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Long-term Follow-up of Patients After Childhood Urinary Tract Infection

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Objective: To evaluate the long-term outcome of children with urinary tract infection (UTI).

Design: Follow-up examination 6 to 17 years after childhood UTI.

Setting: Secondary to tertiary referral center.

Patients: From an original population-based cohort of 1185 children with a history of UTI on whom both ultrasonography (US) and voiding cystourethrography had been performed between January 1, 1993, and December 31, 2003, we excluded 24 cases with major renal dysplasia or obstruction of the urinary tract to form a study cohort of 1161 patients. We took a stratified random sample of 228 patients for follow-up, and a total of 193 (85%) participated. Of the 193 participating patients, 103 (53%) had received antibiotic prophylaxis and 42 (22%) had undergone surgery.

Main Exposure: Urinary tract infection.

Main Outcome Measures: Renal growth and parenchymal damage in US examination, kidney function, and blood pressure.

Results: Unilateral renal parenchymal defect was found in 22 of the 150 patients (15%) studied with US at follow-up, and unilateral kidney growth retardation was found in 5 patients (3%). All but 1 of the renal parenchymal defects seen on US were in patients with grade III to V vesicoureteral reflux. Despite the parenchymal defects seen on US, the serum cystatin C concentration, estimated glomerular filtration rate, and blood pressure were within the normal ranges in all patients.

Conclusions: The risk of long-term consequences from childhood UTI seems to be very low. Owing to the observational nature of our study, we cannot exclude the effects of the given treatment on the outcome of our patients.

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URINARY TRACT INFECTION (UTI) is common in childhood, as approximately 8% of girls and 2% of boys have had symptomatic UTI by age 7 years.[1] For the last 2 decades, the management of children with UTI has included routine imaging of the urinary tract by ultrasonography (US), voiding cystourethrography (VCUG), and, in some countries, dimercaptosuccinic acid scans to identify abnormalities that may increase the risk of recurrent UTIs or permanent renal damage later in life.[2-5] Urinary tract obstruction and major congenital renal dysplasia can undoubtedly lead to permanent renal damage, but the significance of vesicoureteral reflux (VUR) and local renal scars is controversial.

Persistent dimercaptosuccinic acid uptake defects, interpreted as renal scars, are seen in approximately 15% of children studied after UTI, but the long-term implications of these defects are unclear.[6] The oldest studies evaluating the sequelae of childhood UTI were based on highly selected patient series, and the resulting prognoses were quite pessimistic.[7,8] A more recent Swedish population-based study showed no significant deterioration in renal function in patients with a history of childhood UTI.[9] Minor to moderate renal scars, especially if unilateral, seem to be insignificant in the long-term prognosis for children with UTI, and the true etiologic fraction of childhood UTI as a cause of chronic kidney disease is negligible.[10]

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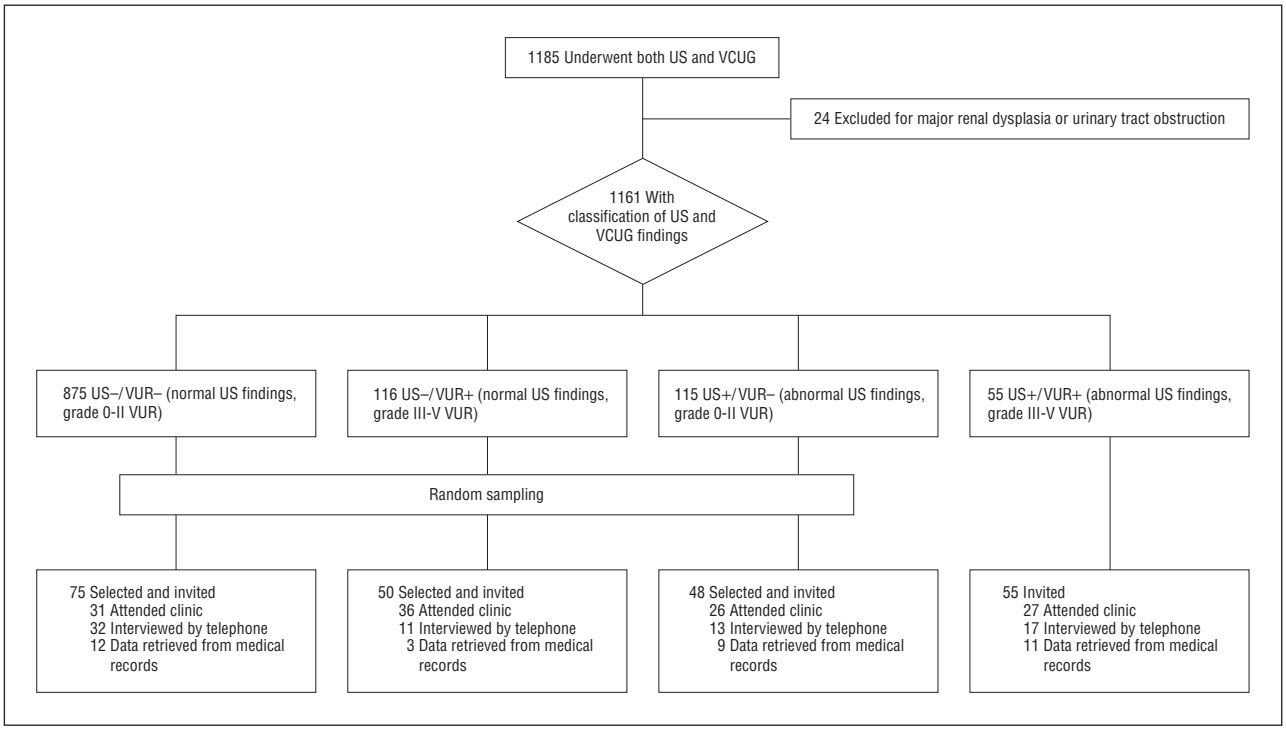

Figure. Classification and sampling of the patients for follow-up. US indicates ultrasonography; VCUG, voiding cystourethrography; and VUR, vesicoureteral reflux.

We describe the long-term clinical outcome in a population-based cohort of patients with a history of childhood UTI.

METHODS

PATIENTS

Between January 1, 1993, and December 31, 2003, 1185 children aged 0 to 14 years (mean [SD], 2.3 [2.5] years) with a history of UTI had undergone both renal US and VCUG at the Department of Pediatrics, University of Oulu. As we were interested in the outcome for children without major renal dysplasia or obstructive uropathy, we excluded 24 patients (2%) in whom these conditions were identified in the primary US. A study cohort of 1161 patients remained (795 girls and 366 boys) (**Figure**). Eighty-two percent underwent radiological imaging following their first UTI, while the remaining patients had recurrent UTI. At the index UTI, 61% of patients had been febrile (temperature >38°C). A radiographic VCUG (rVCUG) had been performed for 933 of 1161 patients (80%) and an isotope VCUG (iVCUG) had been performed for 217 patients (19%). In 11 cases, both rVCUG and iVCUG had been performed.

To obtain a representative and convenient sample of patients with childhood UTI and various abnormalities of the urinary tract, we classified the patients into 4 subgroups based on the findings in the primary US and highest VUR grade: the US–/VUR– group comprised patients with normal US findings and VUR grades 0 to II (n=875), the US–/VUR+ group included patients with normal US findings and VUR grades III to V (n=116), the US+/VUR– group included patients with abnormal US findings and VUR grades 0 to II (n=115), and the US+/VUR+ group included patients with abnormal US findings and VUR grades III to V (n=55). Fifty randomly selected patients in the US–/VUR– group, 50 in the US–/VUR+ group, and 48 in the US+/VUR– group were invited for a follow-up visit, as were all 55 patients in the US+/VUR+ group because we wanted to evaluate the outcome of patients with potentially the most unfavorable prognosis as thoroughly as possible. As the patients in the US–/VUR– group were reluctant to participate, we randomly selected and invited another 25 patients from this group (ie, 75 patients altogether) (Figure).

The follow-up investigations were performed in 2009 and 2010. All of the patients, or the parents of patients aged 15 years or younger, were first contacted by letter and then by telephone. Informed consent was obtained from all of the participating patients or their parents. The study protocol was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District.

Of the 228 patients selected, 193 (85%) participated in the follow-up study (**Table 1**), comprising 120 who attended the clinic and 73 who were interviewed by telephone. Most of the patients (168 of 193 [87%]) had radiological imaging following their first UTI, and 76% of the patients had been febrile at the index UTI. Among the 193 patients, 115 (60%) had their UTI diagnosed and treated at the Department of Pediatrics, while 78 (40%) were treated in outpatient clinics. The mean (SD) follow-up time was 11.1 (3.2) years (range, 5.9-17.3 years). The mean (SD) age at follow-up was 13.0 (3.9) years (range, 6.0-25.2 years), and 19 patients (10%) were older than 18 years. One female had been pregnant without complications. Of the 35 nonparticipating patients, 1 died in a motor vehicle crash, 26 could not be contacted by telephone, and 8 were contacted but declined to participate.

A control VCUG had been performed for 93 of the 193 participating patients (48%) earlier during follow-up (Table 1). All of the 91 patients with grade III to V VUR in primary VCUG (US–/VUR+ and US+/VUR+ groups) had a control VCUG, and an average of 3 VCUGs (range, 1-7 VCUGs) per patient were done. Multiple VCUGs were mostly done on surgically treated patients to evaluate the results of the surgical procedures.

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Table 1. Characteristics, Follow-up Data, and Grouping of the 228 Selected Patients

	Study Group[a]							
	US–/VUR–		US–/VUR+		US+/VUR–		US+/VUR+	
	Participated		Participated		Participated		Participated	
Characteristic	Yes	No	Yes	No	Yes	No	Yes	No
Patients, No.	63	12	47	3	39	9	44	11
Female, No.	41	10	33	3	25	6	33	4
Age, mean (SD), y								
At index UTI	2.2 (2.6)	3.6 (3.0)	1.2 (1.6)	3.5 (2.9)	2.2 (2.4)	5.3 (3.3)	1.7 (2.1)	1.6 (2.0)
At follow-up	13.4 (3.9)	5.7 (5.8)[b]	12.3 (3.9)	7.6 (2.9)[b]	13.6 (4.0)	4.8 (5.5)[b]	12.9 (4.2)	7.0 (4.7)[b]
Follow-up time, mean (SD), y	11.2 (3.2)	5.7 (5.8)[c]	11.0 (3.5)	7.6 (2.9)[c]	11.4 (2.9)	4.8 (5.5)[c]	11.2 (3.1)	7.0 (4.7)[c]
Antibiotic prophylaxis, No. (%)	9 (14)	1 (8)	46 (98)	3 (100)	5 (13)	4 (44)	43 (98)	11 (100)
UTI recurrence, No. (%)	15 (24)	NA	27 (57)	NA	10 (26)	NA	23 (52)	NA
Febrile at UTI recurrence, No. (%)	3/15 (20)	NA	15/27 (56)	NA	2/10 (20)	NA	15/23 (65)	NA
Control VCUG, No. (%)	2 (3)	0	47 (100)	3 (100)	0	2 (22)	44 (100)	9 (90)[d]
Urinary tract surgery, No. (%)	0	0	19 (40)	2 (67)	0	1 (11)	23 (52)	5 (50)[d]

Abbreviations: NA, not applicable; US, ultrasonography; UTI, urinary tract infection; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux.
[a] Among the study groups, US– indicates normal primary US findings; US+, abnormal primary US findings; VUR–, grade 0 to II VUR; and VUR+, grade III to V VUR. Data are given separately for the patients who participated in the follow-up study and those who did not.
[b] Age at the time of the last control visit to the Department of Pediatrics, University of Oulu.
[c] Time elapsing from the index UTI to the last control visit to the Department of Pediatrics, University of Oulu.
[d] Further follow-up data were available for 10 nonparticipating patients in the US+/VUR+ group.

Urinary tract surgery was performed in 42 of the 193 patients (22%) during childhood (Table 1), and 41 of the 91 patients (45%) with grade III to V VUR had antireflux surgery. Vesicoureteral reflux was found to have resolved (grade II or less) in 81 of the 91 patients (89%) in the last VCUG, including in 44 of 50 patients (88%) without active treatment for VUR and 37 of 41 patients (90%) after antireflux surgery. One girl in the US+/VUR+ group had pyelopyelostomy due to an ectopic ureter.

FOLLOW-UP INVESTIGATIONS

The patients attending the clinic were asked to complete a questionnaire concerning UTI recurrences, use and duration of antimicrobial prophylaxis, general health, medication, details of pregnancy, and family history of hypertension. The telephone interview contained the same questions as in the questionnaire. Data of any antireflux surgery and the latest US and VCUG results were retrieved from the medical records of all of the selected patients.

Blood pressure (BP) was measured 3 times from the right arm after 15 minutes in a sitting position, and mean values were calculated for the 120 patients attending the clinic (Dinamap Vital Signs Monitor 8100; Critikon Inc). Recent BP measurements were used from 55 patients interviewed by telephone. Blood samples were obtained for the measurement of serum cystatin C concentration (CysC) in milligrams per liter, and the glomerular filtration rate (GFR) was estimated using the equation published by Filler and Lepage[11]: $GFR = 91.62 \times (1/CysC)^{1.123}$. The urine analyses included dipstick screening, bacterial culture, and the albumin-creatinine ratio. Ultrasonography with a Philips iU22 device (Philips Medical Systems) was performed for 118 patients attending the clinic. In addition, results of the earlier US from 32 interviewed patients were used, contingent on the fact that they had not had UTI recurrences since the last control US.

DEFINITIONS

Primary US findings were considered abnormal in cases where they showed hydronephrosis or a dilated ureter, parenchymal defect, duplex system, renal agenesia, growth retardation of the kidney, or ureterocele. An anteroposterior renal pelvic diameter larger than 10 mm was interpreted as hydronephrosis.[12] A reduction in renal parenchymal thickness and possible corresponding calyceal deformation was interpreted as a renal parenchymal defect, and the defect was considered new renal damage if it was seen only in the control US. Kidney growth retardation was defined as a longitudinal renal dimension smaller than –2 SDs of the mean renal length according to the patient's height.[13]

Vesicoureteral reflux as detected in rVCUG was classified as grades I to V,[14] while that detected in iVCUG was graded as the following: grade I, minimal detectable reflux; grade II, clearly visible reflux that does not increase during voiding or is seen only during voiding; grade III, reflux that increases during voiding; and grade IV, constantly increasing reflux during filling of the bladder with or without increase but no decrease during voiding. The patients with bilateral VUR were assigned to the most severe grade. We regarded grades I and II in iVCUG as corresponding to grades I and II in rVCUG and considered grades III to IV in iVCUG to correspond to grades III to V in rVCUG.

Height was expressed in *Z* scores obtained from Finnish growth charts. Standard age-based pediatric ranges for serum CysC concentration and urine albumin-creatinine ratio were used. An estimated GFR of 90 mL/min/1.73 m^2 or greater was regarded as normal.

STATISTICAL ANALYSIS

The data were analyzed using PASW Statistics version 19 (IBM) and StatsDirect version 2.7.2 (StatsDirect Ltd). In pairwise comparisons, the binomial standard normal deviate test was used for categorical variables and *t* test was used for continuous variables. Because the prevalence of VUR was higher in younger children, we evaluated the influence of grade III to V VUR on the risk of UTI recurrence separately in children younger than 2 years and children aged 2 years or older. The Pearson χ^2 test was used for categorical variables and an analysis of variance with Tukey honestly significant difference post hoc correction was used for continuous variables when comparing the 4 study groups.

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Table 2. Renal Function, Blood Pressure, and Somatic Growth of the 120 Patients Attending the Clinic

Outcome	Study Group[a]			
	US–/VUR– (n = 31)	US–/VUR+ (n = 36)	US+/VUR– (n = 26)	US+/VUR+ (n = 27)
Serum cystatin C, mg/L				
Mean (SD)	0.67 (0.07)	0.66 (0.09)	0.65 (0.08)	0.69 (0.08)
Range	0.51 to 0.82	0.49 to 0.86	0.47 to 0.79	0.52 to 0.82
Estimated GFR, mL/min/1.73 m^2				
Mean (SD)	144 (17)	151 (23)	150 (23)	142 (19)
Range	115 to 195	109 to 204	119 to 214	115 to 191
BP, mm Hg				
Systolic				
Mean (SD)	104 (10)	103 (10)	109 (9)	108 (9)
Range	85 to 128	80 to 123	94 to 133	94 to 124
Diastolic				
Mean (SD)	58 (8)	57 (5)	61 (7)	59 (7)
Range	34 to 77	40 to 65	47 to 74	46 to 74
Height *Z* score				
Mean (SD)	0.1 (0.9)	0.1 (1.0)	0.2 (1.2)	0.6 (1.2)
Range	–2.4 to 2.6	–2.0 to 1.7	–2.3 to 2.9	–1.5 to 3.3

Abbreviations: BP, blood pressure; GFR, glomerular filtration rate; US, ultrasonography; VUR, vesicoureteral reflux.
[a] Among the study groups, US– indicates normal primary US findings; US+, abnormal primary US findings; VUR–, grade 0 to II VUR; and VUR+, grade III to V VUR.

RESULTS

ANTIBIOTIC PROPHYLAXIS AND UTI RECURRENCES

Of the 193 participating patients, 103 had received antibiotic prophylaxis, including 89 (86%) for grade III to V VUR. Altogether, 75 patients (39%) had a recurrence of UTI, and 35 of these patients (47%) had been febrile during at least 1 UTI recurrence (Table 1).

Recurrence of UTI had occurred significantly more often in the patients with grade III to V VUR than in those with grade II or less VUR (50 of 91 patients [55%] vs 25 of 102 patients [25%], respectively; difference, 30%; 95% CI, 17%-43%; $P < .001$). Patients with grade III to V VUR were febrile at UTI recurrence more often than patients with grade II or less VUR (30 of 50 patients [60%] vs 5 of 25 patients [20%], respectively; difference, 40%; 95% CI, 17%-58%; $P < .001$). The difference in the occurrence of UTI recurrences between patients with grade III to V VUR and those without remained significant even after controlling for age.

US FINDINGS

A unilateral parenchymal defect was found on the follow-up US in 22 of the 150 patients (15%), but no cases of a bilateral parenchymal defect were found. Ultrasonography showed a diffuse reduction in parenchymal thickness in 3 of the 22 cases and mild local parenchymal defects in the others. Eighteen of the 22 renal parenchymal defects were considered new renal damage, occurring in 10 of 46 cases (22%) in the US–/VUR+ group and 8 of 43 cases (19%) in the US+/VUR+ group but in none of the patients in the US–/VUR– and US+/VUR– groups. Taking into account the stratified random sampling used, if we extrapolate the total occurrence of new renal defects from these data to the whole study cohort, a total of 36 of 1161 patients (3%) would have potentially developed new renal damage after UTI. Follow-up US also revealed unilateral kidney growth retardation in 4 patients with a parenchymal defect on the same side and in 1 patient without any visible renal parenchymal defect on US.

The patients with a renal parenchymal defect on US at follow-up compared with those without any renal parenchymal defect had experienced UTI recurrence (18 of 22 patients [82%] vs 51 of 128 patients [40%] [51/128], respectively; difference, 42%; 95% CI, 20%-56%; $P < .001$), had received antibiotic prophylaxis (21 of 22 patients [95%] vs 77 of 128 patients [60%], respectively; difference, 35%; 95% CI, 17%-46%; $P < .001$), and had urinary tract surgery (15 of 22 patients [68%] vs 27 of 128 patients [21%], respectively; difference, 47%; 95% CI, 25%-64%; $P < .001$) significantly more often. The patients with and without a renal parenchymal defect did not differ significantly in their distribution by age or sex.

All but 1 of the 22 cases with a renal parenchymal defect and all 5 cases with kidney growth retardation were found in patients with grade III to V VUR. The analysis of renal length on the follow-up US showed no significant difference between kidneys with grade 0 to II VUR and those with grade III to V VUR (mean SD, 0.36 vs 0.18, respectively; difference, 0.18 SD; 95% CI, –0.07 to 0.43 SD; $P = .15$). The rate of VUR resolution in the last VCUG did not differ between the patients with and without a parenchymal defect on US (18 of 21 patients [86%] vs 62 of 69 patients [90%], respectively; difference, 4%; 95% CI, –25% to 9%; $P = .46$).

RENAL FUNCTION, BP, AND SOMATIC GROWTH

The serum CysC concentration and estimated GFR were within normal limits in all patients, with no significant differences between the study groups or between the pa-

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tients with and without a renal parenchymal defect on the follow-up US (**Table 2**). No patients had hematuria or proteinuria.

The mean systolic and diastolic BPs were within the normal range, again with no differences between the study groups or between the patients with and without a renal parenchymal defect on the follow-up US. Two patients had systolic BPs greater than +2 *Z* scores for sex, age, and height; no cases of BP higher than 140/90 mm Hg were found in the 120 patients attending the clinic (Table 2), and none were reported among the 55 patients interviewed by telephone.

Height was normally distributed and within the normal limits in all of the patients, with no significant differences between the 4 study groups or between the patients with and without a renal parenchymal defect on the follow-up US (Table 2).

COMMENT

We found no cases of impaired renal function or hypertension 6 to 17 years after childhood UTI. The follow-up US showed unilateral renal parenchymal defects in 15% of the patients, but renal function and mean BP measurements were within the normal limits in all cases. Renal function remained normal even in the patients with grade III to V VUR and renal parenchymal defects on primary imaging. Because all of the pediatric urological imaging examinations in this district are performed at our hospital, this follow-up study applies to a population-based sample of children with UTI in whom obstructive uropathy and major renal dysplasia had been ruled out with US.

Our results are in agreement with those of a Swedish population-based study that found no significant deterioration in renal function in patients with a history of childhood UTI, with renal function being well preserved in all of the patients after 16 to 26 years of follow-up regardless of the occurrence of renal scarring.[9] There was no difference in 24-hour ambulatory BP between the children with and without renal scars, and the risk of hypertension was small and similar in both groups.[15] Smellie et al[16] monitored 226 patients in a tertiary care center for recurrent UTIs and VUR over a mean of 27 years and found abnormal renal function or hypertension in 8% of the patients at the end of follow-up and no cases in which new renal scars had developed after childhood. Some earlier studies gave significantly higher prevalence figures for hypertension (10%-30%) or renal failure (10%) in patients monitored after UTI in childhood.[7,8] This may be because these studies focused on highly selected series of patients at the time when the diagnosis and treatment of UTIs were not as accurate and prompt as they are now and because children with congenital dysplasia were included in the analyses. In the absence of structural kidney abnormalities, the true etiologic fraction of childhood UTI as the main cause of chronic kidney disease is extremely small.[10]

In this study, patients with grade III to V VUR had recurrences of UTI significantly more often and were more often febrile compared with patients without grade III to V VUR. In previous reports, the presence or absence of VUR did not alter the total numbers of UTI recurrences, although the risk of pyelonephritis was higher in children with grade III or higher VUR compared with those without.[17-20] Most data concerning UTI recurrences were verified from our patients' medical records, but some were based solely on the information given by the patients, entailing a possible recall bias.

All but 1 of the renal parenchymal defects and kidney growth retardation cases found on the follow-up US were in patients with grade III to V VUR. Owing to the observational nature of our study, we cannot exclude the potential effects of the treatment given (antibiotic prophylaxis or surgery) on the natural history of VUR in our patients. On the other hand, surgical correction of VUR does not reduce the risk of new renal scar formation any better than does antimicrobial prophylaxis, and the benefits of prophylaxis in children with VUR are also questionable.[21-23] Ultrasonography is not a sensitive method in finding the smallest renal parenchymal defects. However, renal function, mean BP, and somatic height were within the normal limits in all of our patients at follow-up, indicating that small renal parenchymal defects are unimportant regarding the long-term prognosis for children with UTI.

Some of our patients had undergone up to 7 VCUGs during the follow-up period. Because the average effective radiation dose from a single VCUG in children is 0.9 mSV, there can potentially be long-term sequelae especially if VCUGs are repeated.[24] Furthermore, VCUG is an invasive and expensive procedure that causes pain and psychological stress and carries a risk of iatrogenic UTI.[25-27]

The newly updated guidelines of the American Academy of Pediatrics no longer recommend routine VCUG after the first UTI at which children are febrile, which is consistent with the guidelines issued by the National Institute for Health and Clinical Excellence in 2007. Both guidelines still suggest VCUG for children with certain risk factors and the American Academy of Pediatrics still recommends performing VCUG after a recurrence of UTI.[28,29] However, 2 recent surveys have shown that when US findings are normal, abandoning the use of VCUG carries an extremely low risk of missing a significant renal abnormality.[30,31] The good prognosis for childhood UTI found in this follow-up study together with the recent literature showing no obvious benefits for active treatment of VUR support these more conservative imaging practices.[21-23] We nevertheless wish to emphasize the importance of early perception, correct diagnosis, and prompt treatment of childhood UTI.

In conclusion, the clinical outcome in our population-based group of children with UTI was good after 6 to 17 years of follow-up. When obstructive uropathy and major renal dysplasia are ruled out by US, the risk of long-term complications following childhood UTI seems to be very low. However, we cannot draw conclusions on whether the good outcome was achieved as a result of or despite the given active treatment for VUR.

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