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A Comparison of Inpatient Versus Outpatient Resistance Patterns of Pediatric Urinary Tract Infection

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Abstract

Purpose—Prior single center studies showed that antibiotic resistance patterns differ between outpatients and inpatients. We compared antibiotic resistance patterns for urinary tract infection between outpatients and inpatients on a national level.

Materials and Methods—We examined outpatient and inpatient urinary isolates from children younger than 18 years using The Surveillance Network (Eurofins Scientific, Luxembourg, Luxembourg), a database of antibiotic susceptibility results, as well as patient demographic data from 195 American hospitals. We determined the prevalence and antibiotic resistance patterns of the 6 most common uropathogens, including Escherichia coli, Proteus mirabilis, Klebsiella, Enterobacter, Pseudomonas aeruginosa and Enterococcus. We compared differences in uropathogen prevalence and resistance patterns for outpatient and inpatient isolates using chi-square analysis.

Results—We identified 25,418 outpatient (86% female) and 5,560 inpatient (63% female) urinary isolates. Escherichia coli was the most common uropathogen overall but its prevalence varied by gender and visit setting, that is 79% of uropathogens overall for outpatient isolates, including 83% of females and 50% of males, compared to 54% for overall inpatient isolates, including 64% of females and 37% of males (p <0.001). Uropathogen resistance to many antibiotics was lower in the outpatient vs inpatient setting, including trimethoprim/ sulfamethoxazole 24% vs 30% and cephalothin 16% vs 22% for E. coli (each p <0.001), cephalothin 7% vs 14% for Klebsiella (p = 0.03), ceftriaxone 12% vs 24% and ceftazidime 15% vs 33% for Enterobacter (each p <0.001), and ampicillin 3% vs 13% and ciprofloxacin 5% vs 12% for Enterococcus (each p <0.001).

Conclusions—Uropathogen resistance rates of several antibiotics are higher for urinary specimens obtained from inpatients vs outpatients. Separate outpatient vs inpatient based antibiograms can aid in empirical prescribing for pediatric urinary tract infections.

Keywords

urinary tract infections; drug resistance; anti-bacterial agents; inpatients; outpatients

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Antibiotic resistance in pediatric patients is increasing.[1–3] Fewer than 50% of all pediatric UTIs are susceptible to commonly used antibiotics.[4] Because identification and susceptibilities are not available at the point of care, antibiograms are useful aids for empirical treatment of UTI while cultures are pending. Hospital based laboratory data combine outpatient and inpatient sensitivity and resistance patterns to generate antibiograms for empirical antibiotic prescribing and yet these data may not accurately reflect uropathogen resistance patterns in outpatients.[3,5,6]

Studies from single centers show that antibiotic resistance patterns for pediatric UTI differ by setting with generally higher resistance rates among inpatients than outpatients. Based on these findings these studies suggest that antibiograms should separate data on outpatients from those on inpatients to maximize the usefulness of antibiograms for empirical antibiotic selection for UTI treatment. To our knowledge the extent to which these differences in resistance patterns between outpatient and inpatient UTIs exist more broadly nationally is unknown.

We compared national patterns of antibiotic resistance among common uropathogens between antibiograms obtained for outpatients and inpatients. The results of this study show the importance of developing UTI specific antibiograms stratified by the site where the culture was obtained.

METHODS

Study Design

In this retrospective study of microbiological results of pediatric urine cultures we examined urinary isolates from children younger than 18 years that were collected in the inpatient and outpatient setting from clinical laboratories throughout the United States in 2009.

Data Sources

As previously described,[7] we analyzed data from TSN, an electronic surveillance database. TSN collects strain specific, qualitative and quantitative antimicrobial test results and patient demographic data from clinical laboratories at 195 American hospitals, including academic, nonacademic, pediatric hospitals and governmental hospitals, in all 9 United States Census Bureau regions, including Pacific, Mountain, West North Central, East North Central, New England, Mid Atlantic, South Atlantic, East South Central and West South Central. Data include the antimicrobial agents tested, organisms identified, infection site, institution type and test methodology. Patient demographic information, including age and gender, are also available.

Susceptibility testing is performed at all participating laboratories using standard United States Food and Drug Administration testing methods. Urine isolate test results are interpreted according to the NCCLS (National Committee for Clinical Laboratory Standards). The NCCLS sets the standard for the methodology used for susceptibility testing, including antibiotic selection, minimum inhibitory concentration parameters, quality control and test interpretation.[8] When multiple isolates were collected from the same patient in a 5-day period, the first isolate was used to determine susceptibility patterns.

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Outpatient urine cultures were defined as urine isolates obtained at ambulatory clinics and emergency departments. Inpatient cultures were defined as urinary isolates obtained in the inpatient hospital setting. We excluded from study all urinary isolates from skilled nursing facilities and rehabilitation facilities. To limit an overestimation of uropathogen resistance we used a strict definition of resistance and included only organisms classified as resistant. Bacteria with intermediate susceptibility were not classified as resistant by our definition since many antibiotics are highly concentrated in urine and may be adequate for treatment. To decrease the possibility of contamination we limited isolates for this study to those in which only a single organism grew.

Measurements

We compared resistance patterns in the outpatient vs inpatient setting for the 6 most common uropathogens, including Escherichia coli, Enterobacter, Enterococcus, Klebsiella, Pseudomonas aeruginosa and Proteus mirabilis. We report aggregate data on each organism and each of the 15 antibiotics, including TMP/SMX, ampicillin, amoxicillin-clavulanate, nitrofurantoin, cephalothin, cefuroxime, ceftriaxone, cefazolin, ceftazidime, gentamicin, ciprofloxacin, piperacillin/tazobactam, imipenem, aztreonam and vancomycin. Patients were stratified by gender, age and visit setting.

Statistical Analysis

Summary statistics were performed using the frequency and proportion for categorical data. Chi-square analysis was done to compare differences in uropathogen prevalence and resistance patterns between outpatient and inpatient urinary isolates. All analysis was 2-sided with $p < 0.05$ considered statistically significant. Analyses with fewer than 10 observations were performed with the Fisher exact test.

RESULTS

We identified a total of 30,978 urinary isolates in the database, including all inpatient and outpatient settings. Of the 25,418 outpatient urinary isolates 86% were from females. Of the 5,560 inpatient urinary isolates 63% were from females.

Organism Prevalence

We stratified urinary isolates by gender and visit setting (see figure). E. coli was the most commonly cultured organism in males and females in each setting, followed by Enterococcus. The E. coli prevalence in females was 83% (95% CI 83–84) among outpatients and 64% (95% CI 63–66) among inpatients ($p < 0.001$). The prevalence of E. coli in males in the outpatient setting was 50% (95% CI 48–52) compared with 37% (95% CI 35–39) in the inpatient setting ($p < 0.001$). The prevalence of Enterococcus in females was 5% (95% CI 5–6) among outpatients and 13% (95% CI 12–14) among inpatients ($p < 0.001$). Similarly, in male outpatients the Enterococcus prevalence was 17% (95% CI 16–18) compared with 27% (95% CI 25–29) in inpatients ($p < 0.001$). The difference in outpatient vs inpatient prevalence in males and females for all other uropathogens was less than 10%.

Given the large number of total E. coli isolates, it was possible to stratify the prevalence of E. coli isolates by age. The E. coli prevalence was higher in outpatient than inpatient isolates for each gender in all age groups

Antibiotic Resistance

The table lists the rates of uropathogen resistance to various antibiotics stratified by patient setting. We identified numerous differences between the outpatient and inpatient resistance patterns of these organisms. Inpatient resistance rates frequently exceeded outpatient resistance rates, especially for third generation cephalosporins and ciprofloxacin. Notably, E. coli resistance to TMP/SMX was high for outpatient and inpatient isolates.

DISCUSSION

Using the TSN database we compared outpatient and inpatient resistance patterns for the 6 most common pediatric uropathogens. This study had 2 main findings that may affect the treatment of children with UTIs. 1) Different resistance patterns were noted between outpatient and inpatient settings for 5 of the 6 common pediatric uropathogens using a nationwide database. 2) Prevalence patterns vary based on patient setting, gender and age. These differences should be considered when empirically treating children who present with urinary tract symptoms, and when developing antibiograms. Our findings extend what was previously found in single center studies.[5,9]

The different resistance patterns in outpatient and inpatient settings affect empirical antibiotic choices when treating a child with a UTI. Clinicians must choose an antibiotic with a high likelihood of coverage while considering potential adverse effects and minimizing unnecessary overuse of broadspectrum antibiotics. Since antibiotics are generally prescribed before the return of culture results, antibiograms are published to guide empirical antibiotic choice.

Antibiograms are designed by a set of guidelines[8] using antimicrobial resistance and sensitivity data. At most hospitals combined outpatient and inpatient laboratory data are currently used to create an antibiogram.[10,11]

Dahle et al recently examined different susceptibility patterns of urinary isolates in a single health care system, comparing a community based uropathogen antibiogram to a hospital based uropathogen antibiogram for children in Utah.[5] Similar to our findings, they determined that there was a difference in resistance patterns between outpatient and inpatient uropathogens. We evaluated whether outpatient vs inpatient resistance patterns would follow similar trends on a larger, broader scale.

In addition to finding different susceptibilities, we noted different uropathogen prevalence patterns in male and female patients. As expected, E. coli was the predominant female uropathogen in outpatient cultures. Male outpatient urine cultures had more variability in organisms. These variations in prevalence by gender are important observations that should be used to guide empirical antibiotic selection, especially since nonE. coli uropathogens are less likely to be susceptible to narrow spectrum antibiotics. The relatively high frequency of

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Enterococcus is a particularly important finding in males, which may guide different empirical antibiotic choices based on gender.

As clinicians struggle with the growing rate of resistance, the need to target empirical antibiotics becomes more challenging. Prior studies demonstrated that empirical antibiotics are often chosen incorrectly based on longstanding prescribing habits.[9] This concept was studied by McGregor et al when they tracked the increasing prevalence of MRSA (methicillin resistant Staphylococcus aureus) in the outpatient setting.[12] They observed that physicians changed their choice of empirical treatment of cellulitis when they had access to outpatient based antibiograms with appropriate resistance and sensitivity patterns for community acquired MRSA. However, if they were not provided with antibiograms, physicians often continued with prior prescribing practices. This becomes clinically relevant when selecting an empirical antibiotic for a patient with a UTI at a family practice clinic. Copp et al noted that Bactrim™ is a leading antibiotic prescribed by many physicians for pediatric UTIs[13] but in our study it had a fairly high outpatient resistance rate.

Along these lines, Boggan et al reported that when practitioners are provided with antibiograms that target the specific diagnosis of the patient, physicians select more narrow spectrum antibiotics.[9] The investigators asked physicians to choose an empirical antibiotic for theoretical children of different ages with UTIs. When no antibiogram was available, physicians chose an effective antibiotic 32% of the time. When an antibiogram was available that combined adult and pediatric uropathogen data, physicians chose an effective antibiotic 57% of the time. However, when these physicians had access to a pediatric specific antibiogram, 79% chose an effective antibiotic. The mentioned studies support the fact that when clinicians are aware of resistance and prevalence patterns, more informed and effective antibiotic choices can be made for empirical treatment of UTIs.

This study cannot be used to determine an empirical antibiotic for a specific patient at presentation with a UTI. However, the different urinary isolate resistance patterns of outpatient vs inpatient settings demonstrate the need to create separate antibiograms at institutions.

Relation to Clinical Practice

A patient who presents to a clinic at age less than 2 years with fever and urine studies suggestive of a UTI most likely requires empirical antibiotics. Usually the patient is on empirical antibiotics for at least 48 hours before culture results are available. A local antibiogram based on urine cultures can be an important tool to aid in the selection of an antibiotic with a high likelihood of treating the uropathogen.

When urine cultures are stratified to specifically represent the patient being treated, they are most useful. These stratifications can reflect inpatient or outpatient status, and patient age and gender. For example, it would be clear that cefazolin is an excellent empirical antibiotic for females younger than 2 years since the most common bacteria in that age and gender group is E. coli, which is sensitive to cefazolin 96% of the time. In a male patient younger than 2 years cefazolin would be less likely to be effective because it only treats 69% of UTIs

(E. coli and P. mirabilis). In this case one may consider using a different antibiotic, such as amoxicillinclavulanate, while waiting for cultures to return.

Limitations

This study should be interpreted in the context of some database limitations. It was not possible to determine whether urinary isolates collected in the inpatient setting actually represented infections acquired in the inpatient or outpatient setting. If a patient was admitted to the hospital, the urine culture obtained on hospital day 0 was counted as an inpatient culture. Clearly, the timing of that culture should be considered outpatient but in our data set it was counted as an inpatient culture. While our data prevented us from determining this with certainty, patients from whom urine cultures were obtained during inpatient admission tended to have different resistance patterns than those treated in the outpatient setting.

There is no information in the TSN data set on associated clinical signs or symptoms that would support a UTI diagnosis. Thus, it was not possible to determine whether some positive cultures were related to asymptomatic bacteriuria.

Another limitation of the data set was the inability to identify the specimen source, ie clean catch vs catheterized specimen. Despite this limitation it is unlikely that these cultures represented contamination. Investigators at participating laboratories are instructed to submit only culture data that they deem clinically positive and we only chose specimens with single growth bacteria to minimize the concern for contamination.

Lastly, these aggregate data do not necessarily reflect resistance patterns in specific communities since they were not separated regionally. However, this information is essential to evaluate overall uropathogen resistance patterns and trends in the United States.

CONCLUSIONS

We found significant differences in resistance patterns between outpatient and inpatient urinary isolates for several of the most commonly prescribed antibiotic agents. We also noted that uropathogen prevalence varies by patient gender and visit setting. These findings substantiate the need for separate inpatient and outpatient based antibiograms to optimize empirical antibiotic selection for pediatric UTI treatment.

Abbreviations and Acronyms

TMP/SMX	trimethoprim/sulfamethoxazole
TSN	The Surveillance Network
UTI	urinary tract infection

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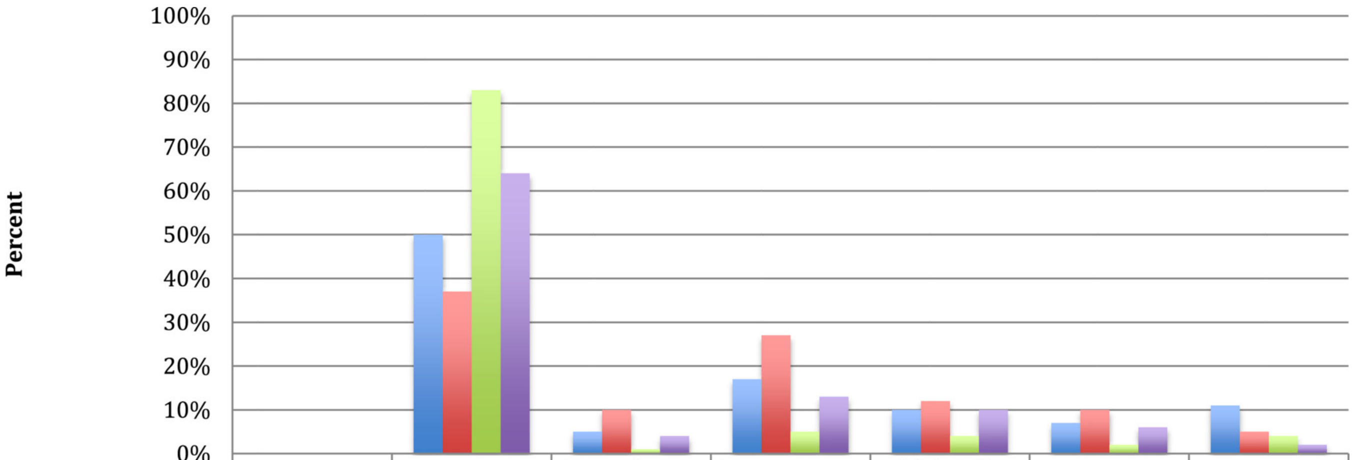

	Organism	E. Coli	Enterobacter spp.	Enterococcus spp.	Klebsiella spp.	P. aeruginosa	P. mirabilis
Male Outpatient		50%	5%	17%	10%	7%	11%
Male Inpatient		37%	10%	27%	12%	10%	5%
Female Outpatient		83%	1%	5%	4%	2%	4%
Female Inpatient		64%	4%	13%	10%	6%	2%

Figure 1.

Uropathogen prevalence by patient setting and gender. spp., species.

Table

Uropathogen resistance rates by setting

	% TMP/SMX (95% CI)	% Nitrofurantoin (95% CI)	% Ampicillin (95% CI)	% Cephalothin (95% CI)	% Cefazolin (95% CI)	% Ceftriaxone (95% CI)	% Ceftazidime (95% CI)	% Amoxicillin-Clavulanate (95% CI)	% Ciprofloxacin (95% CI)	% Vancomycin (95% CI)
E. coli:										Not done*
Outpt	24 (23–24)	Less than 1 (less than 1–less than 1)	45 (44–46)	16 (15–17)	4 (4–4)	Less than 1 (less than 1–less than 1)	Less than 1 (less than 1–less than 1)	5(5–5)	5 (4–5)	
Inpt	30 (29–32)	Less than 1 (less than 1–less than 1)	55 (53–57)	22 (19–25)	8 (7–9)	2 (2–3)	2 (1–2)	6 (5–8)	9 (8–10)	
p Value (chi-square test)	<0.001	0.25	<0.001	<0.001	<0.001	<0.001	<0.001	0.09	<0.001	
Enterobacter:								Not done*		Not done*
Outpt	18 (14–21)	23 (19–27)	78 (74–83)	96 (91–100)	91 (88–94)	12 (9–15)	15 (11–19)		1 (0–2)	
Inpt	13 (10–17)	21 (17–25)	80 (75–85)	98 (94–100)	93 (90–95)	24 (19–29)	33 (28–38)		1 (0–2)	
p Value (chi-square test)	0.08	0.52	0.66	0.69†	0.44	<0.001	<0.001		1†	
Enterococcus:	Not done*			Not done*	Not done*	Not done*	Not done*	Not done*		
Outpt		1 (1–2)	3 (2–3)						5(3–7)	Less than 1 (less than 1–1)
Inpt		5 (4–7)	13 (11–16)						12 (9–16)	6 (5–8)
p Value (chi-square test)		<0.001	<0.001						<0.001	<0.001
Klebsiella:										Not done*
Outpt	15 (13–17)	17 (15–19)	81 (79–84)	7 (3–10)	7 (6–8)	2 (1–2)	2 (2–3)	4 (2–5)	3 (2–4)	
Inpt	17 (14–20)	13 (10–16)	82 (79–86)	14 (8–21)	13 (11–16)	4 (2–5)	4 (3–6)	4 (2–7)	4 (3–6)	
p Value (chi-square test)	0.38	0.06	0.58	0.03	<0.001	0.03	0.03	0.66†	0.2	
P. mirabilis:										Not done*
Outpt	11 (10–13)	94 (92–95)	12 (11–14)	4 (0–not available)	4 (3–5)	Less than 1 (less than 1–less than 1)	Less than 1 (less than 1–less than 1)	1(0–2)	3 (2–4)	

	% TMP/SMX (95% CI)	% Nitrofurantoin (95% CI)	% Ampicillin (95% CI)	% Cephalothin (95% CI)	% Cefazolin (95% CI)	% Ceftriaxone (95% CI)	% Ceftazidime (95% CI)	% Amoxicillin-Clavulanate (95% CI)	% Ciprofloxacin (95% CI)	% Vancomycin (95% CI)
Inpt	13 (8–19)	88 (83–93)	11 (6–16)	0	4 (1–7)	0 (0–0)	Less than 1 (less than 1–2)	0(0–0)	6 (3–10)	
p Value (chi-square test)	0.42	0.01	0.61	0.62†	1†	1†	0.59†	1†	0.02	
P. aeruginosa:			Not done							Not done*
Outpt	94 (92–96)	0 (0–0)				31 (24–38)	4 (3–6)		5 (4–7)	
Inpt	95 (92–98)	0 (0–0)				40 (33–47)	10 (7–13)		11 (8–14)	
p Value (chi-square test)	0.7	Not applicable				0.08	<0.01		<0.01	

*Testing not performed since organism is not susceptible.

†Fisher exact test used when percents used to calculate chi-square statistic were based on fewer than 10 observations.