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Variation in Antibiotic Susceptibility of Uropathogens by Age among Ambulatory Pediatric Patients

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Abstract

We compared uropathogen antibiotic susceptibility across age groups of ambulatory pediatric patients. For *Escherichia coli* (n=5,099) and other Gram-negative rods (n=626), significant differences ($p<0.05$) existed across age groups for ampicillin, cefazolin, and trimethoprim/sulfamethoxazole susceptibility. In *E. coli*, differences in trimethoprim/sulfamethoxazole susceptibility varied from 79% in children under 2 to 88% in ages 16–18 ($p<0.001$) while ampicillin susceptibility varied from 30% in children under 2 to 53% in ages 2–5 ($p=0.015$). Uropathogen susceptibility to common urinary anti-infectives may be lower in the youngest children. Further investigation into these differences is needed to facilitate appropriate and prudent treatment of urinary tract infections.

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Keywords

urinary tract infection; antibiotic resistance; ambulatory care

Introduction

Pediatric urinary tract infections (UTIs) account for more than 1.1 million office visits each year (Chang & Shortliffe, 2006; Hersh, Shapiro, Pavia, & Shah, 2011). Antibiotic selection for pediatric UTI is complicated by varying disease etiology by age and by contraindications for some antibiotic classes in young children. A previous study using national survey data observed that at ambulatory care settings nearly 40% of patients treated for UTI received a broad-spectrum antibiotic. Further among ambulatory pediatric patients receiving an antibiotic (for any indication), broad-spectrum antibiotic use was most frequent in patients less than six years of age (Hersh, et al., 2011). Antibiotic resistance is a complicating factor in the treatment of pediatric UTIs. A study of uropathogens by Gaspari et al. assessed rates of resistance to commonly prescribed antibiotics in the U.S. pediatric population and observed resistance to trimethoprim/sulfamethoxazole (TMP/ SMX) in *Escherichia coli* as high as 22.4% in pediatric females and 31.3% in pediatric males (Gaspari, Dickson, Karlowsky, & Doern, 2005). While this study identified potentially clinically relevant differences in TMP/SMX and ampicillin across age groups, no statistical comparisons of antibiotic susceptibility across age groups were performed.

The American Academy of Pediatrics (AAP) guideline for the treatment UTI in infants and young children was updated in 2011 (Roberts, 2011). The new guideline notes the importance of considering local patterns of antimicrobial susceptibility, particularly to TMP/ SMX and cephalexin, when empirically selecting treatment for UTIs. Because the epidemiology of UTIs differs by age, investigation into the possibility for varying rates of resistance by different pediatric age groups is warranted. For instance, in older pediatric patients sexual intercourse is a risk factor for the development of UTIs. The most common uropathogen transmitted in this manner is *E. coli*, which is generally empirically treated with TMP/SMX. In contrast, in children younger than 5 years of age, the presence of anatomical abnormalities is a risk factor of primary concern (Feigin, 2009). Pediatric patients with anatomical abnormalities are also at risk for UTI due to *Pseudomonas* and *Enterococcus* spp. (Ashkenazi, Even-Tov, Samra, & Dinari, 1991; Bitsori, Maraki, Raissaki, Bakantaki, & Galanakis, 2005), which are associated with multi-drug resistance (Ladhani & Gransden, 2003; Mutnick, Biedenbach, & Jones, 2003; Paterson, 2006). Furthermore, antibiotic use in pediatric patients varies from that in adults, as some antibiotics/antibiotic classes are not approved for use in younger age groups. This may influence the prevalence of antibiotic resistance in uropathogens isolated from children. Our objective was to compare antibiotic susceptibility rates for common uropathogens across different pediatric age groups in a primary care ambulatory setting. To perform this comparison, we summarize clinical microbiology data following Center for Clinical Laboratory Standards Institute guidelines for the analysis and presentation of cumulative antibiotic susceptibility data (Hindler et al., 2009). This approach to summarizing the data is widely employed in hospital settings to produce hospital antibiograms, which are reports of antibiotic susceptibility data used to assist in guiding empiric antibiotic selection for inpatients.

Methods

Study Design

We conducted a retrospective analysis of urinary cultures collected from primary care outpatients in the Kaiser Permanente Northwest (KPNW) healthcare system. KPNW is a

regional, pre-paid group model health maintenance organization that includes over 450,000 members in the Portland, Oregon and Vancouver, Washington metropolitan area. Eighty-nine percent of KPNW members receive their benefits as part of a group membership, primarily through their employer, while the remainder are individual subscribers. Medicare members make up approximately 64% of the individual subscribers. All KPNW clinics have used an electronic medical record system as the sole medical record since 1997. Positive urine microbiology cultures from primary care outpatients (18 years of age or younger) between January 1, 2005 and December 31, 2010 were included in the study. Primary care settings were defined as the non-specialty clinics in the family practice, internal medicine and pediatric departments. Urine cultures yielding less than 50,000 colony-forming units (CFU) per milliliter, or those with greater than two organisms isolated were excluded as negative/potentially contaminated cultures. Note that patients were allowed to enter the dataset multiple times if multiple eligible cultures were collected in different calendar years. This study was reviewed and approved by the KPNW institutional review board.

Data Collection

All data were collected through the KPNW virtual data warehouse. The virtual data warehouse is a data repository for KPNW laboratory, clinical, and administrative data that is maintained for research purposes. Clinical microbiology data, including culture date, organism(s) isolated, and antibiotic susceptibility testing results, were collected. Patient demographic data were also collected.

Data Analysis

Patient age was categorized *a priori* into five groups: less than 2 years, 2–5 years, 6–10 years, 11–15 years, and 16–18 years of age. Antibiotic susceptibility data for all uropathogens were analyzed following clinical guidelines for the development of institutional antibiograms (Hindler, et al., 2009). The mean percent antibiotic susceptibility was calculated for all *E. coli* isolates and stratified by age category. We also calculated the mean percent antibiotic susceptibilities for all other non-*E. coli* Gram-negative rods combined (i.e., *Klebsiella* spp., *Proteus* spp., etc.). Comparisons of antibiotic susceptibilities across age groups were performed using the Pearson's chi-square test. $P<0.05$ was considered statistically significant. Differences in susceptibility frequencies of 10% or greater were considered potentially clinically meaningful. All data were analyzed using SAS version 9.2 (SAS Institute; Cary, NC).

Results

During the 6-year study period, 19,038 urine cultures were ordered for 12,515 pediatric patients at primary care outpatient encounters. Of these, there were 7,659 were positive urine cultures from 4,766 unique patients that met the criteria for inclusion in this study. After restricting the dataset to the first isolate per year per patient, 6,019 microbial isolates from 5,683 urine cultures remained for comparison of antimicrobial susceptibility patterns. Table 1 describes patient and encounter characteristics. In the analysis dataset overall, *Escherichia coli* (84.7%) was the most frequently occurring organism followed by *Proteus mirabilis* (2.9%), *Enterococcus* species (2.3%), coagulase-negative *Staphylococcus* species (2.0%), and enteric-like Gram-negative rods that were not identified by species (2.0%). The frequency of each of the remaining isolated species occurred were less than 2%. In all age groups, *E. coli* was the most frequently isolated organism (range across age groups: 78.1–85.8%).

Table 2 presents antibiotic susceptibilities for *E. coli* isolates stratified by age group (n = 5099). Statistically significant differences across age groups were identified for

susceptibility to ampicillin (p<0.001), cefazolin (p<0.001), ciprofloxacin (p=0.020), gentamicin (p=0.044), tobramycin (p=0.007), and TMP/SMX (p<0.001). However the magnitude of the differences was generally not clinically significant. The exception was susceptibility to ampicillin, where differences in percent susceptibility exceeded 10% between the younger (<2 years and 2–5 years) and older (5–10 years and 11–15 years) age categories. Differences in TMP/SMX approached clinical significance with a 9% difference in susceptibility between the youngest and oldest children. It should be noted that in this healthcare system, microbiology laboratory protocols dictated that susceptibility testing for amoxicillin-clavulanate was performed only for isolates found to be not susceptible to ampicillin (i.e., not all isolates tested for ampicillin susceptibility in general). If it is assumed that all ampicillin susceptible *E. coli* isolates were amoxicillinclavulanate susceptible, then the differences in amoxicillin-clavulanate susceptibility across age groups would then achieve statistical significance (p=0.040) but still not reach the threshold for clinical meaningfulness as the maximum difference between groups would be only 5%.

Table 3 reports the antibiotic susceptibilities for all other Gram-negative rods combined (n = 626), which included *Klebsiella* spp., *Proteus* spp., *Citrobacter* spp., *Serratia* spp., *Enterobacter* spp., *Pseudomonas* spp., *Providencia spp.*, and Gram-negative rods that were not identified by species. Statistically significant and potentially clinically meaningful differences across age groups were identified for susceptibility to ampicillin (p=0.015), cefazolin (p=0.029), nitrofurantoin (p=0.004), tetracycline (p<0.001) and TMP/SMX (p<0.001); and for each of these agents, potentially clinically meaningful differences (≥10%) were observed between at least two of the age groups. If ampicillin-susceptible isolates are assumed to be susceptible to amoxicillin-clavulanate, susceptibility to amoxicillin-clavulanate still would not differ significantly across age groups (p=0.214).

Discussion

Pediatric infectious disease practitioners and public health officials have long recognized the importance of antibiotic stewardship in ambulatory patient care settings (Bradley, 2007; Cohen, 2006; Interagency Task Force on Antimicrobial Resistance; Patel, Larson, Kubin, & Saiman, 2007; Schwartz, Bell, & Hughes, 1997). This includes reduction in unnecessary prescribing, limited use of broad-spectrum or second-line antibiotic therapies, and the use of appropriate dosing and duration of therapy. As much of the antibiotic prescribing performed in ambulatory settings is empiric, clinicians rely largely on patient characteristics, signs and symptoms of disease, and past medical history to select the appropriate antibiotic regimen. Cumulative antibiotic susceptibility reports (i.e., antibiograms), are commonly developed to further inform empiric antibiotic selection by providing institution-specific data on the prevalence of antibiotic resistance among key bacterial pathogens. Prior evaluations have repeatedly demonstrated that stratification of the antibiogram by known risk factors, such as unit (Binkley et al., 2006; Kaufman, Haas, Edinger, & Hollick, 1998; Lalani et al., 2008; Pogue et al., 2011), body site cultured (Green, 2005; Kuster et al., 2008) or relevant patient characteristics (Bosso, Mauldin, & Steed, 2006), may reveal meaningful differences in antibiotic susceptibility patterns. While unit-specific stratification of antibiograms has become increasingly common, a survey of academic and academically-affiliated healthcare systems indicated that only 6% constructed outpatient antibiograms and only 8% constructed pediatric antibiograms (Xu et al., 2012). While outpatient/pediatric antibiograms are not commonly constructed, previous studies suggest that antibiotic susceptibilities among uropathogens do differ significantly between pediatric inpatients and outpatients (Dahle, Korgenski, Hersh, Srivastava, & Gesteland, 2012). Despite the potential benefits of stratifying antibiograms, it should also be noted that stratification inevitably results in smaller stratum-specific sample sizes and thus decreases the precision of the estimates or, in some cases, is prohibitive of reporting susceptibilities for less frequently isolated organisms.

Nonetheless, the identification of risk factors for antibiotic resistance among pediatric ambulatory patients may further support antibiotic stewardship efforts aimed at promoting prudent prescribing practices in this setting.

In this study, age-stratified antibiograms were created to compare antibiotic susceptibilities of pediatric uropathogens across categories of patient age. The youngest age category (children < 2 years) was purposefully created to align with the age group that is the focus of the current AAP guideline for the diagnosis and management of UTI (Roberts, 2011). The guideline recommends the following oral options for empiric therapy: amoxicillin-clavulanate, sulfonamides (TMP/SMX or sulfisoxazole), or cephalosporins (cefixime, cefpodoxime, cefprozil, cefuroxime axetil, or cephalexin). Nationally, TMP/SMX is prescribed for approximately 50% of pediatric (age less than 18) UTIs in ambulatory settings, followed by cephalosporins for approximately 30% and amoxicillin-clavulanate in approximately 5% of UTIs (Copp, Shapiro, & Hersh, 2011). However in this ambulatory population, susceptibility to amoxicillin-clavulanate and cephalothin were below 75% in all age categories. Considering the agents recommended for empiric use, potentially the most clinically relevant differences observed were for TMP/SMX. Among *E. coli*, TMP/SMX susceptibility was lowest in isolates from those less than 2 years of age (79%) and was greatest (88%) in isolates from 16–18 year olds. While among other Gram-negative rods, TMP/SMX susceptibility was lowest in isolates from 2–5 year olds (74%) and greatest in those 16–18 years of age (93%). Though cefazolin susceptibilities differed significantly across age groups among both *E. coli* and other Gram-negative bacilli, clinically meaningful differences were only identified for the Gram-negative bacilli other than *E. coli* where susceptibility ranged from 64% in isolates from patients less than 2 years of age to 82% among patients aged 2–5 years. While few studies have investigated age-specific patterns of antibiotic resistance, an earlier 5-year study identified that of the 26 extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL) identified from patients in a pediatric hospital 50% were from patients less than 2 years of age at the time of their first ESBL infection (Blaschke et al., 2009). Yet without age stratification, potentially clinically meaningful differences in patterns of antibiotic susceptibility may be obscured, as in our study where the overall proportion of TMP/SMX susceptibility was 85% for *E. coli* uropathogens.

This study was conducted among primary care pediatric outpatients in a regional health maintenance organization. Thus, these data may not be generalizable to other geographical regions, or populations with greater proportions of uninsured/lower socioeconomic status patients. Furthermore, this study utilized retrospectively collected clinical microbiology data. Clinical cultures were not reviewed at the patient-level to ensure the presence of true infection; also, not all urinary tract infections may have been cultured. Further, we could not ascertain the source or method of urine specimen collection for approximately 90% of cultures analyzed; this limits our ability to interpret the clinical meaningfulness of these isolates. Also, because patient-level data beyond patient demographics were not available, observed differences in susceptibilities across age groups may be due to differences in comorbidities, medical history, or other risk factors for antibiotic-resistant uropathogens. Further work is needed to explore these associations.

In this manuscript, we did not define a cut-point in susceptibility frequencies at which a particular agent should be avoided. This decision is multifactorial. The prevalence of resistance in a population speaks to the likelihood of treatment failure for a given patient in the absence of patient-specific culture data. However, other factors contribute to the risk of treatment failure as well as contribute to the potential harms associated with failure. As a result, the decision for an appropriate cut-point is beyond the scope of this project and ultimately lies at the discretion of the treating clinician.

As antibiotic-resistant infections become increasing commonplace in ambulatory patient-care settings, local data on the prevalence of resistance among major pathogens are increasingly helpful in guiding appropriate empiric selection of antibiotic therapy. In this study, we identified significantly different patterns of antibiotic resistance among common uropathogens isolated from pediatric patients in an ambulatory patient care setting. These data support further investigation into the differing epidemiology of antibiotic-resistant uropathogens in pediatric patients. Local assessments of trends in antibiotic susceptibility can and should be used to guide management of UTIs in pediatric patients.

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Table 1

Patient and Encounter Characteristics

	N	Percent
Female	5378	94.6%
Age at time of urine culture		
<2 years	389	6.8%
2–5 years	1128	19.8%
6–10 years	1231	21.7%
11–15 years	933	16.4%
16 years and older	2002	35.2%
Race		
White	2034	35.8%
Black	62	1.1%
Asian	59	1.0%
Other	178	3.1%
Multiracial	69	1.2%
Unknown	3281	57.7%
Department of Encounter		
Family Practice	1039	18.3%
Internal Medicine	248	4.4%
Pediatrics	4396	77.4%
Year of Encounter		
2005	800	14.1%
2006	839	14.8%
2007	952	16.8%
2008	1023	18.0%
2009	1146	20.2%
2010	923	16.2%

Table 2

Antibiotic susceptibility of *Escherichia coli* isolated from urine by age group

	Age Category					Chi-square test p-value
	<2 years	2–5 years	5–10 years	11–15 years	16–18 years	
Ampicillin	184 (56%)	544 (56%)	681 (60%)	558 (67%)	1250 (67%)	<0.001
Amoxicillin-clavulanate*	95 (68%)	305 (73%)	321 (74%)	199 (73%)	421 (71%)	0.618
Cefazolin	299 (92%)	887 (92%)	1048 (93%)	799 (96%)	1758 (95%)	<0.001
Cephalothin	224 (69%)	663 (69%)	756 (67%)	580 (70%)	1267 (68%)	0.861
Ciprofloxacin	207 (97%)	589 (98%)	694 (97%)	533 (99%)	1393 (99%)	0.020
Gentamicin	318 (98%)	948 (98%)	1002 (98%)	821 (99%)	1836 (99%)	0.044
Nitrofurantoin	322 (99%)	947 (98%)	1095 (98%)	816 (98%)	1828 (99%)	0.310
Tetracycline	264 (82%)	813 (84%)	944 (84%)	719 (87%)	1592 (86%)	0.130
Tobramycin	318 (98%)	952 (99%)	1112 (99%)	828 (>99%)	1840 (99%)	0.007
TMP/SMX	258 (79%)	789 (82%)	949 (85%)	714 (86%)	1622 (88%)	<0.001

TMP/SMX: trimethoprim/sulfamethoxazole

*Susceptibility testing not routinely reported for ampicillin susceptible isolates

Table 3

Antibiotic susceptibility of Gram-negative rods other than *Escherichia coli* isolated from urine by age group

	Age Category					Chi-square test p-value
	<2 years	**2–5 years**	**5–10 years**	**11–15 years**	**16–18 years**	
Ampicillin	14 (30%)	75 (53%)	46 (38%)	33 (35%)	72 (39%)	0.015
Amoxicillin-clavulanate*	18 (56%)	44 (66%)	44 (59%)	38 (62%)	72 (66%)	0.795
Cefazolin	30 (64%)	117 (82%)	86 (72%)	68 (74%)	147 (81%)	0.029
Cephalothin	31 (67%)	105 (74%)	77 (64%)	60 (65%)	131 (72%)	0.361
Ciprofloxacin	35 (100%)	86 (99%)	55 (100%)	47 (100%)	118 (98%)	0.707
Gentamicin	56 (98%)	151 (97%)	128 (99%)	92 (99%)	176 (97%)	0.486
Nitrofurantoin	21 (45%)	44 (31%)	64 (53%)	38 (41%)	66 (36%)	0.004
Tetracycline	32 (70%)	52 (37%)	78 (65%)	67 (73%)	116 (64%)	<0.001
Tobramycin	56 (98%)	151 (97%)	129 (99%)	96 (100%)	181 (98%)	0.322
TMP/SMX	46 (81%)	116 (74%)	102 (78%)	89 (91%)	172 (93%)	<0.001

TMP/SMX: trimethoprim/sulfamethoxazole

*Susceptibility testing not routinely reported for ampicillin susceptible isolates