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Urinary Tract Infections in Children: Clinical and Antibiotic Susceptibility Data from a Tertiary Care Hospital

Çocuklarda İdrar Yolu Enfeksiyonları: Üçüncü Basamak Bir Hastanenin Klinik ve Antibiyotik Duyarlılık Verileri

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ABSTRACT

Aim: Urinary tract infections (UTIs) are among the most common bacterial infections in children. Empirical antibiotic treatment is recommended until the antibiogram reports of urine culture are available. It is essential to initiate local UTI agents and their antimicrobial susceptibility patterns in specific geographical regions to choose the best empirical antibiotics. The current study aimed to determine causative microorganisms and antibiotic resistance patterns in children diagnosed with UTI.

Material and Methods: The study was carried out retrospectively with 216 children diagnosed with UTIs for the first time. The patients were categorized into two groups according to age (≤1 year and >1 year). Demographic data, presenting symptoms, imaging findings, and urine and culture analysis results were collected and compared between these two groups.

Results: Cefazolin and nitrofurantoin use may be preferred in the empirical treatment of UTIs caused by *Escherichia coli* and *Enterococcus* spp. Additionally, amoxicillin/clavulanate was recommended in the empirical therapy of UTIs caused by *Enterococcus* spp., *Klebsiella* spp., and *Proteus* spp. The trimethoprim-sulfamethoxazole and nitrofurantoin resistance of *E. coli* was found to be statistically significantly higher in the ≤1 year group (p=0.03 and p=0.01, respectively), while the nitrofurantoin resistance of *Klebsiella* was statistically significantly higher in the >1 year group (p=0.01). The gentamicin resistance of *Klebsiella* spp. was statistically significantly higher in the ≤1 year group (p=0.03).

Conclusion: It is important to detect regional antibiotic resistance patterns to manage UTIs and minimize related complications. Antibiotic susceptibility studies are necessary to reduce improper antibiotic use and resistance rates of antibiotics.

Keywords: Antibiotics, children, urinary tract infection, susceptibility

ÖZ

Amaç: İdrar yolu enfeksiyonları (İYE), çocuklarda en sık görülen bakteriyel enfeksiyonlar arasındadır. İdrar kültürü ve antibiyogram sonuçları çıkana kadar ampirik antibiyotik tedavisi önerilir. İYE tedavisi için kullanılabilecek en uygun ampirik antibiyotik seçeneğini belirlemek için o bölgeye özgü İYE ajanlarını ve bunların antimikrobiyal duyarlılıklarını belirlemek esastır. Bu çalışma, bölgemizde İYE tanısı alan çocuklarda etken mikroorganizmaları ve antibiyotik direnç paternlerini belirlemeyi amaçladı.

Gereç ve Yöntemler: Çalışma, ilk kez İYE tanısı alan 216 çocuk ile retrospektif olarak gerçekleştirildi. Hastalar yaşlarına göre (≤1 yaş ve >1 yaş) iki gruba ayrıldı. Bu iki grup arasında demografik veriler, başvuru semptomları, görüntüleme bulguları, idrar ve kültür analiz sonuçları toplandı ve karşılaştırıldı.

Bulgular: *Escherichia coli* ve *Enterococcus* türlerinin neden olduğu İYE'lerin ampirik tedavisinde sefazolin ve nitrofurantoin kullanımı tercih edilebilir. Ayrıca, *Enterococcus* spp., *Klebsiella* spp. ve *Proteus* spp.'nin neden olduğu İYE'lerin ampirik tedavisinde amoksisilin/klavulanat önerilmiştir. *E. coli*'nin trimetoprim-sülfametoksazol ve nitrofurantoin direnci ≤1 yaş grubunda istatistiksel olarak anlamlı yüksek bulunurken (sırasıyla p=0,03 ve p=0,01), *Klebsiella*'nın nitrofurantoin direnci >1 yaş grubunda istatistiksel olarak anlamlı derecede yüksek saptandı (p=0,01). *Klebsiella* türlerinin gentamisin direnci ≤1 yaş grubunda istatistiksel olarak anlamlı derecede yüksek bulundu (p=0,03).

Sonuç: İYE'lerin tedavisinde ve komplikasyonların önlenmesinde bölgesel antibiyotik direnç paternlerini saptamak önemlidir. Uygunsuz antibiyotik kullanımını ve antibiyotik direnç oranlarını azaltmak için antibiyotik duyarlılık çalışmaları gereklidir.

Anahtar Sözcükler: Antibiyotik, çocuk, idrar yolu enfeksiyonları, direnç

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections in children (1), affecting approximately 8% of this population (2). The incidence of UTIs is higher among boys until the age of 1 year; however, girls have more UTIs over 1 year of age. Children experience recurrent UTIs at a rate of up to 30% within the first year of the UTI, and UTIs can cause complications, such as hypertension, renal scarring, and end-stage kidney disease if not treated properly (3). The risk of renal scarring is higher in patients under 1 year of age and those with congenital abnormalities of the urinary tract (CAKUT) (4).

The most common bacterial pathogen is *Escherichia coli (E. Coli)* (1,2). The gold standard for the diagnosis of UTIs is urine culture, but it takes 48-72 hours to identify appropriate antibiotics for treatment in antibiogram reports (5). Empirical antibiotic treatment based on local susceptibilities according to local epidemiologic studies is recommended to prevent the complications of UTIs that may occur due to delayed results (6). However, the inappropriate and widespread use of antibiotics in UTIs has led to an increase in antibiotic resistance globally (7). Therefore, it is essential to initiate local etiological UTI agents and their antimicrobial susceptibility patterns in specific geographical regions.

This study aimed to determine demographic data, causative microorganisms, and antibiotic resistance patterns of these pathogens in children admitted to our hospital and diagnosed with UTIs. The patients were also grouped according to their age as those under and over 1 year of age and compared in terms of demographic characteristics, UTI agents, and antimicrobial susceptibility, which may be helpful to determine appropriate empirical antibiotics for different age groups.

MATERIAL and METHODS

It was a retrospective study carried out with 216 children diagnosed with UTIs for the first time between October 2021 and October 2022 in a pediatric nephrology outpatient clinic after obtaining approval from the local ethics committee (IRB number:127-SBKAEK, date: 29/09/2022). All children with UTIs diagnosed based on positive urine culture results, symptomatology (dysuria, vomiting, abdominal-back pain, fever, anorexia, foul-smelling urine, enuresis, pollakiuria, and hematuria), and positive urinalysis findings of UTIs were included in this study. Patients with a neurogenic bladder, those with incomplete data in hospital records, and those with antibiotic prophylaxis were excluded.

The patients were categorized into two groups according to their age (≤1 year and >1 year). Demographic data (age, age at diagnosis, and the existence of gender, labial synechia, phimosis, constipation, nephrolithiasis, hypercalciuria, CAKUT), presenting symptoms, the results of imaging studies, namely ultrasound (US), voiding cystourethrogram (VCUG), and 99m labeled Technetium dimercaptosuccinic acid (99mTc DMSA) scintigraphy, urine and culture analysis results were collected and compared between these two groups. CAKUT was defined based on the presence of hydronephrosis, vesicoureteral reflux (VUR), or obstructive uropathies (ureteropelvic and ureterovesical junction obstruction).

The midstream clean catch method was used to obtain urine samples in toilet-trained children, while the urine specimen was collected via urethral catheterization in those without sphincter control. Growth of $>10^5$ single colony-forming units (CFU/mL) in the midstream clean catch method and $>5^4$ CFU/mL in the catheterized specimen of urine was considered as UTI (1,2). Urine dipstick analysis with the presence of nitrites or leucocyte esterase or pyuria was documented as positive. Urine culture samples taken in sterile urine containers under aseptic conditions were delivered to the microbiology laboratory at room temperature within 30 minutes according to the quality guidelines of our hospital. The samples were inoculated quantitatively on 5% sheep blood agar and eosin methylene blue agar medium and incubated at 37°C for 18-24 hours. Species identification of microorganisms (*E. coli*, *Enterococcus* spp., *Klebsiella* spp., *Proteus, Pseudomonas spp., Staphylococcus spp., Streptococcus spp.*) considered to be causative was done using conventional methods. Antibiotic susceptibility tests and minimum inhibitory concentration values of microorganisms were performed according to the current European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, using Kirby-Bauer disc diffusion and gradient diffusion methods (8). Extended-spectrum-beta lactamase (ESBL) producing bacteria were also reported. The following antimicrobial drugs were tested: ampicillin, amoxicillin/clavulanate (AMC), trimethoprim-sulfamethoxazole (TMP/SMX), cefazolin, cefuroxime, cefixime, ceftriaxone, ciprofloxacin, fosfomycin, gentamicin, meropenem, nitrofurantoin, and amikacin.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 22.0 (Armonk, NY: IBM Corp.). *P* values of <0.05 were considered statistically significant. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum). The Kolmogorov-Smirnov and Shapiro-Wilk tests, histograms, and probability graphics were used to assess the normality of the distribution of variables. Categorical data were reported as frequency (%) and compared with the chi-squared test. The Mann-Whitney *U* test was carried out to analyze the differences in continuous variables.

RESULTS

The study included a total of 216 (36 male and 180 female) patients with a median age of 6 (range: 0.3-17) years diagnosed with UTIs for the first time. The median age at diagnosis was 5 (range: 0.3-15.5) years. Of these patients, 50 (23.1%) were aged ≤1 year, and 166 (76.9%) were aged >1 year. The majority of the patients in the study group were female (83.3%). Before ≤1 year of age, the male-to-female ratio was 1.3. Over the age of 1 year, the male-to-female ratio decreased to 0.05. Labial synechia was detected in 13.3% of the girls, while phimosis was found in 16.7% of the boys. Dysuria, vomiting, fever, and abdominal pain were the most common presenting symptoms of the children. Constipation was detected in 40 (18.5%) patients. Twenty (9.3%) children had nephrolithiasis, and 24 (11.1%) had hypercalciuria. Forty patients (16 patients under and 24 patients over 1 year of age) had CAKUT. The most common CAKUT was VUR (11.1%), followed by hydronephrosis (5.6%) (Figure 1). There were no significant differences between patients ≤1 year of age and >1 year in terms of hydronephrosis, VUR, ureteropelvic junction obstruction, or posterior urethral valve (p=0.28, p=0.33, p=0.053, and p=0.053, respectively). Twenty patients had abnormalities such as scars, atrophies, or functional loss on DMSA, and 14 (70%) of these patients had VUR. The most common pathogen was identified as *E. coli* (63.9%), followed by *Enterococcus* spp. (11.1%), *Klebsiella* spp. (10.2%), and *Proteus* spp. (6.5%). ESBL (+) uropathogens were found in 6.5% of the patients.

The demographic and clinical data according to age ranges are presented in Table 1. *E. coli* was the most common isolated microorganism in both age groups. There was a significant difference between the two groups according to gender, presenting symptoms such as irritability, abdominal pain, vomiting, dysuria, anorexia, foul-smelling urine, CAKUT, nitrite positivity, ESBL positivity, etc *Klebsiella* spp., and *Proteus* spp. (p<0.001, p<0.001, p=0.002, p=0.041, p<0.001, p=0.001, p=0.011, p=0.023, p=0.048, p=0.041, p<0.001, and p=0.042, respectively).

The antibiotic resistance rates of the most seen pathogens are shown in Table 2. The resistance rates of *E. coli* to ampicillin, AMC, TMP/SMX, cefuroxime, cefixime, and amikacin were found higher at 75.4%, 36.2%, 32.6%, 39.1%, 41.3%, and 40.5%, respectively. Cefazolin and nitrofurantoin (NTF) were found to be useful in the empirical treatment of UTIs caused by *E. coli* and *Enterococcus* spp. Additionally, AMC was recommended in the empirical therapy of UTIs associated with *Enterococcus* spp., *Klebsiella* spp., and *Proteus* spp.

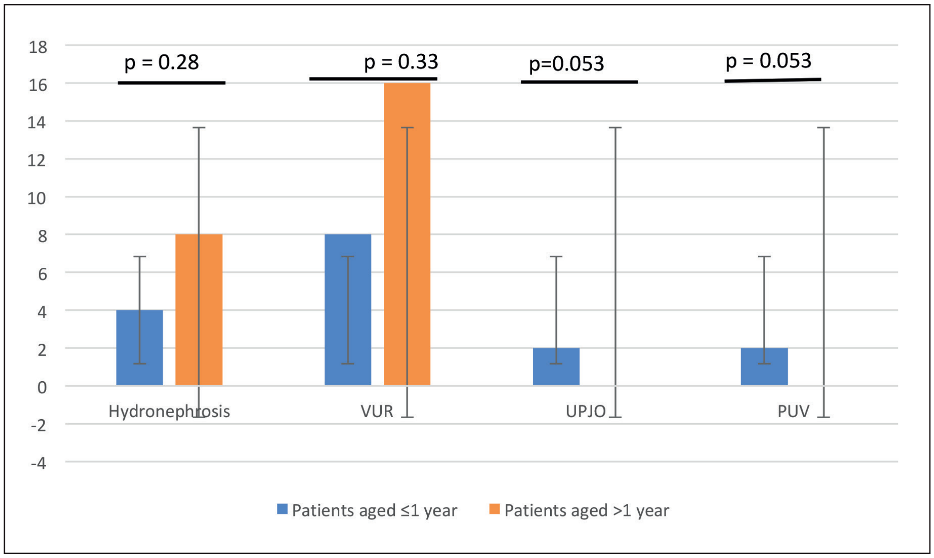

Figure 1: CAKUT detected in the patients.

CAKUT: congenital abnormalities of the urinary tract, **VUR:** vesicoureteral reflux, **UPJO:** ureteropelvic junction obstruction, **PUV:** posterior urethral valve.

The comparison of the antibiotic patterns of the uropathogens according to age groups is presented in Table 3. The TMP/SMX and NTF resistance of *E. coli* was found to be statistically significantly higher in patients aged ≤1 year (p=0.03 and p=0.01, respectively), while the NTF resistance of *Klebsiella* spp. was statistically significantly higher in the >1 year group (p=0.01). The gentamicin resistance of *Klebsiella* spp. was statistically significantly higher in the ≤1 year group (p=0.03).

DISCUSSION

UTIs constitute a common health problem in children due to the risk of long-term morbidity (9). Moreover, the urgent need for empirical treatment without waiting for the results of

Table 1: Demographic data of the patients.

	Patients ≤1 year (n=50)	Patients >1 year (n=166)	p-value
Age (median, min-max, years)	1 (0.3-1)	8 (1.5-17)	**<0.001***
Age at diagnosis (median, min-max, years)	0.5 (0.3-0.9)	7 (2-15.5)	**<0.001***
Gender (F/M)	22/28	158/8	**<0.001****
Presenting symptoms			
• Irritability	24 (48.0)	4 (2.4)	**<0.001****
• Abdominal pain	4 (8.0)	50 (30.1)	**0.002****
• Vomiting	26 (52.0)	30 (18.0)	**0.041****
• Fever	16 (32.0)	42 (25.3)	0.312**
• Dysuria	1 (2.0)	62 (37.3)	**<0.001****
• Hematuria	2 (4.0)	8 (4.8)	0.988**
• Poor feeding	14 (28.0)	16 (9.6)	**0.001****
• Pollakiuria	1 (2.0)	14 (8.4)	0.211**
• Frequency-Urgency	0	20 (12.0)	-
• Foul-smelling urine	12 (24.0)	17 (10.2)	**0.011****
Labial synechia	2 (9.0)	22 (13.9)	0.611**
Phimosis	5 (17.8)	1 (12.5)	0.321**
Constipation	6 (12.0)	34 (20.5)	0.171**
Nephrolithiasis	8 (16.0)	12 (7.2)	0.091**
Hypercalciuria	8 (16.0)	16 (9.6)	0.211**
CAKUT	16 (32.0)	24 (14.5)	**0.023****
DMSA abnormality	0	6 (3.6)	0.512**
Urine analysis			
• LE (+)	38 (76.0)	103 (62.0)	0.081**
• Nitrite (+)	8 (16.0)	50 (30.1)	**0.048****
• LE + nitrite (+)	6 (12.0)	12 (7.2)	0.307**
ESBL (+)	6 (12.0)	8 (4.8)	**0.041****
Uropathogen			
• *Escherichia coli*	28 (56.0)	110 (66.2)	0.182**
• *Enterococcus* spp.	4 (8.0)	20 (12.0)	0.412**
• *Klebsiella spp.*	16 (32.0)	6 (3.6)	**<0.001****
• *Proteus mirabilis*	0 (0.0)	14 (8.4)	**0.042****
• *Pseudomonas* spp.	2 (4.0)	4 (2.4)	0.603**
• *Staphylococcus* spp.	0 (0.0)	10 (6.0)	0.102**
• *Streptococcus* spp.	0 (0.0)	2 (1.2)	0.804**

SD: Standard deviation, **F:** Female, **M:** Male, **ESBL:** Extended-spectrum-beta lactamase, **CAKUT:** Congenital anomalies of the kidney and urinary tract, **DMSA:** Dimercaptosuccinic acid scintigraphy. ***:** Mann-Whitney U , ****:** Chi-square Test the antibiogram and the recent increase in antibiotic resistance to the agents used in empirical antibiotherapy have further complicated the treatment of these infections (1,2). The uropathogens and their antibiotic susceptibility profile may vary between different age groups and geographical areas. To the best of our knowledge, in the literature, there is a lack of data concerning the antimicrobial resistance profile for children with UTIs from our geographical region in Turkey.

The diagnosis of UTIs can be challenging due to the variety of symptoms among age groups (4). In our study, irritability, vomiting, poor nutrition, and foul-smelling urine were more common presenting symptoms in infants compared to older children, which is generally consistent with the study of Shrestha et al., however, these authors found fever to be more common in older children (10). Similar to other studies, female predominance was found in patients with UTIs, but there was a male predominance in the first year of life

Table 2: Antibiotic resistance patterns of the most common pathogens.

Antibiotic resistance	*Escherichia coli* (n=138) (%)	*Enterococcus* spp. (n=24) (%)	*Klebsiella spp.* (n=22) (%)	*Proteus* spp. (n=14) (%)
Ampicillin	104 (75.4)	10 (41.7)	20 (90.9)	1 (7.1)
AMC	50 (36.2)	1 (4.2)	4 (18.2)	0
TMP-SMX	45 (32.6)	16 (66.7)	6 (27.3)	3 (21.4)
Cefazolin	22 (15.9)	4 (16.7)	10 (45.4)	4 (28.6)
Cefuroxime	54 (39.1)	4 (16.7)	8 (36.4)	4 (28.6)
Cefixime	57 (41.3)	4 (16.7)	6 (27.3)	3 (21.4)
Ceftriaxone	32 (23.1)	6 (25.0)	8 (36.4)	0
Ciprofloxacin	26 (18.8)	6 (25.0)	6 (27.3)	0
Fosfomycin	10 (7.2)	4 (16.7)	2 (9.1)	0
Gentamicin	32 (23.1)	4 (16.7)	2 (9.1)	2 (14.3)
Meropenem	2 (1.5)	0	0	0
Nitrofurantoin	10 (7.2)	4 (16.7)	8 (36.4)	10 (71.4)
Amikacin	56 (40.5)	6 (25.0)	0	0

n: Number, **spp:** Species, **AMC:** Amoxicillin/clavulanate, **TMP-SMX:** Trimethoprim-sulfamethoxazole

Table 3: Antibiotic resistance patterns of the most common pathogens according to age groups

Antibiotic resistance	*Escherichia coli* (n=138) (%)			*Enterococcus* spp. (n = 24) (%)			*Klebsiella spp.* (n = 22) (%)			*Proteus* spp. (n = 14) (%)		
	≤1 year (n = 24)	>1 year (n = 114)	p value	≤1 year (n = 4)	>1 year (n = 20)	p value	≤1 year (n = 16)	>1 year (n = 6)	p value	≤1 year (n = 0)	>1 year (n = 14)	p value
Ampicillin	20 (83)	84 (74)	0.41	2 (50)	8 (40)	0.59	14 (87)	6 (100)	0.72	0	1 (7)	-
AMC	9 (38)	41 (36)	0.92	1 (25)	0	-	2 (12)	2 (33)	0.23	0	0	-
TMP-SMX	5 (20)	40 (35)	**0.03**	2 (50)	14 (70)	0.82	4 (25)	2 (33)	0.59	0	3 (21)	-
Cefazolin	4 (17)	18 (16)	0.78	4 (100)	0	-	6 (37)	4 (66)	0.47	0	4 (29)	-
Cefuroxime	8 (34)	46 (40)	0.24	4 (100)	0	-	6 (37)	2 (33)	0.82	0	4 (29)	-
Cefixime	10 (41)	40(35)	0.78	0	4	-	5 (31)	2(33)	0.51	0	10	-
Ceftriaxone	6 (25)	26 (23)	0.59	4 (100)	2 (10)	0.54	6 (37)	2 (33)	-	0	0	-
Ciprofloxacin	4 (17)	22 (16)	0.49	0	6 (30)	-	6 (37)	0	-	0	0	-
Fosfomycin	1 (4)	9 (8)	0.69	0	4 (20)	-	2 (12)	0	-	0	0	-
Gentamicin	7 (29)	25 (22)	0.76	2 (50)	2 (10)	**0.03**	2 (12)	0	-	0	2 (14)	-
Meropenem	0	2 (2%)	-	0	0	-	0	0	-	0	0	-
Nitrofurantoin	5 (20)	5 (5)	**0.01**	0	4 (20)	-	4 (25)	4 (66)	**0.01**	0	10 (71)	-
Amikacin	6 (25)	16 (14)	0.32	2 (50)	4 (20)	0.14	-	-	-	-	-	-

n: Number, **spp:** Species, **AMC:** Amoxicillin/clavulanate, **TMP-SMX:** Trimethoprim-sulfamethoxazole. ***:** Chi-square test

(4,5,11). This is because CAKUT is more common in male infants, as also reported in our study. The rates of labial adhesion and phimosis, which are predisposing factors for UTIs, were similar to previous studies (12,13). Hypercalciuria is an underlying factor in UTIs, causing the impairment of the uroepithelium with calcium oxalate microcrystals (14,15). Stojanovic et al. reported that 10% of their patients with a single UTI had hypercalciuria similar to our study. However, they found this rate to be higher (44%) in children with recurrent UTIs (14). Nacaroglu et al. demonstrated that 66.7% of their hypercalciuric patients had recurrent UTIs (15). To determine the etiology of UTI, it is important to investigate urine calcium excretion, especially in recurrent infections. CAKUT is detected in the US in 18.5% of patients similar to Kumar et al., which showed 17% associated congenital urinary anomalies (16). The most-seen CAKUT in this study is VUR. It is reported that one-third of patients with VUR will develop at least one UTI (17). Thus, it is important to evaluate children with UTIs for CAKUT.

In the current study, gram-negative bacteria were isolated in 92% of the patients, which is compatible with the literature (1,2,16,18). These bacteria are more predominant than gram-positive bacteria in UTIs because they are commonly seen in the intestinal flora and can easily trespass and colonize the periurethral and perineal areas (18). We found *E. coli* to be the most common uropathogen with a rate of 56%, similar to previous studies (16,19,20). In the present study, similar to Mekonnen et al. (21), meropenem and ciprofloxacin were effective and β-lactam antibiotics (ampicillin, cefuroxime, and cefixime) were least effective for *E.coli*. Araújo et al. reported a significant increase in ciprofloxacin resistance between 2021 and 2022 for *E.coli* in an adult study (22). The rate of beta-lactam and other antibiotic resistance is increasing probably due to the continuous use of antibiotics without susceptibility data, easy availability, and misuse of antibiotics.

The World Health Organization has reported ESBL-positive *E. coli* as a key indicator for the surveillance of antibiotic resistance worldwide (23). In the current study, the rate of ESBL (+) uropathogens was found to be 5%, similar to Dejonckheere et al. (24). However, Koçak et al. reported ESBL positivity at a rate of 49% (25). Our lower rate may be due to our inclusion of only patients that were diagnosed with UTIs for the first time and did not receive antibiotic prophylaxis. The long-term and repeated use of antibiotics in UTIs increases ESBL positivity. Patients who required prophylaxis should be chosen carefully, and inappropriate prescriptions of antibiotics should be avoided.

In the current study, patients aged before ≤1 year old had a higher rate of antibiotic resistance than those aged over 1 year, which is consistent with the study conducted by Kurt-Şükür et al. (19). Antibiotic resistance rates may be higher in infants due to the higher prevalence of CAKUT and UTIs with ESBL positivity in this group. Gupta et al. reported that an antimicrobial agent should not be prescribed when the resistance rate is over 20% for empirical treatment (26). According to these data, NTF seems to be a good option in the empirical treatment of UTIs with low rates of resistance. However, according to the American Academy of Pediatrics, NTF is not recommended in febrile infants because serum and parenchymal concentrations may be inadequate for the management of urosepsis or pyelonephritis. In this patient group, TMP/SMX and cephalexin are recommended (27). We also found a higher resistance rate of NTF to *E. coli* in infants than in older children. Moreover, Kurt-Şükür et al. reported an increase in NTF resistance within ten years probably due to its increased use in prophylaxis and treatment (19).

The main limitations of this study are its single-centered retrospective nature and small sample size. In addition, we only evaluated patients that had UTIs for the first time. Children with recurrent UTIs may demonstrate different antibiotic susceptibility patterns.

In conclusion, antibiotic resistance is spreading worldwide. In UTIs, empirical treatment is prescribed until the results of the antibiogram are ready. It is important to detect regional antibiotic resistance patterns to manage UTIs properly by determining the most appropriate empirical therapy and minimizing morbidity and complications associated with these infections. Antibiotic susceptibility studies are also necessary to reduce improper antibiotic use and resistance rates of antibiotics.

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Author Contributions

Esra Nagehan Akyol Önder, Cengizhan Kılıçaslan researched literature and conceived the study. **Esra Nagehan Akyol Önder, Cengizhan Kılıçaslan, Selçuk Turkel** were involved in data acquisition. **Esra Nagehan Akyol Önder, Selçuk Turkel** contributed to data analysis and interpretation. **Esra Nagehan Akyol Önder** wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

No conflict of interest was declared by the authors.

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Ethical Approval

Our research was approved by the Ethics Committee with the decision of the IRB number 127-SBKAEK on 29/09/2022.

Review Process

Extremely peer-reviewed and accepted.

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