

# Vesicoureteral reflux: surgery versus medical treatment

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## Abstract

Vesicoureteral reflux is most often diagnosed after febrile urinary tract infection during childhood or at follow-up after a prenatal ultrasound showing dilated upper urinary tracts. The goal of any medical or surgical treatment is to prevent urinary tract infection, which can result in acquired renal damage and in the long run hypertension and chronic renal failure.

The condition is heterogeneous and is usually regarded as a congenital urinary abnormality, but may just as well occur due to a functional or neurogenic bladder dysfunction. The grade of reflux and the grade of congenital renal damage varies.

The treatment options are surveillance with prompt treatment of febrile urinary tract infection, low dosage antibiotic prophylaxis and different surgical methods to cure the reflux.

Despite grade of reflux the spontaneous resolution rate is high, which makes conservative treatment safe if no complications occur. Asymptomatic children with low-grade reflux need no further follow-up or treatment, but in grade 3–5 reflux, there is no consensus yet about which treatment is the best. The treatment should be designed individually for every patient depending on age, sex, grade of reflux, dilatation of the urinary tract, recurrent UTI and microbial resistance, compliance to treatment, bladder dysfunction and type of renal damage.

## Summary of recommendations

Strategy of treatment depends on age of the child, sex, grade of reflux, co-existing obstruction, recurrent pyelonephritis, bladder dysfunction and renal damage.

The treatment aims to:

- Prevent urinary tract infections
- Prevent progressive renal damage
- Minimize complications or harms from unnecessary treatment

Recommendations:

1. Due to high spontaneous reflux resolution rate of all grades of reflux, most children should be treated conservatively, if no complications occurs (GoR A)
2. Asymptomatic children with reflux grade 1–2 need no further follow-up or treatment (GoR A).
3. Children with reflux grade 3–5 are recommended antibacterial prophylaxis, boys during the first year of life, girls until potty-trained (GoR A).
4. When using antibacterial prophylaxis, side effects and development of bacterial resistance must be taken in consideration (GoR A).
5. Diagnosis and treatment of urinary tract infection must be treated promptly and effectively taking into account that children with VUR more often have infection caused by non-*E. coli* than children with uncomplicated UTI's (GoR B).
6. Bladder and bowel dysfunction increases the risk of recurrent UTI and should probably be treated (GoR B).
7. Circumcision can be considered in predisposed young boys (GoR C).
8. Surgical correction of reflux with endoscopic treatment or open surgery including mini-invasive techniques could be used if recurrent UTI and/or progressive renal damage. It has been shown to reduce incidence of pyelonephritis and may have a modest beneficial effect on reducing the incidence of acquired renal scarring (GoR A).
9. There is no surgical treatment that is superior to any others when it comes to prevention of recurrent UTI and progression of renal damage (GoR C).

## Introduction

Vesicoureteral reflux (VUR) is the pathological retrograde backflow of urine through an incompetent vesicoureteric junction. Normally the oblique entrance of the ureter through the detrusor muscle and the mucosa of the bladder wall creates a valve-mechanism preventing retrograde flow of urine from the bladder to the upper urinary tract. This mechanism can be altered either by a congenital anomaly at the formation of the ureteric orifice or caused by functional or neurogenic bladder-dysfunction. The prevalence of VUR is about 1% in children and it is found in 25–30% investigated after urinary tract infection (UTI) [1], [2]. VUR is diagnosed through voiding cystourethrography (VCU) and is graded 1–5 depending on the severity of ureteral and renal pelvis dilatation [3].

## *VUR and UTI*

VUR does no harm to the kidney per se if the urine is sterile, but it increases the risk of bacterial contamination to the renal pelvis, which could lead to pyelonephritis and renal scarring [4]. Recurrent pyelonephritis should be treated promptly to avoid progress of renal damage [5], [6], which can lead to impaired glomerular function, hypertension and in some cases even end stage chronic kidney disease (CKD) [7], [8], [9], [10]. The main goal in the treatment of VUR is to prevent repeated UTI's and to minimize the risk of acquired renal damage. The risk of recurrent febrile UTI (fUTI) in VUR patients is multifactorial and variables increasing the risk are high-grade (dilated) VUR, bladder and bowel dysfunction, history of prior fUTI, renal damage, male sex during infancy and female sex after the first year of life [10], [11]. In some recent publications computerised models for predicting fUTI in children with primary VUR are presented using multiple variables of the above mentioned for risk grading in the individual patient with accuracy of about 75% [12], [13]. Children with congenital urinary abnormalities more often have infections with non-*E.coli* than other children with UTI [14], [15], which must be taken into considerations when choosing treatment.

## ***VUR and renal damage***

Besides the risk of renal scarring from pyelonephritis, most often seen as defects in the renal contour apically or caudally, high-grade VUR (4–5) is also associated with a congenital renal abnormality shown as a small kidney with generalised poor uptake and/or lowered differential renal function (DRF) seen in technetium DMSA scans [16], [17], [18]. This defect probably represents poor development during gestation (dysplasia or hypoplasia) rather than a consequence of UTI. The risk of renal damage, both acquired (focal) and congenital (generalised) increases with increasing grade of VUR [10].

## ***VUR and lower urinary tract dysfunction (LUTD)***

Many children with high-grade VUR have lower urinary tract dysfunction with a large bladder capacity and increased post void residual (PVR) or overactive bladder (OAB) with symptoms of bladder instability and infrequent voiding and/or constipation [11], [19]. Lower urinary tract dysfunction and renal damage are both risk factors for recurrent UTI, especially in children with VUR [11], [20], [21]. Evaluation of bladder and bowel function through bowel and micturition diary, measurements of flow and post void residual (PVR) is therefore of great importance in the management of children with VUR. Lower urinary tract dysfunction in VUR patients is also associated with less probability of spontaneous resolution of reflux [17], [22], [23].

## ***Special concerns regarding VUR in girls versus boys and younger versus older children***

Generally VUR is more common in girls than in boys with a ratio of 4:1 in children older than 1 year [24]. In infants diagnosed with VUR <1 year of age on the other hand, there is a clear predominance of males where high-grade VUR is often accompanied by congenital renal dysplasia [16], [25]. These infants with high-grade VUR often develop lower urinary tract dysfunction characterized by large capacity bladder with high post void residual (PVR). The risk of recurrent febrile UTI (FUTI) is highest during infancy, especially in boys with declining number of infections after the infant year [26]. Girls with VUR seem to have a continuous risk of new infections even after potty training [27], [28]. Prompt treatment of febrile UTI is considered especially warranted in infants, since the kidneys in children less than two years of age are more prone to renal scarring secondary to ascending infections [29], [30].

## ***VUR and spontaneous resolution***

Spontaneous resolution of VUR over time is seen in 30–50% of children with dilated reflux (grade 3–5) and the resolution rate in undilated reflux (grade 1–2) is up to 80% within 4–5 years of follow-up [31], [32]. Spontaneous resolution is also depending on age, sex (higher in boys during the infant year), uni or bilaterality of VUR, lower urinary tract dysfunction (LUTD), and prevalence of renal damage at diagnosis [17], [23], [31]. Therefore individualized risk evaluation must be made in each patient before choosing optimal treatment.

The optimal treatment of VUR in children is constantly re-evaluated in the dialogue between paediatricians and paediatric urologists. Even though the subject has been the topic of hundreds of publications during the last decades, still the grade of evidence for different treatment options of medical or surgical intervention with the overall aim of making a difference in preserving renal function in a long-term perspective is surprisingly low.

## Methods

A systematic literature search was performed, with end date March 2016, in PubMed and Cochrane databases with the following key words (VUR OR vesicoureteral reflux OR vesicoureteral reflux) AND (treatment OR therapy OR surgery) and the following limitations (filters) Randomized Controlled Trial; Systematic Reviews; Meta-Analysis, English abstract available, only peer reviewed.

A total of 264 publications were identified, which were screened by title and abstract. After exclusion of duplicates, irrelevant or too old publications a total of 43 were included into the review (analysis), supplemented by 2 studies known to the authors published after March 2016.

The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) using ICUD standards (for details see Preface).

## Results

### *Conservative treatments*

#### **Antibiotic prophylaxis (CAP) or surveillance**

For a long time antibiotic prophylaxis has been a standard initial management in children with all grades of VUR. This is questioned today, both because of that new studies have shown that the effectiveness of CAP is doubtful and because of fear of the raising antimicrobial resistance. The poor compliance to treatment, estimated to be only 40% will lower the effectiveness and that must also be taken into consideration [33].

For low grade or asymptomatic reflux there is low or no evidence today that CAP will prevent UTI or renal damage [34], [35], [36], [37], [38], [39], [40] (LoE 1a) but if the child presents with dilating reflux or a history of recurrent UTI's there are studies that have shown that prophylaxis is superior to surveillance concerning prevention of UTI [34], [41], [42], [43] (LoE 1b). In contrast to this, the American RIVUR study showed that CAP reduced the risk for UTI regardless of reflux grade (grade 2–4) [44], which made authors of recent meta-analyses to recommend prophylaxis to children with all grades of reflux [45], [46]. It is shown that CAP increases the risk of infection due to antibiotic resistant bacteria [46], [47] (LoE 1a). In the Swedish reflux study, where 1 year old children with persisting grade 3–4 VUR were randomized to surveillance, CAP or endoscopic treatment and followed for 2 years there was a significant difference between girls and boys, with a higher risk of UTI for girls without prophylaxis. These results led to the recommendation to stop CAP at 1 year of age in boys and continued prophylactic treatment in girls until potty-trained [41].

The evidence for CAP to prevent renal scarring is minimal according to several Cochrane reports [47], [48], [49] (LoE 1a). A study that has been able to show a significant higher risk to develop renal scarring without treatment, was the Swedish reflux study [50]. Furthermore, in a Cochrane report from 2011 [47] it was stated that 33 children would need long-term antibiotic prophylaxis to prevent one more child developing kidney damage over the course of 2–3 years.

Randomised controlled studies evaluating antibiotic prophylaxis versus surveillance in VUR children is summarised in Table 1.

Table 1: Randomised controlled trials evaluating outcome of medical treatment versus surveillance of VUR in children

Author, year	Study size (N=)	Patient age (years)	VUR grade	Intervention and Objectives	Results
Craig et al., 2002 [40]	46	<3 months	1–5	Low dose antibiotic prophylaxis versus placebo in infants with VUR diagnosed after antenatal hydronephrosis or heredity  Primary objective reduction of UTI and prevention of new renal damage	Antibiotic prophylaxis to asymptomatic VUR infants did not significantly reduce the frequency of UTI or new renal damage during the first 3 years of life.
Garin et al., 2006 [36]	236 (113 VUR patients)	<18	0–3	Antibiotic prophylaxis versus surveillance in children diagnosed with acute pyelonephritis  Primary objectives to evaluate the role of VUR in the risk for UTI. Evaluating reduction of UTI and prevention of new renal damage with antibiotic prophylaxis	Mild/moderate VUR does not increase the risk for UTI, pyelonephritis or renal scarring in children after UTI.  Antibiotic prophylaxis does not reduce the risk for UTI, pyelonephritis or renal scarring after 1 year follow-up
Montini et al. (PREDICT), 2008 [37]	338 (128 VUR patients)	<7	0–3	Antibiotic prophylaxis versus surveillance in children after a first febrile UTI  Primary objective reduction of UTI. Secondary objective reduction of new renal damage	Antibiotic prophylaxis does not reduce the rate of febrile urinary tract infections. No difference in renal outcome between treatment groups.
Pennesi et al., 2008 [39]	100	<3	2–4	Antibiotic prophylaxis versus surveillance in VUR children after a first acute pyelonephritis  Primary objectives reduction of UTI and prevention of new renal damage	No difference in pyelonephritic episodes or new renal damage between treatment groups after 2 years of follow-up
Rossey-Kesler et al., 2008 [35]	225	<3	1–3	Antibiotic prophylaxis versus surveillance in young children with low grade VUR  Primary objective reduction of UTI	No difference in occurrence of UTI between treatment groups overall, but antibiotic prophylaxis significantly reduced UTI in boys with grade 3 VUR after 18 months follow-up.

Author, year	Study size (N=)	Patient age (years)	VUR grade	Intervention and Objectives	Results
PRIVENT Craig et al., 2009 [42]	576 (243 VUR patients)	<18	0–5	Low dose antibiotic prophylaxis versus surveillance in predisposed children  Primary objective reduction of UTI	Low dose antibiotic treatment decreases the number of UTI in predisposed children
The Swedish reflux trial in children, Brandström et al., 2010 [41], [50]	203	1–2	3–4	Three armed study evaluating surveillance versus antibiotic prophylaxis versus endoscopic treatment in young children with VUR  Primary objectives reduction of UTI , prevention of new renal damage (and resolution of VUR)	Antibiotic prophylaxis and endoscopic treatment both reduced the number of UTI in girls compared to surveillance and prophylaxis reduced the frequency of new renal damage in girls.  No difference between active treatment and surveillance in boys.
Hari et al., 2014 [38]	93	1–12	1–2, 3–4	Antibiotic prophylaxis versus placebo in children with VUR and UTI  Primary objectives reduction of UTI and prevention of new renal damage	Long-term antibiotic prophylaxis is associated with increased risk of UTI and increased risk of infections with resistant bacteria's  No difference in new renal damage after 1 year follow-up.
RIVUR, Hoberman et al., 2014 [44]	697	0.5–3	1–2, 3–4	Antibiotic prophylaxis versus placebo in children with VUR after first UTI.  Primary objectives prevention of UTI and prevention of new renal damage	Antibiotic prophylaxis reduces the risk of UTI but no difference between treatment groups in new renal damage.

## Probiotics

The use of probiotics has been suggested to reduce the number of UTI in children with VUR, but in a RCT where probiotics was compared to CAP no treatment was superior to the other [51] (LoE 1b).

## **Bladder/bowel dysfunction (BBD)**

Treatment of BBD is considered to be an important factor in the care of children with VUR. Even though identified as a risk factor for persistent reflux and recurrent UTI in several observational studies, there are few RCT and meta analyses that has been able to show a general or specific urotherapeutic treatment that reduces the risk for UTI and renal scars [34] in a pediatric VUR population (LoE 1b). Sillén initiated clean intermittent catheterization (CIC) in a small cohort of VUR patients with recurrent fUTI and bladder dysfunction and found no effect on spontaneous resolution of VUR [52]. In two studies evaluating treatment of bladder dysfunction in VUR patients they found no evidence of advantages of anticholinergic therapy on UTI recurrences [21] or reflux resolution [53]. In one study treatment with alfa blockers in children with BBD resulted in reflux down-grading, but effect on UTI and renal scars were not shown [54].

## **Circumcision**

To reduce number of UTI in children with VUR, circumcision in infant boys is an option, even if there is scarce with evidence (LoE 3). In a study from Turkey it was shown that circumcision decreases colonization of periurethral bacterial pathogenic flora and circumcision plus CAP reduces risk of UTI in boys with low-grade VUR [55].

## ***Surgical treatments***

### **Open surgery**

If reflux resolution is the main goal, it is well known that open surgical procedure with reimplantation of the ureter have good results with abolishing of reflux grade 1–4 in >97% and in grade 5 in >80% [56], [57], [58], [59], [60], [61]. This is to be compared with spontaneous disappearance of the reflux with resolution rates of 30–50% (LoE 1a). In the International Reflux study it was shown that surgery was superior to medical treatment concerning recurrent pyelonephritis but there was no difference in renal outcome, even in long-term follow up of 10 years [29], [62], [63], [64], [65]. The same results were found in another study comparing open surgery to CAP in VUR children [66]. This was shown to be true even in severe bilateral disease [67]. Still it must be considered that open surgery needs a long hospital stay and is a stressful event for the child and family.

### **Endoscopic treatments (ET)**

Endoscopic treatment is today a well established method and meta analyses has shown that ET abolish or down grade the reflux on average in 77% of ureters injected [68] (LoE 1a). This seems to be independently of type of bulking material [69], [70], [71] and perhaps the results could be improved by the injection technique used [72]. The results also depend on the grade of reflux, with lower efficiency in grade 5 and bilateral reflux [60], [73], [74]. This is shown in the Swedish infant high-grade reflux study with 100% success rate in unilateral grade 4 to 30% in bilateral grade 5 [75]. The study shows that it is also doable with ET in infants. In infants, it must be taken into consideration that high grade reflux is often a complex malformation with bladder dysfunction and/or vesicoureteral obstruction, making ET less suitable and patient selection important. ET is more efficient than surveillance and prophylaxis in reflux resolution but a concern is the recurrence rate of about 20% after 2 year follow-up [76], [77].

Looking at the effect on frequency of UTI and renal damage the ET results are comparable to open surgery.

## Minimal invasive methods

Minimal invasive anti-reflux techniques including laparoscopic and robotic assisted surgery are increasing in popularity but there are no randomized studies available supporting the superiority versus other surgical methods (LoE 4). We found one case control study comparing miniureteroneocystostomy to ET presenting greater success of this minimal invasive technique in VUR outcome [78].

Randomised controlled trials comparing surgical intervention with antibiotic prophylaxis are summarized in Table 2.

Extracted Table: Table 2

## Conclusion

Vesicoureteral reflux is a complex topic, and a risk-oriented therapy should account for this complexity. Symptomatic high-grade reflux with recurrent UTI needs therapy, but there is no difference in outcome concerning number of pyelonephritis and acquired renal scars if the child is put on antibiotic prophylaxis or endoscopic treatment or open surgery. In the decision making you must take into account the drawbacks with CAP with compliance to treatment, side effects of the medicine and antimicrobial resistance. On the other hand all operative management needs anesthesia and expensive hospital care. ET is a simpler method but the result concerning reflux resolution is inferior to open surgery.

Conservative treatment also includes treatment of bowel and bladder dysfunction. It is known that BBD is a risk factor for UTI and renal cortical scarring. Reflux resolution and endoscopic surgical success rate is also dependent on BBD. Still, it is hard to prove that general or specific treatments of the dysfunction will change renal outcome or frequency of UTI.

There is minimal evidence in the literature that any treatment of low-grade reflux will reduce number of UTI and renal damage.

Both in Europe and in America guidelines on vesicoureteral reflux are established. In 2012 the EAU guidelines on Vesicoureteral reflux was published [81]. AUA organised in 2005 the Vesicoureteral Reflux Guideline Update Committee and a summary of the work was published in 2010 [34]. The guidelines have in common that the management is based on the goals of minimizing the risk of acute infection and renal injury, while minimizing the morbidity of investigations and management and avoid overtreatment. In the guidelines the management is dependent on age, sex, BBD, UTI and reflux grade and is summarised by Routh et al. in a publication from 2012 (Table 3) [60].

Extracted Table: Table 3

## Further research

Generally when it comes to management of VUR there are few randomised controlled trials comparing different treatment strategies. In recent years there are numerous publications comparing the outcome of VUR resolution with different endoscopic techniques or bulking agents but there are very few with the aim of identifying risk patients for progressive renal damage or interventions that actually means a difference in long-time renal outcome.

Moreover both RCT and observational studies merge cohorts with different ages, different grades of reflux and other risk factors such as LUTD and renal damage. Conclusions about the optimal individualized treatment for each patient can therefore seldom be made. Bladder dysfunction increases the risk of UTI, renal damage and persistence of VUR but very few controlled studies evaluate the role of targeted treatment towards LUTD in VUR patients.

We call for randomised controlled studies with patient stratification that takes into account more risk factors than the primary VUR and with a primary objective significantly reducing the risk of UTI or even more specific saving renal function.

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