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What is the risk of urinary tract infection in children with antenatally presenting dilating vesico-ureteric reflux?

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Summary

Introduction
The incidence of recurrent urinary tract infection (UTI) in children with primary vesico-ureteric reflux (VUR) presenting symptomatically is well documented. The risk of UTI in asymptomatic primary VUR diagnosed on investigation of antenatal hydronephrosis (ANH) is less clear. Paradoxically, several previous studies have suggested a lower risk (1–25%). We ascertain the incidence of UTI amongst antenatally-presenting primary VUR and explore risk factors.

Study design
All patients <16 years managed for primary VUR between 1997 and 2013 were retrospectively reviewed. Patients were identified by searching 'VUR, vesicoureteric reflux' and 'vesico' in the clinical database. Sex, follow up, antibiotic prophylaxis, age at UTI, grade of VUR, radioisotope imaging findings (CRN-congenital reflux nephropathy, NRD-new renal defects), evidence of bladder dysfunction, surgical intervention and resolution were recorded. UTI diagnosis was based on positive urine culture with symptoms including fever. SPSS statistical package and Pearson's Chi-squared test were used to explore significance.

Results
Of 308 patients with primary VUR aged <16 years treated, 242 were diagnosed following presentation with UTI. The remaining 66 (21%) were initially asymptomatic, and VUR was diagnosed on investigation of ANH. All were given prophylaxis from birth. Six months to 16years (median 6years) follow-up was available for 54 (42 males, 12 females). All but two patients had grade III-V VUR (96%), bilaterally in 41 (76%). CRN was evident in 30 (56%; all male) and bladder dysfunction in 12 (22%; 10 males). Twenty-eight patients (52%) developed a UTI. The risk of UTI was 58% in girls, 33% in boys without CRN and 57% in boys with CRN ($p = 0.17$). Bladder dysfunction was a significant risk factor for UTI ($p = 0.03$). All 8 (15%; 7 males) with NRD had had a UTI. A single UTI appeared responsible for the majority of NRD (6/8; 75%). UTI occurred in 6/27 (22%) boys after circumcision compared to 17/25 (68%) prior/without circumcision ($p < 0.05$).

Conclusions
The incidence of UTI in VUR detected after presentation with ANH was 52%. CRN and bladder dysfunction were risk factors for developing a UTI. Circumcision appears to significantly reduce the risk of infection. Antenatal presentation of primary VUR does not carry a reduced risk of UTI. A single UTI, in half before the age of six months, seemed responsible for the majority of NRD. In boys, the highest risk of UTI is in the first few months of infancy, despite antibiotic prophylaxis, and other interventions, particularly circumcision, should therefore be considered as early as possible.

Table

Males	UTI	No UTI	Total
	21	21	42
Bladder dysfunction	8 (80%)	2	10
No bladder dysfunction	13 (40%)	19	32

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Introduction

Vesico-ureteric reflux (VUR) accounts for 10—15% of those with an antenatal diagnosis of hydronephrosis [1,2]. The risk of recurrent urinary tract infection (UTI) in patients found to have VUR on investigation following a UTI is well documented: 5—24% for grades I—II compared with 23—43% for grades III—V [3—6]. However, the risk of UTI in those diagnosed with VUR after investigation for antenatal hydronephrosis (ANH) is less clear. It has been suggested that children with antenatally presenting VUR have a more benign course [7,8]. It seems paradoxical that antenatally presenting VUR, which is dilating and therefore tends to be of higher grade, should have a lower risk of infection than those with high grade VUR that have presented with a UTI. However, previous studies have suggested that the risk of UTI in antenatally presenting VUR is only 1—25% [9—12]. We aim to ascertain the risk of UTI in our cohort of patients with antenatally presenting VUR and to assess the risk factors associated with the development of a UTI.

Methods

We performed a retrospective review with institutional approval of all patients $\leq$16 years managed for primary VUR between 1997 and 2013. Patients were identified using the search terms 'VUR', vesicoureteric reflux' and 'vesico' in the electronic clinical-document database. This was followed by a detailed review of the case notes. Patients presenting with a UTI with normal antenatal scans were excluded, as were those with secondary VUR or duplex systems. We recorded sex, length of follow-up, antibiotic prophylaxis, age at UTI, grade of VUR, initial and follow-up radioisotope imaging findings, evidence of bladder dysfunction, age at surgical intervention, resolution and new renal defects.

In our institution, ANH is defined as renal pelvic dilatation $\geq$7 mm during the second trimester and $\geq$10 mm in the third trimester of pregnancy and postnatally. Indications for micturating cystourethrogram (MCUG) are bilateral hydronephrosis, hydroureteronephrosis and/or an abnormal bladder. VUR was graded according to the International Reflux Study (low grades I—II and high grades III—V) on MCUG. Congenital reflux nephropathy (CRN) and new renal defect(s) (NRD) were diagnosed on functional imaging (DMSA or MAG3 renography) at least 3 months after any UTI.

Follow-up consisted of regular clinic reviews, serial ultrasounds, periodic non-invasive bladder function assessments (BFA), repeat functional imaging and more invasive BFA as indicated. Non-invasive BFA included frequency volume charts, pre- and post-micturition bladder volumes and flow curves. Bladder dysfunction was based on repeat assessments and several voiding episodes, and a post-void residual was deemed significant if >20% of voided volume. It is our recommendation to repeat functional imaging and indirect cystography once the child is fully potty-trained. However, when a child has remained asymptomatic with stable ultrasound imaging and normal non-invasive bladder function assessments, we do not insist on this.

On detection of VUR on postnatal investigation, families are counselled as to the risk of UTI and commenced on prophylaxis, which is discontinued once the child is fully potty-trained. Patients were deemed to have had a UTI based on a positive culture (growth of 1, occasionally 2, organisms to at least 10^5 CFUs/ml) accompanied by symptoms including fever. At times of symptoms, patients were either seen at our hospital or at their local health service with telephone support from our team as required. We do not have the data for the method of urine sample collection in this retrospective study. Asymptomatic bacteriuria, mixed growths, or isolated lower urinary tract symptoms were not classed as a UTI.

Statistical analysis was performed using SPSS statistical package. The Pearson's Chi-squared test was used to explore significance.

Results

We identified 308 patients with primary VUR aged <16 years treated between 1997 and 2013. Of these, 242 were diagnosed following presentation with UTI. The remaining 66 (21%) were initially asymptomatic, and VUR was diagnosed on investigation for ANH. All patients were given prophylaxis from birth. Twelve were followed up elsewhere. Follow-up of 6 months—16 years (median 6 years) was available for 54 patients (42M, 12F). Twenty-eight patients developed a UTI during the follow-up period (25 while on prophylaxis). None of these UTIs were a complication of an intervention such as MCUG. All but two patients had grade III—V VUR, bilaterally in 41. CRN was diagnosed in 30, on the basis of globally small kidneys on initial functional imaging in 28 and presentation in renal impairment in 2, requiring renal replacement therapy from birth in 1. Six patients had a UTI prior to their initial functional imaging performed at age 3—4 months, demonstrating normal kidneys in 1, a globally small kidney without focal defects in 2, focal defects in 1 (interpreted as NRD) and focal defects on a background of a globally small kidney in 2.

There was a high incidence of UTI during the first 6 months of life, all prior to any intervention. There was a further peak at 2—3 years around the age of potty-training. Twenty-five of the 28 were breakthrough UTIs while on prophylaxis. Surgical interventions were undertaken in 31 (1F, 30M), in 17 (1F, 16M) on the basis of breakthrough UTI. Of note, there was a change in practice over time in view of the feasibility of endoscopic injection in early infancy in more recent years, with an increase in the use of endoscopic injection in patients presenting in the latter years. Bladder dysfunction was explored using non-invasive assessment (all) and invasive video-urodynamics in 1 patient (demonstrating low capacity, stable, compliant bladder with exaggerated immature voiding patterns and emptying to 78% at age 6 months, and normal capacity, stable, compliant bladder with persistent incompletely coordinated high-pressure voiding at 18 months). Risk factors for UTI were explored separately in females and males (Table 1).

Females

Seven females developed a UTI (58%); all had a first UTI under 5 years of age. One of the 2 females with low grade