Mika Venhola

VESICOURETERAL REFLUX IN CHILDREN
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IN CHILDREN

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Abstract

The aims of the work were to evaluate the comparability and repeatability of urodynamic studies and to examine whether such examinations are useful for predicting the recurrence of urinary tract infections or the presence of vesicoureteral reflux, to analyse the efficacy of treatments for vesicoureteral reflux (VUR), to validate a pre-established clinical decision rule for targeting voiding cystourethograms efficiently in children and to investigate the occurrence of vesicoureteral reflux.

Reports on urodynamic examinations performed on children were evaluated by analysing inter-observer and intra-observer agreement in their interpretations, and 116 children were followed up to examine whether such examinations can be used to predict the recurrence of urinary tract infections and the presence of vesicoureteral reflux. A meta-analysis of publications on treatments for vesicoureteral reflux was made to analyse their efficacy in children. A group of 406 children were examined to validate a pre-established clinical decision rule for managing vesicoureteral reflux in children after the first urinary tract infection and to investigate the occurrence of VUR in children.

We found poor agreement among the observers in their urodynamic assessments. Neither the occurrence of VUR nor recurrent urinary tract infection could be predicted from the findings in urodynamic studies. The meta-analysis indicated no significant difference between conservative or operative treatment in terms of the recurrence of urinary tract infections, kidney growth or scarring. Our validation of the clinical decision rule showed that it had good specificity but very modest sensitivity in identifying children with dilating vesicoureteral reflux. The overall prevalence of vesicoureteral reflux was 35%, and its occurrence was similar in children without urinary tract infection.

We claim that the occurrence of vesicoureteral reflux in children is higher than the figure of 1% suggested earlier. We could not predict the presence or absence of vesicoureteral reflux from the results of the urodynamic examinations, nor could we predict recurrent urinary tract infections from these findings. We suggest that it is not possible to predict VUR reliably, and that conservative treatment is sufficient for the majority of children with VUR.

Keywords: child, kidney, renal scarring, urinary tract infection, vesicoureteral reflux
Tävitetään

Väitöskirjani tutkimussarjassa selvitimme lapsen virtsateissä tapahtuvan virtsan takaisinvirtauksen (vesikoureteraalinen refluksi, VUR) yleisyyttä ja yhteyttä lasten virtsatieinfektiioihin, arvioimme aiemmin julkaistun tutkimusohjeen käyttökelpoisuutta lasten virtsateiden kuvantamisesta ja toiminnalle. Selvitimme myös virtsarakon toiminnallisten tutkimusten toistettavuutta ja vertailtavuutta lastenkirurgien kesken sekä onko näillä tutkimuksilla mahdollista havaita onko lapsella VUR tai taipumusta uusiutuviin virtsatieinfektiioihin.

Tutkimmassamme 406 lapsen aineistossa virtsan takaisinvirtausta löytyi 39 %:lla virtsatieinfektion sairastaneista lapsista ja 36 %:lla muita tulehdusaiheita sairastaneista. Ero ei ollut tilastollisesti merkittävä ja esiintyvyys on huomattavasti suurempi kuin aiemmin on oletettu. Samassa aineistossa testasimme tutkimusohjetta jonka avulla voitaisi löytää lapset joilla on todennäköisesti VUR. Tuloksemme mukaan tutkimusohje ei ole käyttökelpoinen.

Kirjallisuuteen perustuvassa meta-analyysissä julkaistuista VUR tutkimuksista lapsilla, havaitsimme, ettei leikkauksella korjattujen tai lääkityksellä hoidettujen lasten munuaisten kasvussa, arpeutumisessa tai virtsatieinfektioiden uusiutumisessa ollut eroa.


Lapsilla VUR on mitä ilmeisimmin varsin tavallinen ilmiö myös terveillä lapsilla ja sen esiintyvyys ylittää aiemmin raportoidun 1 %:n esiintyvyysen. Virtsarakon toiminnalliset tutkimukset eivät ennusta VUR:n esiintyvyyttä tai virtsateitulehdusten toistuvuutta ja näiden tulosten hyöty on vähäinen. Virtsan takaisinvirtauksen leikkaukushoitoon on harvoin aihetta eikä arviomamme tutkimusohje auta löytämään VUR:a sairastavia lapsia.

Asiasanat: lapset, munuaistaudit, virtsaelimet, virtsan takaisinvirtaus, virtsatieinfektiio
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And last but not least, thank God it is over.

Oulu September 2011

Mika Venhola
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Atgr2</td>
<td>Angiotensin type 2-receptor gene</td>
</tr>
<tr>
<td>AUA</td>
<td>American Urological Association</td>
</tr>
<tr>
<td>CAKUT</td>
<td>Congenital anomalies of the kidney and urinary tract</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony forming units</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DES</td>
<td>Dysfunctional elimination syndrome</td>
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<tr>
<td>DMSA</td>
<td>99mTc-dimercaptosuccinic acid</td>
</tr>
<tr>
<td>Dx/HA</td>
<td>Dextranomer microspheres with hyaluronic acid</td>
</tr>
<tr>
<td>ESKD</td>
<td>End-stage kidney disease</td>
</tr>
<tr>
<td>Gdnf</td>
<td>Glial-derived neurotrophic factor</td>
</tr>
<tr>
<td>IRR</td>
<td>Intra renal reflux</td>
</tr>
<tr>
<td>iVCUG</td>
<td>Isotope voiding cystourethrography</td>
</tr>
<tr>
<td>IVU</td>
<td>Intravenous urography</td>
</tr>
<tr>
<td>MAG3</td>
<td>99mTc-mercaptoacetyl triglycine renography</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>RNC</td>
<td>Radionuclide cystography</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
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<tr>
<td>VCUG</td>
<td>Voiding cystourethrography</td>
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<tr>
<td>VUR</td>
<td>Vesicoureteral reflux</td>
</tr>
</tbody>
</table>
List of original publications


Contents

Abstract
Tiivistelmä
Acknowledgements 7
Abbreviations 9
List of original publications 11
Contents 13
1 Introduction 17
2 Morphogenesis of the vesicoureteral junction – implications for vesicoureteral reflux 19
   2.1 Morphogenesis of the ureter and kidney ............................................. 19
   2.2 Anti-reflux mechanisms in the ureter ................................................. 20
   2.3 Congenital abnormalities of the ureter and kidney ............................. 21
3 Imaging of vesicoureteral reflux 23
   3.1 Voiding cystourethrogramy ................................................................. 23
   3.2 Radionuclide cystography ................................................................. 23
   3.3 Voiding urosonography .................................................................... 24
   3.4 Magnetic resonance imaging ............................................................ 25
4 Occurrence and classification of vesicoureteral reflux 27
   4.1 General occurrence ........................................................................... 27
   4.2 Classification of vesicoureteral reflux ................................................. 28
   4.3 Intrarenal reflux ................................................................................. 28
   4.4 Primary vesicoureteral reflux ............................................................. 30
   4.5 Secondary vesicoureteral reflux ........................................................... 30
   4.6 Prenatally detected vesicoureteral reflux .......................................... 31
   4.7 Familial occurrence of vesicoureteral reflux ...................................... 31
   4.8 Effect of age, sex and race on the occurrence of VUR ...................... 32
   4.9 Relation of vesicoureteral reflux to multi-organ malformation syndromes ................................................................. 33
   4.10 Vesicoureteral reflux in animals ....................................................... 33
5 Resolution of vesicoureteral reflux 35
6 Vesicoureteral reflux as a pathological phenomenon 37
   6.1 Historical notes on vesicoureteral reflux .......................................... 37
   6.2 After World War II ........................................................................... 38
   6.3 Vesicoureteral reflux, hypertension and chronic renal failure .......... 38
6.4 Vesicoureteral reflux in the neuropathic bladder, bladder outlet obstruction and other conditions ................................................................. 40

7 Vesicoureteral reflux and dysfunctional elimination syndrome 41

8 Vesicoureteral reflux and reflux nephropathy 43
8.1 Occurrence of renal scarring .............................................................. 43
8.2 Pathogenesis of renal scarring ............................................................ 44
8.3 Imaging of renal scarring ................................................................... 45

9 Vesicoureteral reflux and urinary tract infection 49

10 Management of vesicoureteral reflux 51
10.1 Medical management ........................................................................ 51
10.2 Surgical management ....................................................................... 53
10.2.1 Open surgery ............................................................................. 53
10.2.2 Endoscopic therapy .................................................................... 55
10.2.3 Laparoscopic surgery ................................................................. 57

11 Controversies over the management of VUR 59
11.1 No treatment versus treatment ....................................................... 59
11.2 Antimicrobial prophylaxis versus operative treatment ..................... 59
11.3 Open surgical treatment versus endoscopic injection ...................... 60

12 Purpose of the present research 61

13 Results 63
13.1 Urodynamic measurements in children ........................................... 63
13.1.1 Subjects ................................................................................... 63
13.1.2 Methods .................................................................................. 63
13.1.3 Results ................................................................................... 64
13.2 Meta-analysis of vesicoureteral reflux and urinary tract infection in children ................................................................. 65
13.2.1 Materials and methods .............................................................. 65
13.2.2 Results ................................................................................... 66
13.3 Practical guidelines for imaging studies in children after the first urinary tract infection ................................................................. 67
13.3.1 Patients and methods ............................................................... 67
13.3.2 Results ................................................................................... 68
13.4 Occurrence of vesicoureteral reflux in children ................................... 69
13.4.1 Patients and methods ............................................................... 69
13.4.2 Results ................................................................................... 70
13.5 Association of urodynamic findings with vesicoureteral reflux and recurrent urinary tract infections in children ................................. 70
13.5.1 Patients and Methods ................................................................. 70
13.5.2 Results ...................................................................................... 71

14 Discussion
14.1 Vesicoureteral reflux – a benign condition? ............................... 73
14.2 Vesicoureteral reflux – a pathological condition? ....................... 75
14.3 Vesicoureteral reflux – a great swindle? .................................... 77

15 Conclusions .................................................................................. 79
References ......................................................................................... 81
Original publications ........................................................................ 101
1 Introduction

Micturition in infants occurs spontaneously as a spinal cord reflex due to bladder distension. During micturition the striated muscle sphincter relaxes and allows low-pressure bladder emptying. As the bladder fills again the urinary sphincter constricts to prevent incontinence, but bladder compliance allows the bladder to fill without any appreciable rise in bladder pressure. As the child matures, voluntary control over the striated muscle occurs, permitting intentional initiation and termination of micturition.

Vesicoureteral reflux is a retrograde flow of urine from the urinary bladder into the ureter and towards the kidney, supposedly due to a dysfunctional vesicoureteric junction. It is an intriguing phenomenon as its intensity varies and it is usually associated with a high likelihood of spontaneous evanescence. It has been considered a pathological event in children and may be of importance in urinary tract infection (UTI) due to the upward spread of infection in the urinary tract, causing pyelonephritis and consequently renal scarring, hypertension and end-stage renal failure.

The aetiology, natural history, need for treatment, treatment options and significance of vesicoureteral reflux (VUR) are being rewritten due to our evolving understanding of UTI, VUR and renal scarring. The surgical solutions available for abolishing VUR have been around for decades and have stood the test of time, but being invasive and not without complications, they have been accompanied by a search for new treatment options. The recommendations for the management of VUR have been altered, and physicians are faced with dilemmas and conflicting evidence as to the proper standpoint to adopt with regard to VUR.
Morphogenesis of the vesicoureteral junction – implications for vesicoureteral reflux

The vesicoureteral junction is structurally and functionally adapted to allow the intermittent unidirectional passage of urine from the ureter to the urinary bladder and to prevent any backward flow of urine from the bladder to the ureter. The junction separates the low-pressure upper urinary tract from the at times high-pressure urinary bladder, protecting the upper urinary tract from the physiological pressure changes that take place in the latter.

The location at which the ureteric bud exits the mesonephric (Wollfian) duct during embryogenesis is of the utmost significance, as ectopia of the ureteric bud can result in erroneous development of the kidney and urinary tract, leading to varying degrees of hypoplasia and/or dysplasia of the kidney and urinary outflow obstruction in the ureter due to a misplaced ureteral opening or to vesicoureteral reflux (Mackie et al. 1975, Kuwayama et al. 2002). These anomalies are often present simultaneously, and it has been speculated that they may share a common cause (Nishimura et al. 1999).

Morphogenesis of the ureter and kidney

The kidneys and urinary tract develop from the mesonephric ducts. The ureteric bud emerges as an outward pouch of the mesonephric duct during the 4th week of gestation and gives rise to the kidney and ureter. Reciprocal signalling between the ureteric bud and the adjacent metanephros induces the ureteric bud to branch and form the collecting ducts. Simultaneously, the metanephric mesenchyme becomes epithelialised and forms the major part of each nephron. The distal end of the mesonephric duct inferior to the ureteric bud forms the common excretory duct that gives rise to the trigonum of the urinary bladder. Programmed cell death (apoptosis) is involved in directing the insertion of the ureter into the bladder (Batourina et al. 2005).

The regulation of ureteral budding and the growth of the ureter is controlled through a signalling complex that include the glial-derived neurotrophic factor (Gdnf), the tyrosine kinase receptor and the co-receptor Gdnf family receptor (Gfrα1). Prior to ureteral budding Gdnf is expressed in the mesenchyme along the mesonephric duct, but it is then restricted to the metanephric mesenchyme, where
it promotes ureteral budding by binding to tyrosine kinase receptor and Gfrα1 receptors in the mesonephric duct (Murawski & Gupta 2006). The transcription factors Pax2, Eya1, Six1, Sall1 and Hox11 positively regulate Gdnf expression in the metanephric mesenchyme (Bouchard 2004). The bone morphogenetic protein BMP4, the transcription factors Foxc1/Foxc2, the signalling complex Slit2/Robo2 and the receptor tyrosine kinase antagonist Sprouty1 all negatively regulate the Gdnf/Ret signalling pathway (Murawski & Gupta 2006). After controlling budding of the ureter the Gdnf/Ret signalling pathway also regulates the growth and elongation of the distal ureter. All the components of the pathway are regulated by vitamin A (Batourina et al. 2002). These data indicate that vitamin A and the Gdnf pathway are requisites for the formation of a normal vesico-ureteric junction.

2.2 Anti-reflux mechanisms in the ureter

The anatomical and functional factors generally associated with the anti-reflux properties of the ureter are: 1. length of the intramural ureter, 2. attachments to the trigone, 3. an oblique course through the bladder wall, 4. Waldeyer’s sheath (or space), 5. closure of the ureteric orifice when bladder muscle contraction causes micturition due to the muscle attachments that the ureter has with the bladder wall, 6. compression of the intravesical ureter against the bladder muscle as the urine fills the urinary bladder, causing the intravesical pressure to rise, 7. active peristalsis of the ureter, which prevents the reflux of intravesical urine into the ureter.

The vesicouretic junction and ureteric orifice act as a valve with an active and passive flap function to prevent reflux of the vesical contents into the ureter. To achieve this “flap-valve” function, the intravesical ureter has to have an oblique course as it enters the bladder, the length of the intramural ureter must be sufficient and it must have proper muscular attachments to the trigone and bladder wall (Johnston 1962, Tanagho et al. 1965, Zatz 1965). Hutch (1961) showed that the length of the vesical ureter at birth was 0.5 cm, compared with 1.4 cm in adulthood, and that its length correlated inversely with the incidence of VUR (Hutch 1961). The function of the ureter is also of importance, in that the normal ureter propels boluses of urine into the bladder in an antegrade fashion. It is this that enabled Zerin and Paquin to produce VUR in dehydrated rabbits (Zinner & Paquin 1963). In humans, an increase in urine output has been shown to abolish VUR (Ekman et al. 1966). The fact that VUR often resolves spontaneously with
age may partially be explained by the human autopsy findings of Cussen that a progressive increase in muscle cells in the ureter occurs from 12 weeks of gestation to 12 years of age (Cussen 1967). It has also been shown that the length of the intravesical segment of the ureter increases almost linearly with age (Marchal et al. 1982) and the muscular support for the submucosal portion of the ureter expands (Noordzij & Dabhoiwala 1993).

2.3 Congenital abnormalities of the ureter and kidney

There is an association between many congenital urinary tract anomalies and the occurrence of VUR. In children with unilateral renal agenesis the contralateral kidney exhibits VUR in 37–50% of cases (Emanuel et al. 1974, Song et al. 1995). In ureteric duplication VUR occurs in about 50% of the lower pole ureters (King et al. 1974) and in uretero-pelvic obstruction the occurrence of contralateral VUR is about 10% (Lebowitz & Blickman 1983). Vesicoureteral reflux is also common in children undergoing imagery postnatally on account of antenatal hydronephrosis, its occurrence being 38% in Zerin’s study (Zerin et al. 1993).

Congenital anomalies of the kidney and urinary tract (CAKUT) have recently been associated with the angiotensin type 2-receptor gene (Atgr2) (Nishimura et al. 1999). Studies in mutant mice indicate that inactivation of the Atgr2 results in identical CAKUT to those found in man. Also, the characteristic features of CAKUT in Atgr2-null mutant mice and humans having Atgr2 mutations share the same anatomical spectrum and relative frequency of the specific anatomical anomalies. They both have a male preponderance, the anomalies are frequently unilateral and they have a non-typical Mendelian inheritance. Both lack other structural organ anomalies, and the histological patterns of the anomalies present in the urinary tract are similar (Nishimura et al. 1999).
3 Imaging of vesicoureteral reflux

Three modalities are currently employed in the diagnostic imaging of vesicoureteral reflux. Two of these, voiding cystourethrography and radionuclide cystography, are radiological, while the third, voiding urosonography, using ultrasound has gained acceptance since the mid-1990s as a diagnostic method for detecting VUR in children.

Vesicoureteral reflux is usually a radiological observation and a dynamic phenomenon that can be seen intermittently on imaging, although it can fluctuate significantly in grade, so that massive dilating VUR may occur at one bladder filling only to be absent at the next (Cremin 1979, Jequier & Jequier 1989, Fettich & Kenda 1992, Lebowitz 1992). Voiding cystourethrography provides a crude estimate of the occurrence of VUR, and although it is the best method currently available, it would be delusory to believe that by tailoring it to some resemblance of a physiological process it is a reflection of the sequence of events in the urinary bladder of an active child (Cremin 1979).

3.1 Voiding cystourethrography

Cystography or post-contrast conventional radiographs are now virtually obsolete for the imaging of VUR, having been replaced by voiding cystourethrography (VCUG), which should be performed using fluoroscopy, ideally pulsed fluoroscopy. VCUG is the only imaging method that allows VUR grading, detection of intrarenal reflux and visualisation of the urethra. The bladder needs to be catheterized, after which the x-ray contrast medium is instilled and both anterior-posterior and oblique views of the bladder are taken. In case of VUR the ureters and kidneys are visualized. The urethra is also documented during voiding, and a post-void film of the bladder is obtained.

3.2 Radionuclide cystography

There are two methods for radionuclide cystography (RNC): direct RNC and indirect RNC. The procedure for direct RNC is similar to that for VCUG but the urinary bladder is instilled with radionuclide and imaging is performed with a gamma (scintillation) camera connected to a computer. Indirect RNC does not need bladder catheterization, but the examination can only be performed on toilet-trained children following a dynamic renogram preceded by intravenous
administration of the radionuclide. The main disadvantage of indirect RNC is its questionable sensitivity for detecting VUR (Conway & Kruglik 1976, Bower et al. 1985, Majd et al. 1985). Neither direct nor indirect RNC allows precise grading of VUR. The advantages of direct RNC over VCUG are that it allows continuous recording of VUR and results in a lower radiation dose.

3.3 Voiding urosonography

Following the first report of a VUR diagnosis obtained using ultrasound (US), published in 1976 (Tremewan et al. 1976), numerous attempts have been made to implement US for the regular diagnosis of VUR. Both indirect and direct methods have been used. The indirect methods are based on US of the native urinary tract, trying to identify features associated with VUR (upper tract dilatation, pelvic or ureteral wall thickening, absence of corticomedullary differentiation and signs of renal dysplasia). These features are unspecific, however, and a normal US does not exclude VUR (Blane et al. 1993).

Direct US involves instilling various substances intravesically after catheterization or suprapubic puncture of the bladder. The first substance to be used was physiological saline, but this was superseded by US contrast agents such as sonicated albumin and later with contrast agents containing stabilized microbubbles (Darge & Riedmiller 2004).

The limitations of US for VUR imaging include the observations that: it is impossible to exclude VUR even when the US scan is normal, some US contrast agents do not provide a long enough imaging time for detecting VUR on both sides, visualisation of the male urethra is insufficient and US images are not completely convincing for the absence or presence of VUR (Darge & Riedmiller 2004). On the other hand, comparisons of US with VCUG or RNC have given concordance rates of over 80–90% (Berrocal et al. 2001, Radmayr et al. 2002, Ascenti et al. 2003). Contrast-enhanced voiding urosonography provides a radiation-free alternative to VUR imaging but due to the rather high cost of US contrast media and problems in reliable grading of the severity of VUR this approach is not in widespread use. Voiding urosonography can be used in selected situations in order to avoid imposing a radiation burden on children (Darge & Riedmiller 2004).
3.4 Magnetic resonance imaging

To avoid ionizing radiation, several investigators have explored magnetic resonance imaging (MRI) as an alternative to VCUG (Lee et al. 2005, Teh et al. 2005, Takazakura et al. 2007). These examinations were performed under sedation and the urinary bladder was catheterized and filled with gadolinium. The image quality of MRI is inferior to that of VCUG for imaging VUR (Vasanawala et al. 2009). MRI voiding cystography lacks ionizing radiation and has a sensitivity of roughly 90% for VUR as compared with VCUG but needs sedation and catheterizing of the urinary bladder.
Occurrence and classification of vesicoureteral reflux

Vesicoureteral reflux is common in children with urinary tract infection and renal tract anomalies, but its overall occurrence is not well known. Several attempts were made to address this issue during the 1950’s to the 1970’s, and the general conclusion was that the occurrence of VUR in humans is around 0.4% to 1.8% (Sargent 2000). This figure is highly debatable, however, and it is most likely that the occurrence of VUR in normal children is significantly higher than these early estimates would suggest. In a large German study Köllermann and Ludwig found a high occurrence of VUR in children hospitalized for non-UTI conditions such as inguinal hernia etc., and it seems that the reported low occurrence of 1–2% in the general population is implausible (Kollermann & Ludwig 1967).

4.1 General occurrence


Most review articles on VUR suggest that the general occurrence in healthy children is around 1–2% (Eccles & Jacobs 2000, Lama et al. 2000, Mak & Kuo 2003), but the primary studies are more heterogeneous and prevalence rates have been 0–30%. The reason for this wide variance is that the primary studies on healthy children have not used the same cystography methods, and imaging methods differ in their sensitivity in detecting VUR. The populations have also
included children of different ages, and as VUR tends to resolve spontaneously with increasing age, such populations are not intercomparable.

Reports on the occurrence of VUR also give varying results because of differences in study design, heterogeneous patient characteristics and selection bias. The methods used for diagnosing VUR vary and the studies have a certain reporting bias. The occurrence of VUR is also age-related, the highest figures being found in young children (Smellie et al. 1975, Walker et al. 1977, Wennerstrom et al. 1998, Hannula et al. 2010, Venhola et al. 2010b). The vast majority of VUR cases (85%) occur in females. All in all, it may be concluded that the occurrence of VUR in children remains undetermined.

4.2 Classification of vesicoureteral reflux

VUR severity is nowadays graded according to an international classification system (Lebowitz et al. 1985), but unfortunately several different grading systems have prevailed in earlier times, e.g. those of Friedland (1977) (Friedland 1977), Colodny and Lebowitz (1974) (Colodny & Lebowitz 1974), Melick et al. (1962) (Melick et al. 1962), King et al. (1968) (King et al. 1968), Dwoskin and Perlmutter (1973) (Dwoskin & Perlmutter 1973) and Smellie et al. (1964) (Smellie et al. 1964). This has led to a situation in which it is impossible to compare historical and contemporary studies because of the different criteria for defining VUR, and meta-analyses inevitably lack power on account of the problems of combining large numbers of irreconcilable studies.

The severity of VUR has been most commonly reported in terms of the classification used in the International Reflux Study (Lebowitz et al. 1985) which is based on the original work of Heikel and Parkkulainen (Heikel & Parkkulainen 1966). The grading of VUR in voiding cystourethrography is based on whether the contrast medium enters the ureter and reaches the kidney and whether dilatation of the ureter, renal pelvis and calyces is present or not. The now widely accepted classification used in the International Reflux Study does not take into account the possible occurrence of intrarenal reflux.

4.3 Intrarenal reflux

The exact occurrence and significance of intrarenal reflux (IRR) is unknown. The occurrence of intrarenal reflux during retrograde pyelography was first reported by Brodeur et al. in 1965 (Brodeur et al. 1965) and was termed calicotubular
backflow by Amar in 1970 when noting 8 cases during voiding cystography (Amar 1970). In 1975 Hodson et al. observed in experiments on Sinclair miniature pigs that urine could enter the kidney parenchyma in the presence of VUR and elevated bladder pressure (intrarenal reflux, IRR) and that the combination of UTI and IRR led to grave renal scarring (Hodson et al. 1975). They also noted that severe sterile IRR produced focal renal scarring resembling the renal scars found in the kidneys of humans with VUR and postulated that the “water-hammer effect” of sterile VUR pounding on the renal parenchyma on account of IRR could cause permanent renal damage even without UTI (Hodson & Twohill 1984). Later Ransley and Risdon (1975) conducted similar experiments on young Welsh pigs and found that infection was necessary to produce renal scarring in the presence of VUR (Ransley & Risdon 1975). They also noted that sterile VUR could scar the kidney only if the intravesical bladder pressure was elevated for a prolonged time (Ransley et al. 1984). Since then it has been the general opinion that sterile reflux cannot cause renal damage in patients with VUR and normal bladder function.

Ransley and Risdon induced VUR surgically in their animals. The kidneys of the pigs they used had a high proportion of compound renal papillae (having large orifices opening directly onto the calyces) and they were able to demonstrate that renal scarring occurred in segments drained by these compound papillae while the segments drained by simple nipple-shaped papillae (having slit-like orifices opening obliquely into the convex surface of the papillae) did not show IRR or scarring. Later Funston and Cremin (1978) showed that compound and simple papillae occur in a ratio of 1:4 in the human kidney, with the majority of the compound papillae to be found in the upper pole of the kidney, where renal scarring is usually seen in patients with VUR (Funston & Cremin 1978). Since then, Cremin (1979) has noted that the different configurations of the papillary orifices could be the result of post mortem fixation techniques, and that IRR might merely be related to the anatomical site of the orifices on the flat plateau where they are situated (Cremin 1979). Also, intrarenal reflux seems to occur in all areas of the kidneys and not just in the polar regions (Amar 1970, Rolleston et al. 1974).

The current dogma is that the primary cause of renal scarring (reflux nephropathy) is infected urine entering kidney parenchyma due to IRR, even to the extent that a single infection is sufficient to cause such a dramatic effect on a kidney. This “Big Bang” theory was developed by Ransley and Risdon (Ransley & Risdon 1981) and is in contrast to the “water-hammer” theory postulated by
The “Big Bang” theory was supported by the results of Hinchliffe et al. (1992) based on studies of nephrectomy specimens from patients with VUR (Hinchliffe et al. 1992). In contrast, Bernstein and Arant (1992) hypothesized that gross parenchymal scars are formed as a result of a series of “Little Bangs” that lead to a process of renal atrophy (Bernstein & Arant 1992). In 2002 Coulthard et al. repeated the pig studies of Ransley and Risdon but this time using adult pigs, to test whether the kidneys “outgrow” their risk of scarring (Coulthard et al. 2002). The results were in favour of the “Big Bang” theory, as it was concluded that the kidneys remain vulnerable to scarring for as long as VUR prevails. The results of Hannerz et al. (1987) were somewhat at variance with the “Big Bang” theory, as they found renal scarring in 49 out of 2500 children and the scars were usually “polar”, but IRR was found in 14 children and affected all areas of the kidney in 50% of these cases (Hannerz et al. 1987). They also noted that the higher VUR grades more often had “atypical” lateral scars in the kidney parenchyma in areas not considered to have compound papillae.

4.4 Primary vesicoureteral reflux

Primary vesicoureteral reflux is a term indicating a situation where VUR is an isolated finding not related to any known complex congenital urinary tract anomaly, multiorgan malformation syndrome, neuro-muscular bladder dysfunction or bladder outlet obstruction.

The ability of the ureterovesical junction to prevent vesicoureteral reflux is based on the length and function of the extreme distal end of the ureter in the submucosa of the urinary bladder (Tanagho et al. 1969, Mackie et al. 1975). Effective ureterovesical valve function is also dependent on the width of the ureteric opening (Vermillion & Heale 1973), the musculature of the trigone and ureter (Baker & Gomez 1998) and co-ordinated peristalsis in the ureter (Shafik 1996).

4.5 Secondary vesicoureteral reflux

Secondary VUR is caused by bladder outflow obstruction and consequent elevated bladder pressure at rest and during micturition. This obstruction can be either anatomical or functional. The degree and duration of the obstruction influence the severity of the secondary VUR. The most common anatomical obstruction in boys is a congenital posterior urethral valve, and VUR is found in
about 50% of these cases (Henneberry & Stephens 1980). Anatomical obstruction is virtually non-existent in females.

Functional causes are common in both sexes and include neurogenic bladder, non-neurogenic neurogenic bladder and bladder dysfunction. Patients with meningomyelocele often have VUR due to congenital neurogenic bladder (Bauer et al. 1982) as do otherwise healthy children with non-neurogenic neurogenic bladder (Hinman syndrome) (Allen 1977). Constipation, uninhibited bladder contractions, decreased bladder compliance, incomplete bladder emptying during micturition, detrusor decompensation and dyscoordinated micturition have all been associated with functional problems that may cause reflux in the ureterovesical junction (Sillen 1999, Sillen et al. 1999, Chen et al. 2004).

4.6 Prenatally detected vesicoureteral reflux

The occurrence of VUR in children evaluated postnatally for antenatal dilatation of the urinary tract has been between 3–25% (Ring et al. 1993, Zerin et al. 1993, Sargent 2000, Lee et al. 2006, Kitchens & Herndon 2009). In Sargent’s review the figure in the presence of antenatal hydronephrosis was around 20% in the nine eligible studies (Sargent 2000). Unfortunately these data are unreliable because antenatal dilatation is not always present in VUR children and antenatal ultrasound screening does not detect all cases of dilatation.

4.7 Familial occurrence of vesicoureteral reflux

The initial evidence suggesting a genetic basis for VUR came from case reports in monozygotic twins (Stephens et al. 1955). Since that report early evidence of familial clustering (Tobenkin 1964), ethnic difference (King 1972) and increased risk of VUR in first-degree relatives of an index case (Uehling et al. 1992, Kaefer et al. 2000) has been published. Family studies have suggested that the pattern of inheritance could be autosomal dominant with incomplete penetrance (Chapman et al. 1985), autosomal recessive (Pasch et al. 2004), sex-linked (Middleton et al. 1975) or multifactorial (Burger 1971). The main limitations in these studies have been the inability to detect all affected individuals and the lack of control groups, which mean that they result only in hypotheses that VUR is genetically heterogeneous and is caused by a number of genes acting either alone or in combination (Murawski & Gupta 2006).
According to a review of 10 primary studies of siblings with VUR, the occurrence of VUR in these siblings is between 11% and 67% (Hollowell & Greenfield 2002). In his extensive review combining eight eligible studies, Sargent found that the occurrence of VUR in siblings is around 33% (Sargent 2000). However, these sibling studies lacked consistency in the verification of VUR in all family members, and thus it is difficult to estimate the true occurrence of VUR in families when starting out from index cases.

4.8 Effect of age, sex and race on the occurrence of VUR

The detection of VUR is influenced by the age of the child; the highest occurrence is found in young children and figures gradually decrease with increasing age (Smellie et al. 1975, Walker et al. 1977, Wennerstrom et al. 1998, Hannula et al. 2010, Venhola et al. 2010a, Venhola et al. 2010b).

Boys are generally diagnosed with VUR earlier in life than girls, because boys more often have antenatal hydronephrosis as a reason for postnatal VCUG and present with pyelonephritis at an earlier age than girls. Also, the grade of VUR is more severe in boys and renal scarring is found more often (Rolleston et al. 1970, Smellie et al. 1975, Goldraich & Goldraich 1992, Yeung et al. 1997, Nakai et al. 2003, Silva et al. 2006). In contrast, when VUR is diagnosed in connection with the evaluation of UTI later in childhood females predominate (Shopfner 1970, Weiss et al. 1992). In adults, females outnumber males in ratios from 5:1 to 18:1 (Lipsky & Chisholm 1971, Amar et al. 1974, Berquist et al. 1975, Kincaid-Smith et al. 1984, el-Khatib et al. 1990, Kohler et al. 1997), but this is at least partly due to differences in the occurrence of urinary tract infection, in that females have these infections more often than men and are thus examined more actively.

Kunin et al. (1964, 1970) were the first to draw attention to the racial variation in the occurrence of UTIs, VUR and renal scarring (Kunin 1964, Kunin 1970). VUR is significantly less common in African American children with UTI than in Caucasians, but the grade and resolution rate in affected children are similar in both groups (Askari & Belman 1982, Skoog & Belman 1991, Melhem & Harpen 1997). No significant difference exists after the age of 10 years (Melhem & Harpen 1997).
4.9 Relation of vesicoureteral reflux to multi-organ malformation syndromes

Although the vast majority of VUR patients do not have any other organ malformations, VUR can be a part of several syndromes. Renal-coloboma syndrome patients have optic nerve colobomas, renal dysplasia and VUR (Sanyanusin et al. 1995), while patients with Branchio-oto-renal syndrome have renal dysplasia or agenesis, renal and ureteral duplication anomalies and VUR (Ruf et al. 2004). The X-linked recessive form of Kallmann syndrome is characterized by VUR, renal and ureteral duplication anomalies and renal agenesis (Duke et al. 1998), and several other syndromes have also had VUR associated with them (Ahmed 1990, Grisaru et al. 2000, Kolon et al. 2000, Chou et al. 2002). Patients with anorectal anomalies often have VUR (Narasimharao et al. 1983, Parrott 1985, Boemers et al. 1996), as do boys with a congenital posterior urethral valve (Parkhouse et al. 1988, Puri & Kumar 1996, Heikkila et al. 2009).

4.10 Vesicoureteral reflux in animals

The occurrence of vesicoureteral reflux varies among mammals. As in humans, its occurrence is related to the animal’s age. The occurrence in dogs was around 40% in three series (Lenaghan & Cussen 1968, Christie 1971, Newman et al. 1973), and while VUR is rare in adult monkeys but its occurrence was around 80% in young rhesus monkeys (Roberts 1974).

Rats show VUR in about 25% of cases at the age of 7–13 weeks (Angell et al. 1998), but Roberts claims that all rats have VUR (Roberts 1992). The occurrence in rabbits is around 40% (Roberts 1992).
Resolution of vesicoureteral reflux

Vesicoureteral reflux seems to resolve during antimicrobial prophylaxis for the prevention of UTI. This has often been erroneously interpreted as suggesting that the patients have been cured by the antimicrobial prophylaxis, which is obviously not the case. Vesicoureteral reflux has a tendency for spontaneous resolution in many children, and the resolution rate depends somewhat on the initial grade of VUR and the age of the child at presentation. In theory this is a result of the elongation and maturation of the intramural ureter as the ureter and urinary bladder grow (Stephens & Lenaghan 1962). A change in bladder dynamics during the maturation of the child could be another factor affecting the spontaneous resolution of VUR.

Since King et al. (1974) showed that low grade VUR has a high spontaneous resolution rate, cases involving the surgical correction of VUR have gradually decreased in number (King et al. 1974) and subsequent follow-up studies of children with VUR have shown that vesicoureteral reflux tends to resolve spontaneously – a longer time being necessary for the more severe grades. In general, a low grade of VUR and young age at diagnosis correlate with a better chance of spontaneous resolution. An average of 20–30% of low-grade VUR cases are resolved every 2 years (Smellie et al. 1975). The overall resolution rates reported have been 80% for grade I, 60% for grade II and 50% for grade III (Skoog et al. 1987), while Edwards et al. (1977) quote a resolution rate of 41% for grade IV VUR (Edwards et al. 1977) and McLorie et al. (1990) show that even high grade VUR (grades III to V) can resolve in time (McLorie et al. 1990). In the follow-up study of Wennerström et al. 73% of the children with grades III or IV VUR showed resolution (Wennerström et al. 1998). Resolution rates do not seem to vary with age among low-grade VUR cases and grade III VUR has a 50% chance of resolving itself with time even if diagnosed after the age of 10 years – in accordance with the overall resolution rate (Greenfield & Wan 1996). The age of a child with VUR even of a higher grades (III or IV) did not affect the resolution rate in the International Reflux Study of VUR (Weiss et al. 1992).
6 Vesicoureteral reflux as a pathological phenomenon

VUR has long been recognized in connection with renal damage and recurrent UTI, but the recent explosion in clinical and experimental data on the controversial role of VUR in these problems has created a conundrum regarding the “true” nature of VUR. In fact many clinicians now regard VUR not as a disease in itself but rather as a marker of a heterogeneous condition of the whole urinary tract.

6.1 Historical notes on vesicoureteral reflux

Clinical VUR was first visualized over 100 years ago, but notions on the anatomy of the ureter and its function had existed since Roman times. Galen, in the second century, was the first to illustrate the oblique insertion of the ureter into the urinary bladder (Polk 1965), and Leonardo da Vinci made similar detailed descriptions of the vesicoureteral junction. They both discovered that it functions as a one-way valve preventing any retrograde flow of urine from the bladder to the ureter (Lines 1982). Centuries later, Semblinow demonstrated VUR experimentally in rabbits and dogs in his dissertation of 1833 (Semblinow 1883), and a decade later Pozzi accidentally severed a patient’s ureter during a gynaecological procedure and reported the first case of vesicoureteral reflux in humans (Pozzi 1893).

Sampson (1903) attributed the valvular mechanism of the vesicoureteral junction to the obliquity of the ureter and suggested that VUR could be identified by cystoscopy after the instillation of methylene blue solution in the bladder; i.e. immediate cystoscopy after lavage might reveal blue fluid exiting the orifice of a refluxing ureter (Sampson 1903). Between 1923 and 1927 Graves and Davidoff published a series of papers on the ureter, bladder and VUR (Graves & Davidoff 1927). Based on experiments with dogs and rabbits, they demonstrated that reflux was caused by either increased bladder pressure, infection or irritation of the bladder or destruction of the vesicoureteral valve. They also noted that VUR could be missed in single film cystography and found that it could be demonstrated more successfully by fluoroscopy.

Before the emergence of cystography as a routine means of imaging for VUR, investigators had noticed the significant occurrence of VUR associated with many urological diseases, so that Kretschmer (1916) concluded that VUR
was a common cause of renal infection (Kretschmer 1916). Soon afterwards, Bumpus (1924) reviewed a series of 1036 cystograms and concluded that VUR was never observed in normal adults but might be seen in normal children (Bumpus 1924). A year later Eisendrath, Katz and Glasser concluded that VUR was secondary to infection (Eisendrath et al. 1925). Bartrina (1935) was probably the first to recommend routine cystography to be performed during examinations on children with pyuria (Bartrina 1935).

6.2 After World War II

World War II resulted in vast numbers of soldiers with spinal cord injuries, and studies on paraplegics after the war revealed large numbers of VUR cases among these patients. Talbot and Bunts (1949) used “delayed and voiding” cystography and found that this technique increased the sensitivity to of the method for identifying VUR (Talbot & Bunts 1949). They also noted that paraplegics with dilated urinary tracts showed VUR but those with normal urograms did not. A few years later Hutch (1952) described a causal relationship between VUR and chronic pyelonephritis in paraplegics, and this is taken to mark the beginning of the modern era in our understanding of the functional significance of VUR (Hutch 1952). Probably the first to demonstrate the transient nature of VUR was Stewart (1953, 1955), when he reported his experiences with delayed cystography. After filling the bladder he took x-rays every 15 to 30 minutes over a period of one to three hours and observed that VUR could be seen on one film but was absent on the next, only to recur on the following film, thus destroying the concept that VUR was either always present or totally absent (Stewart 1953, Stewart 1955).

6.3 Vesicoureteral reflux, hypertension and chronic renal failure

Vesicoureteral reflux (VUR) has been thought to be a major risk factor for renal scarring, predisposing patients to long-term kidney damage and leading to hypertension, chronic renal insufficiency and complications of pregnancy (Jacobson et al. 1989, Smellie et al. 1998, Wennstrom et al. 2000a). Renal scarring, i.e. reflux nephropathy, is claimed to be a major cause of hypertension (Kincaid-Smith & Becker 1978, Arze et al. 1982, Zucchelli & Gaggi 1988, Jacobson et al. 1989) and a cause of end-stage renal failure in about 8–16% of adult cases in industrialized countries (Fenton et al. 1995, Stewart & Hodson 1995). In children it is said to be the reason for end-stage renal failure in 30–50%

Several long-term follow-up studies have shown that the occurrence of recurrent urinary tract infections does not correlate with the extent of renal scarring (Smellie et al. 1981a, Arze et al. 1982, Jacobson et al. 1989). Primary uncomplicated VUR - regardless of recurrent UTIs, severity of reflux, modality of therapy or presence of renal scarring – is not associated with the development of hypertension (Wolfish et al. 1993), i.e. the prevalence of hypertension in children with renal scarring and dilating VUR has been shown to be identical to that in the general population when the same patients were evaluated as middle-aged adults after 37 years of follow-up (Lahdes-Vasama et al. 2006). Braren et al. (1988) were similarly unable to show any correlation between hypertension and the grade of VUR, renal scarring or changes in renal function (Braren et al. 1988). In a large population survey in Sweden the investigators were unable to demonstrate chronic or terminal renal failure in any children with non-obstructive pyelonephritis between 1986–1994 (Esbjorner et al. 1997). This is in accordance with an earlier report from Sweden (Esbjorner et al. 1990) and the authors stated that the proportion of preventable cases is low among Swedish children with chronic renal failure. Craig et al. achieved similar results in a survey in Australia and New Zealand commenting that the currently advocated diagnosis and treatment protocols for VUR may be of no benefit in the prevention of end-stage renal disease (Craig et al. 2000).

The major problem in evaluating data from reports on children derived from dialysis or transplant registers (Loirat et al. 1994, Warady et al. 1997) in order to address the contribution of UTIs and VUR to end-stage renal disease is that these register do not distinguish between children with and without urinary tract obstruction or major renal abnormalities. It seems that urinary infections per se do not cause end-stage kidney disease (Sreenarasimhaiah & Hellerstein 1998). Furthermore, the male-to-female ratio was reversed among children with chronic renal failure in the ItalKid register as opposed to those suffering from VUR, making it unlikely that the combination of end-stage renal disease and VUR in children could be the result of VUR alone (Ardissino et al. 2003).
6.4 Vesicoureteral reflux in the neuropathic bladder, bladder outlet obstruction and other conditions

In Sargent's review the mean frequency of VUR in neuropathic bladder (commonly meningomyelocele) cases was around 33% (6 eligible studies). More than half of the boys suffering from a congenital posterior urethral valve had VUR (4 studies), and the occurrence of VUR in children with anorectal malformations was around 30% (3 studies). Also, the mean occurrence of VUR among children with congenital renal abnormalities such as multicystic kidney, ureteropelvic junction obstruction and renal agenesis or ectopic kidney was 24% (16 studies), but in duplex systems it was 46% (4 studies) (Sargent 2000).
7 Vesicoureteral reflux and dysfunctional elimination syndrome

Voiding dysfunction was first related to VUR by Koff *et al.* in 1979 (Koff *et al.* 1979), since when the identification and treatment of bladder and bowel dysfunction (dysfunctional elimination syndrome, DES) associated with VUR have been an important area of good clinical practice in children with VUR. Bladder or bowel dysfunction can be associated with a greater risk of febrile UTI and slower resolution of the VUR and it can affect the cure rate of endoscopic therapy for VUR. The rate of postoperative UTI is greater in children with DES than in those without (Peters *et al.* 2010).

The symptoms of DES in toilet-trained children without anatomical or neurological abnormalities include wetting, urgency, frequency and constipation with or without soiling (Koff *et al.* 1998, Shaikh *et al.* 2003). Voiding dysfunction, or DES, is a diagnosis of exclusion, obtained by taking a detailed history and performing a physical examination to rule out any anatomical or neurological aetiology. The only methods for studying the functioning of the lower urinary tract objectively are urodynamic, but the role of urodynamic examinations in the diagnostic work-up of children with UTI and VUR is not well established, due to the inconsistent results obtained (Glazier *et al.* 1997, Greenfield & Wan 2000). The urodynamic procedure is invasive and usually unpleasant for the child, and it is quite possible that the results will not alter the therapy or influence the final outcome (Mattoo 2007). Some authors nevertheless state that urodynamic examinations are important for the evaluating children with VUR and establishing a prognosis (Koff & Murtagh 1983, Homsy *et al.* 1985, Scholtmeijer & Nijman 1994, Yeung *et al.* 1998), some to the extent that they consider the evaluation of a child with VUR and UTI to be incomplete until a thorough examination of lower urinary tract function has been performed (Koff & Murtagh 1983). Urodynamic investigations have detected abnormalities suggestive of DES in up to 76% of children with VUR (Chandra & Maddix 2000). Chen (2004) showed that DES can affect 36% of girls and 20% of boys with VUR (Chen *et al.* 2004), while in a prospective study by Naseer and Steinhart (1997) 77% of the children who developed new renal scars while on antimicrobial prophylaxis were found to have DES (Naseer & Steinhardt 1997).

The most typical findings in urodynamic examinations of children with DES and VUR are bladder instability and dyscoordinated voiding (Koff *et al.* 1979, Homsy *et al.* 1985, Nielsen 1989, Homsy 1994). If clinical evidence and/or a
urodynamic examination is suggestive of DES, the possible options for treatment include behavioural therapy, anticholinergic medication, alpha blockers and the treatment of possible constipation (Peters et al. 2010). The use of anticholinergic drugs for neurologically normal children with VUR resulted in a four-fold reduction in recurrent UTIs and even tripled the resolution of VUR compared with children receiving only prophylactic antibiotics (Koff & Murtagh 1983). In some children, however, the urodynamic dysfunction has been seen to be transient and has shown spontaneous improvement (Chandra et al. 1996).

It is claimed that DES is common and often unrecognized in children with VUR. As DES is arguably associated with delayed VUR resolution, an increased rate of recurrent UTIs and increased failure of reimplantation surgery, it is claimed that the evaluation and management of DES is an integral part of the management of every child with VUR (Koff et al. 1998).
8 Vesicoureteral reflux and reflux nephropathy

The first to use the term reflux nephropathy to describe the coarse renal scarring associated with VUR was probably Bailey in 1973 (Bailey 1973). Prior to his influential work the scarred kidney often seen in conjunction with recurrent urinary tract infection and VUR had been labelled as an outcome of chronic atrophic pyelonephritis, implying that there was a continuous low-grade infection present in the affected kidneys. Bailey underscored the significance of VUR in this condition, however, pointing out that urinary tract infection is not the cause of these small scarred kidneys but that VUR is the essential component in the genesis of the renal injury (Bailey 1979). The doctrine that VUR caused chronic atrophic pyelonephritis (reflux nephropathy) was formulated in the 1960’s (Bialestock 1963, Hutch et al. 1963, Rosenheim 1963, Haran et al. 1967, Hodson 1967, Scott & Stansfeld 1968) and in later series as many as 60% of kidneys associated with VUR showed renal scarring (Scott & Stansfeld 1968, Dwoskin & Perlmutter 1973, Filly et al. 1974, Smellie et al. 1975, Olbing et al. 1992). Characteristically, the scarring is segmental and recognized radiologically by areas of parenchymal thinning or in scintigraphy as a “cold” area or deformation in the renal contour. Intrarenal reflux has been regarded as the link between VUR and segmental renal scarring. Since the 1970’s it has become evident that there are two populations of children with renal scarring associated with VUR: those with congenital abnormalities and those with acquired renal scarring due to pyelonephritis (Wennerstrom et al. 2000b, Murawski & Gupta 2006). It seems that the congenitally unscarred kidneys remain reasonably unscarred, and that clinically it is very difficult to distinguish acquired pyelonephritic scarring from a congenitally abnormal (dysplastic) kidney.

8.1 Occurrence of renal scarring

Children with VUR often present with renal scarring, and there seems to be an increasing occurrence with age: 10% in infants (Bourchier et al. 1984), 26% in children under 8 years of age (Smellie et al. 1975), 47% in children over 8 years of age (Smellie et al. 1975) and 94% adults (Kincaid-Smith & Becker 1978). The highest rate of renal scarring (98%) in children with VUR in the literature seems to be that reported by Shah et al. in 1978 (Shah et al. 1978), although Ditchfield et al. noted that 63% of their children with renal scarring did not show VUR and 55% of those with VUR did not have renal scars in scintigraphy (Ditchfield et al.
Hodson estimated the occurrence of reflux nephropathy in the general population to be 1 in 250 (Hodson 1978). Renal scarring is also associated with the grade of VUR (Dwoskin & Perlmutter 1973, Skoog et al. 1987), but some controversy exists on this point (Zucchelli & Gaggi 1988, Jakobsson et al. 1994). Berg (1992), on the other hand, found that the presence or degree of VUR did not seem to influence renal functioning or scarring, since patients with or without VUR had both a decreased glomerular filtration rate and scarring in a follow-up IVP (Berg 1992).

Acute pyelonephritis can cause renal scarring without VUR (Smellie et al. 1985, Bisset et al. 1987), and renal scarring with VUR can exist without infection (Gordon et al. 1990, Anderson & Rickwood 1991, Risdon 1993, Risdon et al. 1993). There are also children with VUR and urinary tract infections who do not develop renal scars (Smellie et al. 1975). It seems that the prerequisite for acquired renal scarring after infection is the infection itself rather than the presence or absence of vesicoureteral reflux (Rushton et al. 1992).

8.2 Pathogenesis of renal scarring

The pathogenesis of renal scarring can be either a result of abnormal metanephric development, i.e. congenital dysplasia, or acquired segmental scarring due to infection. Acquired scarring is considered to be a sequel of one or more episodes of pyelonephritis caused by bacteria entering the kidney parenchyma (Dillon & Goonasekera 1998). This infection induces an inflammatory and an immune response, and resolution of the infection itself is followed by reperfusion reactions that cause interstitial damage and result in focal segmental scarring of the kidney (Smith 2008). Acquired renal scarring can also result from the combination of VUR and severe bladder outlet obstruction, as demonstrated by Hodson and Edwards (Hodson & Edwards 1960). When infection is present in addition to abnormal bladder pressure and VUR, the scarring is accelerated (Hodson & Edwards 1960). Later Ransley and Risdon – using a pig model, as did Hodson and Edwards – showed that sterile VUR without bladder outlet obstruction does not cause renal scarring, thus challenging the notion of a “water-hammer effect” of sterile reflux (Ransley & Risdon 1979, Ransley et al. 1984). They also defined the possible significance of the renal papillary configuration for renal scarring. The compound papillae usually located in the polar regions of kidneys enable intrarenal reflux and allow bacteria to enter the parenchyma, so that the polar
regions are the most susceptible to scarring (Ransley & Risdon 1974, Ransley & Risdon 1979).

Congenital renal scarring is usually associated with VUR, and the affected kidney is generally smooth and small in appearance (Risdon 1993, Risdon et al. 1993). These infection-free kidneys are dysmorphic, hypoplastic and usually associated with high grades of VUR (Najmaldin et al. 1990, Burge et al. 1992, Marra et al. 1994). In theory, incorrect interplay and regulation of ureteral budding with renal blastema during the first weeks of gestation results in congenital renal scarring that is often indistinguishable from an acquired lesion in either urography or scintigraphy (Mackie et al. 1975, Murawski & Gupta 2006). The involvement of renal dysplasia in the pathological evaluation of lesions in VUR kidneys can be taken as evidence of a congenital origin for these lesions (Gil-Salom et al. 1991). Evidence of dysplasia has been reported in 10 to 50% of nephrectomies of kidneys with VUR (Ambrose et al. 1980, Becu et al. 1988). An element of infective scarring can always be superimposed on dysplastic areas (Risdon 1987).

Findings indicating that new renal scars almost exclusively develop in kidneys that have pre-existing scarring support the theory of congenital renal dysplasia, and new renal scarring hardly ever develops in normal kidneys (Merrick et al. 1995b, Kohler et al. 2001). Also, Matsuoka et al. have demonstrated that profound histological changes can be found in areas of kidneys diagnosed as normal on the basis of DMSA or CT scans and having a histology suggestive of global rather than focal glomerulosclerosis, indicating a cause other than acquired renal scarring (Matsuoka et al. 1994).

8.3 Imaging of renal scarring

Before the advent of modern scintigraphic imaging techniques, renal scars were detected by intravenous urography (IVU). The characteristic appearance of renal scarring and reflux nephropathy in IVU is focal parenchymal thinning of the renal cortex and corresponding calyceal deformity or clubbing (Hodson & Edwards 1960). The scarring can vary from a small single polar lesion to a small, scarred kidney with minimal function. The radiological changes seen indicative of reflux nephropathy can also be generalized calyceal dilatation with cortical atrophy or impaired renal growth with focal scarring or global atrophy (Hodson & Edwards 1960). The problems with IVU include possible adverse reactions to the contrast medium, ionizing radiation obscuring of the kidneys by the bowel contents and
the need to obtain the image directly after injecting the contrast medium (Stokland et al. 1999). Tomography can be helpful in delineating the renal contours, but it adds to the radiation dose. It should also be remembered that other conditions that include loss of tissue, such as renal infarction and papillary necrosis, may simulate scarring (Stokland et al. 1999).

IVU has now been virtually displaced by $^{99m}$Tc-dimercaptosuccinic acid (DMSA) scintigraphy for the detection of renal scarring, with the result that the frequency of renal scars has been shown using DMSA to be about three times higher than the rate of 6–15% obtained with IVU (Jakobsson et al. 1994, Stokland et al. 1996). The advantages of DMSA over IVU include the provision of a quantitative assessment of renal differential function, the reduced radiation dose and the absence of contrast-induced reactions (Dillon & Goonasekera 1998). While DMSA scintigraphy is more sensitive than IVU in detecting renal scars, the significance of the lesions seen in DMSA scintigraphy but not in IVU remains unclear (Leonidas 1997). It is highly likely that most of the small lesions seen in DMSA are of negligible clinical importance (Leonidas 1997, Stokland et al. 1999).

$^{99m}$Tc-mercaptoacetyl triglycine renography (MAG3) is a dynamic examination in which the uptake and excretion of a renal tracer is followed by means of a dynamic acquisition programme for 20–30 minutes post injection. Since the uptake phase in the MAG3 renogram lasts only one or two minutes, the image quality is not as good as with DMSA. Gordon et al. (1992) found that MAG3 renography had a 88% sensitivity and 88% specificity in detecting focal parenchymal defects relative to DMSA scintigraphy. The sensitivity of renal ultrasound in detecting renal scarring is inferior to that of voiding cystourethrography and DMSA (Mahant et al. 2002, Moorthy et al. 2004). Ultrasonography gives a rapid overview of the kidneys, but being highly operator-dependent, it gives only limited information about the calyces and renal parenchymal lesions, and since it is difficult to obtain a reliable follow-up or second opinion on ultrasound images, it is not generally used for diagnosing renal scarring.

Computed tomography (CT) is not routinely used for diagnosing renal scarring in children. It can provide excellent information about the renal outlines but this potential advantage over scintigraphy is usually reduced by motion artefacts, especially in small children. The collecting system is more difficult to visualize in CT than in urography, and calyceal deformities may be difficult to detect. As the calyces are difficult to define, parenchymal thinning of the renal
scar may also be missed (Saxton 1995). The major objections to the use of CT for diagnosing renal scarring are the radiation dose, the need for a contrast medium, the need for sedation in children and the costs involved.

Magnetic resonance imaging (MRI) has high contrast resolution and could be an attractive modality for imaging renal scarring. MRI is not widely used in this context at present due to its limited availability, high costs and long scanning times, requiring sedation or general anaesthesia in children.
9 Vesicoureteral reflux and urinary tract infection

Before Stewart reported inconstant VUR in a series of delayed cystograms the general belief was that pyelonephritis resulted from the lymphatic spread of infection from the perineal area to the kidneys (Stewart 1953). Vesicoureteral reflux seemed to explain the pathogenesis of pyelonephritis and its relation to recurrent UTI by permitting bacteria to enter the upper urinary tract and causing stasis of the urine, thus allowing these bacteria to multiply and establish UTI.

Vesicoureteral reflux is most frequently found in children with UTI because imaging for VUR after a urinary tract infection has for a long time been a recommendation (Koo & Bloom 1999). In a review of 19 studies of children with VUR, Sargent (2000) concluded that the mean occurrence of VUR was 31.1% (Sargent 2000). There were no significant differences between the sexes or based on whether the child had cystitis or pyelonephritis or whether the child was under or over 5 years of age. In the report of the International Reflux Study Committee in 1981 the occurrence of VUR in children with UTI had varied from 29% to 50% (International Reflux Study Committee 1981). Here the children evaluated for VUR due to UTI showed two peaks in occurrence, one in the first year (mostly boys) and the other in the fourth year (mostly girls) (Merrick et al. 1995a). By contrast, Smellie et al. found no age-related differences in the occurrence of VUR in children with UTI and no reliable clinical features that could distinguish children with VUR from those without (Smellie et al. 1981b).


Urinary tract infection (bladder infection) and the accompanying inflammation can also cause VUR by lessening bladder compliance, elevating intravesical pressure and distorting the vesicoureteral junction (Van Gool & Tanagho 1977). Gram-negative bacterial endotoxins can cause ureteral atony, which can also be a contributing factor (Jeffs & Allen 1962). VUR can be transient in some children and occur only during episodes of acute cystitis, resolving after treatment of the infection and the subsequent diminution in inflammation (Kaplan 1980).
10 Management of vesicoureteral reflux

The possible modalities of treatment for VUR are multifarious. The grade and laterality of VUR, renal function and scarring, bladder capacity and function, associated anomalies, the age of the child, the level of compliance and preferences among treatment options must all be considered. There is no consensus as such on whether therapy is needed at all, and if it is considered necessary, what therapy should be chosen.

10.1 Medical management

The medical management of VUR usually aims at preventing recurrences of UTI, and is thus not a treatment for VUR per se. Little attention was paid to medical treatment for children with VUR before 1980, with the exception of Smellie et al., who up to 1960 had just kept children with VUR on antimicrobial prophylaxis and under observation, even in severe cases (Smellie et al. 1998). In 1997 Lohr et al. published a cross-over study comparing nitrofurantoin prophylaxis with a placebo, in which they found that all the symptomatic UTIs occurred during the placebo periods and none during the nitrofurantoin periods (Lohr et al. 1977). There has been no sound demonstration that renal scarring could develop in children with VUR in the absence of UTI. In such cases the medical management usually consists of low-dose prophylactic antibiotics that are continued until the VUR resolves. This approach has been endorsed by several professional societies, including the American Academy of Paediatrics (American Academy of Pediatrics 1999), the Swedish Medical Research Council (Jodal & Lindberg 1999) and the American Urological Association (Elder et al. 1997).

Conservative VUR management should include attention to regular bladder emptying, adequate fluid intake, avoidance of constipation and proper hygiene (Bellinger 1985). Bladder dysfunction should be treated when present (Koff & Murtagh 1983). Periodic urine cultures and repeated radiological examinations to assess the possible resolution of VUR have also been generally advised (Bellinger 1985).

High urinary antibiotic concentrations can be achieved with a variety of medications and can be used to control a broad range of uropathogens. Medication is usually given once a day at a half of the standard therapeutic dose, and night-time administration is generally preferred. The antibiotics used are usually trimethoprim with or without sulfamethoxazole and nitrofurantoin (Wald...
2006, Williams et al. 2006). These medications are not without side-effects, however, and can promote the development of resistant bacteria (Conway et al. 2007).

Long-term antimicrobial prophylaxis has its limitations. It is sometimes ineffective in preventing breakthrough UTI, and recurrent UTI rates in children with VUR range from 25–38% despite prophylaxis (Birmingham Reflux Study 1987, Tamminen-Mobius et al. 1992). Anti-microbial resistance of the bacteria is a major concern individually and globally. Approximately 10% of children with long-term prophylaxis have adverse reactions to the medication (gastro-intestinal symptoms, skin rash, hepatotoxicity, haematological complications and occasionally bone marrow suppression or even Stevens-Johnson syndrome) (Uhari et al. 1996, Karpman & Kurzrock 2004), and compliance may also be questionable in cases of long-term medication (Copp et al., Bollgren 1999).

In 1997 the Pediatric Vesicoureteral Reflux Guidelines Panel of the American Urological Association (AUA) recommended continuous antibiotic prophylaxis as an initial therapy for children with VUR of grades I-IV (Elder et al. 1997). This recommendation was based on expert opinion rather than any clear scientific evidence, and the practise has been challenged more recently. In 2000 Cooper et al. discontinued antibiotic prophylaxis in children with persistent VUR (grades I-IV) and none of them developed any new renal scars (Cooper et al. 2000). A retrospective study by Thompson et al. the following year showed that the children with VUR had similar rates of recurrent UTIs and new renal scarring regardless of whether they were receiving antibiotics or not (Thompson et al. 2001). Similar results have been found in several other studies (Hellerstein & Nickell 2002, Al-Sayyad et al. 2005, Georgaki-Angelaki et al. 2005). In a randomized controlled trial with a hundred patients, Pennesi et al. compared antimicrobial prophylaxis with no treatment over a period of two years (Pennesi et al. 2008) and found that antibiotic prophylaxis was ineffective in preventing recurrent pyelonephritis or renal damage. Kang et al. (2009) found that antibiotic prophylaxis was a significant independent risk factor for recurrent febrile UTI in infants (Kang et al. 2009).

Despite the lack of evidence for its effectiveness, long-term antibiotic prophylaxis has been a common practise in the management of children with VUR for decades. As several uncontrolled studies indicate that antibiotic prophylaxis can safely be discontinued and recent randomized controlled studies show that continuous antibiotic prophylaxis offers no benefit or only limited
benefit relative to intermittent antibiotic therapy, the practise of continuous prophylaxis with antibiotics has been questioned (Costers et al. 2008).

10.2 Surgical management

The surgical abolishment of VUR in children is efficient and historically it has been the treatment of choice in severe cases. On the other hand, the complications of open surgery have led to an active search for less invasive and less problematic means of eradicating VUR. It has never been clear who benefits from surgery relative to the other therapeutic options, when and what kind of surgery should be employed and whether surgery should be the first line of therapy or the last resort when everything else fails. The fundamental principles of all reimplantation techniques are the same: the ureter must be tunnelled through the detrusor muscle and a sufficient submucosal tunnel must be created.

10.2.1 Open surgery

A variety of techniques have been developed for abolishing VUR. These can be categorized anatomically as extravesical, intravesical or combined depending, on the approach to the refluxing ureter. Common to all is an attempt to replicate the normal anatomy of the ureteric orifice and to create a valvular mechanism that prevents VUR but allows an unobstructed flow of urine from the ureter to the urinary bladder.

The earliest attempt to reimplant the ureter surgically was reportedly that of Nussbaum in 1876 (Beer 1933). As early as 1903 Sampson performed a ureteral reimplantation in a human using local anaesthesia (Sampson 1903), and by 1950 the anatomy and function of the ureterovesical junction was well understood, but the importance of VUR was highlighted only after cystographic imaging methods were developed. Then large numbers of VUR cases were detected and the condition was found to be associated with urinary tract infection. This knowledge led to the generation of appropriate surgical operations. The first of these were ureteric advancement techniques (Vermooten et al. 1934, Paquin 1959, Hutch 1963). Stevens and Marshall (1943) were amongst the first to perform a modern reimplantation of the ureter (Stevens & Marshall 1943), much like the technique presented more than a decade later (1958) by Politano and Leadbetter, a technique that is still popular today (Politano & Leadbetter 1958). This means of correcting VUR has been in use since 1958 and was widely accepted internationally soon
after its presentation (Politano & Leadbetter 1958). The method now seems to be declining in popularity, but it is still the preferred technique for many surgeons, especially for unilateral corrections, where it will not interfere with the contralateral ureteric orifice. Success rates of 97–99% in correcting VUR are cited in the literature (Brannan et al. 1973), but higher complication rates than with the Cohen technique have been noted (Carpentier et al. 1982).

Dodson (1946) reported another ureteral reimplantation technique (Dodson 1946) which is in principle identical to that presented later by Lich (Lich et al. 1962) and Gregoir (Gregoir 1964). When Hutch (1950) presented his first method of ureteral implantation for use with paraplegic patients the cure rates for VUR started to be acceptable (Hutch 1952). A few years later he revised his technique (Hutch et al. 1968). Glenn and Anderson advocated a tunnelled advancement of the ureter (Glenn & Anderson 1967), and Paquin tunnelled the ureter outside the bladder (Paquin 1959), both techniques that are still in use today.

The tenet for correcting VUR in the early 1960s was to perform antireflux surgery and also to relieve bladder neck obstruction, as the latter was considered to be present in virtually all cases. The proponents of the concept of bladder neck obstruction (Fisher 1965, King et al. 1965, McGovern & Marshall 1967) were challenged only after negative clinical experiences at the end of the decade showed this not to be an accurate hypothesis (Donohue & Leadbetter 1964, Politano & Harper 1964, Johnston 1966, Harrow et al. 1967). The “gold standard” among surgical antireflux techniques was that first used in 1966 and published in 1975 by Cohen (Cohen 1975). This was adopted enthusiastically and soon superseded the Politano-Leadbetter technique, which had an equally good cure rate but far more complications. This method surpasses all others in ease of performance and an adequate submucous antirefluxing tunnel can be achieved in virtually every patient. Cohen’s cross-trigonal method is versatile and can be used to correct both primary and secondary VUR. Also, it can be used in small children and with small bladders, and especially with thickened neuropathic bladders. Success rates of 97–99% have been reported (Wacksman 1983, Burbige 1991), and complication rates seem to be lower than with the Politano-Leadbetter technique (Carpentier et al. 1982). The Cohen and Politano-Leadbetter techniques have stood the test of time and are still widely used as surgical methods for the correction of VUR.
Cystoscopy has a limited role in the diagnosis of VUR, but historically important in this connection is the study of Lyon, which emphasised cystoscopic visualisation and classification of the ureteric orifices, as some forms were thought to be associated with VUR (Lyon et al. 1969). The “golf-hole” configuration of the ureteric orifice associated with a short intramural tunnel in the ureter had important prognostic implications for the outcome of VUR (King et al. 1974). Orifice configuration has now been found to be of only modest value for the diagnosis of VUR or for predicting the likelihood of its resolution (Duckett 1983).

Endoscopic treatment relies on the theory that any object or (injectable) material placed between the ureter and bladder muscle will enable coaptation of the ureteric orifice and thus reduce or cure VUR. This concept has been adopted and modified from open surgical techniques, but has a certain extra appeal on account of the technical simplicity, acceptable success rate, lessened morbidity and potential cost-effectiveness of endoscopic treatment.

When Matouchek reported the first minimally invasive endoscopic technique for correcting VUR, a new era dawned (Matouschek 1981). After Puri and O’Donnell verified and popularized the method (O’Donnell & Puri 1984, Puri & O'Donnell 1984), it gained huge international success due to its simplicity, effectiveness and fairly low complication rate. The original injectable material, Teflon, raised concerns about safety, and injectable collagen was introduced. Concerns about the safety of collagen and possible adverse reactions to it (Leonard et al. 1990) have nevertheless led to a search for more suitable substances. Any material used in the endoscopic treatment of VUR should be suitable and safe for use in humans. Suitability implies that it should be easy to inject into place and should maintain its volume for the time necessary for preventing VUR. Safety refers to the material’s biocompatibility, non-antigenicity and non-migratory qualities. A vast number of autologous and non-autologous materials have been tested for their ability to meet these criteria. For the present dextranomer microspheres with hyaluronic acid (Dx/HA) have superseded other materials and constitute the most widely used substance for injection treatment, but the long-term results are not encouraging (Chertin & Kocherov 2010)

Several autologous and non-autologous injectable materials have been developed and tested for use in the endoscopic correction of VUR. The first reports on Teflon for the management of VUR were published in 1984 (O'Donnell
& Puri 1984), but this was later abandoned due to particle migration and granuloma formation. Purified bovine dermal collagen, cross-linked with glutaraldehyde, was introduced next, but some children developed serum antibodies to bovine collagen and the substance was no longer widely used for fear of possible connective tissue disease such as dermatomyositis (Leonard et al. 1998). Collagen also decreases in volume with time. Later it was also shown that as many as 13% of patients had submucosal calcifications at the injection site 10 years after the procedure (Knudson et al. 2006). Polydimethylsiloxane has also been used, but has now been withdrawn in the United States due to particle migration and safety concerns. Polyvinyl alcohol was tried as well, but was shown in animal experiments to cause fibroblastic proliferation and tumorigenic effects (Joyner & Atala 1997). Bioglass particles suspended in sodium hyaluronate were studied by Walker et al. (Walker et al. 1992), but the problems with these included difficulties in finding the correct suspension and the laboriousness of injecting them through a small needle. Bioceramics (hydroxyapatite and tricalciumphosphate suspension) have been tried, but they have not achieved popularity. A detachable, self-sealing silicone balloon has also been developed for the endoscopic treatment of VUR (Atala et al. 1992), but, although it has been approved in the United States for the treatment of urinary incontinence, it has not gained popularity for the treatment of VUR. Autologous fat has also been tried, but its long-term stability is not good enough and has gained little acceptance as a treatment for VUR. Human chondrocytes and bladder muscle have been tried as well, but the tedious process of harvesting and the cell technology involved means that they have remained at the level of experimental substances (Joyner & Atala 1997).

The substance used most widely for the endoscopic correction of VUR nowadays is Dx/HA, which has been promoted as a non-migratory, non-immunogenic and non-carcinogenic substance that could be suitable as a first line of treatment for VUR in children (Puri et al. 2006). There is no proof that these statements are true, however, and the systematic review carried out by Routh et al. (2010) shows that there are not enough high-quality studies yet available on this substance (Routh et al.). The authors conclude that there is an urgent need for randomized trials designed to address the utility of Dx/HA injections by comparison with other forms of therapy for VUR. Despite the lack of substantive data, the use of Dx/HA has increased dramatically in recent years (Lendvay et al. 2006). It is disturbing, however, that authors who have followed their patients up for more than a year have reported a significant loss of effectiveness over time.
Lee et al. (2009) quote a success rate of only 46% for the correction of VUR at 1 year (Lee et al. 2009) and Läckgren et al. (Lackgren et al. 2001) and Oswald et al. (Oswald et al. 2002) have also noted a significant failure rate with longer follow-up intervals.

Perhaps the most interesting finding was mentioned by Routh et al. (2010), that the hospital at which the patient receives treatment was the single most important feature that governed the choice of procedure for children with primary VUR (Routh et al.). Although the most appropriate use of endoscopic treatment for VUR is not known, the extreme disparities between hospitals in the United States in their use of injection treatment seem inherently worrying, as these disparities cannot be explained by differences in patient intake between these hospitals.

In a recent meta-analysis of 63 eligible studies, Elder et al. (2006) compared the results of endoscopic therapy with those of open surgical management and found that endoscopic therapy had lower success rates (a VUR resolution rate of 67% compared with 96% for open surgery) (Elder et al. 2006). They also found that if the first injection in endoscopic therapy was not curative the success rates for the second and third injections were 54% and 34%, respectively.

10.2.3 Laparoscopic surgery

Major advances in laparoscopic surgery during the past decade have made this another potential method for correcting VUR. The advantages of laparoscopy over open surgery include smaller incisions, less discomfort, brief hospitalization and quick convalescence. These advantages are less pronounced in VUR surgery, however. Atala et al. (1993) were the first to correct VUR laparoscopically in an animal (Atala et al. 1993), and Ehrlich et al. in children (Ehrlich et al. 1994). There is a long learning curve in laparoscopic surgery for VUR, and patient selection has to be strict. Laparoscopy also requires a team with at least two surgeons, the instruments required are less than ideal for children, the operative time is longer than with open surgery and the costs are considerably higher. This explains why, after some initial enthusiasm, laparoscopic surgery for VUR has not gained wide acceptance.
11 Controversies over the management of VUR

The management of VUR has evolved greatly over the last two decades. The dichotomous paradigm of antimicrobial prophylaxis versus open surgery has been slowly replaced by a more complicated and individualized approach. Patients and physicians can now choose between observation, either with or without antimicrobial prophylaxis, endoscopic injection treatment, open surgery, laparoscopic surgery, or even robotic surgery. Current evidence unfortunately does not indicate which management option would be the treatment of choice for any given patient.

11.1 No treatment versus treatment

If VUR were a significant and modifiable factor in the development of recurrent UTI or new renal scarring, we would have a marked reduction in these outcomes in randomized controlled trials and in the results of meta-analyses based on the published RCTs on this subject. The unanimous conclusion of recent meta-analyses on the treatment of VUR has been that surgical abolishment of VUR entails the same risk of new renal parenchymal injury or recurrent non-febrile UTI as does antimicrobial UTI prophylaxis and spontaneous resolution of VUR (Wheeler et al. 2003, Venhola et al. 2006). This could imply that no treatment could be an option for children with VUR, but no formal studies have yet addressed this possibility. Data from the available RCTs dealing with intervention for children with VUR do not provide evidence as to whether the current practice of diagnosing and treating children with VUR confers important health benefits, as there have been no adequate trials that have included a “no treatment” arm.

11.2 Antimicrobial prophylaxis versus operative treatment

Many children with VUR are initially managed with prophylactic antimicrobials. The major disadvantage of such medical therapy is increased antimicrobial resistance, now a worldwide problem. Since antimicrobials are sometimes ineffective in preventing breakthrough UTI and compliance with long-term medication is questionable, physicians have started to discontinue prophylactic medication, without detrimental results in terms of either renal function or rates of recurrent UTIs. Antimicrobial medication has no effect on the presence of VUR or on its resolution.
There are few absolute indications for surgery to abolish VUR. Most authorities suggest surgery for older children with grade V VUR, and most agree that febrile breakthrough UTI implies mandatory surgery. Some controversy exists even in these matters, however. For years the standard surgical intervention for VUR was open ureteral reimplantation. Open surgery has been shown to be highly effective for treating VUR, but entails a risk of ureterovesical obstruction, incisional pain or postoperative complications.

Trials undertaken to compare surgery and antimicrobial prophylaxis with antimicrobial prophylaxis alone have not demonstrated any additional benefit of surgery except for a reduction in the risk of febrile UTIs (Wheeler et al. 2004).

11.3 Open surgical treatment versus endoscopic injection

A new surgical procedure, endoscopic injection, has become common recently, a procedure that is performed entirely through the child’s urethra and requires no incisions. This is said to reduce postoperative pain and complications, bladder spasms and scarring relative to open surgery, although no formal comparisons of the techniques have yet been performed (Stenberg et al. 2002, Kirsch et al. 2003). A recent meta-analysis has nevertheless revealed that endoscopic treatment has markedly lower success rates than open surgery (Elder et al. 2006). Even so, the use of endoscopic injection therapy has grown tremendously in the past decade and it now constitutes roughly half of all antireflux procedures carried out in the United States (Routh et al., Lendvay et al. 2006). This uncritical enthusiasm for endoscopic injection therapy is due to its ease of performance, the minimal hospitalization required and a good deal of aggressive marketing, in spite of the fact that the procedure is invasive and requires general anaesthesia in children, its short-term and long-term success rates are lower than for open procedures and its long-term safety is unknown. Unfortunately, the surgical management of paediatric VUR remains controversial and the factors governing the choice of procedure for any given patient remain unclear.
12 Purpose of the present research

Vesicoureteral reflux is common in children, but its detection, management and follow-up are controversial. The purpose of this work was to carry out a critical analysis of the literature on childhood VUR management, to explore whether it is possible to limit invasive diagnostic imaging and urodynamic examinations of children suspected of having VUR and to analyse whether the general assumption regarding the occurrence of VUR in children was plausible. The specific aims were:

1. to evaluate the comparability and repeatability of analyses based on urodynamic reports by analysing inter-observer and intra-observer agreement in the interpretations of urodynamic examinations performed on children;
2. to examine whether urodynamic examinations can be used to predict the recurrence of UTI and the presence of VUR in children;
3. to conduct a meta-analysis of the efficacy of medical and surgical treatment for VUR in children using the recurrence of UTIs, renal growth and renal scarring as endpoints;
4. to validate a pre-established clinical decision rule for targeting voiding cystourethrograms more efficiently at children after the first urinary tract infection; and
5. to investigate the occurrence of VUR in children.
13 Results

Five original papers are included in this thesis.

13.1 Urodynamic measurements in children

We evaluated the comparability and repeatability of analyses based on urodynamic reports by analysing inter-observer and intra-observer agreement in the interpretations of urodynamic examinations performed on 15 children. A total of 17 interpretations were obtained, as two sets were analysed twice to assess intra-observer variability.

13.1.1 Subjects

Four paediatric urologists at three university hospitals in Finland produced the 17 assessments of urodynamic data. The cases were chosen at random by a urotherapy nurse from the records of Oulu University Hospital. All the patients’ identification data was removed, but the age and sex of each child were given to enable the evaluation of theoretical maximum cystometric bladder capacity. The urodynamic reports of 6 girls and 9 boys were used and cases numbers 6 and 15 were analysed twice on different occasions to assess intra-observer agreement on their urodynamic curves. The children had undergone urodynamic examinations on account of enuresis, UTI and VUR, posterior urethral valves, dysuria and covert bladder extrophy.

13.1.2 Methods

The urodynamic measurements were performed in 1998 and 1999 using a Dantec Duet urodynamic unit (Dantec Medical A/S, Skovlunde, Denmark). The original colour prints with automatically computed values were used, but the observers were allowed to make their own calculations whenever needed. The observers were given a simple data sheet on which the recorded values were printed. In the case of an abnormal finding the observer was asked to state whether the value was pathologically high or low. Specific suggested urodynamic diagnoses were requested with regard to the urethral pressure profile, bladder compliance, detrusor function during filling and uroflow curves. The urodynamic curves were analysed on 2 occasions 6 months apart and the examinations that were analysed
twice were placed in different sets, since the urologists were not informed that intra-observer variation was being analysed as well. Only methods, definitions and units that are recommended by the International Children’s Continence Society were used. Intra-observer and inter-observer agreement was analysed using kappa statistics.

13.1.3 Results

The kappa values for the analyses of the shape of the urethral pressure profile indicated fair to moderate agreement. The observers were also asked to give an interpretation of overall sphincter function, and in this they agreed only to a fair degree. Detrusor activity during filling was interpreted with good agreement, but the analyses of bladder compliance varied markedly. The observers gave identical replies to the questions on voided volume and maximal flow. The urodynamic diagnoses based on the shape of the flow curve had kappa values indicating a moderate consensus, although further analysis revealed that there was unanimous agreement regarding only 6 pressure flow curves. The remaining 11 results were interpreted as pathological by at least 1 investigator, and most of the patients received 3 different urodynamic diagnoses based on the single pressure flow curve. The urodynamic data for 2 children with enuresis were analysed twice, and all the observers reached exactly the same conclusion on both occasions when considering the urethral pressure profile and the filling phase of voiding cystometry. On the other hand, none of the observers analysed the uroflow curves in the same way on the two occasions.

We found poor agreement among the observers in the interpretation of the uroflow curves, and this discrepancy was especially evident in inconsistencies between the urodynamic diagnoses of flow patterns. We thus found that, despite standardization and the publication of normal reference values, suggested clinical diagnoses based on analyses of urodynamic measurements in children can vary widely among paediatric urologists. Inter-observer variation in analyses also complicates the evaluation of treatment modalities applied to patients with lower urinary tract dysfunction. We suggest that the consistency of the interpretations of urodynamic studies in children be improved before they are accepted as measures for comparing urodynamic diagnoses or the effects of treatment between patient series. Since our patients were all neurologically normal, some of our observations might not be applicable to spina bifida patients.
13.2 Meta-analysis of vesicoureteral reflux and urinary tract infection in children

We evaluated the efficacy of medical and surgical treatment for vesicoureteral reflux (VUR) in children by means of a meta-analysis using the recurrence of urinary tract infections (UTIs), renal growth and renal scarring as endpoints.

13.2.1 Materials and methods

We searched the medical literature for the period January 1966 to August 1998 using the MEDLINE database. The primary Medical Subject Headings search terms were “vesicoureteral reflux” and “kidney” combined, and all subheadings were included when generating the main literature database. An additional search covering the period September 1998 to May 2002 was made later to add the latest publications to the database, and some further articles were identified from the references in those papers accepted from the search for closer review. All the articles were reviewed on the basis of their title or abstract. Case reports, solely neonatal or adult studies, reviews and editorial articles, animal studies, articles about secondary or sibling VUR and publications concerned exclusively with UTI were excluded.

Articles were included only if they reported on children or adolescents (1 to 18 years old) with VUR, had at least one defined treatment group, gave data on either recurrences of UTI or kidney growth or both and were written in English. Information on the following aspects was gathered for a meta-analysis: (1) operative or conservative treatment of VUR, (2) disappearance of VUR, (3) recurrences of UTIs, and (4) kidney growth and possible scarring during follow-up. Kidney growth was assessed as a dichotomous variable (normal or abnormal), as reported in the original articles. Details of the study design (allocation of patients to treatment groups) and data collection (e.g. prospective, retrospective) were also recorded. We reviewed all the accepted articles independently and a consensus was sought on all the data collected from them. The data were then analysed using StatsDirect (Stats Direct Ltd., UK) statistical software to complete the meta-analysis. Before making the final meta-analysis we did tests for heterogeneity between the studies for each endpoint and all the results were insignificant, the lowest p-value being 0.26 for combining the studies on the disappearance of VUR.
13.2.2 Results

The first search yielded 542 publications on VUR and kidney status, and the second 97, making a total of 639 publications. We chose 139 of these for further analysis, and found that five of them met the criteria for the final meta-analysis. These were three randomized controlled trials dealing with childhood VUR, one prospective non-randomized trial and one retrospective controlled study.

We evaluated a vast number of publications, only a few of which were suitable for further analysis and none had information on all the clinically important endpoints. Several studies were concerned with highly selected patient populations and the majority had a retrospective design, merely presenting a series of patients treated at the institution in question. The indications for treatment were not always given and the patient population was seldom described. Only a few publications gave data on the sexes independently, and the results (kidney complications or resolution of VUR) were often reported in terms of the number of kidneys, which sometimes made it impossible to draw conclusions concerning what happened to the patients. The use of four systems for grading VUR made some studies difficult to compare. Many did not monitor the resolution of VUR, and several did not grade the severity of the UTIs during follow-up. We did not notice any marked improvement in study design over time, and the cumulative value of the publications was modest. Thus the modest power of this meta-analysis is partly due to the fact that only five studies were eligible for evaluation according to the criteria described, which reflects the unfortunate state of trials concerning the treatment of VUR in children. It is obvious from our meta-analysis that surgery abolishes VUR effectively, but we could find no significant difference between conservative and operative treatment in terms of the recurrence of UTIs, kidney growth or scarring.

The total numbers of patients treated surgically and medically for resolution of VUR were 329 and 326, respectively. Markedly better resolution of VUR was achieved in the surgically treated cases during a relatively short follow-up period, in terms of both numbers of patients (pooled OR=0.033; 95% CI 0.010–0.107; p<0.0001) and numbers of ureters (405 and 380 in the surgical and medical groups, respectively) (OR=0.020; 95% CI 0.005–0.079; p<0.0001). There were no statistically significant differences in kidney growth (375 kidneys in the surgical group and 377 in the medical group) (OR=2.46; 95% CI 0.74–8.16; p=0.14) or scarring (OR=1.05; 95% CI 0.71–1.55; p=0.80). Similarly, no significant difference in the pooled number of UTIs during follow-up was noted.
between the 247 patients in the surgical group and the 259 in the medical group (OR=0.80; 95% CI 0.49–1.29; p=0.36). We could not assess differences in these parameters between boys and girls because of a lack of data.

On the basis of the results of our meta-analysis we suggest that conservative treatment may be indicated for the vast majority of children with VUR, and that such children could be monitored for some years on conservative therapy before performing any corrective surgery. If there are frequent breakthrough UTIs, or if prophylactic antimicrobials are not tolerated, surgical correction of VUR should be considered.

13.3 Practical guidelines for imaging studies in children after the first urinary tract infection

We sought to validate a pre-established clinical decision rule for target voiding cystourethrograms more efficiently in children after the first urinary tract infection.

13.3.1 Patients and methods

We performed a retrospective evaluation of findings concerning 406 consecutive children, including 143 boys and 263 girls, aged 0 to 5 years who had been treated or referred for consultation for UTI from January 1, 1996 to December 31, 1999, as contained in the patient records of the Central Hospital of Central Finland, Jyväskylä (196 children), and Oulu University Hospital, Oulu (210 children). UTI symptoms, including fever, foul-smelling urine, abdominal pain, dysuria, feeding problems, nausea or vomiting and irritability or lethargy, were recorded together with laboratory blood count and CRP findings, the urine sampling method, and the results of a urinary dipstick screening test and urine culture. We analysed the findings and diagnoses resulting from renal US, VCUG, iVCUG and urography imaging. VUR was examined radiologically by VCUG in 157 cases and by iVCUG in 145. In 50 cases both examinations was performed. The worst VUR finding in each case was used for the analysis. VUR in VCUG was graded according to the international system. For iVCUG we considered VUR extending to the ureter as equivalent to grades I–II in VCUG and VUR extending at least to the pelvis of the kidneys as equivalent to grades III–V in VCUG. Anatomical abnormalities (duplex systems, single agenesis, abnormal kidney positioning and horseshoe kidney), and dilatation of the ureter(s), and/or
renal pelvis and calyces were identified in US. Upper urinary tract dilatation in US was graded as present or absent. All the US and VCUG imaging had been done by experienced paediatric radiologists.

We calculated the VUR risk score using the logistic regression model presented by Oostenbrink et al. (Oostenbrink et al. 2000). In this clinical decision rule the patients gender, age, highest CRP and urinary tract dilatation in US are evaluated to produce a VUR risk score (score = 6*male gender + 7*positive family history – 1*age + 1*CRP + 14*US dilatation). Family history of uropathology was not documented in our case histories and so this factor was not included in the analysis. The statistical analysis was performed with SPSS® 16.0.

13.3.2 Results

The decision rule of Oostenbrink et al. had good specificity (98%) but only modest sensitivity (24%) in identifying children with VUR of grades III–V in logistic regression analysis. This means that if the grade III–V VUR rate were about 30% in children with UTI, the positive predictive value (the proportion of those with a positive decision rule result who had grade III–V VUR) would be 84% and the negative predictive value (the proportion of those with a negative decision rule result who did not have grade III–V VUR) would be 75%. Thus, in this scenario we would have missed 26% of the grade III–V VUR cases when using this decision rule. If the frequency of grade III–V VUR in children with UTI was 10%, the positive predictive value would be 57% and the negative predictive value would be 98%. In that scenario we would have missed 43% of the true grade III–V VUR cases.

Similarly, an abnormality in US did not reliably predict VUR in our patients. If we had performed VCUG only on the children with US abnormalities, 50% would have proved not to have VUR, while we would have missed almost 20% with clinically significant grade III–V VUR, who would have been among those with normal US findings.

Several predictive tools for identifying VUR have been proposed in order to target VCUG better at children with UTI, but we still do not have a useful clinical decision rule for predicting VUR. One could argue, however, that it is uncertain whether identifying and treating children with VUR confers any true clinical benefit, and thus identifying children with VUR may even be unimportant. We suggest that it is not possible to predict VUR reliably. The recent guidelines
recommending a search for VUR cannot be revised using the decision rule of Oostenbrink et al.

13.4 Occurrence of vesicoureteral reflux in children

The reported low occurrence of vesicoureteral reflux in the general population seems implausible, and we therefore wanted to test the hypothesis that reflux is more common and more independent of urinary tract infection than has previously been thought.

13.4.1 Patients and methods

We evaluated retrospectively the findings in 406 consecutive children (143 boys and 263 girls) aged 0 to 5 years with UTI admitted or referred for consultation to the Central Hospital of Central Finland in Jyväskylä (196 patients) and Oulu University Hospital (210 patients) in the interval 1st January 1996–31st December 1999.

Symptoms of UTI (fever, foul-smelling urine, abdominal pain, dysuria, feeding problems, nausea or vomiting and irritability or lethargy), body temperature, laboratory blood count, C-reactive protein (CRP), the method of urine sampling and the results of a urine dipstick screening test and urine culture were recorded. The diagnosis of UTI was considered certain if urine showed pyuria and any growth of a uropathogen in a suprapubic aspirate, or a monoculture of 10^3 colony-forming units/mL (CFU/mL) of uropathogen in a catheterization sample, or a monoculture of >10^5 CFU/mL of uropathogen in at least one midstream or bag specimen in the symptomatic patients (Group A, n = 311/406, 77%). Children who did not fulfil these criteria for certain UTI were classified as having possible UTI (Group B children, n = 56, 14%) or diagnosed as having a non-UTI infection if no pyuria and no significant bacterial growth in the urine was found (Group C, n = 39, 10%).

The renal US, VCUG and isotope voiding cystourethrography (iVCUG) findings were analysed. Vesicoureteral reflux was examined either radiologically by VCUG (n=152) or by the isotope technique (iVCUG, n=145). Both examinations had been performed in 50 cases. Voiding cystourethrographies were usually performed more than 3 months after UTI. Vesicoureteral reflux in VCUG was graded according to the international system, and the iVCUG results were categorized as follows: VUR extending to the ureter in iVCUG was taken as
equivalent to grades I to II in VCUG, and VUR extending at least to the pelvis of the kidneys in iVCUG as equivalent to grades III to V in VCUG.

13.4.2 Results

Voiding cystourethrography had been performed on 347 (85%) of the children, showing some grade of VUR in 120 cases (35%) and grades III–V in 69 (20%). Vesicoureteral reflux was found in 38/131 boys (29%) and 82/216 girls (38%). The children aged less than 2 years had VUR significantly more often than those aged 2–5 years (99/262, 38% vs. 21/85, 25%, p = 0.03) (Fig. 1). There were 98/276 (36%) children with VUR in Group A, 13/46 (28%) in Group B and 9/25 (36%) in Group C. The distribution of VUR grades was similar in Groups A, B and C. The method of VCUG did not alter the frequencies of VUR in the UTI reliability groups.

The overall prevalence of VUR was 35%, and its occurrence was the same in the children without proven UTI. Even the distribution of VUR grades was similar in all the diagnostic reliability groups. The fact that some of the children with non-UTI infection had been examined by VCUG made it possible to assess the prevalence of VUR in those with no reliable evidence of UTI, and our results indicate that the prevalence of VUR in healthy children is considerably higher than the figure of 1% suggested earlier.

13.5 Association of urodynamic findings with vesicoureteral reflux and recurrent urinary tract infections in children

We analyzed whether urodynamic studies can be used to predict the presence of vesicoureteral reflux (VUR) or recurrent urinary tract infections in children.

13.5.1 Patients and Methods

We recruited 136 consecutive children (116 girls) referred to Oulu University Hospital for further examinations after a urinary tract infection diagnosed and treated at outpatient health clinics. During the initial examinations we performed a urodynamic study (water cystometry), voiding cystourethrography (VCUG) and ultrasound imaging of the urinary tract on all the recruited children. After a follow-up period (average 7.8 years) we sent them a questionnaire to collect data on recurrent UTIs, and if we could not get a reply the families were interviewed
over the phone. We obtained full follow-up data on 116 out of the original 136 children (85%, 98 of them girls).

We analysed the results of the urodynamic studies and examined whether they could be used to predict recurrences of UTIs or the presence of VUR in these children. The urodynamic studies were considered abnormal if there was low bladder compliance or an abnormal rise of >15 cm$^3$O in detrusor pressure from the baseline before maximal bladder capacity was reached. Patients with marked perineal EMG activity during voiding and interrupted or staccato voiding were considered to have detrusor-sphincter dyssynergia. A deviation of more than +/- 2 SD from the expected bladder capacity was also considered abnormal.

The renal ultrasound and VCUG examinations were performed by an experienced paediatric radiologist. The anatomy of the kidneys (size, parenchyma, dilatation of calyces or pelvis), ureters (dilatation) and urinary bladder (bladder wall thickness, diverticulae, trabeculation, ureteroceles and residual urine) was analysed. In cases of a renal parenchymal defect or thinning, hydronephrosis (>10 mm anterior-posterior diameter of the renal pelvis), ureteral dilatation (>5mm), bladder wall abnormalities or marked residual urine (>10% of the age-expected bladder capacity) the results were considered abnormal. VUR was graded according to the international reflux grading system.

The initial UTI diagnosis was made in the outpatient clinics. Patients who had had severe symptoms and/or high fever (>38°C) were labelled as having had pyelonephritis, and less severe symptoms were considered to have been cystitis.

The follow-up data collected on questionnaires or in interviews over the phone included the number of recurrent UTIs, use of antimicrobials, presence of either day-time or night-time wetting, symptoms or findings of constipation or possible chronic illnesses.

The results of the primary examinations and follow-up data were analysed statistically with PASW 18.0 (SPSS inc., an IBM company, Chicago, USA).

13.5.2 Results

All 116 children (98 girls, 84%) had previously been healthy and 91/116 (78%) had had cystitis before the initial examination (Group A). The symptoms and findings in 25/116 (22%) were suggestive of a pyelonephritic urinary tract infection (Group B).
The urodynamic studies were abnormal in 18/116 (16%), 14 (15%) in Group A and four (16%) in Group B. Abnormal urodynamic results were seen in three (16%) males and 15 (16%) females.

No clinically important ultrasound abnormalities were found, and 23/116 (20%) of the children had VUR.

During the follow-up 24/116 (21%) had recurrent UTIs, comprising 24/96 in Group A (39%) but none in Group B. Of the children with VUR, 5/23 (22%) had recurrent UTIs while 19/93 (20%) children not having VUR had recurrent UTIs. Of the children having normal urodynamic findings 17/93 (18%) had had at least one recurrent UTI during follow-up, while of those with abnormal urodynamic results 4/18 (22%) had recurrent UTIs. In a logistic regression model a patient age of more than 4 years was associated with abnormal urodynamic examination results (OR=3.03, 95% confidence interval 0.98–9.0), but female gender, recurrent UTI and VUR were not significant risk factors.

We conclude that urodynamic examinations are insensitive as to the presence of VUR and cannot be used as a tool to predict recurrent UTIs in children with a UTI.
14 Discussion

Vesicoureteral reflux is a perplexing phenomenon. We do not know what exactly causes it, whether it is a benign or a pathological condition or what would be the best form of management – if any – for children suffering from it. It has been suggested that it may be associated with urinary tract infections, that it can often be found in patients with renal parenchymal defects and in some children and adults with end-stage kidney disease, but we do not know whether there are any causal relationships involved in these associations.

14.1 Vesicoureteral reflux – a benign condition?

The true occurrence of VUR in humans is uncertain, and the often-cited occurrence rates of 1–2% appear to be claims made without solid evidence. Owing to the invasive nature of imaging for VUR and the radiation burden involved, it is no longer ethically possible to evaluate the occurrence of VUR in healthy children. The reported low occurrence of vesicoureteral reflux in the general population seems implausible. In our work the overall occurrence of VUR was 35%, and its occurrence was the same even in the children without proven UTI (Venhola et al. 2010a). The fact that some of the children with non-UTI infection had been examined by VCUG, made it possible to assess the occurrence of VUR in those with no reliable evidence of UTI, and our results indicate that the occurrence of VUR in healthy children is considerably higher than the figure of 1% suggested earlier (Elder et al. 1997). In a large study carried out in Germany in 1967, Köllermann and Ludwig found a high occurrence of VUR in children hospitalized for non-UTI conditions, and this finding is confirmed by our results (Kollermann & Ludwig 1967). As it would be impossible to perform a study of that kind today, we have to settle for indirect evidence of the occurrence of VUR in healthy children.

The detection of VUR is influenced by the age of the child; the highest occurrence is found in young children and the figure gradually decreases with increasing age (Smellie et al. 1975, Walker et al. 1977, Wennerstrom et al. 1998, Hannula et al. 2010, Venhola et al. 2010a, Venhola et al. 2010b). This reflects the situation observed in other mammals, as VUR is rare in adult monkeys but is around 80% in young rhesus monkeys (Roberts 1974). We were also able to show that the occurrence of VUR was greatest in young children (Venhola et al. 2010a). This could imply that VUR is an age-related benign condition having a
considerable spontaneous resolution rate (Wennerstrom et al. 1998), and is usually explained as a result of the maturation of the uretero-vesical flap-valve and elongation of the intravesical ureter (Stephens & Lenaghan 1962). The dynamic nature of VUR, however, makes it difficult to rule out in any child. It is usually a radiological observation and a dynamic phenomenon that can be seen intermittently upon imaging and can fluctuate significantly in grade – so that massive dilating VUR may occur at one bladder filling only to be absent at the next (Cremin 1979, Jequier & Jequier 1989, Fettich & Kenda 1992, Lebowitz 1992).

In general boys are diagnosed with VUR earlier in life than girls, because boys more often have antenatal hydronephrosis as a reason for postnatal VCUG and present with pyelonephritis at an earlier age than girls. The grade of VUR is also more severe in boys and renal scarring is found more often (Rolleston et al. 1970, Smellie et al. 1975, Goldraich & Goldraich 1992, Yeung et al. 1997, Nakai et al. 2003, Silva et al. 2006). In contrast, when VUR is diagnosed in the evaluation of UTI later in childhood, females predominate (Shopfner 1970, Weiss et al. 1992). We were also able to demonstrate a small gender difference in the occurrence of VUR, but it was not very marked in our patients (Venhola et al. 2010a, Venhola et al. 2010b).

Vesicoureteral reflux can be a risk factor for renal scarring in the presence of UTI through the active transport of microbes from the urinary bladder to the kidney(s), but no causal connection between renal scarring and VUR alone has been established. New renal scars develop only after UTI, with or without VUR, and evidence supporting the role of VUR in leading to pyelonephritis is controversial (Garin et al. 1998). In adults new renal scarring is noted only in previously scarred kidneys and is associated with recurrent UTI (Kohler et al. 2001). Similar findings have been found in children (Garin et al. 1998). Focal or generalized renal scarring is often seen in kidneys without VUR, and it seems that VUR has only a marginal impact on new renal scarring (Winberg et al. 1982).

If VUR were a significant and modifiable factor in the development of recurrent UTI or new renal scarring, we would have a marked reduction in these outcomes in randomised controlled trials and in the results of meta-analyses based on published RCTs on this subject. The unanimous conclusion of recent meta-analyses of the treatment of VUR has been that surgical abolition of VUR entails the same risk of new renal parenchymal injury or recurrent non-febrile UTI as microbial UTI prophylaxis and spontaneous resolution of VUR (Wheeler et al. 2003, Venhola et al. 2006). Our results are in accordance with this.
Vesicoureteral reflux is a fairly common phenomenon that can be associated with congenital renal dysplasia. It does not markedly increase the risk of recurring UTI or new acquired renal scars, and its surgical correction does not prevent recurrences of non-febrile UTI or new renal scars. VUR is a symptom of a developmental maturation defect of the “uretero-vesical valve” in some children, and is often of high grade, resistant to spontaneous resolution and associated with coarse congenital renal dysplasia in infant boys. It seems doubtful whether VUR is an important or modifiable risk factor contributing to recurrent UTI, new renal scarring or ESKD.

14.2 Vesicoureteral reflux – a pathological condition?

Urinary tract infection (UTI) is relatively common in children, and it has been estimated that 8.4% of girls and 1.7% of boys will develop at least one UTI by the age of 7 years (Hellstrom et al. 1991). It is known that UTI can be a marker of abnormalities of the urinary tract, the most common being VUR. The occurrence of VUR appears to be from 30% to 40% in children with UTI and seems to decrease with age (Downs 1999). It is also diagnosed in 9% to 11% of neonates having antenatal hydronephrosis (Farhat et al. 2000, Ismaili et al. 2006), in 32% of siblings (Hollowell & Greenfield 2002) and in 66% of offspring of known VUR patients (Noe et al. 1992). By contrast, the occurrence of VUR in healthy children was less than 2% in surveys conducted between the 1950s and the 1970s (1981). We found a similar high occurrence of VUR (35%) in children imaged on account of an UTI, but almost identical figures in children not likely to have had any UTI (Venhola et al. 2010a).

Children with VUR often present with renal scarring, and there seems to be an increasing occurrence with age: 10% in infants (Bourchier et al. 1984), 26% in children under 8 years of age (Smellie et al. 1975), 47% in children over 8 years of age (Smellie et al. 1975) and 94% in adults (Kincare-Smith & Becker 1978). Congenital renal scarring is usually associated with VUR, and the affected kidney is generally smooth and small in appearance (Risdon 1993, Risdon et al. 1993). These infection-free kidneys are dysmorphic, hypoplastic and usually associated with high grades of VUR (Najmaldin et al. 1990, Burge et al. 1992, Marra et al. 1994). VUR is thought to be a major risk factor for renal scarring, predisposing patients to long-term kidney damage and leading to hypertension, chronic renal insufficiency and complications of pregnancy (Jacobson et al. 1989, Smellie et al. 1998, Wennerstrom et al. 2000a). Renal scarring, i.e. reflux nephropathy, is said
to be a major cause of hypertension (Kincaid-Smith & Becker 1978, Arze et al. 1982, Zucchelli & Gaggi 1988, Jacobson et al. 1989) and to be the cause of end-stage renal failure in about 8–16% of adult cases in industrialized countries (Fenton et al. 1995, Stewart & Hodson 1995). It has also been said to be the reason for end-stage renal failure in children in 30–50% of cases (Pistor et al. 1985). Published guidelines advocate active diagnosis and treatment of VUR to prevent renal scarring, hypertension and the most devastating outcome - end-stage renal failure (Elder et al. 1997, Jodal & Lindberg 1999, Koo & Bloom 1999, Elder 2000, Peters et al. 2010). Long-term follow-up studies have shown, however, that the risk of recurrent urinary tract infections does not correlate with the extent of renal scarring (Smellie et al. 1981a, Arze et al. 1982, Jacobson et al. 1989).

Primary uncomplicated VUR – regardless of recurrent UTIs, severity of reflux, modality of therapy or presence of renal scarring – is not associated with the development of hypertension (Wolfish et al. 1993). Indeed, the occurrence of hypertension in children with renal scarring and dilating VUR has been shown to be identical to that in the general population when the patients were evaluated as middle-aged adults after 37 years of follow-up (Lahdes-Vasama et al. 2006). Braren et al. (1988) were similarly unable to show any correlation between hypertension and the grade of VUR, renal scarring or changes in renal function (Braren et al. 1988).

In a large population survey in Sweden the investigators were unable to point to any children with non-obstructive pyelonephritis having chronic renal failure or terminal renal failure between 1986–1994 (Esbjorner et al. 1997). This is in accordance with an earlier report from Sweden (Esbjorner et al. 1990), and the authors state that the proportion of preventable diseases is low in Swedish children with chronic renal failure. Craig et al. obtained similar results in a survey in Australia and New Zealand, commenting that the currently advocated diagnosis and treatment protocols for VUR may be of no benefit for the prevention of end-stage renal disease (Craig et al. 2000).

Bladder and bowel dysfunction (dysfunctional elimination syndrome, DES) can be associated with a higher rate of postoperative UTI in children, a greater risk of febrile UTI in children with VUR, and slower resolution of VUR, and it also can affect the cure rate of endoscopic therapy for VUR (Peters et al. 2010). Several authors state that urodynamic studies are important for evaluating children with VUR and establishing their prognosis (Koff & Murtagh 1983, Homsy et al. 1985, Scholtmeijer & Nijman 1994, Yeung et al. 1998). Urodynamic
investigations have detected abnormalities suggestive of DES in up to 76% of children with VUR (Chandra & Maddix 2000). The most typical urodynamic findings in children with DES and VUR are bladder instability and dysco-ordinated voiding (Koff et al. 1979, Homsy et al. 1985, Nielsen 1989, Homsy 1994). On the other hand, we could not demonstrate any marked DES symptoms or findings in children with VUR compared with those without (Venhola et al., 2011, submitted), nor could we point to any difference in numbers of recurrent UTI episodes in children with or without DES symptoms or findings in urodynamic examinations.

14.3 Vesicoureteral reflux – a great swindle?

The current data do not support many of the features attributed earlier to VUR. It does not seem to be: (1) caused by bacterial infection in the urinary bladder, (2) a predisposing factor for the development of UTIs, (3) a contributory factor inducing renal parenchymal scars, (4) or a condition leading to hypertension, excessive renal scarring and end-stage renal failure. It could be that it predisposes some children to acute pyelonephritis, but we do not know if we should prevent these infections by abolishing VUR surgically, put the children on continuous antimicrobial prophylaxis or treat each episode of UTI as it occurs.

We have an urgent need to re-evaluate our approach to VUR in children. The aetiology, natural history, need for treatment, treatment options and significance of VUR are being rewritten due to our evolving understanding of urinary tract infection, VUR and renal scarring. The natural course of VUR is spontaneous resolution in 25% to 80% of cases, depending on the severity of VUR and the duration of follow-up. Resolution may be delayed by recurrent UTI, voiding dysfunction or chronic constipation. New insights into the factors contributing to recurrences of urinary tract infections, the development of acute pyelonephritis and renal parenchymal scars and the role of these factors in patients with or without reflux are needed.

The surgical solutions available for abolishing VUR have been around for decades and still stand the test of time, but being invasive and not without complications, they have been challenged by a search for new treatment options. Prospective randomised studies have shown that elimination of VUR is no better than UTI control by conservative means when it comes to preventing renal scarring and end-stage kidney disease. The recommendations for the management of VUR have been altered accordingly and will continue to change in the near
future, but clinicians are now in a situation where no clear evidence exists to
guide treatment decisions on any given child with VUR, leaving room for a wide
measure of personal judgement that could cause extreme differences between the
treatments prescribed for similar patients. Perhaps the most alarming finding was
that of Routh et al. (2010) that the hospital at which the patient received treatment
was the single most important feature that governed the choice of procedure for
children with primary VUR (Routh et al.).

It seems doubtful whether VUR is important as a modifiable risk factor for
recurrent UTI, new renal scarring or ESKD. Since new renal scarring develops
only after recurrent UTI, prompt diagnosis and treatment of UTI seems crucial.
Long-term antimicrobial prophylaxis for UTI in children with VUR is
controversial, and endoscopic treatment of VUR in these children is still of
doubtful benefit relative to prompt treatment of recurrences of UTI. The present
evidence on VUR does not provide a firm basis for searching for it among all
children who have had UTI. Children showing gross congenital kidney
dysmorphology and a high grade of VUR could benefit from surgical correction
of VUR, but it is doubtful whether we can prevent the progression, even of these
kidneys, to ESKD by surgical means. In patients with mild focal renal scarring
and a mild to moderate grade of VUR the emphasis should be on UTI control, and
we should allow time for spontaneous resolution of VUR to occur as the child
matures.
15 Conclusions

On the basis of the work carried out here,

1. We claim that the occurrence of VUR in healthy children is considerably higher than the figure of 1% suggested earlier.

2. We could not predict the presence or absence of VUR from the results of urodynamic examinations of children with a UTI. Nor could we predict possible recurrences of UTI from the urodynamic findings.

3. We suggest that it is not possible to predict VUR reliably. On the other hand, one could argue that it is uncertain whether identifying and treating children with VUR confers any true clinical benefit, and thus it may even be unimportant to identify children with VUR.

4. We suggest that conservative treatment is sufficient for the vast majority of children with VUR, and that such children could be monitored for some years on conservative therapy before performing any corrective surgery and without evaluating them for the occurrence of VUR. If there are frequent breakthrough UTIs, or if prophylactic antimicrobials are not tolerated, renal parenchymal changes should be looked for, and if these are found, then the occurrence of VUR should be evaluated.
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