Vesicoureteric Reflux

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91.1 Introduction

Vesicoureteric reflux (VUR) is a common childhood condition and 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 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 [1].

91.2 Demographics

Although VUR is common, its overall prevalence is difficult to quantify as many sufferers are asymptomatic and invasive investigation leading to diagnosis is only carried out when clinically indicated. Studies carried out from the 1950s to 1970s on healthy children suggest that up to 1.8% of newborns will suffer from VUR. More recently, it is has been shown that approximately a third of children with urinary tract infection will suffer from this condition [2, 3].

There is a well-recognised genetic component to VUR, 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 between 20% and 66% of the offspring of affected parents.

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 vs 0–2 years) with lower grade reflux, often of a functional aetiology. Anatomical factors are more important in the aetiology of male disease.

A study carried out in the USA aiming to investigate 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 sufferers than boys and that white children are three times more likely to have VUR than black children.

91.3 Aetiology of VUR

VUR can be classified as being either primary or secondary in nature. Primary VUR is the product of an anatomical abnormality at the vesicoureteric junction (VUJ), whilst secondary VUR is due to abnormally high pressures within the bladder causing an incompetent VUJ during voiding [4, 5].

91.3.1 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 is dependent of 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.

91.3.2 Secondary VUR

Secondary VUR is associated with conditions such 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, such as a bladder augmentation to reduce pressures in neuropathic bladders. If VUR still persists, specific surgical intervention to reduce VUR can then be carried out.

It is worth noting, however, that this traditional distinction between primary and secondary VUR may have been 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 2 years of life, intravesical voiding pressures are much higher than later when the urinary system matures. These falling pressures will also contribute to the natural resolution of VUR that is seen in some cases.

91.4 Aetiology of Reflux Nephropathy

Reflux nephropathy can be the result of upper tract infections or abnormal renal development associated with VUR [6].

91.4.1 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 where 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 ischemia and fibrosis. The kidneys of children under 3 years of age seem to be particularly susceptible to damage in this way which may be the result of reduced levels of antioxidants such as renal superoxide dismutase.

91.4.2 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. However, it has since become clear 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.

These two forms of renal injury are not mutually exclusive, and 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 between 5% and 12% of the cases of end-stage renal failure (ESRF) in North America, New Zealand and Europe. There is limited data regarding the causes of ESRF in the African setting.

91.5 Grading of VUR

The severity of VUR has been historically 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 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 non-dilating, with or without cortical scarring or dysplasia. This newer classification enables description of VUR from high-resolution ultrasound images and fits better with the natural history of the disease.

91.6 Presentation of VUR

91.6.1 Prenatal Presentation

Antenatal ultrasound will detect dilatation of the upper urinary tracts. This is undertaken routinely in the West, and primary VUR will account for at least 12% of the prenatal uropathies that are detected. Male children are much more likely to suffer from prenatally diagnosed VUR with a male/female ratio of 3:1. Children diagnosed prenatally will often progress through evaluation and treatment without clinically significant illness [7, 8].

91.6.2 Postnatal Presentation

The most common presentation of VUR remains symptomatic urinary tract infection (UTI), with girls being

twice as likely as boys to present in this way. Unfortunately, UTI can be difficult to diagnose in children as signs and symptoms are often non-specific. 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.
- 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 [9].

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

91.7 Investigation

Imaging studies form the basis of diagnosis of VUR. In the UK, it is recommended that all children who suffer from a proven UTI go on to have renal tract ultrasonography. Those with severe or recurrent UTIs are evaluated for VUR with micturating cystourethrogram (MCUG) and DMSA scintigraphy.

91.7.1 Ultrasound

Ultrasound is a commonly used, non-invasive and relatively cheap investigation. Renal ultrasound allows assessment of renal tract dilatation, renal size and renal parenchyma and visualisation of the bladder (Fig. 91.1).

Hydronephrosis in the presence of a dilated ureter is consistent with VUR whilst hydronephrosis with a non-dilated ureter would imply pelvi-ureteric junction obstruction. Observation of changes in hydronephrosis and hydroureter during and after voiding can be used to identify VUR non-invasively.

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, and incomplete bladder emptying may be observed in bladder dysfunction.

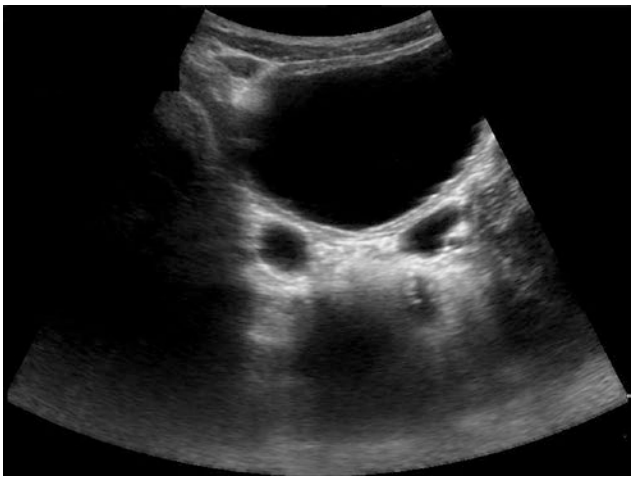

Fig. 91.1 USS showing thick-walled bladder with bilateral ureteric dilatation

However, it is important to appreciate that renal ultrasonography 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 a micturating cystourethrogram (MCUG). Even MCUG will miss VUR in 3–9%.

91.7.2 Micturating Cystourethrography

To perform an MCUG (Fig. 91.2), 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 will also provide 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. However, as an invasive test, it should only be performed if the findings are likely to alter the management. Additionally, MCUG should be avoided during active UTI.

A less invasive alternative to MCUG is dynamic renography using intravenous radioactive mercaptoactyletrigylcerine (MAG3) or diethylenetriaminepentaacetic 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 to follow-up VUR in the older child.

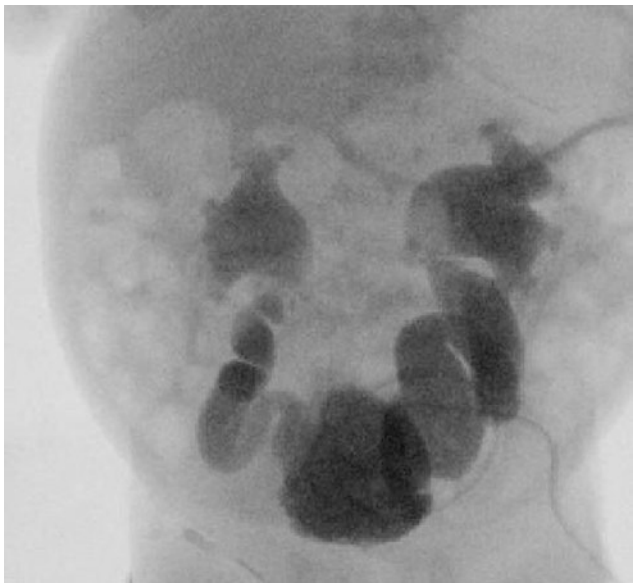

Fig. 91.2 MCUG showing bilateral reflux with tortuous ureters. There is dilatation of the pelvicalyceal system with mild blunting of the calyces

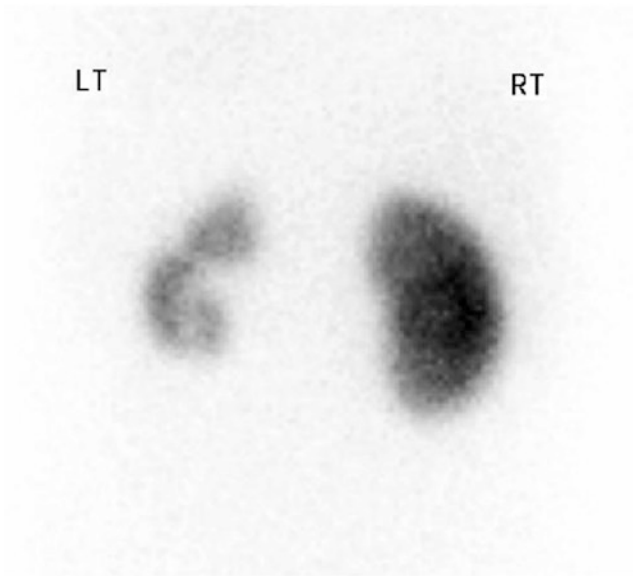

Fig. 91.3 DMSA showing a small left kidney with cortical thinning and upper and lower pole scar. The right kidney is normal

91.7.3 DMSA

DMSA scintigraphy (Fig. 91.3) is considered the best modality for assessing renal scarring and evaluating differential renal function. 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. The scan however does not provide any information regarding VUR itself.

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. High-resolution ultrasonography allows accurate assessment of the renal cortex and cortical loss, and split renal function can be estimated from a 3D calculation of the total cortical volume.

91.8 Management

91.8.1 Medical Management

Many children with VUR are managed non-surgically. The rationale for this being that in the absence of urinary tract infection there will be no further renal damage and 50–85% of cases of mild to moderate VUR will spontaneously resolve.

Initial treatment of UTI has been discussed elsewhere, 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. Once this initial treatment has been completed, prophylactic antibiotics should be considered, typically in the UK trimethoprim (1–2 mg/kg/day). The RIVUR trial conducted in the USA showed that in children with vesicoureteral reflux after urinary tract infection, antimicrobial prophylaxis was associated with a substantially reduced risk of recurrent UTI but not of renal scarring. The Swedish reflux trial however did show a beneficial effect of prophylaxis on scarring in girls aged less than 2 years of age.

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 so as 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 healthcare system does not allow for early and reliable treatment of breakthrough infection, there may be a role for primary surgical intervention [10–13].

91.8.2 Surgical Management

Indications for surgery are relative rather than absolute but 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, is 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 over 18 months of age unless UTIs are particularly severe.

91.8.3 Endoscopic Intervention

The endoscopic subureteric injection of bulking agent to prevent reflux was first popularised by O'Donnell and Puri in the 1980s. 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 as 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 [14–17].

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 classical method is the hydrodistention-implantation technique (HIT). In this case, a pressurised stream of fluid is used to open the ureteric orifice so that 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 has improved our 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.

91.8.4 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/diameter ratio of 5:1 (Paquin's rule) as well as providing good detrusor muscle backing [18].

Cohen pioneered a technique that is now the favoured technique of most pediatric urologists as it has a success rate of over 95% and a low rate of post-operative complications. In this technique, the bladder is opened, the ureter 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/diameter ratio; in this case, the diameter of the distal ureter can be reduced by plication.

Post-operatively, 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. There is however a current trend to leave no stent in situ unless transient obstruction is a concern.

An alternative operation is the extravesical approach of Lich and Gregoir. In this case, the ureter is mobilised extravesically. The detrusor, but not the mucosa, is opened and undermined to create a trough into which the ureter placed. The detrusor can then be closed over the ureter. This technique has the benefits of reduced haematuria and discomfort post-operatively, but is unsuitable for dilated ureters and is associated with post-operative 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 submucosal tunnel, inappropriate placement of the ureteric orifice or insufficient ureteral mobilisation.
- Contralateral reflux may become apparent once the index side has been treated, as it no longer acts as a pressure-relieving valve. The majority of these cases can be managed conservatively or with STING.
- Post-operative 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.

91.8.5 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 enlarged either as an isolated procedure or in combination with ureteric reimplantation.

Transureteroureterostomy 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.

91.9 Prognosis and Outcomes

The outlook for children under 5 years old with reflux of grades I–III is good, with over 50% spontaneously resolving. Even those with higher-grade reflux may resolve with time, but the rates are significantly lower.

For those patients that do not improve with age, endoscopic subureteric injection with Deflux will cure 70% of patients with grade III reflux after only one injection. For those sufferers who are not suitable for, or fail, endoscopic treatment, open reimplantation will definitively treat over 95% of patients [19, 20].

91.10 Prevention

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

91.11 Evidence-Based Surgery

At present there are no randomised control trials guiding the treatment of VUR based in Africa.

Title	The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux
Authors	Brandström P, Jodal U, Sillén U, Hansson S.
Institution	The Queen Silvia Children's Hospital
Reference	J Pediatr Urol. 2011 Dec; 7(6): 594–600
Problem	To evaluate prophylaxis and endoscopic injection for children with dilating reflux compared to surveillance regarding urinary tract infection and new renal damage
Intervention	Antibiotic prophylaxis and endoscopic injection
Comparison	203 children (128 girls and 75 boys), aged 1 to <2 years, with VUR grade III or IV were randomized to antibiotic prophylaxis (n = 69), endoscopic injection (n = 66) or surveillance (n = 68). Voiding cystourethrography, dimercaptosuccinic acid scintigraphy and optional lower urinary tract function assessment were performed before randomisation and after 2 years
Outcome	There were 67 febrile UTIs in 42 girls and 8 in 7 boys (p = 0.0001). In girls, recurrence rate was 19% on prophylaxis, 23% with endoscopic treatment and 57% on surveillance (p = 0.0002). In boys, there was no difference between treatment groups. New damage was seen in 13 girls – 8 on surveillance, 5 in the endoscopic group and none on prophylaxis (p = 0.0155) – and in 2 boys. In 13 children with no or non-dilating VUR after 1 injection, dilating VUR reappeared at the 2-year follow-up
Comments	In girls, prophylaxis reduced the rate of UTI recurrence and new renal damage, and endoscopic injection, the rate of UTI recurrence. Boys did not benefit from active treatment

Key Summary Points

1. Renal injury in VUR may be the result of congenital renal dysplasia associated with VUR or renal scarring secondary to infection or due to 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 only be undertaken after considering medical and endoscopic management.

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