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Predictors of Non-*Escherichia coli* Urinary Tract Infection

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Abstract

We aimed to determine which children are prone to non-*Escherichia coli* coli UTIs. We included 769 children with UTI. We found that circumcised males, Hispanic children, children without fever, and children with Grade 3–4 VUR were more likely to have a UTI caused by organisms other than *E.* coli. This information may guide clinicians in their choice of antimicrobial therapy.

Keywords

Vesicoureteral reflux; *Escherichia coli*

BACKGROUND

The vast majority of cases of community-acquired urinary tract infection (UTI) are caused by *E. coli*. It may be clinically important to predict which children have UTIs caused by organisms other than *E. coli* because these organisms differ in their patterns of antimicrobial susceptibility. A recent study found that the organisms other that *E. coli* were less likely to be susceptible to first generation cephalosporins and nitrofurantoin.[1] Furthermore, some guidelines[2] have suggested that screening for vesicoureteral reflux (VUR) with a voiding cystourethrogram (VCUG) should, at least in part, be based on whether an organism other than *E. coli* is recovered.

Our objectives were (1) to determine clinical characteristics that might be useful in differentiating children with UTI caused by *E. coli* from children with UTIs caused by

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organisms other than *E. coli*, and (2) to understand associations between clinical characteristics, VUR and pathogen type.

Methods

We used data from two prospective, multicenter studies, in which clinical and demographic characteristics were carefully documented, to determine characteristics associated with the type of infecting organism. The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial included 607 children with VUR and the parallel observational Careful Urinary Tract Infection Evaluation (CUTIE) study enrolled 195 children without VUR. We excluded 33 children with missing data (for organism, voiding cystourethrogram, race, ethnicity, antibiotic treatment, or presence of bladder and bowel dysfunction [BBD]), with a resulting analytic sample of 769 children. Methods of the RIVUR and CUTIE studies have been previously reported.[3–5] Briefly, the RIVUR trial enrolled children 2 to 71 months of age presenting with a first or second febrile or symptomatic UTI from both primary and subspecialty care settings at clinical trial centers throughout North America. Children who were found to have grades I to IV VUR after their index UTI were enrolled in the RIVUR trial. Children 2 to 71 months of age with a first or second UTI but without VUR were enrolled in the CUTIE study at 3 of the 19 participating RIVUR sites (Pittsburgh, Philadelphia and Washington, DC). In both studies urine samples were collected by catheterization, suprapubic aspiration or by clean void; bag-collected specimens were not permitted.

We used logistic regression models to test the associations between demographic and clinical characteristics and uropathogen. The clinical model included baseline predictors known or easily measured at a clinical visit: age, gender, race, ethnicity, presence of BBD, use of antimicrobials in the preceding 6 months for infections other than UTIs, number of previous UTIs, type of index UTI (febrile vs. afebrile). We included site (grouped into 6 administrative sites) in the model as a covariate, and categorized age as 2–11 months, 12–23 months, 24–35 months, and 36–72 months. In the association model, we added VUR (a characteristic not known without performance of VCUG) to the clinical model. We also considered unadjusted associations with uropathogens for the following symptoms: suprapubic/abdominal/flank pain or tenderness, urinary urgency, urinary frequency, urinary hesitancy, dysuria, and foul-smelling urine.

Results

Of 769 children included, 703 (91%) were female and 596 (78%) were white. Forty-nine percent of the cohort was 2–11 months of age; 699 (91%) had index UTIs caused by *E. coli*. The 70 children with UTIs caused by organisms other than *E. coli* incuded 21 (30%) with *Proteus* species, 16 (23%) with *Klebsiella* species, 14 (20%) with *Enterococcus* species, 8 (11%) with *Enterobacter* species, and 11 with other species. Data regarding the antimicrobial resistance of the organisms isolated from these children have been previously reported.[1] Children enrolled in the CUTIE study were older (30% vs. 20% were 36–72 months of age), more likely to be non-white (33% vs. 19%) and Hispanic (20% vs. 12%). Further details regarding the demographic makeup of the sample have previously been reported.

In the clinical model, circumcised males (OR=5.5, 95% CI=1.8—17.1, p=0.003, Table) and Hispanic children (OR=2.3, 95% CI=1.1—4.6, p=0.02) were more likely to have infection caused by pathogens other than *E. coli* compared with females and non-Hispanic children, respectively (Table). Children without fever were also more likely to have infections caused by organisms other than *E. coli* (OR=2.8, 95% CI=1.2—6.6, p=0.02). Pathogen type was similar with respect to age, race, presence of BBD, duration of UTI symptoms before presentation, number of previous UTIs, and number of courses of antimicrobials received in the preceding 6 months for conditions other than UTI.

In the association model, children with grade 3–4 VUR had higher odds of non-*E.coli* infections (OR=2.2, 95% CI=1.2—4.1, p=0.01) compared with children with grade 1–2 VUR (Table). Children with no VUR had a similar odds of non-*E.coli* infections compared to children with grade 1–2 VUR. In the association model, odds ratios noted in the clinical model were largely unchanged. Children 4 months or younger with failure to thrive had a higher percentage of non-*E.coli* infections than other children 4 months or younger (24% vs. 11%). Primary pathogens were similar for other individual symptoms.

Discussion

We found that circumcised males, children with grade III or IV VUR, Hispanic children and children without fever were more likely to have UTI caused by organisms other than *E. coli.* The association between gender and organism type has been previously reported.[6,7] Previous studies have also reported the association between VUR and uropathogen.[8,9] High-grade VUR may be necessary for generally less virulent organisms, which lack adhesins prevalent among *E. coli* starins, to ascend to the kidney. The association between Hispanic ethnicity and non-*E. coli* pathogens is novel and may be due to differences in genes involved with susceptibility to UTIs. Fever with infections caused by *E. coli* may be related to the organism's enhanced ability to ascend into the kidney.

Approximately one quarter of circumcised males and one quarter of afebrile children had infections caused by organisms other than *E. coli.* As a group, non-*E. coli* species are more likely to be resistant to first generation cephalosporins and nitrofurantoin.[1] Accordingly, if these data are replicated, clinicians may want to avoid using first-line agents for the treatment of UTIs in these subgroups.; second or third generation cephalosporins would be the preferred agents.

Children with UTIs caused by organisms other than *E. coli* were twice as likely to have high-grade VUR (Grade III and IV), which is consistent with prior studies.[8,9]

The main limitation of this study is that the children we included are not likely representative of all children with UTI because tbecause a relatively large proportion of children had VUR. Nevertheless, after adjusting for VUR, circumcised males and afebrile children had higher rates of infection by organisms other than *E. coli.*

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Table

Predictors of infection with an organism other than *E. coli*; unadjusted, clinical * and association * models

			Unadjusted		Clinical Model		Association model	
	n/N	% Non-*E. coli*	Odds ratio (CI)	P	Odds ratio (CI)*	P*	Odds ratio (CI)*	P*
Age (months)								
2–11	34/374	9	Ref		Ref		Ref	
12–23	5/136	4	0.4 (0.2, 1.0)	0.05	0.4 (0.2, 1.2)	0.10	0.4 (0.2, 1.2)	0.11
24–35	14/89	16	1.9 (1.0, 3.7)	0.07	1.6 (0.7, 3.7)	0.29	1.6 (0.7, 3.8)	0.27
36–72	17/170	10	1.1 (0.6, 2.1)	0.74	0.8 (0.2, 2.6)	0.66	0.7 (0.2, 2.5)	0.61
Race								
White	58/596	10	Ref		Ref		Ref	
Non-White	12/173	7	0.7 (0.4, 1.3)	0.26	0.6 (0.3, 1.1)	0.11	0.6 (0.3, 1.2)	0.12
Gender								
Female	58/703	8	Ref		Ref		Ref	
Uncircumcised Male	7/45	16	2.1 (0.9, 4.8)	0.10	1.6 (0.6, 4.6)	0.35	1.7 (0.6, 4.8)	0.35
Circumcised Male	5/21	24	3.5 (1.2, 9.8)	0.02	5.5 (1.8, 17.1)	0.003	5.3 (1.7, 16.9)	0.005
Ethnicity								
Non-Hispanic	54/663	8	Ref		Ref		Ref	
Hispanic	16/106	15	2.0 (1.1, 3.7)	0.02	2.3 (1.1, 4.6)	0.02	2.4 (1.2, 4.8)	0.02
Bladder Bowel Dysfunction								
No	10/84	12	Ref		Ref		Ref	
Yes	10/95	11	0.9 (0.3, 2.2)	0.77	0.8 (0.3, 2.2)	0.67	0.8 (0.3, 2.1)	0.65
Not toilet trained	50/590	8	0.7 (0.3, 1.4)	0.30	0.7 (0.2, 2.4)	0.58	0.6 (0.2, 2.1)	0.45
Courses of antimicrobials in the preceding 6 months								
0	31/399	8	Ref		Ref		Ref	
1	22/229	10	1.3 (0.7, 2.2)	0.43	1.3 (0.7, 2.5)	0.36	1.3 (0.7, 2.5)	0.38
≥2	17/141	12	1.6 (0.9, 3.0)	0.13	1.6 (0.8, 3.2)	0.16	1.8 (0.9, 3.4)	0.11
Number of previous UTIs								
0	60/700	9	Ref		Ref		Ref	
1	10/69	14	1.8 (0.9, 3.7)	0.11	1.6 (0.7, 3.5)	0.28	1.5 (0.7, 3.4)	0.33

	n/N	% Non-*E. coli*	Unadjusted		Clinical Model		Association model	
			Odds ratio (CI)	P	Odds ratio (CI)*	P*	Odds ratio (CI)*	P*
VUR Grade								
No VUR	12/186	6	0.9 (0.4, 1.8)		N/A *		1.2 (0.5, 2.9)	0.67
Grades I or II	23/314	7	Ref					
Grades III or IV	35/269	13	1.9 (1.1, 3.3)		N/A *		2.2 (1.2, 4.1)	<0.01
Fever								
No	11/46	24	3.8 (1.8, 8.0)	0.0004	2.8 (1.2, 6.6)	0.02	3.3 (1.4, 7.8)	0.008
Yes	49/644	8	Ref		Ref		Ref	
Unknown	10/79	13	1.8 (0.9, 3.6)	0.13	1.4 (0.6, 3.3)	0.43	1.4 (0.6, 3.3)	0.44
Site								
Pittsburgh	20/273	7	Ref		Ref		Ref	
Philadelphia	6/89	7	0.9(0.4, 2.4)	0.85	1.0 (0.4, 2.7)	0.98	1.0 (0.4, 2.8)	0.94
Washington DC	4/77	5	0.7 (0.2, 2.1)	0.52	0.6 (0.2, 1.9)	0.35	0.5 (0.2, 1.8)	0.30
Baltimore	7/78	9	1.3 (0.5, 3.1)	0.63	1.2 (0.4, 3.1)	0.76	1.0 (0.3, 2.7)	0.94
Michigan	14/106	13	1.9 (0.9, 4.0)	0.08	2.1 (0.9, 4.7)	0.08	1.7 (0.7, 4.2)	0.23
New York	19/146	13	1.9 (1.0, 3.7)	0.06	1.8 (0.9, 3.6)	0.13	1.6 (0.7, 3.6)	0.27

Ref, reference category.

*The clinical model adjusted for age, race, ethnicity, gender, BBD, fever, site, number of previous UTIs, and previous antibiotic. The association model adjusted for all of the variables in the clinical model plus vesicoureteral reflux (VUR).