

Antibiotic Resistance Patterns in Children Hospitalized for Urinary Tract Infections

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Background: Children admitted to the hospital with urinary tract infections (UTIs) receive empirical antibiotic therapy. There is limited information on bacterial resistance to commonly prescribed intravenous antibiotics or on the risk factors for increased resistance in these patients.

Objectives: To determine the antibiotic resistance pattern in children admitted to the hospital with UTIs, and to determine if history of UTI, antibiotic prophylaxis, or vesicoureteral reflux increases the risk of resistant organisms.

Design/Methods: We reviewed all of the cases of UTI in children up to 18 years of age who were admitted during a 5-year period to Children's Hospital of Wisconsin, Milwaukee. We recorded age, sex, culture and sensitivity results, imaging that was performed, and past medical history.

Results: We identified 361 patients with UTIs. *Escher-*

ichia coli caused 87% of the infections, although *E coli* was significantly less common in children receiving prophylactic antibiotics (58%; $P < .001$) or in children with a history of UTI (74%; $P < .001$). Resistance to cefotaxime sodium was 3% in the patients not receiving antibiotic prophylaxis, but was 27% in the children receiving prophylactic antibiotics (relative risk, 9.9; 95% confidence interval, 4.0-24.5; $P < .001$). Resistance to aminoglycoside antibiotics was 1% in the children not receiving prophylaxis and 5% in the children receiving prophylactic antibiotics.

Conclusions: Children who are receiving prophylactic antibiotics and are admitted to the hospital for a UTI are often infected with an organism that is resistant to third-generation cephalosporins. These children are more appropriately treated with an aminoglycoside antibiotic.

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URINARY TRACT INFECTION (UTI) is the most common serious bacterial infection during infancy,¹ and many children with UTIs are admitted to the hospital. Most of these children receive antibiotics without knowledge regarding the causative organism or its sensitivity to antibiotics.

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The ability to identify patients at risk for resistant organisms has important implications. Renal scarring is most likely to occur in young children,² and delayed treatment is an additional risk factor for scarring.³ In addition, based on a landmark study⁴ comparing oral and intravenous antibiotics, there is an increased willingness to treat a febrile child with a UTI as an outpatient. This may be inappropriate for patients who are at high risk of

being infected with an organism that is resistant to empirical oral antibiotics.

Resistance of uropathogens to antibiotics is increasing.⁵⁻⁷ Previous studies in adults and children have identified a variety of risk factors for the presence of resistant organisms, including prior antibiotic exposure,⁸ urinary malformations,⁹ and the use of prophylactic antibiotics.⁹ Most prior pediatric studies include either only outpatients or a combination of outpatients and inpatients, some of whom had hospital-acquired infections.^{7,9,10} Thus, the pediatric literature does not include any studies to our knowledge that focus on community-acquired UTIs that are being treated with intravenous antibiotics in the hospital. Risk factors for resistant organisms in this patient population are largely unknown. In addition, many recent reports of antibiotic resistance in children with UTIs are from outside of the United States.^{7,9} Moreover, we are unaware of any pediatric studies that have identified risk factors in children with UTIs

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for resistance to commonly used intravenous antibiotics, such as aminoglycosides or third-generation cephalosporins. We therefore investigated the uropathogens in children treated in the hospital for community-acquired UTIs, focusing on risk factors for resistance to intravenous antibiotics.

METHODS

The Children's Hospital of Wisconsin institutional review board approved this study. We retrospectively reviewed hospital records for all of the patients aged 1 week to 18 years who were discharged from Children's Hospital of Wisconsin with a principal diagnosis of UTI or pyelonephritis (using *International Classification of Diseases, Ninth Revision* codes) for 5 consecutive years (1997-2001). A study¹¹ using this patient population was previously described. A UTI was defined as 10 000 or more colony-forming units (CFUs) per milliliter of a single organism on a catheterized specimen or 100 000 or more CFUs per milliliter on a clean-catch specimen. Patients were excluded if they had received outpatient antibiotics (other than antibiotic prophylaxis) prior to admission, had urologic stents in place, performed regular self-catheterization for spina bifida or other causes of neurogenic bladder, or had a bladder ostomy.

Antibiotic sensitivity was determined using standard techniques.¹² We grouped resistant and intermediate isolates for our analysis. Some organisms are not routinely tested against certain antibiotics. However, based on known sensitivity patterns, enterococci were assumed to be resistant to all cephalosporins, and pseudomonads were assumed to be resistant to cefazolin, cefuroxime, and cefotaxime sodium.

We recorded pertinent medical history, including vesicoureteral reflux (VUR; documented by reviewing radiologic reports), prior UTI, history of renal transplant, sickle cell disease, or posterior urethral valves. We specifically analyzed patients who were diagnosed with VUR after the current infection but had no history of UTI or of receiving prophylactic antibiotics ("previously undiagnosed VUR"). We also recorded the organism and sensitivities with the number of CFUs per milliliter on initial culture.

Comparisons between different populations were analyzed via relative risk (RR) calculations and 95% confidence intervals (CIs). The *P* values were determined using χ^2 or Fisher exact tests.

RESULTS

Our record review revealed 361 patients who met the inclusion criteria. The patient population was 76% female. The ages of the children in our population ranged from 1 week to 18 years (**Table 1**). The median age was 7 months and the mean age was 31 months (mean age, 28 months for boys and 32 months for girls).

There were 73 cultures obtained by clean catch and 283 by catheterization (the method was not documented in 5 patients). Thirteen of the cultures by catheterization had 10 000 to less than 50 000 CFUs per milliliter; the remainder had 50 000 CFUs or more per milliliter.

There were 83 patients with VUR (35 had grades III, IV, or V), including 65 with previously undiagnosed VUR. There were 54 patients with a history of previous UTI, 16 patients with sickle cell disease, 6 patients that had

Table 1. Patient Ages

Patient Age Categories	No. of Cases
0-6 mo	171
6-12 mo	48
1-2 y	35
2-3 y	22
3-8 y	30
8-12 y	32
12-18 y	23

undergone renal transplantation, and 2 patients with posterior urethral valves. The most common organisms were *E coli* (87%), *Klebsiella pneumoniae* (3%), *Pseudomonas aeruginosa* (2%), and *Enterococcus* species (2%). In the children with VUR, *E coli* caused 65 (78%) of the infections (2.2 increased RR of non-*E coli* infection vs those infections in children without VUR; 95% CI, 1.3-3.8; *P* = .004). In the children with previously undiagnosed VUR, 58 (89%) of the infections were caused by *E coli* (vs those in children without VUR, *P* = .80). Among the children with a prior history of UTI, *E coli* caused 40 (74%) of the infections (increased RR of non-*E coli* infection vs children without a history of UTI, 2.7; 95% CI, 1.6-4.7; *P* < .001). Girls (251/277, or 91%) and boys (65/85, or 76%) differed in the likelihood of being infected with *E coli* (increased RR of non-*E coli* in boys, 2.5; 95% CI, 1.5-4.3; *P* < .001).

We identified 26 patients receiving prophylactic antibiotics. This included amoxicillin (4 patients), trimethoprim-sulfamethoxazole (11 patients), penicillin (7 patients), and nitrofurantoin (2 patients); 2 patients did not have the particular antibiotic recorded. Of these 26 patients, 15 had a history of prior UTI, 9 had VUR, 2 had undergone renal transplantation, 6 had other genitourinary anomalies, 6 had sickle cell disease, and 1 had undergone splenectomy for autoimmune hemolytic anemia. The organisms in this group included *E coli* (15 infections; 58%), *Enterococcus* species (4 infections; 15%), *P aeruginosa* (2 infections; 8%), *Klebsiella oxytoca* (2 infections; 8%), *K pneumoniae* (2 infections; 8%), and *Citrobacter freundii* (1 infection; 4%). Patients receiving prophylactic antibiotics were less likely to be infected with *E coli* than those patients not receiving prophylaxis (increased RR of non-*E coli* in patients receiving prophylaxis, 4.2; 95% CI, 2.4-7.2; *P* < .001).

Antibiotic sensitivities among the total patient population, patients with a history of UTI, patients with previously undiagnosed VUR, and patients receiving prophylactic antibiotics are presented in **Table 2**. Among the children receiving prophylactic antibiotic therapy, 7 (27%) had an organism resistant to cefotaxime (vs 9 [3%] of the children not receiving prophylaxis; RR, 9.9; 95% CI, 4.0-24.5; *P* < .001). All of the *E coli* isolates in the group receiving prophylactic antibiotics were sensitive to cefotaxime. The decrease in sensitivity to cefotaxime among the children receiving prophylaxis was owing to the increased percentages of enterococci (4 infections; 15%) and pseudomonads (2 infections; 8%), as well as resistant *K oxytoca* in 1 child (this species was not identified in any children not receiving prophylactic

Table 2. Antibiotic Sensitivity in Children Admitted to the Hospital for a Urinary Tract Infection*

Antibiotic	All Patients (n = 361)	Patients With History of UTI (n = 54)	Patients Receiving Antibiotic Prophylaxis (n = 26)	Patients With Previously Undiagnosed VUR (n = 65)
Amikacin	347/347 (100)	49/49 (100)	22/22 (100)	62/62 (100)
Ampicillin	173/334 (52)	5/25 (20)†	7/21 (33)	32/60 (53)
Aztreonam	285/287 (99)	40/41 (98)	15/16 (94)	51/51 (100)
Cefazolin	261/346 (75)	33/52 (63)‡	11/25 (44)†	45/62 (73)
Cefepime	335/343 (98)	49/53 (92)§	21/25 (84)†	61/62 (98)
Cefotaxime	342/358 (96)	46/53 (87)†	19/26 (73)†	61/64 (95)
Ceftazidime	343/352 (97)	48/53 (91)†	21/26 (81)†	62/63 (98)
Cefuroxime	333/355 (94)	42/53 (79)†	18/26 (69)†	60/63 (95)
Gentamicin	328/333 (98)	47/48 (98)	21/22 (95)	61/61 (100)
Nitrofurantoin	323/346 (93)	45/50 (90)	20/24 (83)‡	59/62 (95)
Tobramycin	306/309 (99)	46/47 (98)	18/19 (95)	52/53 (98)
Trimethoprim-sulfisoxazole	285/345 (83)	33/46 (72)‡	12/20 (60)§	54/61 (88)

Abbreviations: UTI, urinary tract infection; VUR, vesicoureteral reflux.

*Values are expressed as number/total (percentage).

† $P < .001$ vs other patients.

‡ $P < .05$ vs other patients.

§ $P < .01$ vs other patients.

antibiotics). In children receiving prophylactic antibiotics, sensitivity levels increased to 21 (81%) of 26 children receiving ceftazidime, 21 (84%) of 25 children receiving cefepime, 21 (95%) of 22 children receiving gentamicin or tobramycin, and 25 (100%) of 25 children receiving the combination of ampicillin and cefepime. Of children with a history of previous UTI, 7 (13%) of 53 were infected with an organism resistant to cefotaxime (vs 9 [3%] of 305 children without a history of previous UTI; RR, 4.5; 95% CI, 1.7-11.5; $P < .001$). This decreased to 3 (7%) of 41 children with resistance to cefotaxime when children who were receiving prophylactic antibiotics were excluded from the group with a history of UTI (vs 6 [2%] of 295 children without a history of UTI and not receiving prophylactic antibiotics; RR, 3.6; 95% CI, 0.9-13.8; $P = .05$). Three (5%) of 64 children with previously undiagnosed VUR had resistance to cefotaxime, which is comparable to the rate in the total population (16 [4%] of 358 children).

COMMENT

Our study has shown a high rate of resistance to third-generation cephalosporins in subpopulations of children admitted to the hospital for UTIs. The rate of resistance was highest in children receiving prophylactic antibiotics. The increased rate in children with a history of UTI was not significant when the children taking prophylactic antibiotics were excluded. Children with previously undiagnosed VUR had resistance patterns similar to those in the total population.

The dominant cause of UTIs in our patient population was *E coli*, as has been shown in other studies of UTI in both adults^{5,6} and children.^{7,9,10} We observed a lower rate of *E coli* infections in children receiving prophylactic antibiotics, in children with a history of UTI, and in boys. A lower rate of infection with *E coli*

was previously observed⁹ in children with urinary malformations, hospital-acquired infections, a history of UTIs, or receiving prophylactic antibiotics, although that study included children who were managed as outpatients and children with hospital-acquired infections. In another pediatric study,⁷ *E coli* was more common in girls than in boys, and younger patients were less likely than older patients to be infected with *E coli*.

Resistance among uropathogens to a variety of antibiotics is increasing. Prior studies^{5,6} have shown increasing rates of resistance to ampicillin, trimethoprim-sulfamethoxazole, and first-generation cephalosporins. Our study found high rates of resistance to all of these antibiotics, as has been shown in previous studies^{7,9,10} in pediatric patients. In our patient population, resistance to nitrofurantoin was 7%, which is comparable to rates in recent studies in children with community-acquired UTIs^{7,10} and adult women with cystitis.⁶ In contrast, overall resistance to aminoglycosides was approximately 1%. This is consistent with previous studies of community-acquired infections in children⁹ and adults,⁶ although higher rates of resistance to aminoglycosides were found in hospital-acquired infections.⁹ We found an overall 95% sensitivity to cefuroxime, a second-generation cephalosporin. A previous pediatric study⁷ also found 95% sensitivity to cefuroxime. Sensitivity to ceftazidime was high in our study and in another previous pediatric study.⁹

A previous study⁹ in a mixed population of children with UTIs demonstrated that children receiving prophylactic antibiotics were at increased risk for infections with resistance to nitrofurantoin and trimethoprim-sulfisoxazole. The ability of prophylactic antibiotics to produce resistant organisms has been shown in systematic studies of antibiotic prophylaxis.^{13,14} The American Urological Association, Linthicum, Md, recommends antibiotic prophylaxis in children with documented VUR

after UTI.¹⁵ In this setting, prophylaxis is used to prevent recurrent UTIs and renal scarring, which can cause hypertension or chronic renal insufficiency.¹⁶ However, in children with VUR, there have been no controlled, prospective studies to our knowledge evaluating the effectiveness of prophylactic antibiotics for decreasing the recurrence of UTIs or the development of renal scarring.¹⁷ Our study, which found an association between antibiotic prophylaxis and selection for resistant organisms, further supports the need for a prospective study evaluating the practice of routine antibiotic prophylaxis for children with VUR.^{18,19}

The patients receiving prophylactic antibiotics had a high rate of resistance to third-generation cephalosporins, despite the fact that the patients were not receiving third-generation cephalosporins for prophylaxis. In fact, none of the patients were receiving any cephalosporin for prophylaxis. There are a number of potential explanations for this observation. It is possible that prophylactic antibiotics of any type alter the patient's bacterial flora, leading to selection of bacteria that have resistance to multiple antibiotics, as has been shown previously for trimethoprim.²⁰ Alternatively, the patients receiving prophylactic antibiotics had a variety of systemic and urologic diseases that may have predisposed them to acquiring resistant organisms. Finally, it is possible that this patient population may have had previous exposure to third-generation cephalosporins. Other studies have shown that prior exposure to an antibiotic leads to the development of organisms resistant to that antibiotic.⁸ While we could not determine the previous antibiotic exposures of our patients receiving prophylactic antibiotics, the large percentage with a history of UTI, combined with the fact that a third-generation cephalosporin is the standard empirical treatment for a UTI or unexplained fever at our institution, suggests that many children may have received a third-generation cephalosporin in the past. Nevertheless, the overall rate of resistance to third-generation cephalosporins was higher in the patients receiving prophylaxis than in those with only a history of prior UTI. This issue requires further study.

We identified history of UTI as a risk factor for increased antibiotic resistance. Other studies have shown that urinary malformations,^{9,21} history of UTI,²² presence of a urinary catheter,^{9,22} hospitalization within the last year,^{9,21} and recent treatment with antibiotics^{21,22} are additional risk factors for resistant organisms.

We demonstrated a high rate of susceptibility to aminoglycosides, even in patients who had risk factors for antibiotic resistance. This suggests that high-risk patients may be treated with an aminoglycoside. The combination of a cephalosporin with *Pseudomonas* coverage and ampicillin also provided excellent coverage in our high-risk patients. Another alternative might be an extended-generation penicillin such as piperacillin-tazobactam, but we do not have susceptibility data for this approach. Aminoglycosides have the advantage of a much lower cost, but they do require monitoring of drug levels and there is a risk of nephrotoxicity or ototoxicity. Nonetheless, aminoglycosides have a long record of safety and efficacy for the inpatient management of UTI in children.²³

Our study has a number of limitations. First, the conclusions regarding the impact of prophylactic antibiotics are based on a limited number of patients. Second, our study was done at 1 institution and, thus, may not be applicable at other sites. This is especially important since our hospital is a tertiary care center; the results may be less applicable in other settings.²⁴

Our study may have significant implications for outpatient treatment of UTI. Hoberman et al⁴ reported that children with a first febrile UTI may safely be managed as outpatients with an oral third-generation cephalosporin, thereby reducing health care costs. However, their study excluded children with a history of UTI, abnormalities of the urinary tract, or an underlying chronic disease. This would exclude the patients who were receiving prophylactic antibiotics and, therefore, were at the highest risk for being infected with an organism that is resistant to third-generation cephalosporins. This suggests the need for caution in applying the results of the study by Hoberman and colleagues to all of the children being considered for outpatient management of UTI. Young children are more likely to develop renal scarring,² and if they have risk factors for resistant organisms, they may be more appropriately treated as inpatients so that they can receive broader initial antibiotic coverage.

In conclusion, we observed a high rate of resistance to third-generation cephalosporins in children receiving antibiotic prophylaxis who are admitted to the hospital for treatment of UTIs. In such children, empirical treatment with an aminoglycoside provides much better antibiotic coverage than a third-generation cephalosporin.

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Announcement

2006 Certifying Examinations of the American Board of Pediatrics. All applicants for certifying examinations must complete applications online during the registration periods. The requirements for online applications may be found on the ABP Web site: (www.abp.org) or may be obtained by contacting the ABP. Additional information including eligibility requirements and registration dates may also be found on the ABP Web site.

General Pediatrics Examination: October 23 and October 24, 2006.

Sports Medicine: To be determined by ABFM.

Pediatric Cardiology: August 16, 2006.

Pediatric Critical Care Medicine: August 18, 2006.

Pediatric Pulmonology: August 17, 2006.

Pediatric Rheumatology: November 10, 2006.

Pediatric Emergency Medicine: November 16, 2006.

Developmental-Behavioral Pediatrics: November 15, 2006.

Pediatric Hematology-Oncology: November 17, 2006.

Transplant Hepatology: To be determined by ABIM.

Medical Toxicology: November 14, 2006.