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REVIEW ARTICLE

# The Swedish reflux trial: Review of a randomized, controlled trial in children with dilating vesicoureteral reflux

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## KEYWORDS

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**Abstract** *Objectives:* To evaluate prophylaxis and endoscopic injection for children with dilating vesicoureteral reflux (VUR) compared to surveillance, regarding urinary tract infection (UTI) recurrence, new renal damage, VUR outcome, and impact of lower urinary tract (LUT) dysfunction on these outcomes.

*Patients and methods:* 203 children (128 girls and 75 boys), aged 1 to <2 years, with VUR grade III or IV were randomized to antibiotic prophylaxis ( $n = 69$ ), endoscopic injection ( $n = 66$ ) or surveillance ( $n = 68$ ). Voiding cystourethrography, dimercaptosuccinic acid scintigraphy and optional LUT function assessment were performed before randomization and after 2 years.

*Results:* There were 67 febrile UTIs in 42 girls and 8 in 7 boys ( $p = 0.0001$ ). In girls, recurrence rate was 19% on prophylaxis, 23% with endoscopic treatment and 57% on surveillance ( $p = 0.0002$ ). In boys, there was no difference between treatment groups. New damage was seen in 13 girls: 8 on surveillance, 5 in the endoscopic group and none on prophylaxis ( $p = 0.0155$ ), and in 2 boys. In 13 children with no or non-dilating VUR after 1 injection, dilating VUR reappeared at the 2-year follow up. LUT dysfunction at follow up was associated with persistence of VUR.

*Conclusion:* In girls, prophylaxis reduced the rate of UTI recurrence and new renal damage, and endoscopic injection the rate of UTI recurrence. Boys did not benefit from active treatment.

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## Introduction

Vesicoureteral reflux (VUR) in children became a hot subject in the 1950s when voiding cystourethrography (VCU) was more frequently used. In the classical publication of Hodson and Edwards a strong relationship was demonstrated between VUR and 'chronic pyelonephritis' as seen on intravenous urography [1]. It became natural to operate in the case of VUR to prevent development and progression of renal damage, and different surgical techniques were described. It was soon evident that spontaneous resolution of VUR was not unusual, and low-dose antibiotic prophylaxis was introduced as a medical alternative to the surgical approach. However, trials using random allocation to these two treatment options did not show a difference in long-term renal outcome [2,3].

For a long time it was assumed that VUR was a crucial factor in the development of renal damage and the term reflux nephropathy was proposed [4]. As DMSA scintigraphy was introduced, a more sensitive technique to show renal damage, it became clear that VUR was not a prerequisite for damage [5]. Also, the effect of prophylaxis in preventing urinary tract infection (UTI) had not been tested in studies using untreated controls [6].

With the two traditional strategies, antibiotic prophylaxis and reflux surgery, being challenged, the need for randomized studies using untreated controls was evident. On the initiative of Jan Winberg, a Swedish conference on the management of children with UTI was organized [7]. The basis of the new recommended guidelines was a critical review of the literature as well as clinical experience since several issues had not been adequately studied. The aim was to design guidelines that limited renal damage and future complications with minimal discomfort to the child. The new strategy, published in 1999, focused on renal development and function rather than on VUR, a shorter time on antibiotic prophylaxis, and increased attention to lower urinary tract (LUT) dysfunction [8]. Thus, children with febrile UTI who were 2 years of age or older were not recommended for routine VCU, and children with grade I–II VUR would not be followed further unless there was evidence of renal damage.

The new guidelines called for a national study in small children with dilating VUR. The use of antibiotic prophylaxis to reduce the rate of UTI recurrence needed to be tested against an untreated control group. Also, the newly introduced endoscopic subureteric injection of a bulking agent as an alternative to open surgery was promising but had not been challenged in a randomized trial using untreated controls to study recurrent UTI and development of renal damage. Consequently, the Swedish Reflux Trial was set up with random allocation to three treatment alternatives: antibiotic prophylaxis, endoscopic subureteric injection and a control group on close surveillance [9]. The study aim was to compare the rates of febrile UTI, new kidney damage and reflux status after 2 years. Secondary outcomes were complications, and the impact of factors such as VUR grade, gender and LUT dysfunction. Results of the trial were recently published and this review summarizes the highlights of the study [9–13].

## Study design

Two hundred and three patients, 1 to less than 2 years old and with VUR grade III or IV on VCU, were included in this multicenter randomized controlled study; there were 128 girls and 75 boys from 23 pediatric centers. In 194 children the diagnosis of VUR followed one or several UTIs while in 9 it followed the detection of antenatal hydronephrosis. In 135 dilating VUR was found before 1 year of age; they were started on prophylaxis and reinvestigation within a year showed persisting dilating VUR.

DMSA scintigraphy was done before randomization with assessment of focal or generalized renal uptake defects. Abnormal DMSA scintigraphy at entry was seen in 124 children (61%) with bilateral uptake defects in 18 (15%). An optional LUT function assessment was performed in 148 children at entry with a 4-h voiding observation, and in 161 children at follow up with flowmetry, residual urine measured with ultrasound and a structured questionnaire.

Children were randomly assigned to prophylaxis, endoscopic treatment or surveillance. For prophylaxis trimethoprim was the first choice. In the endoscopic group injection was performed with dextranomer/hyaluronic acid copolymer (Deflux<sup>®</sup>, Q-med, Uppsala, Sweden) at one of six regional centers for pediatric surgery. In the case of remaining dilating VUR the child had a second or third injection. The randomization results and adherence to the protocol are outlined in a flow chart (Fig. 1). Follow up was scheduled for 2 years, and study outcomes were febrile UTI recurrence, new renal damage appearing during the 2-year period, and reflux status at study end. All calculations were done according to the intent-to-treat principle.

## Summary of results

### Febrile urinary tract infections [11]

There were more febrile UTI recurrences in girls than in boys (Table 1). In girls there were more and earlier recurrences in the surveillance group (Fig. 2A). In boys there were few recurrences with no differences between treatment groups (Fig. 2B). The rate of febrile recurrence was not related to VUR grade or renal damage on DMSA scan at entry. There was, however, an association between higher VUR grade at 2 years and recurrence rate in girls. A post hoc analysis with Cox proportional hazards is presented in Table 2.

### New renal damage [12]

New renal damage was seen in 2 boys and 13 girls: no girl in the prophylaxis, 5 in the endoscopic, and 8 in the surveillance group ( $p = 0.0155$ , Fig. 3). New damage was more common in the children with febrile UTI recurrence. There was no association between new renal damage and LUT dysfunction at entry or follow up. However, at post hoc analysis we found no case of new renal damage in a selected group of 56 children with normal LUT function both at entry and follow up. On analysis of individual kidneys, new damage occurred only in kidneys drained by

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