Recurrent Urinary Tract Infections in Children
Risk Factors and Association With Prophylactic Antimicrobials

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The evidence regarding risk factors for recurrent urinary tract infection (UTI) and the risks and benefits of antimicrobial prophylaxis in children is scant. Objectives To identify risk factors for recurrent UTI in a pediatric primary care cohort, to determine the association between antimicrobial prophylaxis and recurrent UTI, and to identify the risk factors for resistance among recurrent UTIs.

Design, Patients, and Setting From a network of 27 primary care pediatric practices in urban, suburban, and semirural areas spanning 3 states, a cohort of children aged 6 years or younger who were diagnosed with first UTI between July 1, 2001, and May 31, 2006, was assembled. Time-to-event analysis was used to determine risk factors for recurrent UTI and the association between antimicrobial prophylaxis and recurrent UTI, and a nested case-control study was performed among children with recurrent UTI to identify risk factors for resistant infections.

Main Outcome Measures Time to recurrent UTI and antimicrobial resistance of recurrent UTI pathogens.

Results Among 74,974 children in the network, 611 (0.007 per person-year) had a first UTI and 83 (0.12 per person-year after first UTI) had a recurrent UTI. In multivariable Cox time-to-event models, factors associated with increased risk of recurrent UTI included white race (0.17 per person-year; hazard ratio [HR], 1.97; 95% confidence interval [CI], 1.37-5.51), age 4 to 5 years (0.19 per person-year; HR, 2.47; 95% CI, 1.19-5.12), and grade 4 to 5 vesicoureteral reflux (0.60 per person-year; HR, 4.38; 95% CI, 1.26-15.29). Sex and grade 1 to 3 vesicoureteral reflux were not associated with risk of recurrent UTI. Antimicrobial prophylaxis was associated with decreased risk of recurrent UTI (HR, 1.01; 95% CI, 0.50-2.02), even after adjusting for propensity to receive prophylaxis, but was a risk factor for antimicrobial resistance among children with recurrent UTI (HR, 7.50; 95% CI, 1.60-35.17).

Conclusion Among the children in this study, antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.

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efficacy of prophylaxis have demonstrated no protective effect for preventing recurrent UTI and renal scarring. Moreover, concerns have been raised about the potential harm of antimicrobial prophylaxis because of its potential to breed resistant organisms that can cause recurrent UTIs.

Given the limited information regarding risk factors for recurrent UTI and the risks and benefits of antimicrobial prophylaxis, we sought to (1) identify risk factors for recurrent UTI in a pediatric primary care cohort, (2) examine the association between prophylactic antimicrobials and recurrent UTI, and (3) determine the risk factors for resistance among recurrent UTIs.

METHODS

Design

We assembled a cohort of children aged 6 years or younger who were diagnosed with first UTI between July 1, 2001, and May 31, 2006. Time-to-event analyses were used to determine risk factors for recurrent UTI and effectiveness of antimicrobial prophylaxis. Time to event was defined as the time from first UTI until recurrent UTI (event of interest) or until last clinic visit (observation censored without event occurring). Among children with recurrent UTI, a nested case-control study was performed to identify risk factors for resistant organisms as the cause of the recurrent UTI. Power and sample-size calculations indicated that 77 patients with recurrent UTI were needed to have 90% power to detect a hazard ratio of 1.5, assuming a 15% recurrence rate, type I error of .05, and 1-year follow-up.

Setting

Patients were drawn from a network of 27 primary care pediatric practices spanning 3 states (Delaware, New Jersey, and Pennsylvania) that share a common electronic health record (EHR) managed by The Children’s Hospital of Philadelphia. The practices are located in urban, suburban, and semirural locations. The institutional review board of The Children’s Hospital of Philadelphia approved the study, waiving the need for patient consent.

Data Sources

Data were extracted from the EHR used by the 27 primary care pediatric practices in the research network. In addition to data entered at the point of care, the EHR is automatically populated with administrative and research data from several other sources, including the children’s hospital emergency department and main hospital as well as 2 laboratory vendors in the tri-state area (Quest Diagnostics [Lyndhurst, New Jersey] and LabCorp [Raritan, New Jersey]).

Documents and results obtained from hospitals and emergency departments outside the network also can be scanned or manually entered into the EHR by practice staff. The EHR contains demographic and clinic visit information, laboratory data, radiology results, comorbid conditions coded using the International Classification of Diseases, Ninth Revision (ICD-9), and detailed prescription data that were electronically extracted into the research database. Antimicrobial sensitivity results for urinary pathogens and results for voiding cystourethrogram (VCUG) could not be reliably extracted electronically; therefore, we reviewed the patients’ EHR and manually entered urine antimicrobial sensitivity and VCUG results into the research database.

To minimize missing results from outside the network, we also searched the electronic and paper charts for correspondence from outside hospitals and clinics and included any results obtained outside the network. All data elements were validated with the patient chart as the gold standard on a 5% random sample of patients, and all presumed patients with higher acuity (>2 hospitalizations). Abstracted data agreed with the gold standard for all data elements with greater than 95% sensitivity and specificity.

Patients

The initial cohort (Figure) was defined as all children aged 6 years or younger with at least 2 clinic visits between July 1, 2001, and May 31, 2006 (N=74 974). Two clinic visits were required so that observation time could be accrued. Microbiology records in the EHR for these children were queried for presence of positive urine culture results, defined as 50 000 colony-forming units/mL or greater of a single organism considered to be a urinary tract pathogen, a criterion previously validated for catheterized specimens; 775 children who had experienced a first UTI were identified.

The electronic and paper records (including correspondence from outside hospitals and clinics, problem lists, visit notes, and microbiology results) of all children with positive urine culture results were manually reviewed, and any child with history of a previous UTI was excluded (n=91). To provide sufficient observation time to develop a recurrent UTI (at least 14 days after a typical 10-day treatment course), children with fewer than 24 days of observation time (n=55) were excluded. To assemble a cohort representative of otherwise well children in the community, we excluded 17 children with the following comorbid conditions defined a priori based on ICD-9 codes from the EHR: malignancy (140-239.xx), diabetes (248.xx), cystic fibrosis (279.0), chronic renal failure (586.xx), and Down syndrome (755.xx).
tes (250.xx), human immunodeficiency virus (042), other congenital immunodeficiencies (279.xx), sickle cell disease (282.6), neurogenic bladder and paralytic syndromes (343-344.xx), hypertensive renal disease (403.xx), nephritis and renal failure (580-589.xx), renal calculi (592, 594), kidney disorders (593.xx, except hydroureret and VUR), chronic cystitis (595.xx, except 595.0, acute cystitis), bladder and urethra disorders (596, 598, and 599, except 599.0 UTI), central nervous system malformation (eg, myelomeningocele; 655.0), and congenital anomalies of the urinary system (753.xx). We also excluded 1 child with a urine culture collected from a bag specimen.

Outcomes
Because children entered the cohort at different times and had different lengths of follow-up, time to recurrent UTI was used as the primary outcome. The observation-time end point was defined conservatively as the last clinic visit as opposed to the end of study, because we did not want to assume that children were still within the primary care network past their last documented clinic visit. Recurrent UTI was defined by a second positive urine culture result 2 or more weeks after the termination of therapy for the first UTI.

Of children with documented urine collection methods, only 1 had urine collected via bag specimen (excluded); all but 2 younger than 2 years via catheterization; and all but 1 older than 2 years via clean catch. Since collection included specimens collected via both catheterization and clean-catch, a sensitivity analysis also was performed in which results were recalculated using a cutoff of 100 000 colony-forming units/mL or greater of a single organism.

A survey of network nurse managers indicated that cultures were obtained only if UTI symptoms were present; to validate this claim, we performed a 20% random sample chart review of progress notes at UTI diagnosis to evaluate for presence of symptoms documented consistent with UTI, including fever, dysuria, and/or urinary frequency. In the nested study of children with recurrent UTI, the outcome was resistance among recurrent UTIs. Resistance was defined as a pathogen resistant to any antimicrobial.

Exposures
Exposure variables were defined a priori as age at first UTI, sex, race, VCU result, prophylactic antimicrobial exposure on a daily basis, and other antimicrobial exposure on a daily basis. Antimicrobial prophylaxis prescriptions were identified through a query of electronic prescription records using antimicrobial names, key terms such as prophylaxis, and duration of prescription. Each identified prescription, blinded to the patient’s outcome, was then manually reviewed to verify that it represented UTI antimicrobial prophylaxis. Any antimicrobial prescription not considered UTI prophylaxis was categorized as "other antimicrobial exposure." VUR grade was based on the maximum grade on either side of the urinary collecting system. Results of VUCG were categorized a priori as “not performed,” “normal,” “VUR grade 1-3,” and “VUR grade 4-5.”

Age was analyzed both ordinally by year and dichotomized as age younger than 2 years vs 2 to 6 years, based on guidelines for imaging and prophylaxis specifically applying to children younger than 2 years. Race and ethnicity were reported by parents in the EHR. Less than 3% of the patients were Hispanic, so ethnicity was not evaluated separately. Race was considered as white vs nonwhite, as there were less than 3% Asian and no Native American patients.

Data Analysis
First, the incidence rates were calculated for first and recurrent UTI. Single-variable time-to-event analysis was performed for each exposure variable to determine the hazard ratio (HR) for the outcome of interest, time to recurrent UTI. Sex, race, age at first UTI, and VCU result were considered fixed-time exposures. Prophylactic and other antimicrobial exposure were considered time-varying variables, coded as “0” on days without prescribed antimicrobials and “1” on days that antimicrobials were prescribed. This approach allowed accurate modeling of the intermittent nature of the antimicrobial exposure and accounting for the effect of prophylaxis on a daily basis for each child. Multivariable Cox survival-time regression was then performed to identify risk factors for recurrent UTI.

A stratified analysis (defined a priori) was performed for antimicrobial prophylaxis hazard ratio by sex, age, race, and VUR status to evaluate for effect modification. To control for potential confounding by indication that could occur if physicians prescribed prophylaxis based on factors that increased the risk of recurrence, a propensity score also was developed for receipt of antimicrobial prophylaxis, based on sex, race, age at first UTI, and VUCG result. The propensity score model predicted receipt of prophylactic antimicrobials with good accuracy (c statistic, 0.81). We reanalyzed the effect of prophylaxis in analyses stratified by quintile of propensity score and in multivariable analyses controlling for propensity score as a continuous and categorical (quintiles) variable. For comparison of resistant vs nonresistant recurrent UTIs, univariable logistic regression was performed to measure the association between sex, race, age at first UTI, VCU result, prophylactic antimicrobial exposure, and other antimicrobial exposure to the outcome of resistance. Since this was not a time-to-event analysis, the antimicrobial exposure variable was defined as ever prescribed vs never prescribed. The predicted probability of the recurrent UTI being antimicrobial resistant for each combination of exposures was calculated based on the multivariable model (STATA predict command). All analyses were performed using STATA SE version 9.1 (StataCorp, College Station, Texas); P < .05 was considered statistically significant.

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RESULTS
Clinical Characteristics
A total of 74,974 children aged 6 years or younger had at least 2 clinic visits between July 1, 2001, and May 31, 2006. Among these children, 666 had experienced a confirmed first UTI and had no significant comorbid conditions, resulting in a first-UTI incidence rate of 0.007 per person-year. Fifty-five children had fewer than 24 days of observation, leaving 611 children in the final analytic cohort. Eighty-three percent (13.6%) of these children experienced a recurrent UTI, resulting in a recurrent UTI incidence rate of 0.12 per person-year (12% recurrence per year). Fifty-one (61%) of these recurrent UTIs were caused by a pathogen with antimicrobial resistance. Pathogens included Escherichia coli (78%), other gram-negative rods (16%), Enterococcus (4%), and other organisms (2%). Fifteen percent of children in both the first and the recurrent UTI groups did not have documented urine leukocyte esterase or nitrite results. Of children with results, 473 (91%) of those with first UTI and 68 (95%) of those with recurrent UTI had a positive urinalysis result, defined as presence of leukocyte esterase or nitrites. In review of progress notes for a 20% random sample of first and recurrent UTI events, all children had symptoms consistent with UTI including fever, dysuria, and/or urinary frequency at the time of diagnosis. The mean observation time for the cohort with first UTI was 408 days (median, 310 days; interquartile range, 150-584 days).

The majority of the 611 children with first UTI were female (543 [88.9%]), white (343 [56.1%]), and aged 2 to 6 years (375 [61.4%]). Most did not have a VCUG performed (400 [65.5%]) and had not received antimicrobial prophylaxis (483 [79.1%]) (Table 1). Children younger than 2 years were more likely to have a VCUG performed (137 [58%]) compared with children older than 2 years (75 [20%]). Prophylactic antimicrobials prescribed included cotrimoxazole (61%), amoxicillin (29%), nitrofurantoin (7%), and other antimicrobials including first- through third-generation cephalosporins (3%). Of the 68 male children, there was no documented circumcision status for 32 (47%). Twenty-six (38%) were uncircumcised and 10 (15%) were circumcised.

Table 2. Time-to-Event Analysis for Risk of Recurrent Urinary Tract Infection (UTI)a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable</th>
<th>Multivariableb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Female</td>
<td>1.20 (0.58-2.50)</td>
<td>1.08 (0.51-2.30)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>White</td>
<td>1.99 (1.26-3.16)</td>
<td>1.97 (1.22-3.16)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1 to &lt;2</td>
<td>0.99 (0.43-2.27)</td>
<td>1.05 (0.20-3.37)</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>1.22 (0.51-2.96)</td>
<td>1.26 (0.51-3.07)</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>2.55 (1.33-4.81)</td>
<td>2.75 (1.37-5.51)</td>
</tr>
<tr>
<td>4 to &lt;5</td>
<td>2.17 (1.10-4.29)</td>
<td>2.47 (1.19-5.12)</td>
</tr>
<tr>
<td>5 to &lt;6</td>
<td>1.36 (0.66-2.80)</td>
<td>1.62 (0.73-3.62)</td>
</tr>
<tr>
<td>VUR grade 1-3</td>
<td>1.17 (0.52-2.66)</td>
<td>1.05 (0.43-2.57)</td>
</tr>
<tr>
<td>VUR grade 4-5</td>
<td>4.59 (1.36-15.47)</td>
<td>4.38 (1.26-15.29)</td>
</tr>
<tr>
<td>Antimicrobial prophylaxisa</td>
<td>1.05 (0.57-1.94)</td>
<td>1.01 (0.50-2.02)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; VUR, vesicoureteral reflux.

a Univariable multivariable analysis performed from date of first UTI until event, recurrent UTI, or last clinic visit within the network.

b Time-varying exposure to antimicrobial prophylaxis.

c P < .01.

dP < .05.

TABLE 1. First and Recurrent Urinary Tract Infection (UTI) in The Children’s Hospital of Pennsylvania Primary Care Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>First UTI (n = 611)</th>
<th>Recurrent UTI (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>68 (11.1)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>543 (88.9)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>343 (56.1)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>268 (43.9)</td>
<td>29 (34.9)</td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;2</td>
<td>236 (38.6)</td>
</tr>
<tr>
<td></td>
<td>2-6</td>
<td>375 (61.4)</td>
</tr>
<tr>
<td>VCUG result</td>
<td>Not performed</td>
<td>400 (65.5)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>154 (25.2)</td>
</tr>
<tr>
<td></td>
<td>VUR grade 1-3</td>
<td>50 (8.2)</td>
</tr>
<tr>
<td></td>
<td>VUR grade 4-5</td>
<td>7 (1.1)</td>
</tr>
</tbody>
</table>

Abbreviations: VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

a Among male children, there was no documented circumcision status for 32 (47%); of those with documented status, 26 (38%) were uncircumcised, and 10 (15%) were circumcised.
2- to 6-year olds had significantly increased risk of recurrent UTI (HR, 2.01; 95% CI, 1.20-3.37). Sex, grade 1 to 3 VUR, and other antimicrobial exposure had no effect on risk of recurrent UTI. Among male children in whom circumcision status was known, 5 of 26 (19%) uncircumcised vs 0 of 10 circumcised children had a recurrent UTI (P = .13).

Antimicrobial prophylaxis exposure considered as a time-varying covariate had no significant effect on the risk of recurrent UTI in multivariable analysis (HR, 1.01; 95% CI, 0.50-2.02). In stratified analyses for each of the other covariates (sex, race, age, and VCUG result), antimicrobial prophylaxis had no significant effect in any of the groups. Analyses stratified by propensity score quintile also demonstrated no significant effect of antimicrobial prophylaxis. Similarly, antimicrobial prophylaxis did not decrease the risk of recurrent UTI when controlling for the propensity quintile (HR, 1.03; 95% CI, 0.51-2.08), propensity score as a continuous variable (HR, 1.02; 95% CI, 0.51-2.05), or propensity score combined with all covariates (HR, 1.01; 95% CI, 0.51-2.02). Analysis stratified by type of antimicrobial prophylaxis demonstrated no association between type of prophylaxis and risk of recurrent UTI; however, a HR for nitrofurantoin prophylaxis could not be calculated because 0 of 9 children receiving nitrofurantoin experienced a recurrent UTI.

### Risk of Resistance Among Children With Recurrent UTI

Among the 83 children with recurrent UTI, white race (odds ratio [OR], 0.21; 95% CI, 0.07-0.63) and age 2 to 6 years (OR, 0.26; 95% CI, 0.09-0.80) were associated with decreased risk of resistant infections. Conversely, exposure to prophylactic antimicrobials significantly increased the likelihood of resistant infections (OR, 7.50; 95% CI, 1.60-35.17) (Table 3). This increased risk of resistance associated with antimicrobial prophylaxis persisted when controlling for the antimicrobial receipt propensity score (OR, 6.76; 95% CI, 1.26-30.57) and whether the first UTI was resistant (OR, 8.66; 95% CI, 1.66-45.31). Any exposure to other (nonprophylactic) antimicrobials and exposure to other antimicrobials in the 30 days prior to a recurrent UTI were not significantly associated with resistant infections. Age at first UTI, VUR result, and exposure to antimicrobial prophylaxis were highly correlated (P < .001 for all) among the 83 children with recurrent UTI, likely due to the American Academy of Pediatrics guideline recommending that a VCUG be performed in children younger than 2 years and prophylaxis given to those children with VUR. Since this collinearity prevents the ascertainment of the effect of each individual exposure in a multivariable model and we wanted to provide clinicians with a risk profile based on exposures, we calculated the predicted probability of a recurrent UTI being antimicrobial resistant (Table 4) for each combination of exposures derived from a multivariable regression model that included race, age, presence of VUR, and exposure to antimicrobial prophylaxis. For example, a nonwhite child younger than 2 years who has VUR and is exposed to antimicrobial prophylaxis has the highest probability of resistance, 98.0% (Table 4). In contrast, a white 2- to 6-year-old child who does not have VUR and is not exposed to prophylaxis has only a 40.4% probability of a resistant recurrent UTI. If this same white, 2- to 6-year-old child without VUR is exposed to prophylaxis, our data predict an increased absolute probability of resistance of more than 30% to 73.3%, demonstrating that exposure to antimicrobial prophylaxis has a major impact on risk of resistance in recurrent UTIs.

###COMMENT

To our knowledge, this study is the first large primary care pediatric cohort study to evaluate risk factors for recurrent UTI and the association with antimicrobial prophylaxis. We found that antimicrobial prophylaxis was not associated with lower risk of recurrent infections.
within 6-12 months). The estimate formed without symptoms (20%-48% previously reported from referral populations) was per person-year, or 12% per year) was demonstrated antimicrobial prophylaxis and risk of recurrent UTI. In analyses controlling for antimicrobial exposure, our study found that antimicrobial prophylaxis had no significant effect on risk of recurrence for children with either grade 1 to 3 or grade 4 to 5 VUR, but no firm conclusions could be made in the grade 4 to 5 VUR group, which had only 7 children. Previous randomized trials also have demonstrated the lack of effectiveness of prophylaxis to prevent recurrent UTI and renal scarring in children with grade 1 to 3 VUR. Therefore, it is unclear how much of a role the presence of VUR, especially low-grade VUR, should play in making decisions about starting prophylactic antimicrobials.

Our study demonstrated that age may be an important consideration for risk of recurrent UTI and antimicrobial-resistant infections. Children aged 2 to 6 years, especially those aged 3 to 5 years, were at increased risk of recurrent UTI, possibly related to dysfunctional elimination that previously has been identified as an underappreciated risk factor. The observed increased risk of recurrent UTI in older children is contrary to previous concerns that younger children are at highest risk. Those concerns were based largely on the findings from a study of Swedish children recruited from Goteborg hospital in the 1960s. However, that study included catheterizations performed at set follow-up times irrespective of the presence of symptoms, which may have biased it toward detecting persistent asymptomatic bacteriuria in younger infants, rather than recurrent UTI. Thus our study, which defined recurrent UTI based on physician diagnosis triggered by symptoms, may better reflect the epidemiology of recurrent symptomatic UTI in a pediatric primary care population. Interestingly, a 2006 population-based study from the Netherlands found results similar to ours—in that study, the maximal incidence of UTI in both girls and boys was in year 4 of life.

Race also may play a role in risk of recurrent UTIs and resistant infections. Nonwhites had a decreased risk of recurrent UTI but was associated with increased risk of resistant infection.

Also, to our knowledge, this is the first study to estimate the incidence of recurrent UTI after an initial UTI in a large primary care pediatric cohort. The incidence of first UTI, 0.007 per person-year (4.2% cumulative incidence from ages 0-6 years), is similar to previous population-based first-UTI cumulative incidence rate estimates of 2% to 8%. The rate of recurrent UTI (0.12 per person-year, or 12% per year) was lower than recurrence rates previously reported from referral populations or populations with cultures performed without symptoms (20%-48% within 6-12 months). The estimate of recurrent UTI incidence was the same as that in a study that reported a 12% recurrence rate after diagnosis of first UTI in an emergency department and probably better represents the incidence of symptomatic recurrent UTI in a primary care setting.

No association was found between antimicrobial prophylaxis and risk of recurrent UTI, either in multivariable Cox regression or in propensity score analyses. In addition, exposure to antimicrobial prophylaxis was associated with significantly increased risk of resistant infections. The results did not change significantly when a more stringent colony-count criterion (≥100 000 colony-forming units/mL) was used to define a positive urine culture result. Recent randomized trials of antimicrobial prophylaxis also have demonstrated no reduction in risk of UTI recurrence or renal scarring. Given these previous findings and the unfavorable risk/benefit ratio demonstrated by the current study, we think it is prudent for clinicians to discuss the risks and unclear benefits of prophylaxis with families as they make family-centered decisions about whether to start prophylactic antimicrobials or to closely monitor a child without prescribing antimicrobial prophylaxis after a first UTI.

Currently, antimicrobial prophylaxis is recommended if a child has VUR. In analyses controlling for antimicrobial exposure, our study found no significantly increased risk of recurrence for children with grade 1 to 3 VUR and increased risk of recurrence in children with grade 4 to 5 VUR.

### Table 4. Probability of Recurrent Urinary Tract Infection Being Antimicrobial Resistant Based on Exposures

<table>
<thead>
<tr>
<th>Nonwhite Race</th>
<th>Age &lt;2 y</th>
<th>VUR Present</th>
<th>Prophylactic Antimicrobial Exposure</th>
<th>Probability of Resistance, %a</th>
</tr>
</thead>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>98.0</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>97.2</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>94.2</td>
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<td>−</td>
<td>−</td>
<td>92.4</td>
</tr>
<tr>
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<td>+</td>
<td>−</td>
<td>92.2</td>
</tr>
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<td>+</td>
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<td>−</td>
<td>89.6</td>
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<td>+</td>
<td>+</td>
<td>89.3</td>
</tr>
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<td>+</td>
<td>79.9</td>
</tr>
<tr>
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<td>+</td>
<td>+</td>
<td>−</td>
<td>79.5</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>74.5</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>73.8</td>
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<td>−</td>
<td>+</td>
<td>73.3</td>
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<td>−</td>
<td>−</td>
<td>67.4</td>
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<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>40.4</td>
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</table>

*aProbability of causative organism for recurrent urinary tract infection being resistant to any antimicrobial based on multivariable model including race, age, presence of vesicoureteral reflux (VUR), and antimicrobial prophylaxis exposure.*
of recurrent UTI yet an increased risk of resistant infections. All 9 recurrent UTIs in nonwhites exposed to prophylactic antimicrobials were caused by a resistant organism. We are not aware of literature to explain the mechanism for increased risk of resistance, but it raises questions about whether the benefits of antimicrobial prophylaxis exceed the risks in nonwhite children. Clearly, more studies are needed to validate these findings and to explore the genetic and environmental basis for this observation.

Our study has several limitations. First, as with all studies in which data are gathered via health care delivery networks, we could have missed results from outside the network. We attempted to minimize this loss through incorporation of results from outside hospitals and clinics. Second, if patterns of care were different between groups, then ascertainment bias could have occurred. For example, if whites were more likely than nonwhites to seek or receive care or testing for urinary symptoms, then that pattern of care could explain the observed increased risk of recurrent UTI in whites. However, we found no evidence to support this explanation—there was no significant difference between races in the number of clinic visits per year overall or after first UTI diagnosis.

Third, 65% of the children in our study did not have VCUGs performed; the majority of these children were older than 2 years, for whom the American Academy of Pediatrics guidelines are silent regarding recommendations on screening for VCUG.10 But this prevented us from fully exploring the effect of VUR on recurrent UTI and the effectiveness of prophylactic antimicrobials by VUR grade. Fourth, the lack of circumcision documentation in 47% of male children limited our ability to accurately assess risk based on this important factor. Fifth, we based exposure to antimicrobial prophylaxis on antimicrobial prescriptions and therefore likely overestimated the degree of antimicrobial exposure in children both with and without recurrent UTI, because they may not have adhered to their prescribed regimen. This could have biased the effect of prophylactic antimicrobials toward the null. Sixth, our measure of the effectiveness of antimicrobial prophylaxis could have been affected by confounding by indication. We attempted to minimize this confounding by controlling for plausible observed factors that could influence the decision of a clinician to prescribe prophylaxis, such as sex, race, age, and VUR status, and by performing multiple propensity score analyses.20,31 However, we must recognize that residual unobservable confounding could exist in the assessment of prophylaxis efficacy. Finally, because less than 5% of children underwent dimercaptosuccinic acid renal scintigraphy to assess for pyelonephritis and renal scarring, we could not comment on the effect of prophylaxis on these outcomes.

The major strength of this study is that it is the first study of a large pediatric primary care cohort to simultaneously examine the risks and benefits of antimicrobial prophylaxis for children with first UTI. This study assessed more than 600 children after first UTI in a “natural experiment” setting for, on average, more than 1 year, which is an adequate duration to assess the effectiveness of antimicrobial prophylaxis in practice. Conducting the study in a primary care setting also freed it of the selection bias that has limited the generalizability of previous studies, which typically were performed in referral populations.

Given the limitations of observational studies, further investigation is needed to better understand the risks and benefits of antimicrobial prophylaxis. Specifically, a randomized trial involving children in the community setting after first UTI comparing daily prophylaxis vs close follow-up would significantly improve understanding of the efficacy of antimicrobial prophylaxis. Based on our findings, this type of study should be powered to examine the efficacy of prophylaxis in patient subgroups including nonwhites, older children, and those with and without VUR. It also will be important for future studies to evaluate the potential risks of prophylaxis, such as resistant infections.

CONCLUSIONS

White race, age 3 to 5 years, and grade 4 to 5 VUR were associated with increased risk of recurrent UTI. Sex and grade 1 to 3 VUR were not associated with risk of recurrence. Antimicrobial prophylaxis was not associated with lower risk of recurrent UTI, but prophylaxis was associated with increased risk of resistant infections.

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