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ULTRASONOGRAPHY ALONE IS NOT ENOUGH TO EXCLUDE VESICOURETERAL REFLUX IN ALL SMALL CHILDREN AFTER A URINARY TRACT INFECTION

Marko T. Ristola

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ABSTRACT

Marko T. Ristola

ULTRASONOGRAPHY ALONE IS NOT ENOUGH TO EXCLUDE VESICOURETERAL REFLUX IN ALL SMALL CHILDREN AFTER A URINARY TRACT INFECTION

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As knowledge on vesicoureteral reflux (VUR) and the limited effectiveness of its treatment has increased, several guidelines have been updated, and no longer recommend extensive routine imaging of all children with urinary tract infection (UTI).

We determined the possible consequences of following the most widely used guidelines for imaging children with UTI, in a retrospective cohort of children treated for UTI in Turku University Hospital in the years 2000-2009. Using the same cohort, we identified factors associated with abnormal imaging and UTI recurrence after a first febrile UTI. We also performed a meta-analysis aiming to determine the value of ultrasonography in identifying patients with VUR after UTI.

We found that following the guidelines issued by the National Institute for Health and Care Excellence may lead to missing a substantial number of patients with significant urological anomalies, whereas following the guidelines issued by the American Academy of Pediatrics may lead to fewer patients being missed. Both strategies may lead to avoiding a significant number of unnecessary imaging studies. We identified several factors associated with abnormal imaging and UTI recurrence, and determined a risk score system for predicting the risk for VUR and high-grade VUR. This system had high sensitivity in detecting high-grade VUR in our population. In a meta-analysis of 14 studies, we found that ultrasonography is not sufficiently accurate in predicting the presence or absence of VUR.

The optimal imaging strategy for imaging children with UTI is controversial, and depends ultimately on the significance of VUR and the effectiveness of its treatment.

Keywords: Diagnostic imaging, guidelines as topic, infant, urinary tract infections, vesico-ureteral reflux.

TIIVISTELMÄ

Marko T. Ristola

ULTRAÄÄNITUTKIMUS YKSIN EI RIITÄ POISSULKEMAAN VESIKOURETERAALISTA REFLUKSIA KAIKILLA PIENILLÄ LAPSILLA VIRTSATIEINFEKTION JÄLKEEN

Turun yliopisto, lääketieteellinen tiedekunta, kliininen laitos, lastenkirurgia, Turun yliopiston kliininen tohtoriohjelma.
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Viime vuosikymmenien aikana tieto vesikoureteraalisen refluksista (VUR) ja sen hoidon rajallisesta vaikuttavuudesta on lisääntynyt. Tämän myötä useita suosituksia on päivitetty, eikä kaikkien virtsatieinfektion (VTI) sairastaneiden lasten rutiinikuvantamista enää suositella.

Me selvitimme, mitä mahdollisia seurauksia suosituimpien suositusten noudattamisella olisi ollut potilaskohortissa lapsia, joita hoidettiin Turun yliopistollisessa keskussairaalassa VTI:n vuoksi vuosien 2000-2009 aikana. Samaa potilaskohorttia käyttäen selvitimme tekijöitä, jotka ovat yhteydessä poikkeaviin kuvantamistuloksiin sekä infektion uusiutuvuuteen ensimmäisen kuumeisen VTI:n jälkeen. Suoritimme myös meta-analyysin, jonka tarkoitus oli selvittää, miten hyvin ultraäänitutkimus ennustaa VURia VTI:n jälkeen.

Totesimme, että National Insitute of Health and Care Excellencen suositusten noudattaminen voi johtaa siihen, että huomattava määrä potilaita, joilla on merkittäviä, hoitotoimenpiteitä vaativia urologisia poikkeavuuksia, jäävät löytymättä, kun taas American Academy of Pediatricsin suositusten noudattaminen voi johtaa selvästi pienemmän määrän potilaita löytymättä jäämiseen. Molemmat kuvantamisstrategiat voivat johtaa turhien tutkimuksien selvään vähenemiseen. Tunnistimme useita tekijöitä, joilla on yhteys poikkeaviin kuvantamistuloksiin sekä VTI:iden uusiutuvuuteen, ja muodostimme riskipisteytysjärjestelmän VURin ja korkea-asteisen VURin riskin ennustamiseksi. Riskipisteytysjärjestelmällä oli korkea sensitiivisyys korkea-asteisen VURin tunnistamiselle. Meta-analyysissä, jossa käsiteltiin 14 tutkimusta, totesimme, ettei ultraäänitutkimus ole riittävän tarkka ennustamaan VURia tai sen puuttumista.

Optimaalinen kuvantamisstrategia lapsilla VTI:n jälkeen on ristiriitainen aihe, joka riippuu olennaisesti VURin merkityksestä sekä sen hoidon vaikuttavuudesta.

Avainsanat: Diagnostinen kuvantaminen, imeväinen, ohjesäännöt aiheena, vesikoureteraalinen refluksi, virtsatieinfektio.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
AMP	Antimicrobial prophylaxis
CD68	Cluster of differentiation 68
CFU	Colony-forming unit
CRP	C-reactive protein
CT	Computed tomography
DES	Dysfunctional elimination syndrome
DMSA	Dimercaptosuccinic acid
DRC	Direct radionuclide cystography
DxHA	Dextranomer hyaluronic acid
EAU	European Association of Urology
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
IGF-1	Insulin-like growth factor-1
IRC	Indirect radionuclide cystography
IRR	Intrarenal reflux
IVU	Intravenous urography
MAG	Monoacylglycerol
MAG3	Acetyltriglycine
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NGF	Nerve growth factor
NICE	National Institute for Health and Care Excellence (formerly National Institute for Health and Clinical Excellence)
nVCUG	Nuclear VCUG (see VCUG)

PUV	Posterior urethral valve
RBUS	Renal and bladder ultrasonography
TGF-β1	Transforming growth factor-β1
TNF-α	Tumor necrosis factor- α
UP	Uroplakin
UPJ	Ureteropelvic junction
UR	Ureteral reimplantation
US	Ultrasonography
UTI	Urinary tract infection
UVJ	Ureterovesical junction
VCUG	Voiding cystourethrography
VEGF	Vascular endothelial growth factor
VUR	Vesicoureteral reflux
VUS	Voiding urosonography

LIST OF ORIGINAL PUBLICATIONS

I Ristola MT, Hurme T. NICE Guidelines Cannot Be Recommended for Imaging Studies in Children Younger Than 3 Years with Urinary Tract Infection. Eur J Pediatr Surg 2015; 25: 414-420.

II Ristola MT, Hurme T. Consequences of following the new American Academy of Pediatrics guidelines for imaging children with urinary tract infection. Scand J Urol 2015; 49: 419-423.

III Ristola MT, Löyttyniemi E, Hurme T. Factors Associated with Abnormal Imaging and Infection Recurrence after a First Febrile Urinary Tract Infection in Children. Eur J Pediatr Surg 2016; Feb 8 [Epub ahead of print]

IV Saltychev M, Ristola MT, Laimi K, Hurme T. Accuracy of ultrasonography in predicting vesicoureteral reflux in children: A meta-analysis. Scand J Urol. 2016; 50: 239-245.

1. INTRODUCTION

During normal filling and emptying of the bladder, the vesicoureteral junction functions as a flap-valve mechanism permitting urine flow from the ureters to the bladder, but inhibiting the flow of urine back to the ureters from the bladder. If this valve mechanism fails, retrograde flow of urine from the bladder towards the kidneys (vesicoureteral reflux, VUR) may occur. If the valve mechanism works normally, the kidneys are spared from the intermittently higher pressures that occur in the bladder during filling and with bladder contractions during voiding. In the presence of VUR, however, the kidneys may be exposed to these higher pressures and bacteria may be permitted access to the kidneys during bladder infection, which may lead to infection of the upper urinary tract, *i.e.* pyelonephritis.

Pyelonephritis in the presence of VUR has been associated with permanent renal damage and the development of hypertension and progressive renal failure in some patients[1,2]. In addition, VUR has been associated with decreased body growth and complications in pregnancy[3-7]. The general occurrence of VUR is often estimated at 1-2%, but it has been found to be present in as many as a third of patients with urinary tract infection (UTI)[8-10]. For these reasons, UTI in infancy and early childhood has often led to extensive imaging studies to identify and treat VUR. The treatment of VUR aims at preventing the reflux of infected urine into the kidneys, either by abolishing reflux or by preventing infections. Treatment options include surgical correction of VUR and continuous antimicrobial prophylaxis to prevent UTIs until VUR has resolved.

VUR is diagnosed by voiding cystourethrography (VCUG). VCUG requires catheterizing the child, instilling a radio-contrast agent into the bladder and obtaining x-ray images of the urinary tract, to identify retrograde flow of the contrast agent into the upper urinary tract and possible urinary tract dilatation. The procedure is distressful to the child and entails a significant radiation burden. Due to the invasive nature, radiation burden and relatively high cost involved in VCUG, the routine performance of VCUG in all children with UTI has raised criticism[11-15].

In the recent decades, knowledge on VUR and its treatment has increased. The effectiveness of antimicrobial prophylaxis or surgical correction of VUR has been found to have only modest success in preventing UTI recurrences and new or progressive renal damage. Consequently, the treatment of VUR has not resulted in a significant reduction in the number of children who develop progressive renal failure[16]. This has led to several guidelines being updated, and many of them no longer recommend routine imaging by VCUG after a first UTI in childhood[17-21].

Although one might assume that updating guidelines would lead to physicians being provided with an unambiguous view on which patients to image after a UTI, the imaging strategies formulated during the last decade are manifold and in some cases quite complex, leading to an even more unclear situation for the primary physician. The effects of these guidelines with regard to missed diagnoses and treatment, and on the other hand avoided unnecessary imaging studies are not yet entirely known. In addition, even the significance of VUR remains somewhat unclear[22]. In this thesis, the advantages and disadvantages of some of the most popular imaging strategies are discussed.

2. ETIOLOGY OF VUR

Vesico-ureteral reflux is the retrograde flow of urine from the bladder up the ureter towards the kidney. It is caused by one of three mechanisms. The first is an abnormally short intravesical submucosal ureter in an otherwise anatomically normal urinary tract. In order to function properly as a flap-valve and to prevent reflux, the ratio of the submucosal tunnel length to the diameter of the ureter needs to be 4:1 to 5:1. In patients with VUR, this ratio is on average 1.4:1[23]. The second is anatomical abnormalities of the ureterovesical junction, such as seen in children with bladder extrophy, periureteric diverticula, prune-belly syndrome, ureteroceles, ureteral ectopia or ureteral duplication, although these conditions are also associated with an abnormally short intravesical submucosal ureter. The third is elevated bladder storage and voiding pressure, resulting in decompensation of the UVJ and VUR[24,25]. This can be caused by *e.g.* holding urine for too long, failing to relax the external urinary sphincter during detrusor contraction, neurogenic bladder and posterior urethral valves.

2.1 Embryology of the urinary tract

The kidney is formed of three somewhat overlapping systems, in a cranial to caudal sequence: the pronephros, the mesonephros and the metanephros. At the beginning of week 4 of development, intermediate mesoderm in the lower cervical and upper thoracic regions extending to the cloaca condense to 7 to 10 solid cell groups, forming the pronephros. These cell groups form nephrotomes; vestigial excretory units, which almost completely regress by the end of gestational week 4 (Figure 1)[26].

The mesonephros first appears in the beginning of developmental week 4. As the pronephric system regresses, the first excretory tubules of the mesonephros appear. The tubules lengthen rapidly, and form an S-shaped structure. At the medial extremity forms a tuft of capillaries, that goes on to form a glomeru-

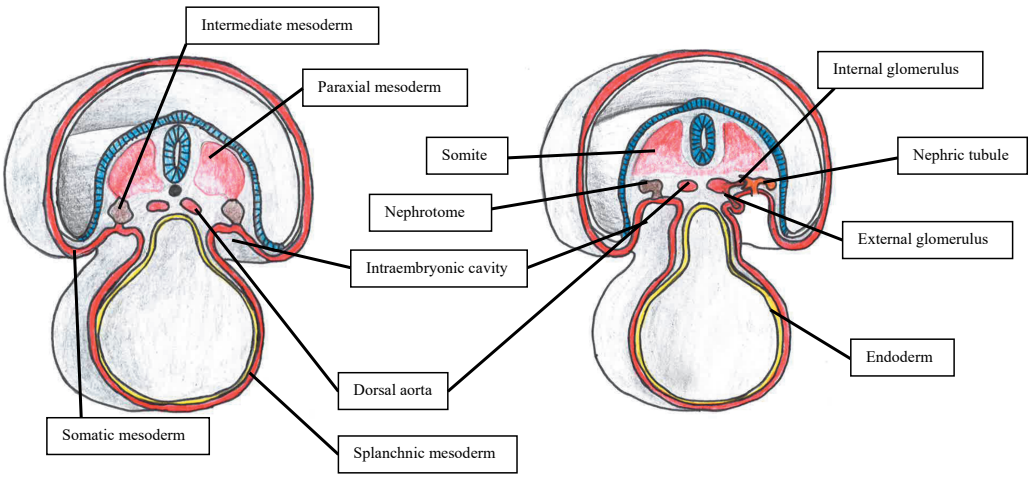

Figure 1. Transverse sections of embryos at 21 days (left) and 25 days (right), showing formation of nephric tubules. Modified from[26].

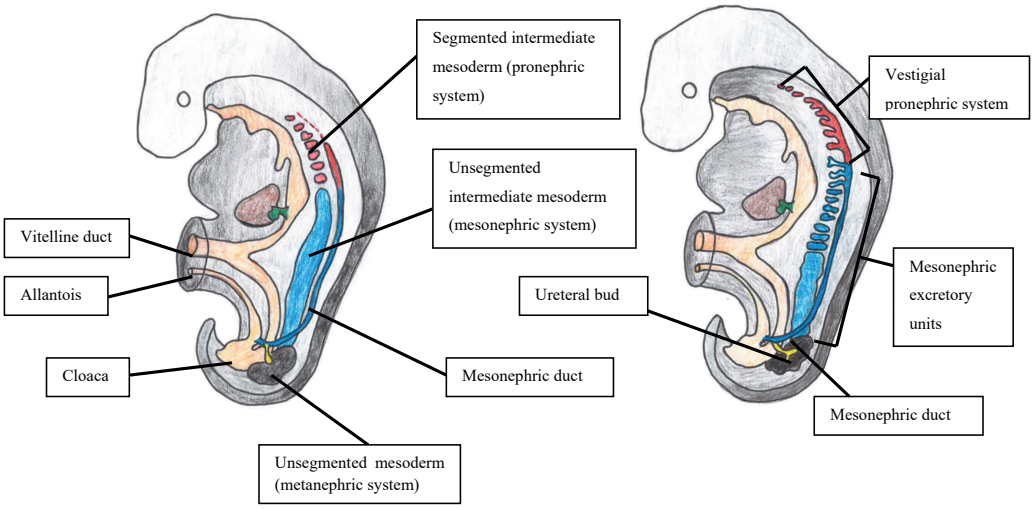

Figure 2. Intermediate mesoderm of the pronephros, mesonephros, and metanephros (left), and excretory tubules of the pronephric and mesonephric systems in a 5-week embryo (right). Modified from[26].

lus. The tubules give rise to Bowman's capsule around the glomerulus, constituting a renal corpuscle together with the glomerulus. Together with the tubule, this structure forms a nephron. Laterally, the tubule enters the mesonephric or Wolffian duct (Figure 2)[26].

At approximately 6 weeks of development, the mesonephros gives rise to an ovoid structure on each side of the aorta. The developing gonad is on its medial side, and together these organs constitute the so called urogenital ridge. At this time, the caudal tubules are still differentiating, but the cranial tubules and glomeruli are degenerating, and by the end of month 2, most have regressed. In the female they disappear completely, but in the male some of the caudal tubules along with the mesonephric duct persist, taking part in the formation of the genital system[26]. At the end of the second month of development, the metanephros is formed. In the 8th week, in a similar fashion to the mesonephric development, the excretory units of the metanephros develop from metanephric mesoderm. Close to the mesonephric duct's entrance to the cloaca, an outgrowth of the mesonephric duct, the ureteric bud is formed. The ureteric bud gives rise to the collecting ducts of the permanent kidney. The bud enters the metanephric tissue, which in turn forms into a cap on the distal end of the bud. The bud dilates to form the primitive renal pelvis, which then splits into cranial and caudal segments, which will later become the major calyces. These calyces each divide again, penetrating the metanephric tissue. The dividing of the buds continues for at least 12 generations. In the periphery of the fetal kidney, tubules keep forming until the end of month 5 of fetal development. The tubules formed in the 2nd generation grow and absorb the tubules of the 3rd and 4th generations, giving rise to the minor calyces of the renal pelvis. Thereafter, the collecting tubules of the 5th and later generations lengthen greatly, converging on the minor calyx to form the renal pyramid. The ureter, the renal pelvis, the major and minor

calyces, and approximately 1 to 3 million collecting tubules are formed from the ureteric bud. Hence, the kidney is formed of two systems: the metanephric mesoderm, which gives rise to the excretory units, and the ureteric bud, which gives rise to the collecting system[26].

The forming of new nephrons continues until birth. At birth there are approximately 1 million nephrons in each kidney. Though the number of nephrons does not increase, nephrons continue to grow after birth. In the neonate, the kidneys have a lobulated appearance, which disappears as a result of the nephrons' growth[26,27].

The fetal development and differentiation of the kidney and ureter require epithelial mesenchymal interactions, specifically interaction between the epithelium of the ureteric bud from the mesonephros and the mesenchyme of the metanephric blastema. The transcription factor Wilms tumor protein (WT1) is expressed in the mesenchyme. WT1 enables the mesenchymal tissue to respond to induction by the ureteric bud and regulates mesenchymal production of glial-derived neurotrophic factor (GDNF) and hepatocyte growth factor (HGF). These proteins, in turn, stimulate branching and growth of the ureteric buds. The RET family tyrosine kinase receptors for GDNF, and MET, for HGF, are synthesized by the ureteric buds epithelium. This creates signaling pathways between the two tissues. The ureteric buds, on the other hand, express fibroblast growth factor 2 (FGF2) and bone morphogenetic protein 7 (BMP7). These growth factors both block apoptosis and stimulate proliferation in the metanephric mesenchyme, and stimulate expression of WT1 (Figure 3).

The ureteric buds also mediate the conversion of the mesenchyme to epithelium, which is required for nephron formation. This happens partly through modification of the extracellular matrix, where laminin and type IV collagen replace fibronectin, collagen I, and collagen III. The transformation of mesenchyme to epithelium also requires the synthesis of the cell adhesion molecules syndecan and E-cadherin. The regulatory genes required for this include paired box gene 2 (Pax2) and Wingless-type MMTV integration site family, member 4 (WNT4)[28].

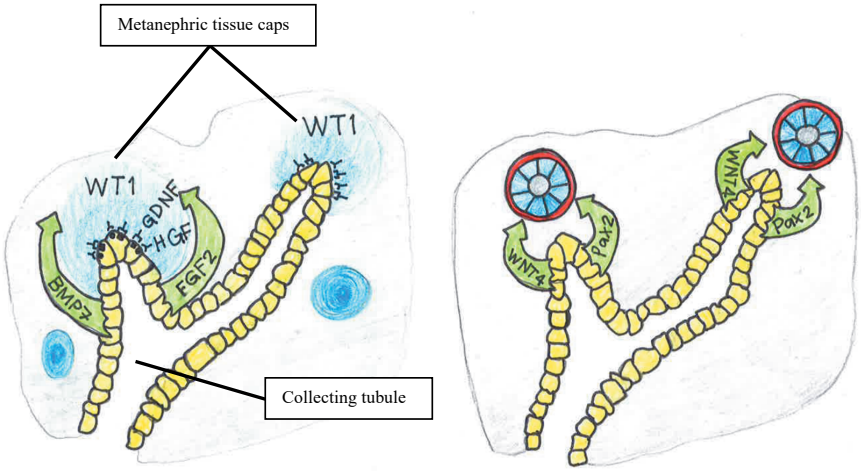

Figure 3. Genes involved in the embryogenetic development of the kidney. Modified from[26].

Pax2 up-regulation and hypomethylation have been associated with VUR[29]

The development of the ureter and ureteral budding requires signaling pathways, as well. This process is regulated through a signaling complex that includes the GDNF, the tyrosine kinase receptor and the co-receptor GDNF family receptor (GFRα1). The mesenchyme of the mesonephric duct expresses GDNF before ureteral budding, but after this, it is expressed only in the metanephric mesenchyme. Here, GDNF binds to tyrosine kinase receptor and GFRα1 receptors in the mesonephric duct, stimulating ureteral budding. In the metanephric mesenchyme, GDNF expression is stimulated by the transcription factors Pax2, Eya1, Six1, Sall1 and Hox11. GDNF expression is negatively regulated by bone morphogenetic protein 4 (BMP4), the transcription factors Foxc1/Foxc2 and the signalling complex Slit2/Robo2 and the receptor tyrosine kinase antagonist Sprouty1.[28] In addition to regulating ureteric budding, the GDNF/RET pathway later regulates the growth and elongation of the distal ureter, as well. This whole signaling pathway seems to be dependent on vitamin A, and disturbances in vitamin A signaling in mice lead to renal hypoplasia, hydronephrosis and mega-ureter, which are also seen in mice with mutations in the proto-oncogene RET[28,30]. In addition, decreased collagen thickness, increased levels of tumor necrosis factor-α (TNF-α) and transforming growth factor-β1 (TGF-β1), and decreased levels of nerve growth factor (NGF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) in the ureteral wall smooth muscle, have been associated with VUR[31-33].

2.2 Normal anatomy and function of the bladder and ureters

The UVJ, in addition to allowing flow of urine from the ureter to the bladder, is essential in protecting the kidney. As intravesical pressure is occasionally physiologically high, the properly functioning UVJ prevents high-pressure retrograde flow of urine, ensuring that the kidney be spared from this high pressure, that might damage the kidney. The extravesical ureter consists of two longitudinal muscle layers and a circular muscle layer in between them. In the bladder wall, the circular muscle layer joins the ureter's adventitia to form Waldeyer's sheath, which attaches the ureter onto the hiatus. This attachment is loose, enabling the hiatus to slide up along the ureter as the bladder fills up. Inside the bladder, as the circular muscle fibers dissipate, the longitudinal layer muscle fibers continue distally past the ureteral orifice into the bladder trigone, joining the contralateral muscle fibers to form Bell's muscle and the posterior urethra. This entity works as a single functional unit, and experimental disturbances of it lead to abnormalities in the ureterovesical angle and VUR. The continuity of the ureterotrigonal complex inihibits excess mobility of the ureteral orifice in relation to the ureter, which is essential in preventing VUR[34].

As the bladder becomes filled, the ureteral lumen becomes flattened between the detrusor muscle and the mucosa, creating an intravesical pressure dependent, more passive than active flap-valve mechanism, preventing retrograde flow of urine from the bladder to the ureter. During voiding, contraction of the detrusor muscle raises intravesical pressure, which can in some cases lead to herniation of the ureteral orifice through the bladder wall. This does not, however,

happen under normal circumstances where the UVJ is attached sufficiently firmly, but disturbances in the fetal development of the trigone and an abnormally lateral ureteral orifice may predispose to this[35]. The active component in the UVJ flap-valve mechanism is comprised of the contraction of the longitudinal ureterotrigonal muscle fibers as the detrusor muscle contracts. The most important factor in the function of the flap-valve mechanism is the occlusion of the ureteral lumen as the raised intravesical pressure compresses it against the detrusor muscle. In order for this to happen, the ureteral orifice must be immobile, *i.e.* get sufficient support from the detrusor muscle.

2.3 Primary VUR

Primary VUR is a congenital phenomenon caused by insufficiency in the flap-valve mechanism of the UVJ and the longitudinal muscle layer of the submucotic ureter. In part, the sufficiency of the flap-valve mechanism is predicted by the ratio of the length of the submucotic tunnel to the diameter of the ureter. In children with no VUR, this ratio is 4:1 to 5:1, whereas in patients with VUR, the ratio is on average 1.4:1[23]. For decades, it was thought that the deficiency in this passive aspect of the flap-valve mechanism was the major cause of VUR. It has later been found, that weakness of the muscle layer of the distal ureter and scarceness of muscle fibers in the extracellular matrix play a crucial role in UVJ incompetence and the emergence of VUR[36].

MMP-2 expression and the amount of CD68 positive macrophages are significantly higher in refluxing UVJs than in normal ones, which may suggest a pathologically increased extracellular matrix remodellation[36-38]. The amount of S-100 positive nerve fibers is also lower, indicating decreased innervations of the active component in the flap-valve mechanism[36,38]. In addition, significantly decreased expression of smooth muscle α-actin, myosin and desmin have been reported in distal ureters of VUR patients[37]. These patients show muscle atrophy and degeneration in the distal ureter and dis-

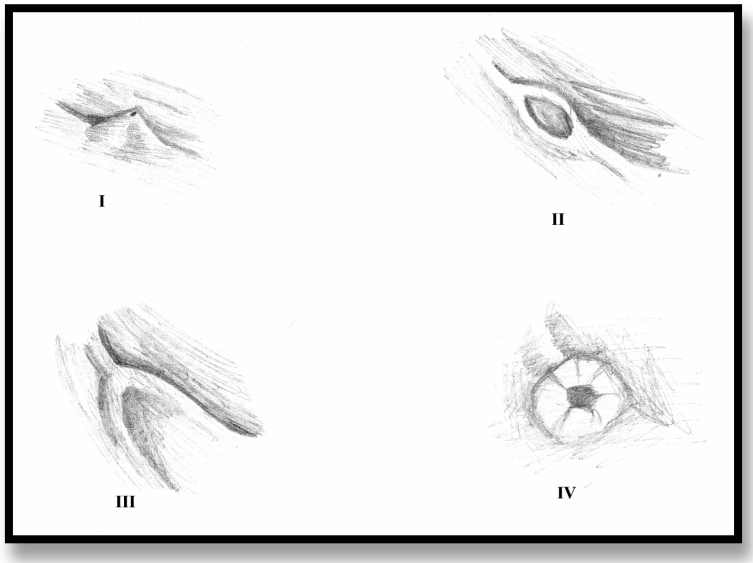

Figure 4. Configurations of ureteral orifices. I: cone (normal), II: stadium, III: horse shoe, IV: golf hole.

ordered fiber arrangement associated with increased extracellular matrix collagen accumulation. In purely primary VUR, obstruction or neuropathic bladder dysfunction do not play any part in the development of VUR. Primary VUR may, however, coincide with secondary VUR.

A clear association to VUR has also been found in abnormally lateral ureteral orifices and unusual ureteral orifice configuration[39]. Lyon et al. described 4 different configurations of ureteral orifices: cone (normal, I), stadium (II), horse shoe (III) and golf hole (IV) (Figure 4.) The prevalence of VUR according to ureteral orifice configuration was reported at 4%, 28%, 83% and 100%, respectively[39]. Stephens later added the so called 'lateral pillar defect', whose appearance is between that of the golf hole and horse shoe orifices[40].

2.4 Secondary VUR

The term 'secondary VUR' is used when reflux is caused by raised intravesical pressure. The most common causes of secondary VUR are neurogenic bladder dysfunction and urinary obstruction. Most commonly it is caused by a posterior urethral valve in boys. Regardless of cause, raised intravesical pressure causes decomepensation of the UVJ, which would under normal circumstances function sufficiently as a flap-valve mechanism, inhibiting reflux.

UTIs may also lead to secondary VUR[41-43]. The infection may on one hand irritate the bladder, causing detrusor contraction and hence raised intravesical pressure. On the other hand, it may disrupt the normal function of the UVJ, leading to decompensation of the flap-valve mechanism. Secondary VUR due to UTI usually resolves spontaneously after the UTI resolves. This is an important factor in why VCUG should be performed several weeks after resolution of the UTI. Recurrent UTIs may also slow maturation of the UVJ, and prolong the period before resolution of VUR[44].

Paraureteral diverticuli may push the intramural ureter outside the bladder, leading to incompetence of the UVJ, and VUR. Ureteral duplication may also be associated with VUR, especially in the case that the two ureters converge at the level of the UVJ.

One of the important causes of secondary VUR is neurogenic bladder dysfunction. Urinary disturbances and uncontrolled detrusor contractions, caused by detrusor-sphincter dyssynergy may be an acquired phenomenon due to abnormal urination patterns, but *e.g.* meningomyeloceles and paraplegia may lead to neurogenic bladder dysfunction, resulting in raised intravesical pressure, predisposing to both VUR and UTIs. Clinically these patients often present with urge, pollakiuria, incontinence and bedwetting due to uncontrolled bladder contractions. Of patients with neurogenic bladder dysfunction, 45-52% have VUR as well[45,46]. On the other hand, 75% of girls with VUR have been found to have signs of uncontrolled bladder contractions in urodynamic investigations[47]. Adequate treatment of neurogenic bladder treatment results in resolution of VUR in 81-90% of patients with low-grade VUR and 47-53% of patients with high-grade VUR[48,49].

Constipation may also cause secondary VUR, as a full rectum presses on the posterior wall of the bladder causing detrusor instability or obstruction. Dysfunctional elimination syndrome (DES), presenting as wetting, urgency, abnormally frequent or infrequent voiding, difficulty in voiding, diffuse abdominal pain, constipation or soiling, has been found in 36-72% and 21-83% of in-

fant females and males with primary VUR, respectively[50-52]. DES is also associated with a higher likelihood of UTI recurrence, delayed spontaneous resolution of VUR and higher failure rate of surgical correction of VUR. In addition to VUR being a possible consequence of DES[53], it has also been speculated that DES and VUR may have a common etiology, a disturbance in the development of the ureteral bud[54]. Constipation is to be considered and, if found, treated in all patients with UTI or VUR.

2.5 Prevalence of UTIs

UTIs in early childhood are common. A meta-analysis by Shaikh et al.[55] reported the total pooled prevalence of UTIs in febrile children before the age of 2 years at 7.0% (95% CI 5.5-8.4%). In febrile boys under 3 months old, not being circumcised is a risk factor for UTI. In girls, the prevalence of UTIs drops drastically after the age of 12 months. In boys, UTI prevalence is highest during the first 3 months of life, and declines rapidly thereafter. White race is also a risk factor for UTI[55].

2.6 Prevalence of VUR

The true prevalence of VUR, especially in healthy children, has been debated for decades, and still remains somewhat unclear. There are, however, plausible estimates of the prevalence of VUR in children after UTI, after antenatally detected hydronephrosis and in family members of patients with VUR. In addition to the situations described below, VUR is often present in certain syndromes, *e.g.* renal-coloboma syndrome, branchio-oto-renal syndrome, the X-linked recessive form of Kallmann syndrome, and alongside anorectal anomalies[56-61].

2.6.1 Prevalence of VUR in healthy children

Very few studies on the prevalence of VUR in healthy children have been conducted, mainly because performing VCUG in otherwise healthy children cannot be easily justified due to the radiation stress, need for catheterization which carries a risk for iatrogenic UTI, and the procedure being uncomfortable and stressful to the child. Based largely on a 6% cumulative incidence of UTI in childhood[8], and the VUR prevalence of one-third to one-fourth after a UTI[10], the overall prevalence of VUR is usually estimated at 1-2%. This is based on the questionable assumption that all children with VUR will eventually have a UTI. In a meta-analysis of 1308 children with antenatal hydronephrosis, Lee et al. found the prevalence of VUR to be 10% in those with moderate or severe hydronephrosis, 4% in those with mild hydronephrosis, and even lower in contralateral, non-hydronephrotic kidneys[62].

In contrast to these estimates, a historical series of urologically healthy children who underwent VCUG found the general prevalence of VUR to be 28%, with a higher, 65% prevalence in infants under 6 months old[63]. Venhola et al. studied the VCUG results of children with certain, possible or false diagnosis of UTI, and found the overall prevalence of VUR to be 35%, with no differences between the three groups[9]. As performing VCUGs in a larger population of healthy children cannot be justified, the true prevalence of VUR in healthy children remains unclear, but the generally used prevalence of 1-2% is not conclusively proven to be accurate. It has been suggested that VUR in early life is a normal, benign condition that may require neither active search nor treatment[22,64,65]. Current studies do not, however, support this notion[16,66,67].

2.6.2 Prevalence of VUR in family members of VUR patients

1st degree family-members of VUR patients are often routinely investigated with VCUG to detect VUR, even in asymptomatic patients. A meta-analysis found the prevalence of VUR to be 27% in siblings and 36% in offspring of VUR patients[68]. This is significantly higher than the commonly used general occurrence of 1-2%, but comparable to the aforementioned occurrence rate of 35% in children aged 0-5 years with UTI, reported by Venhola et al.[9]. A twin study reported the prevalence of VUR in early life at 80-100% in identical twins and 35-50% in fraternal twins[69].

2.6.3 Prevalence of VUR after abnormal antenatal US

Hydronephrosis in antenatal US is one of the most common antenatally diagnosed abnormalities. It is detected in approximately 1-5% of pregnancies[70-73]. The most common (66%) pathology behind antenatally detected hydronephrosis is primary ureteropelvic junction obstruction[74], but many of these patients are diagnosed with VUR in a postnatal VCUG. A meta-analysis found VUR to be present in 8.6% of children with antenatally detected hydronephrosis[62]. In a more recent retrospective study, the same number was 17.4%, although this study reported results by renal unit, while the first study reported results by patient[75]. Neither study found an association between the severity of hydronephrosis and probability for VUR. Unfortunately, neither study reported the frequency of VUR in kidneys with no previously detected hydronephrosis.

2.6.4 Prevalence of VUR after UTI

A recent meta-analysis of 12 studies found the prevalence of VUR after a UTI in children to be 18-35%, with a weighted average of 34%[10]. This number was, however, significantly driven by a massive (n>15,000) retrospective study by Chand et al.[76], and most studies reported the prevalence of VUR at 24% or less. Reported risk factors for VUR after a UTI include, male sex, younger age at presentation, family history of uropathology, abnormal RBUS, non-E. coli infection, plasma CRP >40 mg/l, raised plasma creatinine, raised plasma procalcitonin and jaundice[77-81].

2.7 Spontaneous resolution of VUR

When contemplating the optimal imaging and treatment strategy for VUR, an important factor to consider is the tendency of VUR to spontaneously resolve over time. This tendency is particularly evident in low-grade VUR. A meta-analysis found that low-grade VUR has a spontaneous resolution rate of over 80% in a 5 year follow-up[82]. Children with higher grade (IV-V) VUR, bilateral VUR, ureteral anomalies, such as duplication or paraureteral diverticula, filling phase VUR, older age at diagnosis, or female gender have significantly longer time to resolution or improvement of VUR[83,84]. In one study, grade I-III VUR was found to have spontaneous resolution rates of 40% and 42.9% in children aged under 1 year old and over 1 year old, respectively, while the same numbers for grade IV-V VUR were 35.7% and 0%[85]. Resolution is thought to be a result of elongation of the intramural ureter and maturation of the UVJ resulting in improvement in the active component of the flap-valve mechanism, but the maturation of the micturition process plays a role, with micturition becoming less obstructive and bladder pressure becoming more normal[86].

2.8 Classification of VUR

In 1985, Lebowitz et al., largely based on the work by Heikel and Parkkulainen[87], devised the International system for radiographic grading of vesicoureteric reflux[88], in order to improve comparability among studies on VUR. To this day, the system remains the gold standard by which VUR is graded around the world. It is based on both extent of filling and dilation of the ureter, renal pelvis and calyces, caused by VUR (Figures 10-12). Specific instructions for the performance of a VCUG are also given in the paper (discussed in chapter 4.2).

The grades of VUR are determined as follows. Grade I: Ureter only. Grade II: Ureter, pelvis and calyces; no dilatation, normal calyceal fornices. Grade III: Mild or moderate dilatation and/or tortuosity of the ureter and mild or moderate dilatation of the renal pelvis. No or slight blunting of the fornices. Grade IV: Moderate dilatation and/or tortuosity of the ureter and moderate dilatation of the renal pelvis and calyces. Complete obliteration of the sharp angle of the fornices but maintenance of the papillary impressions in the majority of calyces. Grade 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[88]. (Figures 10-12.) Although the system described above is the only universally accepted one, many studies additionally divide VUR into low-grade (non-dilating) VUR vs. high-grade (dilating) VUR, low grade being grade I-II, and high-grade being grade III-V. This division has been the basis for some recommendation for managing VUR, based on the observation that low-grade VUR is not of clinical significance, and the prognosis of these patients cannot be improved with the treatment of VUR either by antimicrobial prophylaxis or surgical correction of VUR.

3. CONSEQUENCES OF VUR

VUR itself was previously thought to be damaging to the kidneys by direct pressure effect[89]. It has, however, been shown that this occurs only at substantially elevated pressure conditions, which can only be found in obstructive situations, not primary VUR[90]. In other words, sterile VUR may not in itself be a dangerous phenomenon, but may predispose to other situations harmful to the kidney, and it may be associated with damaging phenomena through a common etiology. It has also been suggested that VUR, especially in early childhood, may be of very little consequence, and should not be actively sought or treated[22,64,65].

3.1 Pyelonephritis

VUR is generally considered a risk factor for pyelonephritis. It is thought that, in the presence of VUR, infected urine is transported into the upper urinary tract enabling the infection to spread to the kidneys. It has been demonstrated, that in children with VUR, higher grades of VUR are significantly associated with UTI recurrence[91]. This association is particularly evident with higher grades (IV-V) of VUR, and is more often also associated with renal scarring[92-96]. In addition, successful endoscopic correction of VUR may result in a reduced rate of UTI recurrence at least in girls[97].

3.2 Reflux nephropathy

Reflux nephropathy (RN) is the renal scarring in patients with VUR, most commonly in association with UTI. Renal dysplasia can, however, also be present in the absence of UTI, *e.g.* after hydronephrosis in prenatal US. In these cases, the renal damage is congenital (primary) and results from abnormal renal development and is associated with other abnormalities including hydronephrosis and VUR, whereas acquired (secondary) renal damage is caused by UTI in the presence of VUR. Primary RN is more common in boys, and secondary RN more common in girls[1,2].

The differentiation between primary and secondary RN is unreliable, as patients with UTI and renal damage may also have pre-existing, congenital renal damage. Acquired renal damage is, however, usually more localized, whereas congenital RN often presents as diffuse renal damage. In addition, congenital RN is more common in younger patients, while acquired RN can be found in children of any age. VUR in congenital RN is also usually of a higher grade. Even though secondary RN is usually a slow process, taking several years[98], even a single episode of febrile UTI may cause renal scarring especially in young children, in a process termed "the big bang effect"[99].

The total prevalence of RN is unknown, as some patients may have asymptomatic VUR and renal damage and, on the other hand, some patients' VUR may have spontaneously resolved at the time of being diagnosed with RN. The reported prevalence of RN in patients with UTI and VUR is 36-56%[100,101]. In otherwise healthy children with newly diagnosed hypertension, the prevalence of renal dysplasia diagnosed by DMSA scanning is reported at 21%[102]. The incidence of renal scarring increases with increasing age at VUR diagnosis, being 10% in preterm infants, 26% in children under 8 years old, 47% in children older than 8 years and 94% in adults[103-106]. The high number of adults with

renal scarring in adults with VUR is from a 40-year-old review, where patients were diagnosed with VUR in childhood, and the VUR persisted into adulthood[104]. Nowadays, this is almost never the case due to more aggressive treatment. The most significant risk factors for renal scarring after a first UTI are a temperature of at least 39°C, non-E. coli infection, abnormal RBUS findings, polymorphonuclear cell count of greater than 60%, CRP level of greater than 40mg/L, and presence of VUR (especially grade IV and V)[95]. Higher grades of VUR are more significantly associated with renal damage[107].

Focal segmental glomerular sclerosis (FSGS) has also been associated with RN[108], and FSGS has been found in as many as 21% of nephrectomy specimens from patients with VUR[109]. FSGS has been found to occur in non-scarred parts of the kidney and the contralateral normal kidney in patients with unilateral VUR as well[110]. The pathogenesis of FSGS in RN remains unclear.

RN with significant scarring may lead to hypertension in children. 17-30% of children[111] and 32-38% of adults[112-115] diagnosed with RN are diagnosed with hypertension as well. The factors predisposing to hypertension include the degree of parenchymal damage, bilateral damage, level of kidney failure and age. Microalbuminuria, an early indicator of glomerular damage, preceding overt proteinuria, progressive renal damage and renal failure, has been reported in 51% of patients with renal scarring, while only 14% had raised serum creatinine[116].

3.3 Chronic renal insufficiency

Chronic renal insufficiency is a condition in which the kidneys perform below the normal level for more than three months. Chronic renal insufficiency is classified into five stages according to the decline in the glomerular filtration rate (GFR) as follows. Stage I: GFR 90 ml/min/1.73 m2 or greater, stage II: GFR 60-89, stage III: GFR 30-59, stage IV: GFR 15-29 and stage V: GFR 15 or less[117]. Stage V is also termed end-stage renal disease (or chronic renal failure). Chronic renal failure may lead to the development of hypertension, anemia, azotemia, uremia, hyperkalemia, hyperphosphatemia, hypocalcemia, renal osteodystrophy, and metabolic acidosis. A large portion of patients with chronic renal failure require dialysis before eventually undergoing renal transplantation.

RN accounts for 1.0-6.3% of patients requiring renal transplantation, varying according to age and race[118,119]. In contrast, a systematic review found childhood UTIs to be a minimal (0.3% at most) etiologic factor in the development of chronic renal insufficiency[120]. In an earlier large study, supporting this notion, it was found that treatment of VUR has not led to a reduction in the incidence of chronic renal failure attributable to RN[121]. This supports the notion that the etiology of chronic renal failure in children with high-grade VUR and RN is congenital in nature, and cannot be prevented by abolishing VUR and preventing UTIs.

3.4 Effects on growth

VUR, especially together with recurrent UTIs, may lead to decreased kidney growth[3,4,6]. In addition, VUR has been associated with slightly decreased body growth, and resolution of VUR – either spontaneously or by surgical correction – and medical treatment of VUR patients have been associated with significant catch-up growth[5,7,122,123]. The underlying mechanism is unclear.

3.5 Effects on pregnancy

VUR diagnosed in childhood has been thought to be a predisposing factor for future problems in pregnancy, including UTI, hypertension, pre-eclampsia and fetal morbidity. A review showed, however, that only UTIs were more frequent in pregnant mothers with a history of VUR diagnosed in childhood, while the incidence of hypertension, pre-eclampsia, and fetal morbidity were similar compared to women with no history of VUR. However, renal scarring in women with a history of childhood VUR has been associated with a higher incidence of UTIs, hypertension, pre-eclampsia and low birth-weight[124-126].

4. OTHER ABNORMALITIES FOUND AFTER A UTI

Imaging studies after a childhood UTI are performed to detect more than just VUR. There are several urological abnormalities associated with a higher susceptibility to UTIs, including ureteral duplication, obstruction of the urinary tract, ureterocele, urethral valve, bladder diverticulum. Some of these conditions, as well as VUR and UTIs, can be associated with functional renal impairment, and most of them, or their sequelae, can be detected in RBUS or VCUG. In addition to these abnormalities discussed below, imaging studies after a childhood UTI may reveal several other pathological findings, including single renal cysts, multicystic kidneys, calculi, ureteral dilatation, and dysfunctional renal segments[105,127,128].

4.1 Ureteral duplication

Ureteral duplication is one of the most common urological abnormalities, and it can be found in as much as 0.5-0.9% of the entire population and 2-8% in children after a febrile UTI, with a slight predominance in girls[129-133]. The condition is bilateral in approximately 40% of cases[134,135]. It is characterized by incomplete fusion of the upper and lower poles of the kidney, resulting in duplication of the collecting system. It ranges from only partial duplication of the renal pelvis with a single ureter, to two completely separate collecting systems draining independently to the bladder or to an ectopic focus. The term 'duplex kidney' is used if two separate pelvicalyceal systems drain a single renal parenchyma, 'bifid ureter' is used if the two ureters unite before entering the bladder, and 'double ureter' is used in the case of completely duplicated ureters that drain independently into the bladder or ectopically. In males, the most common ectopic site is the urethra, while in females the vagina is also common, but there are also cases of the ureter's orifice being located in the bladder neck, the seminal vesicle, the vestibule, the ejaculatory duct, and the prostatic utricle[136-139].

Duplication has been found to be associated with other urological abnormalities in 70% of patients diagnosed after a UTI. VUR is the most common, with 66% of complete duplication and 47% of incomplete duplication being accompanied by VUR, and complete duplication is associated with higher grades of VUR and a lower rate of spontaneous resolution of VUR. Complete duplication has been associated with ectopic ureterocele in 20% of cases and with poorly functioning pole moieties in 40% of cases[132]. VUR is more often present in the lower pelvis[140].

Duplication can be detected quite well in RBUS and especially renography, but VCUG also gives additional information on whether or not there is also VUR[140]. Duplication is most often discovered after imaging studies are performed after a UTI, but as duplication is often asymptomatic, it may sometimes be diagnosed incidentally when performing imaging studies, such as a CT scan or MRI, for other reasons[131,132,140]. Some cases may also be diagnosed in a prenatal US[133].

Duplication on its own does not usually warrant surgery or any other particular treatment, but the comorbidities associated with it, such as VUR and UTIs, may require further evaluation and treatment. Additionally, as duplication is associated with a lower rate of resolution of VUR, it may be wise to be taken into consideration when

deciding on treatment of VUR, whether it may be AMP or surgical treatment. Particularly cases of incomplete duplication rarely cause problems, but complete duplication is sometimes associated with UPJ obstruction, particularly of the lower pole, that may warrant surgical treatment, *i.e.* pyelopyelostomy, ureteropyelostomy, pyeloplasty, or even heminephrectomy[133,141]. In addition, ectopic ureteral orifices often require surgery to redirect flow of urine from the ureter only to the bladder[136-139].

4.2 Ureteropelvic junction obstruction

With an incidence of 0.07-0.13%, and accounting for 50-64% of all cases of prenatal hydronephrosis, UPJ obstruction is the most is the most common urologic obstructive abnormality[142-144]. It is defined as an obstruction of the flow of urine from the pelvis to the proximal ureter, which may lead to *e.g.* progressive renal damage and deterioration. The most common causes of this are intrinsic fibrotic stenosis and embryogenetic disturbances, in which the UPJ canalizes inadequately[145,146]. Most cases are detected in prenatal US, but UPJ obstruction is also sometimes detected after UTI in several imaging studies, including RBUS, renography, and VCUG, and in other imaging studies, including intravenous urography, CT, CT urography, MRI, and magnetic resonance urography[147-150].

Left untreated, 15-33% of patients with UPJ obstruction develop progressive renal deterioration[151-155]. It may also be associated with pain, stone formation, and recurrent UTIs[156]. Studies have shown that early surgery in these cases may prevent the progression of renal deterioration in the majority of patients[157-159]. Pyeloplasty is often considered the gold standard of treatment, but endoscopic pyelotomy may also be effective especially in cases of UPJ obstruction resulting from an aperistaltic ureteral segment and ureteral stricture[156,160]. If the affected unit is found to account for less than 10-15% of total kidney function, nephrectomy may be indicated[156]. Uncomplicated UPJ obstruction may also be treated conservatively, with only repeated RBUS, and renography when necessary. If progressive renal deterioration is detected in these studies, surgical treatment may be indicated[156]. As UPJ obstruction has been associated with UTIs, AMP is often recommended in these cases, although there is some controversy regarding the necessity and effectiveness of AMP in these patients[156,161,162].

4.3 Urethral valve

At gestation weeks 5-7, a thick, valve-like membrane called a posterior urethral valve (PUV), derived from tissue from the Wolffian duct may be formed in the posterior male urethra. There are three types of PUVs. The first and most common one occurs when two adjoined mucosal folds at the level of the seminal colliculus extend anteroinferiorly. The second and rarest type occurs when mucosal folds extend along the posterolateral urethral wall from ureteral orifice to the seminal colliculus. This type is no longer considered a true PUV, but a normal variant. The third type occurs when a circular, diaphragm-like membrane with a central orifice forms in the membranous urethra. Type 3 is caused by abnormal canalization of the urethra.

A PUV may obstruct the free flow of urine, resulting in raised bladder pressure during voiding, which may in turn cause secondary VUR and hydronephrosis. Although the majority of cases are diagnosed in prenatal

US, posterior urethral valves (PUV) have been found in up to 2.3-4.8% of boys after a UTI[163,164]. PUV after infancy have also be found in imaging studies done because of voiding dysfunction, difficulty in catheterization, hypospadia, and fistulae[165].

Even with early surgical treatment, PUV is associated with chronic renal failure in as many as 43% of cases, regardless of VUR status, especially if there are signs of renal failure at the time of PUV diagnosis, *i.e.* raised serum creatine levels or plasma renin activity[166]. PUVs require surgical treatment, and are usually treated endoscopically using incision with cold knife, electrosurgery, or laser ablation[167].

4.4 Ureterocele

A ureterocele is a cystic dilatation limited to the distal end of the ureter within the bladder, the urethra, or both. The incidence of ureteroceles is estimated to be 0.03-0.2%[168,169]. They are more common in girls, and are associated with the upper pole of a duplex system in as many as 80%, and have an ectopically located orifice in the urethra in approximately 60% of cases[168,170]. Although most cases are detected in prenatal US, many cases are also found in imaging studies after a UTI[171,172]. Some cases may also be detected due to a palpable abdominal mass or urethral prolapsed of the ureterocele in girls[168]. Most cases are asymptomatic, but ureteroceles are associated with a higher incidence of VUR, recurrent UTIs, antenatal hydronephrosis, urinary stones, renal scarring, bladder outlet obstruction, and urinary retention[170,173,174].

Ureteroceles are often quite well visualized in RBUS and renography, but VCUG provides important information on VUR status. This is particularly relevant, as 50% of the ipsilateral lower pole and 25% of the contralateral renal units have been found to show VUR[168,171]. As ureteroceles are associated with considerable morbidity, surgical treatment is often recommended. The most common surgical options include endoscopic incision of the ureterocele and ablation of the ureterocele with bladder floor reconstruction and ureteral reimplantation. In the case of ureterocele in a single ureter of a complete duplex system, heminephrectomy of the affected pole may be appropriate[174-176].

4.5 Bladder diverticulum

Bladder diverticula are outpouchings of bladder mucosa through the bladder musculature outside the bladder. They can be either congenital (primary) or acquired (secondary). Secondary diverticula are far more common in the entire population, but in the pediatric population there is a substantial amount of primary diverticula. Secondary diverticula can be caused by several conditions causing lower urinary tract obstruction and elevated bladder pressure, such as PUV or neurogenic bladder. They can also be found as a part of some congenital syndromes, such as Ehlers-Danlos syndrome and prune-belly syndrome. Primary diverticula are thought to be caused by a congenital weakness in the Waldeyer's sheath. So called Hutch diverticula are congenital diverticula located near the UVJ, which may lead to obstruction of the UVJ and hydronephrosis. The diverticulum may also distort the UVJ leading to VUR. Hutch diverticula occur almost exclusively in boys, with a prevalence of 1.7%[177]. Roughly 10% of primary diverticula in children so called primary isolated bladder diverticula, *i.e.* diverticula that are not associated with

the UVJ and as such do not cause obstruction nearly as often[178].

Several associated morbidities and complications have been described, including VUR, recurrent UTI, hydronephrosis, pain, and bladder retention[179-181]. Although bladder diverticula have been associated with bladder cancer in the adult population, there is no evidence of this association in children[179]. Bladder diverticula can usually be detected quite well in RBUS, but VCUG provides both a better view of the diverticulum and additional information on VUR status[181]. Due to risk of complications, primary bladder diverticula are usually treated surgically. The most common procedure is extravesical diverticulectomy, often with simultaneous ureteral reimplantation if there is evidence of significant high-grade VUR and/or distortion of the UVJ[180,182].

5. DIAGNOSTICS IN URINARY TRACT INFECTIONS

As stated previously, the total pooled prevalence of UTIs before the age of 2 years is 7.0% (95% CI 5.5-8.4%). In the first few months of life, UTIs are more common in boys, and thereafter the incidence is higher in girls. In febrile infants with no other potential source of fever, urine cultures should always be obtained. Even in the presence of another potential source of fever, urine sampling should be considered especially in the presence of risk factors for UTI, including white race, female sex, uncircumcised boys, history of UTI, malodorous urine or hematuria, abdominal or suprapubic tenderness on examination, or fever of 39.0°C or higher[183,184].

In toilet-trained children, obtaining a clean-catch urine sample is recommended. Thorough cleaning of the external genitalia is important to reduce the risk for bacterial contamination from the skin. In pre-toilet-trained children, the highest diagnostic accuracy is achieved with suprapubic aspiration samples (SPA) or with catheter samples. SPA is considered the gold standard with very low risk for contamination, but is also the most invasive and not always successful. In some centers, special urine collection bags or pads are also used. These sterile bags or pads are tightly attached around the child's genitalia with adhering tape, and the child is monitored until he/she spontaneously voids. Urinalysis is then performed on the gathered urine. These methods of urine collection have been strongly criticized due to the high risk of contamination and a false positive rate of up to 85%[10,185,186] A negative result may, however be considered reliable. Additionally, even when using urine collection bags or pads, a positive nitrite test and a positive leukocyte esterase test have a specificity of 98% and 78% for UTI, respectively[10]. A positive finding in urinalysis of a bag or pad sample should always be confirmed with SPA or a catheter sample, in order to eliminate false UTI diagnoses and unnecessary antibiotic treatment.

Regardless of the method of urine collection, the diagnostic tests for UTI are the same. The urine may first be tested with a dipstick or flow cytometry, which may then be confirmed by microscopy if necessary. In a dipstick test, a positive result for leukocyte esterase and/or nitrite is indicative of a UTI. The leukocyte esterase test is positive in the case of all bacteria, but the nitrite test is positive in the case of only gram negative bacteria, including E. coli, and is most useful when bladder time is at least 4 hours, as bacteria in the bladder need time to produce nitrite. In microscopy, uncentrifuged urine is examined under a microscope. The presence of any bacteria or a higher than normal amount of leukocytes (normally 1-5 leukocytes per high power field) is indicative of a UTI. Both these methods are widely used, but microscopy has been found to have better sensitivity and specificity for UTI, and a negative finding in enhanced urinalysis has a NPV of 99.6-99.8% for UTI [10,187].

Any of the aforementioned results suggestive of UTI should be confirmed with a bacterial culture. The threshold for the amount of bacteria in a culture, indicative of a UTI varies among guidelines and institutions. Most clinicians, however, agree that any growth of a single uropathogen in a SPA sample may be considered certain UTI. No bacterial growth may be considered a negative result regardless of the method of ob-

taining a urine sample. Growth of multiple bacteria in a culture is considered to signify contamination. In catheter samples, the threshold for 'certain UTI' is 10,000-100,000 CFU/ml.[10,19,20] The presence of white blood cells in the urine, or pyuria, determined either by the leukocyte esterase test or by microscopy, can be used to differentiate between true UTI and asymptomatic bacteriuria. The tests' sensitivities for detecting UTI alone, however, are 83% and 73%, respectively, so they cannot be used alone to rule out UTI[10]. Particularly in pre-toilet-trained, preverbal children, UTI diagnostics can be extremely challenging. In these cases, history of UTI, malodorous urine or hematuria, abdominal or suprapubic tenderness on examination, or fever of 39.0°C or higher, and the absence of other potential infection foci are considered to support the UTI diagnosis, and must always be taken into account. Asymptomatic bacteriuria is not an indication for antibiotic treatment in children.

Clinical differentiation between lower UTI or cystitis and upper UTI or pyelonephritis is difficult. Fever of ≥38.0°C, loin pain or tenderness, a CRP level of ≥40 mg/l, as well as any other systemic symptoms or signs in infants and small children are considered suggestive of pyelonephritis[10,17,21]. Due to this difficulty, many clinicians rather differentiate between febrile UTI and afebrile UTI, with the most commonly used threshold of ≥38.0°C for the term 'febrile'. Additionally, small infants, aged 0-3 months, with UTI are often treated as having pyelonephritis even if they are afebrile, in order to minimize the risk of potentially dangerous sequelae of undertreated pyelonephritis.

Bacteremia in children with UTI is associated with feeding problems, abdominal pain, vomiting, higher CRP level, and longer lasting fever. It is more often accompanied by high-grade VUR, and other anatomical or functional abnormalities of the urinary tract, than UTI without bacteremia. Bacteremia cannot, however, be ruled out based on the lack of the aforementioned symptoms, but blood bacterial cultures should be taken with a low threshold in all children with febrile UTI[188].

6. IMAGING STUDIES AFTER A UTI

VUR is the most common urological abnormality detected in imaging studies after a UTI. Other possible abnormalities include hydronephrosis, ureteral duplication, ureterocele, posterior urethral valve, bladder diverticulum and renal abscess. VCUG remains the gold standard for identifying and grading VUR. RBUS is often performed as a first-line screening study for VUR, and to identify other anatomical anomalies of the urinary tract. DMSA scanning has gained some popularity and is the imaging modality of choice for identifying pyelonephritis and renal parenchymal damage. Other imaging studies are usually performed only after a specific concern has arisen based on other imaging studies or other complex clinical situations.

6.1 RBUS

RBUS is a noninvasive study that can often be performed during initial hospitalization for UTI without radiation exposure or significant discomfort to the child. This has been one important factor in the widespread use of RBUS as a first-line investigation in infants and small children with febrile UTI. It can provide important information of kidney size, thickness of the parenchyma, hydronephrosis, significant renal scars and ureteral duplication[128,189,190]. Some information may also be obtained of *e.g.* ureteral dilatation and thickness of the bladder wall, which can be associated with obstruction of the urinary tract. Although RBUS does not provide definitive diagnostic information on a wide range of conditions, it has been thought to be a sufficient screening study in some cases to identify patients who may benefit from further imaging by *e.g.* VCUG[17,18]. VUR itself cannot be diagnosed by conventional RBUS, but it may reveal several conditions associated with VUR, including dilatation of the upper urinary tract. Some studies have found that RBUS on its own after a UTI in children may be of relatively little consequence[163,189,191-193] (Table 1). As a screening study to select certain patients for VCUG, it may be of more value. Abnormal RBUS after a febrile UTI in childhood is listed as an indication for VCUG in most guidelines. Data on the sensitivity and specificity of RBUS to identify patients with VUR, however, are inconclusive[194-196]

Table 1. RBUS studies after a UTI in children with no VUR on VCUG.

	Number of patients	RBUS abnormal (%)	Management altered by RBUS (%)
Alon et al. (1999)[163]	124	19 (15)	1 (0.8)
Hoberman et al. (2003)[189]	309	37 (12)	0 (0)
Zamir et al. (2004)[191]	255	36 (14)	0 (0)
Giorgi et al. (2005)[192]	203	32 (16)	9 (4.4)
Jahnukainen et al. (2006)[193]	155	23 (15)	9 (5.8)
Total	1046	147 (14)	19 (0.9)

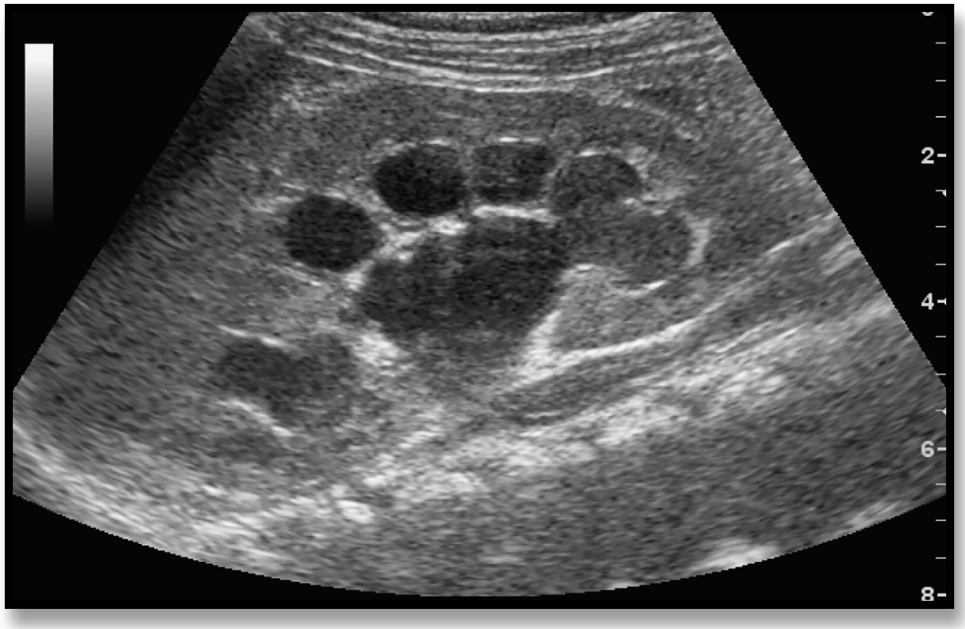

Figure 5. RBUS image of a 6-month-old boy, showing hydronephrosis of the left kidney, with dilatation and blunting of the pelvis and calices. Further studies revealed obstruction of the ureteropelvic junction (UPJ).

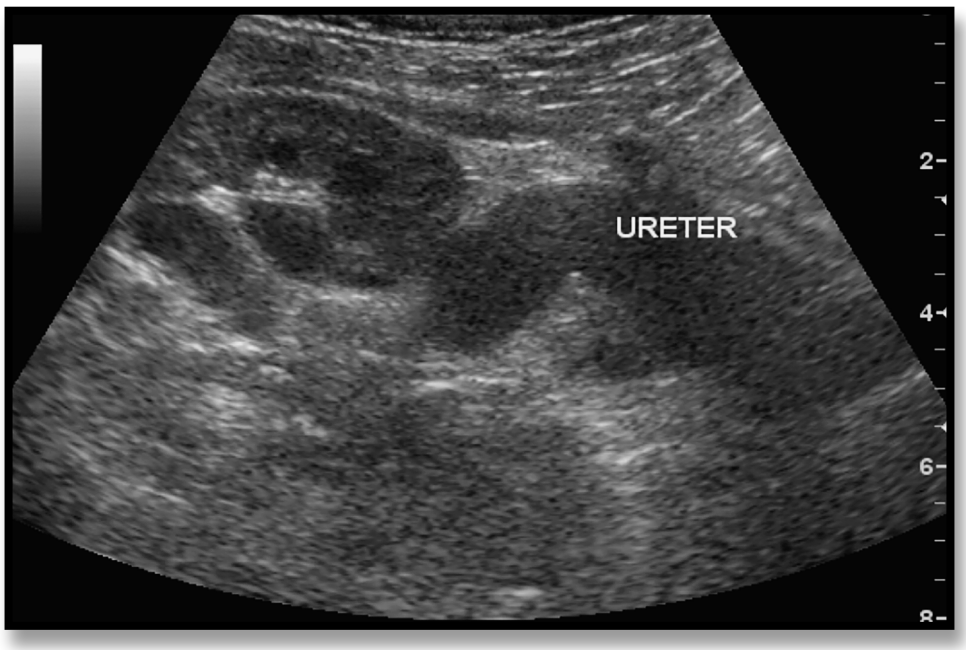

Figure 6. RBUS image of a 6-month-old girl, showing tortuosity and dilatation of the ureter.

6.2 VCUG

VCUG remains the gold standard in diagnosing and grading VUR. In addition to identifying and grading VUR, VCUG can reveal abnormalities of the urethra and bladder, ureteral duplication, bladder diverticula, ureteroceles, posterior urethral valves, and reliably estimate bladder capacity. VCUG is performed, according to the instructions provided by the International Reflux Study in Children[88] as follows. The child is instructed to void, if possible. After this, a urinary catheter is inserted into the bladder and residual urine is measured. Then the bladder is filled by catheter with contrast medium at body temperature, with a concentration of 15-20%, and no more than 30%. The most commonly used contrast agent is the iodine containing agent diatrizoic acid. The bottle should be held at a maximum of 70 cm above the bladder, until the dripping of the contrast medium has stopped while the child is calm and/or has the urge to void. The volume is recorded at this point, and compared with normal bladder volumes according to the age of the child. The aim in successive examinations should be to achieve at least the same volume. Four images should be obtained during voiding: 1) at partial filling, 2) when the bladder is full, 3) at the height of voiding, and 4) immediately after voiding. The highest grade of VUR in all images is recorded. This is often at the height of voiding. At the time of the first VCUG, the lower urinary tract should be visualized, and in boys, a lateral image should be obtained to properly assess the urethra. VUR may sometimes be absent in one study and present in the next. Therefore, many institutes perform several cycles of imaging in one VCUG session. If possible, sedation should be avoided, as this affects voiding pressures.

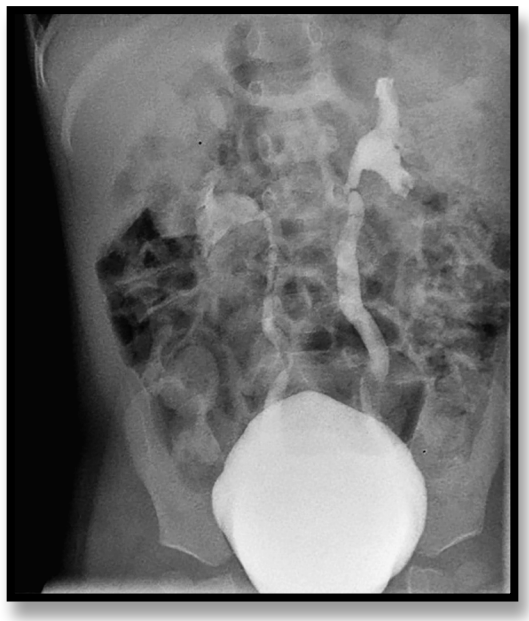

Figure 7. VCUG image of a two-year-old girl, showing grade II VUR on the right side and grade III VUR on the left side.

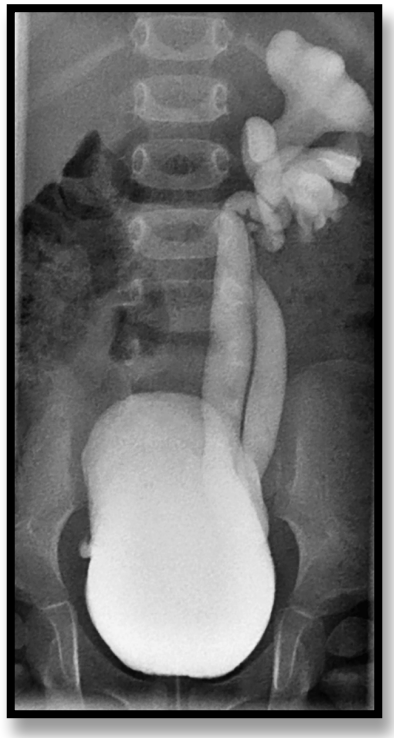

Figure 8. VCUG image of a 20-month-old girls, showing grade I VUR on the right side and grade IV VUR to both the upper and lower poles of a bifid system on the left side.

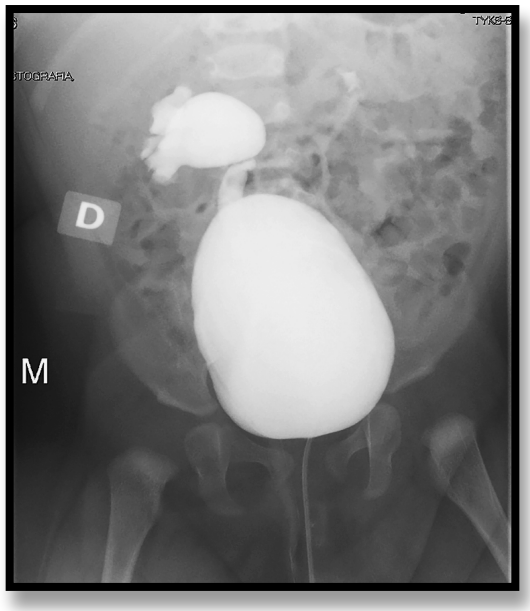

Figure 9. VCUG image of a five-month-old girl, showing grade V VUR on the right side and grade II VUR on the left side.

VCUG has traditionally been performed 3-4 weeks after the acute UTI, mainly because of 50-year-old studies indicating that transient VUR may occur during or immediately after UTI due to edema of the ureterovesical junction, reduced ureteral tone and peristalsis caused by inflammation of the urinary tract[34,41,43]. In a more recent study, however, it was found that the timing of VCUG had no impact on the incidence of VUR detected in VCUG[197].

VCUG has several problems, including a considerable radiation dose of 0.7 to 1.1 mGy in boys and 0.27 to 1.25 mGy in girls[13-15,198], discomfort to the child due to the need for catheterization, and risk of iatrogenic UTI[11,12]. Several attempts have been made to replace VCUG with a less invasive study and/or one that would entail a smaller radiation burden. Of these imaging modalities only direct radionuclide cystography (DRC) and indirect radionuclide cystography (IRC) (discussed in more detail in chapter 4.4) have proven sufficiently accurate for the detection of VUR, and have been accepted for use in some institutes.

6.3 DMSA scintigraphy

DMSA scintigraphy uses intravenously administered technetium 99m-labeled dimercaptosuccinic acid (DMSA) to form an anatomical image of the kidneys, in order to identify anatomical abnormalities and acquired lesions. It has the most implications in detecting cortical abnormalities related to UTI, with a higher sensitivity compared to RBUS or intravenous urography[199-201]. It may be used for both acute imaging to identify acute pyelonephritis and other lesions in the acute phase, and at a later time to detect chronic lesions. DMSA scanning may also be useful in detecting associated abnormalities, including duplex kidney, abnormal kidney size, dysplastic tissue, horseshoe kidney, ectopic kidney and non-functional multicystic kidney. Abnormalities in DMSA scintigraphy have a very good sensitivity for VUR, and can be used as a screening study for VUR as well[202,203].

The lesions detected in DMSA scanning are, however, not specific, and similar lesions can be found in renal abscess, cyst, duplex kidney, and hydronephrosis. Thus, combining DMSA scanning with RBUS provides a more detailed picture of the situation. Another possible factor complicating the interpretation of DMSA scans is that significant dilatation of the upper urinary tract may cause accumulation of tracer in the renal cavities, which may cause differential function of the kidney to be evaluated falsely high. Both transient and permanent lesions can be visualized by DMSA scanning, and late scanning is recommended to be performed approximately 6 months after the acute infection, in order to differentiate between acute inflammatory lesions and permanent renal damage[204].

DMSA scanning is performed, according to the European Association of Nuclear Medicine guidelines, as follows[204]. There are no contraindications for DMSA scintigraphy, but in the case of significant hydronephrosis a dynamic renal scan with Tc-MAG3 is recommended instead of a DMSA scan. Drug sedation is only rarely needed regardless of the age of the child. If sedation is, however, deemed necessary, intranasal or per-rectal midazolam is recommended. 99m-Tc-DMSA tracer is then administered intravenously. Images are obtained approximately 2 to 3 hours after tracer injection, with the child in a supine position. Posterior and posterior oblique images are obtained. An additional

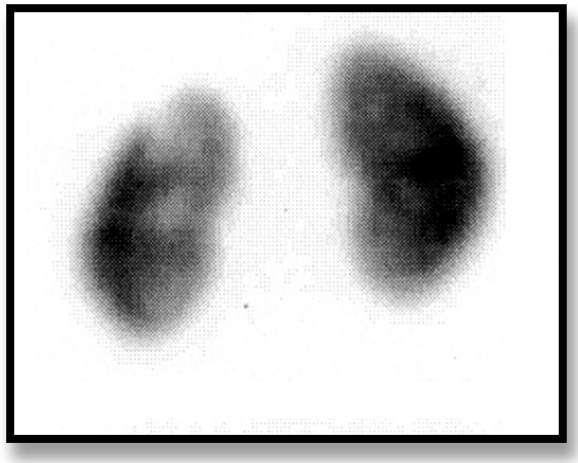

Figure 10. Posterior view of a DMSA scan image of a six-year-old girl, showing uptake defects in each third of the left kidney and in the middle and inferior pole of the right kidney, suggestive of renal scarring. Adapted from Hitzel et al. (2004)[205].

anterior view is recommended when suspecting horseshoe kidney or ectopic kidney. Relative tracer uptake values for each kidney are calculated, normal values lying within 45-55%. The most common abnormal finding is a localized photopenic area, signifying possible cortical loss or scarring. Larger polar hypoactive areas, without deformity of the outlines and with indistinct margins will often heal during follow-up, whereas localized deformity of the outlines or deformed outlines usually correspond to permanent damage[204].

6.4 Other imaging

Due to the various problems surrounding VCUG, many alternative imaging modalities have been studied, in order to find a safer, cheaper, more comfortable way of identifying and grading VUR. Although some of the described methods have proved useful and may have potential as a first-line investigation tool after UTI, no imaging modality has so far been accepted to replace VCUG as the gold standard for identifying and grading VUR.

6.4.1 Direct radionuclide cystography

Of the several alternative imaging studies available to identify VUR, direct radionuclide cystography (DRC) is among the most widely used, and has reasonable sensitivity in detecting VUR; in some studies it has even detected VUR in cases where VCUG did not[206,207]. Whether this may be interpreted as DRC having greater sensitivity or poorer accuracy in detecting VUR is somewhat unclear. In contrast, some studies have found DRC to miss a significant proportion of patients with VUR[208]. One setback of DRC is its inability to grade VUR according to the international system for radiographic grading of VUR. A simplified classification using three grades (grade A: reflux into the ureter, grade B: reflux into the pelvis, grade C: reflux into the pelvis, with apparent dilatation of the ureter or pelvis) is sometimes used[208,209]. Zhang et al.[209] graded DRC simply as "low-grade" vs. "high-grade" and reported a correlation of 100% compared to low-grade (determined as grades I-III) vs. high-grade VUR (determined as grades IV and V) on VCUG. In addition to the difficulties

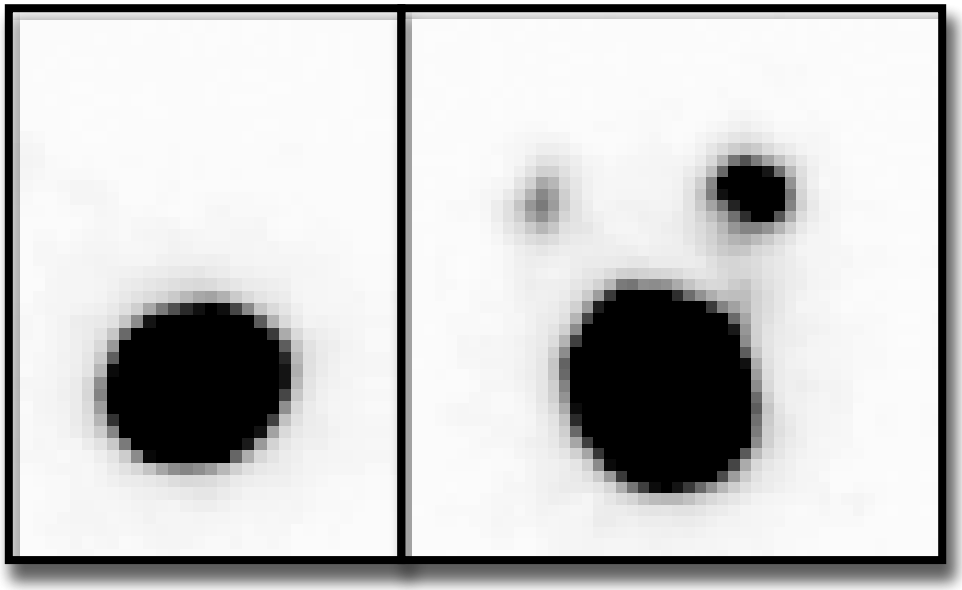

Figure 11. Two DRC images from the same series in a 5-month-old boy. The first image shows normal findings, and the second reveals bilateral VUR.

in grading VUR, adequate visualization of the urethra is not possible using DRC.

DRC is performed, according to the European Association of Nuclear Medicine guidelines, as follows[210] The child, in a supine position, is catheterized and the bladder is emptied. The bladder is then slowly, under hydrostatic pressure filled with tracer (20 MBq for 500 ml saline), warmed to body temperature. The container should be held at no higher than 40-60 cm, and filling should take approximately 10 minutes, to avoid an increase in bladder tone and premature micturition. To approximate the child's bladder capacity, the following formula should be used: V = (Age in years + 1) x 30 ml. Filling is stopped and the child is allowed to void, when bladder capacity is reached, or when flow from the container to the bladder has stopped, or when the child has the urge to void. Voiding should ideally happen with the child in an upright sitting position with the back to the camera. The procedure may then be repeated several times (cyclic DRC), to increase the sensitivity of the study[208].

The effective radiation dose of a single cycle of DRC is approximately 0,048 mSv per 20 MBq of 99mTc. When using 20 MBq of 99m-Tc in 500 ml of saline, the estimated dose to the bladder for children between 1 and 10 years old, is 0,09-0,14 mGy, with an ovarian dose of 0,005-0,01 mGy and an even smaller testicular dose[211-213].

6.4.2 Indirect radionuclide cystography

Many attempts have been made to eliminate the need for catheterization in imaging VUR. Among the most successful is indirect radionuclide cystography (IRC), which is often carried out following a standard or diuretic renogram (see chapter 4.4.3). There are no contrainidications for IRC, but in can only be performed in toilet trained children. According to the European Association of Nuclear Medicine, IRC is performed as follows[214] Before the study, the child should be well hydrated (orally if possible, otherwise

intravenously), and the child should void, if possible. Then the child is positioned in a supine position. A minimum of 15 MBq of 99m-Tc-MAG3 is injected intravenously as a bolus (99m-Tc-ethylenedicysteine or 99m-Tc-hippuran can also be used). At this point, a renogram is often performed. Immediately after the renogram, the child is offered oral fluids freely, and the IRC will begin when the child feels an urge to void. The child is then placed sitting on a commode (girls) or standing (boys) with his/her back close to the camera. The child then voids and images are taken from the time immediately before voiding until voiding is complete. Images should be displayed in 5 seconds/frame. VUR will show in the images as increased activity in the kidneys or ureters, according to the refluxing volume. IRC does not result in any additional radiation burden compared to the dynamic renogram.

In addition to reducing stressfulness of the study to the child, the lack of catheterization makes voiding more physiological. However, the filling phase cannot be studied in IRC. Some studies have found this a weakness, as VUR was identified in many patients only in the filling phase in DRC, resulting in a false negative finding in IRC in an unacceptably large number of patients[215-217] As with DRC, VUR cannot be graded according to the international system for radiographic grading of vesicoureteric reflux in IRC.

6.4.3 Renography

In children with febrile UTI, renography may be useful if suspecting urinary tract

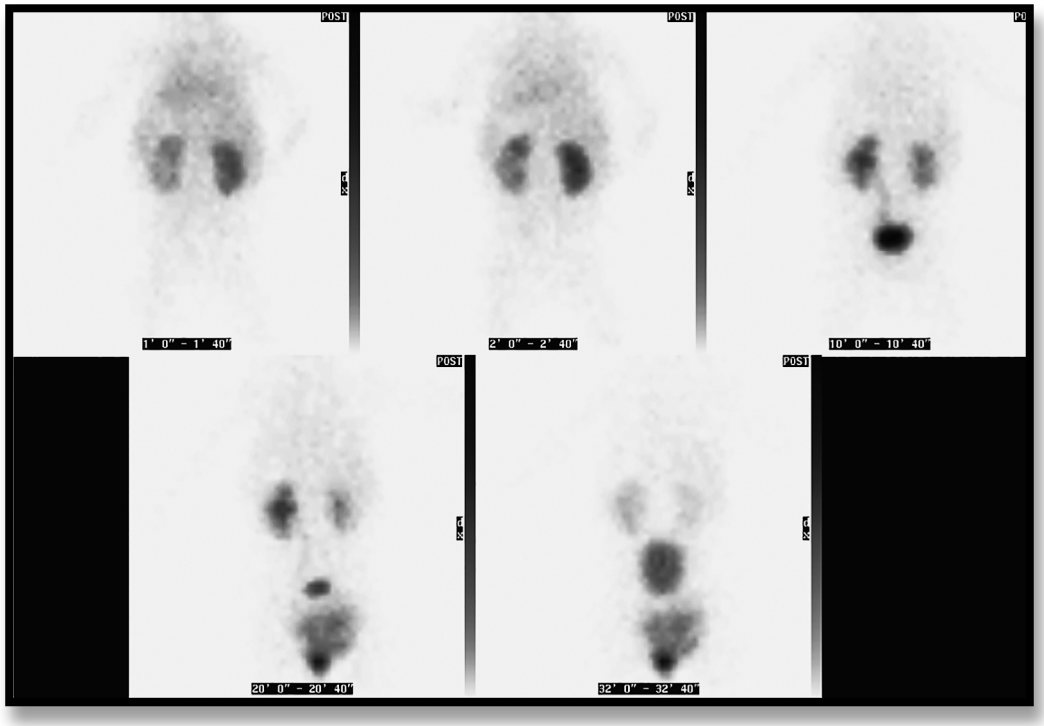

Figure 12. 99m-Tc-MAG3 renogram of a five-month-old boy, showing decreased secretion of the contrast agent on the left side at 20 minutes (frame 4). At 20 minutes, intravenous furosemide is administered, followed by normal resolution of the situation (frame 5). Relative kidney function was slightly decreased on the left side (62/38%).

obstruction or impaired renal function. Although VUR cannot be diagnosed by renography, it provides information on the size, location, function and emptying of the kidney, and may reveal *e.g.* obstruction of the UPJ or unilateral renal function impairment. According to the European Association of Nuclear Medicine, the study is performed as follows[218]. The child is well hydrated (orally if possible, otherwise intravenously), and instructed to void. A minimum of 15 MBq of 99m-Tc-MAG3 is injected intravenously as a bolus. 99m-Tc-ethylenedicysteine, 123-Tc-hippuran or 99m-Tc-diethylenetriaminepentacetate (DTPA) can also be used. Of these, 99m-Tc-DTPA is dependent on glomerular filtration and the others on tubular excretion. Images are obtained in the circulatory phase, parenchymal phase and excretory phase, for a total duration of at least 20 minutes. In a diuretic renography, intravenous furosemide is given to induce excretion of the tracer and identify urinary tract obstruction. The radiation burden of the procedure depends on the contrast agent used. For a five-year-old, the effective doses are 0.54-0.82 mSv for 99m-Tc-DTPA, 0.20-0.38 for 99m-Tc-MAG3 and 0.41-0.70 for 123-Tc-hippuran[212,213]. In the case of renal function impairment, a reduction of the injected activity is required when using 99m-Tc-DTPA or 123-Tc-hippuran[219].

6.4.4 Voiding urosonography

While standard RBUS is a noninvasive study that provides mostly anatomical information, voiding urosonography (VUS) involves catheterization of the child and instillation of a contrast agent into the bladder. The contrast agent can then be visualized with US, and possible reflux into the ureters or kidneys can be identified.

The first fluid to be administered through a catheter in VUS was saline. After administering the saline, dilatation of the renal pelvis or terminal ureter was considered a positive finding for VUR. The method, however, had poor sensitivity[220,221]. Adding color Doppler to this procedure improved the sensitivity in one study[222]. Shaking the normal saline or adding carbon dioxide to produce gas bubbles, which can be detected by US, has also been tried with reasonable results[223,224]. Some other contrast agents, including air and sonicated albumin have been tested with limited success[225,226].

The most promising results have been achieved with special US contrast media. First in 1994, the method had limited success[227]. Later, after the development of a galactose-based contrast agent that contains microbubbles stabilized with a layer of palmitic acid (Levovist, Schering, Berlin, Germany), the procedure became easier to perform, as the microbubbles lasted longer[228]. The diagnosis of VUR is made as microbubbles become visible in the pelvicalyceal system by US. In a review of 1140 renal units, VUS was found to be concordant with VCUG in 92% of cases[229].

VUS, however, has some major disadvantages. The urethra cannot be visualized by VUS. VUR cannot be reliably graded using VUS. VUS still requires either catheterization of suprapubic punction in order to deliver the contrast agent into the bladder. For these reasons, VUS is as of yet not recognized as a feasible imaging modality for identifying VUR.

In addition to VUS, Matsui et al. recently found that the angle of the ureteral jets identified by color Doppler US correlated significantly with the presence of VUR. They found that, at a ureteral jet angle cut-

off point of 50°, color Doppler US had a sensitivity of 90% and 95% for detecting grade III-V and grade IV-V VUR, respectively[230] The method does not require catheterization or radiation, but VUR cannot be graded. The method may, however, have some potential as a screening study to select patients for VCUG.

6.4.5 Magnetic resonance voiding cystourethrography

Magnetic resonance voiding cystourethrography (MRVCUG) has potential to be a radiation-free way of diagnosing VUR as well as providing accurate anatomical data on the urinary tract, including renal scarring, ureteral duplication, abscesses, urethral anomalies and other abnormalities.

The procedure can be performed either without catheterization and an intravesical contrast agent (indirect MRVCUG), or with a contrast agent instilled in the bladder via a catheter. Younger children need sedation before the study. In direct MRVCUG, the bladder is filled with a gadolinium containing contrast agent and the procedure is performed much like a standard VCUG. In indirect MRVCUG, the patient is well hydrated either orally or intravenously, and diuresis is stimulated by intravenous furosemide. Images are taken with the bladder full as well as during and immediately after voiding.

The sensitivities and specificities for detecting VUR are reported at 76-100% and 89-90%, respectively, for direct MRVCUG[231-234], and 77-90% and 89-96%, respectively, for indirect MRVCUG[234,235]. Direct MRVCUG has the added benefit of being able to better visualize the urethra. Be it direct or indirect MRVCUG, a significant problem is the study's cost and limited availability.

6.4.6 Microwave heating and radiometric thermometry

In an attempt to obviate both catheterizing and radiation, Arunachalam et al. introduced a novel imaging method, where urine in the bladder is warmed by microwaves[236]. Temperature changes are then measured in the renal pelvis by microwave antennas, indicating the presence of reflux to the kidney. This method has only been tested in an ex vivo porcine model to show that microwave heating does not result in tissue damage, but sensitivity or specificity for detecting VUR has not been studied[237,238]. Though this imaging modality has some potential as a feasible, noninvasive, radiation-free method of detecting VUR, it has the downside of not being able to visualize the urethra.

7. MANAGEMENT OF VUR

Previously, the detection of VUR has often led to open surgical procedures to repair the anti-reflux mechanism of the ureterovesical junction. In 1984, the endoscopic subureteral injection of polytetrafluoroethylene was introduced as a potentially effective and less invasive way of abolishing VUR[239]. Thereafter, open surgical repair of VUR has slowly lost popularity. With increasing knowledge on VUR and the possibly quite limited effectiveness of its treatment in preventing UTI recurrences and new renal damage, open surgery is now, in some institutions, recommended only in selected special cases of complicated VUR, such as ectopic ureter, megaureter, grade V VUR or after several unsuccessful endoscopic injection treatments[240]. In some institutions, however, the treatment modality of choice for VUR is still open surgery.

In all centers, the grade of VUR is not the only factor affecting the decision regarding treatment modality. Non-complicated cases are often treated more conservatively, while the presence of other anatomical or functional abnormalities, such as ureteral duplication, paraureteral diverticuli, or functional renal impairment may tip the scales in the direction of open surgical treatment. Other treatment options include antimicrobial prophylaxis, endoscopic injection treatment and watchful waiting. The identification of various risk-factors has been recognized as an integral part of VUR patients' treatment. For instance, in recent decades, the treatment of constipation and bladder training has been recognized as an important factor in the prevention of UTI recurrences[241-244].

7.1 Ureteral reimplantation

Ureteral reimplantation (UR) is a procedure in which the ureter or ureters are detached from the bladder and reattached to a new site. The variety of techniques is wide, but they all share a common basic principle; to increase the length of the submucosal tunnel, in order to facilitate the passive closing of the distal ureter as intravesical pressure rises, inhibiting urine from refluxing towards the kidney.

7.1.1 Open ureteral reimplantation

Techniques of open UR can be divided into two distinct categories, intravesical and extravesical techniques. In intravesical techniques, the bladder is opened and the ureter or ureters are mobilized from within the bladder. This entails more tissue trauma and patients require post-operative catheterization. The most commonly used intravesical techniques include the Cohen, Politano-Leadbetter, Hutch-1, Kelalis, Paquin, Mathisen, Glenn-Anderson, and Gil-Vernet techniques.

Of the techniques mentioned above, the Paquin and Mathisen are combinations of intravesical and extravesical techniques. Some techniques, primarily the Paquin, can be combined with the so called psoas hitch, where the bladder is superiorly fixed to the psoas muscle. This is useful in cases of megaureter or failed UR procedures, when the remaining ureteral lentgh is not sufficient[245]. The Glenn-Anderson technique has the advantage of advancing the ureter from its original hiatus, making the risk of ureteral distortion or obstruction minimal. Unlike the other intravesical techniques, the Gil-Vernet technique requires post-opera-

tive catheterization very seldom[246]. The main difference between the various techniques of UR is the position and location of the newly formed submucosal tunnel. Choice of technique is primarily determined by the surgeon's preferences. With a success rate of 96-99%, the Cohen is the most commonly used technique for UR

While the success rate for abolishing VUR is, as mentioned above, close to 100%, a substantial amount of children suffer from UTI recurrences even after successful UR. In a large study, the rate of UTI recurrence after UR during a 2.9 year follow-up was 22%, and the same figure for pyelonephritis was 6.5%[247]. In a quite recent Cochrane review, UR plus antibiotics did not result in a significant reduction in the number of symptomatic UTIs during up to 10 years of follow-up, when compared to antibiotics alone[248]. However, UR did reduce the risk of febrile UTI by approximately half. In the same comparison, UR did not lead to a reduction in the development of new renal damage or the progression of existing defects on intravenous pyelography during up to 5 years of follow-up[248].

A well recognized complication of UR is new contralateral reflux after surgical correction of unilateral VUR. This occurs in 6-18% of patients after successful UR[249-251] The mechanism behind this remains uncertain. It has been shown that this occurs far more often in scarred kidneys than in healthy kidneys[251]. Based on this, it has been speculated that the so-called 'new' contralateral reflux may in fact be a pre-existing condition rather than a new phenomenon[251]. Due to the relatively low incidence, strong tendency to resolve spontaneously and generally benign course of new contralateral reflux, it has not warranted extensive treatment or follow-up imaging[82].

A meta-analysis found that 2% of patients are diagnosed with ureteral obstruction after open UR, and the reoperation rate for obstruction or any other complication was 2%[82]. There was no difference between surgical techniques. Additionally, approximately 3-22% of patients suffer persistent voiding dysfunction, including urine retention, after extravesical UR[252-258]. This has been thought to be caused by damage to the bladder musculature and mucosa and damage to the nerves of the pelvic plexus posterior to the bladder. Hence, attempts have been made to identify the nerves during surgery, in order to avoid damaging them. In one study, the identification and avoidance of the nerves led to a success rate of 100%; *i.e.* no patient developed voiding dysfunction post-operatively[259].

7.1.2 Laparoscopic ureteral reimplantation

In order to reduce the invasiveness of anti-reflux surgery, some surgeons prefer a laparoscopic approach. This may have several advantages, including reduced need for post-operative analgesia, reduced trauma to the bladder decreasing the risk for bladder spasms, reduced risk of ventral hernia due to not dissecting the linea alba and better cosmetic result. The biggest challenge in laparoscopic UR is its technical difficulty.

Just as in conventional open UR, laparoscopic UR may also be performed either intravesically or extravesically. Success rates in terms of abolishing reflux are reported at 93-100%, *i.e.* comparable to those of open UR, but with shorter recovery time, shorter period of catheterization, fewer cases of post-operative hematuria and reduced need for analgesia Some problems may arise from the longer learning curve required for laparoscopic UR.

7.1.3 Robot-assisted laparoscopic ureteral reimplantation

In addition to conventional laparoscopic UR, some surgical centers have begun using a robot-assisted technique. The success rates in terms of abolishing VUR are reported at 91-97%[259-262]

In addition to having a high success rate even when compared to open techniques, the robot-assisted technique has been found to result in shorter duration of catheter drainage, fewer bladder spasms, shorter hospitalization and decreased need for analgesia[260,263]. The technique has not yet become common practice, partly due to the limited availability of the robot equipment. The downside of the procedure is its longer operation time[260,263].

7.2 Endoscopic correction of VUR

Up to the 1980's, VUR was corrected using more invasive surgery. In 1981, Matouschek introduced the endoscopic subureteral injection of a bulking agent for the correction of VUR[264]. O'Donnell and Puri studied the technique in the piglet, and the procedure came to be known as the 'STING' procedure, an acronym that stands for 'subureteral Teflon injection'[239]. Thereafter, open UR has slowly but steadily lost popularity, as endoscopic correction has become more popular as the first-line method for correcting uncomplicated VUR. The original procedure is performed by inserting a catheter ending in a needle through a cystoscope with the bladder filled with saline. The needle is inserted 2-3 mm below the ureteral orifice at six o'clock position, and advanced approximately 0.5 mm into the space behind the intravesical ureter. Then, a small amount (0.2-3.0 ml, depending on the bulking agent used and the age and size of the patient) of the bulking agent is injected subureterally to produce a slit-like shape of the ureteral orifice facilitating passive closing of the ureteral lumen as intravesical pressure rises[239].

In addition to the original STING technique, Kirsch et al. introduced a modified method of STING, where a pressured stream of irrigation fluid is directed into the ureter to define the location of the injection. This process is called hydrodistention. The needle is then inserted within the ureteral submucosa at the 6 o'clock position and a small volume of bulking agent is injected to confirm implant location. The cystoscope is retracted to the bladder neck to visualize subsequent injection. The ureter should appear to be completely coapted with proper injection. Another deeper injection is performed to "anchor" the superficially injected implant. Hydrodistention of the ureter is attempted after the procedure, in order to ensure proper coaptation of the ureter. Later, Kirsch et al. reported on a technique, where the needle inserted further up the ureter, into its mid to distal portion. This technique became known as the HIT method (hydrodistention implantation technique)[265]. A modification of the HIT is the double HIT, which includes intraureteral implantations in both proximal and distal sites, in order to achieve full coaptation of the entire ureteral tunnel[266]. The double HIT technique has a success rate of 90-94%[266-268], and is currently the most commonly used technique for endoscopic correction of VUR among pediatric urologists in the United States[269].

The earliest injection materials included polytetrafluoroethylene and then bovine collagen, polydimethylsiloxane suspended in a hydrogel carrier, and polyacrylate polyalcohol copolymer as bulking agents. Early results were promising, and *e.g.* collagen in-

jections were found to have an initial success rate of up to 93.9% in simple ureters[270]. These early injection materials have, however, been largely replaced by dextranomer hyaluronic acid (DxHA) due to problems with their use. Problems included poor success rates, migration to the pelvic lymph nodes, lungs, brain, kidneys, and spleen, inflammatory reactions in the bladder, allergic reactions, problems with stability, ureterovesical obstruction, and calcification of the implant[271-277].

Among the newest of the commonly used bulking agents is dextranomer/hyaluronic acid (DxHA), commercially available as Deflux (Sweden). DxHA is associated with a minimal volume loss over time, speculated to be related to the in-growth of host collagen[278]. A meta-analysis of three studies found a single injection treatment to be successful in 69% of cases[279]. In successive courses of treatment the success rate rises to 75-100%[265,280-283]. Some serious adverse events have been reported. These include late ureteral obstruction requiring ureteral reimplantation, even years after DxHA injection[284,285]. The histopathologic evaluation of these cases revealed extensive inflammatory foreign body reaction. Apart from these isolated reports, DxHA has not been associated with major adverse events, and is the bulking agent of choice for many pediatric urologists[269].

With modern bulking agents and techniques, endoscopic injection treatment with one or more treatment sessions has a cumulative success rate of 75-100%[265-268,280-283]. These studies focused on VUR grades I-IV, as grade V is often thought to be an indication for open UR. However, a report found endoscopic injection treatment with DxHA to have an 89% success rate in abolishing grade V VUR[286]. Thus, endoscopic correction of VUR may be considered a potential treatment option in patients with any grade of VUR. In duplex systems, however, endoscopic injection treatment has a quite poor success rate; up to 83% of children required UR after injection treatment with collagen in a prospective study of 24 children due to persistent VUR[287].

Regardless of whether or not endoscopic correction of VUR is successful in terms of abolishing reflux, important factors in the treatment of VUR are the rate of UTI recurrence and new or progressive renal damage. A meta-analysis found the rate of cystitis to be low, at 6.0% and febrile UTI as low as 0.75%, after endoscopic correction of VUR[279]. In the Swedish reflux trial in children, the rate of febrile UTI recurrence among girls was 57% in the surveillance group and 23% in the endoscopically treated group. In boys, there was no significant difference in the rate of febrile UTI recurrence between the two groups[288]. The rate of new renal damage was not statistically significantly reduced by endoscopic correction of VUR in either boys or girls[67]. In a meta-analysis of two studies comparing endoscopic correction of VUR plus antibiotics to antibiotics only, the children in the first group had significantly fewer febrile UTIs during a five year follow-up (RR: 0.43 [95% CI: 0.27– 0.70])[66]. In a meta-analysis on endoscopic correction of VUR, only 0.4% of patients developed persistent ureteral obstruction[82].

7.3 Antimicrobial prophylaxis

The management of VUR is based on preventing infected urine from refluxing into the kidneys. This can be done by either abolishing reflux or by preventing infection. Antimicrobial prophylaxis (AMP) to prevent UTIs until VUR has spontaneously resolved

has the advantages of no invasiveness and hence no risk of ureteral obstruction or other complication of open UR or endoscopic correction of VUR. AMP does, however, require good compliance to treatment for a longer period of time from the parents, and entails the usual risks of antibiotics.

The most common antibiotic agent in AMP is trimethoprim–sulfamethoxazole, but trimethoprim, nitrofurantoin, cefalexin, and amoxicillin-clavulanic acid are also used, all at a reduced dose compared to the treatment of acute UTI.

In a recent meta-analysis, AMP significantly reduced the number of UTIs and febrile UTIs at 1-2 years (risk-ratios 0.68 [95% CI 0.39-1.17] and 0.77 [95% CI 0.47-1.24], respectively), compared to surveillance[248]. Though this relative risk reduction is statistically significant, the absolute reduction in UTI recurrences may not be significant, as the 95% confidence interval reaches on both sides of 1.0. Overall, AMP reduced the rate of recurrent afebrile and febrile UTIs, but the result had poor statistical significance. AMP also reduced the number of children developing new or progressive renal damage by 60%. The authors assumed a baseline risk of 8%, and calculated that 33 children would need to be treated with AMP for two to three years, in order to prevent one child developing a new or progressive renal scar[248]. A meta-analysis comparing endoscopic correction of VUR to AMP, found that the only significant difference was in the rate of VUR disappearance, and therefore recommended that children with significant VUR should be treated with AMP, and endoscopic correction should be considered only in case of frequent UTI recurrences during AMP, intolerance to AMP, or persistent significant VUR after several years of conservative treatment[289].

One of the major concerns surrounding AMP is compliance. In randomized studies, compliance has been reported at 71-88%[91,290,291], but there is some suspicion that this number may be driven up by the fact that these patients' parents had higher than average motivation due to being part of a trial. Thus, compliance may be even lower in patients not participating in a trial.

Even if the patient and the family comply fully to AMP, there may be recurrence of UTIs. In these cases, drug resistant pathogens have been found in up to 67-68% of patients on AMP compared to 25% receiving placebo[91,292]. With prophylactic doses, the rate of gastrointestinal symptoms, allergic skin reactions, upper respiratory tract infections or viral infections may be only slightly increased[91,292], and gastrointestinal symptoms are more common when using nitrofurantoin compared to trimethoprim-sulfamethoxazole[293].

Increasing antibiotic resistance in urine bacterial cultures has raised concern regarding the use of antibiotics and AMP in particular[294]. As a result, the use of probiotics as a second-line means of preventing UTIs has been suggested[10,295] Although studied thoroughly and proven effective in the prevention of gastrointestinal infections, evidence on the effectiveness of probiotics in preventing UTIs is scarce. One randomized study compared oral Lactobacillus acidophilus with trimethoprim-sulfamethoxazole, and found it equally effective in preventing both UTI recurrence and new renal damage in DMSA scan[295]. There was no difference in the scausative uropathogens. There was, however a significant difference in the rate of resistance to trimethoprim-sulfamethoxazole (43% vs. 100%) in favor of the group receiving probiotics. The role of probiotics

in the prevention of UTIs in patients with VUR remains unclear.

Cranberry juice and other cranberry products have been recommended for prevention of UTIs, particularly in women with recurrent UTIs. However, a recent Cochrane review on the topic showed that the consumption of cranberry products did not reduce the number of UTIs compared to placebo or no treatment[296]. In addition, many of the studies included in the review reported low compliance, which was attributed mainly to the poor palatability of cranberry juice. Consequently, cranberry products were not recommended for preventing recurrent UTIs.

7.4 Treatment of bladder and bowel dysfunction

Bladder and bowel dysfunction (DES, dysfunctional elimination syndrome) is a common finding in children with VUR. These functional bowel and bladder disturbances that are collectively referred to as DES include bladder instability, infrequent voiding, the Hinman syndrome and constipation[297]. Urodynamic dysfunction is characterized by voiding detrusor pressure of >40 cmH_20, reflex detrusor contractions during bladder filling, or incomplete bladder emptying. Dysfunctional voiding has been noted in as many as 97% of male infants and 77% of female infants after a UTI[298], and in 36-72% and 21-83% of infant females and males with primary VUR, respectively[50-52]. DES has been shown to be a risk factor for breakthrough UTIs, delayed reflux resolution, failure of surgical correction of VUR, and renal scarring[50,299,300]. It is also possible that VUR, partly by increasing the rate of UTI recurrence, may lead to a higher rate of DES, or that VUR and DES have a common developmental etiology[301].

The symptoms of DES are difficult to evaluate in children who are not yet toilet-trained. In toilet-trained children, DES may present as wetting, urgency, abnormally frequent or infrequent voiding, difficulty in voiding, diffuse abdominal pain, constipation, and soiling[302-305].

DES is diagnosed by measuring the function of the lower urinary tract in a study called urodynamics. In addition to the urodynamic study, any underlying anatomical or neurological condition must be ruled out. The study is performed as follows. The child is instructed to empty the bladder. A catheter is then inserted in the bladder and the volume of residual urine is measured. Urine may then be sent to microscopy and culture. The bladder is then filled with saline, until the child has the urge to void. Bladder capacity is measured. The child is then allowed to void. In addition to measuring the urine flow, intravesical and rectal pressures are measured by catheters during voiding to identify the site of possible abnormality. The study may include a measurement of the strength of the urethral sphincter contraction, an EMG, or fluoroscopy, according to the specific suspicion of abnormalities in each case. A perioperative antibiotic is often given to prevent iatrogenic UTI.

The role of urodynamics and whether or not the results have a significant impact on the treatment of the child is controversial, even though some recommend it as a part of the routine studies of children with UTI[20,306,307]. One of the biggest problems with urodynamic studies is its poor consistency of the interpretations[308].

The treatment options of DES are behavioral therapy, anticholinergic medication,

alpha blockers and the treatment of possible constipation[299]. The treatment of DES with anticholinergic drugs has been reported to reduce the rate of UTI recurrences and improve the resolution rate of VUR significantly when compared to only antibiotics[241]. Behavioral and medical treatment of constipation results in a significant reduction in UTI recurrences and enuresis[242-244].

7.5 Surveillance

As stated previously, VUR, especially low-grade of VUR, has a strong tendency to resolve spontaneously over time[82]. Taking into account the relatively limited ability of AMP or surgical correction of VUR to prevent renal damage, one strategy is to simply monitor the child for any symptoms of UTI recurrences and schedule follow-up RBUS and VCUG annually until VUR has resolved. If any fever or symptoms of UTI develop, a urine sample is taken at a very low threshold and prompt antibiotic treatment is initiated if needed. Surveillance may be considered especially in cases of low-grade VUR. Some pediatricians have suggested that even high-grade VUR is of little or no consequence and should not be sought or treated in any case[309]. Most pediatric urologists do not agree with this.

8. GUIDELINES FOR IMAGING CHILDREN WITH UTI

Due to the invasive nature, radiation and cost of some of the imaging modalities used in imaging children with UTI, many guidelines have been formulated in an attempt to direct the imaging studies to those patients who may benefit most of them. Recent studies[10,121,310] have questioned both the significance of VUR as a phenomenon and the possibility to affect the prognosis of VUR patients by treating them with AMP or endoscopic correction of VUR. This in turn has led to several guidelines adopting a more selective approach particularly regarding routine use of VCUG to identify VUR[17-19,311-313].

8.1 NICE guidelines

In 2007, the National Institute for Health and Clinical Excellence issued their guidelines for imaging children with UTI. While the 1991 UK guidelines encouraged performing imaging studies in all young children with UTI[314], the new 2007 guidelines advocate a rather restrictive approach to imaging, and even limit the use of RBUS in infants and children older than 6 months old to those with atypical or recurrent UTI[17]. The detailed guidelines for imaging studies according to NICE are described in tables 1-4.

Table 2. NICE recommendations for imaging infants younger than 6 months with UTI. Modified from[17].

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
RBUS during the acute infection	No	Yes[c]	Yes
RBUS within 6 weeks	Yes[b]	No	No
DMSA 4-6 months following UTI	No	Yes	Yes
VCUG	No	Yes	Yes

[a] See table 5 for definition

[b] If abnormal consider VCUG

[c] In an infant or child with a non-E. coli infection, responding well to antibiotics and with no other features of atypical infection, the RBUS can be requested on a non-urgent basis to take place within six weeks

Table 3. NICE recommendations for imaging infants and children 6-36 months old with UTI. Modified from[17].

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
RBUS during the acute infection	No	Yes[c]	No
RBUS within 6 weeks	No	No	Yes
DMSA 4-6 months following UTI	No	Yes	Yes
VCUG	No	No[b]	No[b]

[a] See table 5 for definition

[b] While VCUG should not be performed routinely, it should be considered if the following features are present:

- Dilatation on RBUS
- Poor urine flow
- Non-E. coli infection
- Family history of VUR

[c] In an infant or child with a non-E. coli infection, responding well to antibiotics and with no other features of atypical infection, the RBUS can be requested on a non-urgent basis to take place within six weeks

Table 4. NICE recommendations for imaging children 3 years or older. Modified from[17].

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
RBUS during the acute infection	No	Yes[b c]	No
RBUS within 6 weeks	No	No	Yes[b]
DMSA 4-6 months following UTI	No	No	Yes
VCUG	No	No	No

[a] See table 5 for definition

[b] RBUS in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after voiding

[c] In an infant or child with a non-E. coli infection, responding well to antibiotics and with no other features of atypical infection, the RBUS can be requested on a non-urgent basis to take place within six weeks

Table 5. Definitions of atypical and recurrent UTI according to NICE. Modified from[17].

Atypical UTI includes
• Seriously ill • Poor urine flow • Abdominal or bladder mass • Raised plasma creatinine • Septicemia • Failure to respond to suitable antibiotics within 48 hours • Non-E. coli infection
Recurrent UTI includes
• Two or more episodes of UTI with acute pyelonephritis/upper UTI, or • One episode of UTI with acute pyelonephritis/upper UTI plus one or more episode of UTI with cystitis/lower UTI, or • Three or more episodes of UTI with cystitis/lower UTI

8.2 AAP guidelines

The earlier, 1999 AAP guidelines[3,15] recommended RBUS for all children aged 2 to 24 months with febrile UTI. VCUG or DRC was 'strongly encouraged'. While the updated 2011[18]guidelines still recommend RBUS for all children aged 2 to 24 months with first febrile (≥38.0°C) UTI, VCUG is no longer routinely recommended. Instead, VCUG is now recommended only if RBUS reveals hydronephrosis, scarring or other findings that would suggest either high-grade VUR or obstructive uropathy, as well as in 'other atypical or complex clinical situations' (Figure 13). AAP does not go on to further clarify these 'other atypical or complex clinical situations', but the atypical situations described by NICE[17] may be considered such situations. VCUG is also recommended in the case of a recurrent febrile UTI.

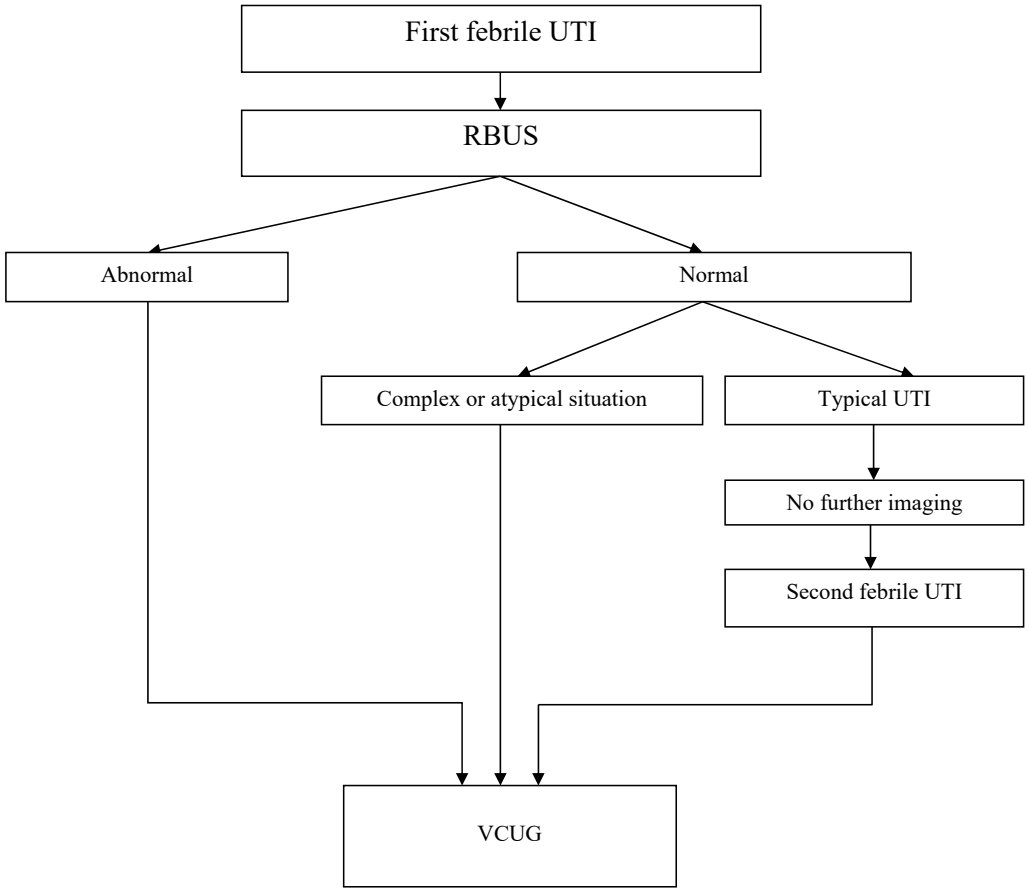

Figure 13. AAP algorithm for imaging studies in infants and children aged 2-24 months with first febrile UTI. Modified from[18].

8.3 EAU guidelines

The European Association of Urology updated their guidelines most recently in 2016[20]. The updated guidelines recommend RBUS for all infants diagnosed with febrile UTI. VUR must be excluded in all infants and girls, and in case of suspicion of VUR and/or pyelonephritis. In other words, only boys over 12 months old, with no suspicion of VUR or pyelonephritis may be followed without studies to identify VUR. Though the guidelines consider VCUG to be the gold standard for diagnosing VUR, they also state that 'DMSA scanning may be used as a first-line diagnostic procedure'[20].

8.4 Italian Society of Pediatric Nephrology guidelines

The Italian Society of Pediatric Nephrology (ISPN) issued their updated guidelines in 2011[19]. The guidelines are limited to infants and children aged 2-36 months with febrile (≥38.0°C) UTI. RBUS is recommended in all patients. Further imaging, consisting of VCUG and a DMSA scan is recommended in case of abnormal RBUS or other risk factors, or after a febrile UTI recurrence (Figure

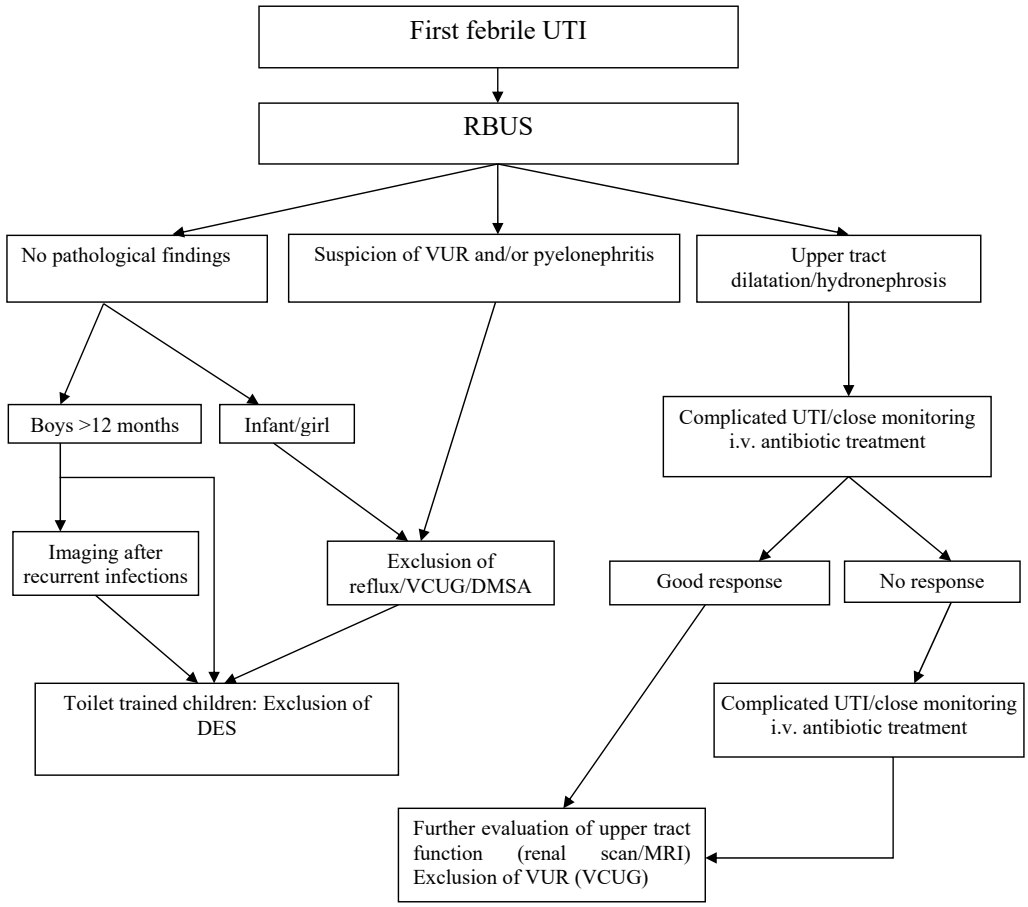

Figure 14. EAU algorithm for managing a first febrile UTI. Modified from[20].

15). Compared to the NICE guidelines, the ISPN guidelines are very similar, the main difference being that RBUS is recommended in all patients with febrile UTI. The ISPN guidelines along with the EAU guidelines are the only strategies where gender affects the decision to perform a VCUG.

8.5 Finnish Current Care Guidelines – Käypä hoito

The Current Care Guidelines21 recommend RBUS for all children with first UTI, regardless of the level of infection, and with no specification of age. A VCUG should be considered only in case of abnormal RBUS findings. Even though the guidelines state that younger age at first UTI and higher level of infection raise suspicion of anatomical abnormalities of the urinary tract, no other indications for VCUG are given. Indications for DMSA scanning are not given. In fact, there is no mention of any imaging modalities other than RBUS and VCUG in the guidelines.

8.6 Other imaging strategies

In addition to the official national guidelines, some studies have been made on alternative imaging strategies. The main objective of these strategies is to identify patients

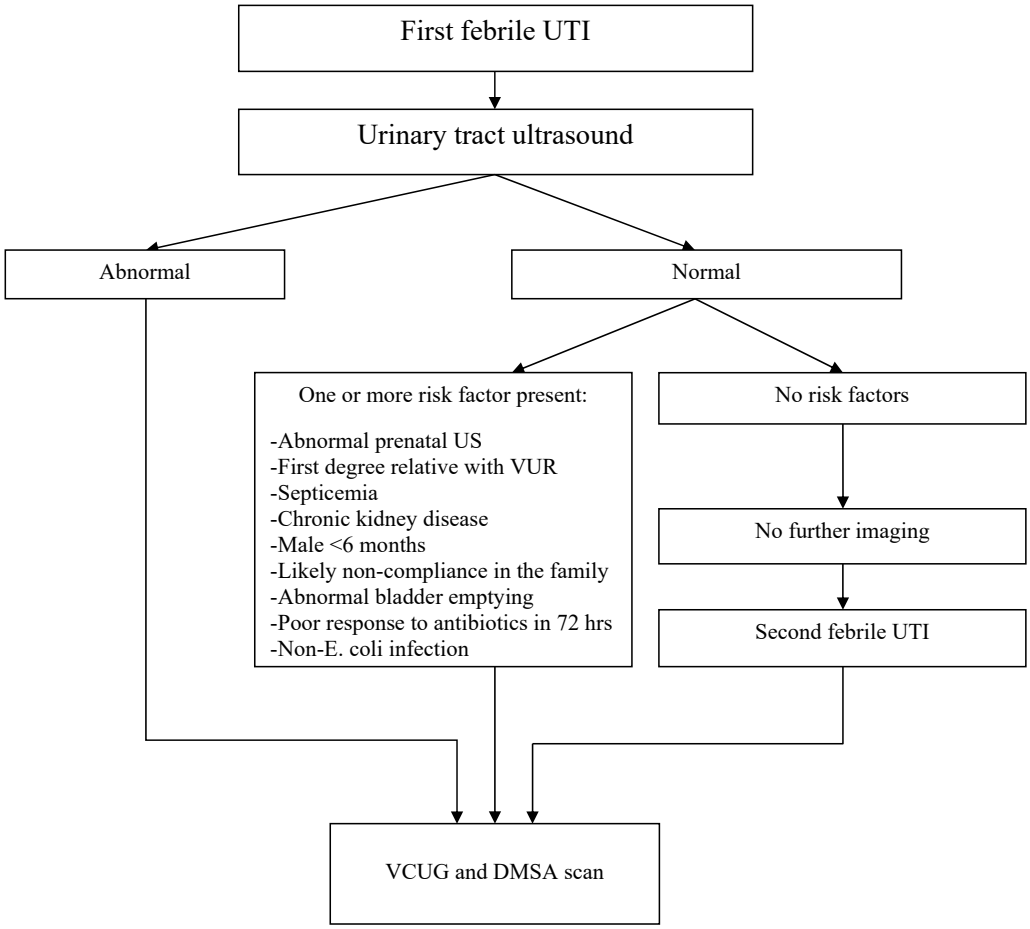

Figure 15. ISPN algorithm for imaging studies after a first febrile UTI. Modified from[19].

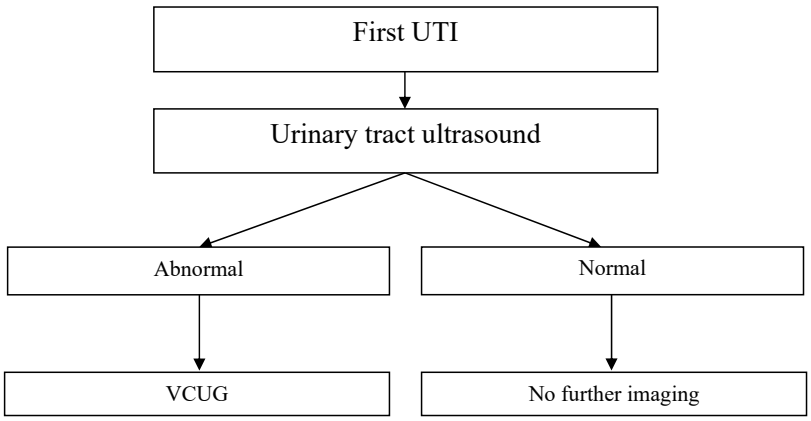

Figure 16. Finnish Current Care Guidelines algorithm for imaging studies after a first UTI. Modified from[21].

most likely to have VUR and to reduce the amount of unnecessary VCUGs.

8.6.1 The top-down approach

In the top-down approach, DMSA scanning (and often RBUS) is performed as a first-line imaging study in children with UTI, and only if abnormalities are found, a VCUG is performed. The initial reports of this strategy were very promising, with sensitivity for detecting high-grade VUR reaching as high as 96%[316]. However, a meta-analysis on the subject showed that with a sensitivity and specificity of 79% and 53%, respectively, for identifying patients with high-grade VUR, DMSA scanning is insufficient as a screening study for VUR[317] The combined strategy of performing both RBUS and a DMSA scan in all children with UTI, and performing VCUG in the case of abnormal findings in either DMSA scan or RBUS has a sensitivity of 83-100% and a NPV of 92-100% for identifying patients with high-grade VUR[318-321] While the top-down approach may have higher sensitivity for detecting VUR and high-grade VUR, it entails a remarkably higher economic and radiation cost compared to other imaging strategies[322].

8.6.2 The procalcitonin strategy

Procalcitonin is traditionally used as a biomarker of serious bacterial infection, but it has also been studied in children with UTI. Raised procalcitonin levels have been found in VUR patients, and a meta-analysis found raised procalcitonin (≥0.5ng/ml) to have a sensitivity and specificity of 83% and 43%, respectively, for identifying patients with high-grade VUR[323]. In another meta-analysis raised procalcitonin had a sensitivity and specificity of 79% and 50%, respectively, for identifying patients who went on to develop renal scars on late DMSA scanning[324]. In the same study, raised procalcitonin was also associated with acute pyelonephritis on DMSA scanning, with a sensitivity and specificity of 71% and 72%, respectively. The strategy of performing VCUG and late DMSA scanning only when serum procalcitonin is raised (≥1.0ng/ml) may, however, result in significantly higher economic and radiation cost compared to the AAP and NICE guidelines[325].

In addition to procalcitonin, variations in uroplakin (UP) gene expression have been associated with VUR. UPIII messenger ribonucleic acid (mRNA) up-regulation and decreased UPIb mRNA levels have been associated with VUR[326,327]. UP investigations are not yet, however, in clinical use, but they may have some potential as a non-invasive screening test for VUR, with a sensitivity and specifity of up to 77.8 and 76.3%, respectively[326]. Further studies are needed to validate their use.

9. AIMS

VCUG is a stressful radiation study, that requires catheterization of the child. In order to reduce the number of unnecessary VCUGs, many guidelines[17-19,311-313] have been formulated, attempting to direct imaging studies to a selected subgroup of patients that may benefit most from them. Limiting imaging studies to only a subpopulation of children with UTI has the risk of missing patients with significant remediable urological anomalies, which must be weighed against the benefit of avoiding unnecessary imaging studies.

The aims of the study were set as the following:

1. To determine the potential consequences of following the NICE guidelines for imaging children under 3 years old with UTI.

2. To determine the potential consequences of following the AAP guidelines for imaging children aged 2-24 months with first febrile UTI.

3. To evaluate factors associated with abnormal RBUS and VCUG, and recurrence of UTIs after a first febrile UTI before the age of 3 years.

4. To assess the value of abnormal RBUS and particularly dilation on RBUS in predicting VUR.

10. MATERIALS AND METHODS

The first three manuscripts' patient materials were subsets of a large retrospective cohort of children. The fourth manuscript was a meta-analysis of 14 original studies on the predictive value of RBUS for the presence of VUR on VCUG.

10.1 Retrospective analyses of children under 3 years old with UTI

We reviewed the patient records of all children treated for UTI in Turku University Hospital between January 1st 2000 and December 31st 2009. Exclusion criteria included 1) previously diagnosed urological abnormalities (*e.g.* hydronephrosis in antenatal ultrasound), 2) any neurological or anatomical abnormalities known to be associated with recurrent UTIs, VUR or renal damage, 3) not having underwent RBUS, and 4) having had the imaging studies performed in another healthcare district or moving to another healthcare district before the imaging studies.

All patients' antenatal US results were reviewed and found normal. All patients' UTI diagnoses were evaluated. A CRP level of 40 mg/l or higher and a fever of 38.0°C or higher were the criteria for pyelonephritis. Signs of renal inflammation on RBUS were also considered confirmatory to the diagnosis of pyelonephritis. Phimosis was determined as obstructed urine flow due to constriction of the orifice of the prepuce, with ballooning of the prepuce, either seen by the physician or reported by the parents. Abnormal RBUS was defined as any abnormal finding as reported by the radiologist, *e.g.* urinary tract dilatation, renal parenchymal defects, abnormal kidney size, bladder diverticulum, ureteral duplication, ureterocele, renal cyst, nephrocalcinosis, and urolithiasis.

Antimicrobial treatment was carried out in accordance with routine procedures in our department. The antibiotic drug of choice was determined according to the antibiogram in each case. Empiric treatment was often started before the antibiogram was available, and the drug of choice for pyelonephritis was intravenous cefuroxime and for cystitis an oral antibiotic, occasionally preceded by a single intramuscular injection of ceftriaxone. Most patients with pyelonephritis received intravenous cefuroxime for three days, followed by an oral antibiotic after discharge from the hospital, for a total treatment period of 10 days. The most commonly used oral antibiotics were trimethoprim–sulfamethoxazole, amoxicillin–clavulanic acid and cefalexine.

VUR was classified according to the international system for radiographic grading of vesicoureteric reflux[88], and the highest grade detected in all studies was recorded for the purposes of this study. High-grade VUR was determined as VUR grades III-V. The common finding in nuclear VCUG (nVCUG), "VUR, reaching the level of the kidney" without reference to dilation, was determined as grade II. However, data regarding dilation in RBUS were combined to the nVCUG finding to determine the grade of VUR as accurately as possible. If the patient had bilateral VUR, the higher grade of the two recordings was used for classifications.

Data were gathered regarding fever, plasma C-reactive protein (CRP) levels, plasma creatinine levels, urine cultures, blood bacterial cultures, family history of VUR, abnormalities in urine flow, findings in RBUS and VCUG, anti-microbial prophylaxis,

anti-reflux procedures and other urological procedures and recurrence of UTIs. Mean follow-up time was 8.5 years (range 3.9–13.9 years).

10.1.1 NICE guidelines for imaging children under 3 years old with UTI

We gathered data on all children with culture proven UTI before the age of three years, treated in Turku University Hospital during the years 2000-2009. All patients UTI diagnoses were evaluated, and were considered certain if there was both pyuria and bacterial growth of 100,000 CFU/ml in two urinary bag specimens or clean catch urine samples, or if there was any growth of a single uropathogen in an SPA sample. Mean follow-up time was 8.5 years (range 3.9–13.9 years). Indications for RBUS and VCUG were determined according to the NICE guidelines[17], with the premise that whenever a study was to be considered, it would be performed. We determined the possible consequences of applying the NICE guidelines to clinical practice in our cohort.

Statistical comparisons between any two groups were done using Fisher's exact test. P-values of <0.05 were considered statistically significant (two-tailed). The statistical analyses were generated using JMP software (version 9.0 for Windows).

10.1.2 AAP guidelines for imaging children aged 2-24 months with UTI

We gathered data on all children with culture proven UTI at the age of 2-24 months, treated in Turku University Hospital during the years 2000-2009. All patients UTI diagnoses were evaluated, and were considered certain if there were both urinalysis results compatible with infection (pyuria and/or bacteriuria) and bacterial growth of at least 50,000 CFU/ml. The term 'febrile' was determined according to the AAP guidelines as ≥38.0°C. Mean follow-up time was 8.1 years (range 3.9–13.9 years). Indications for RBUS and VCUG were determined according to the AAP guidelines[18]. We determined the possible consequences of applying the AAP guidelines to clinical practice in our cohort.
Statistical comparisons between any two groups were done using Fisher's exact test. P-values of <0.05 were considered statistically significant (two-tailed). The statistical analyses were generated using JMP software (version 9.0 for Windows).

10.1.3 Predictive factors for abnormal imaging and infection recurrence after a first febrile UTI

We gathered data on all children with a first culture proven febrile UTI before the age of 3 years, treated in Turku University Hospital, who underwent both RBUS and VCUG. The UTI was considered certain if there was any growth of a single uropathogen in a suprapubic aspiration, or growth of a single uropathogen in the amount of ≥100,000 CFU/ml in one or more samples of clean catch urine or bag specimen. The term 'febrile' was determined as ≥38.0°C.
We determined statistical correlations between clinical factors and 1) abnormal RBUS results, 2) VUR on VCUG, and 3) UTI recurrence, in order to identify patients potentially at higher risk for abnormal imaging and/or recurrent UTIs. Based on these correlations and current knowledge on the predisposing factors for VUR, we formulated a scoring system for predicting the risk for VUR and high-grade VUR.

Data are described as frequencies and proportions. In addition, median was calculated for age. To determine important associated factors for abnormal RBUS, VUR, high-

grade VUR, and UTI recurrence, binary logistic regression models for these responses were generated with multiple factors included. The abnormal RBUS model included non-E. coli infection, gender, poor response to antibiotics, positive blood culture, atypical infection, poor urine flow, phimosis, and family history of VUR as categorical factors, and age, fever, and CRP as numerical factors. The VCUG model included non-E. coli infection, atypical UTI, UTI recurrence, abnormal RBUS, gender, raised plasma creatinine, positive blood culture, poor response to antibiotics, poor urine flow, phimosis, and family history of VUR as categorical factors, and age, fever, and CRP as numerical factors. The UTI recurrence model included non-E. coli infection, gender, poor response to antibiotics, positive blood culture, abnormal RBUS as categorical factors, and age, fever and CRP as numerical factors. Mean follow-up time was 9.8 years (range 3.9–13.9 years).

For significant predictors of VUR and high-grade VUR, sensitivity (%), specificity (%), positive predictive value (PPV) and negative predictive value (NPV) were also calculated.

P-values of <0.05 were considered statistically significant (two-tailed). The statistical analyses were generated using SAS software (version 9.3 for Windows).

10.2 Value of RBUS in predicting VUR

We conducted a meta-analysis on the value of abnormal RBUS after a first UTI in predicting VUR.

10.2.1 Data sources and searches

Criteria for considering studies for this review were the following: 1) participants: children under 16 years old, with first UTI, 2) index test: standard RBUS, with abnormal finding defined exclusively or primarily as dilatation of the urinary tract, 3) target condition: VUR of any grade, 4) reference standard: VCUG. Exclusion criteria were the following: 1) studies focusing exclusively on a particular grade of VUR, 2) results reported per kidney and not per person, 3) any known urinary tract anomaly, and 4) other than standard RBUS techniques.

A systematic literature search was conducted using the databases Medline (via PubMed), Embase, Web of Science and Cochrane Controlled Trials Register (CENTRAL), with no restrictions by date, but limited by age group, language (only English), and full-text availability. The search strategy is presented in Table 6.

10.2.2 Study selection

The meta-analyses were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines. The identified records were recorded to Endnote (Endnote 7.3.1, Thomson Reuters, NY, USA) and one author selected the relevant records (Figure 17). The results of exclusion were presented to the entire team for discussion. Any disagreements were resolved either by consensus or by the senior researcher.

10.2.3 Quality assessment

The methodological quality of the studies was assessed according to the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool[329]. This tool consists of four key domains dealing with patient selection, index test, reference standard, and patient flow through the study, including timing of both the index test and the reference standard. Each domain was evaluated in terms of the risk of bias, and the first three do-

Table 6. Search strategy. Modified from[328]

Database	Strategy
Medline (via PubMed)	((("Ultrasonography"[Mesh] AND "Vesico-Ureteral Reflux"[Mesh] AND "Urography"[Mesh]))) OR ((*sonograp*[TIAB] OR ultrasound* [TIAB]) AND *reflux*[TIAB]) AND (hasabstract[text] AND English[lang] AND (("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) OR "infant"[MeSH Terms])) AND (sensitivity OR specificity OR "true negative" OR "true positive" OR "false negative" OR "false positive")
Embase	'cystography'/exp AND 'echography'/exp AND 'vesicoureteral reflux'/exp AND ([child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim) AND 'article'/it
Web of Science	TS = ((*sonograp* OR ultrasound*) AND *reflux*) AND TS = (sensitivity OR specificity) AND TS = (child* OR infant* OR pediatr* OR paediatr) AND TS = (infection): Timespan: All years; Search language=Auto; Refined by: RESEARCH AREAS: (PEDIATRICS)
Central	#1 MeSH descriptor: [Ultrasonography] explode all trees #2 MeSH descriptor: [Vesico-Ureteral Reflux] explode all trees #3: #1 AND #2 in TRIALS

mains were also assessed in terms of concerns regarding applicability. Risk of bias was determined 'low', 'high' or 'unclear'. If the answers to all signaling questions for a domain were 'low' then the risk of bias was judged low. Otherwise, a study was considered as being 'at risk of bias' or as having 'concerns regarding applicability'. Two independent reviewers conducted the quality assessment, and any disagreements between reviewers were resolved by consensus or by the senior researcher.

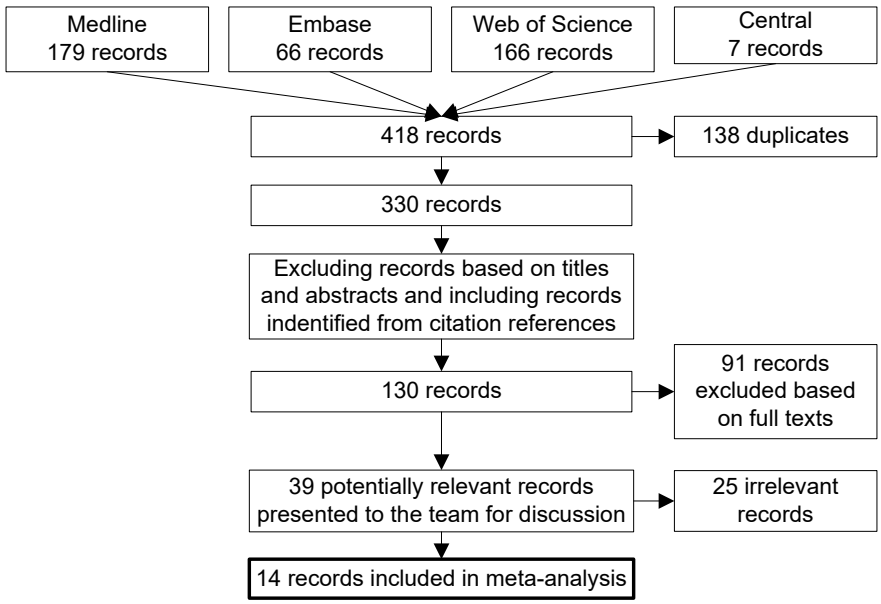

Figure 17. Flowchart of study selection process. Modified from[328].

10.2.4 Data synthesis and analysis

According to the Cochrane collaboration recommendations, data were extracted using a standardized form[330]. A random effects meta-analysis was used to quantify the pooled accuracy of included studies. The pooled results were reported as sensitivity, specificity, positive and negative likelihood ratios, a diagnostic odds ratio (DOR), and a summary receiver operating characteristic curve (SROC) along with an area under the curve (AUC). The main results were presented as forest plots with the corresponding 95% confidence intervals.

The area under the curve of 0.91-1 was considered excellent, 0.81-0.90 good, 0.71-0.80 fair, 0.61-0.70 poor, and 0.51-0.60 was considered fail. Likelihood ratio of >10 was considered large, 5-10 moderate, 2-5 small, 1-2 minimal increase in the likelihood of disease, 1 no change, 1-0.5 minimal, 0.5-0.1 small, 0.2-0.1 moderate, and <0.1 large decrease in the likelihood of disease.

Heterogeneity was tested by using the Chi square, Q, T^2, and I^2 statistics. Due to software limitations, potential publication bias was not evaluated. All calculations for the meta-analysis were performed using the Meta-Analysis of Diagnostic and Screening Test (Meta-DiSc) program, version 1.4 (freeware), (University Hospital Ramon y Cajal, Madrid, Spain).

11. RESULTS

11.1 NICE guidelines for imaging children under 3 years old with UTI

Altogether, there were 672 children with culture proven UTI before the age of 3 years. These included 292 boys (211 aged under 6 months, 81 aged 6-36 months), and 380 girls (117 aged under 6 months, 263 aged 6-36 months). The UTI was termed 'atypical' in 126 children (19%). The NICE criteria for 'recurrent UTI' were fulfilled in 29 patients (4.3%).

11.1.1 RBUS

All 672 patients underwent RBUS, but only 356 patients (53%) had an indication for NICE according to the NICE guidelines. The results were abnormal in 142 patients (21%), including 92 (14%) with dilatation of the urinary tract. Of the 316 patients who underwent RBUS without an indication, the result was abnormal in 44 (14%), including 21 (6.6%) with dilation. The same numbers in the group with an indication for RBUS were 27% and 20%, respectively (table 7).

11.1.2 VCUG

VCUG was performed in 372 patients (55%). VUR was found in 125 (34%) of these, including 64 (17%) with high-grade VUR. A NICE indication for VCUG was found in 165 patients (25%), of whom 129 underwent VCUG (table 7). Of the 243 patients who underwent a VCUG without an indication, 59 (24%) had VUR, including 20 (8.2%) with high-grade VUR. The same numbers in the group with an indication for VCUG were 51% and 34%, respectively. Patients with a NICE indication for VCUG were more likely to have both VUR and high-grade VUR ($p<0.0001$ for both).

In the older age group, boys were more likely to fulfill the indication criteria for VCUG ($p=0.0026$). In the younger age group, there was no difference between boys and girls in the likelihood of fulfilling the indication criteria ($p=0.16$). In both gender groups, younger patients were more likely to fulfill the indication criteria ($p=0.0002$ for boys and $p<0.0001$ in girls).

11.1.3 Treatment of VUR and other urological anomalies

AMP was prescribed to 110 of the 125 patients (88%) with VUR, 49 of whom (45%) had undergone VCUG without an indication. AMP was, however, prescribed quite liberally, and 49 of the 61 patients (80%) with only low-grade VUR received AMP.

Endoscopic correction of VUR was performed on 30 patients, of whom 13 (43%) did not have an indication for VCUG. Of these 30 patients, two had only low-grade VUR. Open UR was performed on five patients, one of whom did not have an indication for any imaging studies.

A nephrectomy was performed on two patients. Both had abnormal RBUS findings and no indication for any imaging studies. Hydronephrosis deteceted in RBUS led to seven patients undergoing pelveoplasty for obstruction of the ureteropelvic junction discovered in further imaging studies. Of these patients, one had no indication for any imaging studies. Ureterocele was surgically treated in three patients, all of whom were diagnosed by RBUS for which they had an indication. A posterior urethral valve was endoscopically ablated in two patients after a RBUS showing dilation of the urinary tract

Table 7. Data on 672 children with UTI. Modified from[331].

Group	Boys <6 months	Girls <6 months	Boys 0.5-3 years	Girls 0.5-3 years	All patients
Total number of patients	211	117	81	263	672
Indication for US	192	104	19	41	356
US performed	211	117	81	263	672
Abnormal US	59	29	15	39	142
Dilation	43	21	7	21	92
Indication for VCUG	90	40	16	19	165
VCUG performed	152	72	37	111	372
VUR on VCUG	46	30	16	33	125
Low-grade VUR	24	13	6	18	61
High-grade VUR	22	17	10	15	64
AMP for VUR	44	27	12	27	110
Surgery	15	10	8	16	49
Endoscopic injection treatment[a]	4	8	3	15	30
Ureteral reimplantation	1	3	1	0	5

[a]Two patients underwent endoscopic injection treatment despite being diagnosed with only low-grade VUR

led to further investigations. Both patients had a positive indication for RBUS. In one patient, a nephrostomy was performed due to a renal empyema that was diagnosed by RBUS for which the patient had an indication. A circumcision was performed on one patient with poor urine flow due to phimosis (table 7).

11.1.4 Missed diagnoses and avoided unnecessary imaging studies

If the NICE guidelines had been applied to clinical practice in our cohort of 672 patients, 44 of the 142 patients (31%) with abnormal RBUS findings would have been missed. These included 21 of the 92 patients (23%) with dilatation on RBUS. The benefit would have been in not performing RBUS in 272 of the 530 patients (51%) with normal RBUS findings.

Of the 125 patients with VUR, 59 (47%) would have been missed, including 20 of the 64 patients (31%) with high-grade VUR. The benefit would have been in not performing VCUG in 184 of the 247 patients (74%) with no VUR on VCUG. Significant diagnoses were missed in all sex and age groups (table 8). On the other hand, it is worth mentioning that some pediatric urologists consider grade IV-V VUR to be of the most importance, and 7 of the 22 patients (32%) with grade IV-V VUR would have been missed. This number is comparable to the 31% of high-grade VUR cases missed.

Following the NICE guidelines would have led to 49 of 110 patients (45%) not being prescribed prophylaxis. Surgical treatment would not have been performed in 17 of 49 patients (35%), including 13 of the 30 patients (43%) who underwent endoscopic correction of VUR and one of the five patients (20%) who underwent open UR.

11.2 AAP guidelines for imaging children aged 2-24 months with UTI

Altogether, there were 394 children with culture proven UTI at the age of 2-24 months.

Table 8. Clinical consequences of following the NICE guidelines in 672 children with UTI. Modified from[332].

Group	Boys <6 months	Girls <6 months	Boys 0.5-3 years	Girls 0.5-3 years	All patients
RBUS avoided in patients with normal RBUS results	15	13	54	190	272
Abnormal RBUS result missed	4	0	8	32	44
Urinary tract dilatation missed	2	0	3	16	21
VCUG avoided in patients with no VUR	65	30	18	71	184
VUR on VCUG missed	16	8	10	25	59
Low-grade VUR missed	13	5	4	17	39
High-grade VUR missed	3	3	6	8	20
AMP for VUR not assigned	15	7	8	19	49
Surgery not performed	1	2	4	10	17
Endoscopic injection treatment for VUR not performed[a]	1	2	1	9	13
Ureteral reimplantation not performed	0	0	1	0	1

[a]Two patients underwent endoscopic injection treatment despite being diagnosed with only low-grade VUR

These included 147 boys and 247 girls. 344 of these patients (87%) had a fever of ≥38.0°C.

11.2.1 RBUS

All 394 patients underwent RBUS, but only 344 (87%) had an indication. The results were abnormal in 87 patients (22%), including 53 (13%) with dilatation of the urinary tract (table 9). Of the 50 patients who underwent RBUS without an indication, the result was abnormal in 7 (14%), including 5 (10%) with dilation. The same numbers in the group with an indication for RBUS were 23% and 14%, respectively.

11.2.2 VCUG

VCUG was performed in 206 patients (52%). VUR was found in 72 (35%) of these, including 36 (17%) with high-grade VUR. An AAP indication for VCUG was found in 126 patients (32%), of whom 100 underwent VCUG (table 9). Of the 106 patients who underwent a VCUG without an indication, 24 (23%) had VUR, including 6 (5.6%) with high-grade VUR. The same numbers in the group with an indication for VCUG were 48% and 30%, respectively. Patients with an AAP indication for VCUG were more likely to have both VUR (p=0.0001) and high-grade VUR (p<0.0001).

11.2.3 Treatment of VUR and other urological anomalies

Antimicrobial prophylaxis was prescribed to 60 of the 72 patients with VUR, 16 of whom had undergone VCUG without an indication. AMP was, however, prescribed quite liberally, and 26 of the 36 patients with only low-grade VUR received AMP.

Endoscopic correction of VUR was performed on 20 patients, of whom four did not have an indication for VCUG. Of these 20 patients, one had only low-grade VUR. Open UR was performed on four patients, all of whom had an indication for VCUG.

Table 9. Data on 394 children with UTI. Modified from[333].

Group	Boys	Girls	All patients
Total number of patients	147	247	394
Indication for US	119	225	344
US performed	147	247	394
Abnormal US	38	49	87
Dilation	22	31	53
Indication for VCUG	52	74	126
VCUG performed	86	120	206
VUR on VCUG	33	39	72
Low-grade VUR	17	19	36
High-grade VUR	16	20	36
AMP for VUR[a]	27	33	60
Surgery	16	18	34
Endoscopic injection treatment[a]	5	15	20
Ureteral reimplantation	2	2	4

[a]26 of the 60 patients that were prescribed AMP had only low-grade VUR

A nephrectomy was performed on two patients – both had abnormal RBUS findings with an AAP indication for RBUS. Hydronephrosis deteceted in RBUS led to four patients undergoing pelveoplasty for obstruction of the ureteropelvic junction. Of these patients, one had no indication for any imaging studies. Ureterocele was surgically treated in three patients, all of whom were diagnosed by RBUS for which they had an indication. A nephrostomy was performed on one patient due to a renal empyema that was diagnosed by RBUS for which the patient had a positive indication. A circumcision was performed on one patient with poor urine flow due to phimosis (table 9).

11.2.4 Missed diagnoses and avoided unnecessary imaging studies

If the AAP guidelines had been applied to clinical practice in our cohort of 394 patients, 7 of the 87 patients (8.0%) with abnormal RBUS findings would have been missed. These included 5 of the 53 patients (9.4%) with dilatation on RBUS. The benefit would have been in not performing RBUS in 43 of the 307 patients (14%) with normal RBUS findings.

Of the 72 patients with VUR, 24 (33%) would have been missed, including 6 of the 36 patients (17%) with high-grade VUR. The benefit would have been in not performing VCUG in 82 of the 134 patients (61%) with no VUR on VCUG.

Following the AAP guidelines would have led to 16 of 60 patients (27%) not being prescribed AMP. Surgical treatment would not have been performed in 5 of 34 patients (15%), including 4 of the 20 patients (20%) who underwent endoscopic correction of VUR (table 10).

11.3 Predictive factors for abnormal imaging and infection recurrence after a first febrile UTI in children

In total, there were 282 patients with culture proven febrile (≥38.0°C) UTI, who underwent both RBUS and VCUG, treated

Table 10. Clinical consequences of following the AAP guidelines in 394 children with first UTI. Modified from[333].

Group	Boys	Girls	All patients
RBUS avoided in patients with normal RBUS results	22	21	43
Abnormal RBUS result missed	6	1	7
Urinary tract dilatation missed	4	1	5
VCUG avoided in patients with no VUR	38	44	72
VUR on VCUG missed	12	12	24
Low-grade VUR missed	10	8	18
High-grade VUR missed	2	4	6
AMP for VUR not prescribed[a]	9	7	16
Surgery not performed	2	3	5
Endoscopic injection treatment for VUR not performed[b]	1	3	4

[a]11 of the 16 patients that were prescribed AMP had only low-grade VUR
[b]One of the three girls who underwent endoscopic injection treatment had only low-grade VUR

in Turku University Hospital between January 1st 2000 and December 31st 2009, before the age of 3 years. These included 135 boys (108 younger than 6 months, 27 aged 6 to 36 months) and 147 girls (55 younger than 6 months, 92 aged 6 to 36 months).

Fever was 39.0°C or higher in 190 patients (67%). Fever was 40.0°C or higher in 62 patients (22%). Plasma CRP levels were measured in 276 patients (98%), and were higher than 40 mg/l in 203 of these (74%). Blood bacterial cultures were taken in 252 patients (89%), and were positive in 17 of these (6.7%). Plasma creatinine levels were measured in 94 patients (33%), and were raised in 29 of these (31%).

Atypical UTI was noted in 82 patients (29%), of which 77 (27%) had an atypical UTI before imaging studies. The uropathogen was other than E. coli in 36 patients (13%), of which 31 (11%) had a non-E. coli infection before imaging studies (Table 11). Poor urine flow during the first UTI was present in three patients (1.1%). Pathologic,

Table 11. Causative pathogens in 282 children with UTI. Modified from[334].

	Number (%)
Escherichia coli	251 (89%)
Klebsiella pneumoniae	7 (2.5%)
Klebsiella oxytoca	5 (1.8%)
Enterococcus faecalis	5 (1.8%)
Enterobacter cloacae	5 (1.8%)
Streptococcus agalactiae	3 (1.1%)
Pseudomonas aeruginosa	3 (1.1%)
Haemophilus parainfluenzae	1 (0.4%)
Streptococcus mitis	1 (0.4%)
Coagulase negative streptococcus	1 (0.4%)

Table 12. Data on 282 children aged 0-36 months with first febrile UTI. Modified from[334].

	Abnormal (%)
Fever	282 (100)
39.0°C or higher	190 (67)
40.0°C or higher	62 (22)
CRP (40 mg/l or higher)	203 (74)
Plasma creatinine level (44 µmol/l or higher)	29 (31)
Blood bacterial culture	17 (6.7)
Failure to respond to suitable antibiotics in 48 hours	3 (1.1)
Poor urine flow	3 (1.1)
Phimosis	2 (0.71)
Family history of VUR	4 (1.4)
Atypical UTI	92 (29)
First UTI atypical	77 (27)
UTI recurrence	57 (20)
Recurrence before imaging	38 (13)
RBUS	90 (32)
VCUG	103 (37)
High-grade VUR	55 (20)

obstructive phimosis, leading to ballooning of the prepuce and poor urine flow was present in two patients (0.71%). Failure to respond to suitable antibiotics during 48 hours was noted in three patients (1.1%). UTI recurrence during follow-up was recorded in 57 patients (20%), of whom 38 (13%) had a UTI recurrence before VCUG. Family history of VUR was present in four patients (1.4%).

Altogether 202 patients (72%) had no potentially predictive factors for abnormal RBUS. RBUS findings were abnormal in 90 patients (32%). A total of 125 patients (44%) had no potentially predictive factors (atypical UTI, recurrent UTI, abnormal RBUS, or family-history of VUR) for abnormal VCUG. VUR was found in 103 patients (37%), including 55 (20%) with high-grade VUR. Of these patients, 29 patients (28%) with VUR and 6 patients (11%) with high-grade VUR had no potentially predictive factors for abnormal VCUG. (Table 12.)

11.3.1 RBUS

The only factor with a strong statistical association with abnormal RBUS was non-E. coli infection. Out of the 31 patients with a non-E. coli infection before undergoing RBUS, 18 (58%) had abnormal RBUS results. Gender, age, level of fever, plasma CRP level, positive blood bacterial culture, failure to respond to suitable antibiotics during 48 hours, atypical infection, poor urine flow, phimosis, family history of VUR and atypical infection were not statistically significantly associated with abnormal RBUS findings. Interestingly, a raised plasma creatinine concentration was associated with a normal RBUS. Out of the 202 patients with no potentially predictive factors for abnormal RBUS, 63 patients (31%) had abnormal RBUS results. (See table 13 for p-values.)

Table 13. Factors associated with abnormal RBUS. Modified from[334].

	***p*-values**
Strong association	
Non-E. coli infection	0.0002
Weak association	
Gender	0.61
Age	0.61
Fever	0.34
Plasma CRP level	0.58
Plasma creatinine level[a]	0.0058
Positive blood culture	0.59
Poor response to antibiotics	0.24
Poor urine flow	1.00
Phimosis	1.00
Family history of VUR	0.31
Atypical UTI	0.57
Recurrent UTI	0.19

[a]Interestingly, raised plasma creatinine was associated with normal RBUS results

11.3.2 VCUG

Non-E. coli infection, atypical UTI, UTI recurrence and abnormal RBUS were all statistically significantly associated with both VUR and high-grade VUR. Gender, age, level of fever, plasma CRP level, raised plasma creatinine, positive blood bacterial culture, failure to respond to suitable antibiotics during 48 hours, poor urine flow, phimosis and family history of VUR were not statistically significantly associated with VUR (Table 14).

Table 14. Factors associated with VUR and high-grade VUR on VCUG. Modified from[334].

	VUR (*p*-value)	**High-grade VUR (*p*-value)**	**Sensitivity[a] (%)**	**Specificity[a] (%)**	**PPV[a] (%)**	**NPV[a] (%)**
Strong association						
Non-E.coli infection	0.0051	0.0002	24	92	42	83
Atypical infection	0.0082	0.011	42	76	30	84
Recurrent infection	0.12	0.0018	27	90	40	84
Abnormal RBUS	0.0036	<0.0001	69	77	42	91
Weak association						
Gender	0.90	0.65				
Age	1.00	1.00				
Fever	0.24	0.50				
Plasma CRP level	0.81	0.91				
Plasma creatinine level	0.50	1.00				
Positive blood culture	0.44	0.12				
Poor response to antibiotics	1.00	0.48				
Poor urine flow	1.00	1.00				
Phimosis	0.13	1.00				
Family history of VUR	0.62	0.58				

[a]Given values are for high-grade VUR

11.3.3 VUR risk score

Patients who had a risk score (Table 15) of 0, were less likely to have VUR and high-grade VUR than those with a risk score of 1 or higher (p<0.0001in both). The higher the risk score, the higher the probability for both VUR and high-grade VUR. (Figures 18 and 19, p<0.0001 in both). In total, 124 patients (44%) had a risk score of 0. Of these patients, only 6 (4.8%) had high-grade VUR, whereas 19 of the 35 patients (54%) with a risk score of 4 or higher had high-grade VUR. (Figure 19.) The same numbers for grade IV-V VUR 0.8% and 26%, respectively.

11.3.4 UTI recurrence

Non-E. coli infection was the only statistically significant predictor of UTI recurrence. Of the 31 patients with a non-E. coli infection during the first UTI, 18 (58%) had a UTI recurrence during a mean follow-up time of 9.8 years, compared to 44 (18%) in the group with E. coli infection. Gender, age,

Table 15. Risk score for high-grade VUR. Modified from[334].

Factor	Score
Abnormal RBUS	2
Atypical UTI	1
Non-E. coli infection	2
Recurrent UTI	2
Family history of VUR	1

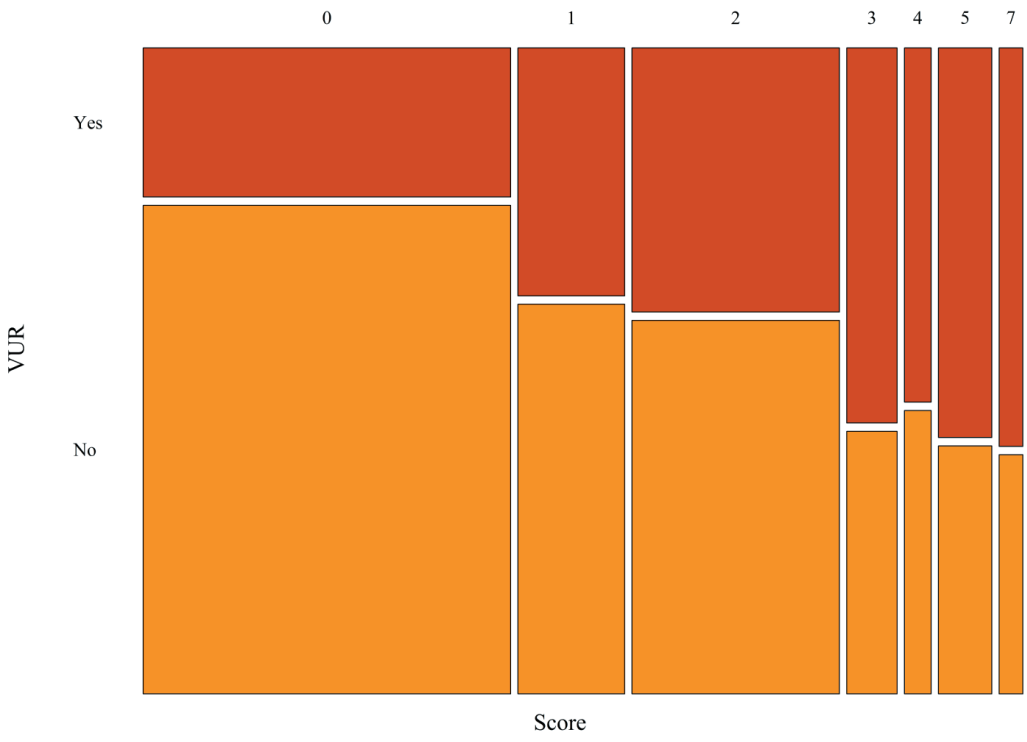

Figure 18. Incidence of VUR according to risk score. Modified from[334].

fever, plasma CRP-level, failure to respond to suitable antibiotics during 48 hours, positive blood culture and abnormal RBUS had no significant correlation with UTI recurrence. (See Table 16 for p-values.) VUR grade was not originally included in the UTI recurrence analyses, because a part of the population underwent VCUG before UTI recurrence and a part had a UTI recurrence before undergoing VCUG. Hence, a number of patients received AMP as a result of being diagnosed with VUR, and data regarding UTI recurrences cannot be considered completely reliable in these cases. We present the numbers for UTI recurrence according to VUR grade in table 17.

11.4 Value of RBUS in predicting VUR

The initial search for studies for the meta-analysis resulted in 418 hits. After removing duplicates, papers published in languages other than English, and clearly irrelevant records the relevance of 39 studies was discussed within the team. One study was excluded due to the full text not being available through contacting the corresponding author or searching on the journal's web site, Science Direct, British Library, and Wiley Online Library[335]. The study by Ismaili et al. was included even though a small portion of the patient sample had congenital abnormalities of the kidney and urinary tract[336].

For the quantitative analysis, altogether 14 studies published in 2000–2015 fulfilled the inclusion criteria (Figure 17 and Table 18). The studies involved 3 544 participants (male/female ratio 1.01). The sample size varied from 98 to 820 participants. Table 18 shows the characteristics of included studies. The risk of bias

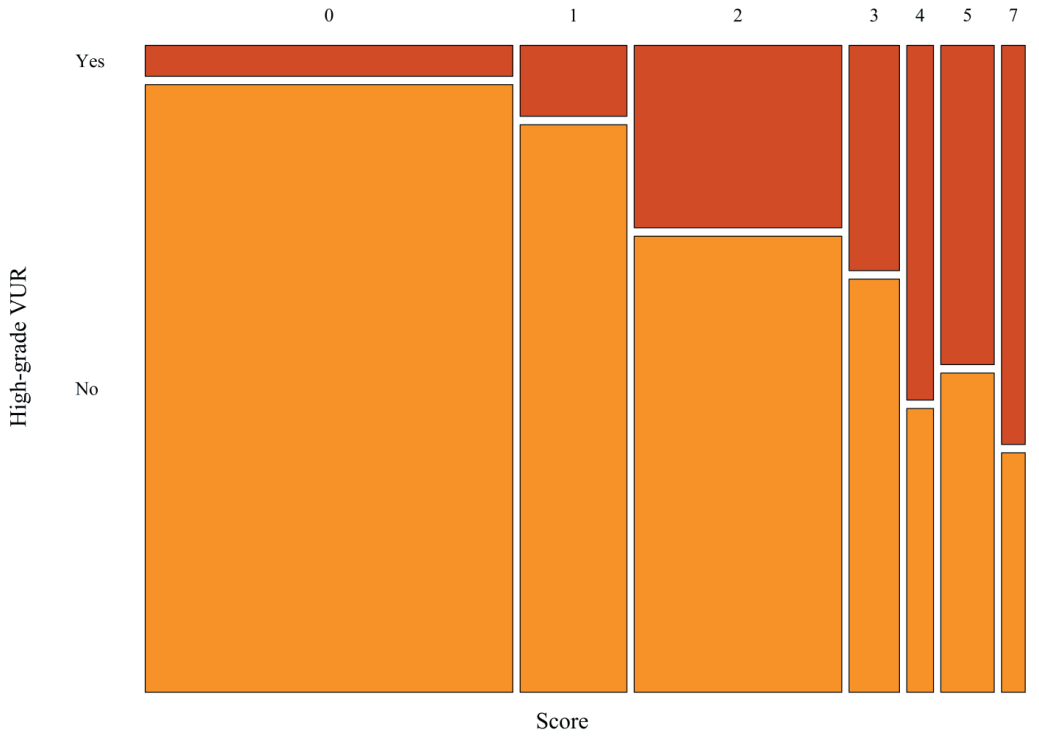

Figure 19. Incidence of high-grade VUR according to risk score. Modified from[334].

Table 16. Factors associated with UTI recurrence. Modified from[334].

	***p*-values**
Strong association	
Non-E. coli infection	0.0020
Weak association	
Gender	0.27
Age	0.13
Fever	0.073
Plasma CRP level	0.19
Positive blood culture	0.29
Poor response to antibiotics	0.45
Abnormal RBUS	0.13

Table 17. UTI recurrence by VUR grade.

VUR grade	**UTI recurrence (%)**
No VUR	27/179 (15)
Grade I VUR	0/8 (0.0)
Grade II VUR	11/40 (28)
Grade III VUR	12/35 (34)
Grade IV VUR	10/16 (63)
Grade V VUR	2/4 (50)
Grade 0-II VUR	38/227 (17)
Grade 0-III VUR	50/262 (19)
Grade III-V VUR	24/55 (44)
Grade IV-V VUR	12/20 (60)

and concern regarding applicability were considered low in ten[128,194,195,318,337-342] and high in four[336,343-345] studies (Table 19). The most frequent source of potential bias and impaired applicability was related to the blinding of index test results.

The sensitivity varied between studies from 0.11 to 0.94. The pooled sensitivity was 0.37 (95% CI 0.34-0.40) with substantial inconsistency of the included studies indicated by I^2 = 96% (Figure 20). The specificity varied between studies from 0.40 to 0.94. The pooled specificity was 0.81 (95% CI 0.80-0.83) with substantial inconsistency of the included studies indicated by I^2 = 97% (Figure 21). Positive likelihood ratio was small at 2.0 (95% CI 1.61-2.50) with substantial heterogeneity indicated by I^2 = 72% (Figure 22). Negative likelihood ratio was minimal at 0.75 (95% CI 0.65-0.86) with substantial heterogeneity indicated by I^2 = 88% (Figure 23). The diagnostic odds ratio (DOR) was 3.03 (95% CI 2.10-4.37) with substantial heterogeneity indicated by I^2 = 68%. Area under the curve was fair 0.72 (standard error 0.03) (Figure 24).

Table 18. Characteristics of included studies. Modified from[328].

Authors Year Country	N	Age	Gender distribution (m*/f**)	Results			
				TP†	FP††	TN‡	FN‡‡
Oostenbrink[337] 2000 Netherlands	140	VUR§ groups mean 1.4 (SD§§ 1.4) years; non-VUR group mean 1.9 (SD 1.6) years	51/89	21	20	83	16
Mahant[343] 2002 Canada	162	Median 85 days	71/91	14	21	97	30
Hoberman[194] 2003 USA	309	Range 1 to 24 months	33/276	12	18	167	105
Zamir[128] 2004 Israel	255	Mean 16 (range 0.3 to 60) months	63/192	7	26	183	36
Alshamsan[338] 2009 Saudi Arabia	130#	Mean 22 months (SD 30, range 0.1 to 132)	38/92	20	18	72	20
Lee[346] 2009 South Korea	220	Mean 4.5 months (range 0.1–21)	162/58	47	44	109	20
Montini[195] 2009 Italy	300	Median 7 months (range 1 to 24)	112/188	18	20	214	48
Müller[339] 2009 Sweden	191	Median 2.7 (m) and 7.2 (f) months	104/87	7	20	155	9
Tse[344] 2009 China	98	>6months	100/34##	3	4	65	25
Preda[340] 2010 Sweden	290	Median 2.7 (m) and 7.4 (f) months	161/129	29	91	147	23
Wong[347] 2010 Hong Kong	820	Median 3.8 (interquartile range 2.3 to 7.1) months	576/244	27	38	579	168
Ismaili[336] 2011 Belgium	209	Median 10 (range 0.2 to 204) months	77/132	18	21	135	35
Tsai[342] 2012 Taiwan	220	Mean 60.2 (SD 22.8, range 6 to 90) days	167/53	40	96	64	20
Kido[345] 2015 Japan	200	Median in VUR-group 4 (interquartile range 2 to 31), in non-VUR-group 5 (interquartile range 3 to 10) months	117/83	65	58	73	4

* Male; **Female; † True positive; †† False positive; ‡ True negative; ‡‡ False negative; § Vesicoureteral reflux; §§ Standard deviation; # There was some inconsistency on the reported number of assessed patients; ## Gender distribution was reported for the entire sample (n=134), numeric data needed for a meta-analysis was reported only for "typical" subgroup (n=98) included in this analysis

Table 19. Risk of bias if the included studies according to QUADAS-2. Modified from[328]

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Oostenbrink	☺	☺	☺	☺	☺	☺	☺
Mahant	☺	☹	☺	☺	☺	☹	☺
Hoberman	☺	☺	☺	☺	☺	☺	☺
Zamir	☺	☺	☺	☺	☺	☺	☺
Alshamsan	☺	☺	☺	☺	☺	☺	☺
Lee H	☺	☺	☺	☺	☺	☺	☺
Montini	☺	☺	☺	☺	☺	☺	☺
Müller	☺	☺	☺	☺	☺	☺	☺
Tse	☺	☹	☺	☺	☺	☹	☺
Preda	☺	☺	☺	☺	☺	☺	☺
Wong	☺	☺	☺	☺	☺	☺	☺
Ismaili	☹	☺	☺	☺	☹	☺	☺
Tsai	☺	☺	☺	☺	☺	☺	☺
Kido	☺	☹	☺	☹	☺	☹	☺

☺ Low risk of bias; **?** Unclear risk of bias; ☹ High risk of bias

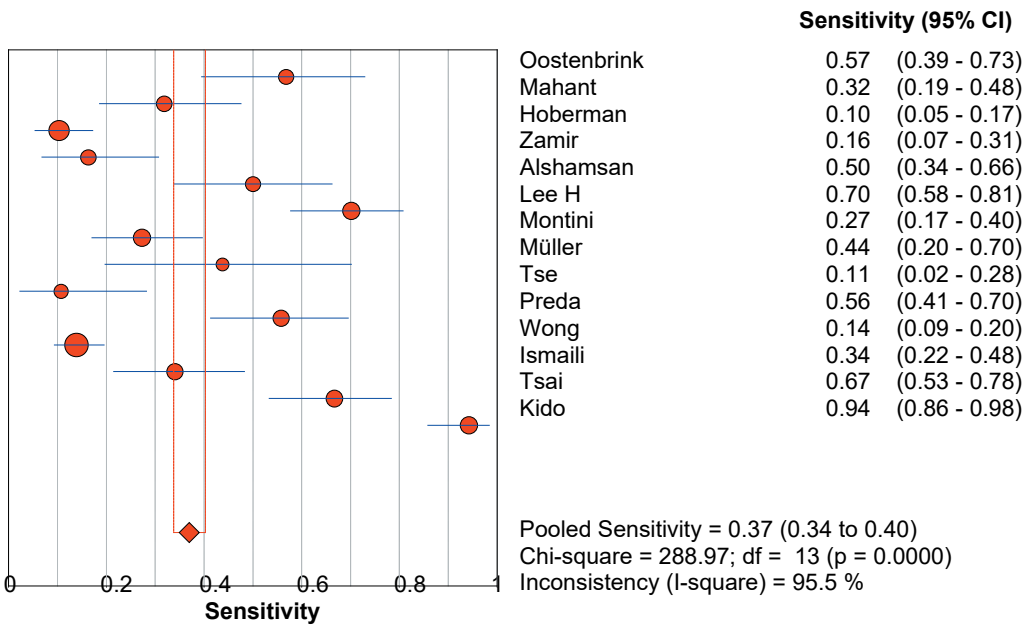

Figure 20. Forest plot of pooled sensitivity. Modified from[328].

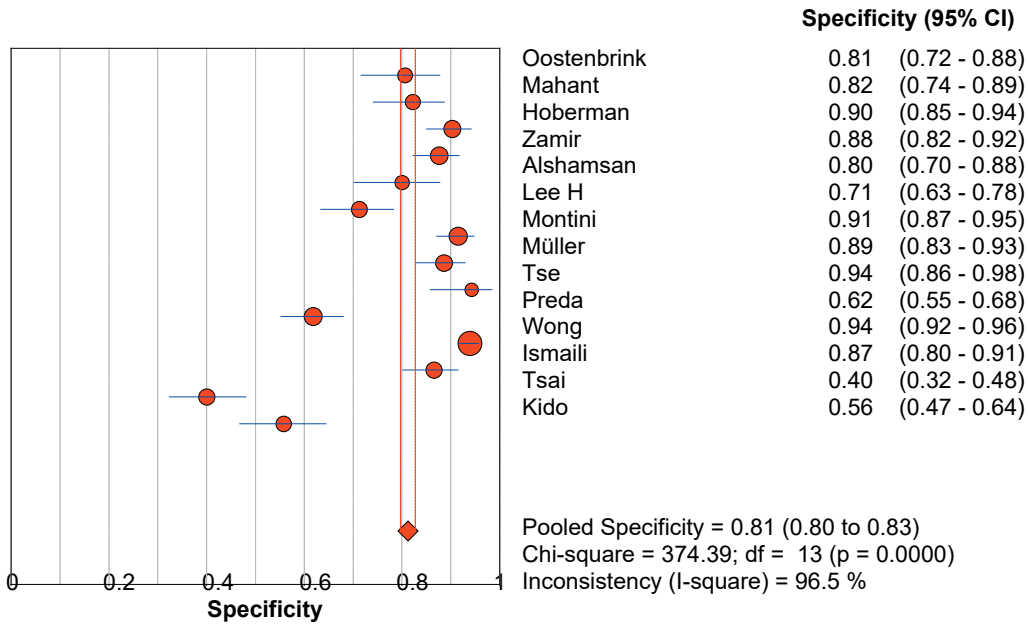

Figure 21. Forest plot of pooled specificity. Modified from[328].

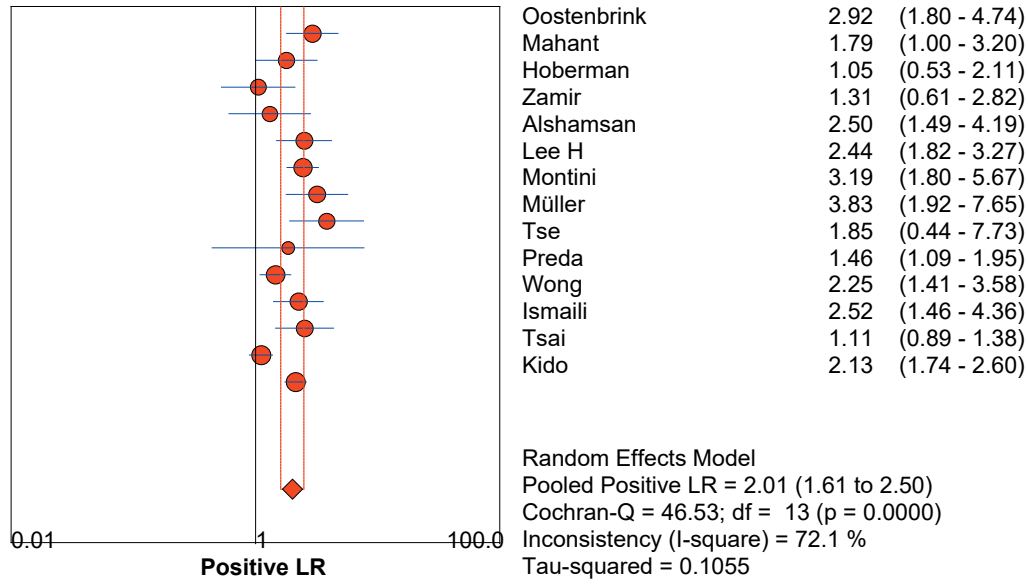

Figure 22. Forest plot of pooled positive likelihood ratio. Modified from[328].

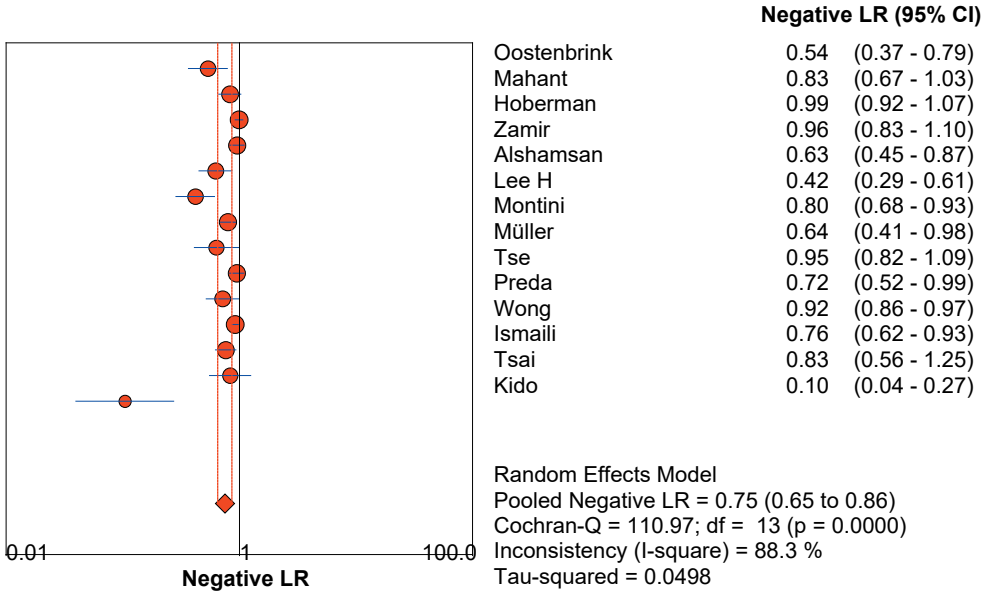

Figure 23. Forest plot of pooled negative likelihood ratio. Modified from[328].

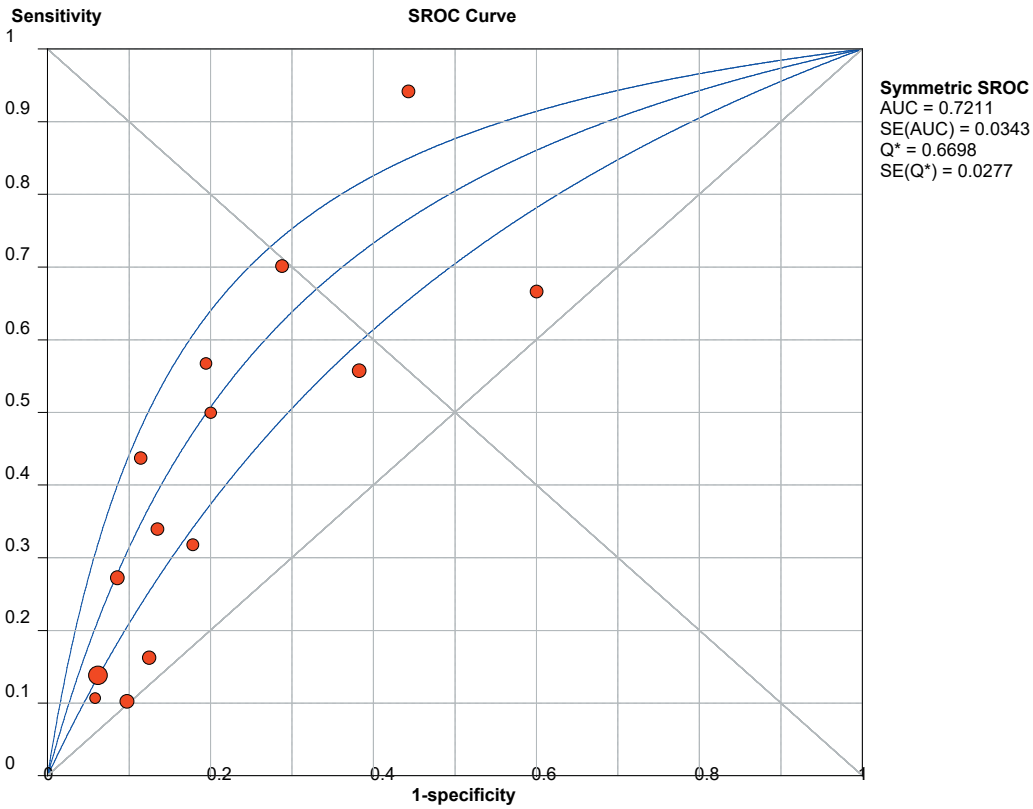

Figure 24. Summary receiver operating characteristic curve (SROC). Modified from[328].

12. DISCUSSION

Most pediatric urologists and nephrologists agree that routine imaging by VCUG should no longer be recommended in all children with first UTI. In addition, most agree that an abnormal RBUS, particularly urinary tract dilatation, after a UTI warrants VCUG. The most controversy revolves around the topic of who to image in the case of a normal RBUS after a UTI. Several factors associated with a higher probability for VUR may be identified, but even in the absence of any of these, patients may have even high-grade VUR. Thus, we are left to balance between high specificity for detecting VUR with the risk of missing patients with VUR, and high sensitivity with significantly higher economic and radiation costs as well as more distress to small children.

12.1 Different strategies for imaging children with UTI

12.1.1 RBUS after UTI

Following the NICE guidelines in our cohort would have led to 31% of patients with abnormal RBUS being missed. These included 23% of the patients with urinary tract dilatation on RBUS. The benefit would have been in not performing RBUS in 51% of patients with normal RBUS findings. In contrast, following the AAP guidelines would have resulted in missing 8.0% of patients with abnormal RBUS, including 9.4% with urinary tract dilatation on RBUS. The benefit would have been in not performing RBUS in 14% of patients with normal RBUS findings.

Although the AAP guidelines do not specifically instruct against performing RBUS in afebrile children, the guidelines pertain to only febrile children. The true cost of performing RBUS in all children with afebrile UTI is difficult to evaluate, as the majority of these children are treated with oral antibiotics outside our institute, without undergoing any imaging studies.

One rationale behind limiting RBUS in small children with UTI has been the assumption that as prenatal US is now performed routinely, most anomalies of the urinary tract would be diagnosed prenatally, and there would be no need to perform RBUS after UTI. In our cohort, however, this was not the case. RBUS was found to be abnormal in as many as 21% of patients, including 14% with dilatation of the urinary tract. We cannot, however, rule out the possibility that there might be differences in the sensitivity of detecting prenatal hydronephrosis by US between Finland and the UK, where the NICE guidelines have been formulated. Naturally, the higher the quality of prenatal US screening and the higher the sensitivity for detecting prenatal hydronephrosis, the smaller the need is to perform RBUS after a UTI in infants and small children. Nevertheless, RBUS is a well tolerated, radiation-free imaging study that can often be performed during initial hospitalization for UTI. Thus, RBUS should be considered in all infants and small children with first febrile UTI, regardless of the results of prenatal US studies.

In our meta-analysis of 3,544 children, RBUS had good specificity (0.81) but poor sensitivity (0.37) in predicting VUR amongst children with first UTI. Area under the curve was only fair 0.7. Both positive and negative likelihood ratios were small. The results of included studies were inconsistent and the observed heterogeneity indexes were high.

Many of the existing guidelines recommend using RBUS as a first-line investigation to screen patients for VUR. While RBUS may reveal other significant, remediable abnormalities of the urinary tract, our findings suggest that with such modest accuracy, RBUS alone can hardly be recommended for screening children for VUR, and other factors should be considered in the decision of whether or not to perform VCUG. Whether or not RBUS can be used as a screening study for grade III-V or IV-V VUR, however, cannot be stated by our studies, but would require another meta-analysis pertaining to particularly high-grade VUR.

As far as we know, ours was the first comprehensive meta-analysis on the topic. Thus, the findings can only be compared with the findings of original studies. The accuracy of RBUS in predicting VUR observed in this meta-analysis was mostly analogous to the figures observed in the included studies. All but one of the included studies reported modest sensitivity of VUR[345]. Respectively, similarly to our results, all but three studies[340,342,345] reported specificity of RBUS being over 0.7. There is no exact explanation to this heterogeneity between studies. It may probably be explained by the differences in samples' age and gender distributions, diverse guidelines used in different settings, the subjective nature of sonography, the differences in sonography equipment, the dissimilar definitions of 'normal or abnormal' RBUS findings, and the dissimilarities in definitions of the grade of dilatation of urinary tract and the grade of VUR. Diverse timing of RBUS and VCUG might also inflict the inconsistency of reported figures. Further research may elucidate the role of these potential sources of heterogeneity. None of the identified studies included an analysis of inter- and intra-observer agreement on the results of RBUS. This "person-related" factor could also be an important topic for further investigation.

12.1.2 VCUG after UTI

Following the NICE guidelines in our cohort would have led to 47% of patients with VUR and 31% of patients with high-grade VUR being missed, with the benefit of 74% of patients without VUR not undergoing VCUG. In comparison, following the AAP guidelines would have led to 33% of patients with VUR and 17% of patients with high-grade VUR being missed, with the benefit of 61% of patients without VUR not undergoing VCUG.

Other studies have found that following the NICE guidelines may lead to missing the VUR diagnosis in 43-71% of patients[322,325,344,348]. This may result in reducing the number of RBUS, DMSA scanning, and VCUG by 27%, 81%, and 68%, respectively, and reduce economic cost by 65-77% and radiation cost by 81%, compared to a strategy where all patients undergo RBUS, DMSA scanning, and VCUG[322,325]. Compared to this all-studies strategy, the AAP guidelines do not reduce the number of RBUS, but the number of DMSA scans and VCUG may be reduced by up to 100% and 65%, respectively. Other studies have reported that following the AAP guidelines may lead to missing the VUR diagnosis in 45-71%[322,325]. These studies did not, however, specify the different 'atypical or complex' situations where VCUG is also recommended by the AAP guidelines. This may lead to evaluating the sensitivity of the AAP guidelines as lower than it would be if all situations even slightly

out of the ordinary were considered 'atypical or complex'.

Some studies have found that while following the NICE guidelines may result in missing a number of patients with VUR, its sensitivity for detecting high-grade VUR may be acceptable[349,350]. After discovering that following the NICE guidelines may results in missing a significant number of children with remediable urological anomalies in boys and in children aged 6-24 months, Wong et al. recommended a revised strategy of performing both RBUS and DMSA scan in all boys, and VCUG in the case of atypical UTI or abnormalities on RBUS or DMSA scan[341]. This strategy yielded a high sensitivity in predicting remediable urological anomalies, but entails a much higher economic and radiation cost. In our cohort of 672 children, performing RBUS to all patients, and VCUG to all with atypical UTI, recurrent UTI or abnormal RBUS, would have led to only 8 of the 64 patients (13%) with high-grade VUR being missed. This seems like a reasonable strategy for imaging children with UTI.

The AAP guidelines state that VCUG is also indicated 'in other atypical or complex situations', leaving room for interpretation. For the purposes of this study, we defined the following as being 'atypical or complex situations': infection with a non-E. coli organism, septicemia, elevated serum creatinine concentration, failure to respond to appropriate antibiotics in 48 hours, poor urine flow, or a family history of VUR. There were 67 patients who fell into this category, and VCUG was performed on 47 of these patients, 24 of whom (51%) had VUR, including 11 (23%) with high-grade VUR. All of these 11 patients had some other indication for VCUG besides the 'atypical or complex situation', *i.e.* abnormal RBUS or recurrent UTI. None of the 25 patients whose only indication for VCUG was 'other atypical or complex situation' underwent surgery. In other words, no high-grade VUR or other findings requiring surgical treatment would have been missed, even if VCUG had not been performed in these 'atypical or complex' situations.

We gathered data from our first three studies to compare the consequences of following them with regards to missed diagnosis in both RBUS and VCUG. This comparison is presented in table 20. Compared to the AAP guidelines and our risk-score system, the NICE guidelines would have resulted in the most abnormalities, VUR, and high-grade VUR being missed. On the other hand, it would have resulted in the smallest number of unnecessary studies. In our opinion, however, the number of missed cases outweighs the benefit of avoiding unnecessary studies in this case.

Some pediatricians have stated that a VCUG should not be performed in any case after a UTI[64]. In our cohort of 672 children, this would have led to missing 125 children with VUR, including 64 with high-grade VUR. Of these 125 children, 43 underwent surgery, although the indication for surgery was not completely clear with some patients with low-grade VUR undergoing endoscopic injection treatment. In general, when deciding whether of not to perform endoscopic injection treatment on a child with VUR, factors favoring operative treatment included grade III-V VUR and breakthrough UTIs despite AMP. The decision to operate was always made individually in concurrence with the parents. Endoscopic correction of VUR was performed in 30 cases, one of whom underwent also UR due to VUR not being resolved at the age of 4

Table 20. Data on following different imaging strategies in 202 children aged 2-24 months with febrile UTI, who underwent both RBUS and VCUG.

Strategy	NICE	AAP	VUR risk-score 1	VUR risk-score 2
RBUS abnormal	71 (35%)	71 (35%)	71 (35%)	71 (35%)
Hydronpehrosis in RBUS	45 (22%)	45 (22%)	45 (22%)	45 (22%)
RBUS avoided in patients with normal RBUS	45 (34%)	0 (0%)	0 (0%)	0 (0%)
Abnormal RBUS results missed	24 (34%)	0 (0%)	0 (0%)	0 (0%)
Hydronephrosis missed	15 (33%)	0 (0%)	0 (0%)	0 (0%)
VUR on VCUG	74 (37%)	74 (37%)	74 (37%)	74 (37%)
Grade I-II VUR on VCUG	36 (18%)	36 (18%)	36 (18%)	36 (18%)
Grade III-V VUR on VCUG	38 (19%)	38 (19%)	38 (19%)	38 (19%)
Grade I-III VUR on VCUG	59 (29%)	59 (29%)	59 (29%)	59 (29%)
Grade IV-V VUR on VCUG	15 (7.4%)	15 (7.4%)	15 (7.4%)	15 (7.4%)
VCUG avoided in patients with no VUR	83 (65%)	68 (53%)	67 (52%)	78 (61%)
VUR on VCUG missed	32 (43%)	24 (32%)	22 (30%)	30 (41%)
Grade I-II VUR missed	21 (58%)	19 (53%)	18 (50%)	24 (67%)
Grade III-V VUR missed	11 (29%)	5 (13%)	4 (11%)	6 (16%)
Grade I-III VUR missed	27 (46%)	23 (39%)	21 (36%)	29 (49%)
Grade IV-V VUR missed	5 (33%)	1 (6.7%)	1 (6.7%)	1 (6.7%)

years. In total, 4 children underwent UR for either high-grade VUR of anatomical anomalies of the UVJ. Two patients with high-grade underwent unilateral nephrectomy after further imaging studies revealed a small, dysfunctional kidney in both. Pyeloplasty was performed on four patients after UPJ stenosis was diagnosed in renography. A ureterocele was surgically removed in three patients. One patient, who had a febrile UTI during the first month of life, underwent RBUS which revealed increased residual urine volume. Cystoscopy revealed a urethral valve, which was immediately ablated. Percutaneous nephrostomy was performed in one case, where RBUS raised suspicion of UPJ stenosis, but renography revealed an obstructing renal empyema. *I.e.*, 1.3% of patients had an obstructive condition of the urinary tract after a normal antentatal US. Most of these patients would have been missed, if they would not have undergone VCUG after a UTI.

12.2 Predictive factors for abnormal imaging and UTI recurrence

Non-E. coli infection was the only strong predictor of abnormal RBUS. These patients represent a relatively small proportion (11%) of the entire population with first febrile UTI. Interestingly, a raised plasma creatinine value was associated with a normal RBUS. This is probably related to the small number of patients having had creatinine values measured. Out of the total 90 patients with abnormal RBUS results after a febrile UTI and a normal prenatal US, 63 (70%) had no predictive factors (such as atypical UTI or recurrence before the initial RBUS) for RBUS abnormalities. Abnormal prenatal US and hospitalization for UTI have also been reported as being risk factors for abnormal

RBUS after a first febrile UTI in children aged 2-24 months[351].

There is a clear association between abnormal RBUS and VUR, but our meta-analysis found the sensitivity of abnormal RBUS to be only 0.37, and RBUS alone cannot be recommended for screening patients with UTI for VUR. If only high-grade VUR is considered to be worth active search, another meta-analysis concentrating particularly on high-grade VUR, is needed. In our retrospective cohort of 282 patients, 31% of patients with high-grade VUR had normal RBUS results, and RBUS had a NPV of 91% for high-grade VUR.

Previous studies have associated age of under one year, male gender, family history of uropathology, recurrent UTI, non-E. coli infection, complicated UTI, plasma CRP >40 mg/l and abnormal RBUS with an increased frequency of VUR[77,78,80,337]. For this reason, we included family history of VUR in the risk score system, despite it having a statistically weak association with VUR in our analyses. In a recent retrospective study of 262 patients[352], recurrent UTIs were not associated with a higher likelihood of VUR or other urologic abnormality in VCUG. In our cohort, UTI recurrence before the initial VCUG correlated with a higher risk for both VUR and high-grade VUR. The sensitivity of UTI recurrence alone was weak (27%), but as a part of the risk score system, it provided additional value.

In earlier studies, non-E. coli infection has been associated with a higher incidence of VUR[80,353,354]. In our cohort, non-E. coli infection was associated with abnormal RBUS and UTI recurrence as well as VUR. These patients represent a subgroup of UTI patients that needs attention. Hence, a non-E. coli infection seems like a potential indication for VCUG and possibly even consideration of anti-microbial prophylaxis.

Non-E. coli infection and elevated post-void residual urine measured by ultrasonography have been shown to be associated with a higher incidence of UTI recurrence[96,355]. Other risk factors for recurrence include younger age, female gender, vesicoureteral reflux (VUR), uncircumcised prepuce in boys, constipation and lower urinary tract dysfunction[356,357]. Although non-E. coli infection was a clear predictor of recurrence, we cannot conclusively assess the rate or predictive factors of UTI recurrence because of the large number of patients (especially those with VUR) receiving anti-microbial prophylaxis.

The VUR risk score system had a strong statistical association with abnormal VCUG results, with the probability for VUR and high-grade VUR rising according to the risk score. There was, however, no clearly definable cut-off point for when VCUG should be performed. But if the goal is to find patients at risk for high-grade VUR and its sequelae, the presence of a risk score of 0 was a good predictor for the absence of high-grade VUR (NPV=95%, sensitivity=89%). As low-grade VUR is no longer considered to be of great clinical significance, these patients may be followed up without extensive imaging studies, and focus may rather be on the prompt diagnosis and treatment of UTI recurrences.

If the cut-off point was set at 1 point, 158 patients (56%) would have undergone VCUG. VUR was found in 74 (47%) of these patients, including 49 (31%) with high-grade VUR, and only 6 patients with high-grade VUR would be missed (NPV=95%, sensitivity=89% for high-grade VUR). If the cut-off point was set at 2 points, 122 patients (43%) would have undergone VCUG. VUR was

found in 60 (49%) of these patients, including 45 (37%) with high-grade VUR, and 10 patients with high-grade VUR would have been missed. *I.e.*, 32 patients without high-grade VUR would not undergo an unnecessary VCUG with the cost of missing 4 patients with high-grade VUR, compared to a cut-off point of 1. Further studies are needed to validate the risk score system in another patient cohort.

12.3 Limitations of the research

The first three studies were retrospective, and have the weaknesses associated with this. Laboratory testing, including plasma CRP, plasma creatinine and blood bacterial cultures, was inconsistent. If all patients had undergone all of these tests, more patients might have had an indication for imaging studies according to the NICE and AAP guidelines, resulting in a higher sensitivity for detecting VUR. The method of gathering urine samples varied. Suprapubic aspiration samples were often attempted unsuccessfully, leading to diagnoses being based on solely bagged specimen in some cases. Inconsistencies in the method of urine sampling may question the reliability of the UTI diagnosis in some cases, and may have lead to a number of patients with no UTI undergoing imaging studies.

A substantial number of children with even febrile UTI are treated outside the university hospital. These patients often have uncomplicated febrile UTI and do not always undergo imaging studies during or after the UTI. Hence, it may be that our studies overestimate the frequency of abnormal imaging results. If all of these patients underwent RBUS and possibly more extensive imaging, it would impose a considerable economical burden and possibly would not lead to detecting a significant number of remediable urological abnormalities.

Diagnostic imaging, particularly VCUG and DMSA scanning, was not performed in all patients, complicating the evaluation of the sensitivity and specificity of guidelines to identify patients with VUR. A number of patients underwent only DRC instead of VCUG, making it impossible to reliably grade these patients VUR. Prophylaxis was prescribed quite liberally at times, even to patients with low-grade VUR. Endoscopic correction of VUR was performed in some cases with only low-grade VUR. This made it difficult to assess the rate of UTI recurrence during follow-up.

Although the VUR risk score system had high sensitivity for predicting high-grade VUR in our cohort, it needs further validation with a separate cohort of patients. Even at a low cut-off point of 1, where 56% of patients would have undergone VCUG, a small number of patients with high-grade VUR would have been missed.

The meta-analysis had two main weaknesses. First, even though the search was systematically designed and results were discussed by the team, the selection process did not assure its best possible objectiveness as only a single researcher conducted most of the search and data extraction. Second, due to software limitations, possible publication bias remained unassessed. The search on four major electronic databases was comprehensive. The methodological quality of included studies was assessed by using a standardized QUADAS-2 framework, recommended for this purpose by Cochrane Collaboration. The pooled sample was large enough to achieve good precision as seen in narrow confidence intervals. It might also be of additional value to perform a similar me-

ta-analysis concentrating especially on the accuracy of RBUS in predicting high-grade VUR, instead of all-grade VUR.

In addition, We did not differentiate between different abnormalities in RBUS, but instead considered all abnormal findings equal. A study on the association between particular abnormalities in RBUS and VUR may be of interest in the future. For instance, ureteral dilatation and uroepithelial thickening in RBUS have been associated with high-grade VUR[358,359]. On the other hand, some abnormal findings in RBUS might not be associated with VUR at all. If abnormal findings in RBUS were looked at more closely, and only certain specific findings were considered indicative of VUR, the specificity of RBUS might have improved, but sensitivity might have been even weaker.

13. CONCLUSIONS

1. Following the NICE guidelines for imaging studies in children with UTI leads to a substantial reduction in the number of performed invasive imaging studies, but also significant diagnoses being missed, in both RBUS and VCUG. RBUS is a well tolerated, non-invasive, radiation-free study that can often be performed during initial hospitalization for UTI. A significant proportion of children with UTI may have abnormal RBUS findings after a UTI despite a normal prenatal US. Thus, RBUS should be performed in all infants and children under 3 years old with first UTI.

2. Following the AAP guidelines for imaging studies in children with UTI leads to a comparable reduction in the number of performed invasive imaging studies, but with significantly less missed VUR diagnoses.

3. A non-E. coli infection is associated with abnormal RBUS and VCUG as well as UTI recurrence. Several other factors are associated with VUR. In the absence of these factors the probability of high-grade VUR may be minimal.

4. The sensitivity of RBUS to identify patients at risk of VUR is insufficient to be recommended as a screening study for VUR. The presence of other atypical factors, family history of VUR, and recurrence of UTIs should be taken into account when considering further imaging studies. Even if VCUG is performed in all patients with abnormal RBUS and/or any atypical situations, there is a small risk of missing patients with even high-grade VUR. This risk needs to be weighed against the invasiveness and radiation burden of VCUG and the limited effectiveness of treatment of VUR.

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15. REFERENCES

1 Marra G, Oppezzo C, Ardissino G, Dacco V, Testa S, Avolio L et al. Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ItalKid Project. J Pediatr. 2004; 144: 677-681.

2 Swerkersson S, Jodal U, Sixt R, Stokland E, Hansson S. Relationship among vesicoureteral reflux, urinary tract infection and renal damage in children. J Urol. 2007; 178: 647-51; discussion 650-1.

3 Smellie JM, Edwards D, Normand IC, Prescod N. Effect of vesicoureteric reflux on renal growth in children with urinary tract infection. Arch Dis Child. 1981; 56: 593-600.

4 Hannerz L, Wikstad I, Celsi G, Aperia A. Influence of vesicoureteral reflux and urinary tract infection on renal growth in children with upper urinary tract duplication. Acta Radiol. 1989; 30: 391-394.

5 Polito C, La Manna A, Capacchione A, Pullano F, Iovene A, Del Gado R. Height and weight in children with vesicoureteric reflux and renal scarring. Pediatr Nephrol. 1996; 10: 564-567.

6 Roihuvuo-Leskinen H, Lahdes-Vasama T, Niskanen K, Ronnholm K. The association of adult kidney size with childhood vesicoureteral reflux. Pediatr Nephrol. 2013; 28: 77-82.

7 Polito C, Marte A, Zamparelli M, Papale MR, Rocco CE, La Manna A. Catch-up growth in children with vesico-ureteric reflux. Pediatr Nephrol. 1997; 11: 164-168.

8 Hellstrom A, Hanson E, Hansson S, Hjalmas K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch Dis Child. 1991; 66: 232-234.

9 Venhola M, Hannula A, Huttunen NP, Renko M, Pokka T, Uhari M. Occurrence of vesicoureteral reflux in children. Acta Paediatr. 2010; 99: 1875-1878.

10 Finnell SM, Carroll AE, Downs SM, Subcommittee on Urinary Tract Infection. Technical report-Diagnosis and management of an initial UTI in febrile infants and young children. Pediatrics. 2011; 128: e749-70.

11 Maskell R, Pead L, Vinnicombe J. Urinary infection after micturating cystography. Lancet. 1978; 2: 1191-1192.

12 Rachmiel M, Aladjem M, Starinsky R, Strauss S, Villa Y, Goldman M. Symptomatic urinary tract infections following voiding cystourethrography. Pediatr Nephrol. 2005; 20: 1449-1452.

13 Sulieman A, Theodorou K, Vlychou M, Topaltzikis T, Kanavou D, Fezoulidis I et al. Radiation dose measurement and risk estimation for paediatric patients undergoing micturating cystourethrography. Br J Radiol. 2007; 80: 731-737.

14 Smans K, Vano E, Sanchez R, Schultz FW, Zoetelief J, Kiljunen T et al. Results of a European survey on patient doses in paediatric radiology. Radiat Prot Dosimetry. 2008; 129: 204-210.

15 Ward VL, Strauss KJ, Barnewolt CE, Zurakowski D, Venkatakrishnan V, Fahey FH et al. Pediatric radiation exposure and effective dose reduction during voiding cystourethrography. Radiology. 2008; 249: 1002-1009.

16 Nagler EV, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. 2011; (6):CD001532. doi: CD001532.

17 CG54 - Urinary tract infection in children - 1 Guidance - National Institute for Health and Clinical Excellence 2012: www.nice.org.uk/guidance/cg54.

18 Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011; 128: 595-610.

19 Ammenti A, Cataldi L, Chimenz R, Fanos V, La Manna A, Marra G et al. Febrile urinary tract infections in young children: recommendations for the diagnosis, treatment and follow-up. Acta Paediatr. 2012; 101: 451-457.

20 Stein R, Dogan HS, Hoebeke P, Kocvara R, Nijman RJ, Radmayr C et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol. 2015; 67: 546-558.

21 Suomalaisen Lääkäriseuran Duodecimin, Suomen Nefrologiyhdistys ry:n, Kliiniset mikrobiologit ry:n, Suomen Infektiolääkärit ry:n, Suomen Kliinisen Kemian Erikoislääkäriyhdistys ry:n, Suomen Lastenlääkäriyhdistys ry:n, Suomen Urologiyhdistyksen ja Suomen yleislääketieteen yhdistys ry:n asettama työryhmä. Virtsatieinfektiot - Käypä hoito. 2015.

22 Venhola M, Uhari M. Vesicoureteral reflux, a benign condition. Pediatr Nephrol. 2009; 24: 223-226.

23 Paquin AJ,Jr. Ureterovesical anastomosis: the description and evaluation of a technique. J Urol. 1959; 82: 573-583.

24 Allen TD, Bright TC,3rd. Urodynamic patterns in children with dysfunctional voiding problems. J Urol. 1978; 119: 247-249.

25 Sillen U, Hjalmas K, Aili M, Bjure J, Hanson E, Hansson S. Pronounced detrusor hypercontractility in infants with gross bilateral reflux. J Urol. 1992; 148: 598-599.

26 Sadler TW: Urogenital system. In: Langman's Medical Embryology, 10th Edition ed. Edited by TW Sadler. Philadelphia: Lippincott Williams & Wilkins 2006.

27 Bouchard M. Transcriptional control of kidney development. Differentiation. 2004; 72: 295-306.

28 Murawski IJ, Gupta IR. Vesicoureteric reflux and renal malformations: a developmental problem. Clin Genet. 2006; 69: 105-117.

29 Zheng Y, Xu J, Guo W, Xu H, Chen J, Shen Q et al. The significance of Pax2 expression in the ureter epithelium of children with vesicoureteric reflux. Hum Pathol. 2015; 46: 963-970.

30 Batourina E, Choi C, Paragas N, Bello N, Hensle T, Costantini FD et al. Distal ureter morphogenesis depends on epithelial cell remodeling mediated by vitamin A and Ret. Nat Genet. 2002; 32: 109-115.

31 Schwentner C, Oswald J, Lunacek A, Pelzer AE, Fritsch H, Schlenck B et al. Extracellular microenvironment and cytokine profile of the ureterovesical junction in children with vesicoureteral reflux. J Urol. 2008; 180: 694-700.

32 Yurtcu M, Gurbuzer N, Findik S, Avunduk MC, Gunel E. Investigation of histopathologic changes in the ureter walls in vesicoureteral reflux. J Pediatr Surg. 2009; 44: 802-805.

33 Izol V, Acikalin AA, Kuyucu Y, Deger M, Aridogan IA, Polat S et al. Ultrastructural and immunohistopathological evaluation of intravesical ureters via electron and light microscopy in children with vesicoureteral reflux. J Urol. 2014; 191: 1110-1117.

34 Tanagho EA, Hutch JA, Meyers FH, Rambo ON,Jr. Primary Vesicoureteral Reflux: Experimental Studies of its Etiology. J Urol. 1965; 93: 165-176.

35 Heale HF: Age of presentation and pathogenesis of reflux nephopathy. In: Reflux nephropathy. Edited by CJ Hodson, P Kincaid-Smith. New York: Masson Publishing USA 1979.

36 Radmayr C, Fritsch H, Schwentner C, Lunacek A, Deibl M, Bartsch G et al. Fetal development of the vesico-ureteric junction, and immunohistochemistry of the ends of refluxing ureters. J Pediatr Urol. 2005; 1: 53-59.

37 Oswald J, Brenner E, Schwentner C, Deibl M, Bartsch G, Fritsch H et al. The intravesical ureter in children with vesicoureteral reflux: a morphological and immunohistochemical characterization. J Urol. 2003; 170: 2423-2427.

38 Oswald J, Schwentner C, Brenner E, Deibl M, Fritsch H, Bartsch G et al. Extracellular matrix degradation and reduced nerve supply in refluxing ureteral endings. J Urol. 2004; 172: 1099-1102.

39 Lyon RP, Marshall S, Tanagho EA. The ureteral orifice: its configuration and competency. J Urol. 1969; 102: 504-509.

40 Stephens FD. Ureteric configurations and cystoscopy schema. Soc Pediatr Urol Newslett. 1980; January 23: .

41 Jeffs RD, Allen MS. The relationship betweeen ureterovesical reflux and infection. J Urol. 1962; 88: 691-695.

42 Schoenberg HW, Beisswanger P, Howard WJ, Klingenmaier H, Walter CF, Murphy JJ. Effect of Lower Urinary Tract Infection upon Ureteral Function. J Urol. 1964; 92: 107-108.

43 Kaveggia L, King LR, Grana L, Idriss FS. Pyelonephritis: a cause of vesicoureteral reflux?. J Urol. 1966; 95: 158-163.

44 Roberts JA, Riopelle AJ. Vesicoureteral reflux in the primate: III. Effect of urinary tract infection on maturation of the ureterovesical junction. Pediatrics. 1978; 61: 853-857.

45 Woods C, Atwell JD. Vesico-ureteric reflux in the neuropathic bladder with particular reference to the development of renal scarring. Eur Urol. 1982; 8: 23-28.

46 Sidi AA, Peng W, Gonzalez R. Vesicoureteral reflux in children with myelodysplasia: natural history and results of treatment. J Urol. 1986; 136: 329-331.

47 Taylor CM, Corkery JJ, White RH. Micturition symptoms and unstable bladder activity in girls with primary vesicoureteric reflux. Br J Urol. 1982; 54: 494-498.

48 Helmy TE, Hafez AT. Vesicouretral reflux with neuropathic bladder: studying the resolution rate after ileocystoplasty. Urology. 2013; 82: 425-428.

49 Zhang P, Yang Y, Wu ZJ, Zhang N, Zhang CH, Zhang XD. Should simultaneous ureteral reimplantation be performed during sigmoid bladder augmentation to reduce vesicoureteral reflux in neurogenic bladder cases?. Int Urol Nephrol. 2015; 47: 759-764.

50 Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol. 1998; 160: 1019-1022.

51 Chandra M, Maddix H. Urodynamic dysfunction in infants with vesicoureteral reflux. J Pediatr. 2000; 136: 754-759.

52 Chen JJ, Mao W, Homayoon K, Steinhardt GF. A multivariate analysis of dysfunctional elimination syndrome, and its relationships with gender, urinary tract infection and vesicoureteral reflux in children. J Urol. 2004; 171: 1907-1910.

53 Leclair MD, Heloury Y. Non-neurogenic elimination disorders in children. J Pediatr Urol. 2010; 6: 338-345.

54 Sillen U. Bladder dysfunction and vesicoureteral reflux. Adv Urol. 2008; 815472.

55 Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J. 2008; 27: 302-308.

56 Narasimharao KL, Prasad GR, Mukhopadhyay B, Katariya S, Mitra SK, Pathak IC. Vesicoureteric reflux in neonates with anorectal anomalies. Br J Urol. 1983; 55: 268-270.

57 Parrott TS. Urologic implications of anorectal malformations. Urol Clin North Am. 1985; 12: 13-21.

58 Sanyanusin P, Schimmenti LA, McNoe LA, Ward TA, Pierpont ME, Sullivan MJ et al. Mutation of the PAX2 gene in a family with optic nerve colobomas, renal anomalies and vesicoureteral reflux. Nat Genet. 1995; 9: 358-364.

59 Boemers TM, de Jong TP, van Gool JD, Bax KM. Urologic problems in anorectal malformations. Part 2: functional urologic sequelae. J Pediatr Surg. 1996; 31: 634-637.

60 Duke V, Quinton R, Gordon I, Bouloux PM, Woolf AS. Proteinuria, hypertension and chronic renal failure in X-linked Kallmann's syndrome, a defined genetic cause of solitary functioning kidney. Nephrol Dial Transplant. 1998; 13: 1998-2003.

61 Ruf RG, Xu PX, Silvius D, Otto EA, Beekmann F, Muerb UT et al. SIX1 mutations cause branchio-oto-renal syndrome by disruption of EYA1-SIX1-DNA complexes. Proc Natl Acad Sci U S A. 2004; 101: 8090-8095.

62 Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. Pediatrics. 2006; 118: 586-593.

63 Kollermann MW, Ludwig H. On vesico-ureteral reflux in normal infants and children. Z Kinderheilkd. 1967; 100: 185-191.

64 Hannula A, Venhola M, Perhomaa M, Pokka T, Renko M, Uhari M. Imaging the urinary tract in children with urinary tract infection. Acta Paediatr. 2011; 100: e253-9.

65 Salo J, Ikaheimo R, Tapiainen T, Uhari M. Childhood urinary tract infections as a cause of chronic kidney disease. Pediatrics. 2011; 128: 840-847.

66 Hodson EM, Wheeler DM, Vimalchandra D, Smith GH, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. 2007; (3): CD001532.

67 Brandstrom P, Neveus T, Sixt R, Stokland E, Jodal U, Hansson S. The Swedish reflux trial in children: IV. Renal damage. J Urol. 2010; 184: 292-297.

68 Skoog SJ, Peters CA, Arant BS,Jr, Copp HL, Elder JS, Hudson RG et al. Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report: Clinical Practice Guidelines for Screening Siblings of Children With Vesicoureteral Reflux and Neonates/Infants With Prenatal Hydronephrosis. J Urol. 2010; 184: 1145-1151.

69 Kaefer M, Curran M, Treves ST, Bauer S, Hendren WH, Peters CA et al. Sibling vesicoureteral reflux in multiple gestation births. Pediatrics. 2000; 105: 800-804.

70 Livera LN, Brookfield DS, Egginton JA, Hawnaur JM. Antenatal ultrasonography to detect fetal renal abnormalities: a prospective screening programme. BMJ. 1989; 298: 1421-1423.

71 Blyth B, Snyder HM, Duckett JW. Antenatal diagnosis and subsequent management of hydronephrosis. J Urol. 1993; 149: 693-698.

72 Gunn TR, Mora JD, Pease P. Antenatal diagnosis of urinary tract abnormalities by ultrasonography after 28 weeks' gestation: incidence and outcome. Am J Obstet Gynecol. 1995; 172: 479-486.

73 Sairam S, Al-Habib A, Sasson S, Thilaganathan B. Natural history of fetal hydronephrosis diagnosed on mid-trimester ultrasound. Ultrasound Obstet Gynecol. 2001; 17: 191-196.

74 Lim DJ, Park JY, Kim JH, Paick SH, Oh SJ, Choi H. Clinical characteristics and outcome of hydronephrosis detected by prenatal ultrasonography. J Korean Med Sci. 2003; 18: 859-862.

75 Hwang HH, Cho MH, Ko CW. The necessity of voiding cystourethrography in children with prenatally diagnosed hydronephrosis. J Int Med Res. 2011; 39: 603-608.

76 Chand DH, Rhoades T, Poe SA, Kraus S, Strife CF. Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. J Urol. 2003; 170: 1548-1550.

77 Haycock GB. A practical approach to evaluating urinary tract infection in children. Pediatr Nephrol. 1991; 5: 401-2; discussion 403.

78 Dick PT, Feldman W. Routine diagnostic imaging for childhood urinary tract infections: a systematic overview. J Pediatr. 1996; 128: 15-22.

79 Oostenbrink R, van der Heijden AJ, Moons KG, Moll HA. Prediction of vesico-ureteric reflux in childhood urinary tract infection: a multivariate approach. Acta Paediatr. 2000; 89: 806-810.

80 Cleper R, Krause I, Eisenstein B, Davidovits M. Prevalence of vesicoureteral reflux in neonatal urinary tract infection. Clin Pediatr (Phila). 2004; 43: 619-625.

81 Juliano TM, Stephany HA, Clayton DB, Thomas JC, Pope JC,4th, Adams MC et al. Incidence of abnormal imaging and recurrent pyelonephritis after first febrile urinary tract infection in children 2 to 24 months old. J Urol. 2013; 190: 1505-1510.

82 Elder JS, Peters CA, Arant BS,Jr, Ewalt DH, Hawtrey CE, Hurwitz RS et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. J Urol. 1997; 157: 1846-1851.

83 Sjostrom S, Sillen U, Bachelard M, Hansson S, Stokland E. Spontaneous resolution of high grade infantile vesicoureteral reflux. J Urol. 2004; 172: 694-8; discussion 699.

84 Kirsch AJ, Arlen AM, Leong T, Merriman LS, Herrel LA, Scherz HC et al. Vesicoureteral reflux index (VURx): a novel tool to predict primary reflux improvement and resolution in children less than 2 years of age. J Pediatr Urol. 2014; 10: 1249-1254.

85 Wildbrett P, Schwebs M, Abel JR, Lode H, Barthlen W. Spontaneous vesicoureteral reflux resolution in children: A ten-year single-centre experience. Afr J Paediatr Surg. 2013; 10: 9-12.

86 Stephens FD, Lenaghan D. The anatomical basis and dynamics of vesicoureteral reflux. J Urol. 1962; 87: 669-680.

87 Heikel PE, Parkkulainen KV. Vesico-ureteric reflux in children. A classification and results of conservative treatment. Ann Radiol (Paris). 1966; 9: 37-40.

88 Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mobius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol. 1985; 15: 105-109.

89 Ransley PG, Risdon RA. Renal papillae and intrarenal reflux in the pig. Lancet. 1974; 2: 1114.

90 Hodson CJ, Maling TM, McManamon PJ, Lewis MG. The pathogenesis of reflux nephropathy (chronic atrophic pyelonephritis). Br J Radiol. 1975; Suppl 13: 1-26.

91 RIVUR Trial Investigators, Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med. 2014; 370: 2367-2376.

92 Park S, Han JY, Kim KS. Risk factors for recurrent urinary tract infection in infants with vesicoureteral reflux during prophylactic treatment: effect of delayed contrast passage on voiding cystourethrogram. Urology. 2011; 78: 170-173.

93 Dias CS, Silva JM, Diniz JS, Lima EM, Marciano RC, Lana LG et al. Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. Pediatr Infect Dis J. 2010; 29: 139-144.

94 Yamazaki Y, Shiroyanagi Y, Matsuno D, Nishi M. Predicting early recurrent urinary tract infection in pretoilet trained children with vesicoureteral reflux. J Urol. 2009; 182: 1699-1702.

95 Shaikh N, Craig JC, Rovers MM, Da Dalt L, Gardikis S, Hoberman A et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. JAMA Pediatr. 2014; 168: 893-900.

96 Chang SJ, Tsai LP, Hsu CK, Yang SS. Elevated postvoid residual urine volume predicting recurrence of urinary tract infections in toilet-trained children. Pediatr Nephrol. 2015; 30: 1131-1137.

97 Brandstrom P, Jodal U, Sillen U, Hansson S. The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. J Pediatr Urol. 2011; 7: 594-600.

98 Shindo S, Bernstein J, Arant BS,Jr. Evolution of renal segmental atrophy (Ask-Upmark kidney) in children with vesicoureteric reflux: radiographic and morphologic studies. J Pediatr. 1983; 102: 847-854.

99 Ransley PG, Risdon RA. Reflux nephropathy: effects of antimicrobial therapy on the evolution of the early pyelonephritic scar. Kidney Int. 1981; 20: 733-742.

100 Rushton HG. The evaluation of acute pyelonephritis and renal scarring with technetium 99m-dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. Pediatr Nephrol. 1997; 11: 108-120.

101 Doganis D, Siafas K, Mavrikou M, Issaris G, Martirosova A, Perperidis G et al. Does early treatment of urinary tract infection prevent renal damage?. Pediatrics. 2007; 120: e922-8.

102 Ahmed M, Eggleston D, Kapur G, Jain A, Valentini RP, Mattoo TK. Dimercaptosuccinic acid (DMSA) renal scan in the evaluation of hypertension in children. Pediatr Nephrol. 2008; 23: 435-438.

103 Smellie J, Edwards D, Hunter N, Normand IC, Prescod N. Vesico-ureteric reflux and renal scarring. Kidney Int Suppl. 1975; 4: S65-72.

104 Kincaid-Smith P, Becker G. Reflux nephropathy and chronic atrophic pyelonephritis: a review. J Infect Dis. 1978; 138: 774-780.

105 Bourchier D, Abbott GD, Maling TM. Radiological abnormalities in infants with urinary tract infections. Arch Dis Child. 1984; 59: 620-624.

106 Dillon MJ, Goonasekera CD. Reflux nephropathy. J Am Soc Nephrol. 1998; 9: 2377-2383.

107 Hannula A, Perhomaa M, Venhola M, Pokka T, Renko M, Uhari M. Long-term follow-up of patients after childhood urinary tract infection. Arch Pediatr Adolesc Med. 2012; 166: 1117-1122.

108 Kincaid-Smith P. Glomerular lesions in atrophic pyelonephritis and reflux nephropathy. Kidney Int Suppl. 1975; 4: S81-3.

109 Hinchliffe SA, Kreczy A, Ciftci AO, Chan YF, Judd BA, van Velzen D. Focal and segmental glomerulosclerosis in children with reflux nephropathy. Pediatr Pathol. 1994; 14: 327-338.

110 Bailey RR, Swainson CP, Lynn KL, Burry AF. Glomerular lesions in the 'normal' kidney in patients with unilateral reflux nephropathy. Contrib Nephrol. 1984; 39: 126-131.

111 Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. J Urol. 2009; 181: 290-7; discussion 297-8.

112 Malek RS, Svensson J, Neves RJ, Torres VE. Vesicoureteral reflux in the adult. III. Surgical correction: risks and benefits. J Urol. 1983; 130: 882-886.

113 Zhang Y, Bailey RR. A long term follow up of adults with reflux nephropathy. N Z Med J. 1995; 108: 142-144.

114 Kohler J, Tencer J, Thysell H, Forsberg L. Vesicoureteral reflux diagnosed in adulthood. Incidence of urinary tract infections, hypertension, proteinuria, back

pain and renal calculi. Nephrol Dial Transplant. 1997; 12: 2580-2587.

115 Simoes e Silva AC, Silva JM, Diniz JS, Pinheiro SV, Lima EM, Vasconcelos MA et al. Risk of hypertension in primary vesicoureteral reflux. Pediatr Nephrol. 2007; 22: 459-462.

116 Karlen J, Linne T, Wikstad I, Aperia A. Incidence of microalbuminuria in children with pyelonephritic scarring. Pediatr Nephrol. 1996; 10: 705-708.

117 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39: S1-266.

118 NAPRTCS Annual Report - Cover Page - annualrept2014.pdf2016:.

119 Jahnukainen T, Bjerre A, Larsson M, Tainio J, Thiesson HC, Jalanko H et al. The second report of the Nordic Pediatric Renal Transplantation Registry 1997-2012: More infant recipients and improved graft survivals. Pediatr Transplant. 2016; 20: 364-371.

120 Salo J, Ikaheimo R, Tapiainen T, Uhari M. Childhood urinary tract infections as a cause of chronic kidney disease. Pediatrics. 2011; 128: 840-847.

121 Craig JC, Irwig LM, Knight JF, Roy LP. Does treatment of vesicoureteric reflux in childhood prevent end-stage renal disease attributable to reflux nephropathy?. Pediatrics. 2000; 105: 1236-1241.

122 Polito C, La Manna A, Mansi L, Rambaldi PF, Papale MR, Marte A et al. Body growth in early diagnosed vesicoureteric reflux. Pediatr Nephrol. 1999; 13: 876-879.

123 Fu LS, Hong YT, Shu SG. Height and weight growth in children with vesicoureteral reflux diagnosed before one year old. Urology. 2009; 74: 1314-1317.

124 Hollowell JG. Outcome of pregnancy in women with a history of vesico-ureteric reflux. BJU Int. 2008; 102: 780-784.

125 Roihuvuo-Leskinen HM, Vainio MI, Niskanen KM, Lahdes-Vasama TT. Pregnancies in women with childhood vesicoureteral reflux. Acta Obstet Gynecol Scand. 2015; 94: 847-851.

126 Geback C, Hansson S, Martinell J, Milsom I, Sandberg T, Jodal U. Obstetrical outcome in women with urinary tract infections in childhood. Acta Obstet Gynecol Scand. 2016; 95: 452-457.

127 Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med. 2003; 348: 195-202.

128 Zamir G, Sakran W, Horowitz Y, Koren A, Miron D. Urinary tract infection: is there a need for routine renal ultrasonography?. Arch Dis Child. 2004; 89: 466-468.

129 Privett JT, Jeans WD, Roylance J. The incidence and importance of renal duplication. Clin Radiol. 1976; 27: 521-530.

130 Bisset GS,3rd, Strife JL. The duplex collecting system in girls with urinary tract infection: prevalence and significance. AJR Am J Roentgenol. 1987; 148: 497-500.

131 Gay SB, Armistead JP, Weber ME, Williamson BR. Left infrarenal region: anatomic variants, pathologic conditions, and diagnostic pitfalls. Radiographics. 1991; 11: 549-570.

132 Siomou E, Papadopoulou F, Kollios KD, Photopoulos A, Evagelidou E, Androulakakis P et al. Duplex collecting system diagnosed during the first 6 years of life after a first urinary tract infection: a study of 63 children. J Urol. 2006; 175: 678-81; discussion 681-2.

133 Rubenwolf P, Ziesel C, Beetz R, Kamal MM, Thuroff JW, Stein R. Presentation, Management and Long-Term Outcome of Ureteropelvic Junction Obstruction in Duplex Kidneys. J Urol. 2015; 194: 427-432.

134 Snyder HM,3rd, Lebowitz RL, Colodny AH, Bauer SB, Retik AB. Ureteropelvic junction obstruction in children. Urol Clin North Am. 1980; 7: 273-290.

135 Ross JH, Kay R. Ureteropelvic junction obstruction in anomalous kidneys. Urol Clin North Am. 1998; 25: 219-225.

136 Gotoh T, Takahashi Y, Kumagai A, Tokunaka S, Koyanagi T. Two cases of ectopic ureter opening into the ejaculatory duct: double vas deferens revisited. J Urol. 1983; 130: 550-552.

137 Pinter A, Jilling A, Vajda M, Baranyi E, Farkas A. Ectopic ureter in infancy and childhood. Orv Hetil. 1991; 132: 1143-1148.

138 Ahmed S, Morris LL, Byard RW. Ectopic ureter with complete ureteric duplication in the female child. J Pediatr Surg. 1992; 27: 1455-1460.

139 Wakhlu A, Dalela D, Tandon RK, Chandra H, Wakhlu AK. The single ectopic ureter. Br J Urol. 1998; 82: 246-251.

140 Dore B, Irani J, De Lustrac JM, Aubert J. Vesicorenal reflux and ureteral duplication. Study of 62 cases. J Urol (Paris). 1990; 96: 303-310.

141 Fernbach SK, Feinstein KA, Spencer K, Lindstrom CA. Ureteral duplication and its complications. Radiographics. 1997; 17: 109-127.

142 Tripp BM, Homsy YL. Neonatal hydronephrosis--the controversy and the management. Pediatr Nephrol. 1995; 9: 503-509.

143 Fefer S, Ellsworth P. Prenatal hydronephrosis. Pediatr Clin North Am. 2006; 53: 429-47, vii.

144 Dias CS, Silva JM, Pereira AK, Marino VS, Silva LA, Coelho AM et al. Diagnostic accuracy of renal pelvic dilatation for detecting surgically managed ureteropelvic junction obstruction. J Urol. 2013; 190: 661-666.

145 Dressler GR, Wilkinson JE, Rothenpieler UW, Patterson LT, Williams-Simons L, Westphal H. Deregulation of Pax-2 expression in transgenic mice generates severe kidney abnormalities. Nature. 1993; 362: 65-67.

146 Taha MA, Shokeir AA, Osman HG, Abd el-Aziz A, Farahat SE. Diagnosis of ureteropelvic junction obstruction in children: role of endothelin-1 in voided urine. Urology. 2007; 69: 560-4; discussion 564-5.

147 Kaya C, Caliskan S. Comparison between intravenous urography and computed tomography urography in diagnosing ureteropelvic junction obstruction. Nephrourol Mon. 2012; 4: 585-586.

148 Muthusami P, Ramesh A. Appearances of the circumcaval ureter on excretory urography and MR urography: A single-center case series. Indian J Radiol Imaging. 2013; 23: 81-85.

149 Arlen AM, Kirsch AJ, Cuda SP, Little SB, Jones RA, Grattan-Smith JD et al. Magnetic resonance urography for diagnosis of pediatric ureteral stricture. J Pediatr Urol. 2014; 10: 792-798.

150 Esmaeili M, Esmaeili M, Ghane F, Alamdaran A. Comparison Between Diuretic Urography (IVP) and Diuretic Renography for Diagnosis of Ureteropelvic Junction Obstruction in Children. Iran J Pediatr. 2016; 26: e4293.

151 Poulsen EU, Kirkeby HJ, Munch-Jorgensen T, Nerstrom B, Mortensen J. Preoperative symptomatology and diagnostic findings in relation to outcome of pyeloplasty in patients with primary hydronephrosis. Urol Int. 1988; 43: 234-238.

152 Ransley PG, Dhillon HK, Gordon I, Duffy PG, Dillon MJ, Barratt TM. The postnatal management of hydronephrosis diagnosed by prenatal ultrasound. J Urol. 1990; 144: 584-7; discussion 593-4.

153 Cartwright PC, Duckett JW, Keating MA, Snyder HM,3rd, Escala J, Blyth B et al. Managing apparent ureteropelvic junction obstruction in the newborn. J Urol. 1992; 148: 1224-1228.

154 Duckett JW,Jr. When to operate on neonatal hydronephrosis. Urology. 1993; 42: 617-619.

155 Palmer LS, Maizels M, Cartwright PC, Fernbach SK, Conway JJ. Surgery versus observation for managing obstructive grade 3 to 4 unilateral hydronephrosis: a report from the Society for Fetal Urology. J Urol. 1998; 159: 222-228.

156 Sutherland DE, Jarrett TW. Surgical options in the management of ureteropelvic junction obstruction. Curr Urol Rep. 2009; 10: 23-28.

157 Mayor G, Genton N, Torrado A, Guignard JP. Renal function in obstructive nephropathy: long-term effect of reconstructive surgery. Pediatrics. 1975; 56: 740-747.

158 King LR, Coughlin PW, Bloch EC, Bowie JD, Ansong K, Hanna MK. The case for immediate pyeloplasty in the neonate with ureteropelvic junction obstruction. J Urol. 1984; 132: 725-728.

159 Thorup J, Mortensen T, Diemer H, Johnsen A, Nielsen OH. The prognosis of surgically treated congenital hydronephrosis after diagnosis in utero. J Urol. 1985; 134: 914-917.

160 Danuser H, Ackermann DK, Bohlen D, Studer UE. Endopyelotomy for primary ureteropelvic junction obstruction: risk factors determine the success rate. J Urol. 1998; 159: 56-61.

161 Song SH, Lee SB, Park YS, Kim KS. Is antibiotic prophylaxis necessary in infants with obstructive hydronephrosis?. J Urol. 2007; 177: 1098-101; discussion 1101.

162 Islek A, Guven AG, Koyun M, Akman S, Alimoglu E. Probability of urinary tract infection in infants with ureteropelvic junction obstruction: is antibacterial prophylaxis really needed?. Pediatr Nephrol. 2011; 26: 1837-1841.

163 Alon US, Ganapathy S. Should renal ultrasonography be done routinely in children with first urinary tract infection?. Clin Pediatr (Phila). 1999; 38: 21-25.

164 Gupta P, Mandal J, Krishnamurthy S, Barathi D, Pandit N. Profile of urinary tract infections in paediatric patients. Indian J Med Res. 2015; 141: 473-477.

165 Zornoza M, Angulo JM, Parente A, Simal S, Burgos L, Ortiz R. Late diagnosis of posterior urethral valves. Actas Urol Esp. 2015; 39: 646-650.

166 Bhadoo D, Bajpai M, Panda SS. Posterior urethral valve: Prognostic factors and renal outcome. J Indian Assoc Pediatr Surg. 2014; 19: 133-137.

167 Pagano MJ, van Batavia JP, Casale P. Laser ablation in the management of obstructive uropathy in neonates. J Endourol. 2015; 29: 611-614.

168 Coplen DE, Duckett JW. The modern approach to ureteroceles. J Urol. 1995; 153: 166-171.

169 Chtourou M, Sallami S, Rekik H, Binous MY, Kbaier I, Horchani A. Ureterocele in adults complicated with calculi: diagnostic and therapeutic features. Report of 20 cases. Prog Urol. 2002; 12: 1213-1220.

170 Gunsar C, Mir E, Sencan A, Ertan P, Ozcan CU. Pediatric ureteroceles: diagnosis, management and treatment options. Iran J Pediatr. 2010; 20: 413-419.

171 Caldamone AA, Snyder HM,3rd, Duckett JW. Ureteroceles in children: followup of management with upper tract approach. J Urol. 1984; 131: 1130-1132.

172 Blyth B, Passerini-Glazel G, Camuffo C, Snyder HM,3rd, Duckett JW. Endoscopic incision of ureteroceles: intravesical versus ectopic. J Urol. 1993; 149: 556-9; discussion 560.

173 Shokeir AA, Nijman RJ. Ureterocele: an ongoing challenge in infancy and childhood. BJU Int. 2002; 90: 777-783.

174 Chowdhary SK, Kandpal DK, Sibal A, Srivastava RN, Vasudev AS. Ureterocele in newborns, infants and children: Ten year prospective study with primary endoscopic deroofing and double J (DJ) stenting. J Pediatr Surg. 2016; .

175 Paye-Jaouen A, Pistolesi F, Botto N, Enezian G, Grapin-Dagorno C, Peycelon M et al. Long-term bladder function after ureterocele decompression in children. J Urol. 2015; 193: 1754-1759.

176 Timberlake MD, Corbett ST. Minimally invasive techniques for management of the ureterocele and ectopic ureter: upper tract versus lower tract approach. Urol Clin North Am. 2015; 42: 61-76.

177 Blane CE, Zerin JM, Bloom DA. Bladder diverticula in children. Radiology. 1994; 190: 695-697.

178 Celebi S, Sander S, Kuzdan O, Ozaydin S, Besik Bestas C, Yavuz S et al. Current diagnosis and management of primary isolated bladder diverticula in children. J Pediatr Urol. 2015; 11: 61.e1-61.e5.

179 Alexander RE, Kum JB, Idrees M. Bladder diverticulum: clinicopathologic spectrum in pediatric patients. Pediatr Dev Pathol. 2012; 15: 281-285.

180 Bhat A, Bothra R, Bhat MP, Chaudhary GR, Saran RK, Saxena G. Congenital bladder diverticulum presenting as bladder outlet obstruction in infants and children. J Pediatr Urol. 2012; 8: 348-353.

181 Khemakhem R, Ghorbel S, Jlidi S, Nouira F, Louati H, Douira W et al. Management of congenital bladder diverticulum in children: A report of seven cases. Afr J Paediatr Surg. 2013; 10: 160-163.

182 Appeadu-Mensah W, Hesse AA, Yaw MB. Giant bladder diverticulum: a rare cause of bladder outlet obstruction in children. Afr J Paediatr Surg. 2012; 9: 83-87.

183 Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D. Prevalence of urinary tract infection in febrile infants. J Pediatr. 1993; 123: 17-23.

184 Shaw KN, Gorelick M, McGowan KL, Yakscoe NM, Schwartz JS. Prevalence of urinary tract infection in febrile young children in the emergency department. Pediatrics. 1998; 102: e16.

185 Lau AY, Wong SN, Yip KT, Fong KW, Li SP, Que TL. A comparative study on bacterial cultures of urine samples obtained by clean-void technique versus urethral catheterization. Acta Paediatr. 2007; 96: 432-436.

186 Kim GA, Koo JW. Validity of bag urine culture for predicting urinary tract infections in febrile infants: a paired comparison of urine collection methods. Korean J Pediatr. 2015; 58: 183-189.

187 Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M. Is urine culture necessary to rule out urinary tract infection in young febrile children?. Pediatr Infect Dis J. 1996; 15: 304-309.

188 Honkinen O, Jahnukainen T, Mertsola J, Eskola J, Ruuskanen O. Bacteremic urinary tract infection in children. Pediatr Infect Dis J. 2000; 19: 630-634.

189 Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med. 2003; 348: 195-202.

190 Jahnukainen T, Honkinen O, Ruuskanen O, Mertsola J. Ultrasonography after the first febrile urinary tract infection in children. Eur J Pediatr. 2006; 165: 556-559.

191 Zamir G, Sakran W, Horowitz Y, Koren A, Miron D. Urinary tract infection: is there a need for routine renal ultrasonography?. Arch Dis Child. 2004; 89: 466-468.

192 Giorgi LJ,Jr, Bratslavsky G, Kogan BA. Febrile urinary tract infections in infants: renal ultrasound remains necessary. J Urol. 2005; 173: 568-570.

193 Jahnukainen T, Honkinen O, Ruuskanen O, Mertsola J. Ultrasonography after the first febrile urinary tract infection in children. Eur J Pediatr. 2006; 165: 556-559.

194 Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med. 2003; 348: 195-202.

195 Montini G, Zucchetta P, Tomasi L, Talenti E, Rigamonti W, Picco G et al. Value of imaging studies after a first febrile urinary tract infection in young children: data from Italian renal infection study 1. Pediatrics. 2009; 123: e239-46.

196 Wong SN, Tse NK, Lee KP, Yuen SF, Leung LC, Pau BC et al. Evaluating different imaging strategies in children after first febrile urinary tract infection. Pediatr Nephrol. 2010; 25: 2083-2091.

197 Soccorso G, Moss G, Roberts J, Godbole P. Infantile urinary tract infection and timing of micturating cystourethrogram. J Pediatr Urol. 2010; 6: 582-584.

198 Leibovic SJ, Lebowitz RL. Reducing patient dose in voiding cystourethrography. Urol Radiol. 1980; 2: 103-107.

199 Bjorgvinsson E, Majd M, Eggli KD. Diagnosis of acute pyelonephritis in children: comparison of sonography and 99mTc-DMSA scintigraphy. AJR Am J Roentgenol. 1991; 157: 539-543.

200 Farnsworth RH, Rossleigh MA, Leighton DM, Bass SJ, Rosenberg AR. The detection of reflux nephropathy in infants by 99mtechnetium dimercaptosuccinic acid studies. J Urol. 1991; 145: 542-546.

201 Benador D, Benador N, Slosman DO, Nussle D, Mermillod B, Girardin E. Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. J Pediatr. 1994; 124: 17-20.

202 Hansson S, Dhamey M, Sigstrom O, Sixt R, Stokland E, Wennerstrom M et al. Dimercapto-succinic acid

scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. J Urol. 2004; 172: 1071-3; discussion 1073-4.

203 Tseng MH, Lin WJ, Lo WT, Wang SR, Chu ML, Wang CC. Does a normal DMSA obviate the performance of voiding cystourethrography in evaluation of young children after their first urinary tract infection?. J Pediatr. 2007; 150: 96-99.

204 2009_RevisedGuidelines DMSA_0909_EANM_format - gl_paed_dmsa_scin.pdf2015:.

205 Hitzel A, Liard A, Dacher JN, Gardin I, Menard JF, Manrique A et al. Quantitative analysis of 99mTc-DMSA during acute pyelonephritis for prediction of long-term renal scarring. J Nucl Med. 2004; 45: 285-289.

206 Nasrallah PF, Nara S, Crawford J. Clinical applications of nuclear cystography. J Urol. 1982; 128: 550-553.

207 Kogan SJ, Sigler L, Levitt SB, Reda EF, Weiss R, Greifer I. Elusive vesicoureteral reflux in children with normal contrast cystograms. J Urol. 1986; 136: 325-328.

208 Fettich JJ, Kenda RB. Cyclic direct radionuclide voiding cystography: increasing reliability in detecting vesicoureteral reflux in children. Pediatr Radiol. 1992; 22: 337-338.

209 Zhang G, Day DL, Loken M, Gonzalez R. Grading of reflux by radionuclide cystography. Clin Nucl Med. 1987; 12: 106-109.

210 Fettich J, Colarinha P, Fischer S, Frokier J, Gordon I, Hahn K et al. Guidelines for direct radionuclide cystography in children. Eur J Nucl Med Mol Imaging. 2003; 30: B39-44.

211 Dimitriou P, Fretzayas A, Nicolaidou P, Gritzali F, Kasfiki A, Karpathios T. Estimates of dose to the bladder during direct radionuclide cystography: concise communication. J Nucl Med. 1984; 25: 792-795.

212 Smith T, Gordon I. An update of radiopharmaceutical schedules in children. Nucl Med Commun. 1998; 19: 1023-1036.

213 Stabin MG, Gelfand MJ. Dosimetry of pediatric nuclear medicine procedures. Q J Nucl Med. 1998; 42: 93-112.

214 Gordon I, Colarinha P, Fettich J, Fischer S, Frokier J, Hahn K et al. Guidelines for indirect radionuclide cystography. Eur J Nucl Med. 2001; 28: BP16-20.

215 Willi U, Treves S. Radionuclide voiding cystography. Urol Radiol. 1983; 5: 161-73, 175.

216 Majd M, Kass EJ, Belman AB. Radionuclide cystography in children: comparison of direct (retrograde) and indirect (intravenous) techniques. Ann Radiol (Paris). 1985; 28: 322-328.

217 De Sadeleer C, De Boe V, Keuppens F, Desprechins B, Verboven M, Piepsz A. How good is technetium-99m mercaptoacetyltriglycine indirect cystography?. Eur J Nucl Med. 1994; 21: 223-227.

218 Gordon I, Piepsz A, Sixt R, Auspices of Paediatric Committee of European Association of Nuclear Medicine. Guidelines for standard and diuretic renogram in children. Eur J Nucl Med Mol Imaging. 2011; 38: 1175-1188.

219 Lassmann M, L. Biassoni, M. Monsieurs, C. Franzius, F. Jacobs, EANM Dosimetry and Paediatrics Committees. The new EANM paediatric dosage card. Eur J Nucl Med Mol Imaging. 2008; 35: 1748-007-0572-5.

220 Martin WG, Schneider K, Lauer O, Fendel H, Pabst HW. Investigations for vesicoureteric reflux in children: ultrasound vs. radionuclide voiding cystography. Uremia Invest. 1985; 9: 253-258.

221 Balbay MD, Ozsan O, Ozbek E, Ozkan S, Gunes A. Comparison of screening of vesicoureteral reflux with renal ultrasound and voiding cystourethrography. Int Urol Nephrol. 1998; 30: 263-266.

222 Haberlik A. Detection of low-grade vesicoureteral reflux in children by color Doppler imaging mode. Pediatr Surg Int. 1997; 12: 38-43.

223 Egghart G, Schlickenrieder JH, Hautmann R. Diagnosis of reflux in children with CO2 and ultrasound. Technic and preliminary results. Urologe A. 1986; 25: 329-332.

224 Hanbury DC, Coulden RA, Farman P, Sherwood T. Ultrasound cystography in the diagnosis of vesicoureteric reflux. Br J Urol. 1990; 65: 250-253.

225 Schneider K, Jablonski C, Fendel H. Contrast sonography of the urinary tract in children. Ultraschall Med. 1986; 7: 30-33.

226 Atala A, Ellsworth P, Share J, Paltiel H, Walker RD, Retik AB. Comparison of sonicated albumin enhanced sonography to fluoroscopic and radionuclide voiding cystography for detecting vesicoureteral reflux. J Urol. 1998; 160: 1820-1822.

227 Kaneko K, Kuwatsuru R, Fukuda Y, Yamataka A, Yabuta K, Katayama H et al. Contrast sonography for detection of vesicoureteral reflux. Lancet. 1994; 344: 687.

228 Darge K, Troeger J, Duetting T, Zieger B, Rohrschneider W, Moehring K et al. Reflux in young patients: comparison of voiding US of the bladder and retrovesical space with echo enhancement versus voiding cystourethrography for diagnosis. Radiology. 1999; 210: 201-207.

229 Darge K. Diagnosis of vesicoureteral reflux with ultrasonography. Pediatr Nephrol. 2002; 17: 52-60.

230 Matsui Z, Asanuma H, Satoh H, Aoki Y, Sakurabayashi K, Mizuno R et al. The new diagnostic approach using ureteral jet angle measurement in children with urinary tract infection. J Urol. 2015; 193: e665.

231 Lee SK, Chang Y, Park NH, Kim YH, Woo S. Magnetic resonance voiding cystography in the diagnosis of vesicoureteral reflux: comparative study with voiding cystourethrography. J Magn Reson Imaging. 2005; 21: 406-414.

232 Vasanawala SS, Kennedy WA, Ganguly A, Fahrig R, Rieke V, Daniel B et al. MR voiding cystography for evaluation of vesicoureteral reflux. AJR Am J Roentgenol. 2009; 192: W206-11.

233 Arthurs OJ, Edwards AD, Joubert I, Graves MJ, Set PA, Lomas DJ. Interactive magnetic resonance imaging for paediatric vesicoureteric reflux (VUR). Eur J Radiol. 2013; 82: e112-9.

234 Johnin K, Takazakura R, Furukawa A, Okamoto K, Murakami Y, Murata K et al. Magnetic resonance voiding cystourethrography (MRVCUG): a potential alternative to standard VCUG. J Magn Reson Imaging. 2013; 38: 897-904.

235 Takazakura R, Johnin K, Furukawa A, Nitta N, Takahashi M, Okada Y et al. Magnetic resonance voiding cystourethrography for vesicoureteral reflux. J Magn Reson Imaging. 2007; 25: 170-174.

236 Arunachalam K, Maccarini PF, De Luca V, Bardati F, Snow BW, Stauffer PR. Modeling the detectability of vesicoureteral reflux using microwave radiometry. Phys Med Biol. 2010; 55: 5417-5435.

237 Birkelund Y, Klemetsen O, Jacobsen SK, Arunachalam K, Maccarini P, Stauffer PR. Vesicoureteral reflux in children: a phantom study of microwave heating and radiometric thermometry of pediatric bladder. IEEE Trans Biomed Eng. 2011; 58: 3269-3278.

238 Snow BW, Arunachalam K, De Luca V, Maccarini PF, Klemetsen O, Birkelund Y et al. Non-invasive vesicoureteral reflux detection: heating risk studies for a new device. J Pediatr Urol. 2011; 7: 624-630.

239 O'Donnell B, Puri P. Treatment of vesicoureteric reflux by endoscopic injection of Teflon. Br Med J (Clin Res Ed). 1984; 289: 7-9.

240 Molitierno JA, Scherz HC, Kirsch AJ. Endoscopic treatment of vesicoureteral reflux using dextranomer hyaluronic acid copolymer. J Pediatr Urol. 2008; 4: 221-228.

241 Koff SA, Murtagh DS. The uninhibited bladder in children: effect of treatment on recurrence of urinary infection and on vesicoureteral reflux resolution. J Urol. 1983; 130: 1138-1141.

242 O'Regan S, Yazbeck S, Schick E. Constipation, bladder instability, urinary tract infection syndrome. Clin Nephrol. 1985; 23: 152-154.

243 Loening-Baucke V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics. 1997; 100: 228-232.

244 De Paepe H, Renson C, Van Laecke E, Raes A, Vande Walle J, Hoebeke P. Pelvic-floor therapy and toilet training in young children with dysfunctional voiding and obstipation. BJU Int. 2000; 85: 889-893.

245 Gearhart JP, Woolfenden KA. The vesico-psoas hitch as an adjunct to megaureter repair in childhood. J Urol. 1982; 127: 505-507.

246 Simforoosh N, Hariri H. Management of vesicoureteral reflux without indwelling catheter and drain, using trigonoplasty technique. J Pediatr Urol. 2008; 4: 445-447.

247 Nelson CP, Hubert KC, Kokorowski PJ, Huang L, Prasad MM, Rosoklija I et al. Long-term incidence of urinary tract infection after ureteral reimplantation for primary vesicoureteral reflux. J Pediatr Urol. 2013; 9: 92-98.

248 Nagler EV, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev. 2011; (6):CD001532. doi: CD001532.

249 Diamond DA, Rabinowitz R, Hoenig D, Caldamone AA. The mechanism of new onset contralateral reflux following unilateral ureteroneocystostomy. J Urol. 1996; 156: 665-667.

250 Noe HN. The risk and risk factors of contralateral reflux following repair of simple unilateral primary reflux. J Urol. 1998; 160: 849-850.

251 Liu C, Chin T, Wei C. Contralateral reflux after unilateral ureteral reimplantation--preexistent rather than new-onset reflux. J Pediatr Surg. 1999; 34: 1661-1664.

252 Fung LC, McLorie GA, Jain U, Khoury AE, Churchill BM. Voiding efficiency after ureteral reimplantation: a comparison of extravesical and intravesical techniques. J Urol. 1995; 153: 1972-1975.

253 Burbige KA, Miller M, Connor JP. Extravesical ureteral reimplantation: results in 128 patients. J Urol. 1996; 155: 1721-1722.

254 Lapointe SP, Barrieras D, Leblanc B, Williot P. Modified Lich-Gregoir ureteral reimplantation: experience of a Canadian center. J Urol. 1998; 159: 1662-1664.

255 Lipski BA, Mitchell ME, Burns MW. Voiding dysfunction after bilateral extravesical ureteral reimplantation. J Urol. 1998; 159: 1019-1021.

256 Minevich E, Aronoff D, Wacksman J, Sheldon CA. Voiding dysfunction after bilateral extravesical detrusorrhaphy. J Urol. 1998; 160: 1004-6; discussion 1038.

257 Barrieras D, Lapointe S, Reddy PP, Williot P, McLorie GA, Bagli D et al. Urinary retention after bilateral extravesical ureteral reimplantation: does dissection distal to the ureteral orifice have a role?. J Urol. 1999; 162: 1197-1200.

258 Marotte JB, Smith DP. Extravesical ureteral reimplantations for the correction of primary reflux can be done as outpatient procedures. J Urol. 2001; 165: 2228-2231.

259 Kasturi S, Sehgal SS, Christman MS, Lambert SM, Casale P. Prospective long-term analysis of nerve-sparing extravesical robotic-assisted laparoscopic ureteral reimplantation. Urology. 2012; 79: 680-683.

260 Smith RP, Oliver JL, Peters CA. Pediatric robotic extravesical ureteral reimplantation: comparison with open surgery. J Urol. 2011; 185: 1876-1881.

261 Chalmers D, Herbst K, Kim C. Robotic-assisted laparoscopic extravesical ureteral reimplantation: an initial experience. J Pediatr Urol. 2012; 8: 268-271.

262 Hayashi Y, Mizuno K, Kurokawa S, Nakane A, Kamisawa H, Nishio H et al. Extravesical robot-assisted laparoscopic ureteral reimplantation for vesicoureteral reflux: initial experience in Japan with the ureteral advancement technique. Int J Urol. 2014; 21: 1016-1021.

263 Marchini GS, Hong YK, Minnillo BJ, Diamond DA, Houck CS, Meier PM et al. Robotic assisted laparoscopic ureteral reimplantation in children: case matched comparative study with open surgical approach. J Urol. 2011; 185: 1870-1875.

264 Matouschek E. Treatment of vesicorenal reflux by transurethral teflon-injection (author's transl). Urologe A. 1981; 20: 263-264.

265 Kirsch AJ, Perez-Brayfield M, Smith EA, Scherz HC. The modified sting procedure to correct vesicoureteral reflux: improved results with submucosal implantation within the intramural ureter. J Urol. 2004; 171: 2413-2416.

266 Cerwinka WH, Scherz HC, Kirsch AJ. Dynamic hydrodistention classification of the ureter and the double hit method to correct vesicoureteral reflux. Arch Esp Urol. 2008; 61: 882-887.

267 Kalisvaart JF, Scherz HC, Cuda S, Kaye JD, Kirsch AJ. Intermediate to long-term follow-up indicates low risk of recurrence after Double HIT endoscopic treatment for primary vesico-ureteral reflux. J Pediatr Urol. 2012; 8: 359-365.

268 Kaye JD, Srinivasan AK, Delaney C, Cerwinka WH, Elmore JM, Scherz HC et al. Clinical and radiographic results of endoscopic injection for vesicoureteral reflux: defining measures of success. J Pediatr Urol. 2012; 8: 297-303.

269 Kirsch AJ, Arlen AM, Lackgren G. Current trends in dextranomer hyaluronic acid copolymer (Deflux) injection technique for endoscopic treatment of vesicoureteral reflux. Urology. 2014; 84: 462-468.

270 Reunanen M. Correction of vesicoureteral reflux in children by endoscopic collagen injection: a prospective study. J Urol. 1995; 154: 2156-2158.

271 Aaronson IA, Rames RA, Greene WB, Walsh LG, Hasal UA, Garen PD. Endoscopic treatment of reflux: migration of Teflon to the lungs and brain. Eur Urol. 1993; 23: 394-399.

272 Smith DP, Kaplan WE, Oyasu R. Evaluation of polydimethylsiloxane as an alternative in the endoscopic treatment of vesicoureteral reflux. J Urol. 1994; 152: 1221-1224.

273 Haferkamp A, Contractor H, Mohring K, Staehler G, Dorsam J. Failure of subureteral bovine collagen injection for the endoscopic treatment of primary vesicoureteral reflux in long-term follow-up. Urology. 2000; 55: 759-763.

274 Kempf C, Winkelmann B, Roigas J, Querfeld U, Muller D. Severe complications after endoscopic injection of polydimethylsiloxane for the treatment of vesicoureteral reflux in early childhood. Scand J Urol Nephrol. 2010; 44: 347-353.

275 Chertin B, Arafeh WA, Zeldin A, Kocherov S. Preliminary data on endoscopic treatment of vesicoureteric reflux with polyacrylate polyalcohol copolymer (Vantris(R)): surgical outcome following single injection. J Pediatr Urol. 2011; 7: 654-657.

276 Eyssartier E, Mourtada H, Dieckmann AK, Maillard R, Lardy H. Chronic limping due to calcification in a subureteric Macroplastique((R)) implant. Arch Pediatr. 2012; 19: 1337-1339.

277 Stredele RJ, Dietz HG, Stehr M. Long-term results of endoscopic treatment of vesicoureteral reflux in children: comparison of different bulking agents. J Pediatr Urol. 2013; 9: 71-76.

278 Stenberg A, Larsson E, Lindholm A, Ronneus B, Stenberg A, Lackgren G. Injectable dextranomer-based implant: histopathology, volume changes and DNA-analysis. Scand J Urol Nephrol. 1999; 33: 355-361.

279 Elder JS, Diaz M, Caldamone AA, Cendron M, Greenfield S, Hurwitz R et al. Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. J Urol. 2006; 175: 716-722.

280 Lackgren G, Wahlin N, Skoldenberg E, Stenberg A. Long-term followup of children treated with dextranomer/hyaluronic acid copolymer for vesicoureteral reflux. J Urol. 2001; 166: 1887-1892.

281 Puri P, Chertin B, Velayudham M, Dass L, Colhoun E. Treatment of vesicoureteral reflux by endoscopic injection of dextranomer/hyaluronic Acid copolymer: preliminary results. J Urol. 2003; 170: 1541-4; discussion 1544.

282 Pelletier AK, Anderson PA, Schwarz RD. Comparison of different substances for subureteric injection in the management of vesicoureteric reflux in children. Can J Urol. 2005; 12: 2774-2777.

283 Moore K, Bolduc S. Prospective study of polydimethylsiloxane vs dextranomer/hyaluronic acid injection for treatment of vesicoureteral reflux. J Urol. 2014; 192: 1794-1799.

284 Rubenwolf PC, Ebert AK, Ruemmele P, Rosch WH. Delayed-onset ureteral obstruction after endoscopic dextranomer/hyaluronic acid copolymer (Deflux) injection for treatment of vesicoureteral reflux in children: a case series. Urology. 2013; 81: 659-662.

285 Christen S, Mendoza M, Gobet R, Bode P, Weber D. Late ureteral obstruction after injection of dextranomer/hyaluronic acid copolymer. Urology. 2014; 83: 920-922.

286 Hunziker M, Mohanan N, D'Asta F, Puri P. Endoscopic treatment of primary grade V vesicoureteral reflux

using hyaluronic acid copolymer (DX/HA). Pediatr Surg Int. 2010; 26: 977-979.

287 Reunanen M. Endoscopic collagen injection: its limits in correcting vesico-ureteral reflux in duplicated ureters. Eur Urol. 1997; 31: 243-245.

288 Brandstrom P, Esbjorner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol. 2010; 184: 286-291.

289 Venhola M, Huttunen NP, Uhari M. Meta-analysis of vesicoureteral reflux and urinary tract infection in children. Scand J Urol Nephrol. 2006; 40: 98-102.

290 Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics. 2008; 122: 1064-1071.

291 Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics. 2008; 121: e1489-94.

292 Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med. 2009; 361: 1748-1759.

293 Brendstrup L, Hjelt K, Petersen KE, Petersen S, Andersen EA, Daugbjerg PS et al. Nitrofurantoin versus trimethoprim prophylaxis in recurrent urinary tract infection in children. A randomized, double-blind study. Acta Paediatr Scand. 1990; 79: 1225-1234.

294 Ladhani S, Gransden W. Increasing antibiotic resistance among urinary tract isolates. Arch Dis Child. 2003; 88: 444-445.

295 Lee SJ, Shim YH, Cho SJ, Lee JW. Probiotics prophylaxis in children with persistent primary vesicoureteral reflux. Pediatr Nephrol. 2007; 22: 1315-1320.

296 Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2012; 10: CD001321.

297 Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol. 1998; 160: 1019-1022.

298 Chandra M, Maddix H, McVicar M. Transient urodynamic dysfunction of infancy: relationship to urinary tract infections and vesicoureteral reflux. J Urol. 1996; 155: 673-677.

299 Peters CA, Skoog SJ, Arant BS,Jr, Copp HL, Elder JS, Hudson RG et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol. 2010; 184: 1134-1144.

300 Sillen U, Brandstrom P, Jodal U, Holmdahl G, Sandin A, Sjoberg I et al. The Swedish reflux trial in children: v. Bladder dysfunction. J Urol. 2010; 184: 298-304.

301 Elder JS, Diaz M. Vesicoureteral reflux--the role of bladder and bowel dysfunction. Nat Rev Urol. 2013; 10: 640-648.

302 DeLuca FG, Swenson O, Fisher JH, Loutfi AH. The dysfunctional 'lazy' bladder syndrome in children. Arch Dis Child. 1962; 37: 117-121.

303 Hinman F, Baumann FW. Vesical and ureteral damage from voiding dysfunction in boys without neurologic or obstructive disease. J Urol. 1973; 109: 727-732.

304 Koff SA, Lapides J, Piazza DH. Association of urinary tract infection and reflux with uninhibited bladder contractions and voluntary sphincteric obstruction. J Urol. 1979; 122: 373-376.

305 Bauer SB, Retik AB, Colodny AH, Hallett M, Khoshbin S, Dyro FM. The unstable bladder in childhood. Urol Clin North Am. 1980; 7: 321-336.

306 Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. Br J Urol. 1997; 80: 319-327.

307 Mattoo TK. Medical management of vesicoureteral reflux--quiz within the article. Don't overlook placebos. Pediatr Nephrol. 2007; 22: 1113-1120.

308 Venhola M, Reunanen M, Taskinen S, Lahdes-Vasama T, Uhari M. Interobserver and intra-observer agreement in interpreting urodynamic measurements in children. J Urol. 2003; 169: 2344-2346.

309 Venhola M, Lanning P, Uhari M. Not Available. Duodecim. 2007; 123: 1076-1082.

310 Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics. 2006; 117: 626-632.

311 Tekgul S, Riedmiller H, Hoebeke P, Kocvara R, Nijman RJ, Radmayr C et al. EAU guidelines on vesicoureteral reflux in children. Eur Urol. 2012; 62: 534-542.

312 Riccabona M, Avni FE, Blickman JG, Dacher JN, Darge K, Lobo ML et al. Imaging recommendations in paediatric uroradiology: minutes of the ESPR workgroup session on urinary tract infection, fetal hydronephrosis, urinary tract ultrasonography and voiding cystourethrography, Barcelona, Spain, June 2007. Pediatr Radiol. 2008; 38: 138-145.

313 Jodal U, Lindberg U. Guidelines for management of children with urinary tract infection and vesico-ureteric reflux. Recommendations from a Swedish state-of-the-art conference. Swedish Medical Research Council. Acta Paediatr Suppl. 1999; 88: 87-89.

314 Mackenzie JR, Murphy AV, Beattie TJ, Azmy AF. Guidelines for the management of acute urinary tract infection in childhood. J R Coll Physicians Lond. 1991; 25: 263.

315 Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Pediatrics. 1999; 103: 843-852.

316 Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. J Pediatr. 2007; 151: 581-4, 584.e1.

317 Mantadakis E, Vouloumanou EK, Georgantzi GG, Tsalkidis A, Chatzimichael A, Falagas ME. Acute Tc-99m DMSA scan for identifying dilating vesicoureteral reflux in children: a meta-analysis. Pediatrics. 2011; 128: e169-79.

318 Lee HY, Soh BH, Hong CH, Kim MJ, Han SW. The efficacy of ultrasound and dimercaptosuccinic acid scan in predicting vesicoureteral reflux in children below the age of 2 years with their first febrile urinary tract infection. Pediatr Nephrol. 2009; 24: 2009-2013.

319 Lee MD, Lin CC, Huang FY, Tsai TC, Huang CT, Tsai JD. Screening young children with a first febrile urinary tract infection for high-grade vesicoureteral reflux with renal ultrasound scanning and technetium-99m-labeled dimercaptosuccinic acid scanning. J Pediatr. 2009; 154: 797-802.

320 Quirino IG, Silva JM, Diniz JS, Lima EM, Rocha AC, Simoes e Silva AC et al. Combined use of late phase dimercapto-succinic acid renal scintigraphy and ultrasound as first line screening after urinary tract infection in children. J Urol. 2011; 185: 258-263.

321 Lee JH, Kim MK, Park SE. Is a routine voiding cystourethrogram necessary in children after the first febrile urinary tract infection?. Acta Paediatr. 2012; 101: e105-9.

322 La Scola C, De Mutiis C, Hewitt IK, Puccio G, Toffolo A, Zucchetta P et al. Different guidelines for imaging after first UTI in febrile infants: yield, cost, and radiation. Pediatrics. 2013; 131: e665-71.

323 Leroy S, Romanello C, Galetto-Lacour A, Bouissou F, Fernandez-Lopez A, Smolkin V et al. Procalcitonin is a predictor for high-grade vesicoureteral reflux in children: meta-analysis of individual patient data. J Pediatr. 2011; 159: 644-51.e4.

324 Leroy S, Fernandez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervaix A et al. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. Pediatrics. 2013; 131: 870-879.

325 Liao PF, Ku MS, Tsai JD, Choa YH, Hung TW, Lue KH et al. Comparison of procalcitonin and different guidelines for first febrile urinary tract infection in children by imaging. Pediatr Nephrol. 2014; 29: 1567-1574.

326 Iwaki H, Johnin K, Kageyama S, Kim CJ, Isono T, Yoshiki T. Up-regulation of urinary UPIII mRNA levels in vesicoureteral reflux patients: potential application as a screening test for vesicoureteral reflux. Int J Urol. 2007; 14: 918-923.

327 Bulut IK, Mir S, Berdeli A, Sozeri B. The predictive value of urinary UPIb mRNA levels in VUR and recurrent urinary tract infections. Clin Nephrol. 2014; 81: 152-158.

328 Saltychev M, Ristola MT, Laimi K, Hurme T. Accuracy of ultrasonography in predicting vesicoureteral reflux in children: A meta-analysis. Scand J Urol. 2016; 50: 239-245.

329 Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155: 529-536.

330 Handbook for DTA Reviews | Diagnostic Test Accuracy Working Group2015:.

331 Ristola MT, Hurme T. NICE Guidelines Cannot Be Recommended for Imaging Studies in Children Younger Than 3 Years with Urinary Tract Infection. Eur J Pediatr Surg. 2014; .

332 Ristola MT, Hurme T. NICE Guidelines Cannot Be Recommended for Imaging Studies in Children Younger Than 3 Years with Urinary Tract Infection. Eur J Pediatr Surg. 2015; 25: 414-420.

333 Ristola MT, Hurme T. Consequences of following the new American Academy of Pediatrics guidelines for imaging children with urinary tract infection. Scand J Urol. 2015; 1-5.

334 Ristola MT, Loyttyniemi E, Hurme T. Factors Associated with Abnormal Imaging and Infection Recurrence after a First Febrile Urinary Tract Infection in Children. Eur J Pediatr Surg. 2016; .

335 Jequier S, Forbes PA, Nogrady MB. The value of ultrasonography as a screening procedure in a first-documented urinary tract infection in children. J Ultrasound Med. 1985; 4: 393-400.

336 Ismaili K, Wissing KM, Lolin K, Le PQ, Christophe C, Lepage P et al. Characteristics of first urinary tract infection with fever in children: a prospective clinical and imaging study. Pediatr Infect Dis J. 2011; 30: 371-374.

337 Oostenbrink R, van der Heijden AJ, Moons KG, Moll HA. Prediction of vesico-ureteric reflux in childhood urinary tract infection: a multivariate approach. Acta Paediatr. 2000; 89: 806-810.

338 Alshamsam L, Al Harbi A, Fakeeh K, Al Banyan E. The value of renal ultrasound in children with a first episode of urinary tract infection. Ann Saudi Med. 2009; 29: 46-49.

339 Muller L, Preda I, Jacobsson B, Sixt R, Jodal U, Hansson S et al. Ultrasonography as predictor of permanent renal damage in infants with urinary tract infection. Acta Paediatr. 2009; 98: 1156-1161.

340 Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Value of ultrasound in evaluation of infants with first urinary tract infection. J Urol. 2010; 183: 1984-1988.

341 Wong SN, Tse NK, Lee KP, Yuen SF, Leung LC, Pau BC et al. Evaluating different imaging strategies in children after first febrile urinary tract infection. Pediatr Nephrol. 2010; 25: 2083-2091.

342 Tsai JD, Huang CT, Lin PY, Chang JH, Lee MD, Huang FY et al. Screening high-grade vesicoureteral reflux in young infants with a febrile urinary tract infection. Pediatr Nephrol. 2012; 27: 955-963.

343 Mahant S, Friedman J, MacArthur C. Renal ultrasound findings and vesicoureteral reflux in children hospitalised with urinary tract infection. Arch Dis Child. 2002; 86: 419-420.

344 Tse NK, Yuen SL, Chiu MC, Lai WM, Tong PC. Imaging studies for first urinary tract infection in infants less than 6 months old: can they be more selective?. Pediatr Nephrol. 2009; 24: 1699-1703.

345 Kido J, Yoshida F, Sakaguchi K, Ueno Y, Yanai M. Ultrasonography and C-reactive protein can predict the outcomes of voiding cystography after the first urinary tract infection. Acta Paediatr. 2015; 104: e216-21.

346 Lee HY, Soh BH, Hong CH, Kim MJ, Han SW. The efficacy of ultrasound and dimercaptosuccinic acid scan in predicting vesicoureteral reflux in children below the age of 2 years with their first febrile urinary tract infection. Pediatr Nephrol. 2009; 24: 2009-2013.

347 Wong SN, Tse NK, Lee KP, Yuen SF, Leung LC, Pau BC et al. Evaluating different imaging strategies in children after first febrile urinary tract infection. Pediatr Nephrol. 2010; 25: 2083-2091.

348 Lytzen R, Thorup J, Cortes D. Experience with the NICE guidelines for imaging studies in children with first pyelonephritis. Eur J Pediatr Surg. 2011; 21: 283-286.

349 Jose SS, Sharif ES. New NICE guidelines for UTI management: what will change?. Arch Dis Child. 2008; 93: 716-717.

350 Schroeder AR, Abidari JM, Kirpekar R, Hamilton JR, Kang YS, Tran V et al. Impact of a more restrictive approach to urinary tract imaging after febrile urinary tract infection. Arch Pediatr Adolesc Med. 2011; 165: 1027-1032.

351 Juliano TM, Stephany HA, Clayton DB, Thomas JC, Pope JC,4th, Adams MC et al. Incidence of abnormal imaging and recurrent pyelonephritis after first febrile urinary tract infection in children 2 to 24 months old. J Urol. 2013; 190: 1505-1510.

352 Friedman AA, Wolfe-Christensen C, Toffoli A, Hochsztein DE, Elder JS, Lakshmanan Y. History of recurrent urinary tract infection is not predictive of abnormality on voiding cystourethrogram. Pediatr Surg Int. 2013; 29: 639-643.

353 Honkinen O, Lehtonen OP, Ruuskanen O, Huovinen P, Mertsola J. Cohort study of bacterial species causing urinary tract infection and urinary tract abnormalities in children. BMJ. 1999; 318: 770-771.

354 Friedman S, Reif S, Assia A, Mishaal R, Levy I. Clinical and laboratory characteristics of non-E. coli urinary tract infections. Arch Dis Child. 2006; 91: 845-846.

355 Park S, Song SH, Lee C, Kim JW, Kim KS. Bacterial pathogens in first febrile urinary tract infection affect breakthrough infections in infants with vesicoureteral reflux treated with prophylactic antibiotics. Urology. 2013; 81: 1342-1345.

356 Dias CS, Silva JM, Diniz JS, Lima EM, Marciano RC, Lana LG et al. Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. Pediatr Infect Dis J. 2010; 29: 139-144.

357 Bulum B, Ozcakar ZB, Kavaz A, Huseynova M, Ekim M, Yalcinkaya F. Lower urinary tract dysfunction is frequently seen in urinary tract infections in children and is often associated with reduced quality of life. Acta Paediatr. 2014; 103: e454-8.

358 Vegar-Zubovic S, Kristic S, Carovac A, Sefic-Pasic I, Dzananovic A, Milicic-Pokrajac D et al. Relationship between ultrasound criteria and voiding ultrasonography (VUS) in the evaluation of vesicoureteral reflux (VUR). Med Glas (Zenica). 2014; 11: 333-338.

359 Gordon ZN, McLeod DJ, Becknell B, Bates DG, Alpert SA. Uroepithelial Thickening on Sonography Improves Detection of Vesicoureteral Reflux in Children with First Febrile Urinary Tract Infection. J Urol. 2015; 194: 1074-1079.