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Original Study

Antibiotic Resistance and Bacteria in Urinary Tract Infections in Pediatric Patients

Çocuk Hastalarda İdrar Yolları Enfeksiyonlarında Antibiyotik Dirençleri ve Bakteriler

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ABSTRACT

Objective: *Antibiotic resistance against bacterial pathogens associated with urinary tract infections (UTI) is rapidly increasing worldwide. In this study, we aimed at determining the causative microorganisms in children under 17 years of age diagnosed with UTI in our hospital and the antibiotic resistance rates of these causes.*
Methods: *We isolated and retrospectively analyzed 4801 urine samples of children under 17 years old who presented with bacterial growth in their urine cultures. The isolated bacteria and their antibiotic resistance profiles were statistically analyzed.*
Results: *Most (2001/77.2%) of 2592 patients included in the study were female and the mean age and median interquartile range (IQR) was 55 (12-98) months. Except for the neonatal period, the female gender was predominant in all age groups (p<0.0001). The most frequently isolated bacteria included Escherichia coli (67.7%), Klebsiella spp. (10.7%), and Enterococcus spp. (8.8%). The most and least resistant antibiotics were ampicillin (66.6%) and meropenem (0.3%) for E. coli, respectively. Although resistance of E. faecalis to ampicillin and ciprofloxacin is at a low level, E. faecium is much more resistant to these antibiotics (p<0.0001).*
Conclusion: *It is important that each center determines its own resistant antibiotics so as to guide empirical treatment. Re-evaluating each antibiotic that is started to be used empirically according to the results of culture and sensitivity in addition to switching to a suitable antibiotic would be very effective in reducing resistance rates.*

Keywords: *Child, urinary tract infection, antimicrobial resistance*

ÖZ

Amaç: *İdrar yolu enfeksiyonu (İYE) ile ilişkili bakteriyel patojenlere karşı antibiyotik direnci, tüm dünyada her geçen gün artmaktadır. Bu çalışmada amacımız hastanemizde İYE tanısı konulan 17 yaş altı çocuklarda etken mikroorganizmaların belirlenmesi ve bu etkenlerin antibiyotik direnç oranlarının saptanmasıdır.*
Yöntem: *Ocak 2018-Temmuz 2019 tarihleri arasında hastanemize başvuran ve İYE ön tanısıyla idrar kültürü tetkiki istenen ve kültürde bakteri izole edilen 17 yaş altı çocuklara ait 4801 örnek retrospektif olarak incelenmiştir. İzole edilen bakteriler ve antibiyotik direnç profilleri istatiksel olarak analiz edilmiştir.*
Bulgular: *Çalışmaya dahil edilen 2592 hastanın 2001 (%77,2)'i kız ve yaş ortalamaları median IQR 55 (12-98) ay idi. Yenidoğan dönemi hariç diğer tüm yaş gruplarında en sık kız cinsiyetin hakim olduğu görüldü (p<0,0001). En sık izole edilen bakteri türleri sırasıyla, Escherichia coli (%67,7), Klebsiella spp. (%10,7), Enterococcus spp. (%8,8) idi. En dirençli ve en az dirençli antibiyotikler Escherichia coli için sırasıyla ampisilin (%66,6), meropenem (%0,3) idi. Enterococcus fecalis'in ampisilin ve siprofloksasine direnç durumu çok düşük olmasına rağmen Enterococcus faecium'un bu antibiyotiklere çok daha dirençli olduğu görülmüştür (p<0,0001).*
Sonuç: *Her merkezin kendi direnç oranlarını belirlemesi ampirik tedaviye yol gösterici olması bakımından önemlidir. Ampirik başlanan her antibiyotiğin kültür ve duyarlılık sonucuna göre yeniden değerlendirilmesinin ve uygun bir antibiyotiğe geçilmesinin direnç oranlarını azaltmada oldukça etkili olacağı göz önünde bulundurulmalıdır.*

Anahtar kelimeler: *Çocuk, idrar yolları enfeksiyonu, antibiyotik direnci*

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INTRODUCTION

Urinary tract infection (UTI) is one of the most frequently encountered problem in children[1]. The frequency of UTI varies according to age, sex, race, and circumcision status[2]. Conversely, congenital kidney and urinary tract anomalies, bladder and bowel dysfunctions, urolithiasis, and incomplete emptying of the bladder are the main risk factors for the development of UTI[3,4].

Approximately 8% of children aged one month to 11 years will have at least one UTI in their lifetime[5]. The most common cause of UTI is *Escherichia coli.* However, in the first year of life, *Klebsiella pneumonia, Enterobacter spp., Enterococcus spp. and Pseudomonas spp.* are more common, and carry a higher risk of urosepsis in this age group compared to adulthood[6].

It may be difficult to distinguish pyelonephritis from cystitis based on clinical symptoms and signs, especially in infants and young children[7]. UTI can lead to acute morbidity in addition to long-term medical problems, such as hypertension and decreased kidney function[8].

The main purpose of treatment in children with UTI is rapid cure of symptoms and prevention of comorbidities, such as sepsis, kidney abscess, and kidney damage[9]. Early diagnosis and prompt, and suitable antibiotic therapy are essential for preventing kidney damage; therefore, empirical antibiotic therapy is usually started before obtaining a urine culture, and antibiotic susceptibility test is also performed[10,11].

Antibiotic resistance against UTI-associated bacterial pathogens is increasing worldwide, especially for widely used antimicrobial agents. Therefore, it is very important to initiate the suitable empirical antimicrobial treatment according to common etiological agents prevalent in specific geographical regions[12,13].

The aim of this study was to determine causative microorganisms in children under 17 years of age who were diagnosed with UTI in our hospital. We also sought to determine the antibiotic resistance rates attributed to these causative agents. In this way, we contribute to the initiation of accurate empirical antimicrobial treatment of pediatric patients diagnosed with UTI.

MATERIALS and METHODS

Study design

We obtained approval for our study from the Kartal Dr. Lutfi Kirdar Training and Research Hospital (2019/514/167/5, dated 06.12.2019). Moreover, the study was conducted in accordance with the principles of the Declaration of Helsinki.

In this study, we investigated urine samples from 4801 children under 17 years of age who had been clinically diagnosed as cases with UTI in our hospital between January 2018 and July 2019.

Urine samples

Mid-stream or catheterized urine samples were collected in a sterile container. According to the guideline of the American Academy of Pediatrics, pyuria and presence of 50,000 or more colonies in a catheterized urine samples were accepted as urinary infection[14]. According to the updated Italian recommendations for the diagnosis and treatment of urinary tract infection in children, the presence of 50.000 or more colonies in mid-stream urine samples was accepted as urinary infection[15].

Those who did not meet these criteria were not included in the study. Identification of bacteria using a matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS; VITEK MS, bioMérieux, France) system, antibiotic susceptibility tests were studied with the VITEK2 (Biomereux, France) automated system. Sensitivity limit values were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Antibiotic susceptibility tests demonstrating Gram-negative bacteria with carbapenem resistance and Enterococci with vancomycin resistance were repeated using an antibiotic gradient test.

Data collection

In this study, we included 2592 samples from patients who had been diagnosed with UTI. In addition to the demographic data of patients diagnosed with UTI, the isolated bacteria and antibiotic resistance profiles were recorded in an Excel file by obtaining information from the hospital automation system.

Statistical analysis

Statistical analysis was performed using portable SPSS 20.0 and MedCalc online free calculator[16]. For descriptive analysis, continuous variables were expressed as median and the first and third IQRS when not normally distributed. Categorical variables were expressed as numbers and percentages. The distribution rates of *E. coli* and *Klebsiella* by age groups, gender, and distribution rate of antibiotic resistance in *Enterococcus spp.* were compared using the Z test[15]. P values of <0.05 were considered statistically significant.

RESULTS

Demographic findings

We included 2592 patients in the study, and the median age with corresponding IQR was 55 (12–98) months with 2001 females out of the total of 2592 patients (77.2%) (Table 1).

Isolated bacterial species and age group distributions

We noted that Gram-negative, and Gram-positive microorganisms were isolated in the bacterial cultures of 89.4% (n=2318) and 10.6% (n=274) of the patients, respectively. The most frequently isolated bacteria were *E. coli* (67.7%), *Klebsiella spp.* (10.7%), *Enterococcus spp.* (8.8%), *Proteus spp.* (5.2%), *Enterobacter spp.* (2.7%), and *Pseudomonas spp.* (2.1%) (Table 1).

Table 1. Distribution of isolated bacteria by age groups.

Age (Month)	*E. coli* N (%)	*Klebsiella spp.* N (%)	*Enterococcus spp.* N (%)	*Proteus spp.* N (%)	*Enterobacter spp.* N (%)	*Pseudomonas spp.* N (%)	Other N (%)	Total N (%)
0-1	30 (31)	35 (36.5)	16 (16.7)	0 (0)	11 (11.5)	4 (4.2)	0 (0)	96 (3.7)
1-24	336 (44)	161 (21.1)	116 (15.2)	45 (5.9)	45 (5.9)	28 (3.7)	32 (4.2)	763 (29.4)
24-72	515 (73.4)	22 (3.1)	48 (6.8)	70 (10)	9 (1.3)	10 (1.4)	28 (4)	702 (27.8)
72-156	781 (83.6)	51 (5.5)	40 (4.3)	15 (1.6)	4 (0.4)	10 (1.1)	33 (3.5)	934 (36)
156-204	67 (69.1)	8 (8.2)	8 (8.2)	4 (4.1)	2 (2.1)	2 (2.1)	6 (6.2)	97 (3.7)
Total N (%)	1729 (66.7)	277 (10.7)	228 (8.8)	134 (5.2)	71 (2.7)	54 (2.1)	99 (3.8)	2592 (100)

Table 2. Distribution of age groups by gender and the most frequently isolated *E. coli.*, and *Klebsiella spp.*

	Gender				Gender			
Age (Month)	Male N (%)	Female N (%)	Total N	P Value	*E. Coli* N (%)	*Klebsiella* spp. N (%)	Total N	P Value
0-1	46 (47.9)	50 (52.1)	96	0.5616	30 (31.2)	35 (36.5)	96	0.4390
1-24	349 (45.7)	414 (54.3)	763	0.0008*	336 (44)	161 (21.1)	763	<0.0001*
24-72	136 (19.4)	566 (80.6)	702	<0.0001*	515 (73.4)	22 (3.1)	702	<0.0001*
72-156	7 (0.7)	927 (99.3)	934	<0.0001*	781 (83.7)	51 (5.5)	934	<0.0001*
156-204	19 (19.6)	78(80.4)	97	<0.0001*	67 (69.1)	8 (8.2)	97	<0.0001*
Total N (%)	557 (21.5)	2035 (78.5)	2592	<0.0001*	1729 (66.7)	277 (10.7)	2592	<0.0001*

**: p<0.05*

Table 3. Antibiotic resistance profiles of isolated bacteria.

Antibiotics	*Escherichia coli* %	*Klebsiella spp.* %	*Enterococcus spp.* %	*Proteus spp.* %	*Enterobacter spp.* %	*Pseudomonas spp.* %
Ampicillin	66.6	-	26.6	48.9	100	-
Piperacillin-Tazobactam	25.3	35.6	-	3.7	36.4	43.4
Cefuroxime Axetil	41.8	36	-	11.5	80.6	-
Ceftazidime	37.1	38.4	-	6.8	40	13
Ceftriaxone	36.7	38.5	-	7.5	39.7	-
Cefepim	40.3	48.4	-	-	-	12
Imipenem	0.4	5.3	-	59.3	4.6	13.2
Meropenem	0.3	5	-	0.7	2.9	9.3
Amikacin	12.1	6.4	-	6.7	4.3	7.4
Gentamycin	10.5	12.8	-	11.7	0	7.4
Ciprofloxacin	24.5	20.6	18.5	15.9	10	3.7
Nitrofurantoin	1.7	35.7	-	99.2	23.8	-
Trimethoprim-Sulfamethaxazole	34	25.2	-	44	10	-
Amoxicillin-Clavunate	43.3	36.1	25.8	9.7	100	-
Fosfomycin	0.5	15.1	-	7.4	27	-
Vancomycin	-	-	4.3	-	-	-
Linezolid	-	-	3	-	-	-
Tobramycin	-	-	-	-	-	0
Levofloxacin	-	-	-	-	-	6.1
Netilmicin	-	-	-	-	-	22.5

Table 4. Distribution of resistance rates among *Enterococcus spp.*

Antibiotics	*Enterecoccus faecalis* N (%) Total N=165	*Enterococcus faecium* N (%) Total N=63	P Value
Ampicillin	1 (0.6)	60 (95.2)	<0.0001*
Ciprofloxacin	8 (4.8)	35 (55.6)	<0.0001*
Amoxicillin	1 (0.6)	57 (93.4)	<0.0001*
Vancomycin	0 (0)	1 (1.6)	-
Teicoplanin	0 (0)	2 (3.2)	-
Gentamycin	5 (3)	12 (80)	<0.0001*
Linezolid	7 (4.7)	0 (0)	-

**: p<0.05*

When the distribution of bacteria by age groups was examined, the most frequently isolated bacteria in all age groups, except the neonatal period was *E. coli* (p<0.0001) (Table 2). The most frequently isolated bacteria in the neonatal period included *Klebsiella spp.* (36.5%) and *E. coli* (31.1%) without any statistically significant difference (p>0.05) (Table 2).

When the distribution of bacteria isolated was examined according to the gender of the patients, it was determined that the female gender was the most prevalent in all age groups except the neonatal period (p<0.0001)

(Table 2). However, the gender distribution in the neonatal period was not significant (Table 2).

Antibiotic resistance profiles of bacteria

The most and least resistant antibiotics were ampicillin (66.6%), and meropenem (0.3%) for *E. coli*, cefepime (48.4%), and meropenem (5%) for *Klebsiella spp.* ampicillin (26.6%), and linezolid (3.1%) for *Enterococcus spp.* (Table 3).

It was observed that 664 (25.6%) isolated microorganisms were susceptible to extended-spectrum beta-lactamases (ESBL). The ESBL positivity rate for *E. coli* was 33.9%.

Although the resistance rates of *E. faecalis* to ampicillin and ciprofloxacin was at a low level (0.6% and 4.8%, respectively), it was observed that *E. faecium* was much more resistant to these antibiotics (95.2% and 55.6%, respectively; p<0.0001) (Table 4). In addition, we found resistance rate of 4.8% to linezolid among *E. faecalis* isolates (Table 4).

DISCUSSION

In this study, we aimed to determine the causative microorganisms in children under 17 years of age diagnosed with UTI in our center and to analyze the antibiotic resistance rates of these microorganisms, and detected that the most common causative microorganism of UTI was *E.coli* (67.7%). However, we found that *Klebsiella spp.* (36.5%) was the most common pathogen for UTI in the neonatal period. We determined that *E. coli* was mostly resistant to ampicillin (66.6%), and *Klebsiella spp.* to cefepime (48.4%).

When we examined similar studies in Turkey, in a study conducted by Kömüroğlu A. et al.[17] in which 4421 cases were evaluated, *E. coli* was determined in the urine cultures of 64.1%, and *Klebsiella spp.* of 17.1% of the cases. In another study conducted by Adem et al.[18] in which 518 patients were evaluated, 69% of urine culture samples tested positive for *E. coli*, and reproduction of *Klebsiella spp.* was observed in 15.94% of the samples. In another study conducted by Erol B. et al.[18] in which 6515 cases were evaluated, the common pathogenic factor was reported as *E.coli* with the rate of 66.8. Similar to our study, it has been reported that the main pathogen causing UTI was *E. coli* in studies reported from different countries[1,2,7].

Although *E. coli* was the most common pathogenic cause of UTI in all age groups, except the neonatal period in our study, *Klebsiella spp.* was found to be the most common causative pathogen in the neonatal period. Similar to our study, in some other studies, *Klebsiella spp.* was determined to be the most common pathogenic agent in the neonatal period[19-21]. However, on the contrary, studies reporting that *E. coli* is the most common etiologic factor in the neonatal period have been published[22,23]. In our study, as the age decreases, especially in children under two years of age, resistance rate of *Klebsiella spp.* increased as it was determined that 57.6% of children with *Klebsiella spp.* identified in urine cultures were in this age group.

UTI is more common in girls and uncircumcised infant boys[1,24]. In our study, it was observed that the female gender was dominant in all age groups in children with UTI. However, it was observed that UTI was more frequently observed in male children <2 years of age as opposed to other age groups. In our study, 71% of male pediatric patients diagnosed with UTI were under the age of two.

Although most children with UTI have a good prognosis, it is important to start treatment as early as possible, because UTIs may cause serious problems, such as sepsis, hypertension, kidney scars, and end-stage kidney disease in some children[10,15]. The increase in widespread and improper use of antibiotics in recent years has led to emergence of increased antibiotic resistance among urinary tract pathogens worldwide[25]. Conversely, urinary tract anomalies and recurrent UTI are risk factors for the development of antibiotic resistance[2]. In UTIs, antibiotic treatment is usually initiated empirically prior to receiving results of antibiotic susceptibility test which contributes to the formation of antibiotic resistance among urinary tract pathogens owing to the use of inappropriate antibiotics[12].

In a study conducted in Turkey by Kömüroğlu et al.[16] in 2017, resistance rates of all Gram-negative microorganisms were reported as follows: ampicillin (75.1%), cefazolin (59%), ampicillin-sulbactam (49.7%), trimethoprim-sulfamethoxazole (TMP-SMX) (45.2%), cefixime (33.1%) and ceftriaxone (31.4%). Also, in another study conducted by Kaya et al.[26] in 2017, resistant rates to ampicillin (64.4%), TMP-SMX (46.6%), amoxicillin-clavulanate (28.8%), and *E. coli* (25%) were as indicated. In another study conducted by

İgan et al.[27] in Turkey, resistance rates of *E. coli* and *Klebsiella spp.* to ampicillin (78.8% vs 71.4%); to amoxicillin-clavulanic acid (67.3% vs 53.6%), and cefazolin (57.7% vs 60.7%, were as indicated. Similar resistance rates have been reported in studies conducted in other countries. In a study reported by Sorlózano-Puerto et al.[28] in Spain in 2017, *E. coli* was found to be highly resistant to amoxicillin-clavulanic acid and TMP-SMX. However, in a 2017 study conducted by Pouladfar et al.[23] in Iran in which 840 urine samples were subjected to antibacterial susceptibility tests, it was reported that *E. coli* was resistant to ampicillin in 86.5%, and *Klebsiella spp.* to amoxicillin in 95.1% of the cases. In Turkey, most of the publications before 2015 were evaluated according to the old versions of CLSI. In these publications, the resistance rates of meropenem, imipenem and ertapenem were very low[9,16,17,21,26]. EUCAST recommends lower cut-off values compared to CLSI criteria in determining carbapenem resistance. EUCAST recommendations for cut-off points have been used in the Clinical Microbiology Laboratory of our hospital since 2017. For this reason, carbapenem resistance rates in our study was found to be higher than those reported in other publications. Considering this situation, we think that the use of EUCAST recommendations should be encouraged to reveal the real antimicrobial resistance status in our country.

Antibiotic resistance of UTI has increased considerably in developing countries. In a meta-analysis conducted by Bryce et al. in which 77,783 *E. coli* isolates were evaluated in 2016, the Organization for Economic Co-operation and Development (OECD) countries and non-OECD countries were compared. Resistance rates were reported for ampicillin (53.4% vs 73.8%), co-amoxilave (8.2% vs 60.3%), and ciprofloxacin (2.1% vs 26.8%)[29]. They reported that antibiotic resistance rates were higher in non-OEDC countries. In our study, we also determined antibiotic resistance rates of *E. coli* for ampicillin (66.6%), amoxicillin-clavulanate (43.3%), cefuroxime axetil (41.8%), and TMP-SMX (34%). *Klebsiella spp.* were shown to have resistance to cefepime (48.4%), amoxicillin-clavulanate (36.1%), cefuroxime axetil (36%), and TMP-SMX (25.2%). ESBL positivity rates of UTI have been gradually increasing[13]. In our study, while the ESBL positivity rate of all of the isolated Gram-negative bacteria was 25.6%, the ESBL positivity rate for *E. coli* was 33.9%.

Enterococcus species have also been reported to develop resistance to commonly used antibiotics[30]. In our study, we determined that *E. faecium* and *E. faecalis* developed resistance to ampicillin (95.2% vs 0.6%), amoxicillin (93.4% vs 0.6%), and gentamicin (80% vs 3%, r). When the antibiotic resistance rates of both bacterial species were compared, we found that *E. faecium* showed greater antimicrobial resistance than *E. faecalis*. We observed that 4.8% of *E. faecalis* isolates were resistant to linezolid. Resistance to linezolid, which is one of the lastly resorted antibiotics in the treatment of serious infections caused by Gram-positive pathogens, has been reported in recent years. It was reported that linezolid resistance in Enterococci is caused by some genes associated with mobile genetic elements affecting 23S rRNA[31]. It was also stated that excessive use of this antibiotic may also be responsible for its associated resistance[32]. In our study, we observed resistance to linezolid in cases with urogenital anomalies, a history of hospitalization for recurrent UTI, and intensive use of antibiotics in whom *E. faecalis* was grown in their bacterial cultures. All resistant pathogens associated with UTI as seen from these studies in Turkey and in other countries have become a major problem. Unfortunately, this problem is on the increase day by day[9,33].

A limitation of this study is the lack of country-wide generalization of the results since data were obtained from a single center. However, as our hospital is an important center in our metropolis, our sample represents a large group. Moreover, we could not obtain data on the clinical findings and predisposing factors for UTI; thus, we could not compare the relationships between resistance profiles and predisposing factors. In addition, the mechanism of resistant isolates could not be confirmed by molecular analyses due to the retrospective nature of the study.

CONCLUSION

The most effective antibiotics against isolates of *E. coli* and *Klebsiella spp.*, which are the most frequently isolated bacterial species in UTI in children were imipenem, meropenem, amikacin, and gentamicin. Resistance against ceftazidime, cefepime, imipenem, meropenem, amikacin, gentamicin, and ciprofloxacin was observed in *Pseudomonas spp.*, which are non-fermentative bacteria that are difficult to treat. Ampicillin, vancomycin, and linezolid were the most effective antibiotics against *E. faecalis*; while vancomycin, teicoplanin, and linezolid were the most effective antibiotics against *E. faecium*. It is important that each center determines its own resistance rates in terms of empirical treatment. It should be taken into consideration that re-evaluating each empirically administered antibiotic based on the results of culture and sensitivity in addition to switching to more suitable antibiotic will be very effective in reducing resistance rates.

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