medical therapy will be needed in this group.

Key Summary Points

1. Renal injury in VUR may be the result of congenital renal dysplasia associated with VUR, renal scarring secondary to infection, or a combination of these two factors.
2. Progressive renal damage may be prevented by the early treatment of UTI and not allowing a pattern of recurrent UTI to develop.
3. Taking steps to manage voiding dysfunction is crucial to effective medical treatment of VUR.
4. In the presence of mild to moderate reflux and breakthrough UTI, endoscopic treatment has an important role.
5. Open surgery should be undertaken only after considering medical and endoscopic management.

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