

The Swedish Reflux Trial

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av

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Fakultetsopponent:
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Avhandlingen baseras på följande arbeten:

- I. **Brandström P, Esbjörner E, Herthelius M, Holmdahl G, Läckgren G, Nevéus T, Sillén U, Sixt R, Sjöberg I, Stokland E, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: I. Study Design and Study Population Characteristics
J Urol 2010; 184: 274-9.
- II. **Holmdahl G, Brandström P, Läckgren G, Sillén U, Stokland E, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: II. Vesicoureteral Reflux Outcome
J Urol 2010; 184: 280-5.
- III. **Brandström P, Esbjörner E, Herthelius M, Swerkersson S, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: III. Urinary Tract Infection Pattern
J Urol 2010; 184: 286-91.
- IV. **Brandström P, Nevéus T, Sixt R, Stokland E, Jodal U and Hansson S**
The Swedish Reflux Trial in Children: IV. Renal Damage
J Urol 2010; 184: 292-7.



The Swedish Reflux Trial

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

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

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

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

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