The Swedish Infant High-grade Reflux Trial

– and a Focus group study of parents' experiences

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To my family

" Reflux is an old hat: now that we have a reliable operation to fix it, it is a boring subject to talk about."

1974 Sir David Innes Williams

Abstract

Background: Vesicoureteral reflux (VUR) is a pathological back-flow of urine from the bladder to the ureter and renal pelvis. VUR is associated with an increased risk of urinary tract infections (UTI) and renal damages. Infants with congenital high-grade VUR (hVUR) often have dysplastic kidneys with diffuse parenchymal defects and a bladder dysfunction with enlarged bladder and poor emptying ability. Spontaneous resolution of VUR with increasing age is common in lower grades of VUR, but is rarely seen in high-grade VUR. The goal of all VUR treatment is to prevent UTIs and minimize the morbidity related to investigation and treatment. Surgical intervention (SI) – endoscopic treatment (ET) or open surgery – can be indicated in case of repeated UTI recurrences or progress of renal damages during antibiotic prophylaxis.

The aim of this research project was to investigate whether hVUR in infants can be treated with endoscopic injection, and whether the VUR outcome is favourable with ET compared with continuous antibiotic prophylaxis (CAP) alone. Furthermore, to determine whether the development of bladder dysfunction during infancy can be prevented by early reflux resolution and whether early ET reduces the risk of UTI and renal scarring during follow-up. Lastly, we aimed to describe parents' experiences of CAP, SI, UTI and renal damage.

The first three papers present the results from the Swedish infant high-grade reflux trial – an open, prospective, randomised, controlled, national multicentre study, in which we compared the outcomes (VUR resolution, bladder function, UTI recurrence and renal scarring) between the two treatment groups (ET vs. CAP). The study did not reveal any differences in bladder function, UTI recurrence or renal scarring between the two treatment groups, despite the superior effect of ET on VUR resolution and the fact that VUR-grade at follow-up correlated with both UTI recurrence and renal deterioration. Although bladder dysfunction could not be prevented by early VUR resolution, it can be seen as an important prognostic factor for VUR outcome.

The fourth paper is based on focus group discussions, held with parents of children with infant hVUR, and describes the parents' experiences of the treatment and outcomes. The focus group discussions revealed that both

CAP and the risk of UTI have a negative, everyday impact on family life, while renal damage appears to be less important to the parents. The concerns relating to SI are related to a single occasion, which can be optimised by proper care.

VUR management should be individualised and risk adapted according to current knowledge and parents' preferences should be considered.

Sammanfattning på svenska

Vid vesicoureteral reflux (VUR) har man ett patologiskt backflöde av urin från blåsan upp genom urinledaren till njurbäckenet. Barn med VUR löper större risk att få upprepade urinvägsinfektioner (UVI) och skador på njurarna. Bland spädbarn med medfödd höggradig reflux (hVUR) har majoriteten även en generell medfödd njurskada. Spädbarnen har dessutom ofta blåsdysfunktion som hos många innebär en onormalt stor blåsa med påverkad tömningsfunktion. VUR kan försvinna spontant med stigande ålder, men vid hVUR är denna chans relativt låg. Målet för all behandling av VUR är att förebygga nya infektioner och samtidigt minimera den morbiditet som är kopplad till utredning och behandling. Kirurgisk refluxbehandling – endoskopisk injektionsbehandling (ET) eller öppen operation – syftar till att skapa en kompetent vesicoureteral övergång och är indicerad vid genombrottsinfektioner eller om progredierande njurskada ses trots antibiotikaskydd.

I delarbete I-III redovisas resultatet av Den Svenska Spädbarnsreflux-studien, där man i en prospektiv, randomiserad, kontrollerad, multicenterstudie undersökt om antibiotikaprofylax eller ET är att föredra vid hVUR hos spädbarn avseende I) nedgradering av reflux, II) blåsfunktion och III) UVI och njurskada. Denna studie fann ingen skillnad i blåsfunktion, förekomst av UVI eller njurskada mellan de två behandlingsgrupperna trots större chans till refluxfrihet i ET-gruppen samt en korrelation mellan hög VUR-grad vid uppföljning, antal UVI-recidiv och njurskada. Blåsdysfunktion kunde inte förebyggas med tidig refluxfrihet, men kan ändå ses som en viktig prognostisk faktor avseende refluxutfall.

I det fjärde delarbetet presenteras en kvalitativ studie där vi använde fokusgruppmetodik för att utforska föräldrars erfarenheter av hVUR hos spädbarn, avseende antibiotikabehandling, kirurgi/endoskopi, UVI och njurskador. Resultatet av fokusgrupperna visade att antibiotikaprofylax och risken för UVI verkar innebära en dagligt återkommande, icke-försumbar påverkan av familjelivet, medan njurskada verkar ha mindre betydelse ur föräldrars perspektiv. Erfarenheterna av kirurgi/endoskopi är relaterade till ett enstaka vårdtillfälle som kan optimeras med små medel och adekvata förberedelser. Föräldraperspektivet bör tas i beaktande vid handläggning av spädbarn med höggradig VUR.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Nordenström, J., Holmdahl, G., Brandström, P., Sixt, R., Stokland, E., Sillén, U., Sjöström, S.

   The Swedish Infant High-grade Reflux Trial: Study presentation and Vesicoureteral reflux outcome

   Journal of Pediatric Urology 2017; 13: 130–138.

II. Nordenström, J., Sillén, U., Holmdahl, G., Linnér, T., Stokland, E., Sjöström, S.

   The Swedish Infant High-grade Reflux Trial - Bladder function

   Journal of Pediatric Urology 2017; 13: 139–145.

III. Nordenström, J., Sjöström, S., Sillén, U., Sixt, R., Brandström, P.

   The Swedish Infant High-grade Reflux Trial: UTI and Renal damage

   Journal of Pediatric Urology 2017; 13: 146–154.

IV. Nordenström, J., Sjöström, S., Dellenmark Blom, M.

   High-grade Vesicoureteral Reflux in Infants - A Focus Group Study of Parents' Experiences

   Submitted

Contents

Abbreviations

BBD	Bowel and bladder dysfunction
BC	Bladder capacity
CAP	Continuous antibiotic prophylaxis
CFU	Colony forming units
Dx/HA	Dextranomer/hyaluronic acid copolymer
ET	Endoscopic treatment
FVO	Free voiding observation
GFR	Glomerular filtration rate
HRQoL	Health-related quality of life
ITT	Intention to treat
LUTD	Lower urinary tract dysfunction
PP	Per protocol
PRE	Patient-reported experience
PRO	Patient-reported outcome
PVR	Post void residual urine
QoL	Quality of life
RCT	Randomised controlled trial
RU	Renal unit
rUTI	Recurrent UTI
SI	Surgical intervention
US	Ultrasound
UTI	Urinary tract infection
VCUG	Voiding cystourethrogram
VUR	Vesicoureteral reflux
hVUR	High-grade vesicoureteral reflux
^{51}Cr-EDTA	^{51}chromium-ethylenediaminetetraacetic acid
^{99m}Tc-DMSA	^{99m}technetium dimercapto-succinic acid
^{99m}Tc-MAG3	^{99m}technetium mercaptoacetyltriglycine

1. Introduction

1.1 Definition

Vesicoureteral reflux (VUR) is the retrograde backflow of urine from the urinary bladder into the ureter and towards the kidney, secondary to a dysfunctional vesicoureteral junction. A functional vesicoureteral junction is dependent on the length of the submucosal ureter, the width of the ureteral orifice, the muscles in the ureter and trigone of the bladder and co-ordinated ureteric peristalsis.

VUR is associated with an increased risk of pyelonephritis and renal scarring, with potentially serious consequences such as hypertension and renal failure. The main goal in VUR management has therefore been the preservation of kidney function by minimising the risk of pyelonephritis. In this summarising chapter, we will discuss whether this approach is still valid and what we can learn from the last 40 years of research.
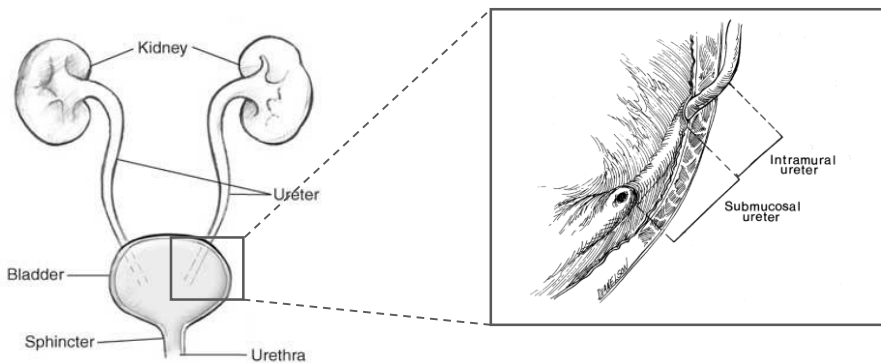
Figure 1 The vesicoureteral junction. Modified from Harrison JH, et al, eds. Campbell's Urology, 4th ed. Philadelphia: WB Saunders, 1979:1597, with permission from Elseiver

1.1.1 Grading

VUR is visualised with cystography and graded by its severity, according to the International Reflux Study in Children standards [1]. The grading depends on the degree of filling and dilatation of the ureter and upper urinary tract, visualised by filling the bladder with contrast. Grades I-II are referred to as non-dilating VUR and grades III-V as dilating VUR.
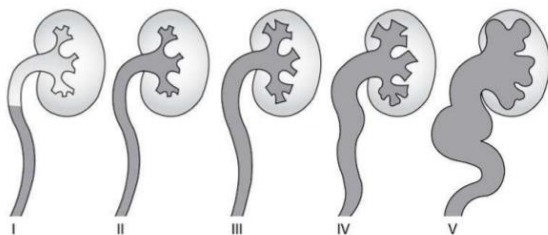
Figure 2 *International grading system of VUR, from www.radipedia.com, with permission.*

The international system for the radiographic grading of VUR

Grade I	Contrast in ureter only
Grade II	Contrast in ureter, pelvis and calyces; no dilatation of calyceal fornices
Grade III	Mild or moderate dilatation of the ureter and the renal pelvis. No or only slight blunting of the calyces.
Grade IV	Moderate dilatation and/or tortuosity of the ureter and moderate dilatation of the pelvis and calyces. Maintenance of the papillary impressions in the majority of calyces.
Grade V	Gross dilatation and tortuosity of the ureter and of the renal pelvis and calyces. The papillary impressions are no longer visible in the majority of calyces.

1.1.2 Prevalence

Studies reporting the frequency of VUR give inconsistent results. Much of the variation can be attributed to study design, particularly the differences in diagnosing VUR, selection bias, large age ranges and sampling bias. Possible confounders when analysing prevalence are the fact that the majority of VUR diagnoses are related to a history of urinary tract infections (UTIs) and that VUR is known to resolve spontaneously with age [2]. Studies of VUR prevalence in

children evaluated for UTI have reported values between 25-40% [3, 4]. Calculating with a cumulative incidence of UTI in children of 5% [5], approximately 1.25-2% of all children will be diagnosed with VUR after a UTI. The stated prevalence of VUR among siblings or first-order relatives of VUR patients is 30-45% depending on age and the study method [6, 7]. In infants with antenatal hydronephrosis, the prevalence is calculated to be 16% [7].

The true prevalence of VUR in otherwise healthy children remains uncertain: 1% is probably an underestimate, and 10% to 20% may be possible, suggesting that VUR is largely asymptomatic [2]. There is a higher prevalence of VUR in males than females during infancy (3:1), but, in children older than two years, the sex ratio has shifted.

1.2 History

The first descriptions of retrograde flow of urine from the bladder to the kidney were given by Claudius Galenos (130–200 AD), a Greek physician, writer and philosopher from Pergamon. He produced hundreds of works in which he marked the history of medicine for almost 1,300 years [8, 9].

In the 15th century, Leonardo da Vinci postulated an anti-reflux mechanism to prevent urine from returning into the ureters [10]. However, it was not until the 1950's that two British radiologists were able to demonstrate the association between post-infectious renal scars and VUR [11].
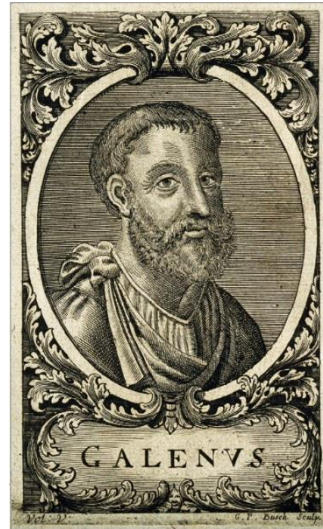
The first anti-reflux surgery was performed in 1952 by Hutch [12] and the first intravesical ureteral re-implantation in 1958, by Victor Politano and Wyland Leadbetter [13]. The extravesical ureteral re-implantation was described in 1961 by Lich et al. [14] and simultaneously and independently, on the other side of the Atlantic, Professor Gregoir in Munich developed a very similar technique [15].
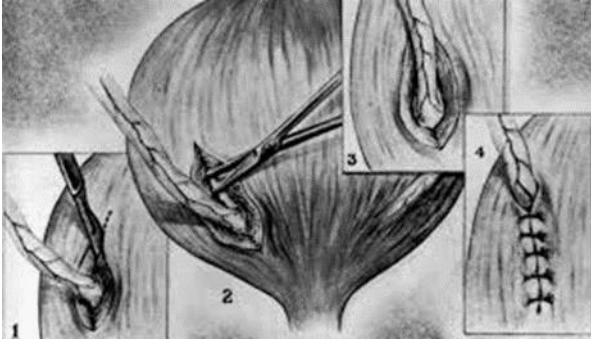
Figure 3 *The Lich re-implant technique. Lich et al. J Ky Med Assoc, 1961*

Ureteral re-implantation, with some modifications here and there, became the gold standard therapy for the treatment of VUR for almost 20 years.

The success of the surgical approach was tempered in the mid-1970s, when Smellie and Edwards et al. demonstrated relatively high rates of the spontaneous resolution of reflux on low-dose continuous antibiotic prophylaxis (CAP) and that CAP lowered the risk of developing new renal scars in most cases [16, 17]. This idea had been presented some years earlier by O'Donnell et al. and Lenaghan, but at that point it had not gained full acknowledgement [18, 19]. All children with VUR were now placed on low-dose prophylactic antibiotics, and, if this failed, surgical correction was recommended. Already at that time, infants with hVUR were regarded as a certain high-risk patient group. Open surgical repair was regarded as technically challenging in the small infant bladder and other temporary solutions such as refluxing ureterostomy were therefore often preferred. Later observational studies by Yeung and Sjostrom reported spontaneous resolution in this group as well [20, 21].

In the mid-1990s, endoscopic treatment (ET) became a safe and effective alternative in the treatment of VUR, especially in older children. The Swedish reflux trial in children was a prospective, randomised study that compared ET with CAP and surveillance in 203 children, aged one to three with VUR grades III-IV in 2000-2009 [22]. During the study period, two of the study's initiators postulated that it could be the extra load of refluxing urine on the infant bladder that caused the development of lower urinary tract dysfunction (LUTD) in small children with hVUR. To investigate their theory, they designed a study where infants < 8 months with high-grade reflux were randomised to either ET or CAP, with the hypothesis that early treatment of VUR would prevent the development of LUTD with a large bladder capacity and poor emptying ability – this was the Swedish infant high-grade reflux trial [23].

1. INTRODUCTION

1.3 Embryology

On day 35 of human gestation, the formation of the ureter and kidney starts with the emergence of the ureteric bud (metanephric diverticulum) from the mesonephric (Wolffian) duct near the urogenital sinus.

The ureteric bud grows towards the primitive kidney (metanephric mesenchyme) which evokes reciprocal signals that induce differentiation. The cranial end of the ureteric bud becomes the renal pelvis and the stalk of the bud becomes the ureter. The common nephric duct (the most posterior part of the mesonephric duct) then undergoes apoptosis which brings the ureters into contact with the urogenital sinus epithelium and, after extensive epithelial remodelling, to their final trigonal positions [24, 25] (Figures 4 and 5).
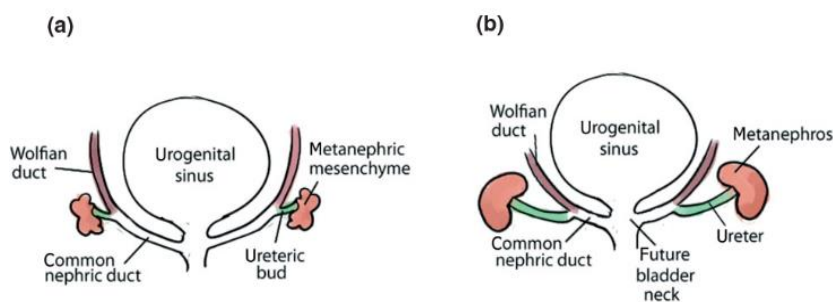
Figure 4 *Urinary tract development and structure.*
(a*) Early development of the urinary tract (fifth week of gestation). The ureteric bud from the mesonephric (Wolffian) duct meets the metanephric mesenchyme.*
(b) Elongation of the ureter and formation of the kidney (metanephros).
Rasouly HM et al. Wiley interdisciplinary reviews. Systems biology and medicine, 2013, with permission from Copyright Clearance Center.
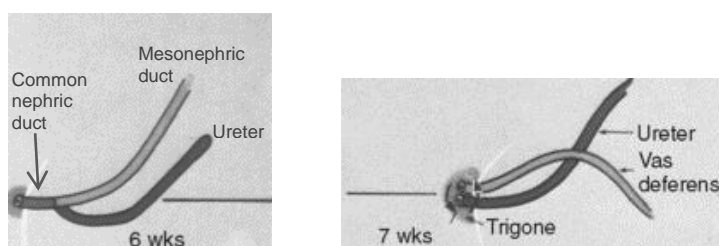
Figure 5 *The common nephric duct is progressively absorbed into the urogenital sinus. By week 7 the ureter and mesonephric (Wolffian) duct have separate openings and rotation takes place.*
https://abdominalkey.com/developmental-anatomy-and-urogenital-abnormalities/

1.3.1 Clinical correlation

The final position of the ureteral orifice depends on the position at which the ureteric bud evaginates from the mesonephric duct, which depends on the location and timing of the contact with the metanephric mesenchyme. For example, excessive caudal budding on the mesonephric duct will result in the poor development of a short intramural tunnel, an incompetent vesicoureteral junction and VUR. Concurrently, ureteral budding from an aberrant site contacts the metanephric mesenchyme at a point where mesenchymal cells are sparse and poorly differentiated, resulting in the development of hypo- and dysplastic kidneys [26].

1.4 Prognosis for VUR

The outcome for most children with VUR is generally excellent. If the VUR prevalence were as high as 3 %, meaning that VUR occurs in 30,000 per million children, approximately 6,000 of them would be diagnosed with a UTI and only five per million children would develop end-stage renal disease [2]. Importantly however, the study population in this study has higher morbidity and a poorer prognosis than VUR children in general, which will be discussed further.

1.4.1 Spontaneous resolution

The spontaneous resolution or downgrading of VUR is dependent on the degree of reflux, age, sex and associated bladder dysfunction. Estrada et al. analysed the frequency of VUR resolution in 2,462 VUR patients. They found that VUR had a high spontaneous resolution rate during the first four to five years of life (60-80% in grades I-II and 30-50% in III-IV) and that male sex, unilaterality and age < 1 year are positive predictors for resolution [27]. Similar results have been presented earlier: 39% downgrade in VUR grades III-V and a significantly higher resolution rate in males during infancy in VUR grades IV-V [21]; 35-45% resolution rate in grades III-IV after five years of follow-up [28] , 48% in grade IV after four years[29] and 51% in grades I-IV after two years [30].

   The presence of bladder and bowel dysfunction (BBD) or lower urinary tract dysfunction (LUTD) is associated with a reduced probability of VUR resolution.

1.5 Infant high-grade VUR

High-grade VUR (grades IV and V) diagnosed early in infancy represents a specific group of VUR children with special characteristics, which are most prominent in bilateral grade V. The latter often have pronounced dilatation of the upper urinary tracts and a large bladder. They are often boys, presenting with a febrile UTI, affected general condition and impaired renal function. This group runs a high risk of developing new renal scars from UTI, especially during infancy, and their risk of UTI is further increased by their high prevalence of bladder dysfunction with high bladder capacity and poor bladder emptying [20, 31, 32]. To save renal function, it is sometimes necessary to treat these children temporarily with bladder drainage or a refluxing distal ureterostomy for a few months.

Moreover, high-grade VUR is often associated with congenital renal abnormalities, such as hypo-dysplastic kidneys, and has a lower likelihood of spontaneous VUR resolution compared with lower reflux grades. In spite of this, there is a small group of children with high-grade VUR, but without the pronounced dilatation of the upper urinary tracts, where early VUR resolution can be seen, preferably during infancy [20, 21, 27].

1.6 VUR-related morbidity

1.6.1 LUTD/BBD

Detecting non-neurogenic bladder dysfunction in children before toilet training is very different from after. After toilet training, the recommendation is to use a standardised bladder-bowel questionnaire with the registration of symptoms and preferably with the addition of flow/residual urine studies. In these studies, there is a clear co-prevalence of VUR and BBD, with some studies describing a BBD prevalence of 40-60% in toilet trained VUR children [33, 34].

In non-toilet trained children, the registration of symptoms is not possible, explaining why non-neurogenic bladder dysfunction is difficult to recognise in infancy. In studies evaluating bladder function in infants with hVUR during the first year of life, characteristics of the urodynamic pattern is often similar to the voiding pattern demonstrated in healthy infants; a small to normal bladder capacity, a normal to high voiding pressure and with dyscoordinated voiding [35-38]. However, during the second year of life, it has been shown that the

urodynamic pattern changes to a high capacity bladder with increased post-void residual urine [37]. In contrast to these observations, one proportion of infants, preferable boys with bilateral VUR grade V mentioned in the previous section, seem to have a large BC already from the start. Whether it is the high volume load from the refluxing urine that affects the bladder and causes the abnormal increase in BC, noted in infants with hVUR, was one of the research questions in the present study [39].

According to the ICCS standardisation document, the term "lower urinary tract dysfunction (LUTD)" should be applied to symptoms from the urinary tract, whereas, if both urinary and bowel symptoms are present, the term should be "bladder bowel dysfunction (BBD)" [40]. LUTD, with or without bowel dysfunction, is associated with an increased risk of recurrent UTI, lower rates of VUR resolution and reduced success of surgical/endoscopic treatment [41-43]. For this reason, early potty training should be encouraged and the management of VUR in toilet trained children should include treatment for bladder/bowel dysfunction, with an individualised selection of behavioural therapy, biofeedback, anticholinergic medications and constipation management [43].
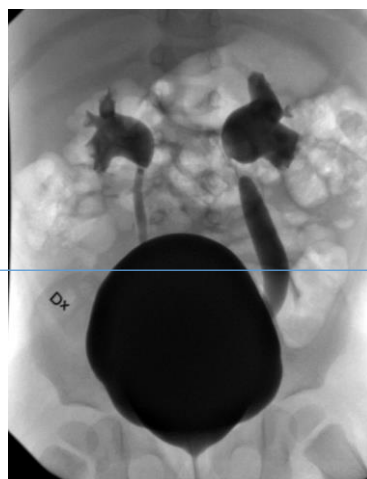
Figure 8 Large bladder capacity with bladder reaching above the iliac crest and bilateral high-grade VUR.

1.6.2 UTI

VUR in itself does not cause UTI, but it does increase the risk of bacteriuria progressing to pyelonephritis. One of the pathogenic mechanisms is probably the endotoxin effects from bacteria which cause ureteral peristalsis to cease. This leads to an atonic ureter and a decreased rate of bacterial clearance from the upper urinary tract [44]. The same effect is seen in bilateral grade V with gross dilatation of the upper urinary tract, even without bacterial influence. UTIs are more common in girls than boys because of anatomic differences, but, among all the children with UTI, boys are more likely than girls to have VUR (29% vs 14%) [45]. The only period when UTIs are more common in boys is during the first six months of life (*Figure 6*) [46].
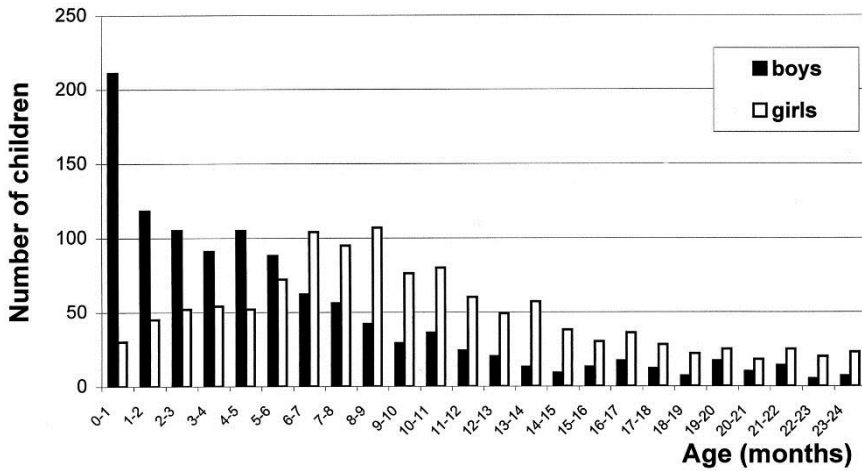
Figure 6 *Age distribution of first known UTI in children aged 0-2 years, divided by sex. Minimum Incidence and Diagnostic Rate of First Urinary Tract Infection. Jakobsson et al. Pediatrics 1999, with permission from Copyright Clearance Center.*

1.6.3 Renal damage

VUR is neither necessary nor sufficient for the development of pyelonephritis and renal scarring. Nevertheless, children with VUR are more likely to develop pyelonephritis and renal scarring compared with those with no VUR. Moreover, children with VUR grades III-V are more likely to develop renal scarring than children with lower reflux grades [43, 47]. A meta-analysis revealed that renal abnormalities occur in 6% of those with grades I-III and in 48% of those with VUR grades IV-V [7].

Reflux nephropathy (RN) is renal scarring diagnosed in patients with VUR and can be either congenital (abnormal renal development) or acquired (pyelonephritis-induced renal injury). Renal dysplasia in VUR children is most probably due to poor nephrogenic differentiation very early in embryogenesis, rather than being caused by the back pressure effect of urine reflux on the developing foetal kidney, as previously suggested [26]. The differentiation between congenital and acquired RN can be challenging, especially when a renal scintigraphy before a pyelonephritis is missing. Congenital RN is almost exclusively seen in infant boys with bilateral VUR grade V [20].

1.7 Family screening for VUR

Despite the increased prevalence of VUR in first-order relatives of VUR patients, the screening of family members is controversial. There are no randomised studies of the clinical outcome of screened versus non-screened children or siblings of reflux patients. Some authors believe that the early identification of children with VUR may prevent episodes of UTI, while others think that the screening of asymptomatic individuals may result in an overtreatment of clinically insignificant VUR. Both European and American guidelines recommend informing parents of the increased risk of VUR in siblings and offspring and, if screening is performed, the recommended modality is ultrasound. VCUG is performed if dilatation or renal scarring is detected on ultrasound or after a febrile UTI [43, 45].

1.8 Treatment of VUR

1.8.1 Continuous antibiotic prophylaxis

The purpose of continuous antibiotic prophylaxis is to keep the urine free from bacteria and thereby reduce the risk of retrograde renal infection. Since many of the reflux cases resolve with time, a conservative approach with CAP as the initial management option is often recommended [43, 45]. Nevertheless, the risk of UTI and acute pyelonephritis has to be weighed up against concerns about the possible side-effects of CAP and the emergence of multi-resistant strains of bacteria.

Many well-constructed trials have been designed to determine the efficacy of CAP in preventing UTI with contradictory results and different conclusions. The International reflux study in children demonstrated an equal incidence of UTI in the two treatment arms (CAP or open surgery) and no difference in renal scarring [48]. The Swedish reflux trial reported significantly more UTI recurrences in girls than in boys, where the rate in girls was higher in the surveillance group compared with both CAP and endoscopy. Further, the rate of new renal damage in girls was higher in the surveillance group. There were no effects of CAP on UTI recurrence or renal damage in boys [49, 50].

The PRIVENT study concluded that CAP had a limited effect on UTI recurrence [51]. The RIVUR trial enrolled 607 children with VUR grades I-IV after a UTI episode, randomised to CAP or placebo, and showed that CAP reduced the risk of UTI recurrences by 50% during the two-year follow-up [30]. According to a recent systematic review, CAP significantly reduced the risk of UTI in children with VUR, although it increased the risk of infection by antibiotic-resistant bacteria and CAP did not impact the occurrence of new renal scarring [52]. In spite of this, it can be concluded that, based on current evidence, CAP can be recommended in the first year of life, especially for children with dilating VUR who are not toilet trained and for patients with bladder bowel dysfunction [53].

1.8.2 Surveillance

Viewing VUR as a generally self-resolving condition makes active surveillance without prophylaxis an option in selected cases. A prerequisite for this approach is easy access to paediatric emergency care and parents being observant of any

sign of UTI, as the early use of antibiotics in the event of pyelonephritis significantly reduces the risk of renal scarring [54].

1.8.3 Surgery

Surgical intervention is an option in patients with persistent reflux, recurrent UTI, deterioration of renal function or parents' preference to avoid CAP [43, 45]. Surgical approaches are open ureteral re-implantation, endoscopic subureteric injection and robot-assisted laparoscopic ureteral re-implantation (RALUR).
The goal of all surgery is to create a functional vesicoureteric junction.

Open surgery

Different intra- and extravesical open surgical procedures have been described. Creating an adequate length of the intramural tunnel is common in all methods. The Lich-Gregoir extravesical anti-reflux technique, Cohen intravesical re-implantation and Politano-Leadbetter combined intra- and extravesical re-implantation techniques are the most widely used methods. Open surgical repair has an excellent success rate (>95%) in experienced hands and older children [55], but it is regarded as technically demanding in the small infant bladder and involves in-patient hospitalisation and significant post-operative morbidity.
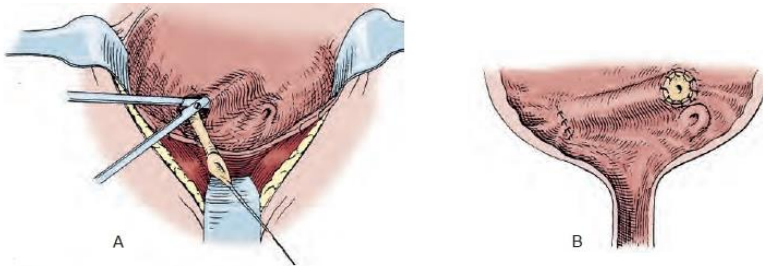
Figure 7 *Cohen intravesical re-implantation where the ureter is inserted into a submucous tunnel. Retik et al. Pediatric Urology. In: Paulson DF, editor. Genitourinary surgery, vol 2. New York: Churchill Livingstone, 1984, p. 764.*

Endoscopic injection

Endoscopic injection with a bulking agent in the submucosal intramural tunnel was introduced in the mid-1990s and it is now a minimally invasive alternative to both CAP and ureteral re-implantation in selected cases.

Many bulking agents have been tested; a polyacrylate polyalcohol copolymer (Vantris®) and dextranomer-hyaluronic acid (Deflux®) are the most commonly used. The rate of reflux resolution has been demonstrated to correlate with the degree of VUR (80-90% in grades I-II, 60-70% in grades III-IV and 50-60% in grade V) and with lower success rates for duplicated compared with single systems [56, 57].

Another factor that has a great impact on success rates is the length of follow-up. Some studies have reported a high (>90%) success rate after four to six weeks [58], while studies with a longer follow-up suggest that the effect may not be lasting [59-61]. It can nonetheless be argued that even a temporary effect of ET can buy the child time for the reflux to resolve, or until it is less prone to recurrent UTIs and more suitable for open surgery [62, 63]. Compared with ureteral re-implantation, endoscopic injection is performed as an outpatient procedure with minimal post-operative morbidity.

Robot-assisted laparoscopic ureteral re-implantation (RALUR)

RALUR was introduced in 2004 and, today, the success rates of laparoscopic and robot-assisted anti-reflux surgery are comparable with those of open surgical techniques according to recent studies. Improved visualisation, ergonomic comfort for the surgeon, a shorter hospital stay and decreasing post-operative pain are some of the benefits. However, robot-assisted surgery has major disadvantages of longer operating times and higher costs [53, 64].

1.10 VUR and quality of life

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

From the Constitution of the World Health Organisation 1946 [65]

In the evaluation of health care, clinical outcome is one component to consider. The other is the care-taker's perceptions of health-related quality of life (HRQoL), which in this study applies to the way the different options of VUR management affect the HRQoL of the patient and parent. Based on the chronicity of the therapy and management of VUR, a potential impact on HRQoL can be anticipated, but the literature on HRQoL in paediatric VUR is still sparse. Previous studies have reported diverse and somewhat contradictory results, both regarding the families' HRQoL [66-68] as well as the parents' satisfaction and preferences [69-73].

The lack of consistency in previous studies can be partly explained by the large-scale diversity in study populations. Many studies have mixed age-groups and all grades of VUR, which makes it difficult to draw any sharp conclusions.

In the fourth paper in this thesis, we therefore chose to focus on a certain age-group and grade of VUR, namely patients with VUR grades IV-V who were diagnosed before the age of six months. We wanted to find out how the parents had experienced the first two years of their child's life.

1.11 Introduction to qualitative research methodology

"Not everything that counts can be counted and not everything that can be counted counts."

From a sign hanging in Albert Einstein's office at Princeton, crediting Cameron, 1963. [74]

Qualitative research seeks to answer questions about experience, meaning and perspective from the standpoint of the participant. Acquiring a rich and complex understanding of a specific social context or phenomenon is central in qualitative research, rather than obtaining data that can be generalised to other areas or

populations. In this way, qualitative research differs from quantitative research. If a *quantitative* approach aims to *quantify* variations and *predict* causal relationships, a *qualitative* approach *describes* variations and *explains* relationships. Where the quantitative approach seeks to *confirm an hypothesis* about phenomena, the qualitative approach seeks to *explore* the phenomena.

With quantitative methods such as questionnaires, the responses are often fixed alternatives, pre-determined by the researcher. This requires a thorough understanding of the best questions to ask, how to ask them and the range of possible responses, but it also allows for comparisons of responses across participants. Instead, by using open-ended questions in interviews or group discussions, the participants are given the opportunity to respond in their own words and create responses that are rich and explanatory and sometimes unanticipated by the researcher [75].

1.11.1 Patient-centred outcomes research

Patient-centred care is defined as "Health care that is compassionate, empathetic, and focused on the patient's own worldview, goals, preference, values and needs" [76]. *Patient-centred outcomes research* makes it easier for patients and their caregivers to make informed health care decisions and helps the patient to assess the value of health care options. This research can be used to increase the quality of healthcare and push the healthcare system towards a more patient-centred approach [76-78].
When investigating patients' subjective experiences of health and received care, patient-reported outcomes (PRO) and patient-reported experiences (PRE) are commonly studied.

In PRO, the report of outcome comes directly from the patient, without any interpretation of the responses by a clinician or anyone else. It includes different health parameters, such as signs, symptoms, functional capacity and health-related quality of life (HRQoL). Patient-reported outcome measures (PROMs) are tools that aim to measure the outcomes, such as indices and questionnaires.

PRE covers aspects of the structure and processes of care, as experienced by the patient. It includes respect for patients' values; information and communication; involvement of family; emotional support; continuity; access to care; and cleanliness of the environment. PREMs measure the patients' experiences of the given care and are distinct from measurements of satisfaction, as the latter are strongly affected by both expectations and outcomes [79, 80].

When assessing the health status of younger children, it is common to only assess the perspective of parents as observers or proxies of the children's

treatment and health outcomes [81]. The family can be considered the child's primary source of strength and support to health and development [82]. In the present study (Paper IV), the intention was therefore to assess the family impact of infant hVUR from the parents' perspectives.

1.11.2 Evaluating qualitative research

Some quantitatively trained researchers view qualitative research with suspicion and regard it as unserious, because it involves small samples which may not be representative of a broader population. Qualitative research can also be criticised for being subjective in the sense that the results may be influenced by the researchers own experiences and opinions. The common knowledge of what constitutes rigour or quality in qualitative research is therefore limited [83]. A qualitative study has the same requirement for procedural description as a quantitative study. The purpose of the study, how it was conducted, including the details of data generation and management, should be transparent and specific. A reviewer should be able to follow the chain of events and understand the logic of the decisions and choices of methodology and methods [84].

In qualitative research, the concepts *credibility*, *dependability* and *transferability* of the study are often used to describe various aspects of *trustworthiness* [85], representing a quality control. In qualitative research, *saturation* and *variation* are discussed instead of significances and p-values. All these concepts are as strict and specific as the ones in quantitative research, and this needs to be fully understood when evaluating the quality of a qualitative study.

1.11.3 Methods of data collection

Examples of methods of data collection include in-depth interviews, observations, fieldwork, focus groups and the study of events, videos, art or texts like diaries, blogs and books, among many others. The choice of method depends on the research question, study population and the time and resources of the project. In this study, we chose focus group discussions as the method of data collection.

Focus group research

Focus groups can be described as "a carefully planned discussion designed to obtain perceptions on a defined area of interest in a permissive, non-threatening environment" [86]. The primary aim of a focus group is to acquire an understanding of a specific issue from the perspective of a selected group of people. Ultimately, focus group discussions encourage a wide range of responses which provide the researcher with different attitudes, behaviour, opinions and perceptions of the participants [87].

> *"The goal of the group is to elicit a discussion that allows the researcher to see the world from the participants' perspectives."*
>
> Heary et al. 2012 [88]

Researchers have used focus groups for the past 90 years. In the 1920s, they were used to assist researchers in identifying survey questions. Later, focus group data were collected and analysed mainly to assess consumer attitudes and opinions in marketing research. In the past 20 years, social science researchers have used focus groups to collect qualitative data in an economical, fast and efficient manner [89].

A focus group usually lasts between one and two hours and consists of three or more participants. The number of participants should be sufficient to yield diversity in the provided information, but too large a group can cause participants to feel uncomfortable about sharing their thoughts and experiences [89]. The use of very small focus groups, "mini-focus groups", with three or four participants, can be used when the participants have specialised knowledge or experiences to discuss within the group [86].

> *"For many novice researchers, analysing qualitative data is found to be unexpectedly challenging and time-consuming."*
>
> Erlingsson and Brysiewicz. 2017 [90]

1.11.4 Methods of data analysis

There are numerous different methods/approaches to analysing qualitative research. Each one has a different theoretical scientific foundation, area of application and specific traits. For example, *phenomenology* is grounded in scientific philosophy and focuses on the perceived world ("lifeworld"), *hermeneutics* focus on language and the interpretation of a "hidden meaning",

ethnography is often used in field work to understand the other's perspective "from the inside" and *phenomenography* has its roots in pedagogics and emphasises variations – "all voices should be heard". *Grounded theory* is a research approach which follows its own very specific set of rules. Data collection (often through individual interviews) and analysis proceed simultaneously and streamline one another. In this study, we chose to use *content analysis*.

> "Regardless of the 'quality' of qualitative data, its sheer quantity can be daunting, if not overwhelming. Hundreds of pages of data can lead the researcher to think that it cannot be managed."
>
> Elo & Kyngäs. 2007 [91]

Qualitative content analysis (QCA)

In contrast to other qualitative research methods, content analysis is not linked to any particular science, which explains why there are fewer rules to follow and the risk of confusion in matters relating to philosophical concepts and discussions is thereby reduced [92]. CA can be used both quantitatively and qualitatively, where the quantitative approach derives from logistic positivism and the qualitative approach from hermeneutics. This makes it possible to work with QCA in many different ways.

In 1952, Berelson defined content analysis as "a research technique for the objective, systematic and quantitative description of the manifest content of communication". He introduced *quantitative* content analysis, in which facts from the text are presented in the form of frequency expressed as a percentage or actual numbers of key categories [93].

In this study, we chose to use *manifest* content analysis, in which the researcher describes what informants say, as close to their own words as possible, representing the visible and obvious in the text. Another form of content analysis is *latent* analysis, where the researcher seeks to find the underlying meaning of the text, on an interpretive level [92].

In the process of QCA, the text is divided into *meaning units*. A meaning unit is the constellation of words or statements that relate to the same central meaning. The meaning units are then *condensed*, a process of shortening while preserving the core. In the *abstraction* phase, the condensed meaning units are labelled with a *code*. Labelling a condensed meaning unit with a code allows the

data to be thought about in new and different ways and should be understood in relation to the context. Finally, the codes are sorted into categories [94].

According to Graneheim and Lundman, the creation of categories is the core feature of qualitative content analysis. [94]. No data should be excluded due to the lack of a suitable category and no data should fit into more than one category. A category answers the question 'What?' [95] and can be seen as a thread throughout the codes. A category refers to the descriptive level of content and is thereby an expression of the manifest content of the text [90].

"Experiencing chaos during analysis is normal."

Erlingsson et al. 2017
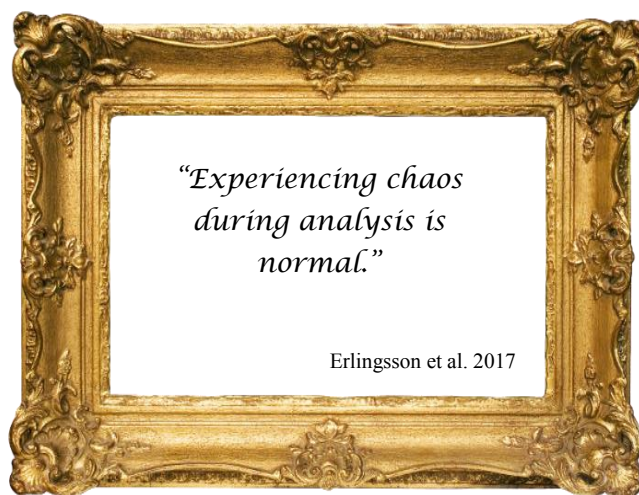
2. Aims

This research project is an attempt to shed some light on the management of infants with vesicoureteral reflux (VUR) grades IV-V. The objective was to evaluate different treatment options for high-grade VUR and to compare the results regarding VUR outcome, bladder function, urinary tract infections and renal damage. Furthermore, we wanted to add the parents' perspective on VUR management, since the patient's experience is central when measuring treatment success and quality of care.

Papers I-III present the results from the Swedish infant high-grade reflux trial, which aimed to:
- determine whether high-grade VUR in infants can be treated endoscopically and whether endoscopic injection is superior to antibiotic prophylaxis in the treatment of VUR
- determine whether the early down-grading of reflux can prevent the development of bladder dysfunction with high bladder capacity and poor emptying ability
- investigate whether successful endoscopic treatment can reduce the risk of UTI recurrence and renal scarring

Paper IV presents selected results from a focus group study with parents of children with infant high-grade VUR, in which we aimed to:
- describe the parents' experiences of different treatment options (antibiotic prophylaxis and surgical intervention), recurrent UTI and the risk of renal damage

3. Patients and Methods

3.1 Papers I-III

3.1.1 Study design

In this randomised, prospective, controlled multicentre trial, infants aged < 8 months, with VUR grades IV-V, were included between 2004 and 2014. A total of 21 referral paediatric centres from different Swedish regions participated. If parents accepted participation, renal scintigraphy and GFR assessment were performed. If no exclusion criteria were met, bladder function was assessed and the child was randomised to either ET (with CAP until resolution) or to CAP alone.

The exclusion criteria were renal function of < 40% of expected, a split function of < 15% in the refluxing kidney, vesicoureteral obstruction, other urological malformation (except duplication), neurogenic bladder dysfunction or suspected parental non-compliance.
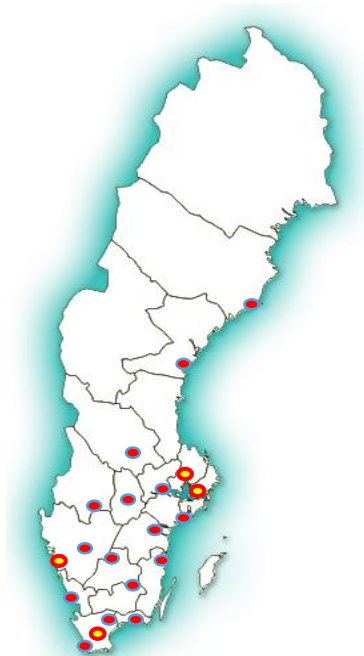
Referral paediatric centres

The randomisation process was computerised to match for sex, presentation, grade of VUR, DMSA abnormalities, bladder size, duplicated system and referral centre.

The result of the ET was evaluated with VCUG and ultrasound two months after injection. Follow-up in both treatment groups was scheduled at two, six, nine and 12 months. Weight, height and blood pressure were recorded on all

visits and antibiotic consumption since the previous contact was registered. Information regarding any breakthrough UTI and possible side effects of treatment was thoroughly analysed and urine cultures were re-examined.

At one year after inclusion, all the study subjects were examined according to study protocol. VUR-grades 0-II at follow-up were regarded as a successful VUR outcome, since no treatment other than surveillance or CAP is recommended for these infants in international guidelines [1].
The primary outcomes in Studies I-III were reflux status, signs of bladder dysfunction, recurrent UTI and a deterioration in renal damage.
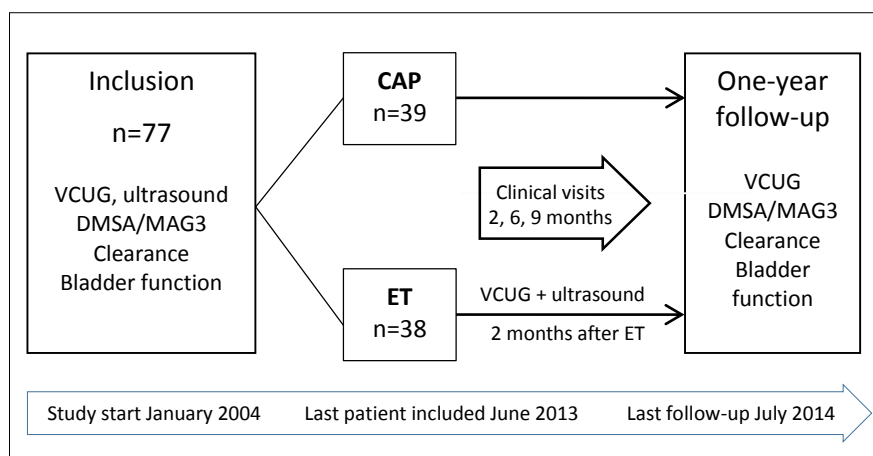
Figure 1 *Study design*

3.1.2 Participants

Seventy-seven infants (55 boys) were included, in whom VUR was diagnosed in the work-up after febrile UTI (n=55), after findings of hydronephrosis on prenatal ultrasound (n=21) or because of heredity (n=1). The median age at presentation was 1.6 months (SD 1.79, range 0-7 months) and the median age at inclusion was 6.7 months. VUR grade IV was seen in 30 and grade V in 47 patients. 52 (68%) had bilateral reflux (18 grade IV and 34 grade V), 39 infants were randomised to CAP and 38 to ET. The baseline characteristics are listed in *Table 1*.

Variable	Total (n=77)	Endoscopic treatment (n=38)	Prophylaxis (n=39)	p-value
Sex				
Girls	22 (29%)	12 (32%)	10 (26%)	
Boys	55 (71%)	26 (68%)	29 (74%)	0.75
Age at presentation (months)	1.6 (1.8) 1.3 (0.0; 6.6)	1.7 (1.8) 1.1 (0.0; 5.6)	1.6 (1.8) 1.4 (0.0; 6.6)	0.82
Age at randomisation (months)	6.7 (1.2) 7.0 (4.1; 9.2)	6.8 (1.2) 7.2 (4.1; 9.2)	6.7 (1.1) 6.9 (4.7; 8.8)	0.65
Presentation				
- UTI	55 (71%)	28 (74%)	27 (69%)	0.86
- Antenatal dilatation	21 (27%)	10 (26%)	11 (28%)	1.00
- Heredity	1 (1%)	0 (0%)	1 (3%)	1.00
Grade of VUR at baseline				
IV	30 (39%)	15 (40%)	15 (39%)	
V	47 (61%)	23 (61%)	24 (62%)	1.00
Bilateral VUR	52 (68%)	25 (69%)	27 (69%)	0.94
Duplex	12 (16%)	8 (21%)	4 (11%)	0.35
Renal damage baseline				
No	10 (13%)	6 (16%)	4 (10%)	
Yes	67 (87%)	32 (84%)	35 (90%)	0.70
Bladder capacity at baseline (normal/large)				
< 150%	42 (58%)	19 (53%)	23 (64%)	
≥ 150%	30 (42%)	17 (47%)	13 (36%)	0.47
Residual volume at baseline (normal/large)				
< 20 ml	54 (75%)	24 (67%)	30 (83%)	
≥ 20 ml	18 (25%)	12 (33%)	6 (17%)	0.17

Table 1 *Baseline characteristics*

Drop-outs

The number of infants assessed for eligibility and their reasons for exclusion have not been registered. Information on the 77 included study subjects is given in detail in the Consort flow diagram, included in the *Appendices* and presented in Paper I [23]. In short, none of the included patients was lost to follow-up and all the patients but one in each treatment group could be analysed according to the ITT principle.

3.1.3 Imaging

VCUG

Voiding cystourethrography remains the gold standard for grading VUR and assessing bladder configuration, despite its invasive nature and concerns about ionising radiation. The average radiation dose for a VCUG in a patient aged 0-2 years is 0.1-0.4 mSv in a standard paediatric radiology setting. The use of VCUG is nowadays often postponed until after evaluation with ultrasound and/or renal scintigraphy in the follow-up after febrile UTI or antenatal hydronephrosis.

In this study, VUR was diagnosed by VCUG and graded according to the International Reflux Study in Children [1]. The highest VUR grade was used to classify each patient with bilateral VUR or duplex.

Urinary tract ultrasound

Ultrasound (US) is the most widely available, inexpensive and radiation-free means of obtaining anatomical information about the urinary tract. It is limited, as it is operator dependent and unable to provide a quantitative assessment of relative function and may not detect all renal scarring. In spite of this, it is recommended as the first standard evaluation for children with antenatal hydronephrosis and after an initial febrile UTI. VUR is rare in infants who have

two consecutive normal postnatal US and, if present, it is almost always low-grade [96, 97].

In this study, a US was performed to evaluate hydronephrosis and to exclude other urogenital abnormalities.

All radiological investigations were re-evaluated at the co-ordination centre by a single paediatric radiologist according to a study protocol.

3.1.4 Assessment of renal function

Renal imaging: MAG3 & DMSA

Renal scintigraphy provides information regarding the degree of renal cortical abnormalities. The limitations include the expense, radiation exposure, possible need for sedation and limited availability. The average radiation dose for one DMSA is approximately 1 mSv and, for MAG3, 0.5 mSv [98]. Internationally, renal scintigraphy is often used in VUR evaluations if VCUG has revealed a reflux. In contrast, both the ESPR (European Society of Paediatric Radiology), the Swedish Paediatric Society and the AAP's revised guidelines endorse a fundamentally different post-UTI recommendation that focuses on kidney involvement. It is known as the *top-down approach* and begins with a US and DMSA renal scan. VCUG should be only performed for recurrent UTI or if renal involvement is identified, based on the belief that no child with a normal initial scan has a clinically significant reflux [99-101]. The benefits would be reduced urethral catheterisations, decreased ionising radiation to the gonads and reduced
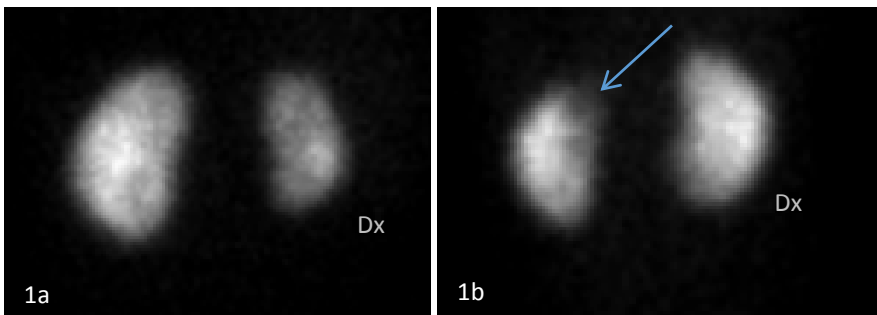
Figure 2. *Example of two DMSA scintigraphies from the study.*
1a. Generalised damage in the right kidney with separate function 71% sin, 29% dx
1b. Focal damage in the left kidney (arrow) with separate function 42% sin, 58% dx

detection of "clinically insignificant" VUR [102-104].

In this study, [99]mTc-DMSA was the first method of choice for renal parenchymal imaging, but [99]mTc-MAG3 scintigraphy was used to rule out ureteric obstruction (if poor drainage of the reflux on VCUG and dilatation on US) or depending on local preferences. The renal damage was characterised as focal, multifocal or generalised. *New* renal damage was defined as an uptake defect in previously normal parenchyma and the *progress* of damage was defined as a reduction in split renal function of ≥4 percentage points in a kidney with a pre-existing parenchymal defect [105]. *Renal deterioration* encompasses both new renal damage and the progress of renal damage.

Clearance

The glomerular filtration rate (GFR) is low at birth, but it increases rapidly during the first months of life. The filtration, related to body surface, increases between 0-2 years of age and then remains stable, with a reference value of 110 ml/min/1.73m^2.

The GFR in this study was assessed with ^{51}Cr-EDTA or Iohexol clearance or, when missing, formula clearance was estimated according to the Schwartz formula:

eGFR(ml/min per 1.73m^2) = 36.5 x (length(cm) / S-creatinine(μmol/l)) [106]

Age-adjusted reference values for filtration rate between 0-2 years of age were calculated using Winberg's algorithm (log y = 0.209 x log(age in days) +1.45) [107] and a filtration rate of < 80% (< 2SD) of expected for age was considered subnormal.

The renal function investigations were performed in accordance with European procedure guidelines [108, 109] and were reviewed by a single paediatric nuclear medicine specialist at the co-ordination centre.

3.1.5 Assessment of bladder function

Free voiding observation (FVO)

VUR and abnormal bladder function are associated with one another and with UTI. VUR outcomes are affected by the presence or absence of bladder dysfunction as mentioned earlier in Section 1.6.1.

In this study, bladder function was evaluated with free voiding observations (FVO), in which the number of voids, voided volume and post-void residual urine (PVR) were registered during a period of four hours [110]. Voided volume was assessed by weighing the diaper and PVR measured with ultrasound.
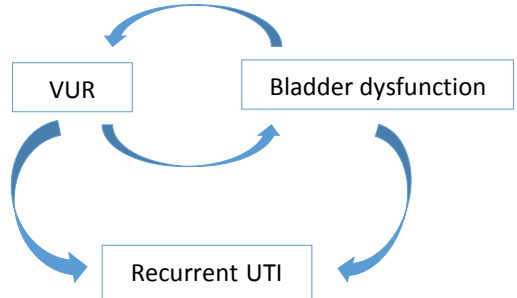
Figure 3 *Four-hour free voiding observation*

The mean residual during four hours was noted as the PVR value and bladder capacity (BC) was estimated as the largest sum of voided and residual volume according to earlier studies of healthy children and the international standardisation document [40, 111]. Abnormal values for BC were ≥ 150 % of expected for age, calculated using the formula (30 + 2.5 x age in months) ml and for PVR ≥ 20 ml. Lower urinary tract dysfunction (LUTD) was defined as BC ≥ 150 % of expected in combination with PVR ≥ 20 ml.

Videocystometry (VCM)

Urodynamic studies investigate the filling and emptying phases of bladder function and are not routinely used to evaluate bladder function in neurologically intact children. A VCM can be explained as a filling and voiding cystometry with a simultaneous VCUG [37].

In this study, VCM was only available at the study centre and was therefore only performed in fewer than a third of the study subjects. The VCM studies gave us information on true post-void residuals and the volume of refluxing urine in those children.
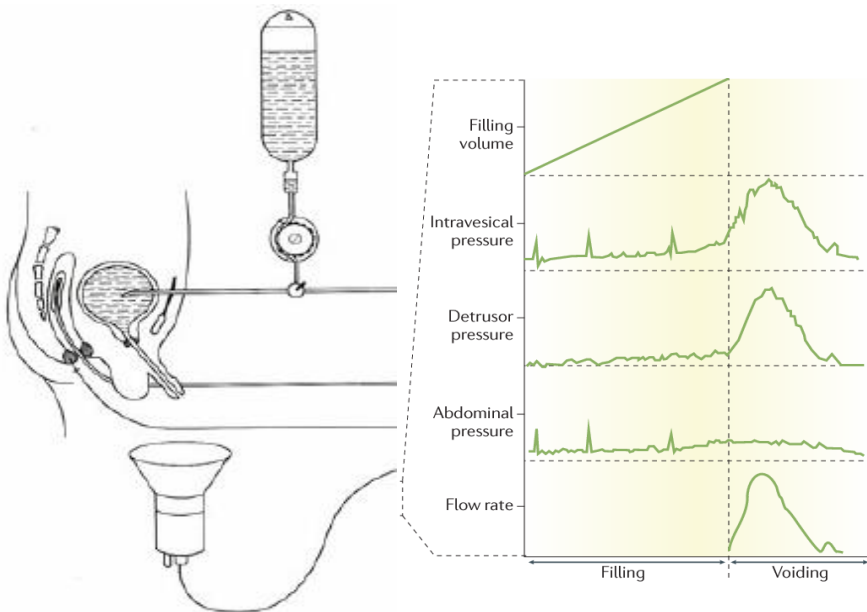
Figure 4. Concept sketch of a cystometry setting. Intravesical and abdominal pressure are measured using one probe in the bladder and one probe in the rectum. In addition, electromyography (EMG) is used to evaluate the activity of the muscles of the pelvic floor. Modified from Aoki, Y. et al. (2017) Urinary incontinence in women. Nat. Rev. Dis. Primers.

3.1.6 Treatment of VUR according to study protocol

Continuous antibiotic prophylaxis (CAP)

All the children were prescribed antibiotic prophylaxis when VUR was diagnosed. The choice of agent was left to the treating paediatrician to decide, but in most cases trimethoprim was used (0.5 to 1 mg/kg once daily), as a single drug or combined with sulfamethoxazole. Optional agents were 1 mg/kg of nitrofurantoin, 5 mg/kg of cefadroxil and 1 mg/kg of ciprofloxacin. Endoscopically treated patients received antibiotic prophylaxis until VUR grades 0-II was observed.

Endoscopic treatment (ET)

ET was performed under general anaesthesia as an outpatient procedure at four paediatric surgical centres. Dextranomer/hyaluronic acid copolymer (Dx/HA) was used as a bulking agent and injected submucosally, according to the standard technique [112].
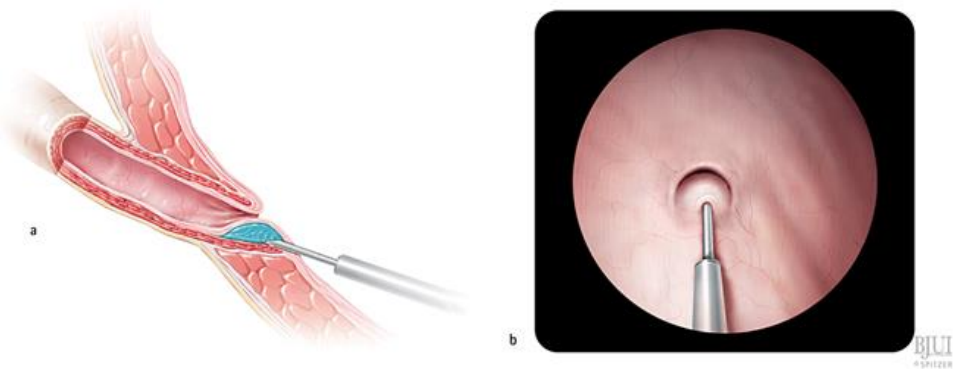
Figure 5 Endoscopic injection technique. Courtesy of Stephan Spitzer, www.medizillu.de

Patients in the ET group had VUR re-graded and dilatation evaluated two months after the first injection. If VUR grade > II persisted, a second injection was performed.

3.1.7 Febrile UTI – definition

In children presenting with fever of > 38°C, the diagnosis of febrile UTI was based on a positive dipstick for leucocyte esterase or nitrite in combination with a significant bacterial count of a pure colony. A significant count refers to $\geq 10^5$ CFU/ml in the clean catch/bag specimen, $\geq 10^4$ CFU/ml in a catheter or any growth in bladder aspiration [113].

3.2 Paper IV – the focus group study

3.2.1 Study design

This study was designed according to well-established methodology and international guidelines [114]. Following a thorough literature review, the authors constructed a VUR-specific focus group manual with nine semi-structured and open questions, included in *Appendices*. We planned for four focus group discussions with approximately five participants in each group, stratified for treatment, sex and pre/postnatal diagnosis of the child. The criteria for the selection of study participants and the sample size were based on recommendations for qualitative studies of this nature [89].

3.2.2 Participants

The inclusion criteria were children born in 2012-2016 with VUR grades IV-V, diagnosed at < 6 months of age and treated at our clinic. The exclusion criteria were renal function < 40% of expected, neurogenic bladder dysfunction, other urogenital anomaly or surgery on the urinary tract, language difficulties and other morbidity that may affect the outcome of QoL and family impact. We identified 82 children, of which 43 were eligible after the exclusion of 39. After stratification, randomisation, invitation and some cancellations, we performed four focus groups with 19 parents (13 mothers) of 15 children (*Figure 6*).

3.2.3 Data collection

Four standardised focus groups were held outside the hospital environment and all the participants were asked identical questions according to the focus group manual. The discussions were led and facilitated by a trained moderator (MDB=1, JN=3) who ensured that the discussions were kept on track, that all the participants were given the opportunity to take part and that no one dominated the discussion. The discussions were recorded digitally and a research assistant (MDB=3, JN=1) was responsible for making field notes of non-verbal communication and group interactions.
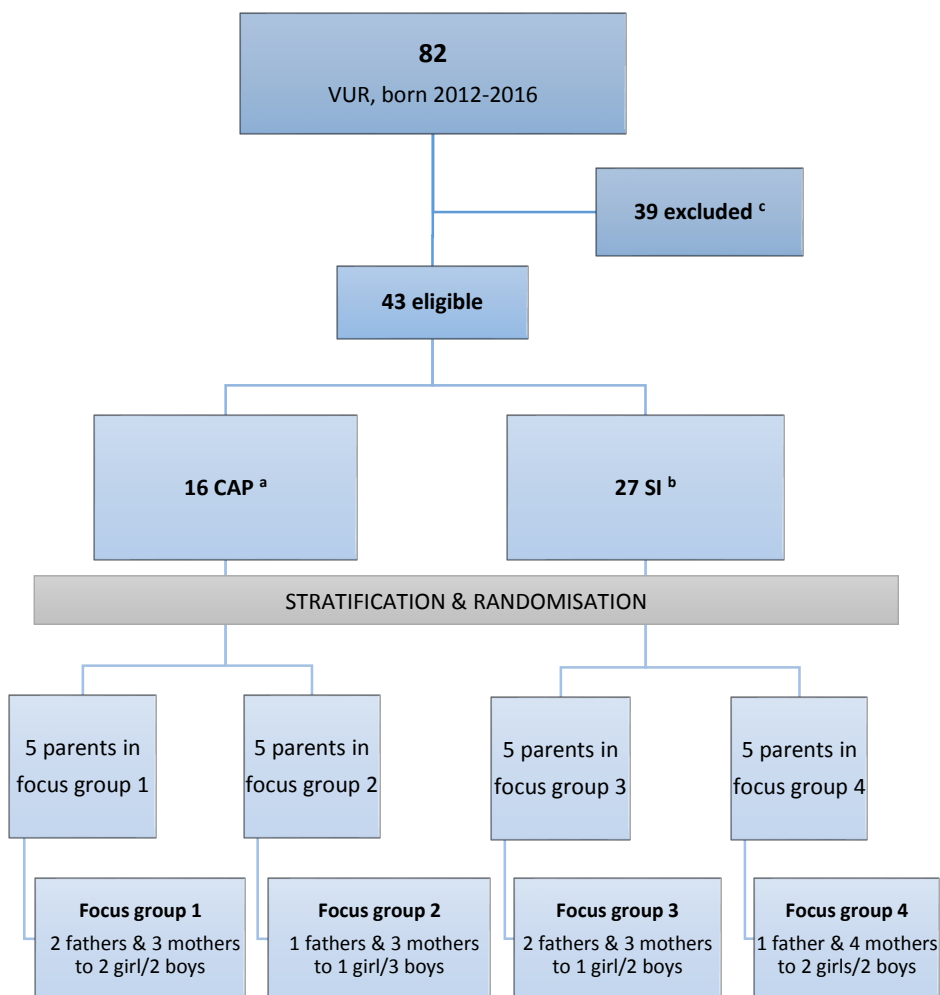
Figure 6 *Flow chart of the inclusion/exclusion/randomisation process.*
[a] *16 patients treated with CAP alone*
[b] *27 patients treated with CAP and SI (endoscopic treatment, ureteric reimplantation and hemi-nephrectomy)*
[c] *Reason for exclusion:*   *VUR grades I-III (n=25)*
                                              Other urogenital anomaly or renal disease (n=7)
                                              Earlier surgery on the urinary tract (n=3)
                                              Non-Swedish speaking (n=2)
                                              ESRD (n=1)
                                              Wrong diagnosis (n=1)

3.2.4 Data analysis

The recorded material was transcribed into text verbatim and used for content analysis. The text analysis was performed using NVivo 11 Pro©, a software program that is useful when sorting and categorising a large amount of data. All experiences were extracted from the transcripts, divided into meaning units and condensed into statements. The statements were then categorised through a reflective, back-and-forward sorting process by two researchers (JN, MDB).

Meaning unit	Condensed MU	Code	Sub-category	Category	Heading
And then it's hard to say: "No, you can't be here, 'cause you've got a cold" – it feels so damn stupid.	Hard asking someone to leave because he/she has a cold.	Avoid seeing people with infections due to the child's risk of being infected.	Restricted social family activities due to ongoing UTI or fear of other infection	Family impact due to the child's UTI	UTI

Table 2 *Examples of the process of text analysis, from raw data to results.*

3.3 Statistical analysis

3.3.1 Papers I-III

Statistical analyses were performed according to a statistical analysis plan, developed by statistical consults in collaboration with the research team. For tests between two groups, Fisher's exact test was used for dichotomous variables. The Mantel-Haenszel chi-square test was used for ordered categorical variables, and the chi-square test for non-ordered categorical variables.

For continuous variables, Spearman's rank correlation coefficient was used between two variables within a group and the Mann-Whitney U-test was used between groups.
In Paper II, for change over time within a group, the sign test was performed with respect to categorical variables, while Wilcoxon's signed-rank test was used for continuous variables.

For probabilities, logistic regression was used. In Papers I and II, the best multivariable model was obtained by using stepwise logistic regression. From these analyses, the odds ratio (OR), 95% confidence intervals (CI), p-value and area under receiver operating curve (ROC) were given. OR is the ratio for the odds of an increase in the predictor of one unit.

All tests were two-tailed and conducted at the 0.05 significance level and all analyses were performed using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA).

The results were analysed and presented according to allocated treatment using the intention-to-treat (ITT) principle, unless otherwise stated.

According to power analysis calculation, a sample size of 68 patients would be needed to detect a difference between the two groups with 80 % power regarding the reflux cure rate and bladder function. The power-calculated number of participants was reached.

3.3.2 Paper IV

Descriptive statistical analysis of the data was performed, and the frequency (%) and distribution of statements according to UTI/renal damage, SI and CAP categories in total/CAP/SI groups were performed using Microsoft Excel 2010.

According to focus group methodology, a larger number of statements within a category indicate greater relevance to the participants. However, p-values are

not applicable in focus group methodology and, as recommended, statistical hypothesis testing was therefore not performed [89].

3.4 Ethical considerations

There are three fundamental research ethics principles, originally published in The Belmont Report [115]. The first is *respect for persons*, meaning respecting all research participants' dignity and autonomy and protecting them from exploitation and vulnerability. *Beneficence* is the second, which commits the researcher to articulating how he/she plans to minimise the risks associated with research (also psychological and social) and maximise the benefits. The third is *justice*, which means ensuring a fair distribution of the risks and benefits resulting from research, i.e. those who are expected to benefit from the knowledge should be the ones who are asked to participate.

The Swedish infant high-grade reflux trial was approved by the regional ethics committee as early as 2003 (Ö 140-03) and also by local ethics committees at every participating centre. The original research question regarded endoscopic treatment of VUR grade V in infants and whether early reflux resolution could prevent the development of bladder dysfunction. The estimated number of 68 patients was calculated, based on the hypothesised difference between the groups in terms of VUR outcome and bladder dysfunction with 80% statistical power. Later, the decision to include patients with VUR grade IV was added to the study. This addition to the research project did not necessitate any ethical considerations. Since the participating surgeons were familiar with ET in older children, no technical issues with the procedure in infants was expected. The advantage of offering a possible cure for the condition outweighed the risks associated with the intervention.

The focus group study was approved by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr 1095-17), and complies with the principles outlined in the World Medical Association Declaration of Helsinki 2009.
When using focus groups, it is important to consider that disclosures by participants are shared not only with the researchers, but also with the rest of the group. Focus group discussions can also create distress in some individuals, which has to be dealt with. We considered the research topic in this study as of a

less sensitive nature, but efforts were still made to minimise stress and discomfort for the participants.

In both the Infant high-grade reflux trial and the Focus group study, the participants received written information about the research study, which was followed-up by a phone call. They were informed that participation was voluntary and that they could withdraw at any time. An informed consent was obtained from each participating family. The identity and integrity of the participants were, and still are, protected at all times and their confidentiality is assured.

4. Results

4.1 Results papers I-III

4.1.1 VUR outcome

In both treatment groups, the reflux status improved during follow-up. Down-grading to VUR grade ≤ II was seen in 30 patients, 22 (59%) in the ET group and eight (21%) in the CAP group (p=0.0014) (*Figure 1*).
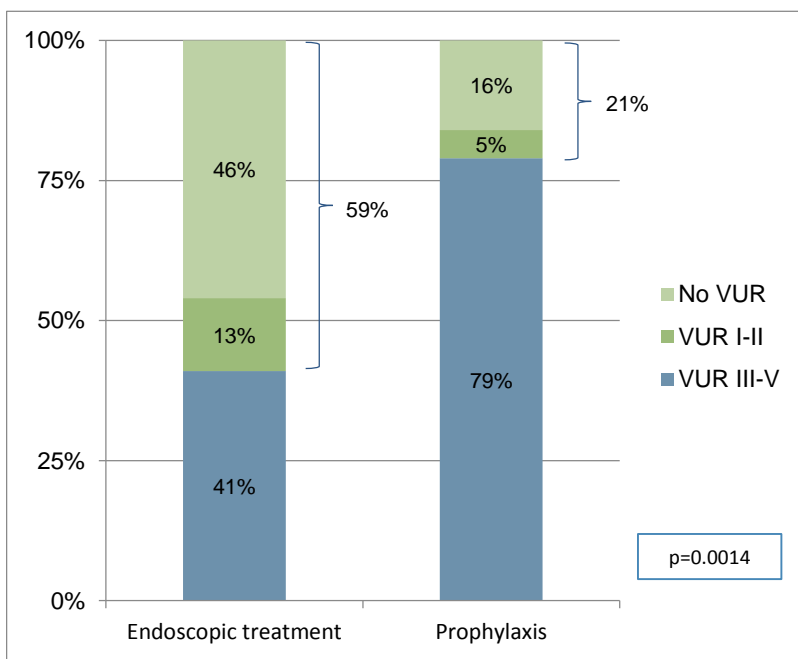
Figure 1 VUR status at the one-year follow-up according to ITT. Green indicates VUR grade ≤ II and blue indicates VUR grades III-V.

The rate of down-grading in the ET group was 100% in unilateral grade IV, 75% in bilateral grade IV, 67% in unilateral grade V, but only 31% in bilateral grade V (*Table 1, bottom*). In the CAP group, dilating VUR remained in 30 patients (79%) at study exit. The down-grading to VUR ≤ II was seen in infants with VUR grade IV (n=6, 40%) and unilateral grade V (n=2, 29%) at baseline, but not in any infant with bilateral grade V at baseline (*Table 1, bottom*).

Variable	Endoscopy group (n=38)	Prophylaxis group (n=39)	p-value
Grade of VUR at follow-up			
VUR=0	17 (46%)	6 (16%)	
VUR=I	2 (5%)	0 (0%)	
VUR=II	3 (8%)	2 (5%)	
VUR=III	6 (16%)	7 (18%)	
VUR=IV	4 (11%)	13 (34%)	
VUR=V	5 (14%)	10 (26%)	0.0007
Grade of VUR at follow-up			
VUR grades 0-II	22 (59%)	8 (21%)	
VUR grades III-V	15 (41%)	30 (79%)	0.0014

	Endoscopy group			Prophylaxis group		
	VUR grade at follow-up			VUR grade at follow-up		
	≤ II	> II		≤ II	> II	
Variable	(n=22)	(n=15)	p-value	(n=8)	(n=30)	p-value
Grade of VUR at baseline						
Unilat IV	7 (100%)	0 (0%)		2 (40%)	3 (60%)	
Bilat IV	6 (75%)	2 (25%)		4 (40%)	6 (60%)	
Unilat V	4 (67%)	2 (33%)		2 (29%)	5 (71%)	
Bilat V	5 (31%)	11 (69%)	0.0094	0 (0%)	16 (100%)	0.037

Table 1. *VUR-grade at the one-year follow-up per treatment group (top) and VUR grade ≤ and > II per treatment group, divided by VUR-grade and uni- or bilaterality at baseline (bottom).*

Endoscopic treatment

Down-grading to VUR grade ≤ II after the first injection was seen in 21 infants of 36 analysed per protocol (58%), of whom 12/14 (86%) had VUR grade IV and 9/22 (41%) had VUR grade V at baseline. VUR-down-grading was seen in another three (67% all together) after the second injection.

Of the 21 infants with a successful first ET, dilating VUR recurred in four (19%), of whom three had bilateral grade V and one had bilateral grade IV at baseline (*Figure 2*).
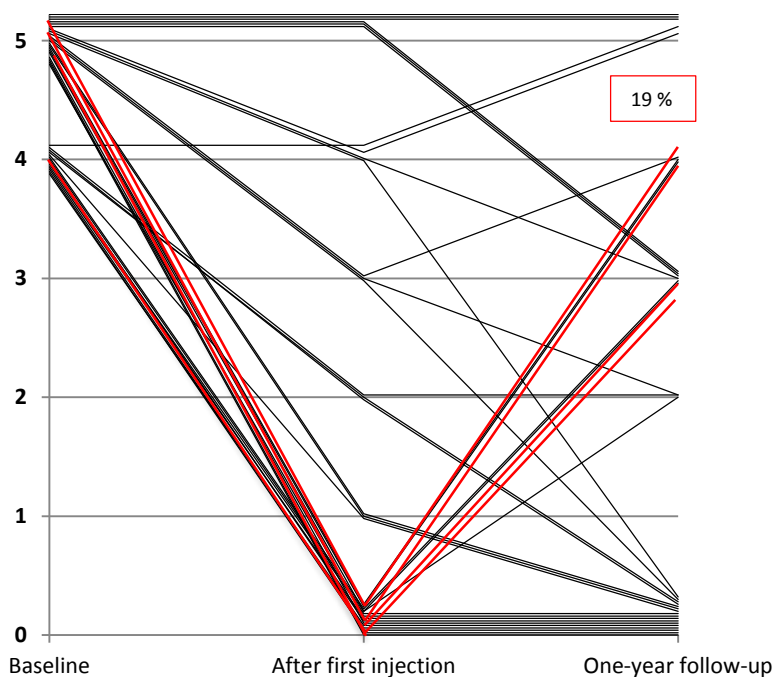
Figure 2 *Grade of VUR at baseline, after first injection and at 1-year follow-up. The red lines representing the four patients with recurrent dilating VUR after a successful first ET.*

Prediction analyses

The prediction analysis of VUR outcome in the total study population identified
ET, VUR grade IV, unilaterality and low PVR at baseline as significant
predictors with univariable logistic regression. Stepwise logistic regression
confirmed these predictors in a multivariable model with an area under the ROC
curve of 0.88 (*Table 2*). This association is graphically illustrated in *Figure 3*
where the decreasing probability of grade ≤ II VUR at one-year correlates with
increasing PVR, increasing VUR grade, bilaterality and prophylactic treatment.

Variable	Value	n (%) of event	Univariable OR (95%CI) VUR grade ≤ II vs. > II at one-year visit	p-value	Multivariable OR (95%CI) VUR grade ≤ II vs. > II at one-year visit	p-value
Group	ET	22 (59%)				
	CAP	8 (21%)	0.18 (0.07-0.50)	**0.0010**	0.03 (0.00-0.23)	**0.0007**
VUR grade at baseline*	IV	19 (63%)				
	V	11 (24%)	0.19 (0.07-0.51)	**0.0011**		
Bilateral VUR	No	15 (60%)				
	Yes	15 (30%)	0.29 (0.10-0.78)	**0.0144**		
VUR grade at baseline, uni/bi	Unilateral IV (ref)	9 (75%)	1.00		1.00	
	Bilateral IV vs ref.	10 (56%)	0.42 (0.08-2.07)	0.2846	0.50 (0.06-3.96)	0.5120
	Unilateral V vs ref.	6 (46%)	0.29 (0.05-1.57)	0.1491	0.51 (0.06-4.22)	0.5312
	Bilateral V vs ref.	5 (16%)	0.06 (0.01-0.31)	**0.0007**	0.02 (0.00-0.25)	**0.0023**
Residual volume (ml)	0-<6.4	14 (56%)				
	6.4-<16	7 (33%)				
	16-83.2	6 (25%)	0.96 (0.92-1.00)	**0.0464**	0.92 (0.86-0.98)	**0.0166**

Table 2. *Univariable and multivariable prediction of VUR grade ≤ II at the one-year follow-
up in the total study population.*
*Maximum grade in bilateral VUR and duplex.
Area under ROC curve with 95% CI for multivariable model = 0.88 (0.81-0.96)
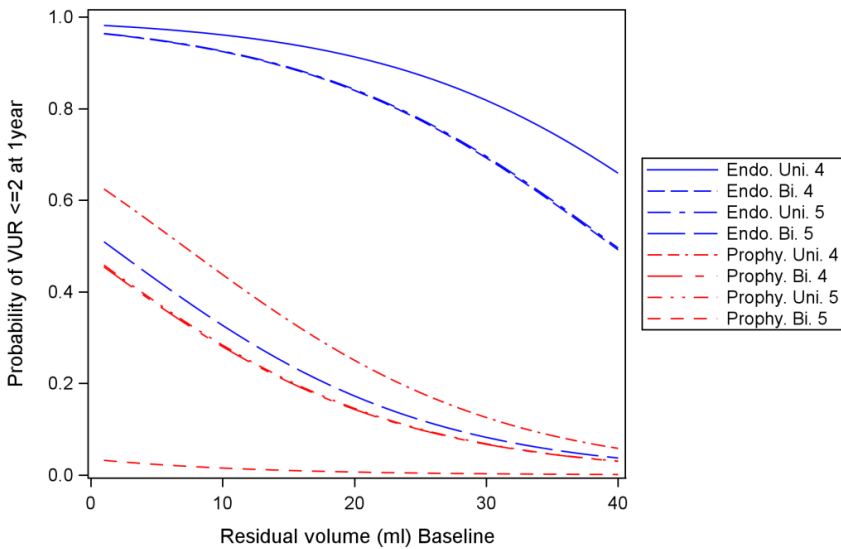
Figure 3 Stepwise multivariable prediction of VUR grade ≤ II at the one-year follow-up with PVR at baseline on the x-axis. Uni- and bilateral VUR separated. Area under ROC-curve = 0.88. Endo (ET), Prophy (CAP).

4.1.2 Bladder function

At baseline, LUTD was seen in 25% (18/72), high BC (from FVO) in 42% and high residual in 36%.

At the one-year follow-up, the BC had decreased in the total study population (high capacity in 34%), with no significant difference between treatment groups, despite the significantly higher reflux resolution in the ET group (p=0.0014).

When analysing the bladder variables compared with VUR grade, independent of treatment group, PVR at baseline was significantly lower in the group with VUR resolution, compared with the non-resolution group (p=0.010) [39].

Since the resolution rate of bilateral VUR grade V was low (31% and 0%) in both the ET and CAP groups, we evaluated a possible correlation between persistent bilateral grade V at follow-up and bladder function. The children with persistent bilateral VUR grade V had a larger PVR at baseline and larger bladder capacity at the one-year follow-up (p=0.0073 and p=0.016), as illustrated in *Figure 4*.
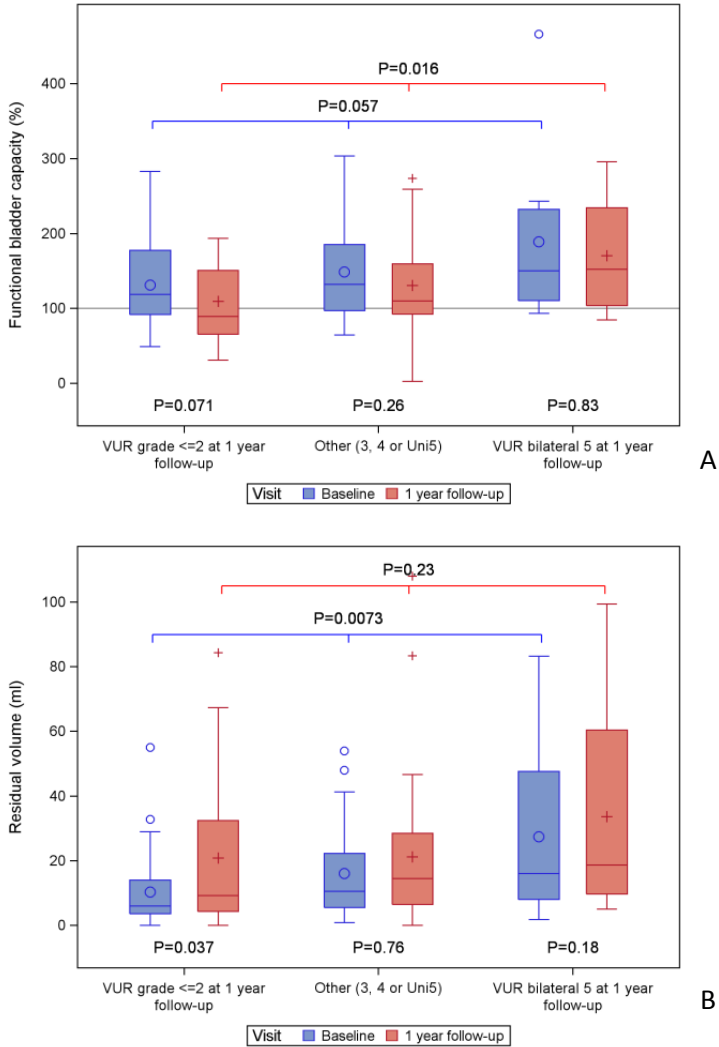
Figure 4 *Functional bladder capacity (A) and residual urine (B) at baseline (blue) and the one-year follow-up (red) in infants with high-grade VUR. Grouping variable VUR at the one-year follow-up. The box plot shows from the bottom: minimum, 25th percentile, median, mean, 75th percentile, maximum and outlier.*

In the explanatory analyses of bladder function vs. outcome, we identified *large PVR at baseline* as a predictor of VUR grade > II at follow-up, bilateral grade V VUR at follow-up, and recurrent UTI (p=0.046, 0.022 and 0.034).

Moreover, *large BC* at follow-up, was seen in infants with remaining bilateral grade V VUR (p=0.025/p=0.027) and in infants with new/progress in existing renal damage (p=0.006) (*Table 3*).

Explanatory variables	Probability of having VUR grade >2 at one-year		Probability of having bilateral VUR grade 5 at one-year		Probability of having febrile UTI during the study until one-year		Probability of having new/progress in renal damage at one-year	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Baseline								
BC, % of expected for age Continuous variable	1.14 (0.97-1.34)	0.12	1.17 (0.99-1.39)	0.060	1.10 (0.94-1.27)	0.22	1.00 (0.80-1.24)	1.00
BC, % of expected for age ≥ 150% vs < 150%	2.73 (0.96-7.78)	0.061	2.02 (0.55-7.40)	0.29	1.29 (0.41-4.06)	0.66	1.16 (0.24-5.63)	0.86
Residual volume (ml) Continuous variable	1.23 (1.00-1.50)	**0.046**	1.22 (1.03-1.45)	**0.022**	1.19 (1.01-1.39)	**0.034**	1.15 (0.95-1.38)	0.15
Residual volume ≥ 20ml vs < 20ml	3.86 (0.99-15.03)	0.051	3.26 (0.85-12.53)	0.085	2.50 (0.74-8.41)	0.14	4.92 (0.98-24.82)	0.053
Lower urinary tract dysfunction (number)	3.86 (0.99-15.03)	0.051	3.26 (0.85-12.53)	0.085	2.50 (0.74-8.41)	0.14	4.92 (0.98-24.82)	0.053
One-year follow-up								
BC, % of expected for age Continuous variable	1.19 (1.00-1.43)	0.050	1.26 (1.03-1.54)	**0.025**	1.10 (0.93-1.30)	0.26	1.38 (1.10-1.73)	**0.006**
BC, % of expected for age ≥ 150% vs < 150%	1.79 (0.61-5.24)	0.29	4.67 (1.19-18.26)	**0.027**	3.38 (1.00-11.39)	0.050	3.04 (0.62-14.99)	0.17
Residual volume (ml) Continuous variable	1.03 (0.93-1.14)	0.54	1.09 (0.97-1.21)	0.15	1.01 (0.90-1.13)	0.86	1.13 (1.00-1.27)	0.051
Residual volume ≥ 20ml vs < 20ml	1.12 (0.40-3.15)	0.83	1.08 (0.28-4.17)	0.91	2.12 (0.64-7.00)	0.22	2.81 (0.57-13.81)	0.20
Lower urinary tract dysfunction (number)	1.56 (0.50-4.83)	0.45	1.67 (0.43-6.59)	0.46	2.31 (0.67-7.89)	0.18	2.20 (0.44-10.98)	0.34

*Table 3 Explanatory analyses of bladder variables in patients with VUR grade > 2 at follow-up, bilateral VUR grade 5 at follow-up, febrile UTI during the study and progress in existing renal damage. Significant p-values in **bold** text.*

4.1.3 UTI and renal damage

Baseline

At inclusion, 67/77 children (87%) had renal parenchymal defects on scintigraphy. The damage was more generalised in boys and only 7% of the boys had a normal baseline scintigraphy (p=0.0097) (*Fig 5*).
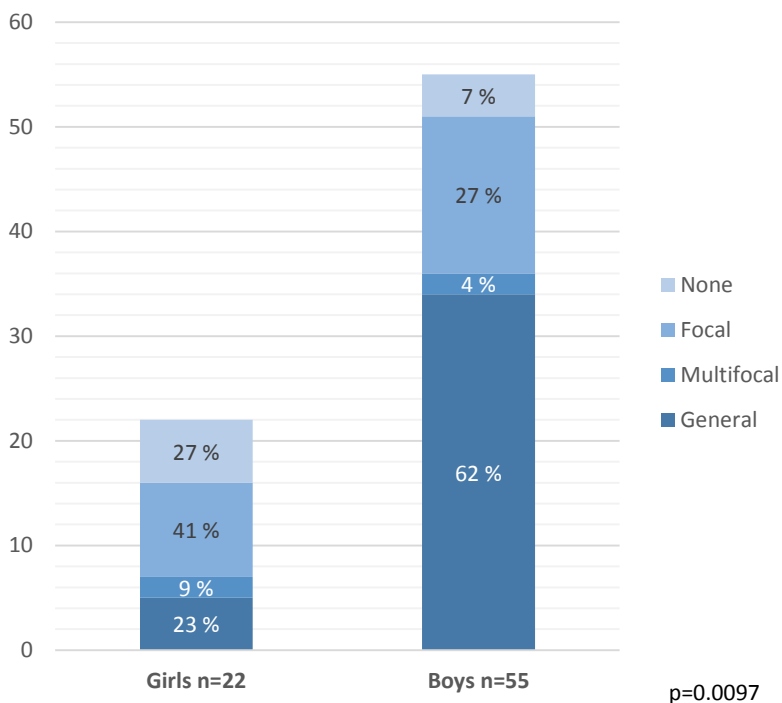
Figure 5 *Bar chart showing renal damage at baseline, number and percentage, in boys versus girls. Light blue indicates none and focal damage, dark blue indicates multifocal or generalised damage*

When analysing the correlation between the character of renal damage at baseline and VUR grade per renal unit, we found that 26 of 32 renal units (81%) with VUR 0-II at baseline had normal renal scans. Generalised renal damage was only seen in the renal units with dilating VUR at baseline (*Table 4*).

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	Girls			Boys		
Variable	VUR grades 0-II at baseline	VUR grades III-V at baseline	p-value	VUR grades 0-II at baseline	VUR grades III-V at baseline	p-value
	n=10 RU	n=34 RU		n=22 RU	n=87 RU	
Character of renal damage at baseline						
None	9 (90%)	17 (50%)		17 (81%)	28 (33%)	
Focal	1 (10%)	10 (29%)		3 (14%)	19 (22%)	
Multifocal	0 (0%)	2 (6%)		1 (5%)	3 (4%)	
General	0 (0%)	5 (15%)	0.045	0 (0%)	36 (42%)	0.0005

Table 4 *The character of renal damage at baseline, analysed per renal unit (RU) and divided by VUR grade 0-II/III-V at baseline.*

Moreover, bilateral renal parenchymal defects at baseline were correlated with a lower GFR, median 72% (44-109) vs 97% (43-140) of expected (p=0.0067).

Fifty-nine of 77 infants had a history of UTI already at inclusion, whereof 33 (56%) were caused by non-Escherichia coli, with no difference between boys and girls. Incidentally, the proportion of index UTI with non-E. coli was larger in the CAP group.

Follow-up

UTI

There were 27 febrile UTIs registered in 16 patients during the study, with no difference between the ET and CAP group (6 vs. 10), but more frequent in girls (8/22, 36%) than in boys (8/55, 15%). Univariable logistic regression showed that female sex and a high PVR at baseline was predictive of febrile UTI (p=0.039 and p=0.034), independent of treatment group. Explanatory analyses also showed that infants with high grade VUR at follow-up had a higher incidence of febrile UTI (p=0.042) (*Table 5*).

	Variable	n missing	Value	Probability of having febrile UTI during the study			Probability of having renal deterioration at follow-up		
				n (% of event)	OR (95%CI)	p-value	n (% of event)	OR (95% CI)	p-value
Baseline	**Group**	0	ET	6 (16%)			3 (8%)		
			CAP	10 (26%)	1.84 (0.59-5.69)	0.29	5 (14%)	1.72 (0.38-7.79)	0.48
	Sex	0	Girls	8 (36%)			4 (19%)		
			Boys	8 (15%)	0.30 (0.09-0.94)	**0.039**	4 (8%)	0.35 (0.08-1.57)	0.17
	Grade of VUR at baseline	0	VUR=IV	6 (20%)			2 (7%)		
			VUR=V	10 (21%)	1.08 (0.35-3.36)	0.89	6 (14%)	2.13 (0.40-11.38	0.38
	BC at baseline	5	Per 20 % of expected increase		1.10 (0.94-1.27)	0.22		1.00 (0.80-1.24)	1.00
	PVR at baseline	5	Per 1 ml increase		1.19 (1.01-1.39)	**0.034**		1.15 (0.95-1.38)	0.15
			Categorised ≥ vs. < 20ml		2.50 (0.74-8.41)	0.14		4.92 (0.98-24.82	0.053
One-year follow-up	**Grade of VUR at one year**	2	VUR=0	2 (9%)			0 (0%)		
			VUR=I	0 (0%)			0 (0%)		
			VUR=II	1 (20%)			0 (0%)		
			VUR=III	3 (23%)			2 (15%)		
			VUR=IV	5 (29%)			4 (25%)		
			VUR=V	5 (33%)	1.41 (1.01-1.98)	**0.042**	2 (15%)	1.85 (1.03-3.35)	**0.041**
	Febrile UTI during study	0	No UTI	-			2 (4%)		
			Any UTI	-	-	-	6 (33%)	13.25 (2.38-73.89	**0.003**
	BC at one year	10	Per 20 % of expected increase		1.10 (0.93-1.30)	0.26		1.38 (1.10-1.73)	**0.006**
	PVR at one year	10	Per 1 ml increase		1.01 (0.90-1.13)	0.86		1.13 (1.00-1.27)	0.051

Table 5 *Explanatory analyses of febrile UTI and renal deterioration. Significant p-values in* **bold** *text.*

During the study, there were 16 recurrences (59%) with non-E. coli and 11 with E. coli. Most recurrences (22/27) occurred during CAP, with bacteria resistant to the given prophylaxis. Multiple recurrences were only seen in patients with remaining dilating reflux at follow-up (p=0.019) (*Fig. 6*).
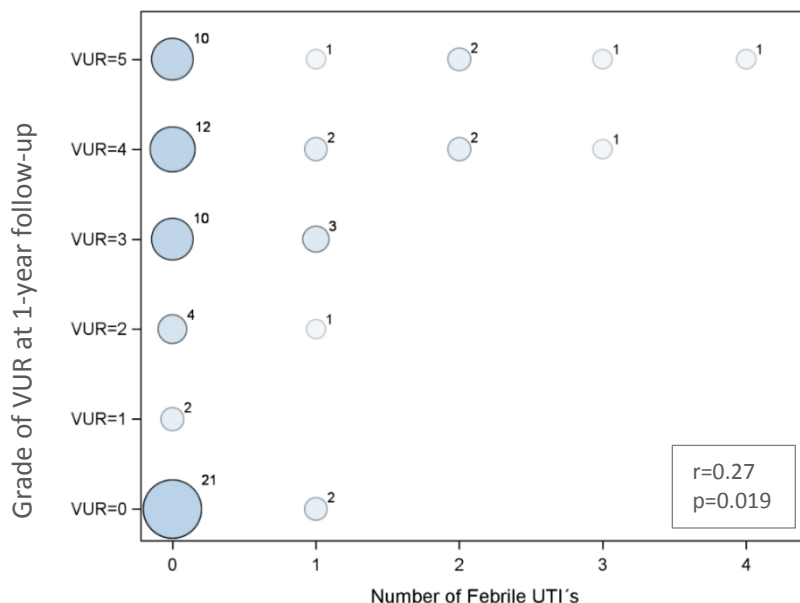
Figure 6 Bubble plot of the number of febrile recurrent UTIs during the study versus VUR grade at one year. The sizes of the circles are related to the number of patients. Multiple recurrences were only seen in patients with remaining dilating reflux at follow up.

4.1.4 Renal damage

Deterioration on scintigraphy at the one-year follow-up was noted in eight children (nine kidneys), with no difference between treatment groups (p=0.48). Seven had progress in old damage (three with additional new scars) and one had a new scar in a previously undamaged kidney. Explanatory analyses showed that 6/8 had one or more febrile UTIs between the first and second scintigraphy, demonstrating that UTI increases the probability of renal deterioration (p=0.003) (*Table 5*). None of the tested baseline variables was able to predict renal deterioration, but high PVR appeared to be important (p = 0.053). However, renal deterioration did correlate with both dilating VUR (p=0.041) and high BC (p=0.006) at follow-up (*Table 5*).

4.1.5 Adverse events Papers I-III

Five children changed treatment arms for reasons listed in the CONSORT flow chart, included in *Appendices* and in Paper I [23].

Four patients required ureteral re-implantation; one with remaining dilating VUR and impaired renal function after two injections, one because of an obstruction after injection and two because of VUJ stenosis detected at cystoscopy (not injected). No adverse events were reported during or after anaesthesia.

The prophylaxis was changed from nitrofurantoin to another agent in three patients, due to nausea and/or vomiting. No other side-effects were reported in the CAP group.

During the study, 164 invasive procedures (112 VCUG and 52 cystoscopies) were performed. We saw only one febrile UTI possibly related, which occurred 15 days after ET (*Figure 7*).
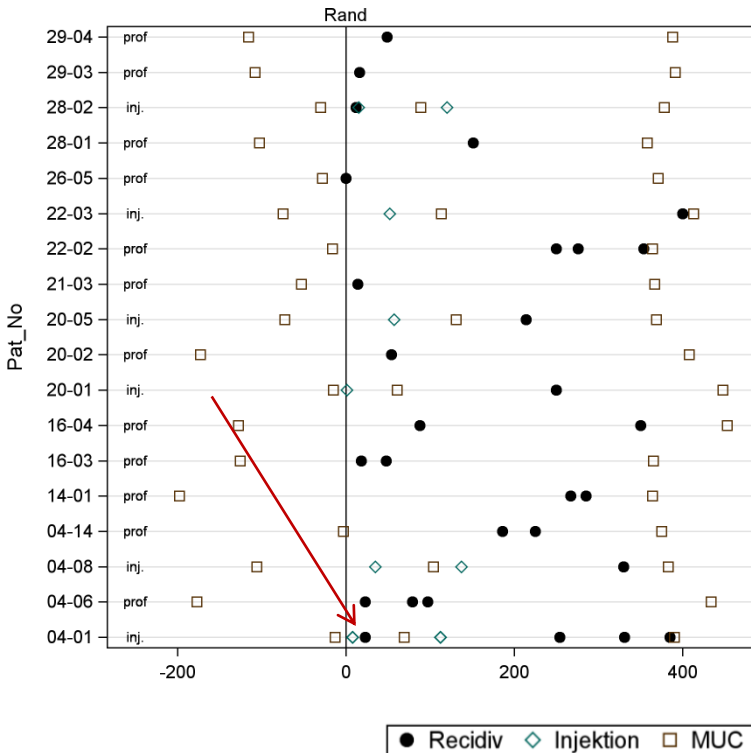
Figure 7

4.2 Results paper IV

Four focus group discussions were conducted with 13 mothers and six fathers of 15 children. The demographic data on the informants are listed in *Appendices*. The children were aged 1.5-6 years at the time of the focus groups. They had all been diagnosed with VUR grade IV or V (47%/53%) before the age of six months. Ten had bilateral reflux (67%), and nine were male (60%). Eight children had been treated with CAP (groups 1-2) and seven children with CAP and SI (groups 3-4). Five children had an antenatal diagnosis of hydronephrosis, one was screened because of heredity and nine presented with a UTI (*Table 6*).

FG	Informant	Parent's sex	Child's age at time of interview (years)	Child's sex	Grade of VUR	Treat-ment	Debut of VUR
1	1	f	3,5	m	Bilat 4	CAP	UTI
	2	f	4,5	m	Bilat 5	CAP	AH[a]
	3	m	2	f	Bilat 5	CAP	UTI
	4[1]	f	4	f	Bilat 4	CAP	Heredity
	5[1]	m	4	f	Bilat 4	CAP	Heredity
2	6	m	2	f	Unilat 4	CAP	UTI
	7	f	1,5	m	Bilat 5	CAP	AH[a]
	8	f	4	m	Bilat 5	CAP	UTI
	9	f	4	m	Unilat 4	CAP	AH[a]
3	10[2]	f	6	m	Unilat 5	Open surgery[c]	UTI
	11[3]	m	6	f	Bilat 4	ET	AH[a]
	12[3]	f	6	f	Bilat 4	ET	AH[a]
	13[2]	m	6	m	Unilat 5	Open surgery[c]	UTI
	14	f	2,5	m	Bilat 4	ET	UTI
4	15[4]	f	4	m	Unilat 5	Open surgery[b]	AH[a]
	16	f	6	m	Bilat 5	ET	UTI
	17	f	4,5	f	Unilat 5	Open surgery[b]	UTI
	18	f	3	f	Bilat 4	ET	UTI
	19[4]	m	4	m	Unilat 5	Open surgery[b]	AH[a]

Table 6 *Sample characteristics. Information on the 15 children of the 19 informants.*
[1, 2, 3, 4] *Both parents participating in the same focus group (FG), light grey child is represented by two parents.*
[a] *antenatal hydronephrosis,* [b] *ureteric re-implantation,* [c] *partial nephrectomy*

A total of 2,897 statements on the parents' experiences of hVUR were identified during the analysis process. These statements were sorted into 10 categories (*Figure 7*). In this study, we focused on the parents' experiences of CAP, SI, UTI and renal damage. These four main topics generated 1,123 statements (39% of all), categorised into nine categories and 33 sub-categories. The main categories and subcategories of CAP, SI, UTI and renal damage are listed in *Table 7* in descending order, according to the frequency of the described experience.
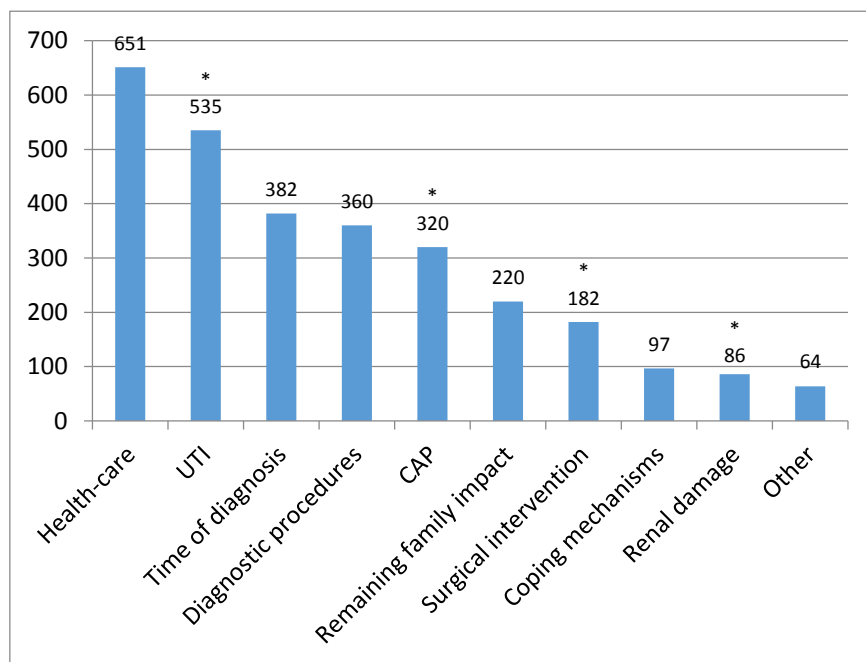
Figure 7 *Number of statements (n=2,897), divided by category.*
*The four main topics of the study.

Categories and sub-categories	Frequency
UTI	535 (48%)
Family impact due to the child's UTI	273 (24%)
-Restricted social family activities due to ongoing UTI or fear of other infection	76
-Emotional stress and worries about the risk of UTI	50
-Difficulties differing between UTI and other infection	48
-UTIs are fewer and easier to recognise with increased child age	39
-Always being prepared to seek immediate medical care	31
-Frequent visits to the emergency department during infancy	22
-Family strains when the child is admitted to hospital	7
Emergency care at suspected UTI of the child	131 (12%)
-Long waits and stressed staff in the emergency department	36
-Determination of need for treatment and level of care	34
-Friendly, fast management in the emergency department	25
-Parents not being heard and symptoms not taken seriously in the emergency department	13
-Inaccessible primary health care	12
-Difficulties with blood samples and iv lines in urgent situations	11
Obstacles and facilitators of sampling and testing of urine	131 (12%)
-Difficulties collecting a urine sample	44
-Challenges handing in a urine sample for analysis	32
-Challenges convincing caregivers to perform a urine culture	26
-Facilitators of sampling and testing of urine	29
CAP	320 (28%)
Emotional stress about the child's CAP intake	140 (12 %)
-Stress making the child take the CAP	103
-Stress about the responsibility/worry if the intake of CAP fails	37
Worries and uncertainties regarding the effects of CAP	140 (12 %)
-Worries about the long-term use of CAP	50
-Thoughts about the therapeutic effect of the CAP	46
-Negative influences on the child's intake of food and other meds	44
The CAP intake was unproblematic	40 (4%)
SI	182 (16%)
Difficulties associated with SI	94 (8%)
-Distress seeing the child at the induction of anaesthesia	30
-Inadequate information and insufficient personal treatment	23
-Difficulties parenting in the postoperative care environment	20
-Troublesome pre-operative preparations	15
-Long waits during surgery	6
Positive experiences related to SI	88 (8%)
-Professional and personal treatment in anaesthesia and surgery	66
-Safe postoperative management	19
-Unproblematic pre-operative preparations	3
Renal damage	86 (8%)
Risk of renal damage	86 (8%)
-Worries about the risk of renal damage	44
-No worries about the risk of renal damage	27
-Existing renal damage	15

Table 7 Parents' experiences (n=1,123) in descending order according to frequency of statements per category and subcategory.

4.2.1 Experiences of CAP (n=320)

Forty (13%) of the CAP experiences were positive, stating that the intake of CAP was unproblematic. The remaining 280 statements described negative experiences, of which the majority (n=103) related to parents' every-day stress when getting their child to take the antibiotics. Other sub-categories regarded parents' stress about the treatment responsibility and concern about missing a CAP dose (n=37), worries about the long-term use (n=50) and thoughts about the therapeutic effect of CAP (n=46). The negative influence on the children's food preference was a matter of concern in all focus groups (n=44).

4.2.2 Experiences of SI (n=182)

Parents' experiences of anaesthesia and surgical care were both positive (n=88) and negative (n=94). The experiences were positively affected by empathic treatment, accurate information and adequate preparation. Among the negative experiences, inadequate information and a feeling of helplessness at the induction of anaesthesia were among the most frequently described concerns. Difficulties parenting in the postoperative care environment were mostly caused by parents being poorly prepared.

4.2.3 Experiences of UTI (n=535)

The majority of parents' experiences of UTI reflected strain (n=408), where most statements described a negative family impact due to UTI, such as restricted social activities and the emotional stress associated with the constantly present risk of UTI.

The experiences of emergency care at suspected UTI encompassed long waiting times, stressed staff and a feeling of not being heard, but also positive experiences of fast, friendly management.

The sampling and testing of urine is a frequent issue for these families; waiting for the child to pee, convincing caregivers, not only to accept the urine sample, but also to perform a urine culture. Among facilitators of urine testing, parents suggested better access to primary care, possibility leaving urine samples at an open clinic and having tubes for urine samples at home.

4.2.4 Experiences of renal damage (n=86)

Parents' thoughts about renal damage varied considerably, both between and within the groups. While 44 statements expressed a constant worry over the risk of renal damage and impaired renal function, 27 described no concern over their children's kidneys. The remaining 15 statements described, in a fairly neutral tone, an awareness of existing renal damage.

5. Discussion

VUR outcome

The Swedish infant high-grade reflux trial is the first randomised study comparing endoscopic treatment with antibiotic prophylaxis in infants with VUR grades IV-V. We found a significantly higher resolution rate in infants treated with ET than in the CAP group and we were able to confirm that the treatment is safe, with few complications even in this young age group. The success rate of ET was related to VUR grade and uni- or bilaterality. ET in VUR grade V has been described previously, but it is not common practice. This study reported fair results in unilateral VUR grade V (65%), but less favourable results in bilateral cases (31%).

In children with a successful first ET, there was a recurrence of dilating VUR in 19%, which is in agreement with previous studies [59, 61].

When discussing VUR outcome, it is essential to take the aspect of spontaneous resolution into account. Even if the rate is lower in higher VUR grades (38-48% in grade IV) [28, 29], it is still a factor to consider and early ET treatment should only be recommended in patients with breakthrough infections and a risk of renal deterioration [43] [45] [21]. Furthermore, infants with megaureter can have both VUR and stenosis, which must be ruled out before suggesting ET.

If a reduction in VUR grade is desired and obstruction is excluded, we regard ET as a safe and attractive first-line alternative, despite the recurrence rate. ET can buy the family and the treating physician time, until the child is less prone to recurrent UTIs and more suitable for other surgical procedures [62, 63].

Bladder function

This study was not able to prove that early endoscopic treatment is superior to prophylaxis in preventing LUTD in infants with high-grade VUR. Instead, we found that bladder function differs from the start and is probably a part of the congenital VUR anomaly. Although, the decrease in bladder capacity in children with non-dilating VUR at follow-up might indicate that refluxing urine still has a role to play in the development of high BC.

High PVR at baseline was an independent negative predictor of VUR resolution in both treatment groups. More interestingly from the clinical point of view, high PVR at baseline also merged as a predictor of recurrent UTI and renal damage at the one-year follow-up. The correlation between LUTD and a lower probability of VUR resolution has previously been shown [21, 116-119] and also that increased PVR correlates with recurrent UTI in infants with hVUR [37, 120].

The question of whether PVR in high-grade VUR actually is reflux urine and that it is therefore related to the grade of VUR rather than to bladder dysfunction has been discussed. According to this study, PVR increased in both resolution and non-resolution groups, which contradicts the hypothesis that PVR mainly consists of reflux urine. In the children investigated with videocystometry, we were also able to demonstrate that PVR consisted of pure reflux urine in a very few patients. In most cases, it was a mixture of both. Whether PVR is reflux urine or true residual or a combination of both is less important, since it is the incomplete bladder emptying that is the risk factor for rUTI and possibly new renal damage.

Shaikh et al. evaluated the effect of bowel and bladder dysfunction on recurrent UTI in children with and without VUR [121]. They analysed the data from the two longitudinal studies, RIVUR [122] and CUTIE (careful urinary tract infection evaluation). In both studies, the inclusion criterion was UTI in children aged two to 71 months and, if VUR grades I-IV was diagnosed, the child was included in the RIVUR trial, with randomisation to CAP or placebo, and, if there was no VUR, the child was included in the CUTIE trial with no treatment. The two trials comprised a total of 802 children from which Shaikh et al. analysed a sample of 181 children who were toilet trained and had data for baseline BBD. Among these, only four were boys and 97 (54%) had BBD at baseline, with no difference between children with and without VUR (p=0.15). In VUR patients with placebo, BBD was associated with a higher rate of rUTI (51% with BBD vs. 20% without BBD, p=0.01). Conversely, in VUR patients with CAP and in patients without VUR and no treatment, the rates of rUTI were similar with and without BBD. In none of the three cohorts was BBD associated with renal scarring, possibly due to the rarity of this event in the cohorts and thereby with limited power to detect differences.

UTI and renal damage

We found no difference in the rate of recurrent UTI or renal deterioration between the two treatment groups in this study. Although, we did see a higher

frequency of UTI recurrences in children with persisting dilating VUR at follow-up. This fact, in combination with the higher resolution rate in the ET group, may still indicate a potential benefit of treating hVUR endoscopically in infants.

The prevalence of renal parenchymal defects of 87% at baseline in this study with 71% boys, corresponds well with the concept that early clinical manifestation indicates a more severe disease, especially in males. The renal damage was strongly correlated with the grade of VUR and was more common and more severe in boys. Similar findings have been reported in previous studies of congenital renal dysplasia in boys versus acquired renal scarring due to febrile UTI in girls [20, 123, 124].

Moreover, we found that febrile UTIs were more likely to occur in girls than in boys (p=0.039), which was also seen in the Swedish reflux trial. The Swedish reflux trial also found that the UTI rate in girls was higher in the surveillance group compared with both CAP and endoscopy. The rate of new renal damage was also higher in the surveillance group in girls, while there were no effects of CAP on UTI recurrence or renal damage in boys [49, 50].

In this study, renal deterioration was found in eight children (10%), significantly related to recurrent UTI and VUR grade on the scarred renal unit, but with no difference between CAP and ET. It is important to mention that the study was not designed to detect differences of this kind between the groups. It is also possible to discuss whether a larger study population or a longer follow-up would have changed the outcome. However, neither the International reflux study in children (aged 0-10 years) [48, 125] nor the Birmingham reflux trial (aged 0-15 years) [126] found any difference in renal scarring or UTI recurrence between CAP and open surgery. Similar to our results, previous studies have also identified hVUR as a risk factor for renal scarring after a febrile UTI [127, 128].

Some authors have started to question whether VUR really predisposes to UTI and renal damage [129], but this mainly relates to lower grades of VUR in older children. So, despite the fact that two RCTs failed to detect a difference in UTI recurrence between children with and without VUR, it is important to consider that all ages were mixed in the analyses and all grades of VUR were included in one [51] and only grades I-III in the other [130]. So, even if there is no convincing evidence that VUR predisposes to renal scars in UTI patients with non-dilating VUR, conclusions cannot be drawn regarding VUR grades IV and V due to a lack of available data [129].

Moreover, the effectiveness of CAP in preventing febrile UTI has been questioned [131-133]. Mattoo et al. performed a meta-analysis of five randomised studies comparing CAP with surveillance or placebo in a total of 809 patients with VUR [29, 51, 130, 134, 135], which revealed no benefit from

prophylaxis in preventing UTI or renal scarring [136]. However, the results should be interpreted with caution, because the study populations differ considerably and most studies excluded children with high-grade VUR. Further, two large trials of CAP and UTI had not yet been analysed and published and were therefore not included in the meta analysis. Firstly, the RIVUR study, where CAP reduced UTI recurrences by 50% [30]. Secondly, the Swedish reflux trial, where they found a significantly higher recurrence rate among girls in the surveillance group (57% compared with 19% on CAP and 23% with ET) [49].

What do parents think?

Many parents in the focus groups described the hesitation they felt when giving antibiotics to their child, both uncertain of the therapeutic effect and scared of long term effects and the risk of increasing bacterial resistance. The concerns about the actual intake and the stress related to the responsibility further increased their reluctance about CAP.

The parents' hassle relating to daily medication administration should not be underestimated. There is a common belief that CAP is the "easy" treatment option and planning for surgical or endoscopic treatment is often a major decision.

When listening to the parents in this study, however, negative experiences of CAP were commonly described (88% of all CAP statements), while the negative experiences of surgical intervention (52% of all SI experiences) were related to a single occasion and could be eased with adequate preparation, information and an empathetic approach.

In studies of parents' preferences, Tran et al. identified 13 themes that influenced the parents' choice of VUR treatment. The four most common were the prevention of future UTI, the efficacy rate of treatment, the burden of daily maintenance and the risk of antibiotic resistance [137]. Capozza et al. evaluated parental treatment preferences in children with VUR grade III who had been on CAP for at least six months. After detailed information about the three treatment options (CAP, ET and open surgery), 80% of all parents would prefer ET [138]. In other studies, the success of the procedure has been regarded as the most important factor for parental satisfaction [69, 70] and increased HRQoL [68, 139].

It was also evident, when analysing the discussions, that the UTI outcome is of great parental relevance. Not surprisingly, the majority of UTI experiences were negative and challenges appeared in different circumstances. The restriction of social activities due to ongoing UTI or the parents' fear of other

infections were frequently described, as were the challenges involved in differentiating between UTI and other infections. Parents' reports on the difficulty associated with handing in a urine sample and obtaining a culture can be relieved by the healthcare system. According to our study results, better access to primary care and the opportunity to leave a urine sample at an open clinic, would facilitate the lives of these families considerably.

The daily negative impact of CAP and UTIs on family life was evident in this study, but it was not identified in previous studies of VUR and HRQoL. One reason for this could be our study material relating to infant high-grade VUR, but also the fact that the methods previously used were not sufficiently sensitive to capture the challenges in these families [66, 140].

In contrast, the parents expressed very little concern about renal damage. Most of the parents were aware that their child had renal damage and that a febrile UTI could cause further scarring. Some of them stated that this knowledge increased their fear of UTIs, but it appeared that in most cases the treating physician had managed to calm them down with the information that "you only need one kidney". The lack of consistency in parents' experiences of renal damages does not make any experience wrong or the result less valid. Instead, it offers an insight into diversity and tells us that the participants dare to have opinions of their own.

When evaluating the quality of this focus group study, one can conclude that we studied experiences of parents to a special sub-group of VUR patients (infants with VUR grades IV-V), stratified for treatment (CAP or SI) with focus on a very limited period of the children's lives (0-2 years of age), which gained homogenous groups and facilitated the data collection. By stratifying for sex and pre/postnatal diagnosis we aimed to achieve *external representativeness* of infants with hVUR [89].

With the focus group manual, the same questions were asked in all focus groups, which increased the study's *dependability*. The data were categorised by two researchers through a reflective, back-and-forward sorting process in order to limit selection bias and to increase the *validity* and the *credibility* of the process [92]. The *credibility*, but also the *transferability,* was further enhanced by a rich presentation of the findings together with representative quotes [89, 94]. Moreover, the use of tables, describing the research process, can aid other researchers to review the different steps of the process, which further strengthened the *trustworthiness* of the study.

Category *saturation* is reached when researchers gather data to the point where no new information is being added [141], and was in this study confirmed through comparison analysis of multiple focus groups.

Importantly, none of the moderators had been involved in the previous care or treatment of the informants' children, which is crucial for the focus group dynamics and complies with the Oxford critical appraisal of qualitative studies [142].

The most vulnerable children

It is important to acknowledge bilateral VUR grade V as a more extensive congenital anomaly, often with renal hypo/dysplasia, a high morbidity rate and a high risk of recurrent UTI. The condition almost exclusively affects boys and presents during infancy, either in the follow-up after antenatal hydronephrosis or after an early febrile UTI.

The prognosis is far worse compared with lower grades of VUR and, in our study, only five of 34 cases of bilateral grade V had resolved at follow-up. All five infants with reflux resolution had normal bladder parameters and they had all been treated with endoscopic injection.
These children pose a true challenge when it comes to managing their treatment and follow-up.

Strengths and weaknesses

The Swedish infant high-grade reflux trial was a randomised, controlled trial, with a selection of high-risk VUR patients, previously excluded from most studies. The recruitment was initially slow, due to the low prevalence of VUR grade V, but also because many eligible infants were excluded when vesicoureteral obstruction could not be ruled out. Nonetheless, the power-calculated number of participants was reached, based on the primary outcome of VUR resolution and bladder function.

In spite of this, the number of patients in each treatment arm was relatively small and the follow-up time was short. With a larger study sample and a longer follow-up, we might have been able to detect a difference in rUTI and renal damage between the treatment groups. In addition, the low success rate of ET in bilateral VUR grade V probably contributed to the finding that no difference in bladder function between the treatment groups was seen and that we were unable to find a statistical correlation between ET and recurrent UTI.

Moreover, information about the eligible patients who declined participation or were excluded has not been registered.

Another limitation of this study is that the type of bacteria in the index UTI was not taken into account in the randomisation procedure. By chance, there was a larger proportion of non-E. coli-caused index UTIs in the CAP group and we do not know if this affected the outcome of UTI and renal deterioration.

The sample size of the focus group study was adequate according to focus group methodology [143] and the study was carefully designed according to current standards, such as involving the target population in evaluation of health care [76, 81, 144]. The study design also complied with the Oxford critical appraisal of qualitative studies [142] and was strengthened by using population characteristics consistent with VUR IV-V infants (3:1 male predominance and 1/3 diagnosed after antenatal hydronephrosis) [20, 62]. If the parents of the same family wanted to participate in the same focus group, this opportunity was given. Therefore, in some cases, the child was represented by two parents. A main reason to give this choice is that it may facilitate the participants' sense of security in the focus group, which is essential for the respondents' openness and provision of reliable information. And even if two parents represent one family, and one child, they still have their own individual experiences. Moreover, the moderator assured that all participants had an opportunity to contribute and that no one dominated the discussion.

Focus group methodology has its limitations: participants may give socially desirable responses and the level of the discussion may not reach the desired depth. All individuals make different numbers of statements and the findings therefore reflect the group rather than the participants [145]. An increased number of statements may indicate the high relevance of an issue, but it cannot be used either to generalise the finding or to determine the actual difference between groups and the extent to which participants are affected by the issue.

6. Conclusion

High-grade VUR in infants can be treated with injection therapy and the resolution rate is higher compared with CAP treatment. ET can be suggested as a safe and effective treatment in infants with VUR grade IV and unilateral grade V. It can also be offered in bilateral grade V, in cases with normal bladder function, where active treatment is necessary.

We were not able to prove that LUTD can be prevented by early VUR resolution, but it can instead be seen as a part of the congenital VUR abnormality. High PVR, as a sign of bladder dysfunction, is an important prognostic factor for VUR outcome in both prophylactic and endoscopic treatment.

There was no difference in UTI recurrence or renal deterioration between the treatment groups. The VUR grade at follow-up correlated with both recurrent UTI and renal deterioration. Female sex and bladder dysfunction, especially high PVR, and are positive predictors of UTI recurrences.

The focus group study revealed that both CAP and the risk of UTI have a non-negligible, everyday impact on family life, while renal damage appears to be of secondary importance to the parents. The parents' concerns in terms of SI are related to an isolated occasion, which can be optimised by simple means.

The management of VUR should be evidence based and risk adapted based on the child's age, sex, reflux grade, history of UTI, renal function and associated bowel/bladder dysfunction – with parents' preferences taken into consideration.

7. Future perspectives

Our results show that endoscopic treatment is a safe and effective treatment alternative in infants with high-grade VUR, particularly in grade IV and unilateral grade V, but also in selected cases of bilateral grade V. We have highlighted the importance of risk grading even among the hVUR patients, to decide what patient would benefit from early intervention. Given how important bladder dysfunction appears to be for the prognosis of VUR, bladder evaluation should be included in the basic investigations.

Concerns regarding the use of antibiotic prophylaxis, with the risk of resistance development, the daily burden of medication administration and the prophylaxis-driven need for repeated renal imaging call for further research regarding the role of CAP in general VUR management. This study did not evaluate the effect of CAP, as the children in the ET group also had CAP until VUR resolution. So, regarding high-grade VUR, no study has yet proven that surveillance is an alternative management form in these children. Randomised studies are needed both to investigate which patients with VUR grades IV and V will benefit from prophylactic antibiotics and to identify factors that contribute to UTI recurrence and renal parenchymal scars. The results from the focus group study demonstrate the parents' need for more information and clearer guidance, which hopefully new studies will be able to provide.

There is also a need to continue questioning the use of invasive investigations and encourage the development of alternative modalities for VUR grading. For VUR grades I and II, repeated VCUG is not needed, but the prompt treatment of any episode of recurrent UTI is recommended. However, in VUR grades III-V, especially grades IV and V, VCUG still has a role to play in detecting spontaneous resolution and, in combination with renal imaging, in choosing the optimal treatment regimen.

This research project was only able to accommodate a small part of the results from the focus group study. The remaining results regarding parents' experiences from the time of diagnosis, diagnostic procedures, remaining family impact and coping mechanisms are yet to be presented. In addition, parents' experiences of the health care that is given, including information, accessibility, personal treatment, continuity and much more besides, will hopefully bring

useful knowledge to the discussion about VUR management and patient-centred care.

A long-term follow-up study of the Swedish infant high-grade reflux trial, from the same research centre with the same study cohort, has recently been proposed. It is to be hoped that it will shed light on some of the study's remaining questions: did ET affect the rate of UTI recurrence or renal damage in the long term, have there been any late complications of ET such as obstruction, what is the long-term result of ET in relation to hVUR and have any late surgical procedures been performed?

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Appendices

CONSORT flow diagram

Assessed for eligibility (not registered)

Enrolment

Excluded (not registered)
- Not meeting inclusion criteria
- Declined to participate
- Other reasons

Randomised

Allocation

Allocated to endoscopic therapy (n=38)
- Received allocated intervention (n=34)
- Did not receive allocated intervention
  (n=4)
  1 VUJ stenosis detected at cystoscopy
  1 delayed treatment and
  spontaneous resolution
  1 parents declined therapy
  → 3 change of treatment arm
  1 VUJ stenosis detected at cystoscopy
  → 1 re-implantation

Allocated to antibiotic prophylaxis alone
(n=39)
- Received allocated intervention (n=37)
- Did not receive allocated intervention
  (n=2)
  2 change of treatment due to
  parents' request

Follow-up

Lost to follow-up (n=0)

Discontinued intervention (n=2)
        2 re-implantations after ET (LOCF)

Lost to follow-up (n=0)

Discontinued intervention (n=0)

Analysis

Analysed PP (n=36)
- Excluded from analysis (n=4)
        4 who did not receive allocated
        intervention
- Added to analysis (n=2)
        2 imported from prophylaxis group

Analysed ITT (n=37)
- Excluded from analysis (n=1)
        1 reimplantation before ET (protocol
        violation)

Analysed PP (n=39)
- Excluded from analysis (n=3)
        2 who did not receive allocated
        intervention
        1 VCUG at follow-up not assessable
- Added to analysis (n=3)
        3 imported from endoscopy group

Analysed ITT (n=38)
- Excluded from analysis (n=1)
        VCUG at follow-up not assessable

Focus group manual

1. Describe how it was for you, as parents or parents-to-be, when your child had the diagnosis VUR (or hydronephrosis)?

2. Children with VUR go through many diagnostic procedures, occasionally with catheter or i.v. line and sometimes blood samples and urine samples are needed.
   How did you experience this and how did this affect you and your child?

3. Infants with high-grade VUR need to take continuous antibiotic prophylaxis to prevent UTI. Describe how this regular medication affected you and your daily life.

4. Despite the CAP, the child can get a breakthrough UTI. How did this risk of UTI affect you and your family?

5. *Only in SI groups:*
   Your children have all been treated with endoscopic therapy or open surgery. How did you experience these interventions?

6. Children with hVUR sometimes have kidney damage from start and the goal of all treatment is to prevent new damages and progress of old. How did this risk of renal damage affect you as parents?

7. Now we would like to learn more about your experiences of the health care system; the provision of service, information and accessibility. What parts of the health care did you appreciate and what parts can be improved?

8. If this first period in the life of your child has been challenging, how did you cope with these challenges?

9. Lastly, how are you as parents and your child affected by the VUR diagnosis today?

Demographic data on the informants

Focus group participants	Value
Mother	13
Father	6
Age (years)	25-44
Number of children per family	1-4
Marital status: Married Cohabitant	 9 10
Country of birth	Sweden
Place of residence: Large city Small town Countryside	 7 4 8
Parent is healthy: Yes No	 16 3
Education: High school University Not finished	 8 8 1
Occupation: Full-time Part-time Parental leave part-time Sick leave	 7 4 4 2
Content with level of occupation: Yes Would like to work more Would like to work less	 11 3 2

Frågor om förälder/vårdnadshavare och barn   Kodnummer....

DEL A. Information om Dig som förälder/ vårdnadshavare

1. **Jag är**
   - ☐ Man
   - ☐ Kvinna

2. **Jag är** ....år gammal.

3. **Jag har** ....antal barn.

4. **Jag är**
   - ☐ Gift
   - ☐ Skild
   - ☐ Registrerad partner
   - ☐ Sambo
   - ☐ Särbo
   - ☐ Ensamstående
   - ☐ Änka respektive änkling/efterlevande partner

5. **Jag är född**
   - ☐ I Sverige
   - ☐ I Europa
   - ☐ I utomeuropeiskt land

6. **Boendeort där barnet bor majoriteten av tiden.**
   - ☐ Storstadsregion (≥ 100 000 invånare)
   - ☐ Stad (< 100 000 invånare)
   - ☐ Landsbygd

7. **Jag (förälder/vårdnadshavare) är**
   - ☐ Frisk
   - ☐ Har en diagnosticerad sjukdom

      Om Du har en diagnostiserad sjukdom, vilken sjukdom är det?

   ....

   ....

1

Frågor om förälder/vårdnadshavare och barn   Kodnummer….

8. Min högsta utbildning

- ☐ Grundskola
- ☐ Gymnasium eller motsvarande
- ☐ Högskola/Universitet
- ☐ Annat,

  vad?...

  ....

9. Det senaste året har jag

- ☐ arbetat heltid
- ☐ arbetat deltid
- ☐ studerat heltid
- ☐ studerat deltid
- ☐ föräldraledig heltid
- ☐ föräldraledig deltid
- ☐ varit sjukskriven heltid
- ☐ varit sjukskriven deltid
- ☐ arbetssökande

10. Deltar du i arbetslivet i den utsträckning Du önskar som förälder?

- ☐ Ja
- ☐ Nej, jag skulle vilja arbeta mer
- ☐ Nej, jag skulle vilja arbeta mindre

11. Erhåller familjen vårdbidrag eller annat ekonomiskt stöd

- ☐ Ja
- ☐ Nej

  Om JA, vilket ekonomiskt stöd erhåller familjen?

....

....

2

Frågor om förälder/vårdnadshavare och barn   Kodnummer....

DEL B. Information om barnet i familjen

1. Mitt barns ålder...................(år)
2. Mitt barns vikt.....................(kg)
3. Mitt barns längd..................(cm)

Frågor om barnets familjesituation

4. Antal helsyskon.........
5. Antal halvsyskon..........

Kryssa i det/de alternativ som stämmer överens med familjesituationen.

	JA	NEJ
6. Bor med båda föräldrar/vårdnadshavare	☐	☐
7. Bor (enbart eller största delen av tiden) med ena vårdnadshavaren	☐	☐
8. Bor växelvis hos båda vårdnadshavarna	☐	☐

Frågor om barnets hälsotillstånd

9. Äter ditt barn antibiotika för att förebygga urinvägsinfektioner?

   ☐ Nej
   Om nej, har ditt barn ätit antibiotika tidigare? Vilket läkemedel?

   ....

   ☐ Ja
   Om ja, vilket läkemedel, vilken styrka och hur ofta? (Ex. Trimetoprim, 2 ml på kvällen)

   ....

Frågor om urinvägsinfektion och njurskada
– om ditt barn aldrig har haft någon urinvägsinfektion kan du hoppa direkt till fråga 14

10. Hur många urinvägsinfektioner har ditt barn haft under det senaste året?

   ☐ 0

   ☐ 1-2

   ☐ 3 eller fler

   ☐

3

Frågor om förälder/vårdnadshavare och barn   Kodnummer....

11. Hade ditt barn feber (>38 grader) vid någon av dessa urinvägsinfektioner?

☐ Nej

☐ Ja

Om ja: *Vid hur många av infektionerna?...*

Var ditt barn inneliggande med intravenös antibiotika (antibiotika direkt i blodbanan)?

☐ Nej

☐ Ja → *Vid hur många av infektionerna?...*

12. Uppskatta hur många urinvägsinfektioner ditt barn hade mellan 0-2 års ålder?

☐ 0

☐ 1-2

☐ 3 eller fler

13. Hade ditt barn feber (>38 grader) vid någon av dessa urinvägsinfektioner?

☐ Nej

☐ Ja

Om ja: *Vid hur många av infektionerna?...*

Var ditt barn inneliggande med intravenös antibiotika (antibiotika direkt i blodbanan)?

☐ Nej

☐ Ja → *Vid hur många av infektionerna?...*

14. Har Ditt barn någon njurskada (ärr på njuren och/eller nedsatt njurfunktion)?

☐ Nej

☐ Vet inte

☐ Ja

Om ja, beskriv vad du vet om den..

...

...

4

Frågor om förälder/vårdnadshavare och barn   Kodnummer....

Frågor om barnets behandling

15. Har ditt barn fått någon behandling med anledning av sin urinvägsreflux (bortsett från antibiotika)?
    - ☐ Nej
    - ☐ Ja, endoskopisk injektionsbehandling
    - ☐ Ja, öppen, kirurgisk behandling (så kallad neoimplantation)

16. Vilka hälso- eller sjukvårdskontakter har ditt barn haft med anledning av sin urinvägsreflux?

    Utgå i svaren från det senaste året
    - ☐ Läkare
    - ☐ Uroterapeut
    - ☐ Sköterska
    - ☐ Annan: ....
    - ☐ Ingen

17. Har ni en planerad uppföljning med anledning av barnets urinvägsreflux? (Ni kallas för kontroll regelbundet)
    - ☐ Ja
    - ☐ Nej

18. Har ni en fast vårdkontakt? (Ni vet var ni ska vända er om ni har frågor, behöver recept eller om ert barn blir sjukt)
    - ☐ Nej
    - ☐ Ja

      Om ja, var någonstans?..

5

Frågor om förälder/vårdnadshavare och barn

Kodnummer....

19. Vilka läkemedel använder Ditt barn idag?

Preparat (namn)	Används ibland (vid behov)	Används regelbundet
1.	☐	☐
2.	☐	☐
3.	☐	☐
4.	☐	☐
5.	☐	☐

20. Om Ni kunde skruva tillbaka tiden – skulle Ni ha föredragit någon annan behandling, av Ert barns urinvägsreflux, än den Ert barn fick?

....

....

....

....

....

....

Information om barnomsorg

21. Vistas barnet idag dagtid i förskola eller motsvarande?

JA ☐   NEJ ☐

22. Hur ofta behöver Ditt barn stanna hemma från förskolan?

Utgå i svaren från det senaste året

☐ Flera gånger varje månad

☐ 1 gång varje månad

☐ 3-5 gånger varje halvår

☐ 3-5 gånger varje år

☐ 1 gång varje år

☐ Har ej frånvaro

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Frågor om förälder/vårdnadshavare och barn   Kodnummer....

23. Om Ditt barn behöver stanna hemma, vilka är orsakerna till barnets frånvaro?

Orsak till frånvaro i förskolan
1.
2.
3.
4.
5.

Avslutande fråga

Beskriv med egna ord. Finns det något som vi glömt att fråga, som berör barnets, förälderns eller familjens situation och som Du skulle vilja tillägga?

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