A Single-Center Experience of Antimicrobial Resistance Patterns in Pediatric Urinary Tract Infection

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Key Words

Antimicrobial resistance • Pediatric infections • Resistance patterns • Susceptibility testing • Urinary tract infection • Uropathogens

Abstract

Objective: To assess the prevalence of urinary tract pathogens and their resistance patterns against antimicrobial agents in a single center. **Patients and Methods:** In children <16 years of age admitted for urinary tract infection (UTI) to the Dr. Sami Ulus Teaching and Training Hospital from January 2004 to December 2008, positive urine cultures were reviewed. **Results:** A total of 3,485 positive urine cultures were identified, of which 2,379 (68%) were from females and 106 (32%) from males. Their mean age was 63.5 ± 40.7 months. *Escherichia coli* was the most common causative agent both in total and among different age groups. Ampicillin had the highest resistance rate from all the pathogens isolated (63.8%), followed by piperacillin (51.8%) and trimethoprim-sulfamethoxazole (TMP-SMX; 48.6%). Cephalotin also had a high resistance rate (32.7%). The least resistance was for imipenem, amikacin, netilmicin and ciprofloxacin (0.13, 1.7, 2.4 and 7.5%, respectively). None of the *Klebsiella* and *Pseudomonas* isolates were resistant to imipenem. None of the *Staphylococcus aureus* isolates were resistant to teicoplanin and

vancomycin. Vancomycin-resistant *Enterococcus* spp. were isolated from two cultures. **Conclusion:** *E. coli* was the most common causative agent of UTI in children. Ampicillin, TMP-SMX or cephalothin and piperacillin had the highest resistance rates against urinary tract pathogens in our center.

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Introduction

Urinary tract infection (UTI) is one of the most common infections in children [1, 2], and early diagnosis and early antimicrobial therapy significantly reduce serious consequences of UTI, such as renal failure and hypertension [2]. Children with UTI are usually treated empirically. Resistance of urinary tract pathogens to antimicrobial agents is an important problem in many countries, with increasing numbers of therapeutic failure after empiric treatment [3]. Resistance patterns to antimicrobial agents vary according to the geographic region [4]; consequently, the choice of antimicrobial empiric treatment should not only be based on the most likely urinary tract pathogens but also on their updated local resistance patterns [5]. Hence the aim of this study was to assess the most likely urinary tract pathogens and their resistance patterns against antimicrobial agents in our center.

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Patients and Methods

We reviewed all urine cultures from January 2004 to December 2008 from children <16 years of age admitted to the Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital. In total, 3,485 positive urine cultures and antibiograms from children with UTI were identified. The study was approved by the Local Ethics Board.

All urine samples were obtained by midstream clean catch, transurethral bladder catheterization and suprapubic aspiration. Sterile urine bag samples were excluded. All urine samples were processed on blood agar and eosin methylene blue by standard loop method and incubated at 37°C overnight. A positive urine culture was defined as growth of a single pathogen of >10⁵ colony-forming units (CFU)/ml in a midstream urine sample, >10⁴ CFU/ml in a urine sample obtained by catheterization [6] and any number of colonies in a sample obtained by suprapubic aspiration [5].

Only the first positive urine culture obtained per patient on admission was included in the analysis to eliminate any possibility of recurrence and nosocomial infection. The polymicrobial cultures and cultures with multidrug-resistant uropathogens were not included in the analysis. Cultures with common contaminants, including coagulase-negative staphylococci and α -hemolytic streptococci, and cultures with *Candida* growth were excluded. Bacterial identification and the determination of sensitivity and resistance patterns of these microorganisms were assessed by the criteria established by the Clinical Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards) protocol [7]. For each UTI patient, age, gender, causative pathogen and antimicrobial resistance to a panel of antimicrobials were recorded. Data were entered into Microsoft Excel and analyzed. Results were reported as percentages. The mean age ($\pm$ SD) was determined. Median resistance to antimicrobial agents was calculated for each causative pathogen.

Results

A total of 3,485 positive urine cultures were identified, 2,379 (68%) cultures were from females and 1,106 (32%) from males. The female/male ratio was 2.1/1.

Of the positive urine cultures, 686 (19.6%) were from infants (aged 0–24 months), 999 (28.7%) from preschool children (2–5 years), 1,783 (51.2%) from school-age children (5–12 years) and 17 (0.5%) from children >12 years. The mean age was 63.5 $\pm$ 40.7 months (range 0–192 months). Sterile urine bag samples were excluded from this study, and the majority of the cultures were from children >2 years. However, urine samples from infants aged 0–2 years (table 1) were obtained by transurethral bladder catheterization and suprapubic aspiration. *Escherichia coli* was the most common causative agent (2,473 isolates; 71%) both in total and among different age groups (table 1), followed by *Proteus mirabilis* (299 iso-

Table 1. Percentage of *E. coli* and various drug resistance rates against *E. coli* according to age groups

	0–2 years	2–5 years	5–12 years	>12 years
<i>E. coli</i>				
%	57	68	80	53
n/total n	391/686	679/999	1,483/1,783	9/17
<i>Resistance, %</i>				
Amikacin	4.2	0.9	0.8	11
Netilmicin	4.6	1.5	1	–
Gentamicin	11.8	7.7	7.4	22.2
Ciprofloxacin	7.5	7.4	9	22.2
Cephazolin	24	17	14	22
Cephalotin	39.7	34.6	28.4	33
Cefuroxime	17.3	10.9	9.2	22
Ceftazidime	13.5	7.8	7.1	22
Ceftriaxone	14.8	8.4	8.1	22
Cefoperazone	19	14	12	22
Cefepime	13.5	8	7.4	22
Ampicillin	69.2	71	60.9	66.7
Amoxicillin-clavulanate	19	21	16.8	–
Ampicillin-sulbactam	40	38	29.9	22
TMP-SMX	51.5	55.5	48.7	44.4
Piperacillin	62.4	63	50	66.7
Imipenem	–	–	0.1	–
Aztreonam	13.9	7.8	7.1	22.2
– = No resistance.				

lates; 8.6%), *Klebsiella* spp. (233 isolates; 6.7%), *Enterococcus* spp. (221 isolates; 6.3%), *Morganella morganii* (39 isolates; 1.1%), *Staphylococcus aureus* (38 isolates; 1.1%), *Pseudomonas* spp. (35 isolates; 1.1%) and others.

From all the pathogens isolated, ampicillin had the highest resistance rate, followed by piperacillin and trimethoprim-sulfamethoxazole (TMP-SMX; 63.8, 51.8 and 48.6%, respectively) and imipenem, amikacin, netilmicin and ciprofloxacin had the least resistance (0.13, 1.7, 2.4 and 7.5%, respectively; table 2).

E. coli presented high resistance to ampicillin, followed by piperacillin and TMP-SMX (65.7, 56.5 and 50.8%, respectively). Resistance against cephalotin was also high (32.7%). Imipenem was the most active agent against *E. coli* with an extremely low resistance rate (0.08%). Only two of the *E. coli* isolates were found to be resistant to imipenem. *E. coli* presented low resistance to amikacin, netilmicin, gentamicin and ciprofloxacin (1.6, 2, 8.5 and 8.8%, respectively; table 2). Urine cultures of

Table 2. Resistance rates (%) of the most frequent urinary tract pathogens against tested antibiotics

Antibiotic	<i>E. coli</i>	<i>K. oxytoco</i>	<i>K. pneumoniae</i>	<i>M. morganii</i>	<i>Proteus</i> spp.	<i>Pseudomonas</i> spp.	Overall resistance
Amikacin	1.6	1.7	3.5	–	1.0	–	1.70
Netilmicin	2.0	1.8	5.7	–	2.8	5.8	2.41
Gentamicin	8.5	5.2	10.3	2.6	10.1	8.6	8.70
Ciprofloxacin	8.8	1.7	2.3	–	1.0	2.8	7.52
Cephazolin	17.2	62.5	36.6	94.8	45.3	NT	23.68
Cephalotin	32.6	61.4	47.1	94.9	33.9	NT	35.58
Cefuroxime	11.3	45.6	23.8	71.1	21.1	NT	14.83
Ceftazidime	9.3	35.0	20.4	–	1.4	14.3	9.65
Ceftriaxone	9.6	40.7	20.8	–	3.1	26.5	10.24
Cefoperazone	14.7	52.6	28.6	2.7	6.6	3.1	15.26
Cefepime	8.9	35.7	18.8	–	1.4	14.3	9.22
Ampicillin	65.7	96.5	93.1	87.2	58.5	NT	63.85
Amoxicillin-clavulanate	18.1	33.3	36.6	84.2	9.7	NT	20.20
Ampicillin-sulbactam	34.4	63.1	55.4	34.2	11.9	NT	34.12
TMP-SMX	50.7	16.1	22.7	41.1	60.6	97.1	48.57
Piperacillin	56.5	63.1	61.7	12.8	21.1	2.8	51.77
Imipenem	0.08	–	–	–	0.3	–	0.13
Aztreonam	9.5	38.6	19.1	–	1.7	15.2	9.9

– = No resistance; NT = not tested.

children aged between 2–5 and 5–12 years constituted 80% of all, and antibiotic resistance patterns against *E. coli* were comparable to total resistance data. Although antimicrobial resistance against *E. coli* was high in children >12 years, the results were ignored because there were only 9 samples in this age group (table 1).

P. mirabilis had significant resistance rates to TMP-SMX, ampicillin and cephazolin (60.7, 58.5 and 45.3%, respectively), with low resistance rates to amikacin, ciprofloxacin and netilmicin (1, 1 and 2.81%, respectively). Only one isolate was found to be resistant to imipenem (table 2).

Klebsiella spp. had considerable resistance rates to ampicillin (93% for *Klebsiella pneumoniae* and 96.5% for *Klebsiella oxytoco*). None of these isolates was resistant to imipenem. Least resistance was observed to amikacin (3.5% for *K. pneumoniae* and 1.7% for *K. oxytoco*) and ciprofloxacin (2.3% for *K. pneumoniae* and 1.8% for *K. oxytoco*; table 2).

P. aeruginosa was most resistant to ceftriaxone (26.5%). None of the isolates was resistant to imipenem and amikacin, and resistance to ciprofloxacin (2.7%), piperacillin (2.8%) and cefoperazone (3.1) was low (table 2).

None of the *M. morganii* isolates was resistant to imipenem, cefepime, amikacin and ciprofloxacin (table 2).

S. aureus was most resistant to penicillin G (86.8%), but resistance to ciprofloxacin was low (8.6%), with no resistance to teicoplanin and vancomycin (data not shown).

Vancomycin-resistant *Enterococcus* spp. were isolated from 2 cultures (data not shown).

Discussion

UTI are generally mediated by Gram-negative bacteria among which *E. coli* is the principal pathogen followed in frequency by *Klebsiella* spp., *Proteus* spp., *P. aeruginosa*, *Enterococcus* spp., *Serratia* spp. and *S. aureus* [8]. In the present study, *E. coli* was the most prevalent pathogen both in total and among different age groups, consistent with previous studies [4, 6, 8]. In this and previous reports [2, 4, 6], the majority of cultures were from females.

According to WHO guidelines, TMP-SMX and ampicillin are the first choice for treatment of pediatric UTI [9], but resistance to TMP-SMX and ampicillin has progressively increased in the last decade [3, 4, 6]. *E. coli* showed high resistance to ampicillin and TMP-SMX in this study. Almost 65% of the uropathogens were resistant to ampicillin and nearly half of them were resistant

to TMP-SMX, indicating that empiric treatment with ampicillin and TMP-SMX is inadequate for UTI in children in our center. The resistance rates to ampicillin and TMP-SMX reported in the present study were similar to other drug resistance studies in our country [4, 10], but much higher than those published in Europe and North America [3, 11, 12] and lower than those reported in other countries, e.g. Iran, Taiwan, the Arab world and India [2, 6, 13–15].

It has been suggested that children with acute pyelonephritis could effectively be treated with oral antibiotics, such as cefixime, cefibuten and amoxicillin-clavulanate, with or without initial intravenous therapy [16]. Based on our results of 15% resistance to cefuroxime and 20% resistance to amoxicillin-clavulanate, we recommend these drugs for common treatment of primary, uncomplicated UTI in children in our center.

The prevalence of resistance to injectable antimicrobial agents was lowest for imipenem, followed by amikacin and ciprofloxacin in our patients, in agreement with previous studies [4, 11]. Nearly all pathogens were found to be sensitive to imipenem. It is highly stable against β -lactamase and has the unusual property of having a post-antimicrobial effect on Gram-negative bacteria. Due to its small molecular size, it can overcome the poor permeability of β -lactams by efficient penetration through the outer-membrane porin D [15].

Aminoglycosides do not negatively impact the intestinal flora, and resistance against aminoglycosides has remained very low (approximately 1–2%) [17]. The prevalence of resistance against amikacin and netilmicin was very low in our patients, confirming the findings of recently published studies [6, 10, 17]. Hence, amikacin or netilmicin monotherapy could be used for the effective and safe management of UTI requiring parenteral treatment in our center.

There are limitations against the routine use of fluoroquinolones in pediatric patients due to the discovery of arthropathies in animal models [18]. However, they can be used in complicated UTI as they decrease hospitalization time [18]. In longitudinal studies, prevalence of ciprofloxacin resistance increased over time [3, 19], reaching almost 20% in countries such as Spain and Portugal [3]. The prevalence of ciprofloxacin resistance seems to be higher in Latin America [3, 18]. In our patients, the prevalence of ciprofloxacin resistance was higher than in reports from North America and European countries [3].

Resistance to other antimicrobial agents like cephalosporins is an emerging issue in children with UTI [4]. One possible reason for this is the widespread use of these

agents in the pediatric population for otitis media and pharyngitis. Widespread cephalosporin use has been associated with the emergence of resistance to extended-spectrum β -lactamase, i.e. β -lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. These include ceftazidime, ceftriaxone, cefotaxime and the oxyimino monobactam aztreonam [4, 20]. In this study, the overall prevalence of resistance to ceftriaxone was almost 10% along with cefepim, ceftazidime and aztreonam, being in contrast to reports from European countries. In a study in Switzerland, no resistance was identified for third-generation cephalosporins [21], and in a study in Austria, resistance to cephalosporins was considerably low [11]. In a study in Jordan, the prevalence of resistance to these agents was higher than in our study, but we could not find a valid explanation for this discrepancy [14]. In countries like Iran and Brazil, the prevalence of resistance to cephalosporins was comparable with our isolates [2, 6]. This class should be used with caution and should not be used if microbiological documentation is available in our country.

Almost 60% of *E. coli* and *Klebsiella* isolates were resistant to piperacillin. The elevated resistance to piperacillin (60%) in this study was almost exclusively due to the primary resistance of *E. coli* and *Klebsiella* spp., as described in the literature [4].

The inappropriate usage of antimicrobial agents, poor hygienic conditions and overcrowded living conditions may result in the selection of resistant bacterial strains causing therapeutic failure [3, 5]. The high resistance rates to antimicrobial agents in this study may be explained by the easy access to antimicrobial agents even in the absence of a prescription since antimicrobial drugs can be purchased in our country without a prescription. A population with a high percentage of young individuals with low socioeconomic status may contribute as another factor since our hospital is in the suburbs of Ankara, the capital of Turkey.

Conclusion

E. coli was the most common causative agent of UTI in children, and ampicillin, TMP-SMX or cephalothin and piperacillin had the highest resistance rates against uropathogens in our center.

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