The Swedish Reflux Trial

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To my family

Abstract

Background Small children with dilated vesicoureteral reflux (VUR) run risk of recurrent urinary tract infections (UTI) and to acquire renal damage. To protect them, antibiotic prophylaxis and surgery to eliminate VUR have been used. Endoscopic injection of bulking agent at the ureteral orifice has evolved as alternative surgical method but with insufficient scientific support of long term effect on VUR and rate of renal damage and UTI recurrence. Regarding prophylaxis, there is increasing concern of bacterial resistance and reports of low protective effect.

Aim The aim of the trial was to evaluate three management strategies for children with dilating VUR, prophylaxis, endoscopic injection and surveillance only. Specific aims were to describe VUR outcome at two year follow-up, pattern and rate of recurrent UTI and how this differs between the three treatment strategies, and to investigate if prophylaxis or endoscopic injection can reduce rate of progression of established renal defects or new damage.

Patients and methods From 23 centers, 203 children, 128 girls and 75 boys, aged 1 to less than 2 years, with dilating VUR grade III or IV were randomized to antibiotic prophylaxis (n=69), endoscopic injection (n=66) or surveillance (n=68) and followed for 2 years by regular visits and telephone contacts with special attention to febrile UTIs. Voiding cystourethrography (VCU) and dimercaptosuccinic acid (DMSA) renal scintigraphy were performed before randomization and after 2 years. Endoscopic injection with dextranomer hyaluronic acid copolymer was followed by postoperative control with ultrasound and VCU. All calculations were done according to the intent to treat principle.

Results Resolution or downgrading to nondilating VUR was seen in 71% in the endoscopic group, more frequent than in the prophylaxis or surveillance groups, 39% and 47% respectively (p=0.0002 and 0.0030). In 13 children (20% of those in the endoscopy group) with no or nondilating VUR after 1-2 injections, dilating VUR reappeared at 2-year follow-up. There were 67 febrile UTIs in 42 girls, significantly more than the 8 infections in 7 boys (p=0.0001). In girls febrile recurrence rate was 8 of 43 (19%) on prophylaxis, 10 of 43 (23%) with endoscopic treatment and 24 of 42 (57%) on surveillance (p=0.0002). The recurrence rate was associated with persistent VUR after 2 years (p=0.0095). In boys recurrence rate was not associated with treatment group or VUR status at entry or follow-up. Renal uptake defect at entry was seen in 124 of 203 children (61%), in 69 of 128 girls (54%) and 55 of 75 boys (73%), being generalized in 30 girls (23%) and in 44 boys (59%) (p<0.0001). The 2-year DMSA scan was performed in 201 children. New renal damage in previously unscarred areas was seen in 13 girls and 2 boys. Of the girls, 8 were on surveillance, 5 in the endoscopic group and none on prophylaxis (p=0.0155). New damage was more common in children with febrile recurrence than without (11 of 49 (22%) vs 4 of 152 (3%), p<0.0001).

Conclusion In small children with VUR grade III-IV, endoscopic injection enhanced the downgrading or resolution of VUR compared to antibiotic prophylaxis or surveillance only. In boys older than 1 year, new renal damage was rare and febrile UTI recurrence rate low with no difference between treatment groups. In girls the rates of new renal damage and UTI recurrence was higher, especially in the control group on surveillance. UTI recurrence was reduced by prophylaxis and endocopic injection. New renal damage was strongly associated with UTI recurrence and was reduced by prophylaxis.

Contents

List of publications

This thesis is based on the following articles:

I. **Brandström P, Esbjörner E, Herthelius M, Holmdahl G, Läckgren G, Nevéus T, Sillén U, Sixt R, Sjöberg I, Stokland E, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: I. Study Design and Study Population Characteristics
J Urol 2010; 184: 274-9.

II. **Holmdahl G, Brandström P, Läckgren G, Sillén U, Stokland E, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: II. Vesicoureteral Reflux Outcome
J Urol 2010; 184: 280-5.

III. **Brandström P, Esbjörner E, Herthelius M, Swerkersson S, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: III. Urinary Tract Infection Pattern
J Urol 2010; 184: 286-91.

IV. **Brandström P, Nevéus T, Sixt R, Stokland E, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: IV. Renal Damage
J Urol 2010; 184: 292-7.

Abbreviations and Acronyms

CRF	case report form
CRP	C-reactive protein
DMSA	^{99m}technetium dimercaptosuccinic acid
Dx/HA	dextranomer/hyaluronic acid copolymer
UTI	urinary tract infection
VCU	voiding cystourethrography
VUR	vesicoureteral reflux

Introduction

Vesicoureteral reflux

Definition

Vesicoureteral reflux is defined as the retrograde flow of urine from the urinary bladder back into the ureter at bladder filling or emptying. It can be diagnosed by radiological techniques with catheterizaton as in voiding cystourethrography (VCU) or by radionuclide or ultrasound techniques with or without urethral catheterization.[1, 2] Its categorization is depending on the technique used for visualization. The most widespread grading system was first used in the International Reflux Study, initially described in 1981 and published in detail in 1985.[3-5] It has become the gold standard for reflux grading on VCU in research and clinical practice. It defines the reflux grade from I, with reflux restricted to a ureter of normal width, to grade V with reflux to severely dilated renal calyces and pelvis and a dilated and tortuous ureter (figure 1 and table1).

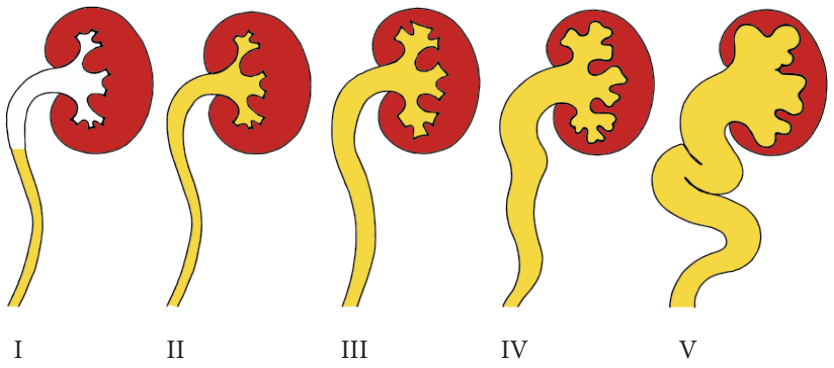


Figure 1. Reflux grading according to the International Reflux Study in Children (image modified)

Table 1. Summary of reflux grading according to the International Reflux Study in Children

Grade	Definition
I	urine refluxing into the ureter but not as far as to the renal pelvis
II	reflux into the pelvis without associated dilatation of ureter or blunting of calices
III	dilatation of the pelvis and calyces with preserved fornices of the calices
IV	further dilatation with rounding of the fornices but preserved papillary impressions
V	blunting and gross dilatation of calyces, with severe dilatation and tortuosity of the ureter.

History

VUR in man was described in 1893.[6] Its significance for UTIs was discussed in 1903 by Sampson and in 1924 Bumpus described the relationship between renal scars and VUR.[7, 8] Although cystography had been known since 1905 it was in the 1950s with the use of fluoroscopy and cine-radiography the association between VUR, UTIs and renal scarring was established, and Hodson and Edwards described the strong association between renal scarring and VUR.[9, 10]

Anatomy

The ureteral orifices are located in the lateral trigonal corners in the lower part of the bladder. The ureters enter the bladder at a sharp angle, run obliquely through the muscular portion of the bladder wall and end in a submucosal tunnel. This serves as a flap valve mechanism to prevent urine from flowing back into the ureters when bladder pressure increases during filling and voiding.

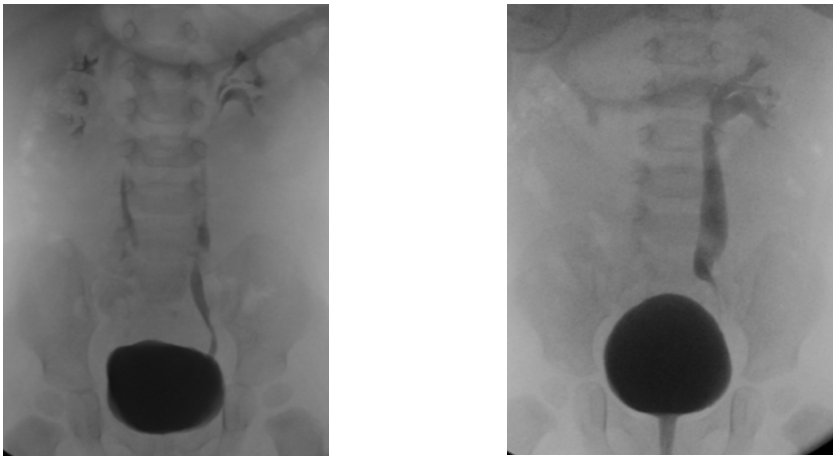
Diagnostic methods

Voiding cystourethrography (VCU)

Radiologic voiding cystourethrography has been used since the 1950s for detecting and grading VUR. A catheter is passed through the urethra and the bladder is filled with contrast medium by free dripping infusion.[5] Radiological images of the bladder, ureters and urethra are obtained during filling and voiding.

This investigation is perceived as painful and stressing for children especially at catherization, and hence stressing also for the parents. Efforts have been made to find ways to ease the pain and distress by the use of sedatives. Midazolam has been used with success and has been shown not to influence the results of the examination.[11, 12]

Intravenous urography can be performed as a complement to VCU for more accurate description of the grade of dilatation at VUR and to detect duplication of the upper urinary tract (figure 2).



Intravenous urography Voiding cystourethrography

Figure 2. Urography and VCU in a child with with VUR grade III during voiding

Other diagnostic techniques for VUR are direct radionuclide cystography where the bladder is filled with radioactive contrast fluid by urethral catheter,[13-15] indirect radionuclide cystography obtained as a byproduct at intravenous radionuclide renography[16] and ultrasound contrast enhanced voiding urosonography, also requiring catheterization.[17] All these methods can reliably detect reflux but are less detailed regarding grading compared to VCU.

Prevalence of VUR

In 1978 Ransley referred to a series of screening studies performed between 1949 and 1966 where altogether 7 of 535 healthy neonates and children were found to have VUR.[18] Of these 3 were associated with extra-urinary abnormalities and 1 with bladder neck obstruction, leading to an estimate of the prevalence of VUR to 0.5-1.3%. In an attempt to determine the prevalence of VUR in children with different clinical conditions Sargent reviewed the literature and found a prevalence of 31% in children with UTI.[19] In other patient groups the prevalence approached or even exceeded that of children with UTI. When screening siblings to children with VUR the prevalence of VUR has been reported to be around 30% in most studies but as high as 51% in one.[20-26] In children where one or both parents are known to have VUR a prevalence as high as 66% has been reported.[27] The differences in prevalence between studies on familial VUR can be contributed to differences in study populations and diagnostic modalities used for detecting VUR. Because of the observed familial accumulation of VUR a genetic explanation has been sought. There is evidence for mechanisms disturbing embryological growth and development of both the kidney and urinary tract, explaining the evident familial inheritance of VUR.[28-30] Many candidate gene loci for inherited VUR have been proposed. However, in a recent whole-genome linkage and association scan in two European populations no such major locus could be identified.[31]

The prevalence of VUR in children investigated after UTI was found to be 30%, with dilating VUR grade III-V in 52% of the VUR cases, in the population based Swedish UTI Study in children.[32]

Natural course of VUR

When managing children with dilating VUR conservatively the reflux was found to disappear or downgrade in a substantial number of cases.[33] This downgrading is more prominent during the first year of life but continuous through childhood.[34, 35] Dilating VUR is downgraded more frequently in boys compared to girls (figure 3).[36, 37]

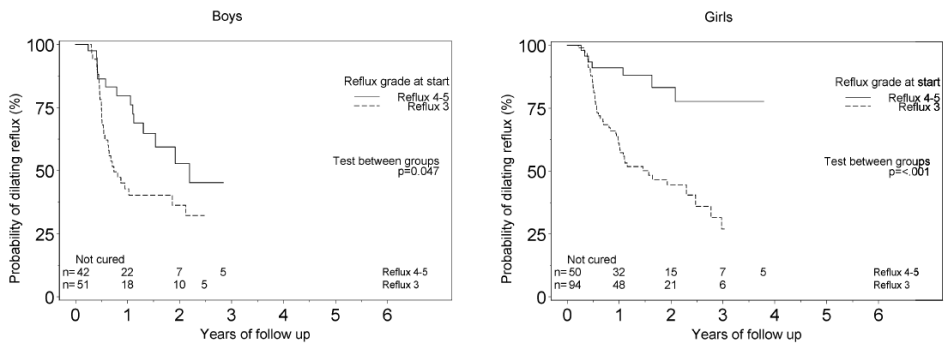


Figure 3. Resolution of dilating VUR to grade 0-II in boys and girls (From Esbjorner et al: Management of children with dilating vesico-ureteric reflux in Sweden. Acta Paediatr 2004; 93: 37-42.[36])

Treatment

Once the association between VUR and renal scarring had been established different open surgical procedures were introduced to treat reflux in order to protect the children from further renal damage.[38] Hutch was the first to describe a technique to elongate the intravesical portion of the ureter and thus creating an antireflux valve.[39] Other techniques have been proposed by pediatric urologists such as Politano-Leadbetter, Lich-Gregoir and Cohen.[40-43] They are all designed to create a sufficient valve mechanism at the ureteral orifice in the bladder wall to stop the backflow of urine into the ureters. Laparoscopic and endoscopic approaches to some of these surgical procedures have been advocated.[44-46]

Matouschek introduced the endoscopic subendothelial injection of bulking agent into the bladder wall right at the orifice of the insufficient ureter in 1981.[47] The technique was further refined by Puri and O'Donnell.[48, 49] Initially polytetrafluorethylene (Teflon™) was used, which gave rise to the acronym STING (Subendothelial Teflon Injection, later referred to as Subendothelial Transurethral Injection). Later other substances were introduced such as polydimethylsiloxane (silicone, Macroplastique™) or injectable bovine collagen.[50] In 1995 dextranomer/hyaluronic acid copolymer (Deflux™, Q-Med Uppsala, Sweden) was introduced.[51] It was approved for endoscopic injection by the Food and Drug Administration, USA, in 2001 and is the most frequently used bulking agent in reflux injection treatment throughout the world (figure 4).

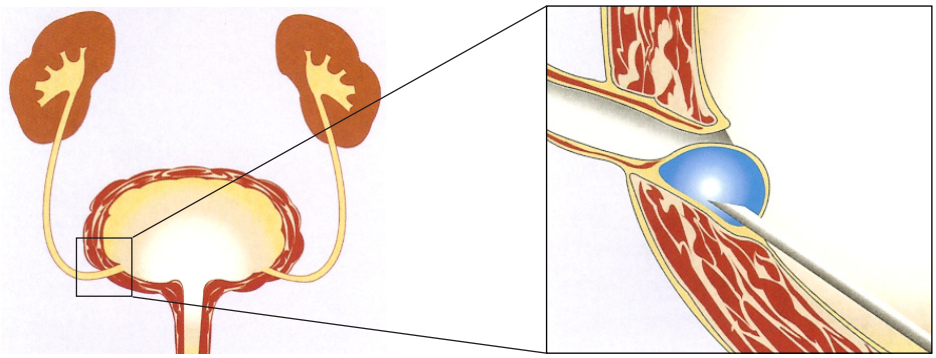


Figure 4. Cystoscopic injection of Deflux™ at the ureteric orifice in the bladder (by permission from Q-Med, Sweden)

The injection technique has constantly been refined and improved.[51] It has been successfully used to manage the reflux also in subgroups of patients initially considered unfit for the treatment, such as children with ureteral duplication and children with bladder dysfunction.[52-54]

Renal damage

Much of our knowledge on renal parenchymal damage and the risk for future mortality and morbidity it incurs has emerged from studies using intravenous urography for detecting and classifying the damages. It may take up to two years for such permanent scarring to develop on urography after an acute pyelonephritis.[55] It has been shown that renal damage seen on urography is associated with risk for hypertension, pregnancy complications, decreased renal function and end stage renal disease.[56-59] These studies were done in patients investigated after pyelonephritis in the 1950s. More recent studies of the long term outcome of children managed for UTI and VUR in the 1970s have shown that in these patients the risk for severe complications in adulthood has been overestimated, except for in women during pregnancy when they are more prone to UTI and elevated blood pressure.[60-63] Ultrasound has been proposed to be used for assessment of renal damage, but the specificity and sensitivity is much lower compared to other modalities and it can not be recommended for evaluation of acute or permanent renal damage.[64, 65]

Renal damage on scintigraphy

Renal scintigraphy has evolved as an alternative to urography in evaluating kidney damage. Gross uptake defects of both kidneys on a DMSA scan is associated with an effect on renal function, but the association between lesser degrees of scintigraphic scarring and renal morbidity has yet to be defined.[66] Of different tracers used DMSA has become the most predominantly used isotope in static scintigraphy. After intravenous injection the tracer is accumulated in the tubular cells and then slowly excreted during many hours. Images are obtained using a collimator and give a good picture of the renal parenchyma and an estimation of the relative function without interference from the pelvicalyceal system. However, in gross dilatation or obstruction the excreted tracer will accumulate in the dilated urinary tract and complicate interpretation of the scan with risk for overestimation of the relative function.[67] DMSA scan is more sensitive than urography to renal parenchymal defects, and uptake defects can be distinguished already at the time of the infection.[68, 69] Aquired permanent renal uptake defects seen after pyelonephritis only develop in areas with acute lesions at the time of infection.[70] Such scarring is a dynamic process from the initial decreased focal uptake with preserved or swollen kidney contour seen at the time of infection, to the cone shaped defect of the renal parenchyma with indentation of the outline of the kidney typical for a permanent scar. But many of the acute defects heal without any signs of remaining damage, a process that most often is completed within 2-6 months. Thus, the evaluation of permanent renal damage after an acute pyelonephritis should not be done until this time has elapsed after the pyelonephritic event.[66, 71]

Renal parenchymal defect seen on DMSA scan can be classified as focal or multifocal, usually attributed to acquired damage associated with recurrent pyelonephritis, or generalized parenchymal reduction, i.e. a small kidney with an even distribution of isotope, more often seen as a congenital malformation or dysplasia. The extent of the damage can be assessed by the relative split function of the affected kidney in unilateral renal damage. In bilateral parenchymal defects the evaluation of the extent of damage has to be individualized since the difference in split function cannot be relied on for the assessment.

Prevalence

Assessment of renal damage has previously been made with excretory urography. DMSA scan is roughly 3 times more sensitive in detecting renal parenchymal damage.[72]

Renal parenchymal uptake defect seen on DMSA scan has been shown to be congenital in many cases, appearing without any history of UTI. It is regarded as a malformation or dysplasia, often in conjunction with urinary tract abnormalities such as dilating VUR or obstruction, and more frequent in boys than in girls.[73, 74] New renal scars are usually acquired after febrile UTIs. The prevalence of renal scarring following UTI differs between reports. One of the first articles on DMSA defects after UTI reported damage in 38% of the children one year after the infection episode.[75] In a more recent studies Hoberman et al found damage in 9% of children under 2 years of age when investigated 6 months after the UTI,[76] while Montini et al found renal scarring 12 months after acute pyelonephritis in 45% of the children, half of them with no VUR.[77]

Urinary tract infection

UTI in children and its serious complications have been reported in the literature since the beginning of the 20th century.[78] But it was the studies of Hodson and Edwards in the 1950s on UTI and its relation to renal damage and VUR that boosted the interest in UTI.[10]

The diagnosis of UTI is based on the findings of bacteria in the urine of a child with symptoms more or less typical for a UTI. The bacteria cause leukocyte infiltration and an inflammatory response in the involved tissue. When confined to the lower urinary tract this causes tenderness and pain in the urinary tract and can lead to mucous membrane bleeding and bladder muscle (detrusor) instability as in urethritis or cystitis. The erythrocyte and leukocyte count is usually elevated and can be detected in urine sediment or with urine dipstick (leucocyterase activity). The total inflammatory response is usually low and the child is afebrile with normal CRP levels. This is contrasted by the upper UTI where bacteria ascend through the ureters to the kidneys where they cause an inflammation of the renal parenchyma, predominantly in the upper and lower poles of the kidney. This leads to a greater inflammatory response with elevated inflammatory markers such as CRP and procalcitonin and raised body temperature.

Diagnostic criteria for UTI

Symptomatic UTI is often diagnosed by the clinical history and the laboratory findings in urine supported by significant growth of a single bacterial strand in a urine culture. The Kass criteria for a UTI are often not applicable in children because of their short bladder incubation time and the low accuracy of recognizable symptoms especially in the young child. Still, the demand for 100,000 cfu/mL has been widely used, except for in catheterization or bladder aspiration specimens known to be significant for UTI with lower bacterial counts.[79] Leukocyturia on a urine dip-stick or at microscopy of urine sediment, has high sensitivity but modest specificity for detecting UTI. The specificity increases with the use of nitrite stick but this is often negative in children in spite of the presence of nitrite producing bacteria in the urine.[80] UTIs are defined as infection of the lower urinary tract, mainly cystitis, and upper UTI, infection of the renal pelvis and renal parenchyma. A UTI is classified as an upper UTI if the child has fever, most but not all centers advocating a temperature of 38.5°C as the lower limit for febrile infection, and an increase in blood levels of inflammatory markers such as CRP or procalcitonin.[81-83]

Epidemiology of UTI

UTI is a common infection during childhood. In comparing the numerous reports on the incidence, it is important to be aware of dissimilarities between studies. There are differences in study design (e.g. screening, retrospective or registry studies), in diagnostic criteria (e.g. demand for symptoms, bacterial count in urine cultures or acute defects on a DMSA scan), in urine sampling technique used, in sex and age distribution and the rate of circumcision in boys.

The minimal incidence of UTI in the Swedish population has been estimated in the Swedish UTI Study.[84] The cumulative incidence of symptomatic UTI the first two years of life was shown to be 2.5% both in boys and girls. There is, however, a gender difference when looking into a detailed age pattern, with a marked male predominance the first 6 months of life, where after girls are more affected (figure 5).

The cumulative incidence of symptomatic UTI for children under 7 years of age was 7.8 % in girls and 1.7 % in boys when studied in a Gothenburg cohort of 3556 school entrants.[85] These figures are from populations where most boys are not circumcised.

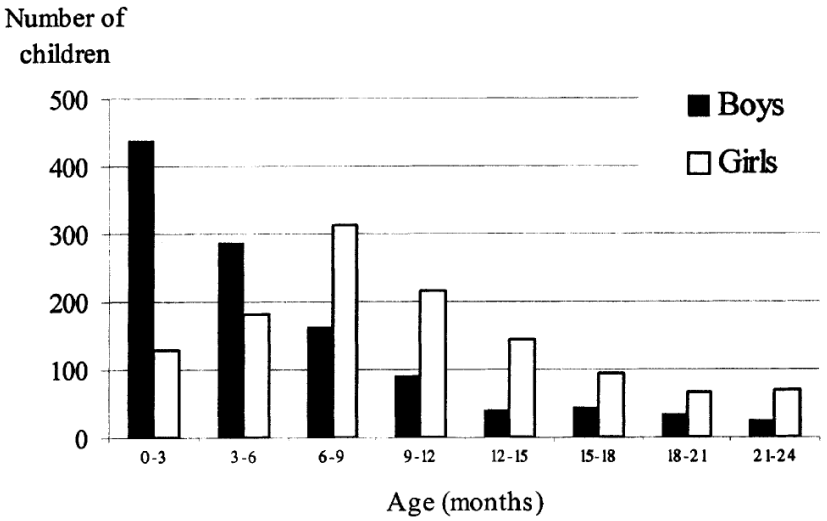


Figure 5. Age distribution of first known clinically diagnosed UTI in children 0-2 years (From Hansson et al: Urinary tract infections in children below two years of age: quality assurance project in Sweden. The Swedish Pediatric Nephrology Association. Acta Paediatr 1999; 88: 270.[32])

Antibiotic prophylaxis

Long term prophylaxis with low dose antibiotics has been used since the1950s to reduce the risk for recurrent UTI.[86] It has been recommended for children who have shown to be prone to recurrent infections and for those with known or presumed disposition to UTI, such as neurogenic bladder dysfunction or dilating VUR.[87] The ideal antibiotic for prophylaxis should have good acceptance, few side effects, be excreted by the kidneys with a high urine concentration to prevent colonization of the urinary tract, combined with a low influence on the bowel bacterial flora, and a low rate of resistance among urinary pathogens. Commonly used drugs have been trimethoprim, with or without sulphametoxazole, and nitrofurantoin.

However, this longstanding concept of protecting children with VUR from recurrent UTI, and in the extension from renal damage, with long-term low-dose antibiotics has been questioned. Concern has been raised regarding the risk of increasing antibiotic resistance and the concept has also been questioned as it was introduced and sustained without adequate scientific support.[88, 89]

Reflux surgery and UTI recurrence rate

The impact of reflux surgery on the rate of UTI recurrence has been the focus of a handful studies. In the International Reflux Study in Children with VUR grade III or IV treated with antibiotic prophylaxis or open neoimplantation, the UTI recurrence rate was similar in the medically and surgically treated children, though the rate of pyelonephritis was lower in the latter group, 10% in the European and 8% in the American arm of the study were afflicted with pyelonephritis.[90, 91] Capozza et al found in a randomized trial of children treated with prophylaxis or endoscopic injection for VUR grade II-IV, a 19% UTI rate in the endoscopic group, whereas there was no infection in the prophylactic group.[92] Chi et al in a retrospective study of 167 children successfully treated with endoscopic injection found a postoperative UTI recurrence rate of 24%, half of them febrile.[93]

VUR, UTI and renal damage

Through the years there have been varying theories about the cause and effect relation between VUR, UTIs and renal parenchymal damage in children. Hutch revealed the strong association between VUR and renal damage in children with neurogenic bladder dysfunction in 1952.[39] Triggered by these findings Hodson and Edwards drew attention to the association between VUR and kidney damage, defined as chronic pyelonephritis, in 1960.[10] Reflux had previously been described in association with bladder outlet obstruction, but they demonstrated the presence of reflux in patients without any obstruction, who had concomitant chronic pyelonephritis, confirmed histologically or with radiograms typical of this entity. From their observations they drew the conclusion that VUR preceded renal changes and that kidneys could not develop normally in the presence of reflux. They also demonstrated that these chronic renal changes could be seen in the absence of urinary tract symptoms or infections.

The term reflux nephropathy was coined by Bailey in 1973.[94] He stressed the observation that gross VUR was highly associated with renal damage even in the absence of UTI. Believing the reflux to be causative of the renal damages he found the term reflux nephropathy more accurate than the term chronic pyelonephritis previously used.

The strong association between renal scarring and UTI coupled to VUR was shown in the studies by Ransley and Risdon in piglets with surgically induced VUR followed by inoculation of bacteria into the bladder.[95]

Risdon, in studying kidneys after nephrectomy due to obstruction or VUR, found dysplasia as sign of a congenital malformation and argued that this was the cause of renal scarring rather than it being acquired from infection.[96] Renal scarring has also been found in children with dilating VUR grade IV or V, detected at screening of siblings to children with known VUR or follow-up of prenatal hydronephrosis, without any history of UTI, even though the rate of renal damage was higher in those with VUR diagnosed after UTI. [97]

In studies of children after pyelonephritis renal scarring has been found in the absence of VUR, even though a strong association between reflux severity and the presence and extent

of renal damage was seen.[67] It has been shown that renal damage is strongly associated with first time UTI, but it is also related to recurrences of febrile UTI.[98]

From more recent studies in children with prenatal hydronephrosis associated with VUR, we have learnt that kidneys with refluxing ureters can be normal at birth and if no UTI occurs they may develop normally.[99] Whether sterile refluxing urine could cause new renal damage was at first a controversy, but it was later established that UTI is a prerequisite for acquired scarring.[100, 101]

The International Reflux Study in Children, a collaborate effort to compare surgical treatment of VUR to antibiotic prophylaxis, was presented at an international workshop on reflux in 1991.[102] Children under the age of 11 years with dilating VUR were randomized to long-term prophylaxis until reflux disappeared or to surgical treatment. There was close to 100 % success rate at surgery, while in the medical group reflux grade was reduced considerably in more than half of the children. There were fewer pyelonephritic attacks in the surgical group but the total number of UTI was similar in both groups. There was no difference between the groups in renal scarring over a 10 year period.[103] Similar results were presented from the Birmingham Reflux Study, comparing neoimplantation to antibiotic prophylaxis in children under the age of 15 years, where no difference in UTI recurrence or scarring could be found between the groups after 5 years of follow-up.[104]

Study initiative

In 1994 Winberg wrote a critical review on the management of vesicoureteral reflux in children.[105] He briefly outlined the state of knowledge of UTI in children and stressed the two main tasks when dealing with these patients: to prevent focal renal scarring and secondly to prevent the suffering caused by recurrent lower UTI. Regarding the management of children with dilating VUR he emphasized the importance of insight into the role of UTIs and their complex biology. To consider the treatment of dilating VUR only in relation to the size of reflux would be too simplistic.

He questioned the assumptions that elimination of VUR would reduce the number of infections and the risk of future renal scarring by referring to studies from USA, Finland and Great Britain.[104, 106, 107] In referring to these studies and the International reflux Study in Children he concluded that operation of VUR was based on insufficient scientific evidence. But he also raised the question whether antibiotic prophylaxis offers any advantage over follow-up combined with short term treatment of symptomatic recurrences.

Winberg called for an agenda for the care of children with VUR and UTI that would apply to both pediatricians and pediatric urologists. In working out such an agenda aspects to consider, other than urological, would be the decrease of susceptibility of kidneys to damage with rising age, immunity in the course of the disease – first infection is probably more dangerous than recurrences, the protective effect of asymptomatic bacteriuria against infection with more virulent strains, and the risk of infections in association with instrumentation. He argued that efficient routines for thorough follow-up ensuring immediate diagnosis and treatment of recurrences in high risk children are more important than stereotyped policies of operation or long-term prophylaxis. Well informed parents as active participants in the management would make a more restrictive regimen of antibiotic prophylaxis possible.

He concluded that audits for the imaging and treatment of children with VUR were urgent. He also stressed the lack of scientific basis for operating on reflux to prevent renal damage. Studies were needed, to define subgroups that would benefit from operation, and to define indications for long-term antibiotic prophylaxis.

In response to this article a national state-of-the-art conference was arranged in Sweden in 1997, with the aim of designing new guidelines for the management of children with VUR.[108] The basis for these guidelines was a critical review of the literature, as well as clinical experience, since there were areas that had not been adequately studied. These guidelines stated that in children with VUR grade I and II the risk for recurrent UTI and future renal damage was not shown to be increased compared to those with no reflux. Thus, children with no VUR or reflux grade I or II were to be treated with neither surgery nor antibiotic prophylaxis. If there was no renal damage seen on urography or DMSA scintigraphy they were even left without further follow-up.

At the conference the need for further studies was identified, and the following remarks and suggestions for future research were made: active treatment for VUR was previously considered so obvious that no studies had been performed with an untreated control group on surveillance only. Since the effectiveness of antibiotic prophylaxis was being questioned such a study was considered both acceptable and necessary. Thus, a study in children with dilating VUR grade III- IV with or without antibiotic prophylaxis was suggested.

The endoscopic subendothelial injection of a bulking agent by the orifice of refluxing ureters to reduce the reflux had been studied regarding its effect on VUR outcome, but mostly on short term. There is also a considerable portion of spontaneous downgrading or resolving of dilating reflux during the first years of life.[36, 109] Furthermore, at the time the impact of the endoscopic treatment on UTI recurrence rate or the development of renal damage had not been addressed.[110] Thus, there was a need for Dx/HA injection to be studied in comparison with a control group on surveillance only. Since there was a dramatic increase in the use of Dx/HA in children with VUR of all grades after it was approved of by FDA in 2001 this question urgently needed to be addressed.

At the time of the planning of the study children with the most grossly dilating VUR grade V were considered a particularly vulnerable group with a higher risk of UTI recurrence and it was not considered ethical to leave them without protective treatment. They were also previously known to have a more pronounced bladder dysfunction and therefore considered unsuitable for endoscopic treatment.[111] For these reasons the study was confined to dilating VUR grade III or IV.

Spontaneous resolution of dilating VUR is known to occur more frequently the first year of life, probably due to alterations of the bladder function seen during this period of life. It was considered inappropriate to perform anti-reflux surgery in children under the age of 1 year, which was the reason for not including them in the study.[37, 73] As we aimed for a study population as homogenous as possible we chose not to include children after the age of 2 years, i.e. before potty training was expected to be introduced.[112]

As a response to these research proposals this prospective, randomized, controlled multicenter study in children 1-2 years of age with VUR grade III or IV was initiated. The study protocol was drawn up by researchers at the University of Gothenburg in collaboration with a nationwide network of researchers. The trial was designed with three treatment arms: antibiotic prophylaxis, endoscopic injection with Dx/HA (Deflux™) or surveillance only.

Aims of the study

The overall aim of the Swedish Reflux Trial was to evaluate the management strategies for children with dilating VUR.

Specific aims

To describe VUR outcome at two year follow-up after endoscopic injection compared to children on prophylaxis or surveillance only.

To describe the pattern and rate of recurrent UTI and the differences between prophylactic antibiotics, endoscopic treatment and surveillance.

To investigate if treatment with antibiotic prophylaxis or endoscopic injection is effective in reducing new renal damage or progression of established renal damage.

Study design

Study design and population characteristics - paper I

The study was randomized, controlled, open and multicenter, with three allocation alternatives, one of them a control group without active treatment. After 2 years with regular contacts, follow-up investigations were performed. The overall study design, including the numbers of patients, is outlined in figure 6.

The characteristics of the population are described in the following section.

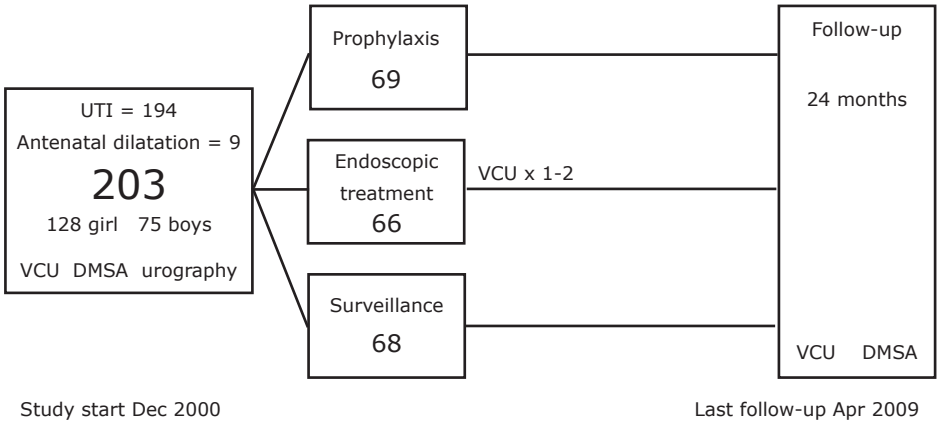


Figure 6. Study design

Patients

Multicenter study

In the 1990s a collaboration network including almost all pediatric departments in Sweden had been formed in the work with the Swedish UTI Study.[36] These pediatric centers were the foundation from which children were recruited into this study.

Twenty-two pediatric centers in Sweden and one in Oslo, Norway, participated in the study. The centers in Sweden covered about 80% of the Swedish childhood population. Principal investigators were appointed at every center. They met at several occasions before the study started and at regular annual meetings during the course of the trial to facilitate similar clinical practice at all centers. The study protocol gave detailed information on recommended procedures of the investigations in the study.

Patient selection

Children diagnosed with VUR grade III and IV between 1 and less than 2 years of age were eligible for the study. There was no prerequisite as to the reason for why the VCU was done. As anticipated, most of the cases with VUR were found at work up after a UTI. In some children the cystography was performed after findings of urinary tract dilatation on prenatal ultrasound. None was included because of known VUR in siblings. In case VUR was diagnosed before 1 year of age the child was to be given prophylactic antibiotics according to the Swedish guidelines at the time, with a repeat VCU within the next year, but before the child's 2nd birthday.

Ultrasound of the kidneys and urinary tract was done in 191 of the 203 children as primary investigation after their first UTI, and was used to rule out obstruction disorders in the urinary tract. Extretory urography for detection of pelvoureteral duplication was done in all children before inclusion.

Children with known stone disease or known neurological disability, affecting the bladder function, were not eligible for the study. Neither were children with malformation of the urinary tract, except duplicated renal pelvis and ureter, or reduced renal function with a glomerular filtration rate below 70 ml/min/m^2 body surface. Surgery in the urinary tract, except circumcision, also excluded the child from the study. In order to be sure the family was able to follow instructions they had to understand spoken and written Swedish.

Power estimation of study size

The power estimation was done on the presumption that the recurrence rate of UTI would be 0.10, 0.40 and 0.60 in the prophylaxis, endoscopic and surveillance groups respectively. In order to have 80% power in finding a difference in recurrence rate at pair wise comparison between these groups and with an aim of equal numbers in all three groups we would need 97 evaluable children in every group. Counting on a 10% drop out rate our target was to recruite 330 patients for inclusion. Based on the experience from the Swedish UTI Study in 1993, we presumed the annual inclusion rate to be 100 children requiring an inclusion period of 3-4 years.[36]

Study population

The first patient entered the study in December 2000. Recruitment proved to be more difficult than expected, partly due to the high rate of spontaneous resolution the first year of life, and the inclusion rate was 30-40 cases a year instead of the presumed 80-100 (figure 7).

Table 2. Baseline characteristics of the patients

	Prophylaxis n=69	Endoscopic n=66	Surveillance n=68
Girls, number of pts (%)	**43**	**43**	**42**
VUR III	27 (63)	32 (74)	29 (69)
IV	16 (37)	11 (26)	13 (31)
Bilateral VUR	25 (58)	21 (49)	21 (50)
Duplication	8 (19)	12 (28)	7 (17)
1st DMSA scan			
normal	21 (49)	20 (47)	18 (43)
abnormal	22 (51)	23 (53)	24 (57)
Prenatal dilatation	1	1	0
UTI before 1st VCU	42	42	42
Age (yrs) at UTI before 1st VCU			
Median (range)	0.81 (0.08-1.83)	0.74 (0.02-1.90)	0.80 (0.15-1.96)
Mean ± SD	0.83 ± 0.43	0.73 ± 0.47	0.83 ± 0.45
1st VCU before age 1 yr, no.	20	25	21
Age (yrs) at randomization			
Median (range)	1.69 (1.32-2.23)	1.67 (1.06-2.40)	1.81 (1.25-2.31)
Mean ± SD	1.75 ± 0.28	1.71 ± 0.35	1.80 ± 0.29
Boys, number of pts (%)	**26**	**23**	**26**
VUR III	14 (54)	10 (43)	14 (54)
IV	12 (46)	13 (57)	12 (46)
Bilateral VUR	15 (58)	13 (57)	16 (62)
Duplication	2 (8)	1 (4)	5 (19)
1st DMSA scan			
normal	5 (19)	7 (30)	8 (31)
abnormal	21 (81)	16 (70)	18 (69)
Prenatal dilatation	2	1	4
UTI before 1st VCU	24	22	22
Age (yrs) at UTI before 1st VCU			
Median (range)	0.24 (0.01-1.26)	0.29 (0.02-1.64)	0.26 (0.04-1.76)
Mean ± SD	0.32 ± 0.35	0.43 ± 0.47	0.46 ± 0.52
1st VCU before age 1 yr, no.	24	20	22
Age (yrs) at randomization			
Median (range)	1.65 (1.13-2.38)	1.64 (1.08-2.19)	1.68 (1.21-2.27)
Mean ± SD	1.66 ± 0.27	1.67 ± 0.32	1.69 ± 0.31

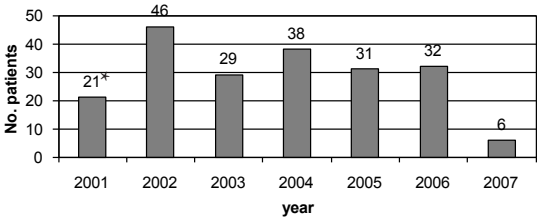


Figure 7. Number of patients included per year during the trial
** including one patient in December 2000.*

Since clinical management shifted away from the study design, and recruitment was harder than expected, it was decided to stop inclusion after 6 years. This decision was made without any knowledge of outcome. The last patient entered the study in February 2007. A total of 203 children were included in the study, 128 girls and 75 boys. Of these, 9 were found after detection and follow-up of prenatal dilatation of the urinary tract and 194 children were diagnosed with dilating VUR at work up after a UTI. The reflux was detected before 1 year of age in 135 patients. These had a second VCU done, between their first and second birthday, showing VUR grade III or IV and were thus eligible for the study.

After the parents had been informed by their local investigator and given their informed consent the children were randomly assigned to one of the three treatment strategies. An optional assessment of bladder function with 4 hour micturition observation was performed before or at inclusion in those centers that had the necessary euipment and personnel available.

See table 2 for baseline characteristics of the children.

Reflux at entry

At study entry VUR was bilateral in 111 children (55%) and 56 of these had VUR with bilateral dilatation. Details of VUR grade in the children are listed in table 3.

Table 3. VUR status at study start.

	Number of patients		
VUR status at entry	Girls	Boys	Total
IV – IV	5	3	8
IV – III	7	10	17
IV – II	6	7	13
IV – I	6	1	7
IV – 0	16	16	32
III – III	21	10	31
III – II	20	11	31
III – I	2	2	4
III – 0	45	15	60
Totals	128	75	203

Urinary tract infections before randomization

In 194 children the first VCU was motivated by a UTI and 135 of those occurred before the age of one year. Median age at first UTI was 0.26 years in boys and 0.77 years in girls. Details for each treatment group are shown in table 2. In the majority of children the first UTI was caused by E. coli, 87% in girls and 58% in boys. Other infectious agents were Klebsiella in boys and girls, enterococci and coagulase negative staphylococci in boys, and one or two infections each were caused by strands of Proteus, Pseudomonas, Enterobacteria, Streptococci, Staphylococcus aureus, Serratia or Haemophilus parainfluenzae.

Recurrent UTI was seen in 58 of the children before they were included in the study, but no details were given on these infections.

Renal status on DMSA at entry

At study start 79 children had normal DMSA scans. Abnormal scans were seen in 124 and were more common in boys than in girls (73% vs 54%, p=0.0088). In children with VUR grade IV there were more damaged kidneys, and the damages were more severe, compared to those with grade III, details in table 4. In 6 patients the kidney with the most severe VUR had no uptake defect, but the correlation between VUR grade and DMSA findings was still significant (p = 0.0001).

Table 4. Renal status at entry in 203 children

DMSA Class*	VUR grade III numbers (%)	VUR grade IV numbers (%)
0	63 (50)	16 (21)
1	17 (13)	15 (19)
2	17 (13)	14 (18)
3	29 (23)	23 (42)
Totals	126	77

** Discordant results in 6 patients.*

Methods

The three treatment arms

Antibiotic prophylaxis

Children with dilated VUR were started on antibiotic prophylaxis at the time when VUR was diagnosed. In 135 of the children in the trial, VUR was detected before the age of one and the prophylaxis was started before they were eligible for the study. The preferred drug in Sweden at the time of the trial, as well as in the study protocol, was trimethoprim 0.5 mg/kg, with the alternative options nitrofurantoin 1 mg/kg or cefadroxil 5 mg/kg.

The child continued the ongoing prophylaxis already given, or started the prophylaxis as soon as possible. The antibiotic was prescribed using regular prescription procedures. During the study the parents were asked about medication and any intercurrent antibiotic treatment for other reasons at every scheduled appointment and contact. Compliance was not otherwise tested for.

Endoscopic treatment

The children allocated to endoscopic treatment were referred to one of the six regional departments of pediatric urology where the endoscopic procedure was performed within a month of the referral. One of thirteen pediatric urologists, with varying levels of experience, performed the injection, done in general anesthesia as an outpatient procedure. With a cystoscope the surgeon entered the bladder and located the ureteral orifices. Subendothelial injection with dextranomer/hyaluronic acid copolymer (Dx/HA, Deflux®, Q-med, Uppsala, Sweden) was performed according to standard technique.[49, 110] Using a prefilled syringe (standard low pressure type) and a 25 cm long, 3.5 Charriere steel needle, a median volume of 0.8 mL (range 0.2-2.0) of Dx/HA was injected submucosally in or below the ureteral orifice at 6 o'clock position to create a prominent bulge and raise the distal ureter and ureteral orifice. In cases of duplication and complete separation of the ureters, injection was done under the refluxing ureter and a second injection was usually given laterally under the distal ureter to ensure that both ureters were elevated.[52] Following the injection the child was checked with ultrasound after 1 month to rule out any post operative obstruction and VCU after three months to control the reflux status. If the child still had a dilating VUR the injection procedure was repeated with the same postoperative controls. In case a third injection was needed the third postoperative VCU was excluded to limit the radiation burden for the child. All children continued the antibiotic prophylaxis until a postoperative VCU showed no or nondilating VUR.

Surveillance

In the surveillance group the child was withdrawn from any prestudy prophylactic treatment. No placebo drug was used.

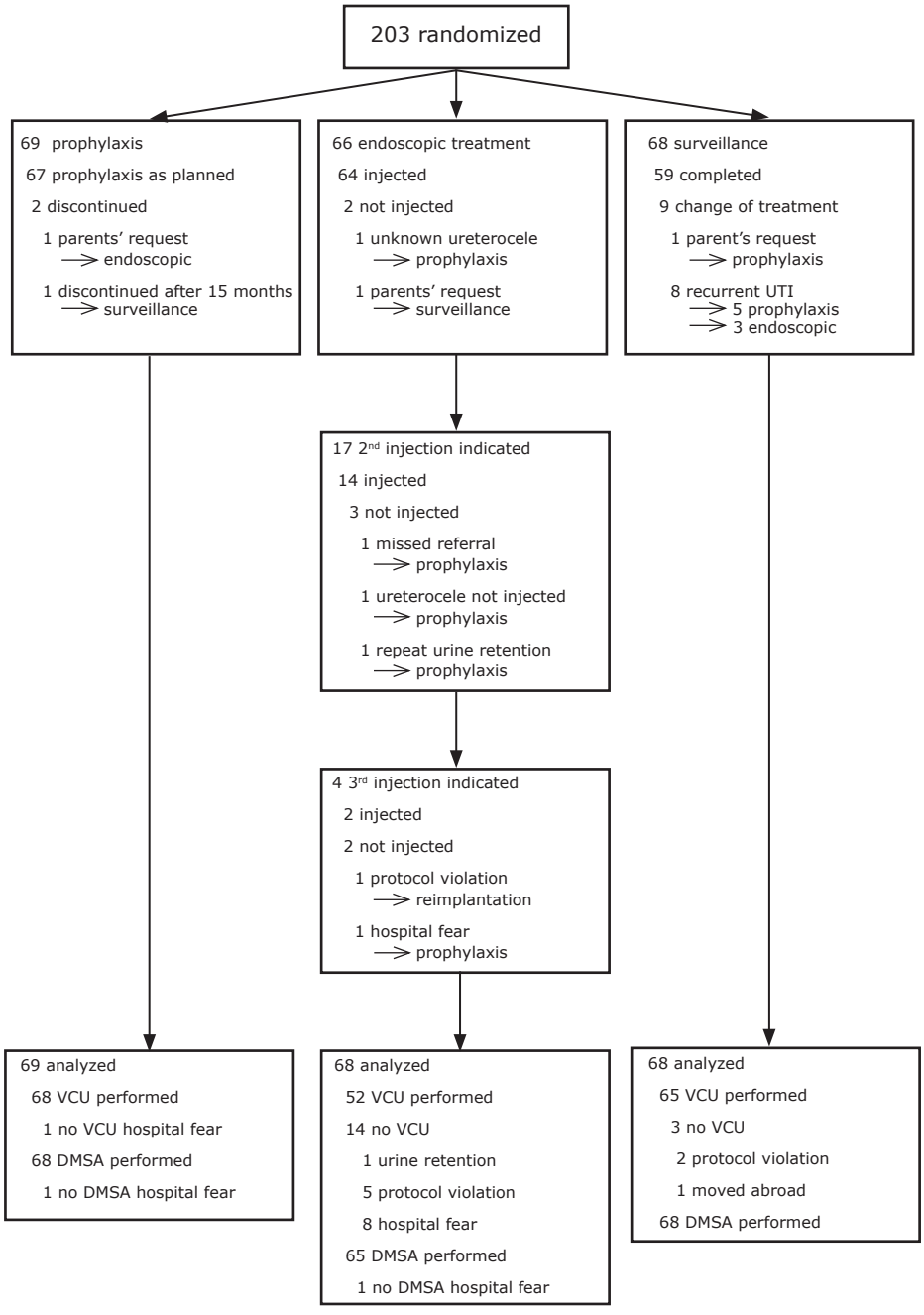


Figure 8. Flow chart of patients after randomization.

Randomization

When the required inclusion information was complete the case was entered into a computerized randomization program at the coordinating center, using the minimization procedure described by Pocock and Simon, to assign the patient to one of three treatment arms.[113] This procedure allotted the first case randomly while the following patients were allocated in a procedure that minimized the differences of, or matched for, gender, previous UTI, VUR grade, DMSA uptake defect, bladder size, duplication and center. The allocation result was faxed to the local study center where the assigned management was started.

Follow-up

Every child was scheduled for follow-up at 3-month intervals for two years with visits every 6 month and telephone interviews between visits. The protocol included questions on fever episodes, illnesses and antibiotic consumption since the previous contact. At every visit height, weight, blood pressure and urinalysis were recorded. Should the child present with symptoms suggesting a UTI, especially fever, the families were instructed to make an extra visit to their local pediatric outpatient clinic. When recurrent UTI was suspected a special protocol was used to report the incidence to the coordinating center, monitoring the urine dipstick and culture results, temperature and serum levels of CRP.

At the end of the study period, two years after randomization, VCU and DMSA scintigraphy were done. Children with recurrent UTI were promptly treated with antibiotics for ten days.

Examinations

Voiding cystourethrography

Guidelines for the VCU procedure coherent with international recommendations were stated in the study protocol.[114] Anterior images were taken during filling and micturition. In boys images from a latereal view was required to detect anomalies of the urethra, especially posterior urethral valves. A postvoid image was taken in all children. The images were assessed and graded I through V according to the staging proposed by the Study Group of the International Reflux Study in Children.[5] Antibiotic prophylaxis was to be given at the examination, sedation with midazolam was optional.

In the analysis, the kidney with the highest grade of reflux was used to characterize the patient. Bladder size was assessed on the VCU images as larger than normal if it reached above an imaginary horizontal line between the iliac crests in the frontal view.

Intravenous urography

Intravenous urography was done according to local routines in all cases to detect duplication of the upper urinary tract. In some centers urography replaced ultrasound for detection of obstructive malformations of the urinary tract.

Ultrasound examination

Ultrasound was not a mandatory investigation in the study but done as part of the primary work up after UTI in most centers, for detection of swollen kidneys, renal anomalies such as small or absent kidneys and dilatation of the urinary tract to exclude obstructive malformations. The bladder was also examined to detect bladder wall anomalies and ureterocele.

All radiologic examinations were electronically transferred from the local radiological department to the study coordinationg center to be assessed by one senior radiologist (Eira Stokland).

DMSA scintigraphy

For DMSA scans, the centers were instructed to follow the European guidelines.[67] In short, static renal scintigraphy was to be done 2-4 hours after injection of DMSA in a dose of 1 MBq/kg body weight (minimum 15 MBq) and planar images obtained by high resolution collimator in 1 posterior and 2 oblique projections with 300,000 counts in the posterior view. All data files were reevaluated at the coordinating center by the same senior nuclear medicine specialist (Rune Sixt), using the Hermes software package (Hermes Medical Solutions, Nuclear Diagnostics AB, Stockholm, Sweden). The relative split function in normal kidneys has been shown to be 50 ±5% (mean ± 2SD). A kidney without uptake defect and a relative (split) function of 45% or more was classified as normal (DMSA class 0), whereas a kidney with reduced or absent uptake in one or more areas or a relative function of <45% was considered abnormal. The extent of kidney damage was graded as class 1 – uptake defect with relative function ≥45%, class 2 – relative function 40-44% and class 3 – relative function <40%. In cases with bilateral renal damage the kidneys were individually classified according to the extent of the uptake defects. In a unilateral duplicated kidney expected mean normal split function is shifted from 50 % to 54 %, consequently the lower limit for normality was set at 49%.[115] On analysis, the kidney with more pronounced involvement was used to characterize the case. Since the focus of the study was to compare three different treatment regimens, special attention was given to DMSA scan development over the study period. A new renal scar was defined as an uptake defect appearing in a previously normal area. Deterioration was defined either as a new renal scar or a decrease of relative (split) function of 4% or more in a kidney with uptake defects at entry.[116] Kidney damage was also classified as focal or generalized.

Bladder function assessment

Bladder capacity on VCU was recorded and a bladder reaching above the line connecting the iliac crests, or with a documented filling volume of 200% or greater of expected normal capacity for age, was considered enlarged. For estimation of normal bladder capacity for age the formula proposed by Hjälmås et al was used: 30 ml + 2.5 ml x age (months).[117]

Four-hour voiding observation, optional at study start, and free voiding flowmetry and post void residual urine, optional at 2-year follow-up, were done in 148 and 161 children, respectively.

These results will not be further discussed in this thesis.

Primary outcomes

Febrile urinary tract infection

For diagnosing a UTI urine was sampled according to the traditions of the local study centre. A diagnosis of UTI required bacteriuria with ≥100,000 colony forming units/mL in urine obtained by midstream or bag technique or any number of bacteria after suprapubic bladder aspiration. To exclude asymptomatic bacteriuria and contaminated urine, only infections with symptoms consistent with UTI and laboratory results in support (elevated CRP, positive nitrite test, or pyuria on dipstick) were approved, body temperature ≥38.5°C defining febrile infection. Children with recurrence were promptly treated with antibiotics for 10 days.

Renal damage

Renal damage was assessed by DMSA scintigraphy performed two years after randomization, in comparison with the scan performed before entry.

Reflux outcome

This was measured by VCU performed two years after randomization and denoted resolution (to grade 0), downgrading to grade I or II, or persistant grade III or IV. There was no case of upgrading of the reflux to grade V during the study.

Data collection

Separate Case Report Forms (CRF) was used for all events in the study including all radiological and scintigraphic examinations, visits at the clinic, telephone contacts and UTI recurrences. All CRFs were filled in locally and sent by fax to the coordinating center where they were manually transposed to the electronic database. The CRFs for the radiographic investigations and DMSA scans were completed at the coordination center by the senior examinator blinded to treatment allocation of the patients.

Every family was equipped with a patient diary in which the parents were to take notes on every UTI or episode of fever. It served as a record and reminder at the regular visits and telephone contacts but was not classified as primary data. It also provided information to the child's local physician about the study, with recommendations for tests and work up in case of a suspected UTI.

Statistical methods

All statistical calculations were done according to allocated treatment on the intent to treat principle.

For comparison between groups the chi-square exact test was used for nonordered categorical variables, the Mantel-Haenszel chi-square exact test for ordered categorical variables, the Kruskal-Wallis test for continuous variables and Spearman's rank correlation coefficient in nonparametric correlation analysis.

In pairwise comparison between groups Fisher's exact test was used for dichotomous variables, the Mantel-Haenszel chi-square exact test for ordered categorical variables and the Mann-Whitney U test for continuous variables.

To compare time to first UTI recurrence between the groups Kaplan-Meier life table analysis was done and survival curves were plotted using Kaplan-Meier estimates and formally tested by the log rank test.

In all analyses $p < 0.05$ was considered significant.

Ethical approval and informed consent

For the coordinating center the study was approved by the regional ethical committee in Gothenburg (protocol Ö462-99), with complementary approvals by the regional committees of all the participating centers. Each family received written information about the study and gave their consent to participate.

Results

The results are primarily presented as totals of the whole study population but will in some respects be presented for boys and girls separately, since there is a striking difference between gender in many of the aspects of the VUR-UTI-renal scarring complex.

Vesicoureteral reflux outcome – paper II

The follow-up VCU after two years was done in 185 of the 203 patients (91%). It was not performed in one of 69 (1%) in the prophylaxis, 14 of 66 (20%) in the endoscopic and 3 of 68 (4%) in the surveillance group. The reason for not completing the 2 year VCU was fear of the investigation in 9 cases, protocol violation in 7, recurrent urine retention after previous catheterizations in 1 and family moved abroad in 1 (figure 8, page 32). The median time span between randomization and the 2-year VCU was 2.04 years. In 9 patients the time span was shorter than 1.8 years and in 5 longer than 2.8 years.

VUR status improved in all three groups, with complete resolution in 13%, 38% and 15% of patients in the prophylaxis, endoscopic and surveillance groups and downgrading to grades I-II in 26%, 33% and 32%, respectively (figure 9). Resolution and downgrading were more common in the endoscopic group than in the prophylaxis and surveillance groups ($p = 0.0002$ and 0.0030 respectively). There was no difference in VUR outcome between the prophylaxis and the surveillance groups ($p = 0.3906$).

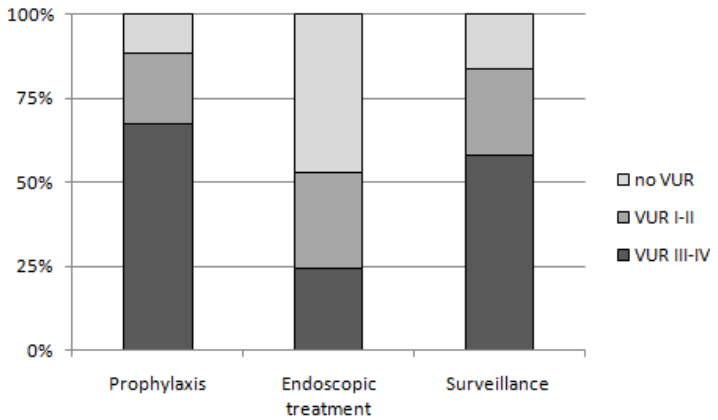


Figure 9. VUR status after 2 years.

Prophylaxis and surveillance groups

The prophylaxis and surveillance groups could be regarded as controls to the actively treated children in the endoscopic group. There were together 85 girls in these groups, 82 of whom underwent VCU after 2 years. VUR grade III at randomization was associated with a better outcome than grade IV (p = 0.0177, table 5). No such difference in outcome was seen in 51 of 52 boys (p = 0.2284). Of children with VUR grade IV at entry 79% of the girls still had dilating VUR after 2 years, but only 54% of the boys. Renal uptake defect at start was associated with higher VUR grade at follow-up in girls but not in boys. Duplicated ureters seen in 22 children (17%) did not correlate with VUR resolution or downgrading (p = 0.3596).

Table 5. VUR grade at 2 years in prophylaxis and surveillance groups

VUR at randomization	2-year VCU* number of patients						Mantel-Haenszel chi2-test
	no VUR	I	II	III	IV	total	
Girls							p = 0.0117
III	10	2	16	22	4	54	
IV	3	2	1	12	10	28	
total	13	4	17	34	14	82	
Boys							p = 0.2254
III	6	2	5	8	6	27	
IV	0	4	7	6	7	24	
total	6	6	12	14	13	51	

** VCU not done after 2 years in 3 girls and 1 boy.*

Endoscopy group

In accordance with the intent to treat principle all 66 children randomized to endoscopic injection treatment were included in the calculations.

Endoscopic treatment was given to 64 of the 66 children. In one case the parents declined therapy after randomization and in one the injection was inhibited due to a previously undiscovered ureterocele detected at cystoscopy.

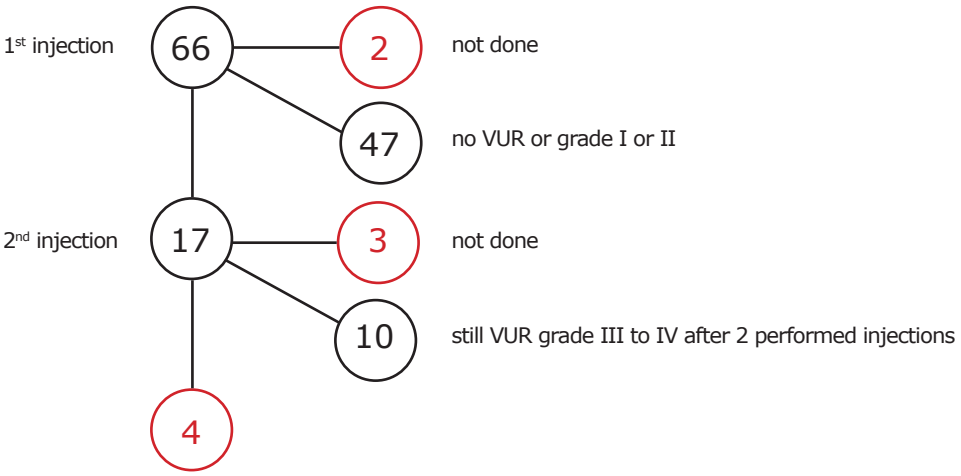


Figure 10. Results in 66 children with endoscopic treatment. Red circles indicate 9 children in whom VUR did not improve.

The results after the first injection was resolution to no VUR in 34, downgrading to nondilating VUR in 13 and dilating VUR remaining in 19 children, including the two not injected (details in figure 10 and table 6). Of the 17 with remaining dilating VUR, 3 were not reinjected due to missed referral, repeat urinary retention after urethral instrumentation and a small ureterocele with unchanged VUR grade after first injection in one case each. The results after 1 or 2 injections in the 66 children, including those not injected or reinjected, was resolution to no VUR in 39, downgrading to nondilating VUR in 18 and VUR grade III or IV in 9. Of these 9 patients with dilating VUR, 2 did not receive the first injection, 3 did not receive the second and 4 were injected twice and still had dilating VUR. In 2 of them a third injection was performed, with resolution to no VUR in one and downgrading to grade II in one case each.

In the endoscopic group 52 of the 66 patients carried out the 2-year VCU. Of the 14 remaining, 9 had no VUR on their last post injection VCU, 2 had grade II, 2 grade III and 1 grade IV.

Table 6. VUR grades in endoscopic group at post injection and 2-year VCU.

	VUR grade number of patients					
	no VUR	I	II	III	IV	Total
after 1 injection*	34	2	11	12	7	66
after 1-2 injections†	39	4	14	6	3	66
after 2 years‡	20	2	15	12	3	52

** 2 pats not injected 1st time, post-op VCU #1 in 64 pats.*
† 2 pats not injected 1st time, another 3 not injected 2nd time, post-op VCU #2 in 14 pats.
‡ 14 pats not completing 2-year VCU

In 13 patients without dilating VUR after the first injection (8 with no VUR, 1 grade I and 4 grade II), VUR grade III or IV reappeared at the 2-year VCU (figure 11). None of the 9 patients with no or nondilating VUR after the second injection was shown to deteriorate to dilating VUR on the 2-year VCU. Duplicated ureter found in 12 patients (2-year VCU missing in 1 patient) did not correlate with VUR resolution or downgrading (p = 0.5403).

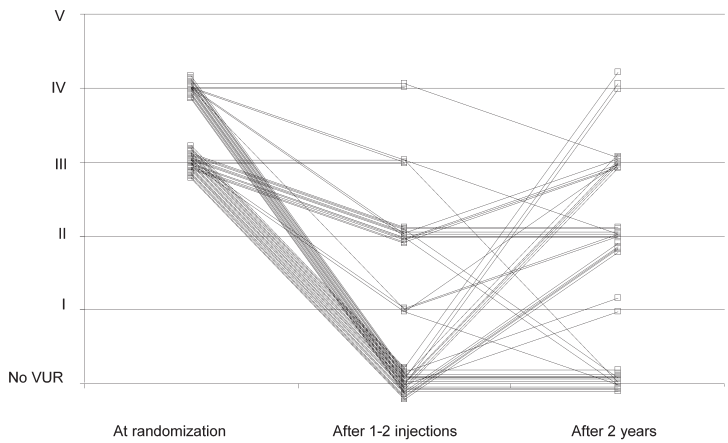


Figure 11. VUR grade at randomization, after 1 or 2 injections and after 2 years in 66 children with endoscopic treatment

Renal units in endoscopic group

The 66 patients allocated to endoscopic treatment had a total of 82 renal units with dilating VUR. After 1 or 2 injections, including the 2 patients who did not receive the first injection, a total of 10 renal units had dilating VUR in 9 patients (one patient had grade II-III at entry and grade III-III after first bilateral treatment, not further injected due to urine retention). After 2 years, 16 of 104 tested renal units had dilating VUR in a total of 15 patients.

Complications

In the endoscopic group there were adverse events in 6 patients. One boy had transient ureteral and renal pelvic dilatation on ultrasound at 1 month after injection. Febrile UTI appeared after injection in 1 boy. Urine retention after the first endoscopic procedure and also after previous VCU was seen in 1 boy. One boy was observed over night in the intensive care unit after aspiration during anesthesia. One girl with abdominal pain during follow-up had pelvic dilatation and decreasing split function due to a crossing vessel at the pelvoureteral junction. In 1 boy a fibrous narrowing of the bulbar urethra without signs of obstruction was detected at first endoscopic procedure. Due to weakening urine flow and an obstructive flow curve pattern a repeat endoscopic investigation was performed, revealing deterioration of the bulbar urethral narrowing. Internal urethrotomy was done.

Urinary tract infection pattern – paper III

Median follow-up, between randomization and the 2-year DMSA scan, was 2.05 years. It was more than 1.8 years in all but 4 patients (98%) and more than 2.8 years in 6 patients (3.0%).

During follow-up 53 of the 203 children, including 45 girls and 8 boys, experienced a total of 91 new symptomatic UTIs. Of these episodes 16 were nonfebrile, including 11 with temperature below 38.0°C, and 5 with temperature between 38.0 and 38.4°C. Only febrile infections are included in the analyses. A total of 67 febrile recurrences were noted in 42 girls and 8 in 7 boys (table 7). The difference between girls and boys was significant ($p = 0.0002$). At recurrence in these 49 patients the sampling technique was bag in 18 (3 on prophylaxis, 5 with endoscopic therapy and 10 on surveillance), midstream in 26 (6 on prophylaxis, 6 with endoscopic therapy and 14 on surveillance), catheter and bladder aspiration in 1 each (endoscopy) and technique not specified in 3 (1 per group).

Girls had more febrile recurrences. In the prophylaxis group, it was seen in 8 of 43 girls (19%) (table 7) with trimethoprim resistant bacteria in 7 (table 8). In the endoscopic group 10 of 43 girls (23%) had recurrence, including 5 with resistance to trimethoprim. In the surveillance group, 24 of 42 girls (57%) had recurrence with trimethoprim resistant bacteria in 9. Recurrence was the reason to change treatment modality in 8 girls, including 5 to prophylaxis and 3 to endoscopic treatment. There was a difference in the number of febrile recurrences between the three treatment groups ($p < 0.0001$), being more frequent in those on surveillance than on prophylaxis or with endoscopic therapy ($p = 0.0002$ and 0.0014, respectively, table 7, figure 12). There was no difference between the prophylaxis and endoscopic groups ($p = 0.53$).

Table 7. Recurrent febrile UTIs by gender and treatment

Treatment	Number of patients with UTI / Total number of patients (number of UTIs)	
	Girls	Boys
Prophylaxis	8 / 43 (11)	2 /26 (2)
Endoscopic	10*/ 43 (14)	4*/ 23 (4) †
Surveillance	24 / 42 (42)	1 /26 (2)
Totals	42 /128 (67)	7 /77 (8)

** No worse VUR outcome after 1 injection than in those without recurrence (31% and 25% with still dilating VUR, respectively)*
† Two UTIs developed within 3 days of urethral instrumentation

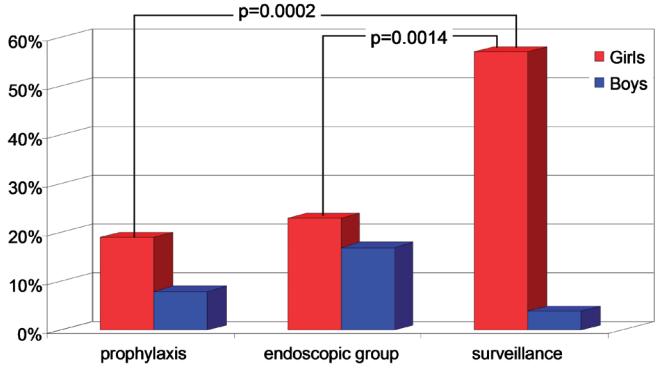


Figure 12. Febrile UTI recurrence rate by gender and treatment group.

There was also a difference in number of girls with febrile recurrences caused by bacteria resistant to trimethoprim between the treatment arms (p=0.0489, table 8). In pairwise comparison between the groups we found that prophylaxis was associated with resistance to trimethoprim compared to surveillance (p=0.038). No such difference was seen between the endoscopic treatment and surveillance (p=0.70) or between prophylaxis and endoscopic treatment (p=0.15).

In boys there were few recurrences with no differences between treatment groups (p=0.28).

Table 8. Girls with febrile UTI recurrences by trimethoprim resistance and treatment group

		Number of girls with febrile UTI	
Treatment	Number of girls	Not trim-resistant	Trim-resistent
Prophylaxis	43	1	7
Endoscopic	43	5	5
Surveillance	42	15	9
Totals	128	21	21

The rate of febrile recurrence was not related to VUR grade at entry. It was 32% in girls with grade III and 35% in those with grade IV (p = 0.38, table 9). Renal damage on DMSA scan at entry did not correlate with recurrence. The rate was 39% in girls with damage and 25% in those without (p = 0.44).

Table 9. Recurrent febrile UTIs in girls during follow-up, by VUR grade and DMSA scan results at study entry

	Number of recurrences						
	0	1	2	3	4	Totals	Mantel-Haenszel chi2 test
At study entry							
VUR grade							p = 0.38
III	60	15	12	1	0	88	
IV	26	9	1	2	2	40	
Total	86	24	13	3	2	128	
DMSA scan							p = 0.44
Normal	44	6	7	1	1	59	
Abnormal	42	18	6	2	1	69	
Total	86	24	13	3	2	128	

There was an association between VUR grade at 2 years and recurrence rate in girls, with more UTIs in those with higher grades of reflux (p=0.0095, table 10). The same association was seen when girls in the surveillance group were analysed separately (p=0.048). No such association was seen in boys.

Table 10. Recurrent febrile UTIs in girls by VUR status at 2 years

	Number of girls with recurrences		
2-year VUR grade	No	Yes	Totals
No VUR	22	5	27
I	4	2	6
II	22	5	27
III	24	19	43
IV	8	8	16
Total	80	39	119 *

** Two-year VCU not done in 9 girls (Mantel-Haenszel chi2 test p = 0.0095)*

In the 7 boys with recurrences all occurred in the group with renal damage already at start, and 6 of them had grade IV reflux at entry. The difference in recurrence rate between boys with different VUR grade at entry was significant (p = 0.045).

Figure 13 shows Kaplan-Meier curves of time from randomization to the first febrile recurrence in girls and boys. In girls median time to the first recurrence was 589 days in the prophylaxis, 380 days in the endoscopic, and 96 days in the surveillance group with a significant difference between groups (log-rank p <0.0001). No such difference was seen in boys (log-rank p = 0.25).

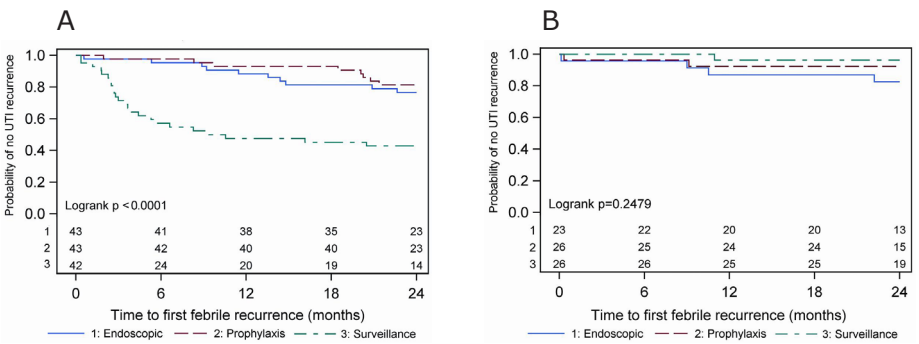


Figure 13. Kaplan-Meyer curves showing time from randomization to first febrile UTI in children with grade III-IV VUR. A: 128 girls B: 75 boys.

Renal damage – paper IV

Median time between DMSA scan before inclusion and randomization was 49 days, interquartile range 22-119 days. Abnormal DMSA scintigraphy at entry was seen in 124 children (61%) with bilateral uptake defects in 18 of them (15%). Generalized renal damage was more frequent in boys, 44 of 75 (59%) than in girls, 30 of 128 (23%) ($p < 0.0001$). Two-year DMSA scan was done in all 203 children except for 2 due to hospital fear. Of these 1 had bilateral class 1 uptake defects at entry and 1 had normal kidneys. Median interval between last reported UTI and follow-up DMSA was 225 days, and was shorter than 6 months in four cases (79, 81, 83 and 114 days respectively). Detailed description of children with progression of renal uptake defect present at entry or new damages at follow-up are given in table 11, published on the internet in association with paper IV.

Deterioration

Renal status deterioration, i.e. new damage in a previously normal area or decreased relative function in a kidney with uptake defects at entry, was seen in 17 girls and 7 boys. The differences between the groups, 4 of 68 (6%) on prophylaxis, 8 of 65 (12%) with endoscopic treatment and 12 of 68 (18%) on surveillance, were not significant ($p = 0.11$).

Deterioration was seen in 15 of 49 children (31%) with recurrent febrile UTI, and in 9 of 152 children (6%) without recurrence ($p < 0.0001$, table 12). There was no difference in deterioration between children with grade III or IV VUR at entry, 12% in each.

New damage

New damage was seen in 13 girls and 2 boys (figure 14). Of the 13 girls 8 were on surveillance, 5 in the endoscopic and none in the prophylaxis group. ($p = 0.0155$). In pair wise comparison between groups new damage was more common in the surveillance than in the prophylaxis group ($p = 0.0054$). This difference was still significant ($p = 0.0258$) after excluding from analysis 2 girls with recurrence during the study period but who also had febrile UTI after first DMSA but before randomization, and where damage from recurrence before randomization could not be ruled out. The difference between the endoscopic and prophylaxis groups did not attain significance and there was no difference between the endoscopic and surveillance groups ($p = 0.0551$ and 0.5477 respectively). Also new damage was more common in children with febrile recurrences, 11 of 49 (22%) than in those without, 4 of 152 (3%) ($p < 0.0001$, table 12). New damage developed in 9 children with normal kidneys and in 6 with abnormal kidneys at study entry.

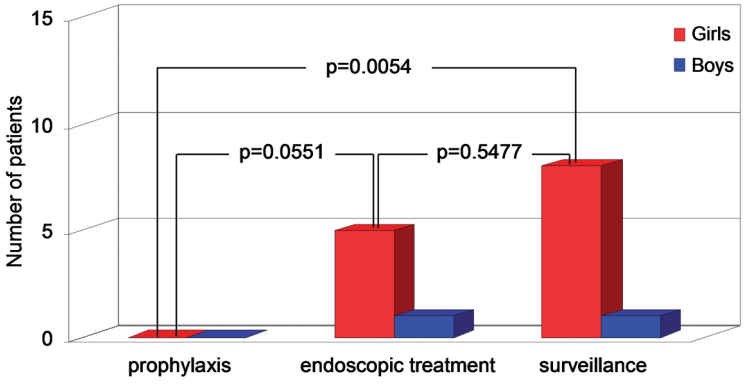


Figure 14. New renal damage in children with dilating VUR by treatment arm

Table 11. Deterioration of renal status at the 2-year DMSA scintigraphy in 24 children. Progression of initial renal uptake defects was seen in 13 and new damage in 15 children (overlapping in 4 girls).*

Patient number	Allocated treatment arm	Sex	At entry				Number of febrile recurrences during F/U	Progress of old damage right-left	New renal damage right-left	Change of split function (%) of the damaged kidney
			Right		Left					
			VUR grade	DMSA class	VUR grade	DMSA class				
1	prophylaxis	girl	I	0	IV	3	4	no-yes	no-no	39 → 32
2	prophylaxis	boy	IV	1	IV	2	0	no-yes	no-no	42 → 33
3	prophylaxis	boy	0	0	IV	2	1	no-yes	no-no	41 → 37
4	prophylaxis	boy	III	3	0	0	0	yes-no	no-no	26 → 21
5	endoscopy	girl	III	1	III	2	0	yes-no	no-no	55 → 51
6	endoscopy	girl	II	0	III	0	2	no-no	no-yes	50 → 43
7*	endoscopy	girl	0	0	III	3	2	no-yes	no-yes	32 → 20
8	endoscopy	girl	III	0	0	0	1	no-no	yes-no	57† → 52
9	endoscopy	girl	0	0	III	0	0	no-no	no-yes	50 → 44
10	endoscopy	girl	0	0	III	0	1	no-no	no-yes	50 → 30
11	endoscopy	boy	IV	3	III	0	1	yes-no	no-no	28 → 21
12	endoscopy	boy	0	0	IV	1	0	no-no	no-yes	48 → 46
13	surveillance	girl	III	0	IV	0	4	no-no	no-yes	54 → 50
14*	surveillance	girl	0	0	IV	1	0	no-yes	no-yes	47 → 37
15*	surveillance	girl	IV	2	0	0	1	yes-no	yes-no	40 → 31
16	surveillance	girl	IV	0	0	0	3	no-no	yes-no	47 → 42
17	surveillance	girl	III	1	II	1	1‡	no-no	yes-no	46 → 44
18	surveillance	girl	II	1	III	0	2‡	no-no	no-yes	54 → 49
19	surveillance	girl	III	0	II	0	2	no-no	yes-yes	54† → 44
20	surveillance	girl	0	0	III	3	0	no-yes	no-no	31 → 25
21	surveillance	girl	0	1	III	3	2	no-yes	no-no	39 → 35
22*	surveillance	girl	III	3	0	0	1	yes-no	yes-no	29 → 22
23	surveillance	boy	III	3	III	0	0	yes-no	no-no	35 → 31
24	surveillance	boy	0	0	III	0	0	no-no	no-yes	48 → 46

* *Both progression of old damage and new damage in 4 girls*
† *Duplex kidney*
‡ *Additional febrile UTI recurrence after the first DMSA scan but before randomization*

Tabel 12. Children with deterioration or new damage by number of recurrences.

	Number of recurrences					
	0	1	2	3	4	Totals
Number of patients* with deterioration						
No	143	22	10	2	0	177
Yes	9	9	3	2	1	24
Totals	152	31	13	4	0	201
with new damage						
No	148	25	10	3	0	186
Yes	4	6	3	1	1	15
Totals	152	31	13	4	0	201

**Follow-up DMSA scan not done in 2 patients.*

Damage in renal units

In analysing individual kidneys we found that deterioration occurred only in kidneys drained by ureters with grade III or grade IV VUR (table 13). In patients with bilateral VUR deterioration always occurred in the kidney with the most severe reflux, except in 1 case. In this girl with normal kidneys and grade II and III VUR at study entry, 2 febrile recurrences and bilateral scars developed (figure 15).

Table 13. Kidneys with deterioration (progression or new damage) by VUR grade at study entry

	Number of kidneys		
VUR grade	Totals*	Progression	New damage
No VUR	92	0	0
I	11	0	0
II	44	0	1
III	173	7	10
IV	83	6	5
Totals	402	13	16

**Follow-up DMSA scan not done in 2 patients.*

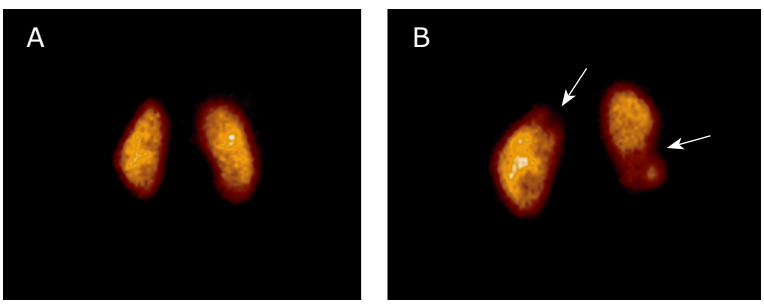


Figure 15. DMSA scan at entry (A) and at 2-year follow-up (B) in girl with bilateral new renal damage (arrows).

Discussion

The role of VUR in renal scarring in children has been studied and debated for half a century. When the association between VUR and scarring was established, it was close at hand, and easy to understand, that surgery became the first option for children with VUR. As the role of pyelonephritis in scar formations was recognized antibiotic prophylaxis was recommended for these children. The complexity of the relationship between VUR, UTI and renal scarring was even more apparent when renal damage was found in children with congenital VUR found at work up of prenatal hydronephrosis without any UTI.

There were still many unanswered questions. Is endoscopic injection an efficient and reliable way to reduce VUR? Is the risk for recurrent UTI or renal damage reduced by VUR elimination or antibiotic prophylaxis? If prophylaxis reduces the UTI recurrence rate, does it also precipitate the spontaneous resolution of VUR? Does prophylaxis increase the risk for antibiotic resistance? Is established renal uptake defect or scarring a risk factor for reduced VUR resolution, increased rate of UTI recurrence or new renal damage?

Does dysfunctional elimination affect the results of injection treatment or the spontaneous VUR resolution? Does it affect the risk of UTI recurrence or renal damage?

What are the differences between boys and girls in these respects?

The answers to these questions will help us decide how to best treat boys and girls with VUR. We might be able to identify subgroups of children that would benefit more from endoscopic treatment, and other subgroups that could be left without follow-up or kept on surveillance only. Indications for antibiotic prophylaxis could be defined and specified.

The Swedish Reflux Trial in children with dilating VUR was set up to answer some of these questions and help us to better tailor the management strategies in accordance with the child's specific features and needs.

On UTI

The Swedish Reflux Trial shows a clear protective effect of long-term antibiotic prophylaxis from recurrent febrile UTI in small children with dilating VUR. This is in contrast to the results of five randomized controlled studies on the role of antibiotic prophylaxis published the last four years (summary of number and age of patients, follow-up and VUR grades in table 14). Comparing prophylaxis to surveillance or placebo they found no, or only modest, benefit to prophylaxis for children with VUR. Garin et al followed 218 patients aged 3 months to 17 years with VUR grade 0-III and found no support for prophylaxis protecting from UTI. However, they only included 37 children with dilating grade III reflux.[118] Roussey-Kesler et al studied 225 children and found no protective effect of antibiotics against UTI in low grade VUR, but among the 54 children with grade III they found a significant reduction of UTI in boys on prophylaxis.[119] Pennesi et al studied 100 children with VUR II-IV, and found no difference in recurrence rate between prophylaxis and non-prophylaxis irrespective of gender or VUR grade.[120] Montini et al found no difference in number of febrile recurrences in 338 children with VUR grade 0-III when comparing prophylaxis to no prophylaxis.[121] However, the rate of febrile recurrences increased with increasing VUR grade. From these studies it was concluded that there was no or very limited benefit of prophylaxis in children with no or low grade VUR but for dilating reflux there was not sufficient data to guide clinicians in their management of the children.[122]

Table 14. Six studies on prophylaxis for UTI

	Pennesi[120]	Montini[121]	Roussey-Kesler[119]	Garin[118]	Craig[123]	Swedish Reflux Trial
number of pats	100	338	225	218	576*	203
age at inclusion	0-2½ yrs	2 m-7 yrs	1 m-3 yrs	3 m-17 yrs	0-18 yrs	1-2 yrs
follow-up	2 yrs	1 yr	1½ yr	1 yr	1 yr	2 yrs
VUR grade						
III (pats)	46	40	54	37	129†	126
IV (pats)	33					77

** VUR grade unknown in 99*
† VUR III-V (VUR grade distribution unknown)

In the most recent published study (PRIVENT) Craig et al compared prophylaxis with placebo in 576 children under the age of 18 years, 369 girls and 207 boys, after one or more UTI.[123] Most children did not have any severe VUR, no VUR in 234 and grade I or II in 114, while dilating VUR was found in 129 (VUR unknown in 99). This is the only of the studies where placebo was used in the control group. They showed a modest reduction of 6-7% in the absolute risk for symptomatic UTI for the prophylaxis group. For febrile UTI these differences were not significant, except for in boys and those younger than 4 years. The risk reduction was constant across subpopulations such as different VUR grades, boys and girls, and whether the first infection was resistant to the trimethoprim-sulfamethoxazole or not. Their results are somewhat different from the Swedish Reflux Trial. Craig et al had lower rate of febrile recurrence altogether and less difference between girls and boys, 11% in girls and 6% in boys, compared to our study where we had much higher recurrence rate in girls compared to boys, 33% and 9% respectively (paper III). The risk reduction for girls receiving prophylaxis, from 15% to 9%, was more modest in the Australian study compared to our results of a reduction from 57% to 19% between surveillance and prophylaxis.

In the Swedish Reflux Trial we found a remarkable gender difference with a low total number of recurrences in boys with no difference between groups as opposed to the much larger number of UTIs in girls. In girls there were significant differences between groups clearly showing the protective effect of prophylaxis.

These differences are probably due to our population being more vulnerable to UTI compared to the children in the other five trials. The children in the Swedish Reflux Trial were more homogenous in age, 1-2 years, and a larger proportion of renal damage on scintigraphy (61%) was found at start. And they all had dilating VUR, as this was the main inclusion criteria in our trial, as opposed to other studies emanating from follow-up of children after UTI.

The recruitment process included only children with a documented dilating VUR between 1 and less than 2 years of age. This procedure excluded a cohort of children with severe VUR in infancy but with regress of reflux grade during the first year of life. One can speculate if this left us with a subpopulation with more severe VUR who were more prone to contract UTI.

Recurrence during prophylaxis can be expected to be caused by resistant bacteria. Sensitivity to the given drug in the bacteria causing a UTI indicates non-adherence to medication.[124] Conway found in a retrospective registry study of 27 primary care pediatric practices that prophylactic antibiotics did not lower the UTI recurrence rate, but rather increased the rate of resistant bacteria at recurrences.[125] This can be seen as a support for the concern that prophylaxis may increase the risk for infections caused by resistant bacteria.

In our study the bacteria causing febrile UTI in the prophylaxis group where more often resistant to trimethoprim than in controls. Similar results have been reported by others.[124, 126] Thus, the proportion of resistant infections in girls with recurrences was largest in the prophylaxis group, even though the total number of girls with resistant infections was similar in all groups.

In interpreting the results on prophylaxis one has to consider the favourable resistance situation in Sweden. At the time of the trial trimethoprim resistance in E. coli from urine cultures showed an increase from 13 to18% according to reports from Strama, the Swedish Strategic Programme against Antibiotic Resistance (figure 16).[127] This is similar to the 17% reported from Italy in 2007.[122]

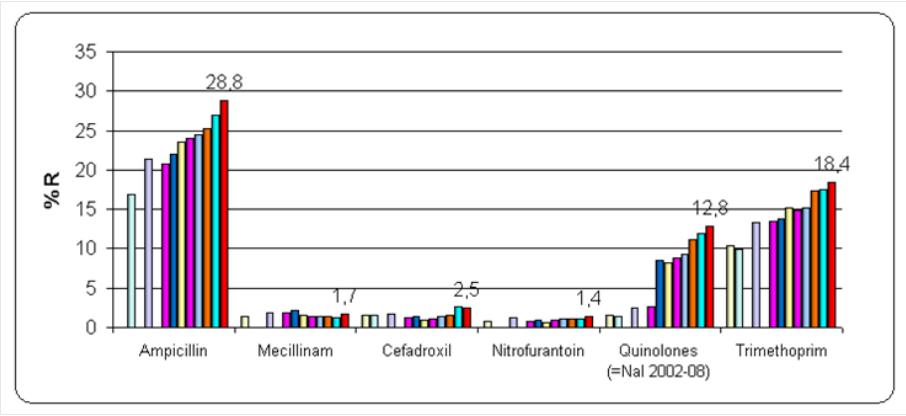


Figure 16. E. coli antibiotic resistance in Sweden 1996-2008 according to STRAMA. (From Kahlmeter et al: Swedres 2009: A Report on Swedish Antimicrobial Utilisation and Resistance in Human Medicine. Swedish Institute for Infectious Disease Control. 2009)[127]

On renal damage

For the first time we have been able to show that prophylaxis reduces the rate of new renal damage in children with dilating VUR, especially in girls as they are more prone to contract UTI.

In boys UTI recurrences were seen in only 7 of 75, but all occurred in the group with renal damage already at start, and 6 of them had grade IV reflux at entry, one grade III. This difference barely attained significance ($p = 0.048$) due to the low total number of recurrences in boys, but is an indication that boys with renal damage at start constitute a group with higher risk for recurrences.

In work up of antenatal urinary tract dilatation boys more often have congenital renal parenchymal reduction or dysplasia compared to girls.[73] In studies of renal damage found at work up after UTI and the progression of renal status over time, boys of young age are more often found to have generalized renal damage at diagnosis, while new renal damage in previously normal areas are more frequent in girls.[128] These findings were confirmed in our study were 54% of the girls and 73% of the boys had renal damage at DMSA scan before entry, while 13 girls and 2 boys (10% and 3 % respectively) obtained new renal scars during follow-up.

The fraction of children with renal damage on DMSA after a UTI differs widely between studies. This is partly due to the lack of a unanimous system for the grading of damage on DMSA. There are many reports on renal damage in DMSA scintigraphy where the renal uptake is reported as normal/abnormal, a dichotomization of the variable. This makes the results easier to evaluate and compare but runs the risk of loosing valuable information about differences between groups, since long term effects of renal damages seen on DMSA can be expected to differ according to the extent of the parenchymal defect. Attempts have been made to define criteria for such a grading system, but consensus has not been reached.[67, 129] We have studied the deterioration of renal parenchyma, as new lesions in previously unscarred areas as well as progression of already established renal damage. The dispersion on definition played a role in our decision to focus on new lesions in the analysis as they are more indisputable and readily defined.

Two other problems in assessing DMSA scintigraphies need to be mentioned. When comparing repeated scans in the same patient to evaluate damage progression, it can be difficult to distinguish between new lesions, and lack of growth potential in an already scarred kidney in combination with compensatory hypertrophy on the contralateral side. Secondly, the time needed for acute DMSA changes to evolve into permanent damage has been estimated to be up to 6 months. This has been questioned in a recent report on 50 children, of whom 18 had VUR grade I-IV, with lesions visible on DMSA 6 months after pyelonephritis. At reexamination after 3 years, complete disappearance was seen in 9 % of these lesions and partial resolution in 63%.[130] This has to be confirmed in more studies but will eventually have implications on future research on renal damage after UTI.

On outcome of reflux

Our postoperative results after endoscopic injection therapy are in agreement with previous studies taking into account the learning curve for some of the participating pediatric urologists. There was a relatively large group of children who relapsed with dilating VUR at two years follow-up. This has previously not been systematically described or looked for. The explanations to these results may be the study population characteristics, with more pronounced VUR, more renal damage at start and greater tendency for UTI recurrence

compared to other studies. This might have left us with a population with more pronounced bladder dysfunction, known to hamper the success of reflux surgery.

The rate of spontaneous resolution or downgrading of VUR did not differ between the prophylaxis and surveillance groups, even though there were less UTI recurrences in the former.

On allocation coherence

There were more children in the surveillance group that were shifted to another treatment, endoscopic treatment in 3 and prophylaxis in 6, and 2 of these 6 were later endoscopically treated because of additional recurrences. The intent to treat principle in the analysis has provided information on the results from the treatment to which the child was randomized, reflecting the situation of choosing a strategy for a real world patient. But the conclusions could be concealing some of the actual treatment consequences, such as fewer UTI recurrences in the surveillance group due to prophylaxis initiated during the study, or lower VUR grade at follow up because of injection performed in some of the children in the prophylaxis and surveillance groups. Since the endoscopic group was given prophylaxis until the VUR was shown to be downgraded that group in a sense was a mixture of endoscopy and prophylaxis, once again a reflection of the real world situation.

On recruitment problems

The study did not meet the goals of recruitment, as has been the situation for other recent studies[121, 123] The results reported are significant, but there are associations not attaining significance that may be examples of type I errors, being excluded as non-significant because of lack of statistical power. The adversity, especially in interventional studies, to reach the set goals of recruitment, often based on thorough power analysis in the planning phase of a study, is a problem in clinical research that need to be highlighted and addressed in future studies.

Implications for clinical management

In combining our results with other's, including recent studies in children with lower VUR grades, it becomes obvious that VUR is not a homogenous entity. The outcome of any management strategy for children with VUR will depend on individual characteristics of the children, not merely the severity of the reflux.

It has been suggested that bladder function could be one of the more important elements to account for, maybe the crucial watershed, in the decision on suitable investigations and follow-up for a child with known VUR or after febrile UTI.[131] In our study population abnormal voiding pattern was shown to be associated with VUR outcome and UTI recurrences, but in retrospect since only the follow-up bladder function tests were significant in this respect.[132] We still do not have any validated method for bladder function assessment in not toilet trained children specific and sensitive enough to help us predict the outcome for the individual child, in terms of VUR resolution, UTI-recurrence or new renal damages, in order to tailor the management according to bladder function at diagnosis.

Until such tests emerge we will have to rely on factors such as shown proneness to UTI, preexisting scarring, VUR grade, female gender and age of the child for an individualized management strategy. The goal of the treatment will also direct the choice of strategy.[133] The detection and prevention of renal infections and parenchymal damage is of great impor-

tance for the well being of the child. The mere cessation of VUR is of many considered a means to reduce the risk for damage and UTI recurrence, not a goal in itself.

The treatment should be safe and sufficient without over treating the patient. In boys over the age of 1 year with dilating VUR active treatment, with endoscopic injection or antibiotic prophylaxis, seems to be of very little value and should be limited to those who have shown to be prone to recurrent UTI. Girls with dilating VUR, on the other hand, benefit from active treatment with reduced rate of recurrence and new renal scarring. Thus, we still need to search for dilating VUR in girls, by VCU or other diagnostic methods, as they are at greater risk, a risk that can be affected by the choice of management.

A flow chart on the management of girls and boys over the age of 1 year with dilating VUR illustrates the results from the Swedish Reflux Trial (figure 17). The study provides evidence for treatment in children between 1-4 years of age with dilating VUR, and the results may have implications for children older than 4 years. But no conclusions can be drawn for infants younger than 1 year. Consideration also has to be taken to the resistance pattern in the area in question, when deciding on the use of prophylaxis and the choice of antibiotic agent.

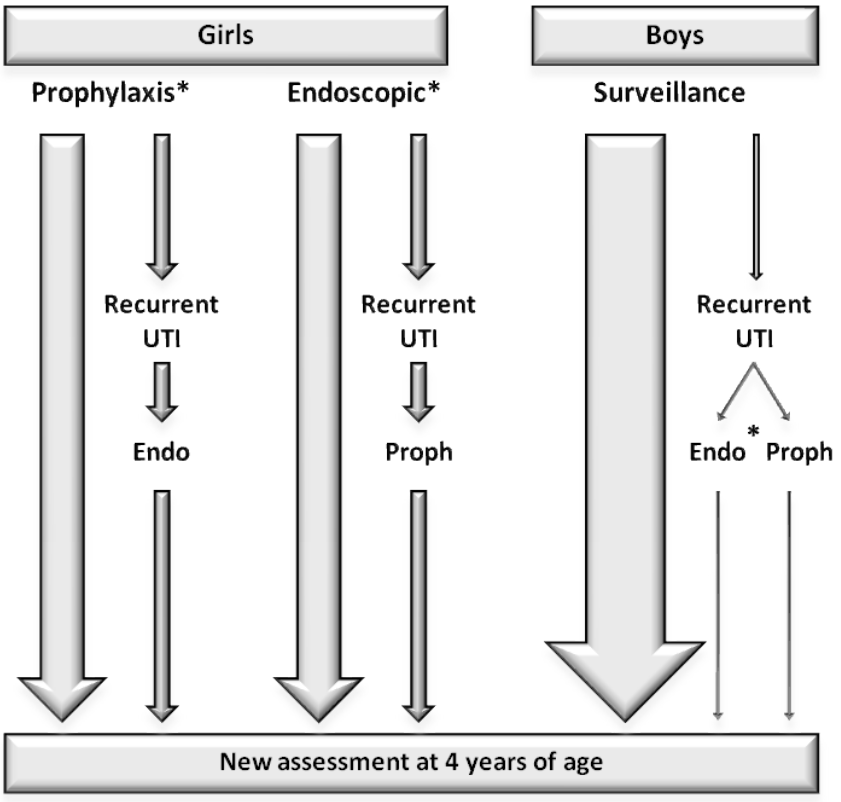


Figure 17. Management strategies for children >1 year of age with dilating VUR.
** No evidence in study for prophylaxis or endoscopic injection being superior.*

Conclusions

We need to be better at individualizing management of children with dilating VUR. The results of the Swedish Reflux Trial have provided evidence to use in tailoring the treatment for these children. Our results are in apparent contrast to other recently published studies in children with VUR where no or little benefit from prophylaxis was shown. However, these different results should be seen as complementary, since our trial included a larger group of children with dilating reflux.

For girls above 1 year of age with dilating VUR there is apparent benefit to active medical and surgical treatment in reducing the recurrence rate. We have also shown that prophylaxis reduces the risk for new renal damage to occur. On the other hand, boys older than 1 year with dilating VUR do not benefit from active treatment.

Sammanfattning på svenska

Bakgrund

Vesikoureteral reflux är den medicinska termen för backflöde av urin från blåsan tillbaka till njuren via urinledaren. Den graderas I-V efter hur mycket de övre urinvägarna vidgas i samband med backflödet. Reflux förekommer hos ungefär 1% av alla barn, men när man undersöker dem som haft urinvägsinfektion hittar man det hos upp till 30%, varav hälften är vidgad (grad III eller mer).

Små barn med vidgad reflux har en ökad risk att få nya urinvägsinfektioner och har på sikt också större risk att utveckla njurskador. Refluxen är oftast medfödd och den njurförändring man ibland finner hos dessa barn finns i många fall redan vid födelsen. Hos en del barn försvinner refluxen spontant. Hos andra finns den dock kvar och riskerna för infektioner och skador ökar ju kraftigare vidgningen är.

För att minska dessa risker började man under andra hälften av 1900-talet operera refluxen eller ge förebyggande antibiotika (profylax) mot nya infektioner. På 1990-talet spreds en ny kirurgisk metod där man via ett titt-instrument (cystoskop) för in en tunn nål till blåsan och sprutar ett biologiskt fyllnadsmaterial in under slemhinnan precis vid urinledarens mynning. På så sätt kan man minska eller helt få bort refluxen, men man saknar kunskap om vad som händer med den på lång sikt. Man vet heller inte om metoden får antalet urinvägsinfektioner och njurskador att minska.

Vetenskapliga studier har visat att antibiotikaprofylax varje dag under lång tid, ofta flera år, är lika effektivt som de äldre operationsmetoderna när det gäller antalet infektioner och njurskador. Men man hade inte jämfört antibiotikaprofylax med en kontrollgrupp. Med tiden dök det upp allt fler rapporter om bakterier som var resistenta mot olika antibiotika och man började också ifrågasätta om profylax var ett så effektivt skydd mot infektioner som man tidigare trott.

För att ta reda på hur man bäst skulle behandla barn med reflux behövde dessa oklarheter studeras. Därför startades den Svenska Refluxstudien.

Studiens design

Studien bestod av tre behandlingsalternativ: antibiotikaprofylax, injektionsbehandling av refluxen och en kontrollgrupp. Snabb behandling vid eventuella infektioner skulle ges i alla tre grupperna.

Metoder

Refluxens utveckling kontrollerades genom att det gjordes en blåsröntgen på alla barn före studiens start och efter 2 års uppföljning.

För att bedöma om njurskada fanns och förvärrades, eller om det uppkom nya skador, gjordes en gammakameraundersökning av njurarna (njurscintigrafi med DMSA), också det före studiens start och efter 2 år.

Patienter

Det var 203 barn med i studien, 128 flickor och 75 pojkar, från 22 olika barnkliniker i Sverige och 1 i Oslo. Den första patienten inkluderades i december 2000 och den sista patienten avslutade sina 2-års-undersökningar i april 2009.

Barnen fördelades slumpmässigt mellan de tre grupperna med hjälp av ett specialgjort datorprogram. De kontrollerades under 2 år med regelbundna besök och telefonkontakter, och varje urinvägsinfektion registrerades.

Resultat

Hos barn som fick antibiotika eller enbart observerades försvann eller minskade refluxen spontant hos 39% respektive 47%. I gruppen som fick injektionsbehandling var den siffran 71% trots att 13 barn som först blev bra efter en injektion fick tillbaka refluxen.

Det var mycket vanligare med febrila urinvägsinfektioner hos flickorna, sammanlagt 67 infektioner inträffade hos 42 av dem, medan det bara var 8 febrila infektioner hos 7 av pojkarna. Hos flickorna var det också stor skillnad mellan grupperna. 19% av dem i profylaxgruppen och 23% i injektionsgruppen hade infektioner, i observationsgruppen var det 57%.

Förändringar i njurarna fanns redan från början hos 61 % av barnen och det var något vanligare hos pojkarna än hos flickorna, 71% respektive 54%. Nya skador var däremot vanligare bland flickorna vilket drabbade 13 av dem, däremot ingen av dem som fått profylax. Av pojkarna var det bara 2 som fick nya skador. Det fanns också ett tydligt samband mellan urinvägsinfektioner och nya skador.

Slutsats

Hos små barn med kraftig reflux kan man påskynda minskningen eller utläkningen av refluxen med injektionsbehandling, Det viktiga är dock att minska risken för infektioner och njurskador. För flickor över 1 år med kraftig reflux kan man minska antalet återkommande urinvägsinfektioner med antibiotikaprofylax eller injektionsbehandling av refluxen. Profylax minskar också risken för ny njurskada.

Hos pojkar däremot är det så ovanligt med urinvägsinfektioner och nya njurskador att de inte har någon nytta av vare sig injektionsbehandling eller antibiotikaprofylax.

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Errata

Paper I: Page 277, table 3 and page 278, table 4:
The percentage of patients with VUR grade III and grade IV, given in brackets (%), should be:

Table 3. *Basic data by treatment arm in 128 girls*

	Prophylaxis		Endoscopy		Surveillance	
No. pts	43		43		42	
No. VUR grade (%):						
III	27	**(63)**	32	**(74)**	29	**(69)**
IV	16	**(37)**	11	**(26)**	13	**(31)**
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.	.	.	.	.	.	.
.	.	.	.	.	.	.

Table 4. *Basic data by treatment arm in 75 boys*

	Prophylaxis		Endoscopy		Surveillance	
No. pts	**26**		**23**		**26**	
No. VUR grade (%):						
III	14	**(54)**	10	**(43)**	14	**(54)**
IV	12	**(46)**	13	**(57)**	12	**(46)**
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.

Paper II: Page 282, right column, line 24:
After 1 or 2 injections, including in the 2 patients who did not receive injection 1, a total of 10 renal units had dilating VUR in 9 patients.
(Not 9 renal units as written.)