Early Discontinuation of Antibiotic Prophylaxis in Patients with Persistent Primary Vesicoureteral Reflux Initially Detected during Infancy: Outcome Analysis and Risk Factors for Febrile Urinary Tract Infection

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Purpose: We retrospectively assessed the incidence of and risk factors for febrile urinary tract infection in children during active surveillance after early discontinuation of antibiotic prophylaxis.

Materials and Methods: We retrospectively evaluated 9 females and 61 uncircumcised males diagnosed with primary vesicoureteral reflux before age 1 year who had persistent reflux on followup voiding cystourethrogram and were subsequently followed under active surveillance without continuous antibiotic prophylaxis. Patients with secondary vesicoureteral reflux or associated urological abnormality were excluded. Clinical outcomes, including incidence of febrile urinary tract infection and new scar formation, were evaluated. Risk factors for febrile urinary tract infection were also analyzed.

Results: Mean age at stopping continuous antibiotic prophylaxis was 21 months, and mean followup was 61 months. During active surveillance 21 patients had febrile urinary tract infection, and the 5-year infection-free rate under active surveillance was 67.5%. One or 2 foci of minimal new scarring developed in 4 of 16 patients who underwent followup dimercapto-succinic acid scan after febrile urinary tract infection. On multivariate analysis dilated vesicoureteral reflux on followup voiding cystourethrogram was the only significant risk factor for febrile urinary tract infection.

Conclusions: This study revealed that about two-thirds of patients with persistent vesicoureteral reflux were free of febrile urinary tract infection during 5 years of active surveillance. Those with dilated vesicoureteral reflux on followup voiding cystourethrogram are at significantly greater risk for febrile urinary tract infection. Accordingly active surveillance, especially in patients with nondilated vesicoureteral reflux on followup voiding cystourethrogram, seems to be a safe option even in children who have not yet been toilet trained.

Key Words: risk factors, urinary tract infections, vesico-ureteral reflux, watchful waiting

Abbreviations and Acronyms

CAP = continuous antibiotic prophylaxis

DMSA = dimercapto-succinic acid

SPECT = single-photon emission computerized tomography

UTI = urinary tract infection

VCUG = voiding cystourethrography

VUR = vesicoureteral reflux

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Study received institutional review board approval.

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ACCORDING to the American Urological Association guideline published in 2010, conservative management with continuous antibiotic prophylaxis is recommended as initial treatment for children with primary vesicoureteral reflux detected before age 1 year, for whom spontaneous resolution is

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expected.[1] However, there are many patients with persistent reflux on followup voiding cystourethrogram without any symptoms. The American Urological Association guideline states that there can be no uniform guidelines on the subsequent management of asymptomatic cases of persistent vesicoureteral reflux. Our strategy in such patients is basically active surveillance, which means that patients are followed without continuous antibiotic prophylaxis under the treatment of bladder-bowel dysfunction if necessary, even if they are not yet toilet trained. While several series have shown that active surveillance in toilet trained patients with primary vesicoureteral reflux is a reasonable option for subsequent treatment,[2–8] reports of active surveillance, including in patients not yet toilet trained, are scarce. We retrospectively reviewed our experience of active surveillance in patients with persistent reflux initially detected during infancy to evaluate the incidence of and risk factors for febrile urinary traction infection during active surveillance after early discontinuation of antibiotic prophylaxis.

PATIENTS AND METHODS

This study was approved by our institutional review board. We retrospectively reviewed the medical charts of 127 patients younger than 1 year with primary VUR who were referred to our hospital between February 1995 and June 2011. Of these patients 70 who had persistent VUR on followup VCUG and were subsequently followed under active surveillance without CAP were enrolled in the study. The timing of discontinuation of CAP varied depending on physician preference and parental opinion, usually at 1 to 2 years after diagnosis of VUR. Since we do not recommend surgery aggressively in patients with asymptomatic persistent VUR, almost all patients with persistent VUR were followed under active surveillance at our hospital. Patients with secondary VUR or associated abnormality such as ureterocele, ectopic ureter, concomitant ureteropelvic junction obstruction, multicystic dysplastic kidney, posterior urethral valve or neurogenic bladder were excluded.

Patients were followed through our outpatient clinic at varying intervals, depending on gender, age and duration since stopping CAP. In general terms interval of followup visit was about 3 months for 1 to 2 years after discontinuation of CAP and about 6 months for 1 to 2 years thereafter. Subsequently regular followup visits at 1 or 2-year intervals were recommended until puberty. Febrile UTI was defined as fever (38C or greater) with significant pyuria on urinalysis and/or significant bacteriuria. We defined significant pyuria as more than 10 white blood cells per high power field and significant bacteriuria as growth of more than 100,000 cfu/ml of a single pathogenic bacteria. Urine samples for urinalysis and culture were collected by clean catch in toilet trained patients and using catheterization or collecting bag in children not yet toilet trained. VUR was classified into 5 grades according to the International Reflux Study in Children.[9] Renal scarring was defined as a focal defect or global renal atrophy (less than 40% split renal function) on DMSA scan with routine SPECT performed 3 months or more after febrile urinary tract infection.

Clinical outcomes such as incidence of febrile UTI during active surveillance and incidence of new scar formation after febrile UTI were evaluated. Risk factors for febrile UTI during active surveillance were also analyzed. Owing to the limited number of events and number of patients per VUR grade, reflux was dichotomized as nondilated (grades I and II) and dilated (grades III to V).

Febrile UTI-free time was calculated from date of stopping CAP to date of first febrile UTI during active surveillance, or date of antireflux surgery or last contact in patients without febrile UTI. Kaplan-Meier curve, log-rank test and Cox proportional hazards model were used for statistical analysis. Sensitivity analysis was performed by omitting patients who were censored at less than 5 years without febrile UTI.

RESULTS

Patient characteristics are outlined in table 1. Of the patients 87% were male and 89% presented with febrile UTI. In addition, 64% of patients had bilateral reflux and 81% had dilated reflux on initial VCUG. On initial DMSA scan abnormalities were identified in 34 patients, consisting of unilateral

Table 1. *Patient characteristics*

Initial evaluation	
No. gender:	
Male	61
Female	9
Mos age range at presentation (mean)	0.1—11.8 (5.4)
No. presenting symptom:	
Febrile UTI	62
Anomaly on ultrasound	8
No. VUR laterality on VCUG:	
Unilat	25
Bilat	45
No. VUR grade on VCUG:	
I	5
II	8
III	15
IV	22
V	20
No. DMSA findings:	
Normal	34
Abnormal	34
Single kidney without scar	1
Not applicable	1
Followup under CAP	
No. breakthrough UTI:	
Pos	8
Neg	62
No. VUR laterality on VCUG:	
Unilat	32
Bilat	38
No. VUR grade on VCUG:	
I	8
II	13
III	24
IV	16
V	9