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The Swedish Infant High-grade Reflux Trial — Bladder function

J. Nordenström [a], U. Sillen [a], G. Holmdahl [a], T. Linnér [b], E. Stokland [c], S. Sjöström [a]

[a]Department of Pediatric Surgery, The Pediatric Uronephrologic Centre, The Queen Silvia Children's Hospital, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

[b]Pediatric Clinical Physiology, The Pediatric Uronephrologic Centre, The Queen Silvia Children's Hospital, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

[c]Pediatric Radiology, The Paediatric Uronephrologic Centre, The Queen Silvia Children's Hospital, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Correspondence to: U. Sillen, Pediatric Uronephrologic Centre, The Queen Silvia Children's Hospital, SE-416 85 Gothenburg, Sweden, Tel.: +46 313434658

ulla.sillen@vgregion.se (U. Sillen)

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Summary

Introduction
It has been suggested that infants with high-grade vesicoureteral reflux (VUR) have lower urinary tract dysfunction (LUTD) that is characterised by large bladder capacity (BC) and increased post-void residual (PVR). However, most of these infants have normal or small BC in early infancy and develop large capacity during the first year of life.

Objective
This study aimed to see whether LUTD development during the infant years in children with high-grade VUR could be prevented by early reflux resolution.

Materials and methods
For early VUR intervention, endoscopic treatment (ET) was used in a randomised trial comprising 77 infants (55 boys) aged <8 months with VUR grade 4–5 (n = 30/n = 47); 39 were randomised to antibiotic prophylaxis and 38 to ET. Voiding cystourethrogram, free voiding observation (FVO) and renal scintigraphy were performed at baseline and after 1 year. Bladder capacity and PVR were obtained from FVO. LUTD was defined as a BC of ≥150% of expected and a PVR of ≥20 ml.

Results
There were no differences in bladder function variables seen between the treatment groups, despite significant differences in VUR resolution. Analysing bladder function related to VUR outcome (VUR grade ≤2 vs grade >2), independent of treatment, showed that VUR grade ≤2 was associated with a smaller BC at 1 year ($P = 0.050$) (a tendency already seen at baseline) and a lower PVR at baseline ($P = 0.010$). PVR increased from baseline to 1 year ($P = 0.037$) in children with grade ≤2 VUR (Summary Table).

The group with persistent bilateral grade 5 VUR at 1 year had more abnormal bladder variables compared with other study subjects, with a tendency of larger BC ($P = 0.057$), higher PVR ($P = 0.0073$) and more LUTD ($P = 0.029$) at baseline and a larger BC at 1 year ($P = 0.016$).

In explanatory analyses, using logistic regression, a high PVR at baseline was identified as a predictor of VUR grade >2 ($P = 0.046$), persistent bilateral grade 5 VUR ($P = 0.022$), recurrent urinary tract infection ($P = 0.034$), and only a tendency was seen regarding new renal damage ($P = 0.053$).

Conclusion
There was no between-group difference seen in bladder function. In children with VUR resolution at follow-up, independent of treatment, BC decreased, whereas PVR increased. High PVR at baseline was a predictive factor for both non-resolution of high-grade VUR and recurrent urinary tract infection. The results suggest that LUTD cannot be prevented by early VUR resolution, but rather is an important prognostic factor for VUR outcome in both endoscopic and prophylactic treatment.

Summary Table Bladder variables by grade ≤2 vs grade >2 VUR at 1-year follow-up.

Variable	Total (n = 74)	Within-group *P*-value	Grade ≤2 VUR at 1 year (n = 29)	Grade >2 VUR at 1 year (n = 45)	Between-group *P*-value
Bladder capacity (%)					
• Baseline	126 (49–466)		120 (49–283)	138 (65–466)	0.14
• 1 year	113 (3–296)	0.075	90 (31–194)	121 (30–296)	**0.050**
• Large (≥150%) baseline	28 (41%)		7 (27%)	21 (49%)	0.12
• Large (≥150%) 1 year	22 (33%)		7 (26%)	15 (39%)	0.43
Residual urine (ml)					
• Baseline	9 (0–83)		6 (0–55)	11 (1–83)	**0.010**
• 1 year	14 (0–108)	**0.025**	9 (0–84)	16 (0–108)	0.41
Lower urinary tract dysfunction					
• Baseline	17 (24%)		3 (12%)	14 (33%)	0.087
• 1-year follow-up	18 (27%)		6 (22%)	12 (31%)	0.63

Continuous variables: median (minimum–maximum), categorical variables: n (%).

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Introduction

Lower urinary tract dysfunction (LUTD) in infants with high-grade VUR was described in studies published in the early 1990s [1–3]. Characteristics of the dysfunction were suggested from urodynamic studies showing detrusor overactivity during filling, low bladder capacity, high voiding pressure levels, and dyscoordination at voiding. However, some years later, most of these signs were also found in urodynamic studies of healthy infants, and could therefore not be interpreted as signs of LUTD [4,5]. Instead, the opposite bladder characteristics (i.e. large bladder and incomplete emptying) were shown in a longitudinal follow-up of infants with high-grade VUR [6]. About half of the infants changed their bladder pattern to large capacity at the 1-year follow-up, but there were also a small percentage of infants (about 20%) who already had a large bladder from early infancy. This LUTD pattern with a large-capacity bladder and incomplete emptying was already demonstrated in 1987 by Griffiths and Scholtmeijer in children aged 1–3 years with high-grade VUR, and was interpreted as being caused by dyscoordination between the detrusor and sphincter [7].

The question from the above findings was whether the increase in bladder capacity during infant years in children with high-grade VUR was induced by the extra load of refluxing urine volume or whether it was a part of the congenital abnormality. To address this, the present study explored whether an early reflux intervention could prevent increase in bladder capacity. This was one of the aims of the Swedish Infant High-grade Reflux Trial. Another aim was to see whether residual urine decreased with early reflux resolution, which would indicate that residual urine mainly consists of reflux urine in infants with high-grade VUR.

For the early treatment of VUR, endoscopic treatment (ET) with dextranomer/hyaluronic acid copolymer (Dx/HA) was used in this randomised study, with two allocation alternatives: prophylaxis or ET. Bladder function was investigated before treatment and at the 1-year follow-up. A comparison of bladder outcome was made between the two treatment groups and between groups with early VUR resolution vs non-resolution, irrespective of treatment.

Material and methods

Study design

In this randomised, controlled, multicentre trial, 77 infants (55 boys) aged <8 months and with grade 4–5 VUR were included. A VCUG and urinary tract ultrasound (US) were performed at presentation. Before inclusion, renal scintigraphy (DMSA and/or MAG-3) and clearance studies were performed. After inclusion, bladder function was evaluated with 4-hour free voiding observation (FVO) and, in the children examined at the study co-ordination centre, with the addition of videocystometry (VCM).

The study subjects were randomised either to ET or to continuous antibiotic prophylaxis (CAP). The children who received ET were investigated with US and VCUG 2 months after the treatment. If grade >2 VUR persisted, a second injection was performed. Recurrent UTIs were registered during the study. A follow-up was performed 1 year after inclusion, with VCUG (or VCM), a renal scan, clearance studies and FVO. For details of the study design, see Nordenström et al. [8].

Patients and methods

A total of 39 infants were randomised to CAP and 38 to ET (Dx/HA copolymer). The mean age at inclusion was 6.7 months. For baseline demographic variables, see Table 1. All the children were prescribed antibiotic prophylaxis at diagnosis.

Bladder function was evaluated by FVO [9]. The number of voids, voided volume, post-void residual urine (PVR), and bladder capacity (largest sum of voided and residual volume) were recorded and analysed during a 4-hour period. PVR was assessed using US and voided volume by weighing the diaper. For description of the method see Jansson et al. [10]. PVR was given as the mean residual during the 4 h. The limits for abnormal values in the FVO were taken from earlier longitudinal FVO investigations of bladder function in healthy children and the International Children's Continence Society (ICCS) standardisation document [10,11]. All BC values were presented in % of expected for age, according to the formula (30 + 2.5 x age in months) ml. This allowed between-age comparison in the growing infant. Abnormal values were PVR of ≥20 ml and BC ≥150% of expected for age. Lower urinary tract dysfunction (LUTD) was defined as both elevated PVR (≥20 ml) and a large BC (≥150% of expected).

The BC and PVR values in this study were derived from the FVO investigations. VCM, a technique available only at the study centre, was performed in 21 children at inclusion and in 25 at the 1-year follow-up. From the VCM studies, information relating to true post-void residual and volume of refluxing urine was collected. VCM has previously been described in detail [6].

Statistical methods

Statistical analyses were performed according to a statistical analyses plan (SAP).

Table 1 Study population demographics.

Variable	Total (n = 77)
Sex	
Females	22 (29%)
Males	55 (71%)
Age at presentation (months)	1.6 (0–7)
Age at randomisation (months)	6.7 (4–9)
Presentation	
- UTI	55 (71%)
- Antenatal dilatation	21 (27%)
- Hereditary	1 (1%)
Grade of VUR at baseline	
4	30 (39%)
5	47 (61%)
Bilateral VUR	52 (68%)
Duplex	12 (16%)

Continuous variables: mean (minimum–maximum), categorical variables: n (%).