Distrubution of Antibiotic Resistance in Urinary Tract Infections in Children; a Five-Year Evaluation

Çocuklarda İdrar Yolu Enfeksiyonlarında Antibiyotik Direnç Dağılımı; Beş Yıllık Bir Değerlendirme

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Abstract

Objective: In our study, we aimed to evaluate the prevalence of microorganisms, antibiotic resistance rates, and changes over a five-year period in order to plan timely and appropriately the treatment of urinary tract infections in children.

Material and Methods: In this retrospective study, data were obtained by screening the microbiology laboratory records from the automation system of our hospital. Urine samples were collected by the midstream urine or bag culture. 105 colonies with a single microorganism in a urine culture were evaluated as positive urine culture. A total of 4938 urine cultures were retrospectively screened over a five-year period.

Results: Of the total 613 (12.4%) positive urine cultures, 83.4% were identified as gram-negative and 16.6% as gram-positive. The most common bacteria in gram-negative growth was *Escherichia coli* (68.3%), followed by *Proteus* spp. (16.4%) and *Klebsiella* spp. (10.6%). The most common bacteria in gram-positive agents was *Enterococcus* spp. 42.2%. While the ratio of the extended-spectrum beta-lactamase (ESBL) (+) organisms in 2013 was 9/96 (9.4%), it was found to be 22/102 (21.6%) in 2017. The highest ampicillin resistance was observed in *Klebsiella* strains (79.6%) and the lowest in *Proteus* strains (44%). Increased ampicillin resistance (54.2% to 66.7%) and decreased trimethoprime/sulfamethoxazole resistance (54.2% to 45.1%) were found over the years.

Conclusion: We think that aminoglycosides and nitrofurantoin can be effectively used as an alternative option in empirical treatment due to increased resistance to ESBL, ampicillin, and amoxicillin clavulanate. Antibiotic selection should be customized according to the results of urine culture antibiogram.

Keywords: Antibiotic resistance, child, urinary tract infections

Öz

Giriş: Çalışmamızda çocukluk çağında görülen üriner sistem enfeksiyonlarının zamanında ve uygun tedavisini planlayabilmek için son 5 yıl içindeki etken mikroorganizmaları, antibiyotik direnç oranlarını ve yıllar içindeki değişimini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamızda, veriler hastanemiz otomasyon sisteminden mikrobiyoloji laboratuvar kayıtları taranarak elde edildi. İdrar kültürleri orta akım veya torba kültürü ile toplandı. İdrar kültürlerinde tek bir mikroorganizmada 105 koloni üreme olması pozitif idrar kültürü olarak değerlendirildi. Beş yıllık sürede toplam 4938 idrar kültürü geriye dönük olarak tarandı.

Bulgular: Gram-negatif (%83.4) ve gram-pozitif (%16.6) etkenlerden olmak üzere toplam 613 (%12.4) pozitif idrar kültürü tespit edildi. Gram-negatif üreyen etkenlerde en fazla *Escherichia coli* %68.3 oranında bulunurken, bunu *Proteus* spp. %16.4, *Klebsiella* spp. %10.6 oranı ile takip etti. Gram-pozitif etkenlerde ise en fazla *Enterococcus* spp. %42.2 oranıyla görüldü. Genişlemiş spektrumlu beta-laktamaz (GSBL) (+) organizmaların oranı 2013 yılında %9.4 (9/96) iken 2017 yılında bu oranın %21.6 (22/102)'ya çıktığı tespit edildi. Ampisilin direnci en yüksek *Klebsiella* suşlarında (%79.6) görülürken en düşük (%44) *Proteus* suşlarında görüldü. Yıllar içinde ampisilin direncinde artış (%54.2'den %66.7'ye), trimetoprim-sülfametoksazol direncinde azalma (%54.2'den %45.1'e) olduğu belirlendi.

Sonuç: Hastanemizde GSBL direncinin artması, yüksek oranda ampisilin, amoksisilin-klavulanik asit direnci, %24 civarında bulunan seftriakson direnci nedeniyle aminoglikozidlerin ve nitrofurantoinin ampirik tedavide tercih edilebileceğini düşünüyoruz. Antibiyotik seçiminin idrar kültür antibiyogram sonucuna göre özelleştirilmesi ve akılcı antibiyotik kullanımına yönelinilmesi gerekir.

Anahtar Kelimeler: Antibiyotik direnci, çocuk, üriner sistem enfeksiyonları

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Introduction

Urinary tract infections (UTIs) are among the most common infections in childhood and an important cause of morbidity. Failure to properly and timely treat these infections with appropriate antibiotics can lead to serious consequences, such as renal failure, high blood pressure, and retardation in growth and development (1,2). UTIs are difficult to diagnose since they may occur with non-specific symptoms during infancy (3). Empirical treatment is recommended for these patients due to complications known in clinical practice. Most commonly, ampicillin, amoxicillin clavulanic acid, trimethoprim-sulfamethoxazole (TMP-SMX) and cephalosporin group antibiotics are preferred in empiric treatment (4). However, it is well evidenced that empiric treatments eventually lead to severe antibiotic resistance (5). Therefore, it is necessary to investigate the organisms and antibiotic resistance of UTIs in different geographical regions to determine the appropriate antibiotic in order to significantly reduce morbidity and mortality. The aim of our study was to identify the optimum antibiotic regimen for our region by investigating the microorganisms that caused UTIs in the study area, the antibiotic resistance rates, and changes over a five-year period.

Materials and Methods

After obtaining the approval of the regional ethics committee (25.07.2018/80576354-050-99/144), patients, aged 0-16 years, admitted to the pediatric outpatient clinic of our hospital between January 1, 2013 and January 1, 2018 were included in the study. Data were obtained by screening the microbiology laboratory records from the automation system of our hospital. The urine samples were kept in 5% blood agar and eosin methylene blue agar (EMB) for 18-24 hours at 37°C. The microorganisms reproducing in culture were identified by a conventional method using the IMVIC tests. Antibiotic susceptibilities were determined by the Kirby-Bauer disk diffusion method on the Mueller-Hinton agar based on the EU-CAST criteria. The Phoenix system (PHX) was used for manually unidentifiable bacteria. PHX is a fully automated system for the rapid identification of bacteria and antimicrobial susceptibility testing. The presence of 10^5 colonies with a single microorganism was evaluated as positive urine culture. Urine samples were collected by the midstream urine or bag culture. Urine was collected with bag culture in children under 2 years old or who were not toilet trained yet. In children over the age of 2 or with toilet training, instructions were explained to their families and urine was collected by taking clean midstream urine. Patients with recurrent UTIs or urinary tract anomalies, those that required urinary catheters, and those that were in intensive care unit were excluded from the study. A total of 4.938 urine cultures were retrospectively screened over a five-year period. Since only samples sent to the laboratory were studied, patient consent was not required.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS ver. 20.0 Inc. Chicago, IL, USA) 22.0 package proGram was used for all statistical evaluations. The Kolmogorov-Smirnov test was conducted to test the normality assumption, and descriptive and frequency analyses and the chi-square test were used for the comparison of categorical variables.

Results

A total of 4.938 urine samples obtained from patients aged 1 month to 16 years were analyzed. Growth was seen in 613 samples (12.4%), of which 83.4% were gram-negative and 16.6% were gram-positive. The number of male and female patients with positive urine cultures was 251 (40.9%) and 362 (59.1%), respectively. The age of the patients was 55.11 ± 48.18 months. While 38.7% of the patients were ≤ 2 years old, 61.3% were over two years of age. The proportion of boys under two years was greater than girls at 57%, while the ratio of girls over two years of age was 72.6%.

The microorganisms identified were *Escherichia coli* in 60% of the patients (n= 349), *Proteus* spp. in 15% (n= 84), *Klebsiella* spp. in 9% (n= 54), and *Enterococcus* spp. in 8% (n= 43) (Figure 1). Gram-negative bacteria were the most frequent isolates, with *E. coli* 68.3% being the most common, followed by *Proteus* spp. and *Klebsiella* spp. at 16.4% and 10.6%, respectively. The increase in *Klebsiella* strains was statistically significant over the years (p= 0.00) (Table 1). Extended-spectrum beta-lactamase (ESBL) positivity was not detected in gram-positive bacteria and was only found in gram-negative bacteria. The incidence of ESBL positivity was 14.9% for *E. coli* and 7.4% for *Klebsiella* spp. While the ratio of ESBL (+) organisms was 9/96 (9.4%) in 2013, it increased to 22/102 (21.6%) in 2017 (Figure 2). In gram-positive microorganisms, *Enterococcus* was the most common agent seen at a rate of 42.2%, followed by coagulase-negative staphylococcus (CNS) at 23.5%, *Staphylococcus aureus* at 22.5%, and *Streptococcus* spp. at 7.8%. Over the five-year period, the number of methicillin-resistant strains increased (Table 2). No distinction between agent and contamination was made in CNS. Urine culture was only requested for patients with clinical suspicion. In order to prevent contamination, the patients were asked to wash the area with soapy water before urination. Antiseptics were not considered as appropriate to use before urine collection as it could cause false negatives.

Among the gram-negative bacteria, there was high resistance to ampicillin, amoxicillin clavulanate, and TMP-SMX at rates of 58.3%, 28%, and 42.2% respectively, while there was low resistance to amikacin, meropenem, piperacillin at 3.1%, 4.1%, and 2.2%, respectively. Gentamicin resistance was seen in 7.4% of the patients and ceftriaxone resistance in 20.7%. The incidence of ampicillin resistance increased from 54.2 to
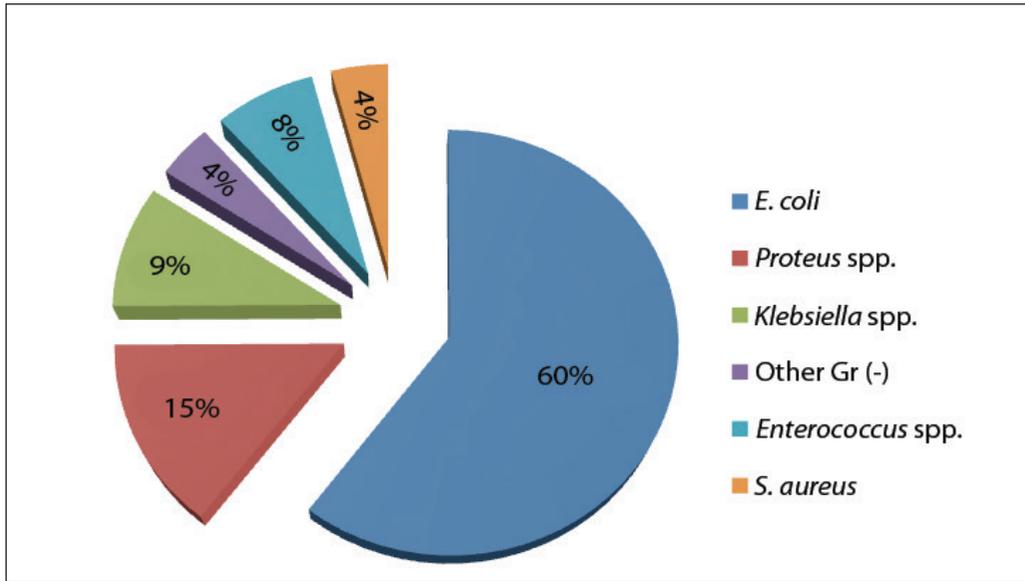
Figure 1. Distribution of microorganisms isolated from urine cultures.

Table 1. Distribution of gram-negative bacteria by years

	2013 (n)	2014 (n)	2015 (n)	2016 (n)	2017 (n)	Total
Escherichia coli	62	86	71	67	63	349
Proteus spp.	21	9	16	21	17	84
Klebsiella spp.	8	4	8	17	17	54
Pseudomonas aeruginosa	1	3	3	0	3	10
Diğer*	4	5	0	3	2	14
Toplam	96	107	98	108	102	511
* Other: *Enterobacter*, *Morganella*, and *Citrobacter* (p< 0.05)						
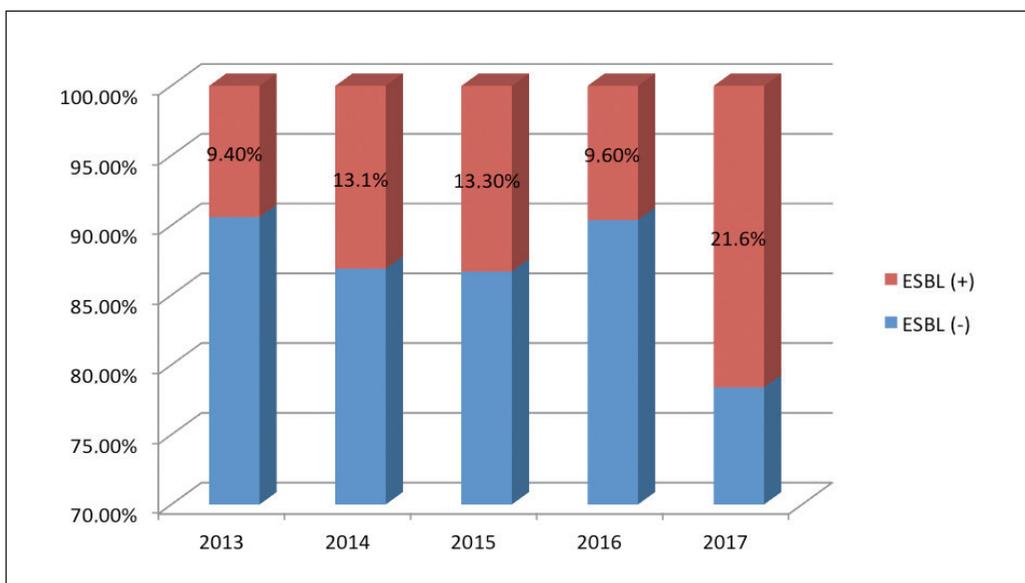
Figure 2. ESBL positivity over five years.

Table 2. Distribution of gram-positive bacteria by years

	2013 (n)	2014 (n)	2015 (n)	2016 (n)	2017 (n)	Total
Enterococcus spp.	12	15	9	4	3	43
MSKNS/MRKNS*	7 (7/0)	3 (3/0)	2 (2/0)	5 (3/2)	7 (4/3)	24
Staphylococcus aureus (MSSA/MRSA)**	15 (12/3)	2 (1/1)	1 (1/0)	3 (2/1)	2 (2/2)	23
Streptococcus spp.	2	1	0	5	0	8
Other***	1	1	2	0	0	4
Total	37	22	14	17	12	102

* MSKNS: Methicillin-sensitive coagulase-negative *Staphylococcus*, MRKNS: Methicillin-resistant coagulase-negative *Staphylococcus*.
** MSSA: Methicillin-sensitive *S. aureus*, MRSA: Methicillin-resistant *S. aureus*.
*** Edwardsiella tarda, *Bacillus* spp.
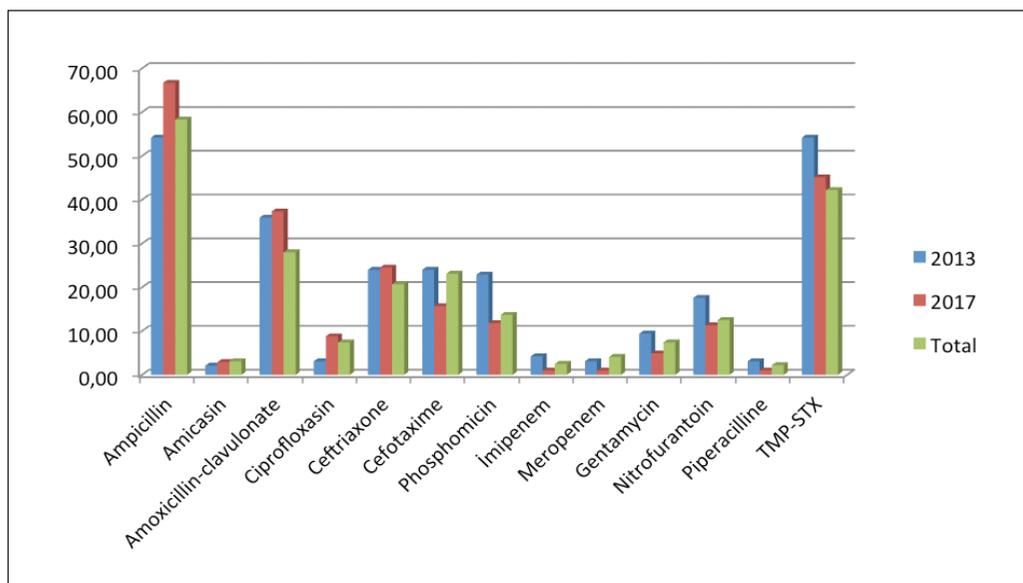
Figure 3. Antibiotic resistance of gram-negative bacteria over five years.

66.7% over the five years while TMP-SMX resistance was reduced from 54.2 to 45.1%, phosphomycin resistance from 22.9 to 11.8%, cefotaxime resistance from 24 to 15.7%, and gentamicin resistance from 9.4 to 4.9% (Figure 3).

When antibiotic resistance rates of the most common gram-negative microorganisms were investigated, ampicillin resistance in *E. coli* strains was 57.6%, amikacin resistance was 2.1%, amoxicillin-clavulanate resistance was 29.1%, and TMP-SMX resistance was 57.2%. For the *Proteus* strains, amikacin resistance was seen at a rate of 6.1%, cefotaxime resistance at 21.4%, and TMP-SMX resistance at 54.8%. Ampicillin resistance had the highest incidence among *Klebsiella* strains (79.6%) and the lowest in *Proteus* strains (44%). Piperacillin resistance was not detected in any of the *Proteus* strains, while it was found in 1.9% of the *E. coli* strains and 2.6% of *Klebsiella* spp. Nitrofurantoin resistance was most common in *E. coli* at 5.6%. Ceftriaxone resistance was also most frequently seen in *E. coli* at 24.4%, but phosphomycin resistance had the highest incidence in *Proteus* strains at 15.5% (Table 3).

In gram-positive bacteria, resistance to penicillin, ampicillin, erythromycin, cefoxitin, clindamycin, and TMP-SMX was found to be 55.6%, 48.5%, 49.5%, 32.3%, 39.6%, and 44.1%, respectively. Vancomycin, linezolid and cefepime resistance was low, seen in 1%, 7.1% and 8.6% of the samples, respectively. Over the five years, penicillin, ampicillin, erythromycin, cefoxitin and clindamycin resistance was found to decrease (Figure 4). Since only samples sent to the laboratory were studied retrospectively, patient consent was not required.

Discussion

UTIs are among the most common infections in children. They can lead to significant complications if not treated timely with appropriate antibiotics. Since they constitute an important cause of morbidity when untreated, empiric treatment is recommended. Amoxicillin-clavulanate, TMP-SMX, cefuroxime, and cefixime are the most commonly used agents for oral treatment while ceftriaxone, cefotaxime, gentamicin, and piperacillin are mostly preferred for parenteral treatment. However, empiric treatment has brought along

Table 3. Antibiotic resistance rates of the most common gram-negative bacteria

|	*Escherichia coli* %	*Proteus* spp. %	*Klebsiella* spp. %
Ampicillin	57.6	44	79.6
Amikacin	2.1	6.1	3.7
Amoxicillin-clavulanate	29.1	12.2	31.5
Cefotaxime	22.9	21.4	27.8
Ceftriaxone	24.4	9.5	27.8
Ciprofloxacin	9.2	3.6	3.7
Ertapenem	6	2.4	5.6
Imipenem	2	1.8	1.9
Phosphomycin	13.2	15.5	13
Gentamicin	6.3	9.5	9.3
Nitrofurantoin	5.2	13.6	16.7
Norfloxacin	7.7	9.5	9.3
Meropenem	4	3	1.9
Levofloxacin	8.7	3.6	1.9
Piperacillin	2.6	0	1.9
TMP-SMX	57.2	54.8	64.8
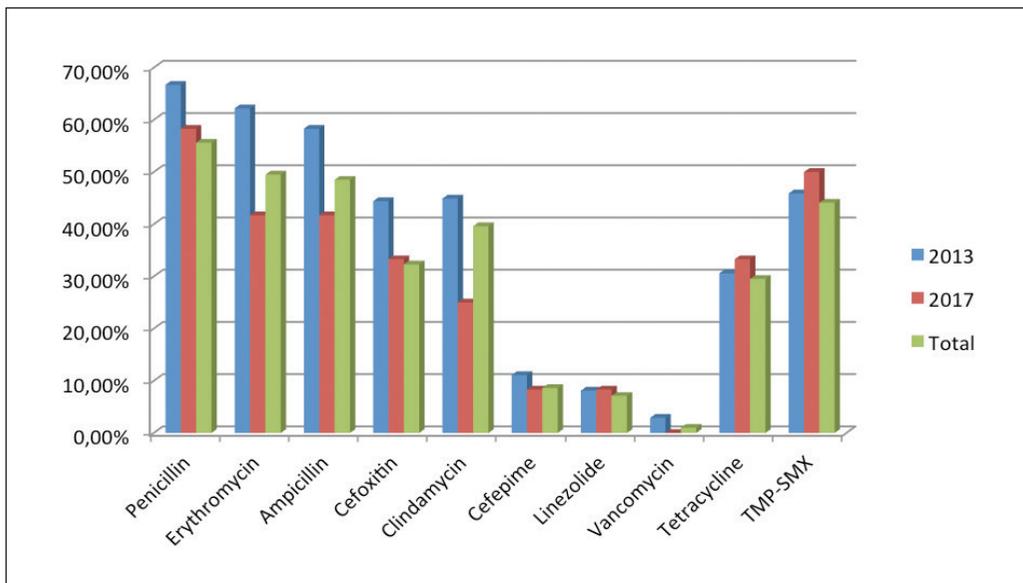
Figure 4. Antibiotic resistance of gram-positive bacteria over five years.

the problem of antibiotic resistance over time (5-7). Therefore, it is important to determine the patient's age, sex, regionally the most common microorganism, and antibiotic resistance rate.

UTIs are more common in girls than in boys. However, in younger children (under two years), the situation is the opposite (8). In the current study, 59.1% of the patients were females. In boys under two years of age, UTIs were more common at 57%, whereas over two years, this rate was 72.3% in

girls. The age range of our patients was 1 month-16 years (mean 55 months).

The most common cause of UTIs in children are gram-negative bacilli with *E. coli* being the most frequent agent (9). Although *E. coli* is the most common bacteria in many studies conducted in Turkey, the second and third frequent bacteria vary according to the geographical region. In our study, we detected the second most common agent as *Proteus* spp. and the third as *Klebsiella* spp., which is consistent with the

reports of Ipek et al. and Senel et al. (10,11). In some studies, *Klebsiella* spp. take the second place, while Enterobacter spp. rank third (12,13). In another study, CNS were found to be the second most common bacteria (14). In the current study, we determined the most common agent among gram-positive bacteria as *Enterococcus*. Despite the availability of similar data in the literature, there are also studies that have reported CNS and *S. aureus* strains to be the most common gram-positive bacteria (15,16). We also found an increase in *Klebsiella* strains and methicillin-resistant forms of Staphylococcus spp. over the years. The resistance of *Klebsiella* strains to common antibiotics was higher than *E. coli*. These two findings suggest that rational antibiotic use should be encouraged.

Another problem was the increase in ESBL-positive bacteria. The production of beta-lactamase is one of the most important resistance mechanisms of gram-negative bacteria against beta-lactam antibiotics. If a bacterium is synthesizing beta-lactamase, it can cleave the amide bonds in the beta-lactam ring of the beta-lactam group of antibiotics and make this antibiotic ineffective. This acquired property can be synthesized by the genetic structure of the bacteria and transferred (17). In studies, ESBL positivity in *E. coli* isolates has ranged from 13% to 20.8% of the urine cultures while a meta-analysis has reported that ESBL incidence reached 28.4% (18-20). In our study, ESBL positivity was 14.9% for *E. coli* strains and 7.4% for *Klebsiella* strains, and it was 9.4% in 2013 and 21.6% in 2017. Although this is consistent with the literature, the increase over the years is worrying.

In gram-negative bacteria, resistance to ampicillin, amoxicillin-clavulanate, and TMP-SMX, which are the most preferred oral drugs, has been reported to be high in many studies (21-27). In the current study, in agreement with the literature, ampicillin resistance was found to be 57.6%, amoxicillin-clavulanate resistance was 29.1%, and TMP-SMX resistance was 57.2% in *E. coli* strains. The highest ampicillin resistance was observed in *Klebsiella* strains (79.6%) and the lowest in *Proteus* strains (44%). In previous studies, the ampicillin resistance rate of *Klebsiella* strains has been reported to be 93.2% by Çoban et al., 88.2% by Güner et al., 67% by Mir et al., and 76% by Yaşar et al. (24,27-29). Although there was an increase in ampicillin resistance in our study, TMP-SMX resistance decreased but remained high at 45.1% in 2017. On the other hand, it was positive to see that phosphomycin, cefotaxime and gentamicin resistance had decreased.

In this study, gram-negative bacteria had the lowest resistance to amikacin, meropenem and piperacillin, and oral nitrofurantoin. Before 2010, there were studies reporting no meropenem and amikacin resistance. However, in recent studies, resistance to these agents has been reported with increasing frequency. Our results were in agreement with those reported in studies conducted in Turkey (30,31,33). Most

common bacteria and antibiotic resistance rates in some recent studies are listed in Table 4.

We found among the gram-positive agents that resistance to penicillin, ampicillin and TMP-SMX was high; whereas, vancomycin, linezolid and cefepime resistance was low. In studies conducted, while penicillin resistances are generally high, ampicillin resistances vary from region to region. In a study by Kalal et al., the ampicillin and ciprofloxacin resistance of *Enterococcus* strains has been determined as 87.5% and 75%, respectively while these rates have been found as 20% for both antibiotics in the study by Saeed et al. (32, 34). Özdem et al. have not found vancomycin resistance, but observed ampicillin resistance at a rate of 6.3%, penicillin resistance at 47.2% and TMP-SMX resistance at 14.8% (35). Similarly, Yenişehirli et al. havew found no resistance to vancomycin, but calculated ampicillin, penicillin and ciprofloxacin resistance rates as 8.7%, 60.9% and 15.2%, respectively (36). Vancomycin-resistant enterococci strains present as an important problem, especially in patients in intensive care, with significant risk factors being the use of multiple parenteral antibiotics, application of invasive procedures, and underlying secondary diseases (37,38). Vancomycin resistance is not expected in patients referred from outpatient clinics (39). In the current study, patients with recurrent UTIs, those receiving intensive care, and those that required the use of a catheter were not included. We found vancomycin resistance and cefepime resistance rates to be low at 1% and 9.2%, respectively, but ampicillin resistance was higher than previously reported in studies conducted in Turkey. A positive finding was that penicillin, ampicillin and cefoxitin resistance was observed to decrease over the five years. However, the presence of vancomycin resistance albeit at low rates and high resistance to common antibiotics (ampicillin, TMP-SMX) were concerning.

A limitation of our study was that we were not able to evaluate the symptoms and findings of the patients when they gave the urine samples; thus, there was the possibility of growth with incompatible with the clinical findings. Another limitation was that the collected urine was not removed by catheter or by suprapubic aspiration. So, the risk of contamination was high due to the midstream urine or bag culture.

This is the first comprehensive study conducted in our region investigating urine culture and antibiotic resistance of children. Based on the results we obtained, we consider that aminoglycosides and nitrofurantoin should be preferred in empirical treatment due to the increased resistance to ESBL, ampicillin, amoxicillin clavulanate, and ceftriaxone. Antibiotic selection should be customized according to the results of urine culture antibiogram and rational antibiotic use should be encouraged considering the high rates of unnecessary use of antibiotics. Our study could be further elaborated by eliminating contamination. Biochemical markers will be useful for future studies.

Table 4. Antibiotic resistance rates according to some recent studies

	Year	Number of significant growth/Total collected sample	Method of urine collection	Most common bacteria	ESBL (+) (%)	Highest Antibiotic Resistance % (according to the most common bacteria)	Lowest Antibiotic Resistance % (according to the most common bacteria)
Temiz et al[31].	2008	889/6535	Bag culture/midstream urine	E. coli		Ampicillin (76.1%) Amoxycillin clavulanate (65.7%)	Amikasin (0) Meropenem (0)
Üstün et al[30].	2009	175	Midstream urine/chateterisation	E. coli	-	Ampicillin (48%) Tmp-Smx (39%)	Gentamicin (8%) Amicasin (0)
Deveci et al[19].	2010	483/14301	Bag/midstream/suprapubic aspiration	E. coli	13	Amoxycillin clavulanate (94.4%) Ampicillin sulbactame (88.9%)	Amikasin (11.1%) Imipenem(11.1%)
Şanlı et al[23].	2010	1015 Gram-negative agent	Bag/midstream/chatetherisation/suprapubic aspiration	E. coli		Ampicillin (71%) Tmp-Smx (55%)	Imipenem (0) Nitrofurantoin(10.3)
Salduz et al[34].	2010	197	Bag culture/midstream urine	E. coli	-	Ampicillin (71.3%) Tmp-Smx (52.7%)	Cefixim (5.5%) Aminoglicoside (0)
Erdoğan et al[26].	2011	51	Bag culture/midstream urine	E. coli	-	Ampicillin (71.7%) Tmp-Smx (54.3%)	Amikacin(2.2%) Ciprofloksasin (2.2%)
Güner et al[24].	2012	2544	Bag culture/midstream urine	E. coli	0.1-0.6	Ampicillin (69.9%) Tmp-Smx (49.8%)	Imipenem (0) Nitrofurantoin (0.7%)
Gündem et al[18].	2013	362	Bag culture/midstream urine	E. coli	20.8	Sefuroxim(100%) (ESBL+) Tmp-Sxm (84.4%)	Amicasin (7.8%) (ESBL+) Imipenem (4.7%)
Çoban et al[28].	2014	392/10691	Urine bag	E. coli		Tmp-Smx (43.1%) Cefalotin(37.9%)	Meropenem (0) Amicasin(3.2%)
Aylanç et al[25].	2014	217	Bag/midstream/chatetherisation/suprapubic aspiration	E. coli		Ampicillin (51%) Tmp-Smx (29.5%)	Amikasin (4%) Nitrofurantoin (6.5%)
Saeed et al[32].	2015	130/300	Bag/midstream/chatetherisation	E. coli	-	Penicilline (100%) Ampicillin (95.8%)	Amikasin (6.3%) Phosfomicin (14.6%)
Ekwealor et al[21].	2016	215	Midstream/bag	S. aureus		Amoxycillin clavulonic acid (82.8%) Cefuroxime(65.5%)	Nitrofurantoin (6.9%) Gentamicin(34.5%)
Kalal et al[35].	2017	62/342	Bag culture/midstream urine	E. coli	-	Cephalosphorin(87.5%) Fluroquinolones (81.7%)	Nitrofurantoin (30%) Aminoglycoside (38.5%)
Yaşar et al[27].	2018	518/1711	Bag culture/midstream urine	E. coli	-	Ampicillin (80%) Tmp-Smx (45%)	Meropenem (0.1%) Amikasin (0.2%)
This Study	2020	613/4938	Bag culture/midstream urine	E. coli	14.9	Ampicilin (57.6%) Tmp-Smx (57.2%)	Amicasin (2.1%) Nitrofurantoin (5.6%)

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