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Annukka Hannula

IMAGING STUDIES OF THE URINARY TRACT IN CHILDREN WITH ACUTE URINARY TRACT INFECTION

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU, FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE, DEPARTMENT OF PAEDIATRICS

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ANNUKKA HANNULA

IMAGING STUDIES OF THE URINARY TRACT IN CHILDREN WITH ACUTE URINARY TRACT INFECTION

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Abstract

The aims were to evaluate the occurrence of vesicoureteral reflux (VUR) in children, to assess the frequency of significant ultrasonography (US) abnormalities and to study whether abandoning the use of voiding cystourethrographies (VCUG) is safe in children with urinary tract infection (UTI).

We analysed reports on US and VCUG in a consecutive series of 406 paediatric patients and in a large population-based group of 2036 children with UTI. Based on the urine culture data, we analysed the frequencies of VUR and US abnormalities in relation to the reliability of the UTI diagnoses. Using a cohort of 1185 children on whom both VCUG and US had been performed, we evaluated whether US imaging alone is sufficient. In a follow-up study, we excluded 24 cases with major renal dysplasia or obstruction of the urinary tract from this cohort of 1185 children leaving a series of 1161 cases, of which 228 were randomly selected for follow-up and 193 (85%) participated, with a mean follow-up time of 11 years (range 6 to 17 years).

The occurrence of VUR was similar among the children with proven (37%) or certain (36%) versus false (35%) or improbable (36%) UTI and decreased with increasing age. Significant US abnormalities were found in 10% and the frequency increased as the diagnostic reliability improved (15% in the proven UTI class and 8% in the false class). In the cohort of 1185 children, initial US was normal in 861 (73%), out of whom VCUG identified two cases of urethral valves and 40 cases of grade III to V VUR who could have benefited from surgical treatment, giving a figure of 42/861 (5%) for pathological findings that might have been missed if VCUG had not been performed. In the follow-up study, unilateral renal parenchymal defect was found in 22 (15%) out of the 150 patients who underwent control US, all except one of these being in patients with grade III to V VUR. Serum cystatin C concentration, estimated glomerular filtration rates and blood pressure were within the normal ranges in all the patients despite the defects seen in US.

We conclude that VUR is a common age-related phenomenon in children and is not as closely associated with UTI as was previously thought. Children with UTI could be examined using US alone. Once obstructive uropathy and major renal dysplasia have been ruled out, the risk of long-term consequences in a case of childhood UTI is very low.

Keywords: child, renal ultrasonography, urinary tract abnormality, vesicoureteral reflux, voiding cystourethrography

Hannula, Annukka, Virtsateiden kuvantamistutkimukset virtsatieinfektion sairastaneella lapsella.

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Tiivistelmä

Tutkimuksen tavoitteena oli selvittää virtsan takaisinvirtauksen (vesikoureteraalinen takaisinvirtaus, VUR) esiintyvyyttä lapsilla sekä arvioida merkittävien virtsateiden rakennepoikkeavuuksien yleisyyttä ja ultraäänitutkimuksen (UÄ) riittävyyttä virtsatieinfektion (VTI) sairastaneilla lapsilla.

Analysoimme sairastetun VTI:n vuoksi tehtyjen UÄ- ja miktiokystografiatutkimusten löydökset 406 lapsen potilassarjassa ja 2036 lapsen väestöpohjaisessa aineistossa. Virtsaviljelytulosten pohjalta luokittelimme potilaat VTI-diagnoosin luotettavuuden mukaan. Väestöpohjaisen aineiston 1185 lapselle oli tehty sekä UÄ-tutkimus että miktiokystografia, ja tässä kohortissa arvioimme pelkän UÄ:n riittävyyttä virtsateiden kuvantamisessa. Seurantatutkimusta varten 1185 lapsen kohortista jätimme pois 24 potilasta, joilla oli todettu munuaisdysplasia tai virtsateiden virtauseste. Jälkitarkastukseen kutsuimme tästä 1161 potilaan tutkimusaineistosta ryväsotannalla 228 potilasta, joista 193 (85 %) osallistui. Keskimääräinen seuranta-aika oli 11 vuotta (vaihtelu 6–17 vuotta).

Tutkimuksemme mukaan VUR on yleinen myös lapsilla, jotka eivät ole sairastaneet varmennettua VTI:ta. Näillä lapsilla VUR:n esiintyvyys oli 35–36 %, joka oli sama kuin varman VTI:n sairastaneilla (36–37 %), ja esiintyvyys väheni merkittävästi iän myötä. Merkittävä UÄ-poikkeavuus todettiin kaikkiaan 10 %:lla, ja riski oli suurin varman VTI:n sairastaneilla. 1185 lapsen kohortissa UÄ-tutkimus oli normaali 861:lla (73 %). Miktiokystografiassa heistä 42/861:lla (5 %) löydettiin merkittävä virtsatieanomalia (n = 2) tai VUR, joka oli hoidettu kirurgisesti (n = 40). Jälkitarkastuksessa 22:lla (15 %) UÄ:llä tutkitusta 150 potilaasta todettiin toispuoleinen munuaisarpi, ja yhtä tapausta lukuun ottamatta arvet löytyivät niiltä, joilla oli lapsena ollut III−V asteen VUR. Todetuista munuaisarvista huolimatta kaikilla seurantatutkimukseen osallistuneilla potilailla oli normaali munuaisten toiminta ja verenpaine.

Aiemmasta käsityksestä poiketen VUR näyttäisi olevan yleinen, kasvun myötä häviävä ilmiö myös terveillä lapsilla. Virtsatieinfektion sairastaneilla lapsilla UÄ-tutkimus riittää virtsateiden kuvantamiseen ja kun synnynnäinen munuaisdysplasia ja virtsateiden virtauseste on poissuljettu, riski merkittäviin myöhäiskomplikaatioihin on hyvin pieni.

Asiasanat: lapsi, miktiokystografia, ultraäänitutkimus, virtsan takaisinvirtaus, virtsateiden rakennepoikkeavuus

To my family

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Abbreviations

ABP	ambulatory blood pressure
BP	blood pressure
CFU	colony-forming unit
CI	confidence interval
CKD	chronic kidney disease
CRP	C-reactive protein
DMSA	dimercapto-succinid acid
ESKD	end-stage kidney disease
iVCUG	isotope voiding cystourethrography
MRI	magnetic resonance imaging
OR	odds ratio
RR	relative risk
rVCUG	X-ray voiding cystourethrography
SND test	standard normal deviate test
SPA	suprapubic aspiration
US	ultrasonography
UTI	urinary tract infection
VCUG	voiding cystourethrography
VUR	vesicoureteral reflux
VUS	voiding urosonography

List of original publications

This thesis is based on the following original papers, which are referred to in the text by their Roman numerals.

I Venhola M, Hannula A, Huttunen NP, Renko M, Pokka T & Uhari M (2010) Occurrence of vesicoureteral reflux in children. Acta Paediatr 99(12): 1875–1878.

II Hannula A, Venhola M, Renko M, Pokka T, Huttunen NP & Uhari M (2010) Vesicoureteral reflux in children with suspected and proven urinary tract infection. Pediatr Nephrol 25(8): 1463–1469.

III Hannula A, Venhola M, Perhomaa M, Pokka T, Renko M & Uhari M (2011) Imaging the urinary tract in children with urinary tract infection. Acta Paediatr 100(12): e253–259.

IV Hannula A, Perhomaa M, Venhola M, Pokka T, Renko M & Uhari M (2012) Long-term follow-up of patients after childhood urinary tract infection. Manuscript.

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1 Introduction

Urinary tract infection (UTI) is a common bacterial illness in children (Hellström *et al.* 1991, Winberg *et al.* 1974) and can indicate a structural abnormality of the urinary tract or the presence of vesicoureteral reflux (VUR) (Sargent 2000). Vesicoureteral reflux is found in around 30% of children with UTI, but its true occurrence in general paediatric population is unknown (Coulthard 2008, Sargent 2000).

Some decades ago there were a number of reports of high rates of renal scarring in children with UTI, especially in those with VUR (Hodson & Edwards 1960, Hutch 1952). Based on this assumed causal association between VUR and renal scarring and on the belief that anti-reflux surgery or antimicrobial prophylaxis could prevent UTI recurrences and further scar formation, the paediatric associations recommended imaging of the urinary tract in children with UTI by ultrasonography (US) and voiding cystourethrography (VCUG) (American Academy of Pediatrics *et al.* 1999, Jodal & Lindberg 1999, Lautala *et al.* 1992, MacKenzie *et al.* 1991).

The effectiveness of these routine imaging studies in improving the long-term outcome for children with UTI was never verified (Westwood *et al.* 2005), and a growing understanding of the origin of renal scarring and the natural history of VUR has subsequently challenged the long-held notions of a causal relation between VUR and renal scars and the overall benefits of treating VUR (Farhat *et al.* 2000, Gordon *et al.* 2003, Venhola *et al.* 2006). In addition, the widespread use of foetal US has led to a decrease in the number of obstructive uropathies diagnosed following UTI (Gelfand *et al.* 2000a). The trend has been towards less routine imaging, particularly the use of invasive tests such as VCUG, although there is a lack of firm evidence as to whether this is a safe direction to follow (National Institute for Health and Clinical Excellence 2007, South 2009).

This present study was designed to assess the necessity and justification for routine imaging studies in children with UTI.

2 Review of the literature

2.1 Acute urinary tract infection in children

Given that the urine is normally sterile, acute UTI develops when bacteria invades the urinary tract, causing inflammation which is manifested as pyuria and acute symptoms.

2.1.1 Epidemiology

Urinary tract infection is diagnosed in 7.5% to 10% of febrile infants with no apparent explanation for the fever (Hoberman *et al.* 1993, Newman *et al.* 2002). A report from Sweden has stated the cumulative incidence of symptomatic UTI by the age of seven to be 8.4% in girls and 1.7% in boys (Hellström *et al.* 1991), while data from the UK suggest that 11.3% of girls and 3.6% of boys will have UTI during childhood (Coulthard *et al.* 1997). A survey based on hospital discharge records found the rate of symptomatic UTIs in Finnish girls to decrease from 2.67/1000 in 1978 to 1.88/1000 in 1984, but to remain more or less the same in boys (0.85/1000 in 1978 and 0.59/1000 in 1984) (Uhari & Nuutinen 1988). During the following 10 years, the rate of UTI episodes remained stable or continued to decline, except in boys aged less than four years, in whom a slight increase from 2.05/1000 in 1987 to 2.58/1000 in 1994 was seen. The authors suggested that these changes in childhood UTI rates could be explained by changes in diagnostics and the ascertainment of UTIs rather than by true changes in incidence (Nuutinen *et al.* 1999). Potentially life-threatening bacteraemic UTIs are rare, and the calculated annual incidence of bacteraemic UTI in children under the age of 16 years in Finland is 1.5/100 000 (Hoberman *et al.* 1999, Honkinen *et al.* 2000, Newman *et al.* 2002).

The occurrence and clinical manifestation of UTIs is greatly influenced by the gender and age of the child. The occurrence is higher in boys in the neonatal period up to three months of age, but girls overtake them around six months and there is a striking female preponderance beyond infancy (Hansson *et al.* 1999, Preda *et al.* 2007, Smellie *et al.* 1964, Wennerström *et al.* 1998). The proportion of febrile UTIs is highest in both sexes during infancy, while cystitis occurs mostly in girls at age over 2 years and only rarely in boys (Mårild & Jodal 1998).

The risk of UTI recurrence in children has been shown to be 15% to 30% with most of the recurrences appearing within six to twelve months of the first UTI (Conway *et al.* 2007, Nuutinen & Uhari 2001, Panaretto *et al.* 1999, Winberg *et al.* 1974). Young age at the time of the first UTI, female sex, grade III or higher VUR and dysfunctional voiding have been suggested as risk factors for UTI recurrence (Conway *et al.* 2007, Dias *et al.* 2010, Panaretto *et al.* 1999).

2.1.2 Pathogenesis and aetiology

Urinary tract infection is usually an ascending infection in which periurethral bacteria rise via the urethra to invade the bladder, causing cystitis, and on some occasions may ascend to the kidney, causing pyelonephritis. Only rarely, mainly in neonates, UTI may develop from a haematological spread of bacteria to the urinary tract (Hoberman *et al.* 1999, Honkinen *et al.* 2000). The most common causative agent of childhood UTI is *Escherichia coli* (in approximately 80% of cases), while other important causative bacteria are *Klebsiella*, *Enterococcus*, *Proteus* and *Enterobacter* species (Hoberman *et al.* 1999, Honkinen *et al.* 1999, Jantunen *et al.* 2001). Factors contributing to UTI include bacterial virulence factors such as P fimbriae of *Escherichia coli*, which facilitate bacterial adherence to the uroepithelium, and host defence mechanisms such as inadequate urine flow due to obstruction (Tullus *et al.* 1991).

2.1.3 Symptoms and diagnosis

The symptoms of acute UTI are unspecific and vary considerably which may cause a delay in diagnosis (Hoberman *et al.* 1993, Pylkkänen *et al.* 1979). Fever is the most common symptom in infants and young children, and can be the only one, so that the possibility of pyelonephritis should always be ruled out in infants with unexplained fever (Hoberman *et al.* 1993). Other common unspecific symptoms of UTI in infants and young children are irritability or lethargy, feeding difficulties, vomiting and diarrhoea. In older children, fever, abdominal or flank pain and nausea or vomiting are manifestations of pyelonephritis, while cystitis usually presents with dysuria and frequent voiding with or without a slight fever (Hoberman *et al.* 1993, Honkinen *et al.* 2000, Smellie *et al.* 1964).

The diagnosis of UTI requires sampling of the urine for urinalysis and quantitative bacterial culture. It is difficult to obtain uncontaminated urine samples from infants and young children, and the results can easily lead to false

positive diagnosis, over treatment and unnecessary examinations (Al-Orifi *et al.* 2000). Although suprapubic aspiration (SPA) is regarded as the gold standard for urine sampling in infants, its limited success rate (approximately 50%) and invasiveness has restrained its use (Newman *et al.* 2002, Pollack *et al.* 1994). Sterile bags and urine pads are reliable when screening infants and young children for possible UTI, but as these collection methods involve a significant contamination rate, the final diagnosis should be based on bacterial culture from either a SPA or a catheterization sample (Al-Orifi *et al.* 2000, Aronson *et al.* 1973, Etoubleau *et al.* 2009, Liaw *et al.* 2000, Pylkkänen *et al.* 1979, Rao *et al.* 2004). In older children, who are able to control their bladder, bacterial cultures from two clean voided urine samples are sufficient (Huttunen *et al.* 1970, Kass 1957, Pylkkänen *et al.* 1979). In clinical practice many UTI diagnoses are nevertheless based on bag or pad samples only (Hansson *et al.* 1999, Liaw *et al.* 2000, Newman *et al.* 2002).

Quantitative bacterial culture of the urine is used to establish a diagnosis of UTI. The concentration of bacteria in the urine, presented in colony-forming units (CFU), offers a measure of the likelihood that bacteria in the urine sample represent a true infection rather than contamination (Kass 1957). The universally accepted concept that $\geq 10^5$ CFUs per ml of clean voided urine indicates UTI is based on a study by Kass *et al.* from the 1950s. They analysed urine samples from adult women with no symptoms and with clinically suspected pyelonephritis and found the threshold of 10^5 CFUs to best separate cases of true bacteriuria from contamination. Thus, the definition of a positive urine culture is operational and not absolute, and it has never been formally validated in children. The used thresholds for significant bacterial growth also depend on the urine collection method used (Table 1) (Aronson *et al.* 1973, Hoberman *et al.* 1994, Jodal *et al.* 1975, Pylkkänen *et al.* 1979).

Table 1. Thresholds of significant bacterial growth in the urine according to the collection method used to define urinary tract infection in children.

Urine collection method	Number of colony-forming units (CFU)/ml
Suprapubic aspiration	Any growth
Catheterization	$\geq 5 \times 10^4$
Clean voided urine	$\geq 10^5$
Bag specimen	$\geq 10^5$
Pad specimen	$\geq 10^5$

Urine dipstick screening is the most widely used test for rapid urine analysis. The presence of either leukocyte esterase and/or nitrite is interpreted as positive dipstick test. Positive leukocyte esterase has 79% sensitivity and 87% specificity and is as accurate as urine microscopy for white blood cells, while nitrite has only 49% sensitivity, but 98% specificity for UTI (Williams *et al.* 2010). To obtain reliable urine dipstick analysis, however, the urine has to be stored in the bladder for at least four hours which reduces the reliability of the method in infants and young children. The nitrite test works only in UTIs caused by Gram-negative rods, but not with other uropathogens. Urine microscopy with Gram stain for the detection of bacteria would be the best single rapid test for UTI diagnosis, but it is expensive, time-consuming and rarely available in primary care. It has been claimed that rapid urine tests are negative in around 10% of children with UTI, and thus they should not take the place of urine culture (Williams *et al.* 2010).

Determination of the level of UTI is difficult and cannot be reliably achieved by reference to any symptoms or laboratory tests (Jaksic *et al.* 2011). Methods such as a bladder washout test or measurement of renal concentration capacity were used in earlier studies, but although the osmolality test appeared to be the more promising of the two, both tests showed rather poor sensitivity and significant overlapping between children with clinical cystitis and pyelonephritis (Jodal *et al.* 1975, Mårild *et al.* 1989). Acute-phase dimercapto-succinid acid (DMSA) scintigraphy is considered the best technique for detecting renal parenchymal involvement and confirming a diagnosis of pyelonephritis, but in view of its invasive nature, expense and radiation burden, its routine clinical use is questionable (American Academy of Pediatrics *et al.* 1999, Jaksic *et al.* 2011, National Institute for Health and Clinical Excellence 2007, Rushton & Majd 1992). In clinical practice, especially with infants and young children, fever ≥38°C is often used as a clinical marker of pyelonephritis (American Academy of Pediatrics *et al.* 1999). Indirect markers of systemic inflammation such as serum C-reactive protein (CRP) or procalcitonin concentrations can be helpful (Fernandez-Menendez *et al.* 2003, Jodal *et al.* 1975, Jodal & Lindberg 1999, Pecile *et al.* 2004, Stokland *et al.* 1996). It has been recently suggested that serum procalcitonin may be more sensitive than CRP for detecting pyelonephritis, as assessed by renal parenchymal involvement in a DMSA scan (Pecile *et al.* 2004).

2.2 Abnormalities of the urinary tract in children with urinary tract infection

Urinary tract infection in children can be the presenting symptom of an underlying structural urinary tract abnormality or VUR (American Academy of Pediatrics *et al.* 1999). The risk of significant abnormality is highest in infants and young children with febrile UTI and in cases where the causative bacteria are of a strain other than *Escherichia coli* (Bourchier *et al.* 1984, Honkinen *et al.* 1999, Jantunen *et al.* 2001, McKerrow *et al.* 1984, Ring & Zobel 1988, Smellie *et al.* 1981).

2.2.1 Structural abnormalities

Depending on the patient characteristics, structural abnormalities of the urinary tract are found in 10% to 15% of children examined after UTI, the most common abnormalities being hydronephrosis, obstructive uropathies and duplex kidneys (Gelfand *et al.* 2000a, Hoberman *et al.* 2003, Honkinen *et al.* 2000, Jahnukainen *et al.* 2006, Jantunen *et al.* 2001, Ring & Zobel 1988, Zamir *et al.* 2004).

Obstruction of the urinary tract

Obstructive uropathies are important cause of chronic renal failure in children, accounting for 15% to 20% of all paediatric cases of end-stage kidney disease (ESKD) (Esbjörner *et al.* 1997, Miklovicova *et al.* 2005, Roth *et al.* 2002, Warady *et al.* 1997, Warshaw *et al.* 1982). Obstruction of the urinary tract in children is mostly congenital and its clinical effects depend on its level, extent of involvement and duration (Elder 2007, Roth *et al.* 2002). Severe bilateral obstruction in early foetal life results in irreversible renal failure and major renal dysplasia, often leading to early neonatal death (Elder 2007, Roth *et al.* 2002, Warshaw *et al.* 1982). Partial or unilateral obstruction leads to various degrees of dilatation of the upper urinary tract and milder renal cortical dysplasia which can be symptomless for a long period of time (Elder *et al.* 1995, Elder 2007, Roth *et al.* 2002). Ureteropelvic junction obstruction is the most common obstructive uropathy in children, while a posterior urethral valve is the most common cause of severe obstruction. Other reasons for obstruction are ureterovesical junction obstruction, an ectopic ureter and ureterocele (Elder 2007, Roth *et al.* 2002).

Obstruction of the urinary tract blocks adequate urine flow and causes urine stasis, predisposing the child to UTI and enabling even the less virulent non-*Escherichia coli* bacteria to invade the urinary tract (Honkinen *et al.* 1999, Jantunen *et al.* 2001). Song *et al*. found that 36% of children with antenatally diagnosed severe obstructive hydronephrosis not treated with prophylactic antibiotics experienced UTI (Song *et al.* 2007), whereas Roth *et al*. found the rate of UTIs in a similar group of children not receiving prophylaxis to be only 4.3% (Roth *et al.* 2009). Most studies of children with UTI have found the occurrence of an obstructive uropathy to be around five per cent or less, but the figure has varied from 0% to 23% (Bourchier *et al.* 1984, Hoberman *et al.* 2003, Honkinen *et al.* 1986, Honkinen *et al.* 2000, Hsieh *et al.* 2009, Jantunen *et al.* 2001, McKerrow *et al.* 1984, Preda *et al.* 2010, Ring & Zobel 1988). During the past two decades, since the adoption of routine foetal US screening, most children with severe congenital obstructive uropathies have been diagnosed antenatally and the rate of post-UTI diagnosed obstructions has decreased (Gelfand *et al.* 2000a).

Other structural abnormalities

Duplex, solitary, ectopic and horseshoe kidneys and simple renal cysts are occasionally detected when evaluating the urinary tract after a child's UTI (Gelfand *et al.* 2000a, Giorgi *et al.* 2005, Hoberman *et al.* 2003, Huang *et al.* 2008, Jahnukainen *et al.* 2006, Lee *et al.* 2009b, Ring & Zobel 1988). Apart from simple renal cysts, these abnormalities have been reported to be associated with other urological abnormalities such as obstruction and VUR (Calisti *et al.* 2008, Cascio *et al.* 1999, Guarino *et al.* 2004, Siomou *et al.* 2006). When US does not show any significant dilatation of the urinary tract, however, the risk of associative abnormalities is extremely low (Calisti *et al.* 2008, Siomou *et al.* 2006). Thus uncomplicated duplex, solitary or ectopic kidneys do not seem to increase the risk of a UTI recurrence (Calisti *et al.* 2008, Siomou *et al.* 2006).

2.2.2 Vesicoureteral reflux

Vesicoureteral reflux is the retrograde flow of urine from the bladder into the ureter and towards the kidney due to a dysfunctional vesicoureteric junction. The vesicoureteric junction usually functions like a one-way valve allowing urine to flow from the ureter to the bladder and preventing it from flowing backwards

during voiding, when intravesical pressure rises (Stephens & Lenaghan 1962). Vesicoureteral reflux is common in children examined after UTI, but its true occurrence in an unselected healthy paediatric population is uncertain (Coulthard 2008, Sargent 2000). It has been assumed that VUR is the cause of the renal scarring and subsequent renal damage observed in children with UTI, indicating that an active search for VUR and treatment of it is essential for preventing the possible adverse outcomes of childhood UTIs (Bailey 1973, Cohen 1977, Hodson & Edwards 1960, Jacobson *et al.* 1989, Politano & Leadbetter 1958).

Classification of VUR

The severity of VUR is graded in five categories according to the International Reflux Study System (Table 2) (Lebowitz *et al.* 1985). This system was developed to ensure compatible results of VCUGs and to enable reliable evaluation of various approaches for managing VUR in this multicentre study and is based on the original work of Heikel and Parkkulainen (Heikel & Parkkulainen 1966).

Table 2. International Reflux Study grading system (Lebowitz *et al*. 1985).

Grade	Interpretation
I	Ureter only
II	Ureter, pelvis and calyces. No dilatation, normal calyceal fornices.
III	Mild or moderate dilatation and/or tortuosity of the ureter, and mild or moderate dilatation of the renal pelvis but no blunting of the fornices.
IV	Moderate dilatation and/or tortuosity of the ureter, and moderate dilatation of the renal pelvis and calyces. Complete obliteration of the sharp angles of the fornices but maintenance of the papillary impressions in the majority of the calyces.
V	Gross dilatation and tortuosity of the ureter. Gross dilatation of the renal pelvis and calyces. The papillary impressions are no longer visible in the majority of the calyces.

Occurrence and natural history of VUR

The occurrence of VUR among children with UTI varies from 25% to 40% (Table 3) (Chand *et al.* 2003, Hoberman *et al.* 2003, Sargent 2000, Smellie *et al.* 1981), and several authors have confirmed that VUR resolves spontaneously in most children as they mature (Chand *et al.* 2003, Edwards *et al.* 1977, Gelfand *et al.* 2000b, Sargent & Stringer 1995, Schwab *et al.* 2002, Smellie *et al.* 1975). The spontaneous resolution rate for grade I to III VUR is 13% per year (Schwab *et al.*

2002), and the tendency of grade III to V VUR to disappear spontaneously is also favourable, with 73% of children having grade I or less after 10 years of follow-up (Wennerström *et al.* 1998).

Studies of the siblings of children with VUR have shown VUR occurrence rates of 35–50%, which has led to the conclusion that VUR is a hereditary condition (Table 3) (Ataei *et al.* 2004, Connolly *et al.* 1997, Parekh *et al.* 2002, Tombesi *et al.* 2005). Unfortunately these sibling studies lack controls, and thus this potentially overestimates the hereditability of VUR. Numerous attempts have been made to establish genetic associations with VUR (Carvas *et al.* 2010, Williams *et al.* 2008).

Postnatal VCUG has shown VUR in 12% to 38% of neonates with antenatally diagnosed hydronephrosis (Table 3) (Brophy *et al.* 2002, Farhat *et al.* 2000, Najmaldin *et al.* 1990, Ring *et al.* 1993, Sargent 2000, Zerin *et al.* 1993). Knowing that VUR does not necessarily cause hydronephrosis and that not all dilatations are detected by antenatal US, it is impossible to extrapolate the occurrence of VUR from these findings to the general new-born population.

In animals, VUR has been found to be common among infant mammals and to occur in almost 100% of rats. Almost all monkeys have VUR during the first months of life, but the frequency decreases as they grow and VUR resolves by adulthood (Roberts 1992).

The precise occurrence of VUR in the general population is unknown, as it is unethical to perform VCUGs on healthy subjects and no large population-based studies have been carried out. The often-used figure around 1% for the occurrence of VUR is based on estimates (Coulthard 2008). Historical studies of healthy children aged 0 to 14 years showed the occurrence of VUR to vary from 1% to 30% (Table 3) (Gibson 1949, Iannaccone & Panzironi 1955, Jones & Headstream 1958, Kretschmer 1916), but should be noted that none of these earlier studies used the same cystography method and in some cases only single non-voiding X-ray images was taken. In one historical study from Germany VCUG was performed to 102 children with no urinary tract pathology by a comparable method to that used nowadays and VUR was found in over 60% of the infants and its occurrence to decrease with increasing age (Köllermann & Ludwig 1967).

Table 3. Occurrence of vesicoureteral reflux (VUR) in children with or without predisposing condition.

Study	Description	Age	n	VUR, %
Children with a history of UTI[1]				
Smellie 1981	Hospital records of children studied after UTI[1]	0 to 12 yrs	744	33
Sargent and Stringer 1995	Hospital records of children studied after the first UTI[1]	1 wk to 15 yrs	309	29 in girls 30 in boys
Gelfand 2000b	Results of VCUG[2] in a cohort of 844 children with UTI[1]	not stated	743	25
Chand 2003	Results of VCUG[2] or radionuclide cystography in children with UTI[1]	0 to 21 yrs	9912	31 in girls 18 in boys
Hoberman 2003	Hospital records of children with first febrile UTI[1]	1 to 24 mo	309	39
Lee 2009b	Hospital records of children with first febrile UTI[1]	2 mo to 2 yrs	699	30
Siblings of children with VUR				
Connolly 1997	Results of radionuclide cystography performed on asymptomatic siblings	2wk to 13 yrs	482	37
Parekh 2002	Results of VCUG[2] screening of 77 asymptomatic siblings and 1 with UTI[1]	7wk to 5 yrs	78	51
Ataei 2004	Results of VCUG[2] of 35 asymptomatic siblings and 5 siblings with a history of UTI[1]	6 mo to 12 yrs	40	43
Tombesi 2005	Results of VCUG[2] screening of asymptomatic siblings	< 8 yrs	146	36
Children with antenatal hydronephrosis				
Ring 1993	Results of postnatal VCUG[2]	neonates	117	21
Zerin 1993	Results of postnatal VCUG[2]	neonates	130	38
Farhat 2000	Results of postnatal VCUG[2]	neonates	260	12
Brophy 2002	Results of postnatal VCUG[2]	neonates	234	21
Children without a predisposing condition				
Kretschmer 1916	Results of single-multiple non-voiding cystograms	3 to 10 yrs	10	30
Gibson 1949	Results of single non-voiding cystogram	0 to 12 yrs	43	5
Iannaccone and Panzironi 1955	Results of multiple non-voiding cystograms	0 to 6 mo	50	2
Jones 1958	Results of single pre- and postvoiding cystograms	0 to 14 yrs	100	1
Köllerman and Ludwig 1967	Results of single voiding cystograms	0 to 5 yrs	102	28

[1]UTI = urinary tract infection, [2]VCUG = voiding cystourethrography

Vesicoureteral reflux and urinary tract infection

The high occurrence of VUR in children with UTI has led to assumption that VUR plays a major role in the pathogenesis of UTI, especially in pyelonephritis. It has been hypothesized that VUR may predispose the child to pyelonephritis by transporting the bacteria from the bladder to the ureter and renal pelvis.

In previous reports the presence or absence of VUR has not altered the total numbers of UTI recurrences (Conway *et al.* 2007, Garin *et al.* 2006, Montini *et al.* 2008, Panaretto *et al.* 1999, Shaikh *et al.* 2010), although multivariate analysis has shown that a small subgroup of children with grade III or higher VUR experienced UTI recurrences more often than those without VUR or with grade I to II (Conway *et al.* 2007, Panaretto *et al.* 1999). The same observation of a higher UTI recurrence rate in children with grade III to V VUR was made in a Finnish retrospective survey (Nuutinen & Uhari 2001). Screenings of siblings of children with VUR have shown, however, that VUR is largely asymptomatic (Connolly *et al.* 1997, Parekh *et al.* 2002, Tombesi *et al.* 2005).

A recent large meta-analysis showed that children with UTI and VUR have a higher risk of developing acute-phase DMSA scan abnormalities interpreted as pyelonephritis than children without demonstrable VUR (Shaikh *et al.* 2010). After an initial UTI, grade III or higher VUR has been shown to be associated with an increased risk of recurrent pyelonephritis (Jakobsson *et al.* 1994, Swerkersson *et al.* 2007). Surgical elimination of VUR does not reduce the total number of symptomatic UTI recurrences, but it does decrease the risk of acute pyelonephritis (Nagler *et al.* 2011, Venhola *et al.* 2006). Thus, VUR does not seem to increase the overall occurrence of UTI in children, but when infection occurs, it is more likely to be pyelonephritis than cystitis.

Vesicoureteral reflux and renal scarring

After World War II, Hutch published observations on adults with a neurogenic bladder due to spinal cord injury. These paraplegic patients presented with gross VUR and renal damage, i.e. chronic atrophic pyelonephritis, and the idea of the causality between VUR and renal scarring was established (Hutch 1952). Some years later, in 1959, Hodson and Edwards recognized an association between VUR and scarred kidneys in children with recurrent UTIs (Hodson 1959, Hodson & Edwards 1960). Using a piglet model, Hodson *et al*. unroofed the intramural ureter and created a bladder outlet obstruction by placing a constricting ring

around the urethra, which produced VUR and led to severe secondary renal scarring. They suggested that sterile VUR per se can cause renal scarring, but this scarring is accelerated when UTI occurs (Hodson *et al.* 1975). The term "reflux nephropathy" was introduced into the medical literature in the 1970s, when Bailey suggested that VUR itself is the predominant factor causing renal damage and not UTI (Bailey 1973). In the late 1970s Ransley and Risdon, in their piglet model, created VUR by unroofing the intramural ureter as Hodson *et al.* had done, but they did not cause urethral obstruction in all the animals. In contrast to the results reported by Hodson *et al*., they did not observe any renal scarring in the presence of sterile, non-obstructive VUR (Ransley & Risdon 1979). The evidence for a direct causal relation between sterile VUR and renal scarring in these historical studies was based on animal experiments and observations of adults in situations where obstruction co-existed with VUR and the renal damage seen was likely to have been caused, or at least accelerated, by abnormally high bladder pressure.

Post-UTI DMSA scans have shown that the risk of renal scarring is higher in children with VUR than in those without VUR (Shaikh *et al.* 2010). A recent meta-analysis including 33 studies on a total of 4891 children showed that the occurrence of renal scarring was 2.6 times higher among the children with VUR (41%) than among those without (17%) (Shaikh *et al.* 2010). Nevertheless, Gordon *et al*. had concluded in their earlier meta-analysis that VUR is a weak predictor of renal scarring (Gordon *et al.* 2003). High grade VUR predisposes a child to febrile UTIs and thus potentially to new parenchymal damage, but it has not been shown that VUR itself could cause renal damage without infection (Moorthy *et al.* 2005, Taskinen & Rönnholm 2005). Another frequently observed phenomenon is that pyelonephritis, even in the presence of VUR, does not always cause renal scarring (Moorthy *et al.* 2005, Shaikh *et al.* 2010).

The widespread use of foetal US screening has led to the detection of antenatal hydronephrosis and the diagnosis of VUR in the early neonatal period. Severe foetal VUR is often associated with congenital renal scarring and in this population radiological scarring in urography and defects in DMSA scans are seen before any UTI (Anderson & Rickwood 1991, Farhat *et al.* 2000, Najmaldin *et al.* 1990, Risdon 1993, Stock *et al.* 1998, Ylinen *et al.* 2003). The same association between VUR and non-infectious renal scarring has been observed in screenings of asymptomatic siblings of index reflux patients (Ataei *et al.* 2004, Cascio *et al.* 2003, Tombesi *et al.* 2005), and it has been suggested that the renal scars observed in young children with significant VUR, especially in boys, may in

most cases reflect a pre-existing complex congenital uropathy (Anderson & Rickwood 1991, Becu *et al.* 1988, Goldman *et al.* 2000a, Najmaldin *et al.* 1990, Ring *et al.* 1993, Risdon 1993, Stock *et al.* 1998). Thus VUR seems to be a sex-related heterogeneous phenomenon with male infants presenting with gross, frequently antenatally diagnosed VUR in association with dysplastic kidneys and progressive renal failure, even without UTI and despite all efforts to cure VUR (Wennerström *et al.* 2000). In older girls with otherwise normal kidneys, mild to moderate VUR is diagnosed after recurrent UTIs and is rarely associated with significant kidney damage (Wennerström *et al.* 2000).

Renal scarring does occur in the absence of VUR, and pyelonephritis itself can cause renal scarring (Ditchfield *et al.* 2004, Jakobsson *et al.* 1994, Moorthy *et al.* 2005, Rushton *et al.* 1992, Smellie *et al.* 1975, Winberg *et al.* 1974). In fact, a recent meta-analysis has shown that most renal scarring occurred in children without VUR (Shaikh *et al.* 2010). Renal scarring has been shown to correlate better with the presence of recurrent UTIs than with the presence of VUR (Jakobsson *et al.* 1994, Panaretto *et al.* 1999, Swerkersson *et al.* 2007, Wennerström *et al.* 2000). Surgical abolishment of VUR has not been shown to reduce the risk of renal scarring, suggesting that VUR is neither sufficient on its own nor essential for the development of renal scarring (Craig *et al.* 2000, Nagler *et al.* 2011, Venhola *et al.* 2006).

Management of vesicoureteral reflux

Soon after the idea of causality between VUR and radiological renal scarring was established in 1950s, anti-reflux surgery, with over 95% success rate, was eagerly adopted into clinical practice (Burbige 1991, Cohen 1977, Hutch 1952, Politano & Leadbetter 1958). In the late 1970s it became evident that VUR resolves spontaneously in most children, and antibiotic prophylaxis was increasingly used to prevent recurrent UTIs and protect the kidneys from acquired scarring (Edwards *et al.* 1977). As happened with anti-reflux surgery, antibiotic prophylaxis was introduced without any controlled studies or clear evidence of a possible long-term advantage for the patients. Later on, in the 1980s, another form of surgical correction of VUR by means of endoscopic injections was developed (Matouschek 1981). Being simple, less invasive and carrying a lower risk of postoperative complications than open surgery, this endoscopic injection therapy became popular among paediatric urologists, although it was not as curative as open surgery, achieving a 67% resolution rate for VUR (Elder *et al.*

2006). As the International Reflux Study, comparing a combination of surgery and antibiotic prophylaxis with antibiotic prophylaxis alone, found no significant differences in the risk of UTI recurrences or renal scarring, antibiotic prophylaxis was adopted as the first-line treatment for VUR and surgery mostly came to be limited to patients for whom prophylaxis failed (Jodal *et al.* 1992, Olbing *et al.* 1992).

Long-term antibiotic prophylaxis has been widely used for children with VUR until the time when spontaneous resolution of VUR has been documented (American Academy of Pediatrics *et al.* 1999, Jodal & Lindberg 1999). The major disadvantage of the antibiotic prophylaxis is increasing antimicrobial resistance (Craig *et al.* 2009, Montini *et al.* 2008, Pennesi *et al.* 2008, Roussey-Kesler *et al.* 2008). Although low-dose antibiotics are usually well tolerated, some minor, most likely gastrointestinal, adverse effects can occur (Craig *et al.* 2009, Montini *et al.* 2008, Uhari *et al.* 1996). Other concerns that have been raised regarding prophylaxis are breakthrough UTIs, poor compliance with long-term medication and the financial costs involved (Panaretto *et al.* 1999, Smyth & Judd 1993).

Evidence emerging from the recent literature has created controversies over the management of VUR. Anti-reflux surgery does abolish VUR efficiently, but meta-analyses comparing surgical correction of VUR with antimicrobial prophylaxis alone have not shown any differences in the risk of new renal scar formation, which is the most significant endpoint (Nagler *et al.* 2011, Venhola *et al.* 2006). Active surgical treatment of VUR seems to prevent febrile UTI recurrences, but eight surgical corrections for VUR combined with antibiotic prophylaxis are needed to prevent one episode of febrile UTI over a period of five years, without any reduction in the risk of new renal scarring (Nagler *et al.* 2011). The authors of these meta-analyses concluded that the additional benefit of surgery over antibiotics is modest at best. Despite the active search for VUR and its treatment during recent decades, no evidence of the hoped-for reduction in the occurrence of ESKD attributable to reflux nephropathy has yet emerged (Craig *et al.* 2000).

The evidence to be found in the current literature does not support the use of antibiotic prophylaxis in children with VUR. Four randomized placebo-controlled studies which involved 899 patients altogether have failed to show any efficacy for antibiotic prophylaxis in preventing recurrent UTIs in children without VUR or with grade I to IV VUR (Garin *et al.* 2006, Montini *et al.* 2008, Pennesi *et al.* 2008, Roussey-Kesler *et al.* 2008), although when subgroups were analysed separately some slight evidence of efficacy was observed in boys with grade III

VUR (Roussey-Kesler *et al.* 2008). In the PRIVENT study, 576 children aged 0 to 18 years with UTI were randomly assigned to receive either antibiotic prophylaxis or a placebo for one year. Recurrent UTI occurred in 13% of the prophylaxis group and 19% of the placebo group, thus giving a relatively modest, although statistically significant, reduction in the absolute risk. However, the time-event analysis showed that the effect was not sustained and up to 14 children would need to have been treated to prevent one recurrence by twelve months. The efficacy of prophylaxis did not differ significantly between the children with or without VUR, and as 17% of the patients had no VCUGs and half of those who did undergo a VCUG examination did not have VUR, no evaluations of the effect of prophylaxis relative to the grade of VUR could be made (Craig *et al.* 2009). It has been argued that the lack of any reduction in UTI recurrences seen in these trials may have resulted from methodological limitations and insufficient statistical power rather than from the lack of efficacy of the antibiotic prophylaxis (Hoberman & Keren 2009, Mathews *et al.* 2009).

A recent Swedish Reflux Trial compared antibiotic prophylaxis, endoscopic surgery and surveillance only in order to evaluate the risk of UTI recurrences and new renal damage in 203 children aged one to two years with grade III to V VUR. The girls who received antibiotic prophylaxis or endoscopic treatment had fewer febrile UTI recurrences (19% and 23% respectively) than those placed under surveillance only (57%), but among the boys the overall rate of UTI recurrences was low and no differences between the three treatment options were found. After two years of follow-up, new renal damage was found in 15 children in the endoscopic treatment and surveillance groups combined, but none in those receiving prophylaxis. In summary, antibiotic prophylaxis was the most effective treatment in young girls, but boys did not benefit from active treatment (Brandström *et al.* 2010a, Brandström *et al.* 2010b).

2.2.3 Renal scarring

Type and occurrence of renal scarring

Renal scarring can be either congenital or acquired. Congenital renal scarring, i.e. congenital dysplasia, originates from maldevelopment or developmental arrest of the renal parenchyma or from antenatal obstruction of the urinary tract, or both. Congenital scarring is often seen in neonates, mostly boys, with high grade VUR.

In these small, dysmorphic kidneys VUR is only part of a complex developmental abnormality of the urinary tract and not the cause of the observed scarring (Anderson & Rickwood 1991, Farhat *et al.* 2000, Najmaldin *et al.* 1990, Ring *et al.* 1993, Risdon 1993, Stock *et al.* 1998, Wennerström *et al.* 2000). Histological examinations of such kidneys often show dysplasia, typically primitive ductal structures resulting from abnormal metanephric differentiation, suggesting a genetic cause for the combination of ureteral and renal parenchymal defects (Anderson & Rickwood 1991, Becu *et al.* 1988, Gil-Salom *et al.* 1991).

Acquired, i.e. post-infectious, renal scarring is mainly seen in older girls and is associated with low grade or no VUR at all (Panaretto *et al.* 1999, Swerkersson *et al.* 2007, Wennerström *et al.* 2000). It is difficult to differentiate congenital dysplasia from acquired renal scarring on a DMSA scan, however (Biassoni & Chippington 2008, Ditchfield *et al.* 2004). Pyelonephritis is more likely to give rise to focal segmental uptake defect associated with loss of contours or cortical thinning of mild to moderate severity, whereas a small kidney with a uniform uptake of isotope is more commonly congenital in origin (Najmaldin *et al.* 1990, Risdon 1993, Stock *et al.* 1998). Acquired renal scarring may coexist with pre-existing congenital dysplasia, but once infection has supervened, it becomes virtually impossible to determine the relative contributions of the congenital and acquired renal components.

Urography has shown renal scarring in approximately 10% to 20% of children after pyelonephritis (Bourchier *et al.* 1984, Hellström *et al.* 1989, Smellie *et al.* 1964, Winberg *et al.* 1974). Being more sensitive for detecting renal parenchymal defects, DMSA scintigraphy has virtually replaced urography (Elison *et al.* 1992, Rushton & Majd 1992). Acute-phase DMSA scans show lesions of the renal cortex consistent with pyelonephritis in approximately 60% of children with febrile UTI, but most of them resolve and persistent DMSA uptake defects, i.e. renal scars, are seen in approximately 15% of children (Shaikh *et al.* 2010). The occurrence of renal scarring detected after UTI seems to be decreasing, as recent studies have reported lower figures for renal scarring than those published before 2002 (Shaikh *et al.* 2010).

Pathogenesis and risk factors for acquired renal scarring

When bacteria from the renal pelvis invade the parenchyma, localized inflammation develops, triggering the innate immune system through multiple pathways. If renal parenchymal infection is limited, in extent and in duration, full

recovery can occur. Continued inflammation, however, may lead to impairment of the microvasculature causing ischaemia, micro-abscess formation and necrosis. If the renal parenchyma is unable to recover from these injuries, permanent fibrotic renal scarring can result (Montini *et al.* 2011). It has been observed that acquired renal scars occur exclusively in sites corresponding exactly to the areas of pyelonephritis demonstrated in DMSA during acute infection (Hitzel *et al.* 2004, Pecile *et al.* 2004, Rushton *et al.* 1992).

Recurrent pyelonephritis is the most significant risk factor for acquired renal scarring (Jakobsson *et al.* 1994, Panaretto *et al.* 1999, Swerkersson *et al.* 2007, Wennerström *et al.* 2000). New renal scars mostly develop in kidneys with pre-existing scarring, i.e. dysplastic kidneys, and the presence of pre-formed renal scars has been shown to be an independent indicator of the development of new scarring in children with VUR (Soylu *et al.* 2008). Obstruction of the urinary tract per se, especially when accompanied by UTI, carries a significant risk of scar formation, while the role of VUR remains unclear, as discussed earlier (Elder 2007, Roth *et al.* 2002, Warshaw *et al.* 1982). The conventional view that the risk of acquired renal scarring is greatest in infancy and during early childhood (American Academy of Pediatrics *et al.* 1999, Olbing *et al.* 1992, Vernon *et al.* 1997), has been challenged by several contradicting results suggesting that post-UTI scarring is more common in older children (Benador *et al.* 1997, Jakobsson *et al.* 1994, Taskinen & Rönnholm 2005). A delay in providing appropriate treatment for acute pyelonephritis has been shown to increase the likelihood of defects on acute-phase DMSA scans (Fernandez-Menendez *et al.* 2003, Pecile *et al.* 2004), but has not been associated with any significant increase in the risk of permanent scar formation (Doganis *et al.* 2007, Hewitt *et al.* 2008, Taskinen & Rönnholm 2005).

2.3 Imaging studies of the urinary tract in children with urinary tract infection

The rationale for urinary tract imaging is to find abnormalities that may predispose the child to recurrent UTIs and renal scarring leading to permanent renal damage (American Academy of Pediatrics *et al.* 1999). Imaging studies after UTI reveal some abnormality of the urinary tract in 20 to 80% of children (Bourchier *et al.* 1984, Hoberman *et al.* 2003, Montini *et al.* 2009, Ring & Zobel 1988, Smellie *et al.* 1981). Identification of such abnormalities would be reasonable only if subsequent treatment were truly capable of reducing the risk of

further UTIs and long-term consequences. As it is, our growing understanding of the origin of renal scarring and the natural history of VUR has challenged the long-held view of a causal relation between VUR and renal scars and the overall benefits of treating VUR (Farhat *et al.* 2000, Gordon *et al.* 2003, Venhola *et al.* 2006). Doubt has been raised as to whether any routine imaging is necessary after UTI in children.

2.3.1 Ultrasonography

Ultrasonography is used to assess the structure of the urinary tract and is sensitive in ruling out dilatation and hydronephrosis, which can be indicative of obstruction (Honkinen *et al.* 1986, Preda *et al.* 2010). As US is a non-invasive and feasible test that carries no risk of ionizing radiation, it has been widely used as a first-line imaging technique in cases of childhood UTI.

Ultrasonography adequately describes renal size, the thickness of the renal cortex and structural kidney abnormalities such as duplex collecting system, renal agenesis or ectopia and horseshoe kidneys. Advances in US technology have improved its usefulness for assessing the renal vasculature and detecting focal perfusion defects, as observed in pyelonephritis or renal scars (Dacher *et al.* 1996, Riccabona *et al.* 2001). Ultrasonography is useful for detecting infectious complications of UTI such as renal abscesses or pyonephrosis (Wippermann *et al.* 1991). Conventional US also gives valuable information on the bladder, e.g. on the thickness or trabeculation of the bladder wall, ureteroceles and the amount of residual urine. It is poor for the anatomical evaluation of the urethra and ureters, however.

The sensitivity of US for detecting grade III to V VUR ranges from 18% to 46% when only urinary tract dilatation is considered abnormal (Hoberman *et al.* 2003, Mahant *et al.* 2002, Wong *et al.* 2010, Zamir *et al.* 2004), but increases to 63% to 86%, when other US findings such as parenchymal dysplasia or a thickened bladder wall are included (Lee *et al.* 2009a, Lee *et al.* 2009b, Preda *et al.* 2010). Ultrasonography has been shown to identify 48% of the parenchymal changes consistent with acute pyelonephritis seen in DMSA scans and its ability to detect parenchymal changes is shown to improve with increasing severity of the DMSA defects (Preda *et al.* 2010). The sensitivity of US for detecting renal scarring, using a DMSA scan as the gold standard, has been found to range from 37% to 100% and its specificity from 65% to 99% (Roebuck *et al.* 1999). It is

unclear whether the additional sensitivity of a DMSA scan in identifying renal scars translates into additional clinical information.

Ultrasonography usually identifies abnormalities in around 15% of children examined after UTI (Gelfand *et al.* 2000a, Giorgi *et al.* 2005, Hoberman *et al.* 2003, Jahnukainen *et al.* 2006, Montini *et al.* 2009, Wong *et al.* 2010, Zamir *et al.* 2004), but there are some reports that found US abnormalities in up to 29% to 56% of cases (Table 4) (Huang *et al.* 2008, Lee *et al.* 2009b, Preda *et al.* 2010). It has been argued that post-UTI US imaging produces a quite low yield of clinically significant abnormalities, and that the results rarely alter the management, as most children with obstructive uropathies are already detected antenatally by foetal US nowadays (Gelfand *et al.* 2000a, Hoberman *et al.* 2003, Miron *et al.* 2007, Montini *et al.* 2009, Zamir *et al.* 2004). Although US has apparently lost some of its value, a Finnish study has shown that US has retained its position for imaging children with UTI, since the management of 9 (6%) out of 155 children with UTI was significantly changed on the basis of US findings only (Jahnukainen *et al.* 2006). Similarly, in a group of 203 children with UTI and normal VCUG, US revealed significant abnormalities in 9 (4.4%) (Giorgi *et al.* 2005). Furthermore, US has been reported to have found all the significant structural abnormalities and would have changed the management further in 10% of a series of 290 children with UTI (Preda *et al.* 2010).

Table 4. Frequencies of abnormal ultrasonography (US) findings and obstruction of the urinary tract in children with urinary tract infection.

Study	n	Age	Abnormal US, %	Obstruction, %
Gelfand 2000b	844	not stated	17	not stated
Hoberman 2003	309	1 to 24 mo	12	none
Zamir 2004	255	≤5 yrs	14	none
Giorgi 2005	282	5 d to 6 mo	16	2
Jahnukainen 2006	155	≤16 yrs	15	3
Huang 2008	390	<5 yrs	29	none
Lee 2009b	699	2 mo to 2 yrs	56	not stated
Montini 2009	300	1 mo to 2 yrs	13	0.3
Preda 2010	190	<1 yr	41	5
Wong 2010	820	<2 yrs	9	0.7

2.3.2 Imaging of vesicoureteral reflux

There are several methods available for detecting VUR, including VCUG, direct and indirect isotope cystography, voiding urosonography (VUS) and magnetic resonance imaging (MRI), and each has its own advantages and disadvantages.

Voiding cystourethrography

Voiding cystourethrography is considered the gold standard for detecting VUR. In VCUG urine reflux from the bladder to the ureter(s) and kidney(s) is simulated by filling the bladder with contrast medium by drip infusion through a catheter (or alternatively through suprapubic puncture) and taking serial X-ray pictures during filling and voiding. The child lies supine and the bladder is filled to its estimated maximal capacity or until the child needs to void or feels discomfort. As VUR is known to be intermittent, cyclic filling of the bladder enhances the ability of VCUG to detect VUR in infants, but increases the radiation burden significantly (Paltiel *et al.* 1992). A standardized technique for performing VCUG was introduced by the International Reflux Study Committee to ensure the compatibility of results between institutions (Lebowitz *et al.* 1985), but despite these detailed instructions for the procedure, there is considerable methodological variation in practice (Palmer *et al.* 2011).

Voiding cystourethrography is the only method that allows the grading of VUR according its severity and it thus remains a reference method (Lebowitz *et al.* 1985). It also provides detailed anatomical information on the outline of the bladder and is the only imaging technique that can reliably evaluate the male urethra. It has been common practice to perform VCUG as an initial test for evaluating the presence and severity of VUR and excluding other anatomical abnormalities.

The major limitation of VCUG is radiation exposure, especially to the gonads (Perisinakis *et al.* 2006, Stefanidis & Siomou 2007). The average effective radiation dose from a single VCUG in a child is 0.9 mSV, which corresponds to 30 chest X-rays (Perisinakis *et al.* 2006). Especially when VCUGs are repeated, the cumulative radiation burden is considerable and may lead to long-term sequelae (genetic anomalies, carcinogenesis) (Perisinakis *et al.* 2006). Furthermore, the catheterization and the whole procedure are unpleasant, causing pain and psychological stress and carry a potential risk of iatrogenic UTI (Rachmiel *et al.* 2005, Rao *et al.* 2011).

Radionuclide cystography

The isotopic methods available for detecting VUR include direct and indirect cystography. Direct isotope cystography is performed by retrograde filling of the bladder through a catheter, while indirect cystography is obtained via an intravenous injection of a radiopharmaceutical (Biassoni & Chippington 2008).

Direct isotope cystography offers the advantage of continuous monitoring of the kidneys during bladder filling and emptying, thus potentially affording even higher sensitivity than VCUG while entailing a significantly lower radiation exposure (average 0.07 mSV) (Lebowitz 1992, Stefanidis & Siomou 2007, Sukan *et al.* 2003). The disadvantages are the need for catheterization, radiation, although this is less than in VCUG, poor anatomical resolution and the inability to grade VUR accurately, and thus this technique is mostly used to verify VUR resolution in the follow-up of children with VUR or after anti-reflux surgery (Biassoni & Chippington 2008, Lebowitz 1992, Sukan *et al.* 2003). In cases where the clinical suspicion of VUR is low, or in girls with UTI in whom urethral pathology is uncommon, direct isotope cystography can be considered a first-line test for detecting VUR (Lebowitz 1992, Sukan *et al.* 2003).

One technique for detecting VUR that does not need catheterization is indirect isotope cystography, although it does require an intravenous catheter and it is essential that the child is toilet-trained as the child needs to void in front of a gamma camera. The main advantage of this method is that VUR can be detected with a physiologically filled and emptying bladder, but as with direct isotope cystography, the anatomical resolution is poor and no exact grading of VUR can be achieved (Biassoni & Chippington 2008). The sensitivity of indirect isotope cystography for detecting VUR ranges between 22% and 51% which is far lower than in direct cystography (De Sadeleer *et al.* 1994).

Voiding urosonography

Contrast-enhanced VUS with microbubbles containing contrast medium has been shown to achieve similar or even higher sensitivity for detecting VUR than VCUG and direct isotope cystography (Darge 2008, Piscitelli *et al.* 2008). Voiding urosonography seems to offer a radiation-free, safe and sensitive method for imaging VUR. Its disadvantages, however, are the need for catheterization, less accurate grading of VUR and poorer anatomical information on the ureters and urethra. In addition, the US contrast agents are expensive and the method is

operator-dependent, quite challenging and time-consuming. If VUS was to become as the primary modality for searching for VUR, there would be an urgent need to standardize the modality of US and the contrast agent to be used, and also documentation of the results (Darge 2010).

Magnetic resonance imaging

Magnetic resonance cystography by either a direct or an indirect method has been used and found feasible, but its sensitivity is not equal to that of conventional VCUG, being in the range of 76% to 90% for detecting VUR with 90% to 96% specificity (Lee *et al.* 2005, Takazakura *et al.* 2007, Vasanawala *et al.* 2009). The advantages of MR cystography are the lack of ionizing radiation and the possibility for combining it with MR scanning of the structure of the urinary tract and the renal parenchyma for assessment of possible scarring during the evaluation for VUR (Lee *et al.* 2005, Vasanawala *et al.* 2009). Sedation is necessary in young children and catheterization is required if the direct method of MR cystography is used (Takazakura *et al.* 2007).

2.3.3 Dimercapto-succinic acid scintigraphy

Renal cortical scintigraphy with ^{99m}Tc-DMSA is considered the gold standard for detecting parenchymal defects in pyelonephritis and renal scarring (Dacher *et al.* 2005, National Institute for Health and Clinical Excellence 2007). Acute-phase DMSA scanning has been shown to have excellent sensitivity (about 90%) and high specificity (100%) in finding renal parenchymal defects associated with pyelonephritis (Rushton & Majd 1992). Defects are seen in acute-phase DMSA in around 60% of children with their first UTI (Shaikh *et al.* 2010). On the other hand, it is not clinically important in most cases to confirm upper urinary tract involvement in acute UTI, so that acute-phase DMSA is not recommended as a part of routine care (National Institute for Health and Clinical Excellence 2007).

In order to assess permanent renal scarring DMSA scan should be performed at least six months after acute pyelonephritis to be able to distinguish reversible inflammatory parenchymal defects from permanent renal scars (Biassoni & Chippington 2008, Jakobsson & Svensson 1997). Permanent renal scars have been shown to occur at the sites of defects seen during pyelonephritis, and acute-phase DMSA scans have proved to possess 100% negative predictive value for

acquired scarring – i.e. if a DMSA scan is normal during acute UTI, it will remain normal (Hitzel *et al.* 2004, Rushton *et al.* 1992).

The major disadvantage of a DMSA scan is that congenital dysplasia cannot be reliably differentiated from acquired renal scarring (Biassoni & Chippington 2008, Ditchfield *et al.* 2004). Other concerns are its invasiveness, in that it requires intravenous access, rather high costs and risks of ionizing radiation. A single DMSA scan exposes a child to a radiation dose of approximately 1.1mSV, and the cumulative radiation burden can be considerable when DMSA scans are repeated several times (Stefanidis & Siomou 2007).

It has been suggested that VCUG could be replaced by an acute phase DMSA scan for evaluating children with febrile UTI. The rationale of this top-down strategy is that children with a normal DMSA scan during acute febrile UTI rarely have high-grade VUR and have an extremely low chance of developing renal scarring as evaluated in a follow-up DMSA twelve months later, even in the presence of VUR (Hansson *et al.* 2004, Hitzel *et al.* 2004, Preda *et al.* 2007, Rushton *et al.* 1992). Conversely, an abnormal acute-phase DMSA would detect any child with potentially harmful, high-grade VUR (Preda *et al.* 2007, Tseng *et al.* 2007). Nevertheless, a recent meta-analysis including eight cohort studies with marked heterogeneity found the pooled sensitivity of acute-phase DMSA for detecting high-grade VUR to be 79% with only 53% specificity (Mantadakis *et al.* 2011).

2.3.4 Current imaging recommendations

The association between UTI, VUR and renal scarring has formed the basis for various imaging recommendations which have been focused on the detection of VUR. For the last two decades, the management of children with UTI has included routine imaging of the urinary tract with US and VCUG, and in some countries with a DMSA scan as well, to identify abnormalities that may increase the risk of recurrent UTIs or permanent renal damage later in life (American Academy of Pediatrics *et al.* 1999, Jodal & Lindberg 1999, Lautala *et al.* 1992, MacKenzie *et al.* 1991).

The effectiveness of these routine imaging examinations in improving the long-term outcome for children with UTI has not been verified scientifically, however (Westwood *et al.* 2005). In fact, it has become clear in the course of time that the majority of children with UTI have normal imaging results. Despite the guidelines given, there has been considerable variability in using imaging studies,

particularly in ordering invasive tests such as VCUG, for children with UTI (Cohen *et al.* 2005, Hansson *et al.* 1999, Williams *et al.* 2007). The trend has been towards less routine imaging, although no new consensus on guidelines in this respect has been reached (South 2009). In 2007, the National Institute for Health and Clinical Excellence (NICE) in Britain recommended more selective imaging and encouraged abandonment of the practice of using VCUG on every child with UTI, but admitted that its guidelines were mostly based on a clinical consensus rather than on firm evidence, which was lacking in the literature (National Institute for Health and Clinical Excellence 2007). The previously mentioned top-down approach has been suggested recently, shifting the focus from VUR to evaluation of the status of the renal parenchyma with DMSA scans (Hansson *et al.* 2004, Preda *et al.* 2007).

2.4 Consequences of childhood urinary tract infection

Childhood UTIs, especially when accompanied by VUR, have been thought to predispose children to renal scarring, leading to long-term consequences such as hypertension, complications in pregnancy, chronic kidney disease (CKD) and potentially to ESKD later in life (Goonasekera *et al.* 1996, Jacobson *et al.* 1989, Lahdes-Vasama *et al.* 2006). The results of population-based studies have nevertheless suggested that the overall long-term consequences of childhood UTIs are not as serious as was previously thought and that the clinical outcome seems to be determined by the presence and extent of renal scarring, i.e. the number of functioning nephrons in the kidneys, not by the presence of VUR (Smellie *et al.* 1998, Sreenarasimhaiah & Hellerstein 1998, Wennerström *et al.* 2000a, Wennerström *et al.* 2000b).

2.4.1 Renal function

There is considerable variation in the literature evaluating the frequency of CKD and ESKD after UTI in childhood. One study identified 30 patients with UTI in childhood and non-obstructive renal scarring through a retrospective review of urographies performed between 1951 and 1967 and noted that after a mean interval of 27 years 10% had developed ESKD and all the remaining patients had significantly lower glomerular filtration rates (GFR) than healthy age-matched controls (GFR 91 vs. 108 ml/min/1.73 m²) (Table 5) (Jacobson *et al.* 1989). A larger follow-up study reported outcomes for 226 patients treated in a tertiary

centre for recurrent UTIs and VUR. After 10 to 41 years, abnormal renal function was found in 11 (7%) of 162 adults, all of whom had already had renal scarring identified before the age of ten years while none had developed new renal scars after childhood. Two of these 11 patients with abnormal renal function had received renal transplants and one had died of malignant hypertension (Table 5) (Smellie *et al.* 1998). Similarly, 12 (4.5%) of the patients in a Finnish cohort of 267, who had been diagnosed with VUR as children between 1955 and 1965, had died of kidney-related disease and 8 (3%) had developed ESKD. Moderate-to-severe renal insufficiency was found in 4 (3%) of the 127 patients who participated in the follow-up evaluation (Table 5) (Lahdes-Vasama *et al.* 2006). These studies represent highly-selected patient series from tertiary centres examined at a time when our knowledge of the diagnosis and treatment of childhood UTIs was not as accurate and readily available as nowadays and it is likely that patients with congenital renal abnormalities and pre-existing hypodysplasia were included in these studies.

By contrast, a population-based study in Sweden found no significant deterioration in renal function in patients with a history of childhood UTI. Renal function for 57 children with renal scarring and 51 matched controls without were reported out of an original cohort of 1221 children with UTI. After 16 to 26 years of follow-up, they had preserved their renal function well in all cases with or without renal scarring (median GFR 99 ml/min/1.73 m²). Altogether there were eight (7%) patients whose GFR had fallen below 80 ml/min/1.73 m², six of them with scars and two without (Table 5) (Wennerström *et al.* 2000b). Thus minor-to-moderate renal scars, especially if unilateral, seemed to be of negligible importance in terms of the long-term prognosis for children with UTI.

The few prospective studies to have been performed have found a low risk of CKD after childhood UTI. In the International Reflux Study in Children only one (0.8%) out of the 133 children with UTI and VUR had GFR <70ml/min per $1.73m^2$ after 10 years of follow-up (Table 5) (Jodal *et al.* 2006). Likewise, a survey of 111 girls with UTI followed up until adulthood found GFR <80ml/min per $1.73m^2$ in seven cases (6%), four with severe renal scarring and three without scarring, but none had GFR <70ml/min per $1.73m^2$ (Table 5) (Martinell *et al.* 1996).

Registers of ESKD or kidney transplants show that the commonest cause of ESKD in childhood is congenitally malformed kidneys (either obstructive uropathy or congenital dysplasia), accounting for one third of all cases, while the percentage of reflux nephropathy/acquired renal scarring is around 5% (ranging

from 0% to 19%) (Esbjörner *et al.* 1997, Miklovicova *et al.* 2005, Orr *et al.* 2009, Warady *et al.* 1997). It is impossible, however, on the basis of the information available from these registers, to assess the true risk of developing ESKD as a result of childhood UTI as they do not necessarily describe the specific causes of ESKD or distinguish between congenital and acquired renal scarring nor do they specifically address UTIs as a risk of ESKD. Moreover, as discussed earlier, clinical differentiation of congenital dysplasia from acquired renal scarring is difficult. Registers from Australia and New Zealand, show that the proportion of reflux nephropathy as a cause of childhood ESKD has declined with time. This phenomenon most likely reflects the improved antenatal recognition of renal dysplasia, so that children who would previously have been labeled as having reflux nephropathy are nowadays categorized as having congenital dysplasia (Orr *et al.* 2009).

In order to determine the frequency with which UTI could cause severe renal insufficiency in the absence of concomitant underlying abnormalities, Sreenarasimhaiah & Hellerstein reviewed the medical histories of 102 patients with ESKD. Three patients were found to have had reflux nephropathy as the main cause of ESKD, but only in one case (<1% of the whole series), presenting with renal scarring at the time of first imaging examinations, had the progression to ESKD been potentially accelerated by recurrent febrile UTI episodes. The authors concluded that UTIs per se do not cause ESKD and suggested a reconsideration of routine imaging following childhood UTI (Sreenarasimhaiah & Hellerstein 1998). In accordance with this, a recent survey of 366 patients with CKD treated at Oulu University Hospital, found 13 who had a history of UTI in childhood, all with structural abnormalities in initial imaging scans and only in one case could recurrent UTIs in childhood possibly have contributed to the further development of CKD. Thus, in the absence of structural kidney abnormalities, the true aetiologic fraction of childhood UTIs as the main cause of CKD is extremely small, 0.3% at most (Salo *et al.* 2011).

Attempts have been made to estimate the life-time risk of developing ESKD after UTI in childhood (Round *et al.* 2012, Stark 1997). Based on the reported incidence figures for UTI and information on the causes and annual or cumulative incidences of ESKD obtained from registers, Round *et al*. found considerable variation and uncertainty in the relationship between childhood UTI and the risk of ESKD in the light of the currently available data. The calculated estimates of the risk of developing ESKD after the first UTI ranged from 1/154 to 1/199900

and were heavily dependent on the assumptions made and the source of data used, so that no confident predictions of the true risk could be made (Round *et al.* 2012).

2.4.2 Hypertension

As blood pressure (BP) increases with age and depends on an individual's physical size, it is difficult to define hypertension in a paediatric population. The most commonly used definition is a statistical one based on the normal distribution of BP in healthy children and states that all individuals with a BP above +2SD or the 95th percentile (for gender, age and height) are hypertensive (National High Blood Pressure Education Program 2004). This means that hypertension occurs at the same frequency throughout childhood and even in healthy neonates. When considering the true harmful consequences of high BP, i.e. target-organ damage, defining hypertension as a BP above 140/90 mmHg is probably as useful in children as in adults (Uhari *et al.* 1991). Studies using the statistical definition for hypertension have found 3 to 28% of children with a history of UTI and VUR, and most of those with renal scarring, to be hypertensive (Patzer *et al.* 2003, Simoes e Silva *et al.* 2007). On the other hand, an earlier study concluded that, regardless of the presence of acquired renal scarring, VUR does not increase the risk of hypertension in adolescents unless accompanied with renal dysplasia (Wolfish *et al.* 1993). In accordance, hypertension needing medical treatment was diagnosed in less than 2% of patients in the International Reflux Study in Children after 10 years of follow-up (Table 5) (Jodal *et al.* 2006).

Reports on adults followed up after childhood UTI quote variable figures for hypertension, depending on patient selection, the extent of renal scarring and the follow-up-time. Some earlier studies based on highly selected series of patients with reflux nephropathy have found hypertension in up to 23% of cases (Table 5) (Goonasekera *et al.* 1996, Jacobson *et al.* 1989), while in a Finnish cohort of 127 adults treated for VUR during childhood 11% had been diagnosed earlier as having hypertension and were on antihypertensive medication and a further 29% had either systolic BP >140mmHg or diastolic BP >90mmHg at the follow-up visit. The overall occurrence of hypertension in this series did not differ from that in a normal Finnish adult population, however (Table 5) (Lahdes-Vasama *et al.* 2006). Two further retrospective cohort studies have also found a relationship between hypertension and renal scarring, but the risk of developing hypertension after childhood UTI was relatively low (3 to 11%) and only those with severe

renal scarring had an increased risk (Table 5) (Martinell *et al.* 1996, Smellie *et al.* 1998).

By contrast, the only population-based epidemiological study from Sweden showed no difference in mean 24h ambulatory BP (ABP) in patients followed up for 16 to 26 years after a first UTI in childhood. The risk of hypertension was low and only 9% patients with renal scarring and 6% without scarring were regarded as hypertensive (Table 5) (Wennerström *et al.* 2000a).

It seems that the occurrence of hypertension is relatively high in the general population and from late adolescence onwards the predominant cause is essential hypertension even in those with a history of UTI in childhood (Wolfish *et al.* 1993). Severe, bilateral renal scarring associated with childhood UTI may increase the risk of hypertension in some individuals, but the additional risk is likely to be small.

2.4.3 Pregnancy-related complications

Although some reports exist on pregnancy outcomes in women with reflux nephropathy or surgically corrected VUR, there are only few studies concerned with gestational morbidity in women followed up after UTI in childhood (Hollowell 2008, Martinell *et al.* 1990, Smellie *et al.* 1998). The limited evidence to be gained from these suggests that severe renal scarring found after childhood UTI rather than the presence of VUR may be associated with a slightly increased risk of hypertension especially during the first pregnancy (Martinell *et al.* 1990, Smellie *et al.* 1998).

Table 5. Follow-up studies evaluating consequences of childhood urinary tract infection (UTI).

Study	Description	Age at follow up, yrs	Renal function	Hypertension
Jacobson 1989	30 patients with UTI, renal scars in all and ≥gr III VUR[1] in 21	25 to 41	10% (3/30) ESKD[2] mean GFR[3] 91ml/min/1.73m^2 in others	23% (7/30) BP[4] >140/90 mmHg
Goonasekera 1996	100 patients with UTI, renal scars and VUR[1] in all	20 to 31	not stated	18% (18/100) systolic or diastolic BP[4] >+2SD
Martinell 1996	111 women with childhood UTIs, renal scars in 54 and VUR[1] in 69	16 to 31	6% (7/111) GFR[3] 70-79ml/min/1.73m^2 4/54 with renal scars 3/57 without renal scars	3% (3/111) BP[4] >140/90 mmHg all with renal scars
Smellie 1998	226 patients with UTIs, renal scars in 85 and VUR[1] in all	26 to 52	7% (11/162) elevated creatinine all had renal scars 1/11 had died, 2/11 had ESKD[2]	11% (24/226) BP[4] >140/90 mmHg 21/24 had renal scars
Wennerström 2000a+b	108 patients with UTI, study group: 57 with non-obstructive renal scars and VUR[1] in 43 control group: 51 matched subjects without scars, presence of VUR[1] not stated	17 to 34	median GFR[3] 99ml/min/1.73m^2 for all 8% (8/107) GFR[3] 69-79ml/min/1.73m^2 6/57 (11%) in the study group 2/51 (4%) in the control group	8% (8/100) mean 24h ABP[4]>+2SD 5/53 (9%) in the study group 3/47 (6%) in the control group
Jodal 2006	252 patients with UTI, renal scars in 113 and gr III-IV VUR[1] in all	not stated	<1% (1/133) GFR[3] <70ml/min/1.73m^2 with renal scars	<2% (4/252) systolic or diastolic BP[4] >95th percentile
Lahdes-Vasama 2006	127 patients from a cohort of 267 children with UTIs and VUR[1] in all, no data on renal scars in childhood	33 to 55	4% (12/267) died of kidney disease 3% (8/267) ESKD[2] 3% (4/127) GFR[3] <60 ml/min/1.73m^2	11% (14/127) hypertension 29% (37/127) systolic BP[4] >140 or diastolic BP[4] >90 mmHg

[1]VUR = vesicoureteral reflux, [2]ESKD = end stage kidney disease, [3]GFR = glomerular filtration rate, [4]BP = blood pressure

3 Aims of the present research

In order to assess the necessity and justification for routine imaging studies in children with UTI, we aimed:

1. To evaluate the occurrence of VUR in a general paediatric population using the reliability of a diagnosis as a marker of true UTI in children with proven and suspected UTI.
2. To examine the occurrence of clinically significant US abnormalities in children with UTI.
3. To study whether US alone is sufficient for imaging the urinary tract in children with UTI and whether any significant information would have been missed if VCUG had not been performed.
4. To analyse the value of imaging studies by assessing the clinical outcome for patients with a history of UTI in a large population-based cohort.

4 Patients and methods

4.1 Vesicoureteral reflux in children (I and II)

Study I

We evaluated retrospectively the findings in 406 consecutive children (143 boys and 263 girls) aged 0 to 5 years with suspected UTI admitted or referred for consultation to the Central Hospital of Central Finland in Jyväskylä (196 patients) and Oulu University Hospital (210 patients) between 1st January 1996 and 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, CRP, the method of urine sampling and the results of a urine dipstick screening test and urine culture were recorded and the renal US and VCUG findings were analysed.

The method of urine sampling was SPA in 134 (33%) cases, clean catheterization in one and a clean voided or a bag specimen in 271 (67%). The diagnosis of UTI was considered certain if the urine showed pyuria and any growth of a uropathogen in a SPA, or a monoculture $\geq 10^3$ CFU/ml of uropathogen from a catheterization sample, or a monoculture $>10^5$ CFU/ml of uropathogen from at least one clean voided urine or bag specimen in symptomatic patients (Group A, n=311/406, 77%). Children who did not fulfil the criteria for certain UTI were classified as having possible UTI (Group B, n=56, 14%) or improbable UTI if no pyuria and no significant ($<10^4$ CFU/ml) or mixed bacterial growth was found in the urine (Group C, n=39, 10%).

Of the 406 children studied, 291 (72%) were under the age of 2 years at the time of diagnosis, comprising 161 (55%) girls and 130 (45%) boys, while those in the age group 2 to 5 years ($p<0.001$) were predominantly girls (102/115, 89%). The children in Group A (mean age 1.3 years) were younger than those in Group B (mean age 1.8 years, difference -0.6 years, 95% confidence interval (CI) -1.03 to -0.11, p=0.01) or Group C (mean age 2 years, difference -0.8 years, 95% CI -1.32 to -0.23, p=0.002).

Ultrasonography imaging had been performed on 399 (98%) patients, and 347 (85%) had had a VCUG. The presence of VUR had been ascertained either radiologically (rVCUG), in 152, or by the isotope technique (iVCUG), in 145. In 50 cases both examinations had been performed.

Study II

We reviewed retrospectively the reports on renal or abdominal US and VCUG examinations performed at the Department of Paediatrics, University of Oulu, between 1st January 1993 and 31st December 2003. A list of all the patients on whom such examinations had been performed was obtained from the hospital database and data were collected from the patients' medical records.

Altogether 8567 patients were identified during the 11 years, 2145 of whom were younger than 15 years and had had their first imaging examination performed after UTI. Patients with a known urinary tract abnormality or other significant medical condition that could predispose them to UTI, such as meningomyelocele, were excluded (n=36). As we wanted to construct a population-based patient series, patients who had been referred from other hospital districts were also excluded (n=73) and finally 2036 patients were identified who fulfilled the inclusion criteria.

We classified the UTI diagnoses into 5 reliability classes based on the data on the urine cultures (Table 6). In 332 (16%) cases UTI had been diagnosed in an outpatient clinic and the referral did not include any data on urine cultures (classified as having of no microbial data).

Table 6. Classification of diagnostic reliability in 2036 children with proven or suspected urinary tract infection (UTI).

Reliability class	Children (%)	Type of urine sample	No. of samples	Urine bacterial culture (CFU/ml)
Proven UTI	583 (29)	clean voided or bag specimen	2	$\geq 10^5$ and species known, same bacteria in both samples
		suprapubic aspiration	1	any growth
Likely UTI	621 (31)	clean voided or bag specimen	1-2	$\geq 10^5$ in one or $\geq 10^5$ in one and $\geq 10^{4-5}$ in the other sample
Unlikely UTI	355 (17)	clean voided or bag specimen	1-2	10^{4-5} or growth unknown but species known
False UTI	145 (7)	clean voided or bag specimen	1-2	$<10^{3-4}$ or mixed bacterial flora[1]
		suprapubic aspiration	1	no bacterial growth
No microbial data	332 (16)			no data

[1]with no significant growth of uropathogenic bacteria

The survey population comprised 1481 (73%) girls and 555 boys, with a mean age of 3.2 years (standard deviation [SD] 2.9) (range from 1 day to 14.9 years), 76% being less than 5 years old at the time of diagnosis (Table 7). The majority of the children (60%) had had their UTI diagnosed and treated in outpatient clinics, mainly by general practitioners. The diagnosis of UTI was based on a SPA sample in 257 (13%), clean voided urine in 1137 (56%) and a bag specimen in 635 (31%) cases. In 7 cases the sampling method was unknown. About half (54%) of the UTI episodes had been febrile (temperature above 38°C). Eighty-two per cent had had radiological imaging following their first UTI, while the remaining 18% had had more than one episode of UTI before any imaging examination (Table 7). We gathered information on previous urine cultures from the 22/145 (15%) patients in the false UTI class who had a history of possible recurrent UTI. In 11 cases none of the previous urine cultures showed significant bacterial growth and in 9 cases no data on previous cultures were available. In 2 cases there was some evidence of possible previous UTI.

The children in the class of proven UTI were younger (mean 2.0 years, SD 2.4) than those in the other classes ($p<0.001$), they included more boys, they were more often febrile and most of them had their first UTI diagnosed and treated in hospital ($p<0.001$ for all variables). Those in the other diagnostic reliability classes, being more often referral patients, tended to be afebrile girls who had more often had recurrent UTIs (Table 7).

Table 7. Characteristics of the patients. Clinical and laboratory variables for the children with proven and suspected urinary tract infection (UTI) are shown by diagnostic reliability classes. Data were missing in some cases.

Characteristic	Reliability class				
	Proven UTI	Likely UTI	Unlikely UTI	False UTI	No microbial data
Children, n (%)	583 (29)	621 (31)	355 (17)	145 (7)	332 (16)
Age years, mean SD	2.0 (2.4)	3.4 (2.9)	3.2 (2.8)	3.0 (2.8)	4.7 (2.9)
Female, n (%)	370 (63)	467 (75)	263 (74)	107 (74)	274 (83)
Fever, n (%)	406 (71)	266 (46)	168 (52)	86 (61)	60 (28)
Bacteraemia, n (%)	15 (5)	9 (7)	0	3 (7)[a]	0
Recurrent UTI, n (%)	39 (7)	129 (21)	57 (16)	22 (15)	125 (38)
Outpatient, n (%)	156 (27)	432 (70)	234 (66)	73 (50)	327 (98)
Highest CRP, mg/L, mean (SD)	93 (73)	88 (80)	72 (72)	92 (72)	52 (52)

[a]Three neonates were classified as false UTI as they had bacteraemia caused by *Escherichia coli* but there was no bacterial growth in the urine sample.

Renal US had been performed on all of the children and 1185 (58%) had had a cystogram examination. Most patients 957/1185 (81%) had had an rVCUG to detect possible VUR, while 217 had had an iVCUG. In 11 cases VCUG had been performed by both methods. Out of 1552 children under the age of five, 531 (34%) did not have any VCUG performed.

4.2 Ultrasonography imaging in children with urinary tract infection (III)

Out of the population-based series of 2036 children who had undergone radiological imaging of the urinary tract because of UTI, 1185 patients on whom both US and VCUG had been performed were included in the present analysis. We were especially interested in 285 patients with a normal initial US but abnormal VCUG and collected further follow-up data on these cases (Figure 1).

The case histories of 1185 children (808 girls and 377 boys) with a mean age of 2.3 years (SD 2.5, range from 1 day to 14 years) were reviewed. About half the children (640/1185, 54%) had had their UTI diagnosed and treated at the Department of Paediatrics, while 545 had been diagnosed and treated in outpatient clinics. Eighty-two per cent had had radiological imaging following their first UTI, while the remainder had had recurrent UTI. In 61% of cases, the UTIs had been febrile (temperature above 38 °C).

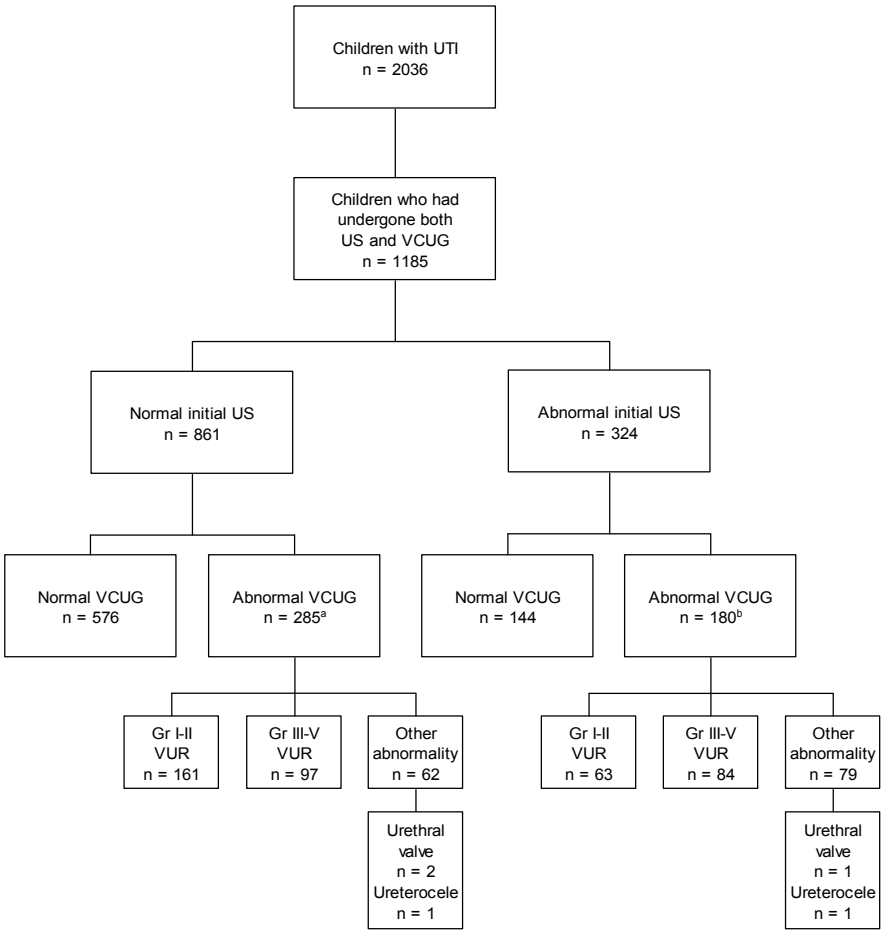

Fig. 1. Survey profile (III). [a] 35 patients had two abnormal findings in VCUG. [b] 46 patients had two abnormal findings in VCUG.

4.3 Prognosis for patients with a history of childhood urinary tract infection (IV)

In this follow-up study we wanted to evaluate the outcome of children with UTI, but without any underlying major renal dysplasia or obstructive uropathy. From our population-based cohort of 1185 children with UTI, we excluded 24 patients (2%) in whom one or other of these conditions had been identified in the primary US and were left with a study cohort of 1161 patients (795 girls and 366 boys)

(Figure 2). Eighty-two per cent of these had had radiological imaging following their first UTI and in 61% of the cases the index UTI had been febrile (temperature above 38 °C). All of them had had a US examination, and an rVCUG had been performed on 933/1161 (80%) and an iVCUG on 217. In 11 cases both rVCUG and iVCUG had been performed.

To obtain a representative and convenient sample of patients with childhood UTI and various abnormalities of the urinary tract, we classified the patients into four subgroups based on the findings in primary US and the highest VUR grade: the *US−VUR−* group comprised patients with normal US and VUR grades 0 to II (n=875), the *US−VUR+* group patients with normal US and VUR grades III to V (n=116), the *US+VUR−* group patients with abnormal US and VUR grades 0 to II (n=115) and the *US+VUR+* group patients with abnormal US and VUR grades III to V (n=55). Fifty randomly selected patients in the *US−VUR−* group, 50 in the *US−VUR+* group and 48 in the *US+VUR−* group were invited for a follow-up visit, as were all 55 patients in the *US+VUR+* group, as we wanted to evaluate the outcome for patients with potentially the most unfavourable prognosis as thoroughly as possible. As the patients in the *US−VUR−* group were reluctant to participate, we randomly selected and invited another 25 patients from this group (i.e. 75 patients altogether) (Figure 2).

The follow-up examinations were performed at the Department of Paediatrics and Department of Radiology, University of Oulu, in 2009 and 2010. All the patients, or the parents in the case of patients aged 15 years or less, were first contacted by letter and then by phone.

Of the 228 patients selected, 193 (85%) participated, comprising 120 who attended the clinic and 73 who were interviewed by phone (Figure 2). Majority of the participating patients 168/193 (87%) had had radiological imaging following their first UTI and the index UTI had been febrile in 76%. Sixty per cent (115/193) of the patients had had their UTI diagnosed and treated at the Department of Paediatrics, while 78 were treated in outpatient clinics. The mean follow-up time was 11.1 years (SD 3.2, range 5.9 to 17.3 years) and the mean age at follow-up was 13.0 years (SD 3.9, range 6 to 25.2 years) (Table 8). Of the 35 non-participating patients, one had died in a motor vehicle accident, 26 could not be contacted by phone and 8 were contacted but declined to participate.

A control VCUG had been performed on 93 (48%) of the 193 participating patients earlier during the follow-up (Table 8). All 91 patients with grade III to V VUR in their primary VCUG (groups *US-VUR+* and *US+VUR+*) had a control VCUG, and an average of three VCUGs (range one to seven VCUGs) per patient

were performed. Multiple VCUGs were mostly performed on surgically treated patients to evaluate the results of the surgical procedures.

Urinary tract surgery had been carried out on 42 (22%) of the 193 patients during childhood or adolescence, and 41 (45%) of the 91 patients with grade III to V VUR had had anti-reflux surgery (Table 8). Vesicoureteral reflux was found to have resolved (grade II or less) in 81 patients (89%) in the last VCUG, including 44/50 (80%) patients without active treatment for VUR and 37/41 (90%) patients after anti-reflux surgery. One girl in the *US+VUR+* group had had pyelopyelostomy due to an ectopic ureter.

Fig. 2. Study profile (IV). Classification and sampling of the patients for follow-up.

Table 8. Characteristics, follow-up data and grouping of the 228 selected patients. Data are given separately for the patients who participated in the follow-up study and for those who did not.

Characteristic	Study group							
	US-VUR-[1] Participated		US-VUR+[1] Participated		US+VUR-[1] Participated		US+VUR+[1] Participated	
	Yes	No	Yes	No	Yes	No	Yes	No
Patients, n (female, n)	63 (41)	12 (10)	47 (33)	3 (3)	39 (25)	9 (6)	44 (33)	11 (4)
Age at index UTI[2], years, mean (SD)	2.2 (2.6)	3.6 (3.0)	1.2 (1.6)	3.5 (2.9)	2.2 (2.4)	5.3 (3.3)	1.7 (2.1)	1.6 (2.0)
Age at follow-up, years, mean (SD)	13.4 (3.9)	5.7 (5.8)[a]	12.3 (3.9)	7.6 (2.9)[a]	13.6 (4.0)	4.8 (5.5)[a]	12.9 (4.2)	7.0 (4.7)[a]
Follow-up time, years, mean (SD)	11.2 (3.2)	5.7 (5.8)[b]	11.0 (3.5)	7.6 (2.9)[b]	11.4 (2.9)	4.8 (5.5)[b]	11.2 (3.1)	7.0 (4.7)[b]
Antibiotic prophylaxis, n (%)	9 (14)	1 (8)	46 (98)	3 (100)	5 (13)	4 (44)	43 (98)	11 (100)
Recurrence of UTI, n (%)	15 (24)		27 (57)		10 (26)		23 (52)	
Febrile recurrence, n (%)	3/15 (20)		15/27 (56)		2/10 (20)		15/23 (65)	
Control VCUG[3], n (%)	2 (3)	0	47 (100)	3 (100)	0	2 (22)	44 (100)	9 (90)[c]
Urinary tract surgery, n (%)	0	0	19 (40)	2 (67)	0	1 (11)	23 (52)	5 (50)[c]

[1]US −/+ indicates normal/abnormal primary ultrasonography and VUR −/+ indicates grade 0 to II/grade III to V vesicoureteral reflux, [2]UTI = urinary tract infection, [3]VCUG = voiding cystourethrography, [a]Age at the time of the last control visit to the Department of Paediatrics, [b]Time elapsing from the index UTI to the last control visit to the Department of Paediatrics, [c]Further follow-up data were available for ten non-participating patients in the US+VUR+ group.

Follow-up examinations

The patients attending the clinic were asked to complete a questionnaire concerning their history of UTI recurrences, use and duration of antimicrobial prophylaxis, general health, medication, details of pregnancy and family history of hypertension. The telephone interview contained the same questions as this questionnaire. The medical records of all the selected patients were reviewed and data on any anti-reflux surgery and the latest US and VCUG results were retrieved.

The follow-up visit included a clinical examination, measurements of weight, height and BP, laboratory tests and renal US. Blood pressure was measured three times from the right arm after 15 minutes in a sitting position and mean values were calculated (Critikon Dinamap^{TM} Vital Signs Monitor 8100). In addition to the BP measurements obtained for the 120 patients attending the clinic, use was also made of recent BP measurements performed on 55 of the patients interviewed by phone. Blood samples were obtained for the measurement of serum cystatin C concentration (CysC) (mg/L), and the glomerular filtration rate (GFR) was estimated using the equation based on serum CysC concentration published by Filler and Lepage ($GFR=91.62x(1/CysC)^{1.123}$) (Filler & Lepage 2003). The urine analyses included dipstick screening, bacterial culture and the albumin-creatinine ratio. Ultrasonography with a Philips iU22 device (Philips Medical System, Bothell, WA, USA) was performed on 150 patients (78%) altogether, including 118 who were attending the clinic and 32 examined earlier during the follow-up period.

Height was expressed in Z-scores obtained from Finnish growth charts. Standard age-based paediatric ranges for serum CysC and U-alb/U-creat levels were used. An estimated GFR ≥90ml/min/1.73 m² was regarded as normal.

4.4 Definitions

Vesicoureteral reflux detected in rVCUG was graded into I to V according to international system (Lebowitz *et al.* 1985). The grading of VUR in iVCUG was: grade I - detectable minimal reflux; grade II - clearly visible variable reflux which does not increase during voiding or is only seen during voiding; grade III - reflux which increases during voiding; grade IV - constantly increasing reflux during filling of the bladder. For the purposes of this analysis we regarded grades I-II in iVCUG as corresponding to grades I-II in rVCUG and grades III to IV in iVCUG

as corresponding to grades III to V in rVCUG. The most severe grade was recorded in patients with bilateral VUR. In the control cystograms, VUR was considered resolved if it was grade II or less in the last VCUG. Bladder wall trabeculation, marked residual urine, widened posterior urethra and bladder diverticulum in rVCUG were defined as bladder abnormalities.

In study I dilatation of the upper urinary tract in US was graded as present or absent, while in studies II, III and IV a more precise definition was used: an antero-posterior pelvic diameter of more than 10 mm in US was defined as hydronephrosis (Avni *et al.* 2001) and a diameter of 7 to 10 mm was defined as mild dilatation of the upper urinary tract. A thickened bladder wall (thickness >5 mm with an almost empty bladder and >3 mm with a full bladder), marked residual urine and bladder diverticulum were interpreted as bladder abnormalities (Dinkel *et al.* 1985). A renal scar/parenchymal defect in US was defined as a reduction in renal parenchymal thickness and possible corresponding calyceal deformation. Kidney hypoplasia/growth retardation was defined as a longitudinal renal dimension smaller than −2 standard deviations (SD) of the mean renal length according to the patient's height (Ring & Riccabona 2001).

The abnormalities in US in studies II and III were classified as either clinically significant or insignificant. Clinically significant US abnormalities comprised hydronephrosis, dilated ureter, duplex system, renal scar/parenchymal defect, renal agenesis, kidney hypoplasia/growth retardation, ureterocele, polycystic kidney disease and renal tumour. Mild dilatation of the upper urinary tract, bladder abnormalities, ectopic kidney, horseshoe kidney, simple renal cysts and ovarial cysts were defined as clinically insignificant US abnormalities. In the follow-up study IV, the primary US was considered abnormal in cases where it showed at least one of the previously defined clinically significant US abnormalities.

4.5 Statistical methods

The data were analysed with SPSS for Windows (version 16.0) or PASW Statistics (versions 18 and 19, IBM Company, Chicago, IL, USA) and with StatsDirect (version 2.7.2, StatsDirect Ltd, Cheshire, UK).

In the pairwise comparisons categorial variables were tested using either the Pearson χ^2 test or the binomial SND (standardized normal deviate) test and continuous variables with the Student's t-test. In study II the linear association between age and VUR was examined by means of the trend test, and the relative

risks (RR) of VUR and US abnormalities in the proven and false UTI classes and their 95% CIs were calculated. A multivariate logistic regression analysis was performed for study II to evaluate the influence of the reliability of the UTI diagnosis on the risk of VUR after adjusting for possible confounding factors (age, gender and history of recurrent UTI), and the results of the multivariate analysis are given as adjusted odds ratios (ORs) with 95% CIs. When analysing the differences between the diagnostic reliability classes in studies I and II and between the groups in study IV the Pearson χ^2 test was used for categorial variables and an ANOVA test with Tukey's HSD (Honestly Significance Difference) *post hoc* correction for continuous variables.

4.6 Ethical considerations

The protocol of study IV was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District. Informed consent was obtained from all the participating patients or from their parents in the case of patients aged 15 years or less. Studies I, II and III were register-based surveys with no contact with or consequences for the patients, and thus approval from the Ethics Committee was unnecessary.

5 Results

5.1 Vesicoureteral reflux in children (I and II)

Study I

Voiding cystourethrographies showed 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 to 5 years (99/262, 38% vs. 21/85, 25%, p=0.03). 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.

Abnormal US findings were recorded for 31/141 (22%) boys and 40/258 (16%) girls. There were 56/284 (20%) children under the age of 2 years and 15/115 (13%) older children who had abnormal US (p=0.11). The majority of the abnormal US findings in boys were recorded in infants aged less than 6 months (25/31, 81% of all US abnormalities in boys) and no US abnormalities were recorded over the age of 2 years. Among the girls, 8/40 (20%) of the US abnormalities were found in infants under the age of 6 months as compared with 15/40 (38%) over the age of 2 years. Ultrasonography showed upper urinary tract dilatation or anatomical abnormality in 58/305 (19%) of the children in Group A, in 4/55 (7%) in Group B and in 9/39 (23%) in group C (p=0.08). Where 34/58 (59%) of the US abnormalities in Group A were considered clinically significant (hydronephrosis and/or dilated ureter), this was the case in 3/9 (33%) in Group C.

Vesicoureteral reflux was noted in 69/205 (34%) of the children under the age of 2 years with normal US and in 39 (19%) it was of grades III-V. Among the children over the age of 2 years with normal US, VUR was found in 14/70 (20%) and was of grades III-V in 4 (6%) cases.

Fever was the most common clinical symptom in all the patient groups (documented in 337 patients, of whom 257 [76%] had temperature ≥38 °C). The mean body temperature was 38.9 °C for the children with VUR and 38.7 °C without (difference 0.2° C, CI - 0.5 to 0.5, p=0.11). None of the other clinical symptoms of UTI recorded (foul-smelling urine, abdominal pain, dysuria, feeding problems, nausea or vomiting, irritability or lethargy) was predictive of the

presence of VUR. The mean CRP values for the children with and without VUR were 94 mg/l and 81 mg/l (difference 13 mg/L, CI 1.4 to 27, p=0.08).

Study II

Vesicoureteral reflux of any grade was found in 405/1185 (34%) cases and grades III to V in 181 (15%) cases. Unilateral VUR was found in 208 cases and bilateral in 197. The occurrence of VUR was similar among those with proven and false UTI (37.4% vs. 34.8%, RR 1.08, 95% CI 0.7 to 1.7, p=0.75) and did not increase towards the higher diagnostic reliability classes (p=0.58 for trend) (Figure 3). Similarly, the frequencies of grade III to V VUR did not differ between the reliability classes (Figure 3). There was a significant negative trend in the occurrence of VUR with increasing age (p=0.001 for trend) (Figure 4). In a subgroup analysis of children younger than 2 years of age the occurrence of grade III to V VUR was similar in the false and proven UTI classes (20.0% vs. 18.6%, RR 0.93, 95% CI 0.45 to 2.15, p=0.61).

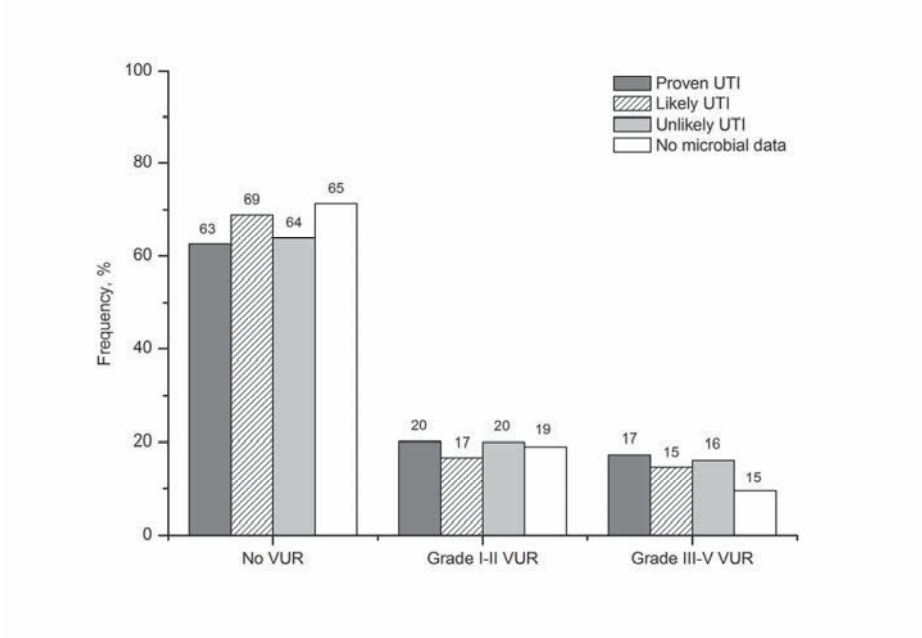

Fig. 3. Vesicoureteral reflux in 1185 children with proven and suspected urinary tract infection (UTI). Frequencies are shown in diagnostic reliability classes.

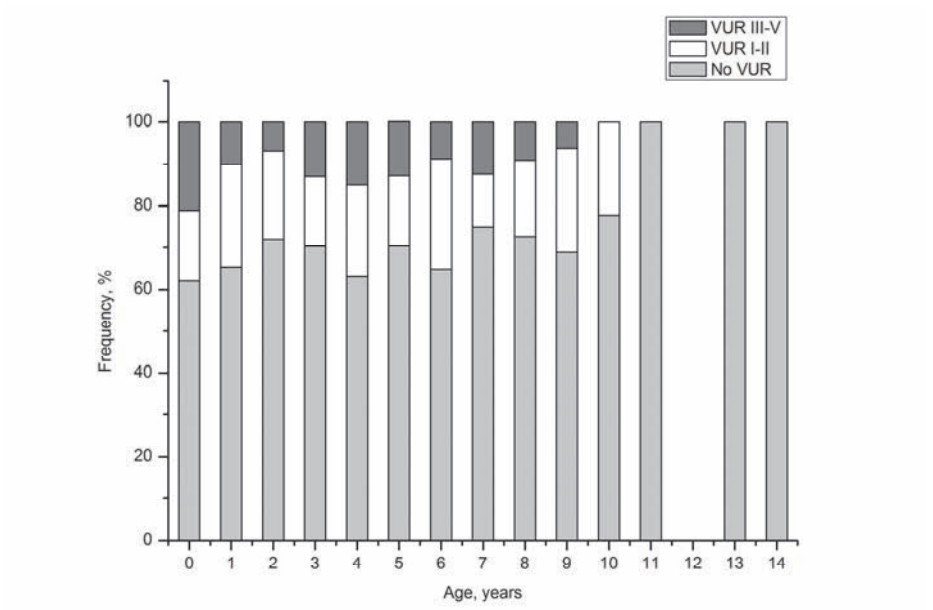

Fig. 4. Frequencies of vesicoureteral reflux (VUR) of grades I to II and of grades III to V by age groups among the 1185 children with proven and suspected urinary tract infection.

Ultrasonography was abnormal in 424 (21%) cases (Table 9). Clinically significant US abnormalities occurred in 206/2036 (10%): in 87/583 (14.9%) of the patients with proven UTI, in 57/621 (9.2%) of those with likely UTI, in 31/355 (8.7%) of those with unlikely UTI, in 11/145 (7.6%) of those with a false UTI diagnosis and in 21/332 (6.3%) of those with no microbial data. The risk of clinically significant US abnormalities increased as the reliability of the UTI diagnosis improved, the RR in cases where the diagnosis of UTI was proven being 1.96 (95% CI 1.1 to 3.6, p=0.02) as compared with that in cases with a false UTI diagnosis. Grade III to V VUR was found in 97/861 (11%) cases with a normal US.

Our multivariate logistic regression analysis showed the occurrence of VUR to decrease with increasing age (OR 0.92, 95% CI 0.86 to 0.98, p=0.01) and to have a significant association with female gender (OR 1.74, 95% CI 1.29 to 2.34, p<0.001). Neither a history of recurrent UTI (OR 1.00, 95% CI 0.99 to 1.02, p=0.61) nor the reliability of the UTI diagnosis (OR 1.14, 95% CI 0.60 to 2.17, p=0.41) was associated with VUR after adjusting by other variables.

Table 9. Findings on renal/abdominal ultrasonography (US) in 2036 children with proven and suspected urinary tract infection (UTI). Frequencies are shown in the whole survey population and by diagnostic reliability classes.

US finding	All, n (%)[a]	Reliability class				
		Proven UTI, n (%)[a]	Likely UTI, n (%)[a]	Unlikely UTI, n (%)[a]	False UTI, n (%)[a]	No data, n (%)[a]
Normal	1612 (79)	439 (75)	492 (79)	289 (81)	126 (87)	266 (80)
Clinically significant US abnormality						
Hydronephrosis or dilated ureter	124 (6)	61 (10)	32 (5)	16 (5)	5 (3)	10 (3)
Duplex system	66 (3)	20 (3)	22 (4)	9 (3)	5 (3)	10 (3)
Renal scar	17 (<1)	4 (<1)	4 (<1)	7 (2)	1 (<1)	1 (<1)
Hypoplastic kidney	14 (<1)	4 (<1)	7 (1)	0	1 (<1)	2 (<1)
Ureterocele	7 (<1)	4 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Renal agenesia	4 (<1)	1 (<1)	2 (<1)	1 (<1)	0	0
Polycystic kidney disease	1 (<1)	1 (<1)	0	0	0	0
Kidney tumour	1 (<1)	0	0	1 (<1)	0	0
Clinically insignificant US abnormality						
Mild dilatation	120 (6)	48 (8)	33 (5)	20 (6)	6 (4)	13 (4)
Bladder abnormality	146 (7)	31 (5)	54 (9)	17 (5)	3 (2)	41 (12)
Ectopic kidney	3 (<1)	0	1 (<1)	2 (<1)	0	0
Horseshoe kidney	1 (<1)	1 (<1)	0	0	0	0
Simple renal cyst	4 (<1)	2 (<1)	1 (<1)	1 (<1)	0	0
Ovarial cyst	11 (<1)	3 (<1)	6 (<1)	2 (<1)	0	0

[a]88 patients had ≥ 2 ultrasonographic abnormalities

5.2 Ultrasonography imaging in children with urinary tract infection (III)

Baseline data

The initial US had been abnormal in 324/1185 cases (27%), and 261 abnormalities in 191 patients (16%) were considered clinically significant (Figure 1). The most common US abnormalities were hydronephrosis, seen in 120, a duplex system, in 60, renal scarring, in 16, and hypoplastic kidney, in 9 patients. In 17 cases (1.4%) with US showing dilatation of the upper urinary tract, a surgical procedure other than anti-reflux surgery was needed: four obstructions of the ureteropelvic junction, four obstructions of the ureterovesical junction, four

double collecting systems with obstructive ureteroceles, two obstructive double collecting systems, two urethral valves and one double collecting system with a dysplastic upper moiety. Ultrasonography also showed one non-functioning dysplastic kidney, which was removed.

Out of the 324 patients with abnormal initial US, VCUG was considered abnormal in 180 cases (56%) (Figure 1) and showed non-VUR abnormalities in 79, 31 of which were additional to the initial US findings. In two cases out of these 31 (one urethral valve and one obstructive ureterocele), VCUG revealed the cause of the hydronephrosis seen in US, and these patients were operated on. In the remaining 29 cases VCUG found no clinically significant non-VUR abnormalities (six uncomplicated duplex systems, two non-obstructive ureteroceles, one horseshoe kidney and mild bladder abnormalities in the others).

The initial US had been normal in 861/1185 cases (73%), VCUG being considered abnormal in 285/861 of these (33%) (Figure 1). Grade III to V VUR was found in 97/861 (11%) (Figure 1 and Table 11). In three cases, VCUG showed clinically significant non-reflux abnormalities not seen in US: two infant boys had non-obstructive posterior urethral valves and one girl had bilateral non-obstructive ureteroceles (Table 11). Boy A had had one episode of febrile UTI caused by *Escherichia coli* at the age of three months and boy B had had two cystitis episodes by the age of six months and his UTIs were diagnosed and treated in an outpatient clinic, so that the referral did not include any data on urine cultures. Neither of the boys had a history of a poor urinary stream. Although US did not show any dilatation of the upper urinary tract, VCUG showed mild tapering of the urethral caliber implying the possibility of a urethral valve, but no bladder wall thickening, trabeculations or VUR. Both boys had endoscopic valve ablation, and no further complications had occurred during 4-year follow-up. The girl (aged seven months) with the bilateral ureteroceles had been observed closely without surgical intervention and no obstruction had occurred.

Table 10. Findings in voiding cystourethrography (VCUG) in 861 children with urinary tract infection and normal initial ultrasonography.

VCUG finding	No. of patients (%)[a]
Normal	576 (67)
Vesicoureteral reflux grade I-II	161 (19)
Vesicoureteral reflux grade III-V	97 (11)
Duplex system (non-obstructive)	13 (2)
Urethral valve (non-obstructive)	2 (0.2)
Ureterocele l.a. (non-obstructive)	1 (0.1)
Bladder abnormality	46 (5)

[a]35 patients had 2 abnormal findings in VCUG

Follow up data on 97 patients with normal initial US and grade III to V VUR

In 97/181 patients (54%) with grade III to V VUR, initial US showed no dilatation of the ureters or pelvis (Figure 1). This group comprised 71/97 girls (73%) and 26 boys (27%), their age ranging from 1 day to 10 years (mean age 1.5 years, SD 1.8) (Table 11). The patients were followed up by our hospital for a mean time of 6.9 years (range 3.3 to 12.2 years). The choice of treatment (operative or antimicrobial prophylaxis) was based on a clinical decision. Fifty-seven patients (59%) received no active treatment for VUR, while 29 (30%) had endoscopic treatment and 11 open surgery (Table 11). In the endoscopic treatment group, eight patients needed one re-injection for correction of VUR and one needed two re-injections. Two patients in the open surgery group had had two unsuccessful endoscopic injections before open surgery. An average of three VCUGs (range one to seven) was performed per patient during the follow-up, although one patient with no active treatment for VUR refused to have any follow-up VCUGs. Multiple VCUGs were mostly performed on surgically treated patients to evaluate the results of the procedures. Antibiotic prophylaxis was given in 93/97 cases (96%), with a mean duration of 2.3 (SD 1.9) years, and UTI recurrences occurred in 35/97 cases (36%). The patients in the endoscopic and open surgery groups had had recurrent UTIs during follow-up more often than those who received no active treatment for VUR (24/40, 60% vs. 11/57, 19%, difference 41%, 95% CI 21% to 57%, $p<0.001$) (Table 11). Vesicoureteral reflux had resolved in 88/97 (91%) cases by the end of follow-up, including 50/57 (88%) patients without active treatment for VUR, 27/29 (93%) after endoscopic surgery and 11/11 (100%) after open surgery (Table 11).

Follow-up US examinations were performed on 89/97 (92%) of the patients, the last US being considered abnormal in 25 cases (28%). The US abnormalities comprised hydronephrosis in three cases, small-sized kidney in eight, a duplex system in six, mild dilatation of the upper urinary tract in two and a bladder abnormality in one, while 11 patients had developed new renal scars detectable in US. Six patients had two of the above mentioned US abnormalities. The treatment given for VUR did not alter the occurrence or nature of abnormal findings in follow-up US.

The eleven patients (eight girls and three boys) with new renal scars visible in US had had longer antibiotic prophylaxis (3.6 vs. 2.2 yrs, $p<0.001$) than those without new scars and their VUR was more persistent (resolution of VUR in 7/11, 64% vs. 80/86, 93%, difference 29%, 95% CI 7% to 58%, $p<0.01$). The patients with or without new renal scars did not differ statistically significantly in terms of age, gender, fever, bacteraemia, a causative organism other than *Escherichia coli* at presentation, recurrence of UTI during follow-up or the treatment given for VUR. No impairment of renal function was observed during clinical follow-up in these 11 children with renal scars.

Table 11. Baseline characteristics and follow-up data for 97 patients with normal initial ultrasonography (US) and grade III to V vesicoureteral reflux (VUR) by treatment groups.

Characteristic	No treatment for VUR	Endoscopic treatment	Open surgery
Children, n (%)	57 (59)	29 (30)	11 (11)
Age at index UTI[1], yrs, mean (SD)	1.2 (1.5)	2.2 (2.3)	0.9 (1.1)
Female, n (%)	38 (67)	23 (79)	10 (91)
Antibiotic prophylaxis, n (%)	54 (95)	28 (97)	11 (100)
Duration of prophylaxis yrs, mean (SD)	2.4 (1.7)	1.9 (1.5)	3.6 (1.7)
Recurrence of UTI[1], n (%)	11 (19)	17 (59)	7 (64)
New renal scar in US, n (%)	4 (7)	4 (14)	3 (27)
Resolution of VUR, n (%)	50 (88)	27 (93)	11 (100)

[1]UTI = urinary tract infection

Out of our series of 861 children with UTI and a normal initial US, 40 with grade III to V VUR and two with significant non-reflux pathology may have benefited from surgical treatment, giving total number of 42/861 (4.9%) potential cases of pathological findings that could have been missed if VCUG had not been performed.

5.3 Prognosis for patients with a history of childhood urinary tract infection (IV)

Antibiotic prophylaxis and UTI recurrences

Of the 193 participating patients, 103 had had antibiotic prophylaxis, including 89 (86%) for grade III to V VUR. Altogether 75 (39%) patients had had a recurrence of UTI and at least one UTI recurrence had been febrile in 47% of these cases (Table 8).

A recurrence of UTI had occurred significantly more often in the patients with grade III to V VUR than in those with grade II or less (55% [50/91] vs. 25% [25/102], difference 30%, 95% CI 17% to 43%, $p<0.001$) and UTI recurrences had more often been febrile in the patients with grade III to V VUR (60% [30/50] vs. 20% [5/25], difference 40%, 95% CI 17% to 58%, $p<0.001$). The difference in UTI recurrences between the patients with grade III to V VUR and those with grade II or less remained significant even after controlling for age.

Ultrasonography findings

A unilateral parenchymal defect was found in the follow-up US in 22 (15%) of the 150 patients, but no cases of a bilateral parenchymal defect were found. Follow-up US showed a diffuse reduction in parenchymal thickness in three of the 22 cases with unilateral renal parenchymal defects and mild local parenchymal defects in the others. Eighteen of the 22 renal parenchymal defects were considered to represent new renal damage and occurred in 10/46 (22%) cases in the *US−VUR+* group and in 8/43 (19%) in the *US+VUR+* group, but in none of the patients in the *US−VUR−* or *US+VUR−* groups. Taking account of the stratified random sampling used, if we were to extrapolate the total occurrence of new renal defects from these data to the whole study cohort, a total of 36 out of the 1161 (3%) patients could potentially have developed new renal damage after UTI. Follow-up US also revealed unilateral kidney growth retardation in five patients: four with a parenchymal defect on the same side and one without any renal parenchymal defect visible in US.

The patients with a renal parenchymal defect in US at follow-up had significantly more often experienced a UTI recurrence (82% [18/22] vs. 40% [51/128], difference 42%, 95% CI 20% to 56%, $p<0.001$), had antibiotic prophylaxis (95% [21/22] vs. 60% [77/128], difference 35%, 95% CI 17% to 46%,

p<0.001) and undergone urinary tract surgery (68% [15/22] vs. 21% [27/128], difference 47%, 95% CI 25% to 64%, p<0.001) than those without any renal parenchymal defect. The patients with and without a renal parenchymal defect did not differ significantly in their distribution by age or gender.

All except one of the 22 cases with a renal parenchymal defect and all five cases with kidney growth retardation were found in patients with grade III to V VUR. The analysis of renal length (expressed as SD scores for the mean renal length according to height) in the follow-up US showed no significant difference between kidneys with grade 0 to II and those with grade III to V VUR (mean SD +0.36 vs. +0.18, difference 0.18 SD, 95% CI -0.07 to +0.43 SD, p=0.15). The rate of VUR resolution in the last VCUG did not differ between the patients with and without a parenchymal defect in US (resolution of VUR in 86% of cases [18/21] vs. 90% [62/69], difference 4%, 95% CI -25% to 9%, p=0.46).

Renal function, blood pressure and somatic growth

Serum CysC and estimated GFR levels were within normal limits in all the patients, with no significant differences between the study groups or between the patients with and without a renal parenchymal defect in the follow-up US (Table 12). None of the patients had haematuria or proteinuria.

Mean systolic and diastolic BP values were within the normal range, again with no differences between the study groups or between the patients with and without a renal parenchymal defect in the follow-up US. No cases of BP above 140/90mmHg were found in the 120 patients attending the clinic (Table 12), nor were any reported among the 55 patients interviewed by phone who had data available on recent BP measurements.

Height was normally distributed and within the normal limits in all the patients, with no significant differences between the four study groups or between the patients with and without a renal parenchymal defect in the follow-up US (Table 12).

Table 12. Renal function, blood pressure and somatic growth in the 120 patients attending clinic in different study groups.

Parameter	Study group			
	US-VUR-[1] (n=31) mean (range, SD)	US-VUR+[1] (n=36) mean (range, SD)	US+VUR-[1] (n=26) mean (range, SD)	US+VUR+[1] (n=27) mean (range, SD)
Serum cystatin C, mg/L	0.67 (0.51-0.82, 0.07)	0.66 (0.49-0.86, 0.09)	0.65 (0.47-0.79, 0.08)	0.69 (0.52-0.82, 0.08)
Estimated GFR[2], ml/min/1.73m²	144 (115-195, 17)	151 (109-204, 23)	150 (119-214, 23)	142 (115-191, 19)
Systolic BP[3], mmHg	104 (85-128, 10)	103 (80-123, 10)	109 (94-133, 9)	108 (94-124, 9)
Diastolic BP, mmHg	58 (34-77, 8)	57 (40-65, 5)	61 (47-74, 7)	59 (46-74, 7)
Z-score of height	+0.1 (-2.4 to +2.6, 0.9)	+0.1 (-2.0 to +1.7, 1.0)	+0.2 (-2.3 to +2.9, 1.2)	+0.6 (-1.5 to +3.3, 1.2)

[1]US −/+ indicates normal/abnormal primary ultrasonography and VUR −/+ indicates grade 0 to II/grade III to V vesicoureteral reflux, [2]GFR = glomerular filtration rate, [3]BP = blood pressure

6 Discussion

We found in two consecutive studies that the overall occurrence of VUR was around 35% and that its frequency did not increase as the reliability of UTI diagnosis improved, since the frequencies were similar among the children with proven (37%) or certain (36%) UTI versus false (35%) or improbable (36%) UTI. This supports claims that VUR is not associated with UTI as closely as was reported earlier and that VUR is more common even among healthy children than has been thought.

In both studies I and II, there was a significant negative trend in the occurrence of VUR with increasing age. The tendency of VUR to resolve spontaneously as the child grows is well known and this maturation phenomenon was again documented here (Chand *et al.* 2003, Edwards *et al.* 1977, Gelfand *et al.* 2000b, Sargent & Stringer 1995). Although young age and female gender increased the risk of VUR, our multivariate analysis showed that neither recurrent UTI nor improved reliability of the UTI diagnosis had this effect. Vesicoureteral reflux was not significantly related to UTI and occurred frequently even in children without proven UTI.

Our findings are in accordance with those of Köllerman and Ludwig in the late 1960s, who found that VUR was common in healthy children without UTI or any other urinary tract pathology and that the frequency of VUR decreased with increasing age (Köllermann & Ludwig 1967). Since it is unethical to perform VCUGs on healthy subjects and it would be impossible to perform a study of that kind today, we have to settle for this indirect evidence of the occurrence of VUR in healthy children. In our large population-based cohort of 2036 children, the diagnosis of UTI was based on SPA only in 13% cases and a bag specimen was used in about a third of all cases. The fact that the children in our survey with unreliable or even false UTI diagnosis were examined by means of VCUG gave us the opportunity to analyse the frequency of VUR among children with proven and suspected UTI and even without UTI. One could argue that as we did not have full documentation on all the urine cultures obtained, there might be some overlapping between the classes of proven, likely and unlikely UTI, i.e. some children with unlikely UTI might indeed have had UTI. Nevertheless, the children in the false UTI class did not have UTI according to any used criteria and yet they still had VUR as often as the children with proven UTI.

It has traditionally been thought that VUR is found only rarely in healthy children. However, the often-used figure of 1% for the occurrence of VUR in a

general paediatric population is based on estimates and historical patient series using cystograms very distinct from the VCUG technique used nowadays (Coulthard 2008). If these traditional estimates were true, it would not be possible to find as high frequencies of VUR in children with no proven UTI as we did in our series. Even when calculated mathematically the assumed low occurrence of VUR in healthy children seems underestimated. If we take the cumulative incidence of childhood UTI to be about 6% (Hellström *et al.* 1991), some 600 in a population of 10 000 children would have UTI and one third of them (200 children) would have VUR, giving a VUR occurrence of around 2% (200/10 000) in the whole child population. This is twice the commonly used estimate of 1% in healthy children (Coulthard 2008), and would also mean that all the children with VUR would ultimately have to have UTI. Yet screenings of the siblings of children with VUR have shown that only less than one-third of siblings with VUR have a history of UTI and in most of them VUR is asymptomatic (Ataei *et al.* 2004, Connolly *et al.* 1997, Parekh *et al.* 2002, Tombesi *et al.* 2005). If we agree that VUR is largely asymptomatic, it means that the previously reported low occurrence of VUR in the general population is implausible and the importance of VUR in children with UTI has been overestimated.

Ultrasonography showed abnormality of the urinary tract in 21% of our population-based series of 2036 children examined after UTI, and such abnormalities were considered clinically significant in 10%. The overall frequency of abnormal US results was of same magnitude as reported earlier (Gelfand *et al.* 2000a, Giorgi *et al.* 2005, Jahnukainen *et al.* 2006). Contrary to the occurrence of VUR, we found that the frequency of clinically significant US abnormalities increased as the diagnostic reliability improved, with an almost two-fold relative risk. Operative treatment for obstructive uropathy was eventually needed in 1.4% of all cases. In addition, US revealed one kidney tumour, one case of polycystic kidney disease and one non-functioning dysplastic kidney, which was removed. In study I the US abnormalities were considered clinically significant nearly twice as often in the children with certain UTI as in those without proven UTI. Our findings indicate that structural abnormalities identifiable by means of US show a significant association with UTI.

It is likely that most of the children in our series had been screened antenatally, as foetal US has been part of maternal surveillance in Finland for almost two decades. However, the latest US scans are usually performed at around 20 to 22 weeks of gestation which is too early to reliably detect all

significant urinary tract abnormalities, and thus foetal screening has not significantly altered the utility of post-UTI US in Finnish children (Goldman *et al.* 2000b, Grandjean *et al.* 1999, Jahnukainen *et al.* 2006). If later pregnancy scans, beyond 30 to 32 weeks of gestation, become common practice, the need for US after UTI should be reconsidered, as recently suggested (Mathews *et al.* 2009, Miron *et al.* 2007, Montini *et al.* 2011). Since US is not unpleasant and involves no risk to the patient, performing US is easy to endorse.

We further analysed the sufficiency of US scanning solely for imaging the urinary tract in 1185 children with UTI who had undergone both US and VCUG imaging. In our series of 861 patients with a normal initial US, VCUG revealed two non-obstructive urethral valves in infant boys, who were treated surgically and bilateral ureteroceles in one girl, in whom no obstruction occurred during follow-up. In addition grade III to V VUR was found in 97 patients. The choice of treatment in these 97 patients was based on a clinical decision, and eventually 40 had anti-reflux surgery, while VUR resolved spontaneously in 50 cases. At the end of follow-up, 11 of these 97 reflux patients had developed new renal scarring, but no renal impairment occurred. Altogether, two patients with significant non-reflux pathology (urethral valve) and 40 patients with high grade VUR out of our 861 patients with a normal initial US may have benefited from surgical treatment, giving a total number of 42/861 (5%) pathological findings that could have been missed if VCUG had not been performed. Thus in case of a normal US, abandoning the use of VCUG carries a low risk of missing significant renal abnormality. Nevertheless, the possibility of urethral valve in infant boys should be kept in mind. In accordance, an earlier Finnish survey evaluating the usefulness of US in 76 children with febrile UTI showed that US is a reliable screening procedure, as it found all significant urinary tract abnormalities except one case of obstructive uropathy and one case of dilating VUR (Honkinen *et al.* 1986). Furthermore, in a recent series of 209 children no clinically significant urinary tract abnormalities were found by VCUG after normal post-UTI US (Ismaili *et al.* 2011).

Our follow-up study found no cases of impaired renal function or hypertension 6 to 17 years after childhood UTI. The follow-up US showed unilateral renal parenchymal defects in 15% of the patients, but renal function and mean BP measurements were within the normal limits in all cases. Renal function remained normal even in the patients with grade III to V VUR and renal parenchymal defects in primary imaging, and no cases of hypertension were found. Since all the paediatric urological imaging examinations in this district are

performed at our hospital, we think that these results represent a population-based sample of children with UTI in whom obstructive uropathy and major renal dysplasia have been ruled out with US.

Our results are in agreement with a Swedish population-based study that found no significant deterioration in renal function or risk of hypertension in patients with a history of childhood UTI (Wennerström *et al.* 2000a, Wennerström *et al.* 2000b). Some earlier studies have given significantly higher figures for the occurrence of hypertension (10 to 30%) or renal failure (10%) in patients monitored after UTI in childhood (Goonasekera *et al.* 1996, Jacobson *et al.* 1989, Lahdes-Vasama *et al.* 2006). This may be because these studies were based on highly selected series of patients in tertiary centres and because all heavily scarred kidneys were referred as reflux nephropathy earlier, indicating that renal scars were caused by VUR and UTIs without noting that in most cases the true aetiology was probably congenital dysplasia.

Although UTIs are common in children, the occurrence of ESKD is rare and the presumed likelihood that UTI will cause ESKD is also low. Post-infectious renal scars are small and infrequent, as 85% of children with UTI will not develop scarring, and they are likely clinically inconsequential (Shaikh *et al.* 2010, Wennerström *et al.* 2000b). As reviews of the medical histories of patients with ESKD have demonstrated, UTI in children without congenital obstructive uropathy or dysplastic kidneys rarely, if ever, leads to significant renal scarring and subsequent long-term sequelae such as ESKD (Salo *et al.* 2011, Sreenarasimhaiah & Hellerstein 1998).

In the present study IV, recurrences of UTI occurred significantly more often and were more often febrile in patients with grade III to V VUR than in those without. This observation differs from those in previous reports, where the presence or absence of VUR has not substantially altered the total numbers of UTI recurrences, although the risk of pyelonephritis has been higher in children with grade III or higher VUR than in those without (Conway *et al.* 2007, Garin *et al.* 2006, Montini *et al.* 2008, Panaretto *et al.* 1999). The observed higher risk of UTI recurrences in our patients with grade III to V VUR may be explained by higher awareness and suspicion of UTI in these children, and thus urine cultures were obtained more eagerly than in children with no or low-grade VUR, and also by the fact that urine was cultured routinely before the control VCUGs, so that cases of asymptomatic bacteriuria may have been treated as true UTI recurrences. Our findings that VUR seems to be fairly common in young children and that

high-grade VUR increases the risk of pyelonephritis may explain why UTIs are more often febrile in infants and toddlers than in older children. All except one of the unilateral renal parenchymal defects and kidney growth retardation cases in the follow-up US examination were found in patients having grade III to V VUR and most presenting with recurrent UTIs. Due to the observational nature of our approach, we cannot exclude the potential effects of the treatment given (antibiotic prophylaxis or operative treatment) on the natural history of VUR in our patients. On the other hand, the data also showed that although patients with recurrent UTIs were more likely to be operated on, the rate of VUR resolution in the last VCUG did not differ between the patients with and without a parenchymal defect in US. This finding is in accordance with previous reports showing no superiority of operative treatment over antimicrobial prophylaxis for preventing new renal scars in patients with VUR, and based on the current data available, antibiotic prophylaxis as well seems to be ineffective in treating children with VUR (Brandström *et al.* 2010b, Finnell *et al.* 2011, Nagler *et al.* 2011, Venhola *et al.* 2006). Nonetheless, renal function, mean BP measurements and somatic height were within the normal limits in all our patients at follow-up, indicating that small renal parenchymal defects are unimportant as far as the long-term prognosis for children with UTI is concerned.

Some of our patients had undergone up to seven VCUGs during the follow-up period, causing a significant radiation burden that can lead to long-term sequelae in terms of an increased risk of cancer and hereditary effects due to gonadal radiation (Perisinakis *et al.* 2006, Stefanidis & Siomou 2007). Moreover, VCUG is one of the most unpleasant radiological procedures, which causes pain and psychological stress and may lead to iatrogenic UTI (Rachmiel *et al.* 2005, Rao *et al.* 2011). When we contacted the patients or their parents by phone to enquire whether they would be willing to participate in our follow-up study, most of them stated that they would not do so if a control VCUG was needed. The unpleasant fact is that our traditional, although well-meaning, recommendations on routine imaging of children with UTI have led to practices in which thousands of children have undergone VCUGs with modest or no benefit in the majority of cases.

The limitations of this thesis include its retrospective and observational nature. To achieve reliable frequency data on rare but important urinary tract abnormalities, the number of patients has to be large. Our sample of over 2000 patients was large enough to reveal even rare urinary tract abnormalities and together with the diagnostic uncertainty of UTIs, gave us the opportunity to evaluate the occurrence of VUR among children without a history of true UTI. It

would be difficult to collect data of this magnitude prospectively and reprehensible to expose healthy children to VCUGs, but we believe that the information obtained by means of this retrospective analysis is reliable. The follow-up time in our study IV was relatively short and a more prolonged follow-up time might be needed to ensure favourable outcome of the childhood UTIs observed, although there is no evidence in the current literature to support the view that UTI by itself could lead to ESKD (Salo *et al.* 2011, Sreenarasimhaiah & Hellerstein 1998).

No worldwide conclusion on what imaging studies, if any, are needed in children with UTI has yet been reached. Nonetheless, the intensive debate surrounding the causal relationships between VUR, UTI and renal scarring and the ineffectiveness of interventions for VUR has certainly raised questions among clinicians as to whether to order invasive radiological studies or not. In Australia a considerable nationwide reduction in the numbers of VCUG and DMSA examinations performed on children was observed between 1993 and 2008, the decline in VCUGs being most evident from 1999/2000 onwards. On the contrary, there was no significant change in ordering renal US examinations (South 2009). The newly updated guidelines of the American Academy of Pediatrics (AAP) no longer recommend a routine VCUG after the first febrile UTI, which is consistent with the 2007 guidelines of the National Institute for Health and Clinical Excellence (NICE). Both guidelines still suggest VUCG for children with certain risk factors, and unlike the NICE, the AAP still recommends performing VCUG after a UTI recurrence also in children aged more than six months (American Academy of Pediatrics *et al.* 2011, National Institute for Health and Clinical Excellence 2007). In accordance with Ismaili *et al.* in their survey, we found in study III that given a normal US, abandoning the use of VCUG carries a low risk of missing a significant renal abnormality (Ismaili *et al.* 2011).

In summary, VUR seems to be a common age-related phenomenon in children and is not as closely associated with UTI as was previously thought. This finding and the good prognosis for childhood UTIs observed in our follow-up study challenge the need for searching for and treating VUR in children with UTI and support more conservative imaging practices. We suggest that children with UTI could be examined using US alone and that VCUG should be used only after additional indications, e.g. in infant boys with a clinical suspicion of a urethral valve. Nevertheless, we want to emphasize the importance of an early suspicion of childhood UTIs, correct diagnosis and prompt treatment.

7 Conclusions

Based on the results presented here:

1. We claim that the occurrence of VUR in children without proven UTI is significantly higher than the traditional estimates, and that VUR seems to be a rather common age-related phenomenon.
2. We suggest that US imaging is still needed in children with UTI, as structural abnormalities of the urinary tract were significantly associated with UTI and US identified clinically important urinary tract abnormalities in 10% of the children in our series.
3. We state that, in the case of a child with UTI having normal US results, abandoning the use of VCUG entails a 5% risk of missing a significant renal abnormality.
4. We conclude that when obstructive uropathy and major renal dysplasia have been ruled out by US, the risk of long-term complications following a childhood UTI is very low.

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