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Antibiotic Resistance Patterns of Outpatient Pediatric Urinary Tract Infections

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Abstract

Purpose—We characterize the current national patterns of antibiotic resistance of outpatient pediatric urinary tract infection.

Materials and Methods—We examined outpatient urinary isolates from patients younger than 18 years in 2009 using The Surveillance Network®, a database with antibiotic susceptibility results and patient demographic data from 195 United States hospitals. We determined the prevalence and antibiotic resistance patterns for the 6 most common uropathogens, ie Escherichia coli, Proteus mirabilis, Klebsiella, Enterobacter, Pseudomonas aeruginosa and Enterococcus. We compared differences in uropathogen prevalence between males and females using chi-square analysis.

Results—We identified 25,418 outpatient urinary isolates. E. coli was the most common uropathogen overall but the prevalence of E. coli was higher among females (83%) than males (50%, $p < 0.001$). Other common species among males were Enterococcus (17%), P. mirabilis (11%) and Klebsiella (10%). However, these uropathogens each accounted for 5% or less of female isolates ($p < 0.001$). Resistance among E. coli was highest for trimethoprim-sulfamethoxazole (24%) but lower for nitrofurantoin (less than 1%) and cephalothin (15%). Compared to 2002 Surveillance Network data, E. coli resistance rates increased for trimethoprim-sulfamethoxazole (from 23% to 31% in males and from 20% to 23% in females) and ciprofloxacin (from 1% to 10% and from 0.6% to 4%, respectively).

Conclusions—E. coli remains the most common pediatric uropathogen. Although widely used, trimethoprim-sulfamethoxazole is a poor empirical choice for pediatric urinary tract infections in many areas due to high resistance rates. First-generation cephalosporins and nitrofurantoin are appropriate narrow-spectrum alternatives given their low resistance rates. Local antibiograms should be used to assist with empirical urinary tract infection treatment.

Keywords

anti-bacterial agents; drug resistance; bacterial; pediatrics; urinary tract infections; uropathogenic Escherichia coli

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Urinary tract infection is a common medical condition in children. The cumulative incidence in the first 6 years of life is 7% in girls and 2% in boys.[1] Collectively urinary tract infection accounts for 1.5 million to 1.75 million doctor visits annually.[2] Understanding antibiotic resistance patterns helps guide effective empirical antibiotic selection and decrease treatment failure. Ineffective empirical antibiotic therapy may contribute not only to increased morbidity, but also to increased costs due to prolonged antibiotic treatment, recurrent office or emergency room visits and hospital admissions.[3]

There are limited data regarding the antibiotic resistance patterns of pediatric urinary tract infections in the outpatient setting. A previous study indicates that the most commonly used antibiotics for pediatric UTIs are TMP/SMX and broad-spectrum agents, especially third-generation cephalosporins.[2] There is not a clear explanation for these prescribing patterns, but it has been suggested that the increasing levels of antimicrobial resistance in the last decade have impacted antibiotic choice for a wide range of pathogens.[4] We describe the current national resistance patterns for the 6 most common uropathogens, ie Escherichia coli, Proteus mirabilis, Klebsiella, Enterobacter, Pseudomonas aeruginosa and Enterococcus.

METHODS

Study Design

We performed a retrospective observational study examining urinary isolates from patients younger than 18 years collected in the outpatient setting from clinical laboratories in the United States in 2009.

Data Sources

We analyzed data from The Surveillance Network, an electronic surveillance database that collects strain specific, qualitative and quantitative antimicrobial test results and patient demographic data from clinical laboratories across 195 U.S. hospitals across all 9 Census Bureau regions, ie Pacific, Mountain, West North Central, East North Central, New England, Mid Atlantic, South Atlantic, East South Central and West South Central. Data include antimicrobial agents tested, target organisms, infection site, institution type and test methodology. Patient demographic information including age, gender and site of infection are also available, although variables such as race and socioeconomic status are not available.

Each participating laboratory performs its own susceptibility testing. Positive culture data along with corresponding de-identified demographic data are sent to TSN for incorporation into the master data set. All participating laboratories use standard U.S. Food and Drug Administration testing methods with results interpreted according to the National Committee for Clinical Laboratory Standards, which specifies standardized methods for susceptibility testing including information about drug selection, interpretation and quality control with clear guidelines for minimum inhibitory concentrations.[5] If multiple isolates are collected from the same individual within a 5-day period, only the first isolate is used to determine susceptibility pattern.

We limited our data analysis to urine cultures obtained in the outpatient setting, defined as visits that took place at clinics or emergency departments. Isolates that grew more than 1 organism were considered contaminated and excluded. We also excluded urine samples obtained from outpatient skilled nursing and rehabilitation facilities. Finally, to prevent overestimation of resistance patterns, we imposed a strict definition of resistance and included only organisms that were truly resistant. Organisms with intermediate susceptibility were not included as "resistant" because numerous antibiotics concentrate in the urine and, therefore, can successfully eradicate certain bacteria in the urinary tract despite intermediate susceptibility.

Measurements

We analyzed antibiotic resistance patterns for the 6 most common pediatric uropathogens in the data set, ie E. coli, P. mirabilis, Klebsiella, Enterobacter, P. aeruginosa and Enterococcus. We report aggregate data for each organism and each of the 15 antibiotics (TMP/SMX, ampicillin, amoxicillin-clavulanate, nitrofurantoin, cephalothin, cefuroxime, ceftriaxone, cefazolin, ceftazidime, gentamicin, ciprofloxacin, piperacillin-tazobactam, imipenem, aztreonam and vancomycin). Broad-spectrum antibiotics were defined as amoxicillin-clavulanate, quinolones, macrolides, and second and third-generation cephalosporins.[2] Oral treatment options with a first-generation cephalosporin for outpatient UTI should be based on cephalothin susceptibility patterns since cephalothin is more predictive of cephalexin susceptibilities compared to cefazolin.[6,7] Further stratifications included patient demographic information (age, gender and geographic region). Age was evaluated as a categorical variable, with categories of younger than 2, 2 to 5, 6 to 12 and 13 to 17 years, because the prevalence of UTI varies by age in a nonlinear fashion.[8]

Statistical Analysis

Summary statistics were performed using frequencies and proportions for categorical data. Chi-square analysis was used to compare differences in uropathogen prevalence between males and females. All analyses were 2-sided, and $p \leq 0.05$ was considered statistically significant.

RESULTS

There were a total of 25,418 outpatient urinary isolates in 2009 from the 195 hospitals contributing data to TSN (table 1). The majority of these isolates (86%) were from females. Age distribution of isolates differed by gender. The smallest percentage of isolates in females was from children younger than 2 years (13%), while isolates were similarly distributed among the remaining age groups (28% in patients 2 to 5, 29% in patients 6 to 12 and 30% in patients 13 to 17 years). Conversely the majority of isolates in males were from children younger than 2 years (37%), and isolates from the remaining age groups were more variable (18%, 29% and 16%, respectively). Additionally, all 9 U.S. Census Bureau regions are represented, although not evenly so, with most isolates from the Pacific (greater than 20%) and South Atlantic (greater than 20%) regions, and few samples (less than 5%) from the Mountain, New England and East South Central regions.

E. coli was the most common uropathogen, accounting for 79% of urinary isolates overall. The prevalence of E. coli was significantly greater among females (83%) than males (50%, $p < 0.001$). All other species were more common in males than in females ($p < 0.001$), with Enterococcus (17%), Proteus (11%) and Klebsiella (10%) being the next most common isolates in males. Among females these uropathogens each accounted for 5% or less of the urinary isolates (p <0.001). This pattern applies for each age group, with the percentage of E. coli isolates significantly higher among all females compared to males (p <0.001), and the remaining 5 pathogens being more prevalent in males.

Resistance in E. coli was highest for ampicillin and TMP/SMX, while it was lower for cephalothin and nitrofurantoin (table 2). Klebsiella isolates were often resistant to ampicillin but had lower levels of resistance to nitrofurantoin, TMP/SMX and cephalothin. In contrast, Proteus isolates had lower levels of resistance to ampicillin but high resistance to nitro-furantoin. Proteus resistance levels were also low for TMP/SMX and cephalothin. Finally, resistance to amoxicillin-clavulanate and ceftriaxone was low in E. coli, Klebsiella and Proteus.

Enterococcus and Pseudomonas isolates are not tested for susceptibility to a number of the previously mentioned antibiotics since these bacteria are known to be uniformly resistant. Resistance to ampicillin, nitrofurantoin and vancomycin was low in Enterococcus. Pseudomonas was uniformly nonresistant to nitrofurantoin and infrequently resistant to ceftazidime but was highly resistant to TMP/SMX. Enterobacter had high levels of resistance to cephalothin but was less resistant to TMP/SMX, nitrofurantoin and ceftriaxone. Finally, resistance to ciprofloxacin was low in all 6 uropathogens.

Evaluation of these data by gender demonstrated only slight differences in resistance patterns between males and females. In males E. coli had higher levels of resistance to TMP/SMX and ciprofloxacin than in females (31% vs 23% and 10% vs 4%, respectively). Enterobacter had increased levels of resistance to TMP/SMX in females than in males (20% vs 15%). Finally, Proteus isolates were more resistant to TMP/SMX and ampicillin in males than in females (17% vs 9% and 18% vs 10%, respectively). All other observed differences in resistance patterns by gender were less than 5%.

DISCUSSION

While several studies have described antibiotic resistance patterns of pediatric UTIs at individual hospitals and outpatient facilities,[8,9] few have addressed resistance patterns on a broader scale.[10] We used the TSN data set to evaluate antibiotic resistance patterns among patients younger than 18 years, and found that the majority of UTIs in males and females were caused by E. coli. For the remaining 5 uropathogens there were marked differences in prevalence by gender. However, antibiotic resistance was similar in both genders.

Prior research has shown that the majority of outpatient UTI visits result in prescription of either a broad-spectrum antibiotic (32%) or TMP/SMX (49%).[2] Broad-spectrum antibiotics are more often administered to younger patients, females and children with fever.[2] While these subpopulations are at increased risk for UTIs and associated complications,[8] the current study suggests that most of the time a narrow-spectrum agent is a reasonable option. However, consideration should be given regarding whether TMP/SMX, the most commonly prescribed narrow-spectrum antibiotic, is the best empirical treatment option given that resistance to this agent was 24% in the present study. Guidelines suggest that when resistance rates are known to exceed 20%, TMP/SMX should not be used empirically.[11] On the other hand, resistance levels for other narrow-spectrum agents such as nitrofurantoin and first-generation cephalosporins are low, yet these antibiotics are infrequently prescribed. Given the low resistance rates to narrower spectrum antibiotics, the prescription of broad-spectrum antibiotics for a third of pediatric UTI visits not only is likely unnecessary, but also may add avoidable costs. Antibiotics comprise upward of 30% of hospital pharmacy budgets.[12] However, narrow-spectrum generic agents are extremely cost effective due to their low purchase price.[13]

These 2009 data can be compared to the 2002 to 2004 data presented by Gaspari et al from the same TSN database.[10] E. coli remains the most prevalent uropathogen in UTI, and was similar in 2009 and 2002 to 2004 for females (86% vs 84%) and males (50% vs 56%). However, we observed an increase in E. coli resistance levels for some antibiotics. TMP/SMX resistance rates increased between the 2 periods studied in males (31% vs 23%) and females (23% vs 20%), and there was a tenfold increase in resistance to ciprofloxacin (10% vs 1% in males and 4% vs 0.6% in females).

Although ciprofloxacin is infrequently prescribed for pediatric UTIs,[2] its use has increased in adults in the last decade and could potentially be responsible for changes in resistance patterns observed in pediatric isolates.[14] The increase in resistance to ciprofloxacin and the high level of resistance to trimethoprim combinations have been noted nationally and internationally.[15] In contrast, nitrofurantoin and first-generation cephalosporins (which we suggest are underused) have maintained low antibiotic resistance.

The study by Gaspari et al did not address cephalothin resistance rates.[10] However, the authors did report rates for cefazolin, which remained stable in the present study compared to 2002 to 2004 (7% vs 6% in males and 4% vs 3% in females). While cefazolin resistance does not perfectly correlate with cephalothin resistance, this finding suggests that resistance rates for first-generation cephalosporins in general have not changed substantially.

Although our series and that of Gaspari et al[10] are derived from TSN databases, the contributing hospitals have changed with time and methodologies between the studies are not identical. The number of contributing sites decreased from approximately 484 hospitals in 2002 to 2004 to 195 in 2009. However, the decrease was random and, therefore, should not create a systematic bias between data sets. Furthermore, given the large number of contributing sites and the high volume of isolates in 2009, a change in the total number of hospitals would likely not have an appreciable effect on the overall results. Moreover, organism prevalence and the majority of uropathogen resistance patterns remained similar between the 2 study periods. In addition, the earlier study did not limit positive cultures to those isolates that grew only 1 organism, nor did it exclude urine samples obtained from out-patient skilled nursing and rehabilitation facilities. The more selective sampling in our current study would tend to decrease resistance rates compared to the earlier study. Therefore, the observed trends in increased resistance rates for E. coli are likely still relevant.

Limitations

The Surveillance Network does not include patient information regarding conditions that may place individuals at risk for resistant uropathogens, such as presence of genitourinary anomalies, history of UTIs, prior antibiotic exposure and recent hospitalizations. Hence, the prevalence of E. coli in males in our series may be artificially low. There is a possibility that boys with genitourinary abnormalities are overrepresented in our sample since these patients are more likely to contract UTIs and more likely to undergo culture for suspected UTIs due to known higher rates of uropathogen resistance.[16] In addition, without clinical information it is impossible to reject positive cultures related to asymptomatic bacteriuria. The data set also does not specify the urine source (clean catch specimen, catheterized specimen, etc) or the number of colony forming units in each culture. However, contamination is limited as individual laboratories only submit culture data to the data set that they deem clinically positive and for which they determine susceptibilities. Moreover, we limited isolates for this study to those that grew only a single organism to further decrease the possibility of contamination.

Finally, these are aggregate data across the entire country and do not necessarily apply to a single patient in a specific community. Uropathogen resistance may vary at the regional level, and clinicians with access to this information should use local antibiograms.[17] However, national information remains critical to clinicians without local information and is valuable in assessing overall trends in uropathogen resistance in the United States.

Relation to Clinical Practice

Although TMP/SMX continues to be the most commonly prescribed antibiotic for pediatric UTI, our study reveals not only that TMP/SMX resistance rates have increased in the last decade, but also that the current national resistance rate exceeds the recommended level of resistance for empirical TMP/SMX prescribing. In addition, this study reinforces that there may be an opportunity to prescribe underused narrow-spectrum agents, such as nitrofurantoin and first-generation cephalosporins, which have demonstrated persistently low resistance rates through time.

Despite these national findings, prescribing patterns must be tailored to local data. Although different U.S. regions are represented in TSN, the distribution is not nationally representative. Therefore, breaking down resistance patterns by region may not accurately represent these patterns. Use of local antibiograms can improve empirical therapy decision making by increasing knowledge of local outpatient uropathogen prevalence and antibiotic resistance patterns.[18] However, Ernst et al found that only 60% of surveyed U.S. hospitals publish a complete antibiogram.[19] Moreover, most antibiograms are from hospital based laboratory data, and a recent study from Dahle et al showed that these data may provide inaccurate information about antibiotic resistance patterns for ambulatory pediatric patients.[20] Thus, the goal should be to promote separate institutional guidelines for hospital and community based patients derived from local data to optimize empirical prescribing choices and reduce the use of unnecessarily broad agents or antibiotics with known higher resistance rates.

CONCLUSIONS

This study reveals that uropathogen prevalence varies significantly by gender, although E. coli is the most prevalent uropathogen in both genders. In many regions it is likely that narrow-spectrum antibiotics are appropriate for empirical UTI treatment, including first-generation cephalosporins and nitrofurantoin in the absence of fever. It is noteworthy that TMP/SMX, although the most commonly prescribed antibiotic for outpatient pediatric UTIs, is likely not the best option for an empirical narrow-spectrum agent in many areas given its resistance patterns. If available, physicians should consult regional antibiograms for assistance with empirical antibiotic selection since resistance patterns will vary at this level.

Abbreviations and Acronyms

TMP/SMX	trimethoprim-sulfamethoxazole
TSN	The Surveillance Network
U.S	United States
UTI	urinary tract infection

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Table 1

Urinary isolates by age and gender

	E. coli	Enterobacter	Enterococcus	Klebsiella	P. mirabilis	P. aeruginosa	No. Pts
% Gender:							
Females	83	1	5	4	4	2	21,981
Males	50	5	17	10	11	7	3,437
p Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
% Younger than 2 yrs:							
Females	79	2	8	6	2	2	2,931
Males	59	5	17	9	6	3	1,280
p Value	<0.001	<0.001	<0.001	0.01	<0.001	0.09	
% 2–5 Yrs:							
Females	80	1	8	3	7	2	6,046
Males	41	3	19	6	24	6	619
p Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
% 6–12 Yrs:							
Females	88	1	4	4	2	2	6,380
Males	45	6	19	11	10	8	1,005
p Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
% 13–17 Yrs:							
Females	84	2	4	5	4	1	6,624
Males	47	6	10	17	6	14	533
p Value	<0.001	<0.001	<0.001	<0.001	0.01	<0.001	

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Table 2

Antibiotic resistance in urinary isolates

	% Antibiotic Resistance					
Antibiotic	**E. coli**	**Enterobacter**	**Enterococcus**	**Klebsiella**	**P. mirabilis**	**P. aeruginosa**
TMP/SMX	24	18		15	11	94
Ampicillin	45	78	3	81	12	
Amoxicillin-clavulanate	5	91		4	1	
Nitrofurantoin	Less than 1	23	1	17	94	0
Cephalothin	16	96		7	4	
Cefuroxime (oral)	2	33		7	0	
Cefuroxime (parenteral)	1	42		6	Less than 1	
Ceftriaxone	Less than 1	12		2	Less than 1	31
Cefazolin	4	91		7	4	
Ceftazidime	Less than 1	15		2	Less than 1	4
Gentamicin	4	2		3	5	10
Ciprofloxacin	5	1	5	3	3	5
Piperacillin-tazobactam	1	7		3	Less than 1	5
Imipenem	Less than 1	Less than 1		Less than 1	2	3
Aztreonam	Less than 1	13		3	Less than 1	4
Vancomycin			Less than 1			

Testing was not performed for antibiotics to which organisms are known to be nonsusceptible.