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Predictors of Antimicrobial Resistance among Pathogens Causing Urinary Tract Infection in Children

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Abstract

Objective—To determine which children with urinary tract infection (UTI) are likely to have pathogens resistant to narrow-spectrum antimicrobials.

Study design—Children, 2 to 71 months of age (n=769) enrolled in the RIVUR or CUTIE studies were included. We used logistic regression models to test the associations between demographic and clinical characteristics and resistance to narrow-spectrum antimicrobials.

Results—Of the included patients, 91% were female and 76% had vesicoureteral reflux. The risk of resistance to narrow-spectrum antibiotics in uncircumcised males was approximately 3 times that of females (OR=3.1; 95% CI: 1.4—6.7); in children with bladder bowel dysfunction (BBD) the risk was 2 times that of children with normal function (OR=2.2; 95% CI: 1.2—4.1). Children who had received one course of antibiotics during the past 6 months also had higher odds of harboring resistant organisms (OR=1.6; 95% CI: 1.1—2.3). Hispanic children had higher odds of harboring pathogens resistant to some narrow-spectrum antimicrobials.

Conclusions—Uncircumcised males, Hispanic children, children with BBD, and children who received one course of antibiotics in the past 6 months were more likely to have a UTI caused by pathogens resistant to one or more narrow-spectrum antimicrobials.

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Keywords

Antibiotic; sensitivity; resistance; vesicoureteral reflux; *Escherichia coli*

The majority of cases of community-acquired urinary tract infection (UTI) are treated (72%) (1) with narrow spectrum antimicrobials, defined here as first generation cephalosporins, trimethoprim sulfamethoxazole, nitrofurantoin, and amoxicillin. However, emerging resistance among uropathogens threatens to limit the efficacy of these antimicrobials. In order to promote continued judicious use of narrow-spectrum antimicrobials, it would be important to determine characteristics of children who can continue to safely and appropriately receive these agents. Available data suggest that young age,(2, 3) female sex, (2, 4) black race,(5) and recent exposure to antimicrobials(5) may be associated with antimicrobial resistance. However, the majority of these data were obtained through retrospective analyses of cross-sectional databases assembled for other reasons, and many of them lacked detailed descriptions of patients.

In this investigation, we used data from two prospective, multicenter studies, in which clinical and demographic characteristics were carefully documented, to determine if patient characteristics could be used to predict resistance to narrow-spectrum antimicrobials. Participant characteristics linked with resistance were further investigated using a mediation model. In these models we assessed whether pathogen type (*E. coli* vs. non- *E. coli*) could explain any observed associations between patient characteristics and resistance.

METHODS

Our database included 607 children with vesicoureteral reflux (VUR) enrolled in the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial and 195 children without VUR enrolled in the parallel observational Careful Urinary Tract Infection Evaluation (CUTIE) study. We excluded 33 children with missing data (organism, voiding cystourethrogram, race, ethnicity, antibiotic treatment, or presence of BBD), resulting in a sample of 769 children. Methods of the RIVUR and CUTIE studies have been previously reported.(6–8) 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 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). None of the children enrolled in either study were receiving antimicrobial prophylaxis for VUR at the time of diagnosis of the index UTI. BBD, which refers to an abnormal pattern of elimination characterized by bowel and bladder incontinence and/or withholding, was assessed at the time of enrollment in both studies. The reported research has been approved an the institutional review board.

Resistance patterns of urinary pathogens were reported according to each laboratory's protocol. Although all laboratories were certified through the Clinical Laboratory Improvement Amendments (CLIA) process, not all laboratories tested for the same

antimicrobials. Accordingly, the total number of specimens differs for each antimicrobial. For the purposes of this analysis, we combined intermediate and full resistance. We grouped antimicrobials according to class because pathogens generally exhibit the same resistance profile for all antimicrobials in a given class (i.e., a pathogen will either be resistant or sensitive to all first generation cephalosporins tested). If a pathogen was resistant to any member of a class, it was classified as resistant. First-generation cephalosporins included cefadroxil, cefazolin and cephalexin; second-generation cephalosporins included cefotetan, cefoxitin, cefuroxime; third-generation cephalosporins included cefotaxime, cefixime, ceftazidime and ceftriaxone; and quinolones included ciprofloxacin, gemifloxacin, levofloxacin and norfloxacin. We did not include cephalothin in the first-generation cephalosporin group because, in our data and in other studies, resistance to cephalothin is inconsistent with resistance to other first-generation cephalosporins.(2) We grouped amoxicillin and ampicillin together.

We used logistic regression models to test the independent association between demographic and clinical characteristics and resistance to narrow-spectrum antimicrobials. The following baseline predictors were considered: age, site (grouped into 6 administrative sites), organism, sex, 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), and symptom duration (0 days, 1–2 days, 3–4 days, 5+ days, unknown). Age was categorized as 2–11 months, 12–23 months, 24–35 months, and 36–72 months. Unadjusted effects for the following symptoms were also considered: suprapubic/abdominal/flank pain or tenderness, urinary urgency, urinary frequency, urinary hesitancy, dysuria, and foul-smelling urine. Because vesicoureteral status is unknown at the time of diagnosis, we did not include this variable in our prediction model. We did, however, separately examine whether presence or grade of VUR was associated with resistance to narrow-spectrum antimicrobials.

To explore whether the relationship between characteristics and resistance to narrow-spectrum antimicrobials was mediated by organism type, we used the approach suggested by Imai, Keele, and Tingly.(9)

RESULTS

Table I describes clinical and demographic characteristics of the sample. Of 769 children, 703 (91%) were female and 596 (78%) were white; 49% of the cohort was aged 2–11 months; 699 (91%) had index UTIs caused by *E. coli*. Children enrolled in the CUTIE study were older (30% vs. 20% age 36–72 months), more likely to be non-white (33% vs. 19%) and Hispanic (20% vs. 12%).

Of 889 instances in which two or more antimicrobials of the same class were tested on the same isolate, we identified 16 discrepancies (1.8%) in antimicrobial resistance within a class (7 among second-generation cephalosporins, 2 among third-generation cephalosporins and 7 among quinolones). As previously noted, we assumed resistance to a class of antimicrobials when resistance was observed for any member of the class.

The proportion of children with pathogens sensitive to the various classes of antimicrobials is shown in the Figure. Overall, sensitivity to amoxicillin was low, with little difference noted between *E. coli* 55%) and organisms other than *E. coli* 61%). Sensitivity to first-generation cephalosporins and nitrofurantoin was generally high among *E. coli* pathogens (93% and 99%, respectively), but not so for non-*E. coli* pathogens (72% and 40%, respectively). The opposite was the case for trimethoprim-sulfamethoxazole with *E. coli* pathogens exhibiting lower sensitivity than non-*E. coli* pathogens (81% vs. 98%, respectively). Sensitivity to second-generation cephalosporins, third-generation cephalosporins, gentamicin, tobramycin and quinolones was >90% for both *E. coli* and non-*E. coli* organisms and considerably higher than sensitivity to amoxicillin clavulanate.

Predictors of resistance to narrow-spectrum antimicrobials

The risk of resistance (Table II) in uncircumcised males was approximately 3 times that of females for first-generation cephalosporin (OR=3.2; 95% CI=1.2—8.8) and amoxicillin (OR=3.2; 95% CI=1.5—6.7). Receipt of one dose of antibiotics in the past 6 months also increased the odds of resistance to first-generation cephalosporin (OR=2.1; 95% CI=1.1—4.0) and amoxicillin (OR=1.5; 95% CI=1.0—2.1), but receipt of 2 or more courses of antimicrobials did not modify the odds of resistance to narrow-spectrum antimicrobials. Hispanic children had higher odds of harboring pathogens resistant to trimethoprim-sulfamethoxazole (OR=2.5, 95% CI=1.5—4.1, p<.0001) and exhibited the same trend with other antimicrobials. Particularly high rates of resistance to amoxicillin (66%) and trimethoprim-sulfamethoxazole (40%) were found in children from Washington D.C. Presence of BBD was associated with resistant pathogens for 2 of the 4 antibiotics. Age, race, and fever were not associated with resistant uropathogens. We examined rates of resistance by VUR grade (grouped as 0, 1–2, 3–4) for antimicrobials listed in Table II. Only nitrofurantoin had a significant difference in resistance by VUR grade (4% in VUR grade 0, 4% in VUR grades 1–2, and 9% in VUR grades 3–4, chi-square p-value=0.04). Rates of resistance for other antimicrobials did not differ by VUR grade (p≥0.31).

The associations between sex/circumcision, BBD, and Hispanic ethnicity and resistance to trimethoprim sulfamethoxazole, amoxicillin, or first generation cephalosporins were consistent after adjusting for pathogen type (data not shown). This indicates that pathogen type did not mediate any of the associations between characteristics and resistance to these 3 antibiotics. Resistance to nitrofurantoin, however, was dominated by the effect of primary pathogen (OR=690.3, 95% CI=140.6—3389.5).

DISCUSSION

The desire to use narrow-spectrum antimicrobials relates to cost, safety and concerns regarding antimicrobial resistance. Accordingly, the ability to determine accurately the risk of resistance to narrow-spectrum antimicrobials is desirable. This information may allow clinicians to use clinical factors available at the time of diagnosis to select effective antimicrobials more judiciously; children with risk factors for resistance should be treated with broader-spectrum agents, thus potentially reducing the incidence of treatment failure

and scarring,(10–13), and children with low risk could safely be treated with narrow-spectrum agents.

We identified predictors of resistant pathogens to the most frequently used narrow-spectrum antimicrobials. Uncircumcised males, Hispanic children, and children with BBD were more likely to have a UTI caused by pathogens resistant to one or more narrow-spectrum antimicrobials. The higher rates of resistance for some antimicrobials in children with BBD are intriguing. Perhaps, children with BBD, who may incompletely empty their bladders, have UTIs caused by bacterial strains with different virulence factors and different resistance patterns. The reasons for the higher rates of resistance in Washington D.C. are not clear. Similar to previous reports,(5) we found that the use of antimicrobials during the past 6 months increased the risk of resistance to narrow-spectrum antimicrobials. However, our data showed an inconsistent dose-response trend, i.e., more exposure to antibiotics did not result in increased likelihood of resistance. Unlike one previous study,(5) we did not find that age <1 year, female sex, or black race were risk factors for resistance to narrow-spectrum antimicrobials.

Resistance to amoxicillin was high; approximately 40% of children had organisms resistant to this antimicrobial. Accordingly, use of the antimicrobial for the treatment of UTI is not appropriate. Of note, resistance to amoxicillin clavulanate was also relatively high in our sample; 17.5% of children had organisms that were resistant to this antimicrobial (Figure). Accordingly, this broad-spectrum antimicrobial is not an ideal choice for children who have risk factors for resistance to narrow-spectrum antimicrobials; a second or third generation cephalosporin would be a more appropriate choice in such children.

We investigated possible mediation of resistance by pathogen type. We found that for all narrow-spectrum antibiotics except nitrofurantoin, resistance was largely independent of pathogen type. In contrast, resistance to nitrofurantoin was mediated by pathogen type; circumcised males, Hispanic children, and children with an afebrile UTI were more likely to have infections with organisms other than *E. coli*, and because of this exhibited resistance to nitrofurantoin.

Based on our results we would treat children with a high likelihood of renal involvement (high fever with or without back pain), with a second- or third-generation cephalosporin; the predicted probability of resistance to first-generation cephalosporins, trimethoprim sulfamethoxazole, amoxicillin is relatively high and the tissue concentrations of nitrofurantoin may not be adequate to eradicate the causative organism. In contrast, in an afebrile child with low risk of renal involvement, a first-generation cephalosporin would be considered as the most appropriate option; the predicted probability of resistance to trimethoprim sulfamethoxazole and amoxicillin are relatively high and nitrofurantoin needs to be given more frequently and is more likely to cause gastrointestinal symptoms.

This report has some limitations. Different local laboratories were involved and they did not always test for resistance to the same antibiotics. Nevertheless, all laboratories were certified CLIA. Additionally, children participating in the RIVUR and CUTIE studies are not representative of all children with UTI; for example, the majority of our participants had

VUR. However, with one exception (nitrofurantoin) the presence of VUR was not associated with resistance to narrow-spectrum antimicrobials.

Importantly, our results are not meant to replace the use of local antibiograms. Rather our goal was to explore generalizable risk factors for resistance. If a local antibiogram is available, especially if it is restricted to ambulatory,(14, 15) pediatric patients,(16) it should be used to guide therapy. Clinicians treating children with UTI can use these data to more judiciously select children who can appropriately receive narrow-spectrum antimicrobials.

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List of abbreviations

OR	odds ratio
CI	confidence interval
BBD	Bladder and Bowel Dysfunction
VUR	Vesicoureteral reflux
UTI	urinary tract infection
RIVUR	Randomized Intervention for Children with Vesicoureteral Reflux
CUTIE	Careful Urinary Tract Infection Evaluation study

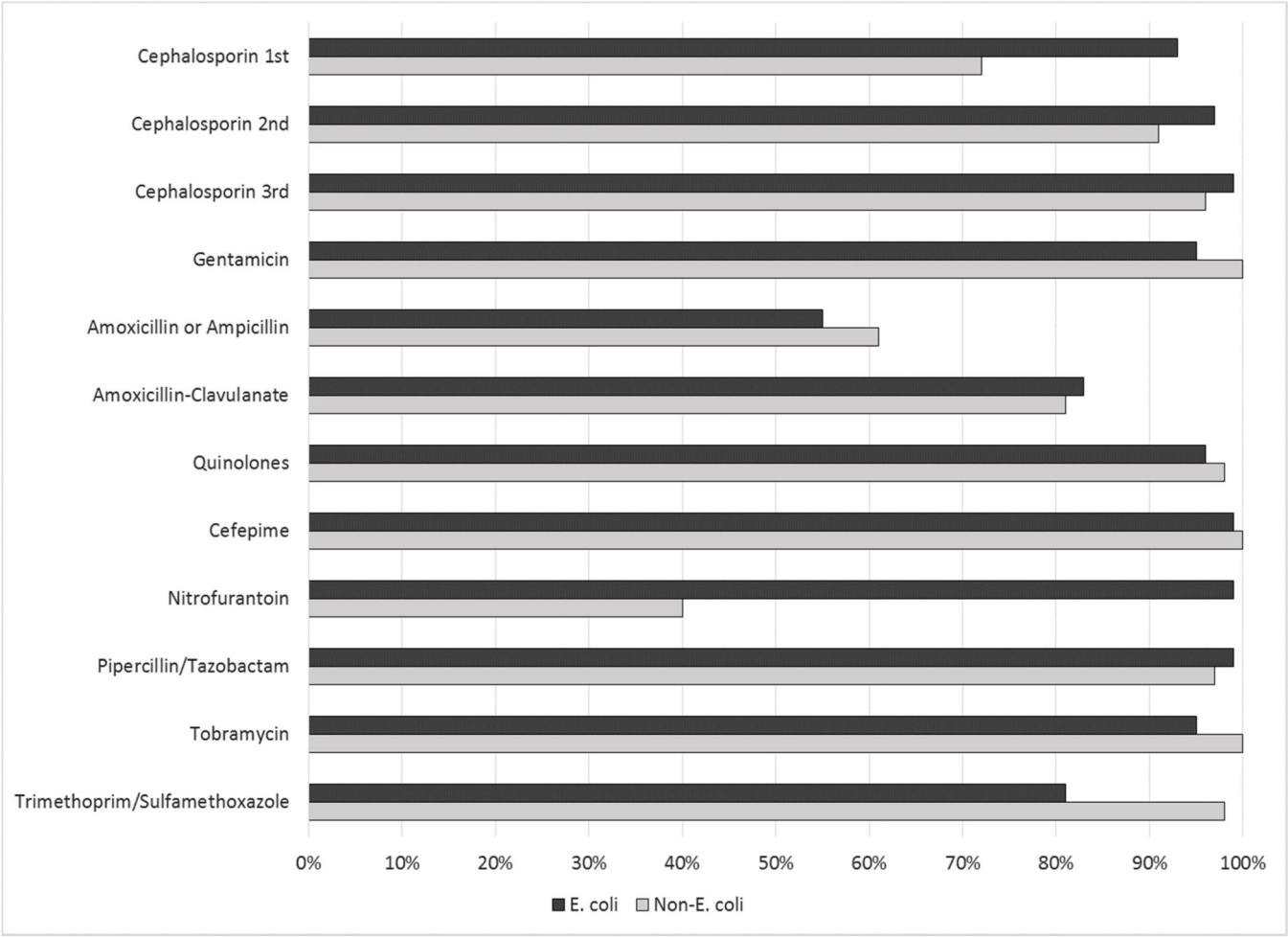

Figure 1.
Proportion of pathogens susceptible to each class of antibiotic

Table 1

Demographic and clinical characteristics of children with urinary tract infection

Characteristic	Total (n=769) N (%)
Age (months)	
2–11	374 (49)
12–23	136 (18)
24–35	89 (12)
36–72	170 (22)
Sex	
Female	703 (91)
Uncircumcised male	45 (6)
Circumcised male	21 (3)
Race	
White	596 (78)
Non-White	173 (22)
Ethnicity	
Hispanic	106 (14)
Non-Hispanic	663 (86)
Vesicoureteral reflux	
No vesicoureteral reflux	186 (24)
Vesicoureteral reflux grades I-II	314 (41)
Vesicoureteral reflux grades III-IV	269 (35)
Bladder Bowel Dysfunction	
Yes	95 (12)
No	84 (11)
Not toilet trained	590 (77)
Number of prior UTIs	
0	700 (91)
1	69 (9)
Number of times antimicrobials prescribed in preceding 6 months	
0	399 (52)
1	229 (30)
≥2	141 (18)

Table 2

Predictors of resistance to frequently used antimicrobial agents in children with urinary tract infection

	Any Narrow-spectrum Antibiotic (N=755)			1st generation cephalosporin (N=659)			Trimethoprim sulfamethoxazole (N=725)			Nitrofurantoin (N=718)			Amoxicillin (N=729)		
	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*
Age (months)															
2–11	52	Ref		8	Ref		20	Ref		5	Ref		47	Ref	
12–23	48	0.89 (0.58, 1.34)	0.57	8	0.90 (0.39, 2.04)	0.79	23	1.21 (0.72, 2.04)	0.47	4	0.81 (0.28, 2.30)	0.69	41	0.82 (0.54, 1.26)	0.36
24–35	63	1.62 (0.93, 2.81)	0.09	8	0.90 (0.30, 2.70)	0.85	16	0.84 (0.39, 1.80)	0.65	13	1.64 (0.57, 4.72)	0.36	48	1.19 (0.69, 2.08)	0.53
36–72	47	0.76 (0.36, 1.63)	0.48	9	0.79 (0.17, 3.72)	0.76	18	0.67 (0.23, 2.00)	0.48	4	0.44 (0.08, 2.33)	0.33	42	0.94 (0.44, 2.03)	0.88
Sex															
Female	50	Ref		8	Ref		18	Ref		5	Ref		43	Ref	
Uncircumcised Male	77	3.08 (1.41, 6.69)	0.005	19	3.21 (1.16, 8.84)	0.02	38	1.94 (0.90, 4.17)	0.09	10	1.36 (0.37, 5.04)	0.65	73	3.15 (1.50, 6.63)	0.002
Circumcised Male	60	1.82 (0.71, 4.66)	0.21	7	1.12 (0.14, 9.22)	0.92	26	2.15 (0.72, 6.44)	0.17	6	0.95 (0.11, 8.48)	0.97	40	0.94 (0.37, 2.39)	0.89
Race															
White	52	Ref		8	Ref		19	Ref		6	Ref		46	Ref	
Non-White	49	0.81 (0.56, 1.17)	0.26	9	0.91 (0.46, 1.81)	0.78	21	0.95 (0.60, 1.50)	0.82	4	0.62 (0.26, 1.50)	0.29	43	0.89 (0.62, 1.29)	0.55
Ethnicity															
Non-Hispanic	49	Ref		8	Ref		17	Ref		5	Ref		43	Ref	
Hispanic	65	1.40 (0.87, 2.25)	0.16	13	1.53 (0.68, 3.41)	0.30	39	2.47 (1.49, 4.11)	<0.001	9	2.29 (0.93, 5.62)	0.07	57	1.22 (0.76, 1.95)	0.41
Site															
Pittsburgh	46	Ref		8	Ref		14	Ref		6	Ref		42	Ref	
Philadelphia	43	0.81 (0.49, 1.33)	0.40	9	1.03 (0.39, 2.67)	0.96	23	1.54 (0.82, 2.91)	0.18	2	0.40 (0.09, 1.87)	0.25	34	0.64 (0.37, 1.08)	0.09
Washington	71	2.19 (1.21, 3.97)	0.01	10	0.99 (0.34, 2.88)	0.99	40	2.45 (1.27, 4.72)	0.008	6	0.71 (0.20, 2.54)	0.60	66	2.08 (1.16, 3.74)	0.01
Baltimore	55	1.15 (0.67, 1.96)	0.62	6	0.73 (0.23, 2.34)	0.59	19	1.10 (0.53, 2.30)	0.80	7	1.06 (0.34, 3.27)	0.92	47	1.04 (0.61, 1.79)	0.88
Michigan	50	0.98 (0.60, 1.62)	0.95	10	1.18 (0.45, 3.05)	0.74	18	1.06 (0.54, 2.07)	0.87	9	1.73 (0.64, 4.67)	0.28	39	0.71 (0.43, 1.20)	0.20
New York	55	1.19 (0.78, 1.82)	0.43	8	0.90 (0.39, 2.05)	0.80	20	1.17 (0.66, 2.08)	0.60	4	0.66 (0.24, 1.84)	0.43	49	1.07 (0.69, 1.65)	0.76

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	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*	% Resistant	Odds ratio (CI)*	P*
Bladder and bowel dysfunction															
No	40	Ref		10	Ref		11	Ref		6	Ref		31	Ref	
Yes	60	2.19 (1.17, 4.12)	0.01	9	0.89 (0.29, 2.79)	0.85	26	2.69 (1.12, 6.45)	0.03	4	0.72 (0.17, 2.96)	0.64	55	2.46 (1.27, 4.74)	0.007
Not toilet trained	52	1.23 (0.56, 2.69)	0.61	8	0.74 (0.15, 3.55)	0.70	20	1.02 (0.32, 3.28)	0.98	6	0.84 (0.19, 3.72)	0.82	45	1.60 (0.71, 3.60)	0.26
Courses of antimicrobials in the preceding 6 months															
0	49	Ref		7	Ref		19	Ref		6	Ref		44	Ref	
1	57	1.62 (1.14, 2.30)	0.008	11	2.07 (1.07, 4.02)	0.03	24	1.52 (0.97, 2.37)	0.07	5	0.90 (0.41, 1.99)	0.79	48	1.44 (1.01, 2.07)	0.05
≥2	51	1.14 (0.76, 1.70)	0.54	9	1.55 (0.71, 3.40)	0.27	16	0.94 (0.54, 1.63)	0.82	5	0.83 (0.33, 2.07)	0.68	43	1.02 (0.68, 1.55)	0.91
Fever															
No	61	Ref		10	Ref		16	Ref		11	Ref		48	Ref	
Yes	51	0.79 (0.40, 1.56)	0.50	8	0.89 (0.28, 2.87)	0.85	21	1.68 (0.67, 4.23)	0.27	4	0.40 (0.12, 1.28)	0.12	45	1.07 (0.54, 2.12)	0.84
Unknown	51	0.87 (0.39, 1.91)	0.72	11	1.31 (0.33, 5.20)	0.70	12	1.00 (0.32, 3.14)	0.99	12	1.46 (0.39, 5.37)	0.57	42	1.06 (0.48, 2.35)	0.89

*Adjusted for age, site, race, gender, BBD, ethnicity, number of prior UTIs, recent antibiotic use, and fever.

C-statistic for narrow spectrum antibiotics, 1st generation cephalosporins, trimethoprim sulfamethoxazole, nitrofurantoin, and amoxicillin were 0.63, 0.61, 0.66, 0.70, and 0.62 respectively.