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

Nader Shaikh, MD, MPH[1], Alejandro Hoberman, MD[1], Ron Keren, MD[2], Anastasia Ivanova, PhD[3], Nathan Gotman, MS[3], Russell W. Chesney, MD[4,*], Myra A. Carpenter, PhD[3], Marva Moxey-Mims, MD[5], and Ellen R. Wald, MD[6]

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

Study design Children, 2-71 months of age (n = 769) enrolled in the Randomized Intervention for Children with Vesicoureteral Reflux or Careful Urinary Tract Infection Evaluation 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, the risk was 2 times that of children with normal function (OR 2.2; 95% CI 1.2-4.1). Children who had received 1 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 bladder bowel dysfunction, and children who received 1 course of antibiotics in the past 6 months were more likely to have a urinary tract infection caused by pathogens resistant to 1 or more narrow-spectrum antimicrobials. *(J Pediatr 2016;171:116-21)*.

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 2 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 (*Escherichia 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 bladder and bowel dysfunction [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 2-71 months of

BBD	Bladder and bowel dysfunction
CUTIE	Careful Urinary Tract Infection Evaluation
RIVUR	Randomized Intervention for Children with Vesicoureteral Reflux
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

From the [1]Division of General Academic Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; [2]Division of General Pediatrics, Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, PA; [3]Department of Biostatistics, Collaborative Studies Coordinating Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN; [5]National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; and [6]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI

*Deceased.

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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-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 had been approved by 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 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 (ie, 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, and 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, and 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 et al.[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 2 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

Table I. Demographic and clinical characteristics of children with UTI

Characteristics	Total (n = 769), N (%)
Age (mo)	
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)
VUR	
No VUR	186 (24)
VUR grades I-II	314 (41)
VUR grades III-IV	269 (35)
BBD	
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 mo	
0	399 (52)
1	229 (30)
≥2	141 (18)