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Antibiotic resistance in childhood urinary tract infections: A single-center experience

Çocukluk çağı idrar yolu enfeksiyonlarında antibiyotik direnci; tek merkez deneyimi

Serhat Samancı[1], Muhittin Çelik[2], Muhammet Köşker[3]

[1]Department of Pediatrics, Diyarbakır Children's Diseases Hospital, Diyarbakır, Turkey
[2]Division of Neonatology, Department of Pediatrics, Diyarbakır Children's Diseases Hospital, Diyarbakır, Turkey
[3]Division of Infectious Diseases, Department of Pediatrics, Diyarbakır Children's Diseases Hospital, Diyarbakır, Turkey

The known about this topic

The causative agent in childhood urinary tract infections is generally Gram-negative bacteria. Antibiotic resistance tends to increase throughout the world and in our country.

Contribution of the study

In community-acquired UTI, ceftriaxone resistance was found as 35% and carbapenem and aminoglycoside resistance rates were low. In empirical treatment, antibiotic resistance rates and regional differences should be considered, as well as the grown causative agents.

Abstract

Aim: Urinary tract infections are the most common genitourinary tract disease in children, and inappropriate antibiotic and/or dose selection increase the likelihood of resistance. The aim of this study was to determine the prevalence of urinary tract infection pathogens, patterns of resistance to antibiotics, and empirical treatment options.

Material and Methods: Between January 2013 and December 2017, urine culture and antibiogram results of pediatric patients aged 0 days to 16 years were analyzed retrospectively. Antibiotic susceptibilities were determined using disc diffusion according to methods of the Clinical and Laboratory Standards Institute.

Results: Of the 1326 children with culture growth, 1070 (80.6%) were female and 256 (19.3%) were male. The most common microorganism found was (1138, 85.8%) *E. Coli*, followed by *Klebsiella* spp. (71, 5.3%), *Enterobacter* spp. (44, 3.3%), and *Proteus* spp. (28, 2.1%). High frequency of resistance to ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime axetil, as TMP-SMX was detected in all microorganisms, whereas resistance to amikacin, meropenem, imipenem, ertapenem, fosfomycin, and nitrofurantoin was low.

Conclusion: *E. coli* was the most common causative agent of urinary tract infections in childhood. High resistance to ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime axetil, and TMP-SMX was detected in all agents in our center.

Keywords: Antibiotic resistance, *E. Coli*, urinary tract infection

Öz

Amaç: Çocuklarda idrar yolu enfeksiyonları en sık karşılaşılan genito-üriner sistem hastalığı olup tedavide uygun olmayan antibiyotik ya da doz seçimi direnç olasılığını artırmaktadır. Bu çalışmada, idrar yolu enfeksiyonu patojenlerinin yaygınlığı, antibiyotiklere karşı direnç paternleri ve ampirik tedavi seçeneklerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2013–Aralık 2017 tarihleri arasında, 0 gün–16 yaş arası çocuk hastaların idrar kültür ve antibiyogram sonuçları geriye dönük olarak analiz edildi. Antibiyotik duyarlılıkları "The Clinical and Laboratory Standards Institute" yöntemlerine uygun olarak disk difüzyon yöntemi ile yapıldı.

Bulgular: Kültürde üremesi olan toplam 1326 çocuk hastadan 1070'i (%80,6) kız, 256'sı (%19,3) erkek cinsiyetteydi. En sık üreyen mikroorganizma 1138 (%85,8) *E. coli*, daha az sıklıkta *Klebsiella* spp. 71 (%5,3), *Enterobacter* spp. 44 (%3,3), *Proteus* spp. 28 (%2,1) idi. Tüm mikroorganizmalarda yüksek oranda ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime-axetil, TMP-SMX direnci saptanırken, amikacin, meropenem, imipenem, ertapenem, fosfomycine ve nitrofurantion'a karşı direnç düşük orandaydı.

Çıkarımlar: Çocukluk yaş grubunda idrar yolu enfeksiyonunun en sık etkeni *E. coli* olarak saptandı. Merkezimizde tüm etkenlerde ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime-axetil, TMP-SMX'e karşı yüksek düzeyde direnç saptandı.

Anahtar sözcükler: Antibiyotik direnci, *E. coli*, idrar yolları enfeksiyonu

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Corresponding Author/Sorumlu Yazar: Serhat Samancı E-mail/E-posta: samanciserhat@hotmail.com
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Introduction

Urinary tract infection (UTI) is the most common genitourinary tract disease and its incidence has been reported as 3–28/1000 in girls and 1.5–7/1000 in boys (1). Empirical antibiotic therapy is generally preferred for treatment. Inappropriate antibiotic and dose selection cause treatment failure and increased resistance to antibiotics. Recurrent UTIs, in particular, may lead to permanent injuries such as renal parenchymal scarring, disruption in renal functions, high blood pressure, and chronic renal disease (2). In addition, frequent antibiotic use or urinary tract malformations are risk factors for the development of resistance. Although there are regional differences, resistance to antibiotics used in empirical treatment is gradually increasing throughout the world and in our country (3–5). The most frequently grown microorganism and antibiotic resistance should be considered in the selection of empirical antibiotic therapy.

The objective of this study was to find antibiotic resistance patterns of microorganisms grown most frequently in our center and to determine empirical treatment options according to the results obtained.

Material and Methods

Urine culture results of 11 360 patients aged below 16 years who presented to our hospital between January 2013 and December 2017 were examined. The culture and antibiogram results of 1326 urine samples in which growth was detected were analysed retrospectively. The subjects' sexes, ages, species that grew in urine culture, and antibiotic resistance/sensitivities were recorded. For urine culture, midstream urine samples or clean urine samples collected in urine drainage bags depending on the age, and urine samples obtained by urinary catheter in newborns, were used. The samples collected were planted in 5% sheep blood agar and eosin methylene blue medium and were evaluated after storage at 37°C for 24–48 hours. Growth of $>10^4$ colonies (CFU/mL) in samples obtained by urine drainage bags and $>10^5$ colonies (CFU/mL) in other samples, and growth of a single microorganism were considered positive culture. Antibiotic sensitivities of the bacteria grown were tested in accordance with the Clinical and Laboratory Standards Institute (CLSI) methods using disc diffusion method; *in vitro* sensitivity tests for commonly used antibiotics including ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, amikacin, gentamicin, cefixime, cefuroxime, cefuroxime axetil, cefoperazone, ceftriaxone, cefepime, cefoxitin, ceftazidime, ciprofloxacin, colistin, ertapenem, imipenem, meropenem, fosfomycin, vancomycin, piperacillin/tazobactam, tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX) and nitrofurantoin, were performed. The primary culture results of patients who had a history of recurrent UTI and who were followed up in hospital were evaluated to exclude recurrent and nosocomial infections. Patients who had growth of candida and/or urinary system anomaly were excluded from the evaluation.

Ethics committee approval was obtained from the Health Sciences University Gazi Yaşargil Education and Research Hospital Ethics Committee for the study (20/6/2018/104). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The Statistical Package for the Social Sciences 20.0 (SPSS Inc., Chicago, Illinois, USA) program was used for statistical analysis. The patients' distributions by age and sex were evaluated using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results

A total of 1326 urine samples in which bacterial growth was found were included in the evaluation. One thousand seventy of the samples were obtained from female patients (80.6%) and 256 urine samples (19.3%) were obtained from male patients; the female/male ratio was 4:1. A statistically significantly higher rate of *E. coli* growth was found in the girls ($p<0.001$) (Table 1). The mean age of the patients was 10.7±4.3 months.

The microorganism which was grown most commonly was *E. coli* (1138, 85.8%) and this was followed by *Klebsiella* spp. (71, 5.3%), *Enterobacter* spp. (44, 3.3%), and *Proteus* spp. (28, 2.1%) (Table 2). *Staphylococcus* epidermis was grown in 10 patients (0.8%) and *Pseudomonas* spp. were grown in eight patients (0.6%).

High rates of ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime axetil, TMP-SMX resistance were found in all microorganisms, whereas resistance to amikacin, meropenem, imipenem, ertapenem, fosfomycin, and nitrofurantoin was found with a low rate (Table 3).

The highest rates of resistance were found against ampicillin (61.2%) and TMP-SMX (38.7%); resistance to cefuroxime (30.2%), cefixime (28.9%), and ceftriaxone (27.2%) was found with lower frequencies for *E. coli*. The lowest rates of resistance were found against meropenem (2%), amikacin (0.4%), colistin (0.6%), ertapenem (1.5%), and imipenem (1.7%) (Table 3). Resistance rates for *E. coli* by years are shown in Figure 1.

For *Klebsiella* spp., the most prominent resistance was found against ampicillin, cefuroxime, ceftriaxone, and TMP-SMX (97%, 47.1%, 42%, and 39.4%, respectively),

Table 1. Distribution of the microorganisms grown by sex

Microorganism	Sex						p†
	Male		Female		Total		
	n	%	n	%	n	%	
Escherichia coli,	177	69.1	961	89.8	1138	85.8	
Adjusted Residual	-8.5		8.5				
Klebsiella spp.	30	11.7	41	3.8	71	5.4	
Adjusted Residual	5.0		-5.0				
Enterobacter spp.	19	7.4	25	2.3	44	3.3	
Adjusted Residual	4.1		-4.1				<0.001
Proteus spp.	15	5.9	13	1.2	28	2.1	
Adjusted Residual	4.6		-4.6				
Other*	15	5.9	30	2.8	45	3.4	
Adjusted Residual	2.4		-2.4				
Total	256	100	1070	100	1326	100	

†: The microorganisms' distribution by sex was evaluated with "adjusted standardized residual". *Escherichia coli* was found with a significantly higher rate in the female sex. *: *Staphylococcus* epidermis, *Pseudomonas* spp., Candida, Group B streptococcus

Table 2. Distribution of the microorganisms grown by years

	2013 n=142		2014 n=340		2015 n=329		2016 n=326		2017 n=189	
	n	%	n	%	n	%	n	%	n	%
Escherichia coli	114	80.3	298	87.6	279	84.8	292	89.6	155	82
Klebsiella spp.	14	9.9	7	2	22	6.7	14	4.3	14	7.4
Enterobacter spp.	10	7	13	3.8	10	3	4	1.2	7	3.7
Proteus spp.	0	0	8	2.3	6	1.8	5	1.5	9	4.8
Other	4	2.8	14	4.1	12	3.6	11	3.4	4	2.1

whereas amikacin, meropenem, imipenem, fosfomycin, and gentamicin resistances were found with low rates (2.9%, 2.9%, 4.3%, 11.8%, and 14.5%, respectively).

For *Enterobacter* and *Proteus* spp., resistance to ampicillin, imipenem, nitrofurantoin, and TMP-SMX was found with high rates.

Discussion

Urinary tract infection is observed commonly in children. Its incidence was found as 9.6/1000 in girls and 2.4/1000 in boys in our study, in accordance with the literature. Infection generally occurs with the colonization of the lower urinary tract by Gram-negative microorganisms. It may extend up to the bladder and kidney depending on the pathogen's characteristics. Infection by the hematogenous route is observed more rarely and occurs as a result of the transfer of the agent to the urinary tract by hematogenous spread during sepsis. Vesicoureteral reflux, voiding dysfunctions, neurogenic bladder, urinary continence, constipation, bladder neck obstruction, and the presence of a catheter are predisposing factors for UTIs (6). Another factor is familial and genetic predisposition (7).

In UTI, the causative agent is generally Gram-negative bacteria; the main pathogen is *E. coli*, and *Klebsiella*, *Enterobacter*, and *Proteus* spp. have been reported with lower rates (8–10). In line with previous studies, we found that the most common causative agent was *E. coli*, and female sex predominated in our study.

Clinical findings in UTI in children vary by age, location in the urinary tract, and the severity of the infection (11). In the neonatal period and infancy, the signs are mostly nonspecific (12). The diagnosis is mostly based on the patient's symptoms, physical examination findings, and urinalysis, and treatment is generally initiated empirically (13). However, increased antibiotic resistance in the present time brings treatment failures. Antibiotic resistance, which is an important problem for nosocomial infections, has also become an important problem for community-acquired agents (14). It is recommended that the resistance rate should not exceed 10–20% to initiate empirical treatment (15). Therefore, the American Infectious Diseases Society emphasizes that regional pathogenic agents and antibiotic sensitivities in UTIs should be known (16).

Table 3. The microorganisms' antibiotic resistances

	Escherichia coli n=1138 (%)	*Klebsiella* spp. n=71 (%)	*Enterobacter* spp. n=44 (%)	*Proteus* spp. n=28 (%)
Amikacin	0.4	2.9	–	3.6
Amoxicillin-clavulanate	21.9	32.4	–	4.2
Ampicillin	61.2	97.1	91.3	62.5
Ampicillin-sulbactam	41.3	100	66.7	25
Cefepime	6.7	33.3	–	–
Cefixime	28.9	43.9	87.5	–
Cefoperazone	7.8	12.5	–	4.3
Cefoxitin	6.2	14.9	87.5	4
Ceftazidime	15.1	35.7	9.1	–
Ceftriaxone	27.2	42	12.5	–
Cefuroxime	30.2	47.1	14.3	7.7
Cefuroxime axetil	29.9	47.8	75	7.7
Ciprofloxacin	7.9	15.7	11.1	3.7
Colistin	0.6	–	–	75
Ertapenem	1.5	9.5	14.3	4.5
Fosfomycine	2.1	11.8	28.6	5.6
Gentamicin	9.6	14.5	19.2	10.7
Imipenem	1.7	4.3	42.9	51.9
Meropenem	2	2.9	–	3.6
Nitrofurantion	2.6	14.9	28	100
Piperacillin/tazobactam	16.1	26.9	–	8
Tetracycline	32.7	50	69.7	100
Trimethoprim-sulfamethoxazole	38.7	39.4	68	57.7
Vancomycin	–	–	14.3	–

Antibiotic resistance of *E. coli* is increasing gradually. In a study conducted in Croatia, it was shown that the most commonly isolated strain was *E. coli*, which had a high level of resistance to ampicillin and TMP-SMX (17). In a study conducted in the United States with 25 418 patients who were diagnosed as having UTIs, high rates of ampicillin and TMP-SMX resistance were reported (18). Similarly, studies conducted in different countries showed that *E. coli* had high rates of ampicillin, TMP-SMX, and amoxicillin-clavulanate resistance (19–22). In studies conducted in our country, on the other hand, the resistance rates were reported as 44–89% for ampicillin, 43–61% for TMP-SMX, and 28–65% for amoxicillin-clavulanate (23–27). The data of this study were found to be compatible with other studies conducted in our country, but there are proportional differences compared with some data from abroad. We think that this can be explained by the difference in the prevalence of antibiotic use between countries.

In the childhood age group, oral agents are preferred more frequently in terms of ease of use in empirical treatment. A high resistance to antibiotics, which can be used by the oral route, such as ampicillin, amoxicillin-clavulanate, and TMP-SMX, was found for *E. coli*, which was the most commonly isolated microorganism. This shows that the above-mentioned antibiotics are not an option in empirical treatment. The gentamycin resistance rate was found as 4.6% in England, 17.5% in Iran, 19.5% in Korea, and 10.9% in Turkey (19, 28–30). In our study, gentamycin resistance was compatible with the literature. Amikacin and meropenem resistance rates were reported as 4%–1.7% (31, 32). In the study conducted by Çoban et al. (33), the amikacin resistance rate was 3.2% and no meropenem resistance was found. In our study, the rates of amikacin and meropenem resistance were found as 0.4% and 2%, respectively.

In studies conducted in our country and in other countries, gradually increasing resistance rates have been reported for third-generation cephalosporins within years (7.5–48%). Broader areas of use of these antibiotics, using an antibiotic as the first-choice antibiotic, prophylactic

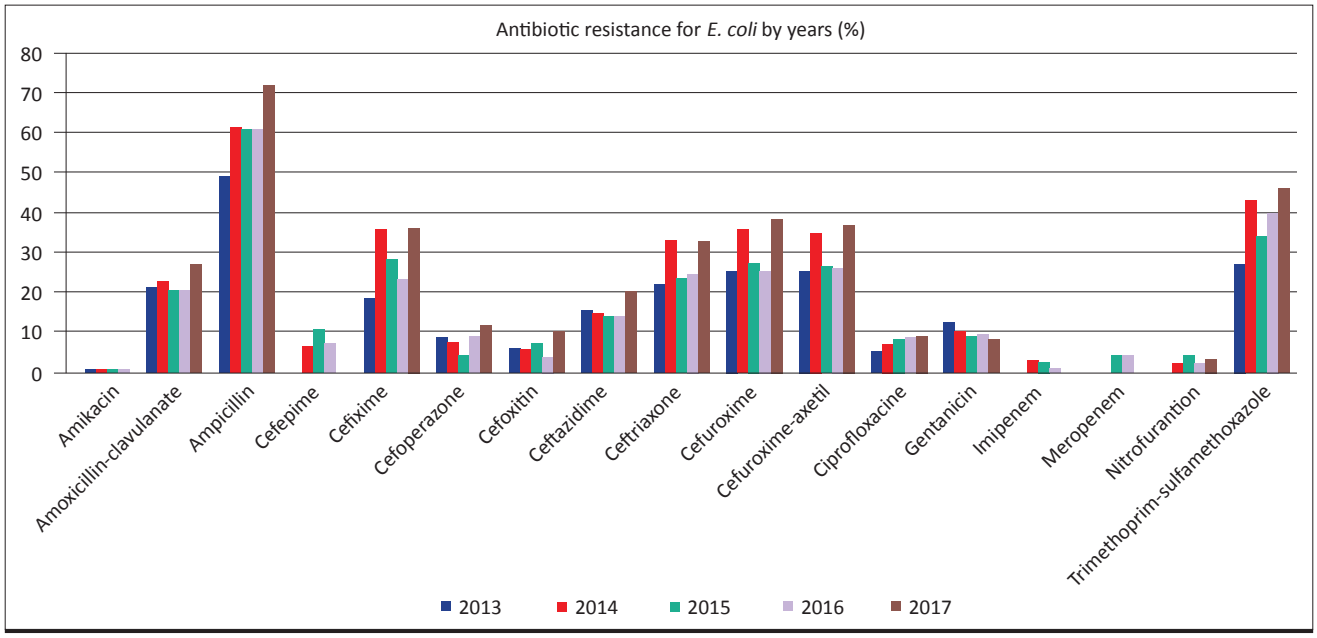

Figure 1. Resistance by years (*E. coli*)

antibiotic use, hospitalization, and nosocomial infections have been blamed for the development of resistance (9, 34). A high level of resistance to third-generation cephalosporins was also found in our study.

In the present study, *Klebsiella* spp. was the second most common agent, and the ampicillin, TMP-SMX, cefixime, amoxicillin-clavulanate, ceftriaxone, meropenem, amikacin, and cefoperazone resistance rates were found higher compared with the other studies conducted in our country (23–27). A more careful approach should be pursued in treatment in terms of using these antibiotics due to high resistance rates.

Amikacin, ciprofloxacin, meropenem, and ceftriaxone resistance was not found, high ampicillin, TMP-SMX, and cefepime resistance rates were found for *Proteus* spp.; the results were similar to those found in other studies (33).

As seen in our study and other studies, antibiotic resistance has become one of the serious health problems throughout the world and in our country. Rates of resistance to ampicillin, ampicillin/sulbactam, amoxicillin-clavulanate, TMP-SMX and second-generation cephalosporins, which are initiated empirically, are high. Ceftriaxone resistance has been found with a rate of 35% in community-acquired UTI. On the other hand, rates of resistance to carbapenem and aminoglycosides are low.

For rational antibiotic use, urine culture should be performed, resistance patterns should be examined, and treatment protocols should be established accordingly. Treatment should be planned considering the region's or country's general resistance rates.

This study was conducted retrospectively, and reliable information regarding the regular use of antibiotics initiated and clinical signs and symptoms could not be obtained, which are limitations of our study.

In conclusion, resistance to antibiotics continues to be an important problem in UTIs. High rates of resistance to ampicillin, ampicillin/sulbactam, amoxicillin-clavulanate, TMP-SMX, and second-generation cephalosporins, which are preferred in empirical treatment of UTIs, were found. We think that resistance to ceftriaxone, which has been used frequently as a parenteral antibiotic in recent years, should be considered specifically. We believe that empirical treatment should be planned considering resistance rates and regional differences.

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