Risk Factors for Recurrent Urinary Tract Infection and Renal Scarring

Ron Keren, MD, MPH[a,b], Nader Shaikh, MD, MPH[c], Hans Pohl, MD[d], Lisa Gravens-Mueller, MS[e], Anastasia Ivanova, PhD[e], Lisa Zaoutis, MD[a], Melissa Patel, MD[a], Rachel deBerardinis, BA[a], Allison Parker, MA[a], Sonika Bhatnagar, MD[c], Mary Ann Haralam, MSN CRNP[c], Marcia Pope, RN[c], Diana Kearney, RN CCRC[c], Bruce Sprague, BS[d], Raquel Barrera, MS[d], Bernarda Viteri, MD[d], Martina Egigueron, MD[d], Neha Shah, MD[d], Alejandro Hoberman, MD[c]

abstract

OBJECTIVES: To identify risk factors for recurrent urinary tract infection (UTI) and renal scarring in children who have had 1 or 2 febrile or symptomatic UTIs and received no antimicrobial prophylaxis.

METHODS: This 2-year, multisite prospective cohort study included 305 children aged 2 to 71 months with vesicoureteral reflux (VUR) receiving placebo in the RIVUR (Randomized Intervention for Vesicoureteral Reflux) study and 195 children with no VUR observed in the CUTIE (Careful Urinary Tract Infection Evaluation) study. Primary exposure was presence of VUR; secondary exposures included bladder and bowel dysfunction (BBD), age, and race. Outcomes were recurrent febrile or symptomatic urinary tract infection ($_{F/S}$UTI) and renal scarring.

RESULTS: Children with VUR had higher 2-year rates of recurrent $_{F/S}$UTI (Kaplan-Meier estimate 25.4% compared with 17.3% for VUR and no VUR, respectively). Other factors associated with recurrent $_{F/S}$UTI included presence of BBD at baseline (adjusted hazard ratio: 2.07 [95% confidence interval (CI): 1.09–3.93]) and presence of renal scarring on the baseline ^{99m}Tc-labeled dimercaptosuccinic acid scan (adjusted hazard ratio: 2.88 [95% CI: 1.22–6.80]). Children with BBD and any degree of VUR had the highest risk of recurrent $_{F/S}$UTI (56%). At the end of the 2-year follow-up period, 8 (5.6%) children in the no VUR group and 24 (10.2%) in the VUR group had renal scars, but the difference was not statistically significant (adjusted odds ratio: 2.05 [95% CI: 0.86–4.87]).

CONCLUSIONS: VUR and BBD are risk factors for recurrent UTI, especially when they appear in combination. Strategies for preventing recurrent UTI include antimicrobial prophylaxis and treatment of BBD.

[a]*Division of General Pediatrics, Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania;* [b]*Departments of Pediatrics and Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania;* [c]*University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania;* [d]*Division of Urology, Children's National Health System, Washington, DC; and* [e]*University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*

Dr Keren conceptualized and designed the study, contributed to the analysis and interpretation of the results, and drafted the initial manuscript; Drs Shaikh, Pohl, and Hoberman conceptualized and designed the study, contributed to the analysis and interpretation of the results, and critically revised the manuscript for important intellectual content; Ms Gravens-Mueller and Dr Ivanova conducted the initial analyses and reviewed and revised the manuscript; and Dr Zaoutis, Dr Patel, Dr Bhatnagar, Dr Viteri, Dr Egigueron, Dr Shah, Ms deBerardinis, Ms Parker, Ms Haralam, Ms Pope, Ms Kearney, Ms Barrera, and Mr Sprague coordinated and supervised the data collection at their respective sites and critically reviewed the manuscript. All coauthors agreed to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Vesicoureteral reflux is recognized as an important risk factor for recurrent urinary tract infection and renal scarring. Less is known about the contribution of other risk factors to these outcomes.

WHAT THIS STUDY ADDS: This study found that information about vesicoureteral reflux and bladder and bowel dysfunction can be used to identify children at low, medium, and high risk of recurrent urinary tract infection, information that clinicians could use to select children for specific preventive therapies.

Urinary tract infection (UTI) is the most common serious bacterial infection in young children. Up to 8.4% of girls and 1.7% of boys will have a UTI in the first 6 years of life.[1] UTIs cause short-term morbidity such as fever, dysuria, and pain and may also result in permanent kidney scarring.[2–5] Many factors, such as age, gender, race, and circumcision status, are believed to increase the risk of recurrent UTI,[6–8] but over the last few decades, no factor has received more attention than vesicoureteral reflux (VUR). In this condition, which occurs in 30% to 40% of children who have had a UTI,[9] urine flows backward toward the kidneys during bladder contraction. VUR is associated with an increased risk of recurrent UTI and renal scarring,[10–12] but it is neither necessary nor sufficient for either of these outcomes.[3,13–17] In recent years, there has been increased appreciation that other factors, such as bladder and bowel dysfunction (BBD)[18] and defects in innate immunity,[19,20] may also be important contributors to the recurrence of UTI. BBD, also known as dysfunctional voiding and dysfunctional elimination syndrome, refers to abnormalities in the filling and/or emptying of the bladder, which manifest as urinary frequency, urgency, and incontinence; holding maneuvers; dysuria; prolonged voiding intervals; and abnormal bowel patterns, including constipation and encopresis. BBD is relatively common in the pediatric population,[1] is often underdiagnosed and undertreated by primary care physicians,[18] and is a risk factor for VUR persistence[21–23] and renal scarring.[24,25]

Between 2007 and 2011, the RIVUR (Randomized Intervention for Children With Vesicoureteral Reflux) study randomized 607 children with VUR identified after a first or second febrile or symptomatic UTI ($_{F/S}$UTI) to receive daily antimicrobial prophylaxis or placebo for 2 years.[26] Recognizing that one-half of the children participating in the RIVUR study would be observed while taking placebo, 3 of the larger clinical trial centers collaborated on an ancillary study (ie, CUTIE [Careful Urinary Tract Infection Evaluation]) to assemble a complementary cohort of children who were screened for inclusion in the RIVUR study but were found not to have VUR. These children received the same follow-up and evaluation as RIVUR participants, but no antimicrobial prophylaxis was administered. Combining the RIVUR study placebo cohort with the CUTIE study cohort provided a unique opportunity to study the natural history of children after a UTI. Thus, the goal of the present study was to compare rates of recurrent UTI and renal scarring between children with and without VUR and to identify risk factors for recurrent UTI and renal scarring.

METHODS

Study Design and Eligibility Criteria

The present study combined data from 2 cohorts of children with UTI who were enrolled prospectively in parallel. The first cohort included children with grades I through IV VUR randomized to the placebo arm of the RIVUR study; the second cohort included children who did not have VUR who were enrolled in the CUTIE study. Screening for the RIVUR and CUTIE studies took place between June 2007 and May 2011, and May 2008 and September 2011, respectively. Children in the RIVUR study were enrolled at 19 clinical sites across the United States, and children in the CUTIE study were enrolled at Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh of UPMC, and Children's National Medical Center. Children were recruited for both studies from primary and subspecialty care offices, pediatric urgent care clinics, emergency departments, and pediatric wards. With the exception of VUR, eligibility criteria for enrollment were identical for both cohorts.

Children 2 to 71 months of age who had experienced 1 or 2 febrile or symptomatic urinary tract infections ($_{F/S}$UTI) were eligible. Fever was defined as a documented temperature of at least 38°C (measured anywhere on the body), either at home or in the office, within 24 hours before or after urine collection. Symptoms included suprapubic, abdominal, or flank pain or tenderness; urinary urgency, frequency, or hesitancy; dysuria; foul-smelling urine; or, in infants ≥4 months old, failure to thrive, dehydration, or hypothermia. UTI diagnosis also required the presence of pyuria on urinalysis (defined as ≥10 white blood cell count/mm^3 [uncentrifuged specimen] or ≥5 white blood cell count/HPF [centrifuged specimen], or ≥1+ leukocyte esterase on dipstick); and culture-proven infection with a single organism (defined as $\geq 5 \times 10^4$ CFU/mL (catheterized or suprapubic aspiration urine specimen) or $\geq 10^5$ CFU/mL (clean voided specimen). We excluded children with comorbid urologic anomalies, history of other renal injury or disease, congenital or acquired immunodeficiency, complex cardiac disease, and syndromes known to be associated with VUR or BBD.

Study Procedures

All children were evaluated within 4 weeks of diagnosis of the index UTI with a renal/bladder ultrasound and a contrast voiding cystourethrogram. Renal scanning with ^{99m}Tc-labeled dimercaptosuccinic acid (DMSA) was performed at baseline and after 1 year (RIVUR study participants only) and after 2 years (RIVUR and CUTIE study participants). In both studies, parents were educated at the time of their child's enrollment about the potential sequelae of untreated UTI and the benefits of prompt and adequate treatment. Specimens for urine culture were obtained at the time of febrile illnesses and when children had symptoms localized to the urinary tract. Parents were contacted by telephone or e-mail every 2 months to ascertain intercurrent illnesses, and children were seen at routine follow-up

visits at 6, 12, 18, and 24 months. At each study visit, an interim history and physical examination were performed.

Outcomes

Recurrent $_{F/S}$UTI was defined based on the same stringent criteria used at study entry. Two pediatric nuclear medicine physicians assessed the extent of renal cortical defects semi-quantitatively by dividing the cortex into 12 segments and determined severity on the basis of the number of segments affected. Cortical defects were defined as focal or diffuse decreased uptake of DMSA with and without loss of contours or cortical thinning with decreased volume. Using criteria established by Majd et al,[27,28] defects were classified as acute pyelonephritis or renal scarring.

Exposures

Exposure variables were defined a priori as follows: VUR grade, age, race, ethnicity, gender, presence of BBD, type of index UTI (first versus second; febrile versus afebrile), causative organism for index UTI (*Escherichia coli* versus other), parental education, insurance type (public versus commercial), presence of ureter duplication on renal ultrasound, and presence of scarring on baseline DMSA scan. VUR was graded according to the 5-grade system of the International Reflux Study Group.[29] We assessed for BBD at study entry and at the 12- and 24-month visits by using a modified version of the dysfunctional voiding scoring system reported by Farhat et al.[30] The scoring system asks parents to report on the frequency of daytime enuresis, bowel movement and voiding frequency, constipation, holding maneuvers, urinary urgency/hesitancy, and dysuria. The BBD variable had 3 levels: (1) not toilet-trained; (2) BBD; and (3) no BBD or "toilet-trained and unknown BBD."

Statistical Analysis

The primary end point was time to recurrent $_{F/S}$UTI during the 2-year observation period. Secondary end points included the proportion of children who had renal scarring (at 2 years, new, and according to severity). The Kaplan-Meier method was used to estimate the proportions of children with and without VUR who experienced a recurrent $_{F/S}$UTI during the 2-year observation period. All exposure variables were treated as fixed-time exposures.

Single-variable time-to-event analysis was performed for each exposure variable to determine the hazard ratio (HR) for the primary outcome (ie, time to recurrent UTI). We tested interactions between VUR and other factors (gender, age, index UTI type, and BBD at baseline) to determine if any exposures modified the association between presence of VUR and risk of recurrent $_{F/S}$UTI. *P* values for tests of interaction were based on the Wald test for the interaction of subgroup with VUR. A multivariable time-to-event model was then built by using a forward stepwise procedure. Variables with univariable *P* values $<.25$ were considered for entry into the model and remained in the model if the resulting *P* value was $<.20$. Finally, using the variables that remained statistically significant in the multivariable model at the $P < .05$ level (VUR grade and BBD), classification and regression tree analysis was performed to determine the main subgroups with distinct rates of UTI recurrence.[31] Presence of renal scarring at baseline was not included because this condition was uncommon at baseline, and this information is not generally available to clinicians. The classification and regression trees were fitted through binary recursive partitioning by using R software version 2.3.1 (R Development Core Team, Vienna, Austria). Institutional review boards at all participating sites approved the RIVUR and CUTIE study protocols.

RESULTS

Study Participants

A total of 2355 children were assessed for eligibility for the CUTIE study (Fig 1). Of the 732 children who were eligible, 195 (27%) enrolled, 164 (84%) attended the 1-year follow-up visit, and 176 (90%) attended the 2-year follow up visit. Details of the RIVUR study enrollment and follow-up have been reported previously.[26] A total of 305 RIVUR study participants were assigned to receive placebo daily; 262 (86%) attended the 1-year study visit, and 259 (85%) attended the 2-year study visit. Of the children with VUR, 167 (55%) had grade I or II disease and 138 (45%) had grade III or IV disease.

Children with and without VUR were similar in terms of gender, number of previous UTIs, index UTI organism, presence of BBD and constipation, male circumcision status, and presence of abnormalities on ultrasound. Children without VUR were more likely to be aged >3 years, African American, publically insured, toilet-trained, and have experienced a nonfebrile (symptomatic only) index UTI; they were less likely to have severe renal scarring at baseline and have a primary caregiver with more than a high school education (Table 1).

Risk Factors for Recurrent Febrile or Symptomatic UTIs

Children with VUR had higher 2-year rates of recurrent $_{F/S}$UTI than children with no VUR (Kaplan-Meier estimate: 25.4% vs 17.3%; adjusted HR: 1.58 [95% confidence interval (CI): 1.04–2.42]). Children with grade III or IV VUR had the highest rate of recurrent $_{F/S}$UTI (Kaplan-Meier estimate: 28.9%) (Table 2). The Kaplan-Meier curves in Fig 2 show that the difference in risk of recurrent $_{F/S}$UTI emerged in the first 6 months after enrollment and remained fairly constant thereafter.

In exploring whether any other factors (gender, age, index UTI type, or BBD at baseline) modified the association between presence of VUR and risk of recurrent $_{F/S}$UTI, there appeared to be a stronger association between VUR and recurrent $_{F/S}$UTI in

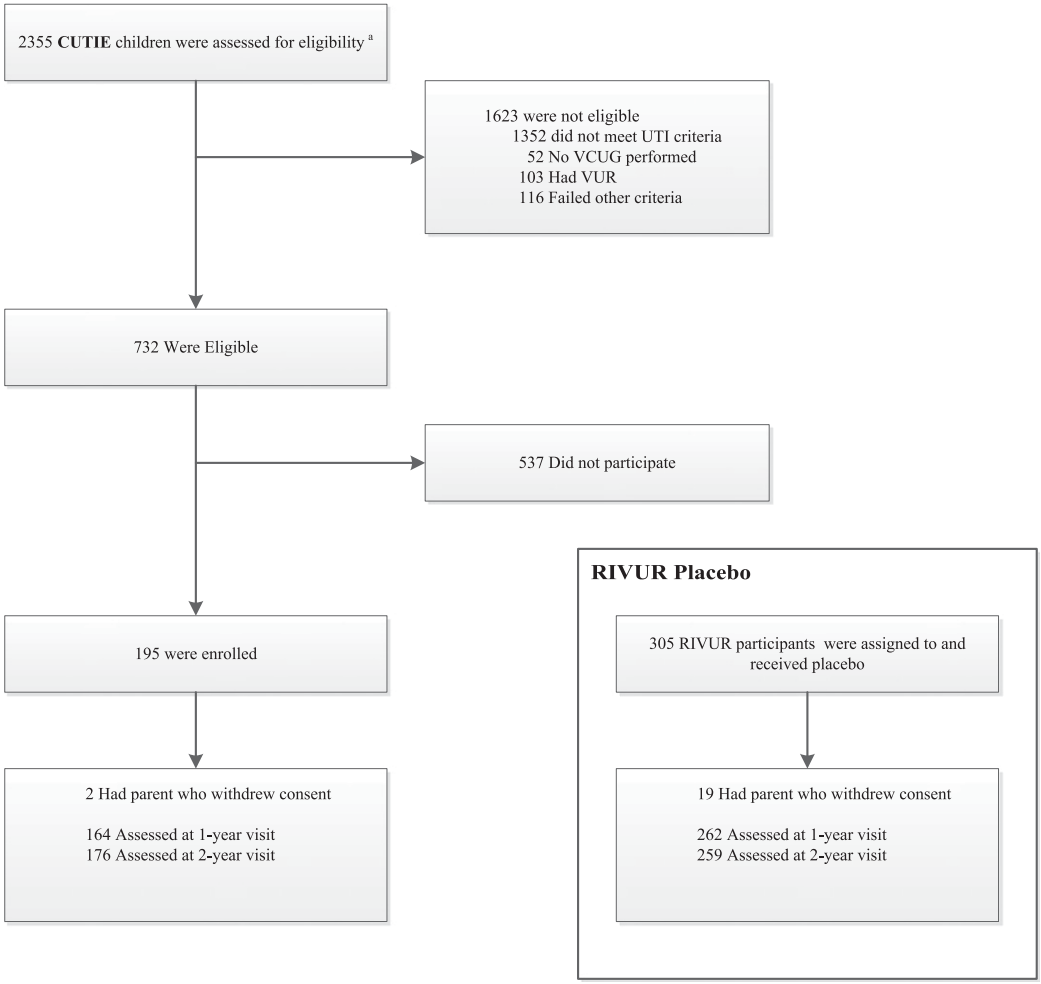

FIGURE 1

[a]Children were enrolled at various clinical sites (emergency and radiology departments and primary care, urology, and nephrology offices), resulting in diverse criteria for screening (eg, abnormal urinalysis results, positive urine culture). VCUG, voiding cystourethrogram.

children aged <24 months (HR: 2.37 [95% CI: 1.25–4.50]) than those aged ≥24 months (HR: 1.06 [95% CI: 0.60–1.84]) and children with BBD at baseline (HR: 1.77 [95% CI: 0.80–3.91]) compared with those without BBD at baseline (HR: 0.55 [95% CI: 0.19–1.62]), but the *P* values for interaction did not reach statistical significance (*P* = .06 and .09, respectively).

In univariable time-to-event analyses, other factors associated with recurrent $_{F/S}$UTI included age 36 to 71 months (HR: 2.49 [95% CI: 1.61–3.85]), white race (HR: 1.70 [95% CI: 1.01–2.86]), presence of BBD (HR: 2.01 [95% CI: 1.07–3.76]), second UTI at enrollment (HR: 2.08 [95% CI: 1.24–3.50]), *E coli* as the causative organism of the index UTI (HR: 0.56 [95% CI: 0.32–0.99]), parental college graduate or higher (HR: 1.84 [95% CI: 1.14–2.97]), and renal scarring on baseline DMSA scan (HR: 3.21 [95% CI: 1.40–7.33]) (Table 3). In the multivariable time-to-event model, only VUR grade, presence of BBD at baseline, and presence of renal scarring at baseline were associated with recurrent UTI.

Probability of Recurrent $_{F/S}$UTI: Classification and Regression Tree Analysis

The classification and regression tree analysis identified splits and 6 risk groups based on the presence or absence of BBD at baseline and the grade of VUR (Supplemental Table 4). Children with BBD and any degree of VUR had the highest risk of recurrent $_{F/S}$UTI (56%), followed by children with BBD but no VUR (35%) and children with no BBD and grade 0 to II VUR (29%). Non–toilet-trained children with grade III or IV VUR and toilet-trained children with no BBD and grade III or IV VUR had intermediate risks of recurrent $_{F/S}$UTI (27%). Non–toilet-trained children with no VUR and grade I or II VUR had the lowest risk of recurrent $_{F/S}$UTI (10% and 16%, respectively).

Renal Scarring

The presence of renal scars (Table 1) at the time of enrollment was rare in both the VUR group (3%) and the no VUR group (2%), although the VUR

TABLE 1 Baseline Demographic and Clinical Characteristics

Characteristic[a]	No VUR (n = 195)	VUR (n = 305)[b]	P
Age			
Median, mo	13	12	.71
25th and 75th quartile, mo	5–42	6–30	
Age group			.023
2–11 mo	91 (47)	147 (48)	
12–23 mo	32 (16)	59 (19)	
24–35 mo	12 (6)	36 (12)	
36–71 mo	60 (31)	63 (21)	
Gender			.25
Male (circumcised)	6 (3)	7 (2)	
Male (uncircumcised)	18 (9)	17 (6)	
Female	171 (88)	281 (92)	
Race[c]			<.001
White	131 (68)	237 (79)	
African American	35 (18)	17 (6)	
Multiracial	17 (9)	20 (7)	
Other	10 (5)	25 (8)	
Hispanic ethnicity group[c]	41 (21)	46 (15)	.085
Education level of primary caregiver			.071
High school graduate or lower	70 (36)	80 (26)	
Some college or 2-y degree	42 (22)	78 (26)	
College graduate or higher	82 (42)	145 (48)	
Health insurance[d]			<.001
Commercial	103 (53)	211 (70)	
Public	92 (47)	91 (30)	
No. of index UTIs			.40
First episode	174 (89)	279 (91)	
Second episode	21 (11)	26 (9)	
Type of index UTI			.003
Febrile only	60 (31)	100 (33)	
Symptomatic only	46 (24)	37 (12)	
Febrile and symptomatic	89 (46)	168 (55)	
Index UTI organism			.73
E coli	177 (91)	274 (90)	
Other	18 (9)	31 (10)	
Toilet-trained	60 (31)	67 (22)	.029
Bladder and bowel dysfunction at baseline[e]	26 (46)	37 (59)	.15
Constipation[f]	8 (13)	8 (13)	.89
Ultrasound abnormalities			
Hydronephrosis[g]	11 (6)	13 (4)	.46
Ureter duplication	4 (2)	15 (5)	.15
Renal scarring			.014
None	187 (98)	281 (97)	
Mild	3 (2)	0	
Moderate	0	2 (1)	
Severe	0	2 (1)	
Global atrophy	0	5 (2)	

[a] Statistics are reported as number (percent) unless otherwise indicated.
[b] Four children with central assessment of no VUR were included in grade I, and 1 child with central assessment of grade V was included in grade IV (enrollment based on local readings).
[c] Race and Hispanic ethnicity categories were self-assigned by parents.
[d] Three children with no insurance were classified into the public category.
[e] Defined as a score >6 for female subjects and >9 for male subjects on 120 toilet-trained children (57 in the no VUR group and 63 in the VUR group), based on modification of the Dysfunctional Voiding Scoring System.
[f] Defined as ≥2 conditions according to modified Paris Consensus on Childhood Constipation Terminology Group criteria (frequency of bowel movements <3 per week, >1 episode of fecal incontinence per week, passing large stool that obstructed toilet, retentive posture and behavior, and pain during defecation). Based on 124 toilet-trained children.
[g] Classified as less than grade 4 according to the Society for Fetal Urology guidelines.

group was more likely to have more severe scarring at baseline (2 with moderate scarring, 2 with severe scarring, and 5 with global atrophy compared with 0 in the no VUR group [P = .014]). At the end of the 2-year follow-up period (Table 2), 8 (5.6%) children in the no VUR group had renal scars (6 [4.3%] with new renal scars, and none with severe renal scars). In the VUR group, 24 (10.2%) had renal scars (19 [8.4%] with new renal scars and 6 [2.6%] with severe renal scars, 2 of which were known to be new scars compared with the baseline scans). Children with VUR had approximately twice the proportion of overall and new renal scarring compared with children without VUR, but none of these comparisons reached statistical significance.

DISCUSSION

In this 2-year study, we prospectively followed up 2 groups of children who had experienced 1 or 2 $_{F/S}$UTIs: 1 group that had grade I to IV VUR and the other with no VUR. None of the children received antimicrobial prophylaxis for the duration of the study. Children with VUR had a higher risk of recurrent $_{F/S}$UTI, but children without VUR still had a considerable risk of recurrent $_{F/S}$UTI. In addition to VUR, other factors associated with an increased risk of recurrent $_{F/S}$UTI included BBD and presence of renal scarring at baseline. In addition, there was a trend toward presence of BBD and age<24 months modifying (ie, strengthening) the association between VUR and recurrent UTI, but this trend was not statistically significant. In our recursive partitioning analysis, children who had both BBD and VUR had the highest risk of recurrent $_{F/S}$UTI, whereas non–toilet-trained children with no VUR had the lowest risk. Renal scarring was not commonly observed at 2 years, and although it was more frequent in children with VUR than in those without VUR, the difference did not reach statistical significance.

Our study corroborates results from earlier research. BBD,[8] white race,[32] and high-grade VUR[7,8,32] have been associated with an increased risk of recurrent UTI in other observational studies. However,

TABLE 2 Clinical Outcomes According to VUR Status

Outcome	VUR Status, *n* (%)				Unadjusted Comparison of VUR Versus No VUR Group	Adjusted Comparison of VUR Versus No VUR Group[a]
	No VUR	VUR	Grade I-II	Grade III-IV		
Recurrent $_{F/S}$UTI[b]	(*n* = 195)	(*n* = 305)	(*n* = 167)	(*n* = 138)	HR (95% CI)	
	33 (17.3)	72 (25.4)	35 (22.4)	37 (28.9)	1.52 (1.01–2.29)	1.58 (1.04–2.42)
Renal scarring[c]	(*n* = 144)	(*n* = 235)	(*n* = 126)	(*n* = 109)	OR (95% CI)	
Overall[d]	8 (5.6)	24 (10.2)	9 (7.1)	15 (13.8)	1.93 (0.84–4.43)	2.05 (0.86–4.87)
Mild	7 (4.9)	13 (5.5)	5 (4.0)	8 (7.3)		
Moderate	1 (0.7)	5 (2.1)	1 (0.8)	4 (3.7)		
Severe	0 (0)	4 (1.7)	3 (2.4)	1 (0.9)		
Global atrophy	0 (0)	2 (0.9)	0 (0)	2 (1.8)		
New[e]	6 (4.3)	19 (8.4)	8 (6.5)	11 (10.6)	2.06 (0.80–5.28)	2.05 (0.77–5.48)

[a] Adjusted for BBD at baseline (absent or present, not toilet-trained), age in months (2–11, 12–23, 24–35, and ≥36), race (white versus non-white), and type of index UTI (febrile versus symptomatic).

[b] Percentages based on Kaplan-Meier 2-year estimates.

[c] Defined as decreased uptake of tracer that was associated with loss of contours or the presence of cortical thinning with decreased volume. Due to the limited number of children with severe scarring, odds ratios were calculated by using Firth's penalized likelihood method.

[d] Refers to scarring present at the end of 2 years, whether it was new or present at study entry.

[e] Defined as scarring on the outcome renal scan with DMSA that was not present at baseline. N's for new scarring were as follows: no VUR, *n* = 141; VUR, *n* = 227; grade I and II, *n* = 123; and grade III and IV, *n* = 104.

in several studies,[7,8,33] younger age (<6 months) rather than older age was associated with increased risk of recurrent UTI. This observation is likely due to selection bias in those studies, which enrolled children who presented to the emergency department or were hospitalized for UTI, a common scenario for infants with UTI. This method is in comparison with the present study and the study by Conway et al,[6] which enrolled and followed up many children from the primary care setting (ie, the setting in which the majority of UTIs in older children are managed).

Due to the observational nature of the present study, some limitations were unavoidable. For example, once BBD was identified, some sites provided guidance to families on strategies for managing this condition, which may have reduced the rate of recurrent UTI. Thus, our recurrence rates may underestimate the true rate in a population of children that are not managed as closely and/or assessed every 6 months for BBD. Our study was also limited to some extent by sample size, especially in the group of children with no VUR. Small sample size and the relatively low frequency of renal scarring prevented us from detecting clinically important differences in the development of renal scars and identifying other risk factors for renal scarring. Even for the more frequently occurring clinical outcome of recurrent $_{F/S}$UTI, our sample size did not permit risk stratification by >2 variables.

Nonetheless, our study had several strengths. To our knowledge, this trial is the largest observational study to prospectively follow up a group of children with a history of UTI who did not receive antimicrobial prophylaxis. We designed our studies (RIVUR and CUTIE) to avoid certain limitations of previous studies,[34] which thus strengthened the validity and generalizability of our findings.

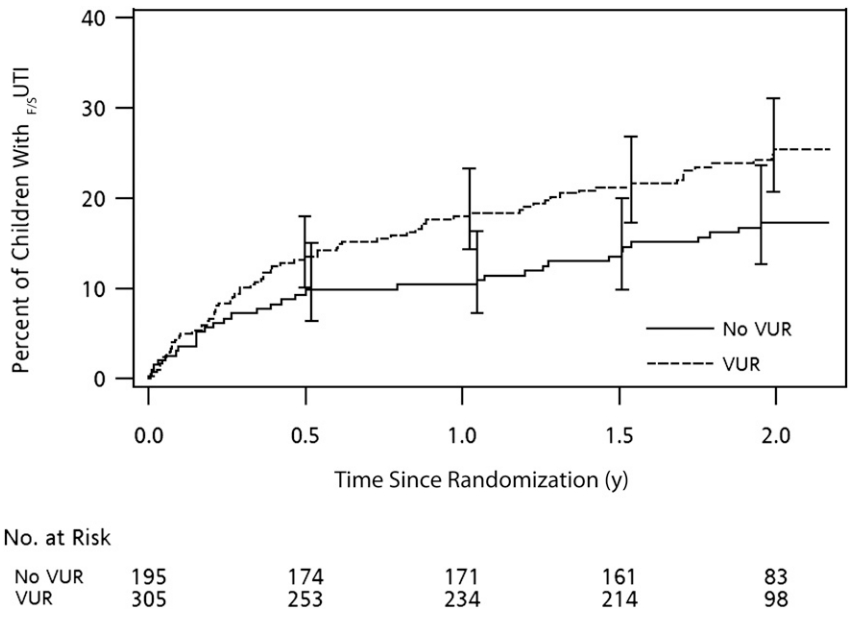

FIGURE 2
Time to first recurrent febrile or symptomatic UTI. Kaplan-Meier estimates are displayed of the cumulative percentage of children who had a recurrent febrile or symptomatic UTI according to presence or absence of VUR. Fewer children in the no VUR group had a recurrent UTI than children in the group with VUR (*P* = .045 by log-rank test). Bars indicate 95% CIs.

TABLE 3 Time-to-Event Analysis for Risk of Recurrent Febrile or Symptomatic UTI

Variable	Univariable			Multivariable[a]		
	HR	95% CI	*P*	HR	95% CI	*P*
VUR grade						
No VUR	Ref			Ref		
Grade I–II	1.32	0.82–2.13	.25	1.49	0.91–2.42	.11
Grade III–IV	1.77	1.11–2.83	.02	1.88	1.14–3.11	.01
Age						
2–11 mo	Ref					
12–23 mo	1.06	0.59–1.90	.84			
24–35 mo	0.87	0.39–1.94	.73			
36–71 mo	2.49	1.61–3.85	<.01			
Race						
Non-white	Ref					
White	1.70	1.01–2.86	.05			
Ethnicity						
Non-Hispanic	Ref					
Hispanic	0.68	0.38–1.22	.20			
Gender						
Female	Ref					
Male	0.44	0.18–1.09	.08			
BBD						
No	Ref			Ref		
Yes	2.01	1.07–3.76	.03	2.07	1.09–3.93	.03
Not toilet-trained	0.60	0.34–1.05	.07	0.66	0.36–1.20	.18
History of UTI						
First	Ref			Ref		
Second	2.08	1.24–3.50	.01	1.70	0.98–2.95	.06
Index organism						
Other	Ref			Ref		
E coli	0.56	0.32–0.99	.04	0.61	0.33–1.11	.10
Education						
High school graduate or lower	Ref			Ref		
Some college or 2-y degree	1.06	0.58–1.93	.84	0.79	0.42–1.49	.47
College graduate or higher	1.84	1.14–2.97	.01	1.39	0.85–2.27	.19
Insurance type						
Public	Ref					
Commercial	1.46	0.96–2.24	.08			
Ureter duplication						
No	Ref					
Yes	2.01	0.94–4.34	.07			
Baseline renal scarring						
None	Ref			Ref		
Scarring	3.21	1.40–7.33	.01	2.88	1.22–6.80	.02

[a] Multivariable model derived from forward stepwise procedure. Variables with univariable *P* values <.25 were considered for entry into the model and remained in the model if the resulting *P* value was <.20.

A representative sample of children with varying degrees of VUR (including no VUR) were enrolled from a variety of clinical settings (including primary care), and we applied stringent diagnostic criteria and used standardized scales to identify risk factors.

CONCLUSIONS

Our study has important implications for clinical practice. Assuming that the antimicrobial prophylaxis treatment effect observed in the RIVUR study would apply to children with no VUR (as suggested by the Australian PRIVENT [Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts] study[35]), and given the relatively high rate of recurrent $_{F/S}$UTI observed in our no VUR group, clinicians might consider using prophylaxis to prevent recurrence of UTI. Although prophylaxis has not been shown to prevent renal scarring, recurrent UTIs may be associated with significant morbidity, including pain, discomfort, fever, vomiting, loss of appetite, office visits, emergency department visits, and occasionally hospitalization. Therefore, clinicians must help families decide whether the benefits of prophylaxis outweigh the risks and inconvenience. Prophylaxis may be particularly effective in children while they are being treated for BBD, and it is important to prevent UTI recurrences, which can interfere with bowel and bladder retraining. Our study also highlights the need for larger studies to identify and validate predictors of recurrent UTI. The risk/benefit ratio of antimicrobial prophylaxis is likely to be more favorable in subgroups of children who have the highest risk of recurrent UTI. In addition to BBD, there may be other high-risk profiles defined by using clinical, demographic, or even genetic characteristics. Given the increasing concerns regarding the contribution of antimicrobial prophylaxis to the emergence of bacterial resistance and the unknown impact on the microbiome, more accurate risk stratification will permit more judicious use of antimicrobial prophylaxis in the future. Before risk stratification strategies can be used to selectively identify patients for antimicrobial prophylaxis, additional research is needed to validate the risk factors and profiles that we identified.

ABBREVIATIONS

BBD: bladder and bowel dysfunction
CI: confidence interval
DMSA: ^{99m}Tc-labeled dimercaptosuccinic acid
$_{F/S}$UTI: febrile or symptomatic urinary tract infection
HR: hazard ratio
UTI: urinary tract infection
VUR: vesicoureteral reflux

Address correspondence to Ron Keren, MD, MPH, Children's Hospital of Philadelphia, ABR 1347, Philadelphia, PA 19104. E-mail: keren@email.chop.edu

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