

# Antibiotic Drug Resistance Pattern of Uropathogens Seen in The First Episode of Community-Acquired Pediatric Urinary Tract Infections At A Tertiary Care Hospital

## Üçüncü Basamak Bir Hastanede Görülen Toplum Kaynaklı İlk İdrar Yolu Enfeksiyonlarındaki Üropatojenlerin Antibiyotik Direnç Paternleri

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### ABSTRACT

**Objective:** Increased antibiotic resistance is a significant problem associated with higher morbidity, mortality, and costs in managing urinary tract infections (UTI). This study aims to analyze the antimicrobial resistance profile of uropathogens isolated from children with the first attack of community-acquired UTI.

**Material and Methods:** This retrospective cohort study was conducted between January 2010-December 2016, with the patients aged one month to 18 years diagnosed with the first attack of community-acquired UTI at the pediatric outpatient clinic of a tertiary care hospital. Patients' age, sex, UTI history, clinical findings at admission, urine analysis, urine culture, and antibiogram results were recorded.

**Results:** A total of 1086 patients and 1086 cultures were included in the study. The male/female ratio was 1/5.3. The mean age of the children was 73.7±47.1 (0.4-215.9) months. 16.0% were aged 1-24 months. *E. coli* was the most common causative agent found to be 85.1% in frequency. The overall antimicrobial resistance was found to be highest for ampicillin, followed by piperacillin and trimethoprim-sulfamethoxazole (63.5, 41.6 and 38.1%, respectively). Imipenem, amikacin, and tobramycin had the least resistance (0.5, 0.5, and 7.6%, respectively). The overall antimicrobial resistance against amoxicillin-clavulanate, ampicillin-sulbactam, cefuroxime, ceftriaxone was 19.4, 24, 25.9 and 21.1%; respectively. Extended-spectrum beta-lactamase positivity was detected in 5.6% (n=61) of samples.

**Conclusion:** Our study showed significant increase in antimicrobial resistance to the most common antibiotics which are prescribed before urine culture results and antibiotic sensitivities are available. The resistance rates for amoxicillin-clavulanate, ampicillin-sulbactam, cefuroxime, ceftriaxone was almost 20% or above in children with the first UTI attack in an outpatient setting.

**Key Words:** Antimicrobial resistance, Antimicrobial susceptibility, Urinary tract infection



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**Ethics Committee Approval / Etik Kurul Onayı:** This study was conducted in accordance with the Helsinki Declaration Principles. Ankara Hematology-Oncology Hospital Ethics Committee approved the study (2017-021/10.04.2017).

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## ÖZ

**Amaç:** Artan antibiyotik direnci, idrar yolu enfeksiyonlarının (İYE) yönetiminde daha yüksek morbidite, mortalite ve maliyetlerle ilişkili önemli bir sorundur. Bu çalışma, ilk kez toplum kökenli İYE geçiren çocuklardan izole edilen üropatojenlerin antimikrobiyal direnç profilini analiz etmeyi amaçlamaktadır.

**Gereç ve Yöntemler:** Bu retrospektif kohort çalışması, Ocak 2010-Aralık 2016 tarihleri arasında, üçüncü basamak bir çocuk hastanesinin polikliniklerinde ilk toplum kökenli İYE atağı tanısı konan bir ay ile 18 yaş arasındaki hastalarla yapıldı. Hastaların yaşı, cinsiyeti, İYE öyküsü, başvuru klinik bulguları, idrar analizi, idrar kültürü ve antibiyogram sonuçları kaydedildi.

**Bulgular:** Çalışmaya toplam 1086 hasta ve 1086 kültür dahil edildi. Erkek/kadın oranı 1/5.3'dü. Çocukların yaş ortalaması 73.7±47.1 (0.4-215.9) aydı. %16'sı 1-24 aylıktı. *E. coli* sıklık olarak %85.1 ile en sık etken etkendi. Genel antimikrobiyal direncin ampisilin için en yüksek olduğu, ampisilini piperasilin ve trimetoprim-sülfametoksazolün (sırasıyla %63.5, %41.6 ve %38.1) takip ettiği bulundu. İmipenem, amikasin ve tobramisin en düşük dirence sahipti (sırasıyla %0.5, 0.5 ve %7.6). Amoksisilin-klavulanat, ampisilin-sulbaktam, sefuroksim, seftriakson'a karşı genel antimikrobiyal direnç oranı sırasıyla %19.4, 24, %25.9 ve %21.1'di. Örneklerin %5.6'sında (n=61) geniş spektrumlu beta-laktamaz pozitifliği saptandı.

**Sonuç:** Çalışmamız, idrar kültürü ve antibiyotik duyarlılık sonuçları belirlenmeden önce reçete edilen en yaygın antibiyotiklere karşı antimikrobiyal dirençte önemli artış olduğunu göstermiştir. Amoksisilin-klavulanat, ampisilin-sulbaktam, sefuroksim, seftriakson için direnç oranları, ayakta tedavi ortamında ilk İYE atağı olan çocuklarda neredeyse %20 veya üzerindedir.

**Anahtar Sözcükler:** Antibiyotik direnci, Antibiyotik duyarlılığı, Üriner sistem enfeksiyonu

## INTRODUCTION

Urinary tract infections (UTI) are among the most common bacterial infections in children (1). *Escherichia coli* is the most common bacterial pathogen responsible for UTI (1,2). Following a UTI there is concern with recurrences which can lead to renal scarring associated with long-term complications, hypertension, and renal failure (1-4). Clinical guidelines about UTI in children encourage rapid diagnosis and early treatment with an appropriate agent to prevent kidney scarring and long-term complications (4-7). Antibiotic resistance is strikingly increasing among the uropathogens, and bacterial resistance causes problems for clinicians due to limited treatment options (1,2,6,7). Data are available on the antimicrobial susceptibility patterns of endemic uropathogens in different countries of the world, but it is necessary to update the changing patterns of resistance to determine the appropriate treatment plans (1,2,6-9). Since treatment to reduce UTI-related morbidity is usually started early before the results of urinary microbiology are obtained, current data on the most common uropathogens and local antibiotic resistance patterns will help to choose accurate empirical therapy.

This study was conducted to determine the antimicrobial resistance patterns of uropathogens isolated from patients with the first episode of community-acquired urinary tract infections to choose appropriate empirical UTI treatment in children.

## MATERIAL and METHODS

This observational study was conducted between January 2010-December 2016, with children aged one month to 18 years diagnosed with their first episode of UTI at pediatric outpatient polyclinics at Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital. Ankara Hematology-

Oncology Hospital Ethics Committee approved the study (2017-021/10.04.2017).

Urine samples for microbial examination were collected by midstream clean-catch method in the toilet-trained and urethral catheterization method in non-toilet-trained children. No samples in the study were collected by the bag or suprapubic aspiration. A positive urine culture (UC) was defined as the growth of a single pathogen of at least 10<sup>5</sup> colony forming units (CFU)/ml for midstream sampling, and 10<sup>4</sup> colonies/ml for catheter specimens (10).

Only a single positive culture per patient was included in the analysis. The diagnosis of UTI was then based on only clinical findings and positive UC. Abnormal urine tests (nitrite and/or leucocyte esterase positivity) and/or abnormal urine microscopy but a negative UCs were not diagnosed as UTI.

Children with urinary tract abnormalities, recurrent UTIs, vesicoureteral reflux (VUR), urolithiasis, complicated urinary tract infections, known chronic or other medical disorders, polymicrobial culture results, culture results defined as contamination by medical microbiology expert and using antibiotics before admission or already on antibiotic treatment and hospitalized children were excluded from the study.

All urine samples were tested using standard procedures and were cultivated into MacConkey agar and incubated at 37 °C for 48 h. The VITEK 2 automated microbial identification system was used to identify uropathogens and antimicrobial "susceptible" or "resistant" status.

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) guidelines (11). Patients' sex, age, clinical findings,

urine analysis (UA), urine culture and susceptibility rates of etiologic agents to different antimicrobials were recorded retrospectively. The patients' previous UTI history was asked to parents and checked by hospital records if they had applied to our hospital before. Patients were classified as *E. Coli* and non-*E. Coli* UTI, according to urine culture results. Statistical analysis was performed in SPSS for Windows 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are given as mean, the standard deviation for continuous variables, and frequency, the percentage for categorical variables. Comparisons were performed using the t-test, Mann-Whitney u test, and chi-squares test, where  $p < 0.05$  was considered as statistically significant.

## RESULTS

### Clinical and demographic characteristics

The 1086 cultures of 1086 patients with first UTI episodes were enrolled in the study. Of these patients; 15.8% (n=172) were male, 84.2% (n=914) were female. The male/female ratio was 1/5.3. The number of girls was significantly higher than boys ( $p < 0.001$ ). The mean age was  $73.7 \pm 47.1$  (0.4-215.9) months. Of the 1086 positive UCs, 16.0% (n=174) were from children aged 1-24 months. 82.4% of UCs were obtained by midstream clean catch. 17.6% were obtained by catheterization. Demographical and clinical characteristics were shown in Table I. UTI with non-*E. Coli* isolates were younger than patients with UTI with *E. coli* isolates, more seen in males, and had more normal urinalysis (Table II).

**Table I: Demographic characteristics of the patients.**

	n (%)
The mean age (months)*	73.7±47.1
Age groups	
<2 years	174 (16.0)
2-5 years	296 (27.3)
6-10years	467 (43.0)
11-18 years	149 (13.7)
Sex	
Male	172 (15.8)
Female	914 (84.2)
Symptoms	
Fever	789 (72.7)
Urinary complaints	293 (27.0)
Abdomen/flunk pain	67 (6.1)
Vomiting	38 (3.4)
Irritability	48 (4.4)
Other (malnutrition, prolonged jaundice)	35 (3.2)
Urine analysis	
Positive nitrite	557 (52.0)
Positive leukocyte esterase (LE)	846 (77.6)
Nitrite and LE positivity	452 (42.2)
Normal urine microscopy	134 (12.5)
Normal results in urinalysis and microscopy	84 (7.8)

\* mean±SS

**Table II: Demographic and clinical characteristics of *E. Coli* and non-*E. Coli* groups.**

Characteristics	<i>E. Coli</i>	Non- <i>E. Coli</i>	p
Mean age (years)	6.3±3.7	4.7±4.4	< 0.01
< 2 years of age (%)	13.1	32.3	< 0.01
Male sex (%)	9.8	49.3	< 0.01
Fever positive (%)	21.4	14.8	0.056
Normal urinalysis	5.8	19.3	< 0.01

**Table III: Antibiotic resistance frequencies according to isolated uropathogens.**

Antibiotics	<i>E. Coli</i> n (%)	<i>Proteus</i> n (%)	<i>Klebsiella</i> n (%)	Total UCs n (%)
Ampicillin	561 (62.7)	33 (41.8)	68 (95.8)	668 (63.5)
Piperacillin	182 (44.5)	3 (9.1)	13 (39.4)	198 (41.6)
Amoxicillin-clavulanate	173 (19.4)	6 (7.5)	23 (33.3)	208 (19.8)
Ampicillin-sulbactam	216 (24.6)	4 (5.2)	25 (36.2)	248 (24)
Piperacillin-tazobactam	67 (11.1)	1 (1.7)	9 (17.3)	78 (10.9)
Aztreonam	107 (19.3)	0/37 (0)	17 (35.4)	124 (19.4)
Cephazolin	94 (16.5)	5 (9.3)	13 (27.7)	114 (16.9)
Cephalotin	142 (29.2)	5 (11.9)	12 (30)	161 (28.2)
Cefepime	64 (12.3)	0/40 (0)	5 (13.5)	69 (11.4)
Cefuroxime	156 (25.4)	5 (11.4)	18 (38.3)	184 (25.9)
Cefixime	10 (18.9)	0/20 (0)	-	10 (17.5)
Ceftriaxone	37 (21.5)	0/46 (0)	19 (35.2)	157 (21.1)
Cefotaxime	55 (10.7)	0/40 (0)	12 (30.8)	67 (11.3)
Ceftazidime	128 (21.1)	0/46 (0)	18 (36.7)	146 (20.7)
Nitrofurantoin	22 (5.5)	33 (94.3)	10 (33.3)	68 (14.4)
Trimethoprim-sulfamethoxazole	336 (37.5)	41 (52.6)	23 (32.9)	400 (38.1)
Gentamicin	86 (9.5)	4 (5.1)	10 (14.1)	100 (9.5)
Amikacin	4 (0.5)	2 (2.4)	1 (1.4)	5 (0.5)
Tobramycin	33 (7.7)	1 (2.6)	4 (11.4)	38 (7.6)
Imipenem	2 (0.4)	0/39 (0)	1 (2.6)	3 (0.5)
Ciprofloxacin	68 (9.1)	1 (1.5)	5 (8.1)	74 (8.4)

### Isolated uropathogens

*E. coli* (85.1%, n=924) was the most common causative agent in all age groups followed by *Proteus species* (7.6%, n=82), and *Klebsiella species* (6.5%, n=71). Other isolates (*M. morgagni*, *Enterobacter*, *Streptococ spp*, *S. aureus*) were 0.8% (n=9) in frequency (Table III).

### Antibacterial susceptibility

Among all isolates, the overall antimicrobial resistance was found to be highest for ampicillin, followed by piperacillin and TMP-SMX (63.5, 41.6, and 38.1%, respectively). The overall antimicrobial resistance against amoxicillin-clavulanate,

ampicillin-sulbactam, cefuroxime, ceftriaxone was 19.4, 24, 25.9, and 21.1%; respectively. Imipenem, amikacin, and tobramycin had the least resistance (0.5, 0.5, and 7.6%, respectively). The antimicrobial resistance patterns of the uropathogens were shown in Table III.

*E. coli* demonstrated high resistance to ampicillin, piperacillin, and TMP/SMX (62.7, 44.5, and 37.5%, respectively). The least resistance was for imipenem and amikacin and nitrofurantoin (0.4, 0.5, 5.5%, respectively) (Table III).

*Proteus spp* represented high resistance to nitrofurantoin, TMP-SMX, and ampicillin (94.3, 52.6, and 41.8%, respectively). *Proteus spp* had no resistance against third-generation cephalosporins and imipenem (Table III).

*Klebsiella spp* had the highest resistance to ampicillin (95.8%). Cephalosporins other than cefepime and cephazolin had a resistance frequency of  $\geq 30\%$ . The least resistance was for amikacin, imipenem, and ciprofloxacin. (1.4, 2.6, 8.1%, respectively) (Table III). The extended-spectrum beta-lactamase (ESBL) producer isolates were detected in 61 samples (5.6%,  $n=61/1086$ ). Of these,  $n=55$  were among *E. coli* isolates,  $n=6$  were among *Klebsiella species*. Extended-spectrum beta-lactamase positive strains showed high resistance to ampicillin (100%), ceftriaxone (96.5%), and nitrofurantoin (33.3%). They revealed the least resistance for amikacin (8.5%) and imipenem (7.1%).

## DISCUSSION

Uropathogens are showing a rising trend in the antimicrobial resistance throughout the world (2,7,8,12-20). Oral 3rd-generation cephalosporins such as cefixime are considered to be the treatment of choice for oral outpatient therapy. For

hospitalized children, parenteral treatment with ceftriaxone or cefepime or cefotaxime is a reasonable choice until culture results are back to determine (21). Our study showed a significant increase in antimicrobial resistance to the most common antibiotics prescribed for UTI in childhood with the first UTI attack even in an outpatient setting. The resistance rates for amoxicillin-clavulanate, ampicillin-sulbactam, cefuroxime, ceftriaxone were almost 20% or above in our study. This result is striking because the frequency of cephalosporin resistance was nearly half in the previous study conducted at our center between 2004-2008 years, which included all positive UCs by not taking into consideration the comorbid factors, including urinary tract anomalies, recurrent UTI which assumed to increase the frequency of antimicrobial resistance (19). A comparison of antimicrobial resistance against uropathogens in consecutive (2004-2008, 2010-2016) periods in our center was shown in Figure 1. These results indicate that UTI treatment will be troublesome in the future, even in an outpatient setting. These results are important because of heralding the risk of UTI complication burden. The significant increase in resistance to third-generation cephalosporins also harbors significant risks not only in UTI but also in other childhood disease treatments.

Ghadageet al. (22) reported increased resistance to commonly used empirical therapy -ampicillin and co-trimoxazole- for UTI in India. Kothari and Sagar (23) also reported low susceptibility to amoxicillin, amoxicillin/clavulanate, ciprofloxacin, co-trimoxazole in uropathogens. Prais et al. (24) reported that empirical treatment with co-trimoxazole or cephalexin as the initial drug is inadequate in approximately one-third of UTI cases, but that nitrofurantoin and nalidixic acid maintained their very high efficacy against urinary pathogens in Israel. The European Centre for Disease Prevention and Control reported the increasing resistance to antibiotic treatments,

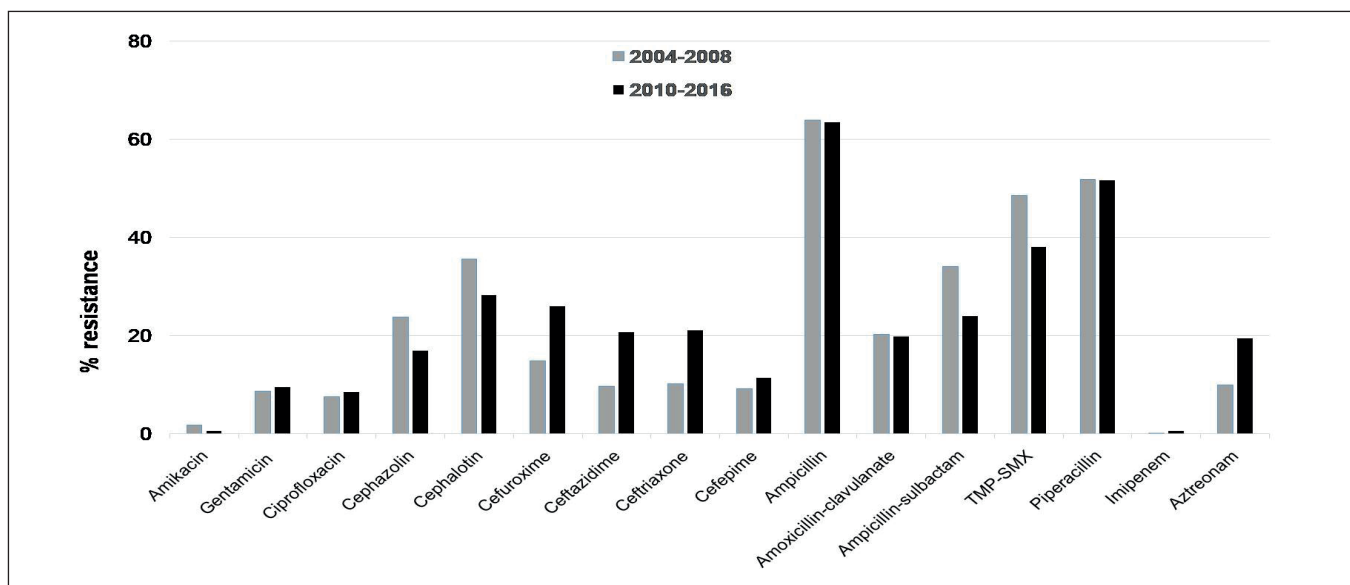


Figure 1: Comparison of antimicrobial resistance against uropathogens in two consecutive period in the same center.

including carbapenems (25). Imipenem-resistant *E. coli* rates were reported at 1.4-3.5% in Turkey (8,26). In our study, while resistance to ampicillin, piperacillin, and TMP-SMX was high among all isolates, imipenem, amikacin, and tobramycin had the lowest resistance. All *Klebsiella* isolates are sensitive to imipenem and amikacin in our study, as in a study by Abuhandan et al. (27) However, Wang et al.(6) reported resistance to imipenem and amikacin at a frequency of 21.12% and 6.83%, respectively. These results may vary because of the different patient inclusion criteria in different studies. *Proteus* isolates also revealed no resistance to third-generation cephalosporins and imipenem in our study. The overall ESBL positivity has been reported to be 5% in Europe, 39% in Asia, and 30% -50% in Turkey (28,29). Kurt-Şükür et al. (8) reported a prominently increase in overall ESBL positivity from 7.8% to 23.5% within ten years. ESBL positivity in our study was 5.6% in frequency, which is lower than the reports of other studies. This may be because all of our patients had the first UTI episode without comorbid conditions and frequent antibiotic usage for UTI treatment. The increase of resistant strains can be attributed to either availability of the drugs for unnecessary and improper use of many antimicrobials, or by empirical treatment (30,31). Therefore, continuous surveillance, new strategies, and multidisciplinary actions should be developed against over consumption and unnecessary antibiotic treatments. Recently, in this context, the Turkish Ministry of Health restricted antibiotic intake without prescription and planned projects to improve rational antibiotic use, such as public education campaigns, to increase awareness about this topic. Studies in the future will show the results of these precautions. Our study has the following limitations. The major limitation was its retrospective nature. The history of previous UTI episodes was limited to the family expression and the investigations performed in our hospital. Another limitation relates to in vitro susceptibility testing, which may not be fully reflected in clinical outcomes, as in-vivo sensitivity may be different. Also, the results obtained from our study may not be valid for other patients in different regions.

## CONCLUSION

The present study showed that initial empirical treatment with amoxicillin, trimethoprim-sulfamethoxazole, and first-generation cephalosporins are no longer appropriate, but fluoroquinolones, cefepime, imipenem, amikacin and nitrofurantoin (for *E. Coli*) maintained their high efficacy against urinary pathogens in Turkey. Almost one in five children have antimicrobial resistance against antimicrobials which are the ones likely to be prescribed before culture results and antibiotic sensitivities are available to the clinician. This result reveals upcoming future challenges in the successful treatment of pediatric UTI, even in an outpatient

setting. The present results may be of significant value to assist physicians in the appropriate choice of antibiotics, and to prevent the misuse or excessive use of antibiotics.

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