Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20240205 • *J Pediatr Inf 2024;18(2):e98-e108*

Comparison of Clinical and Laboratory Characteristics of Pediatric Patients Diagnosed with *E. coli* and non-*E. coli* Urinary Tract Infections

E. coli ve non-*E. coli* Üriner Sistem Enfeksiyonu Tanısı Alan Çocuk Hastaların Klinik ve Laboratuvar Özelliklerinin Karşılaştırılması

Selin Akgül[1](İD), Abdulrahman Özel[1](İD), Meltem Erol[1](İD), Aslıhan Tenekecigil[2,3](İD), Özlem Bostan Gayret[1](İD)

[1] *Clinic of Pediatrics, Health Sciences University Faculty of Medicine, Bağcılar Training and Research Hospital, İstanbul, Türkiye*
[2] *Clinic of Medical Biochemistry, Health Sciences University Faculty of Medicine, Bağcılar Training and Research Hospital, İstanbul, Türkiye*
[3] *Department of Medical Biochemistry, Gazi University Faculty of Medicine, Ankara, Türkiye*

Cite this article as: Akgül S, Özel A, Erol M, Tenekecigil A, Bostan Gayret Ö. Comparison of clinical and laboratory characteristics of pediatric patients diagnosed with *E. coli* and non-*E. coli* urinary tract infections. J Pediatr Inf 2024;18(2):e98-e108.

Abstract

Objective: The objective of this study was to determine the antibiotic susceptibility of *E. coli* and non-*E. coli* bacteria and contribute to the determination of empirical antibiotic treatment with the retrospective evaluation of urinary tract infection (UTI) patients diagnosed in our clinic.

Material and Methods: The data of patients aged 0 to 16 years, who were diagnosed with UTI in our clinic between 2018 and 2021, were retrospectively evaluated by using digital medical records. Patients with *E. coli* and non-*E. coli* growth in urine culture were defined as possible participants. Sixty-six patients were included in each study group.

Results: Our study was conducted on 132 children. The rate of *E. coli* infection was higher among female patients. Underlying risk factors were found in 47% of children. Regarding the *E. coli* group, urinary erythrocyte and bacterial counts were higher in the non-*E. coli* group. Neutrophil to lymphocyte ratio, C-reactive protein, urea, creatinine, and blood urea nitrogen values were higher in patients with urinary system anomalies compared to those without urinary system anomalies. Antibiogram results demonstrated a high rate of antibiotic resistance in both groups.

Conclusion: In our study, the underlying risk factors were more common in patients with non-*E. coli*, and abnormality in urinary tract imaging was more frequent. In addition, high rates of antibiotic resistance were determined in our study. We conclude that antibiotics should be chosen very carefully, and the healthcare personnel should be educated in unnecessary antibiotic use.

Keywords: Antibiotic resistance, children, *E. coli*, non-*E. coli*, urinary system infection

Öz

Giriş: Kliniğimizde üriner sistem enfeksiyonu (ÜSE) tanısı alan hastaları retrospektif inceleyerek *E. coli* ve non-*E. coli* gram negatif bakterilerin antibiyotik duyarlılıklarını tanımlamak ve ampirik antibiyotik tedavilerinin seçimine katkı sağlamak amaçlanmıştır.

Gereç ve Yöntemler: 2018-2021 yılları arasında kliniğimizde ÜSE tanısı alan 0-16 yaş arasındaki hastaların verileri bilgisayar kayıtlarından retrospektif olarak incelendi. İdrar kültüründe *E. coli* ve non-*E. coli* üremesi gözlenen hastalar katılımcı olarak belirlendi. Her iki gruptan 66 hasta çalışmamıza dahil edildi.

Bulgular: Çalışmamız 132 çocuk ile yapılmıştır. *E. coli* enfeksiyonu tespit edilenlerde kızların oranı daha yüksek bulunmuştur. Çocukların %47'sinde altta yatan risk faktörleri bulundu. *E. coli* grubu için idrarda eritrosit ve bakteri sayıları non-*E. coli* grubundan yüksek bulunmuştur. Üriner sistem anomalisi olanlar nötrofil lenfosit oranı, C-reaktif protein, üre, kreatinin ve kan üre azotu değerleri üriner sistem anomalisi olmayanlara kıyasla yüksek bulunmuştur. Antibiyogramda ise her iki grupta da yüksek antibiyotik dirençleri dikkati çekmektedir.

Sonuç: Çalışmamızda non-*E. coli* saptanan hastalarda altta yatan risk faktörleri daha sık görülmüş, üriner görüntelemede ise etkilenmenin daha fazla olduğu belirlenmiştir. Ayrıca çalışmamızda yüksek antibiyotik dirençleri dikkati çekmektedir. Hastalar tedavi edilirken antibiyotik seçiminde çok dikkatli davranılmalı, halk ve sağlık personeli bu gereksiz antibiyotik kullanımı konusunda bilinçlendirilmelidir.

Anahtar Kelimeler: Antibiyotik direnci, çocuklar, *E. coli*, non-*E. coli*, üriner sistem enfeksiyonu

Correspondence Address/Yazışma Adresi

Abdulrahman Özel

Clinic of Pediatrics, Health Sciences University Faculty of Medicine,
Bağcılar Training and Research Hospital,
İstanbul, Türkiye

E-mail: dr.abdulrahman.ozel@gmail.com

Received: 30.08.2023 **Accepted:** 16.11.2023 **Available Online Date:** 26.06.2024

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Available online at www.cocukenfeksiyon.org

Introduction

Urinary tract infection (UTI) is one of the most prevalent bacterial infections in children (1). UTI can affect any region of the urinary system and can cause serious complications in children leading to various morbidities and mortality (2). These complications include hypertension, chronic kidney disease, renal failure, and urosepsis (3).

Escherichia coli is the most common bacterium among the pathogens causing UTIs. *E. coli* is found in the normal flora of the urinary system. However, it can become pathogenic under certain conditions. In addition to *E. coli*, some other bacteria such as *Klebsiella, Proteus, Enterococcus,* and *Pseudomonas* can also cause UTIs. These bacteria are called non-*E. coli* (4).

UTI is a treatable infection, and uropathogens and antimicrobial resistance play an important role in the treatment. Early initiation of treatment in patients with suspected UTI reduces morbidity. Therefore, selection of the appropriate antibiotic is critical. Administration of inappropriate and ineffective antibiotics can lead to treatment failure and the emergence of resistant species. UTI pathogens have been often reported to have different rates of antibiotic resistance (4-8).

Our objective in this study was to determine the distribution and frequency of *E. coli* and non-*E. coli* growth in subjects followed for UTI according to the demographic data such as age and sex, to determine the underlying predisposing factors, to evaluate the laboratory results and the presence of the underlying urinary system anomalies and antibiotic susceptibilities of the pathogens, and to contribute to the selection of the correct antibiotic treatment in light of these findings.

Materials and Methods

Patients aged between one month to 16 years, who were diagnosed with UTI between 2018 and 2021 in our Pediatrics clinic at University of Health Sciences, Bağcılar Training and Research Hospital, were selected as participants. Patients with *E. coli* and non-*E. coli* growth in their urine cultures were divided into two groups. Patients with *E. coli* growth were included in Group 1 and patients with non-*E. coli* growth were included in Group 2. Each group consisted of 66 patients.

Patient data was obtained retrospectively from digital medical records. As 66 patients were considered suitable for the non-*E. coli* group, another 66 patients, who fulfilled the inclusion criteria and had *E. coli* growth in their urine culture between 2020-2021 were included in the *E. coli* group.

In order to include only community-acquired UTI cases, children who developed UTI during hospitalization or within 48 hours after discharge were excluded from the study. In addition, patients with neurogenic lower urinary tract dysfunction, chronic renal failure, and immunodeficiency were excluded from the study. In patients with UTI, a urine culture with a growth of 100.000 colonies or more in the midstream urine and 10.000 colonies or more in the bladder catheterization urine was considered a positive urine culture (9). Patients with a pathogen growth below the abovementioned colony counts or with multiple growths in the urine collected with a urine bag were excluded from the study. Gender, age, month of admission, complete urinalysis results, culture antibiogram results, and radiologically confirmed urinary pathology findings were recorded for all patients diagnosed with UTI.

Pediatric urinary tract infections with *E. coli* and non-*E. coli* growth in the urine culture were grouped by using statistical methods with the data obtained from the medical records and epidemiologic, laboratory, and urinary imaging findings were compared.

Ethics committee approval was obtained from a local ethics committee and the study was conducted in accordance with the Declaration of Helsinki (Date: Jan 6, 2022, No: 27).

Statistical Analysis

The data obtained in the study were analyzed using the IBM SPSS Statistics 22 software package (IBM SPSS, Türkiye). Normal distribution of the study parameters was evaluated with the Shapiro-Wilks test. The Student's t-test was used to evaluate the comparison of the quantitative data along with descriptive statistical methods (mean, standard deviation, frequency) and intergroup comparison of the parameters that showed normal distribution. The Mann-Whitney U test was used for comparison between the groups of parameters that did not show normal distribution. Chi-squared test, Fisher's exact test, Fisher-Freeman-Halton test, and continuity (Yates) correction were used for the comparison of the qualitative data. Statistical significance was evaluated at the level of $p< 0.05$.

Results

The study was conducted on 132 children. Fifty-two (39.4%) were males and 80 (60.6%) were females. Mean age was 38.73 ± 48.42 months. The age at diagnosis was between 0-3 months in 29.5% of children, between 3-24 months in 28.8%, between 24-60 months in 14.4%, and over 60 months in 27.3% of children (Table 1).

In Group 1 (*E. coli*), mean age of the children was 38.89 ± 42.59 months. Of these, 27.3% were aged 0-3 months, 24.2% were aged 3-24 months, 19.7% were aged 24-60 months, and 28.8% were older than 60 months. In Group 2 (non-*E. coli*), mean age was 38.58 ± 53.97 months. Of these, 31.8% were aged 0-3 months, 33.3% were added 3-24 months, 9.1% were aged 24-60 months, and 25.8% were older than 60 months. There was no statistically significant difference between the groups on behalf of the examination age, examination date distribution rates, and examination age group distribution rates ($p> 0.05$) (Table 1).

Table 1. Evaluation of the general characteristics between the groups

		Group 1 (*E. coli*)	Group 2 (non-*E. coli*)	Total	
		Mean ± SD	**Mean ± SD**	**Mean ± SD**	**p**
Mean Age at Examination (months)		38.89 ± 42.59	38.58 ± 53.97	38.73 ± 48.42	0.3291
		n (%)	**n (%)**	**%**	
Age at Examination	1-3 months	18 (27.3%)	21 (31.8%)	29.5	0.2763
	3-24 months	16 (24.2%)	22 (33.3%)	28.8	
	24-60 months	13 (19.7%)	6 (9.1%)	14.4	
	>60 months	19 (28.8%)	17 (25.8%)	27.3	
Sex	Boys	16 (24.2%)	36 (54.5%)	39.4	0.0014*
	Girls	50 (75.8%)	30 (45.5%)	60.6	

[1]Mann-Whitney U Test.
[2]Fisher-Freeman-Halton Test.
[3]Chi-square Test.
[4]Continuity (Yates) Correction.
*p< 0.05

While 24.2% of the patients in Group 1 were boys, 75.8% were girls. The same rates in Group 2 were 54.5% and 45.5%, respectively. The rate of girls in Group 1 was significantly higher than the same rate in Group 2 (p< 0.05) (Table 1).

The most common symptom among the participating children was fever (65.2%), and the patients had presented to the hospital with complaints of vomiting (20.5%), irritability (18.2%), flank pain (12.1%), dysuria (15.9%), abdominal pain (12.1%), macroscopic hematuria (5.3%), bad odor in urine (10.6%), new-onset urinary incontinence (4.5%), pollakiuria (3%), loss of appetite (3.8%), burning sensation during micturition (0.8%), and oliguria (0.8%). There was no statistically significant difference between the groups for the symptoms at admission (p> 0.05) (Table 2).

In Group 2 (non-*E. coli*), the following bacteria were isolated in the urine cultures: *Klebsiella pneumoniae* (54.5%), *Klebsiella oxytoca* (%3), *Klebsiella ornithinolytica* (1.5%), *Staphylococcus aureus* (3%), *Staphylococcus epidermidis* (1.5%), *Morganella morganii* (1.5%), *Pseudomonas aeruginosa* (4.5%), *Enterobacter cloacae* (4.5%), *Proteus vulgaris* (1.5%), *Enterococcus gallinarum* (1.5%), *Proteus mirabilis* (6.1%), *Enterococcus faecalis* (9.1%), *Enterobacter aerogenes* (3%), *Serratia marcescens* (1.5%), *Streptococcus agalactiae* (1.5%), and in *Acinetobacter baumannii* (1.5%) (Table 3).

Table 2. Evaluation of the complaints at admission between the groups

	Group 1 (*E. coli*)	Group 2 (non-*E. coli*)	Total	
Complaints at admission	**n (%)**	**n (%)**	**%**	**p**
Fever	49 (74.2%)	37 (56.1%)	65.2	**0.0451***
Vomiting	13 (19.7%)	14 (21.2%)	20.5	1.0001
Irritability	10 (15.2%)	14 (21.2%)	18.2	0.4981
Flank pain	9 (13.6%)	7 (10.6%)	12.1	0.7901
Dysuria	12 (18.2%)	9 (13.6%)	15.9	0.6341
Abdominal pain	7 (10.6%)	9 (13.6%)	12.1	0.7901
Hematuria	4 (6.1%)	3 (4.5%)	5.3	0.5002
Bad odor in the urine	8 (12.1%)	6 (9.1%)	10.6	0.7771
Urinary incontinence	3 (4.5%)	3 (4.5%)	4.5	0.6602
Pollakiuria	3 (4.5%)	1 (1.5%)	3	-
Loss of appetite	3 (4.5%)	2 (3%)	3.8	0.5002
Dysuria	0 (0%)	1 (1.5%)	0.8	-
Oliguria	1 (1.5%)	0 (0%)	0.8	-

[1]Continuity (Yates) Correction.
[2]Fisher's Exact Test.
*p< 0.05
Note: P value is not given for the parameters, whose numbers were suitable for statistical analysis, their distribution according to the groups was given.

Table 3. Distribution of urine culture pathogens and risk factors

		Group 1 (*E. coli*)	Group 2 (non-*E. coli*)	Total	
		n (%)	n (%)	%	p
Pathogens Detected in Urine Cultures	*Klebsiella pneumoniae*		36 (54.5%)		-
	Klebsiella oxytoca		2 (3%)		
	Klebsiella ornithinolytica		1 (1.5%)		
	Staphylococcus aureus		2 (3%)		
	Staphylococcus epidermidis		1 (1.5%)		
	Morganella morganii		1 (1.5%)		
	Pseudomonas aeruginosa		3 (4.5%)		
	Enterobacter cloacae		3 (4.5%)		
	Proteus vulgaris		1 (1.5%)		
	Enterococcus gallinarum		1 (1.5%)		
	Proteus mirabilis		4 (6.1%)		
	Enterococcus faecalis		6 (9.1%)		
	Enterebacter aerogenes		2 (3%)		
	Serratia marcescens		1 (1.5%)		
	Streptococcus agalactiae		1 (1.5%)		
	Acinetobacter baumannii		1 (1.5%)		
Presence of Urinary Anomaly	No	21 (31.8%)	41 (62.1%)	47	**0.0001***
	Yes	45 (68.2%)	25 (37.9%)	53	
Urinary System Anomaly	Hydronephrosis	3 (14.3%)	8 (19.5%)	17.7	0.4472
	Calculi	5 (23.8%)	12 (29.3%)	27.4	0.8773
	VUR	10 (47.6%)	18 (43.9%)	45.2	0.9933
	Duplicated ureter	1 (4.8%)	0 (0%)	1.6	-
	Cyst	1 (4.8%)	0 (0%)	1.6	-
	Malrotated left kidney	1 (4.8%)	0 (0%)	1.6	-
	Bladder exstrophy	1 (4.8%)	0 (0%)	1.6	-
	Ureter stricture	0 (0%)	1 (2.4%)	1.6	-
	UPJ stenosis	0 (0%)	3 (7.3%)	4.8	-
	Duplex collecting system	0 (0%)	1 (2.4%)	1.6	-
	Horseshoe kidney	0 (0%)	1 (2.4%)	1.6	-
	Unilateral renal agenesis	0 (0%)	1 (2.4%)	1.6	-
	Cystic mass	0 (0%)	1 (2.4%)	1.6	-
	PUV	0 (0%)	1 (2.4%)	1.6	-
	Ureterocele	0 (0%)	1 (2.4%)	1.6	-

[1]Mann-Whitney U Test.
[2]Fisher-Freeman-Halton Test.
[3]Chi-square Test.

A urinary system anomaly was detected in 47% of participants, while no urinary system anomaly was detected in 53% of participants. The rates of urinary system anomalies in Group 1 and Group 2 were 31.8% and 62.1%, respectively. The rate of urinary system anomalies in Group 2 was significantly higher than in Group 1 ($p< 0.05$) (Table 3).

Regarding patients in Group 1, 47.6% had vesicoureteral reflux (VUR), 23.8% had calculi, 14.3% had hydronephrosis, 4.8% had duplicated ureter, 4.8% had cyst, 4.8% had malrotated left kidney, and 4.8% had bladder exstrophy. Considering patients in Group 2, 43.2% had VUR, 29.3% had calculi, 19.5% had hydronephrosis, 7.3% had uteropelvic junction (UPJ) stenosis, 2.4% had ureteral stricture, 2.4% had duplex collecting system, 2.4% had horseshoe kidney, 2.4% had left kidney agenesis, 2.4% had cystic mass, 2.4% had posterior urethral valve (PUV), and 2.4% had ureterocele. No statistically signifi-

cant difference was found when the prevalence of urinary system anomalies was compared between the groups. (p> 0.05) (Table 3).

Mean urine leukocyte, erythrocyte, and bacterial counts in the urine of the children were 188.62 ± 355.54, 60.3 ± 273.77, and 10.84 ± 24.33, respectively. Mean urinary density was 1012.72 ± 8.34 and the mean urine pH was 6.34 ± 0.63. Proteinuria test was negative in 49.2% of the children, while erythrocyte dipstick test was negative in 27.3% of the children. Urine nitrite test was positive in 40.2% of patients, while all participants had a positive urine leukocyte esterase test (Table 4).

Urine erythrocyte count, bacterial count, and positive urine nitrite test rates were significantly higher in Group 1 compared to Group 2 (p< 0.05). There was no statistically significant difference between the groups for urine leukocyte count, proteinuria, positive leukocyte dipstick rate, positive erythrocyte dipstick rate, urine density, and urine pH values (p> 0.05) (Table 4).

Regarding the complete blood count of the children, mean neutrophil/lymphocyte ratio was 2.3 ± 2.87, mean platelet count was 371.81 ± 130.8, mean MPV was 9.78 ± 0.95, mean CRP was 57.69 ± 65.42, mean urea level was 19.62 ± 8.65, and creatinine level was 0.31 ± 0.15. CRP levels in Group 1 were significantly higher than in Group 2 (p< 0.05). There was no statistically significant difference between the groups for neutrophil/lymphocyte ratio, platelet count, MPV, urea, creatinine, and BUN parameters (p> 0.05) (Table 5).

Table 4. Evaluation of urinalysis between groups

		Group 1 (*E. coli*)	**Group 2 (non-*E. coli*)**	**Total**	
Urinalysis		**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**p**
Leukocyte		172.36 ± 213.09	165.88 ± 331.84	188.62 ± 355.54	0.092[1]
Erythrocyte		31.12 ± 40.48	28.92 ± 53.05	30.02 ± 47.01	**0.027[1]***
Bacteria		16.2 ± 30.78	5.48 ± 13.69	10.84 ± 24.33	**0.003[1]***
Density		1013.14 ± 7.49	1012.3 ± 9.15	1012.72 ± 8.34	0.200[1]
pH		6.3 ± 0.49	6.38 ± 0.74	6.34 ± 0.63	0.904[1]
		n (%)	**n (%)**	**(%)**	
Proteinuria	Negative	26 (39.4%)	39 (59.1%)	49.2	0.067[2]
	Positive	40 (60.6%)	27 (40.9%)	50.8	
Nitrite	Negative	28 (42.4%)	51 (77.3%)	59.8	**0.000[3]***
	Positive	38 (57.6%)	15 (22.7%)	40.2	
Leukocyte esterase	Positive	66 (100%)	66 (100%)	100	
Erythrocyte dipstick	Negative	13 (19.7%)	23 (34.8%)	27.3	0.140[2]
	Positive	53 (80.3%)	22 (65.2%)	73.7	

[1]Mann-Whitney U Test.
[2]Chi-square Test.
[3]Continuity (Yates) Correction.
*p< 0.05

Table 5. Evaluation of the laboratory findings between groups

	Group 1 (*E. coli*)	**Group 2 (non-*E. coli*)**	**Total**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**p**
Neutrophil/Lymphocyte Ratio	2.45 ± 3.28	2.14 ± 2.41	2.3 ± 2.87	0.675[1]
Platelet (10^3/μL)	352.26 ± 130.7	391.36 ± 128.92	371.81 ± 130.8	0.086[2]
MPV (fL)	9.73 ± 0.86	9.83 ± 1.03	9.78 ± 0.95	0.565[2]
CRP (mg/L)	69.53 ± 68.95	45.86 ± 59.9	57.69 ± 65.42	**0.028[1]***
Urea (mg/dL)	19.18 ± 8.3	20.07 ± 9.02	19.62 ± 8.65	0.679[1]
Creatinine (mg/dL)	0.3 ± 0.13	0.31 ± 0.16	0.31 ± 0.15	0.879[1]
BUN (mg/dL)	8.85 ± 3.73	9.46 ± 4.14	9.15 ± 3.94	0.531[1]

[1]Mann-Whitney U Test.
[2]Student's t test.
*p< 0.05

Antibiotic resistance according to the antibiograms of the microorganisms in Group 1 and Group 2 is shown in the table/figure (Table 6). In the *E. coli* group, 33 (50%) bacteria and in the non-*E. coli* group, 25 (46%) bacteria were extended-spectrum beta-lactamase-positive.

The resistance rates of nitrofurantoin and ertapenem in Group 2 were significantly higher than Group 1 (p< 0.05) (Table 6).

We divided patients into two groups according to the presence or absence of urinary anomalies detected in ultrasonography (US) examination and found that neutrophil/lymphocyte rate, CRP, urea, and creatinine levels were significantly higher in the group with anomalies compared to the group without anomalies (p< 0.05) (Table 7).

Table 6. Comparison of antibiotic susceptibility and resistance rates between groups

		Group 1 (*E. coli*)	**Group 2 (non-*E. coli*)**	
Antibiotics		**n (%)**	**n (%)**	**p**
TMP-SMX	Susceptible	30 (45.5%)	36 (54.5%)	0.296[1]
	Resistant	36 (54.5%)	30 (45.5%)	
Ciprofloxacin	Susceptible	36 (63.2%)	35 (70%)	0.588[1]
	Resistant	21 (36.8%)	15 (30%)	
Ceftriaxone	Susceptible	22 (45.8%)	26 (47.3%)	0.884[1]
	Resistant	26 (54.2%)	29 (52.7%)	
Cefotaxime	Susceptible	9 (39.1%)	17 (58.6%)	0.264[2]
	Resistant	14 (60.9%)	12 (41.4%)	
Ceftazidime	Susceptible	20 (34.5%)	21 (39.6%)	0.492[3]
	Resistant	38 (65.5%)	31 (58.5%)	
Cefepime	Susceptible	8 (40%)	10 (45.5%)	0.964[2]
	Resistant	12 (60%)	12 (54.5%)	
Cefuroxime	Susceptible	27 (40.9%)	24 (40%)	0.917[1]
	Resistant	39 (59.1%)	36 (60%)	
Cefixime	Susceptible	13 (43.3%)	10 (34.5%)	0.667[2]
	Resistant	17 (56.7%)	19 (65.5%)	
Piperacillin-Tazobactam	Susceptible	39 (78%)	28 (62.2%)	0.145[2]
	Resistant	11 (22%)	17 (37.8%)	
Nitrofurantoin	Susceptible	51 (94.4%)	22 (59.5%)	**0.000[2]***
	Resistant	3 (5.6%)	15 (40.5%)	
Meropenem	Susceptible	57 (98.3%)	48 (87.3%)	-
	Resistant	1 (1.7%)	7 (12.7%)	
Ertapenem	Susceptible	57 (95%)	42 (75%)	**0.005[2]***
	Resistant	3 (5%)	14 (25%)	
Gentamicin	Susceptible	51 (77.3%)	38 (61.3%)	0.077[2]
	Resistant	15 (22.7%)	24 (38.7%)	
Ampicillin	Susceptible	10 (15.2%)	10 (15.2%)	1.000[2]
	Resistant	56 (84.8%)	56 (84.8%)	
Amoxicillin-clavulanate	Susceptible	18 (27.3%)	23 (34.8%)	0.452[2]
	Resistant	48 (72.7%)	43 (65.2%)	
Amikacin	Susceptible	63 (98.4%)	56 (87.5%)	-
	Resistant	1 (1.6%)	8 (12.5%)	

[1]Chi-square Test.
[2]Continuity (Yates) Correction.
[3]Fisher-Freeman-Halton Test.
*p< 0.05
Note: P value is not given for the parameters whose numbers were suitable for statistical analysis, their distribution according to the groups was given.

Table 7. Evaluation of the laboratory findings for the presence of urinary system anomalies

	Presence of Anomalies in the Urinary System		
	Yes	No	
	Mean ± SD	Mean ± SD	p
Neutrophil/lymphocyte Ratio	2.68 ± 3.19	1.69 ± 2.17	**0.004**[1*]
Platelet (*bin/µL)	358.38 ± 132.29	393.14 ± 126.76	0.138[2]
MPV (fL)	9.7 ± 0.99	9.91 ± 0.87	0.231[2]
CRP (mg/L)	64.81 ± 67.22	46.39 ± 61.43	**0.038**[1*]
Urea (mg/dL)	21.17 ± 9.35	17.18 ± 6.79	**0.009**[1*]
Creatinine (mg/dL)	0.33 ± 0.15	0.27 ± 0.13	**0.005**[1*]
BUN (mg/dL)	9.85 ± 4.22	8.04 ± 3.18	**0.009**[1*]

[1]Mann-Whitney U Test.
[2]Student's t Test.
*p< 0.05.

Discussion

Urinary tract infections are one of the most common infections in children and *E. coli* is the top-ranked pathogen in terms of etiology. Other pathogens causing UTI, which are less common, are classified in a single group as non-*E. coli* pathogens. This group includes *Klebsiella, Proteus, Pseudomonas* species, *Enterococci*, coagulase-negative *Staphylococci*, and other bacteria (10). In our study, the most common non-*E. coli* pathogen was *K. pneumoniae* (27.3%), as in other studies in the literature.

In our study, in patients with UTI, a urine culture with a growth of 100.000 colonies or more in the midstream urine and 10.000 colonies or more in the bladder catheterization urine was considered a positive urine culture (9). The American Academy of Pediatrics (AAP) defines positive culture as the growth of at least 50.000 CFU/mL colonies in a urine sample obtained by bladder catheterization for the diagnosis of UTI (11). However, in many guidelines published in the European region, of which our country is a part, 10.000 CFU/mL (or even 1.000 CFU/mL) and more colonies in the bladder catheter sample is considered as positive culture (9,12-14). Since it has been reported that early diagnosis and treatment in a child with a suspected UTI reduces the incidence of renal scarring we think that the guidelines published from the European region are more reliable (9,14).

In the first three months of life, UTI is more common in males than in females, but then becomes more common in females (15,16). After the first three months of life, girls are significantly more likely to have UTI than boys (17-19). Regarding the total number of patients in our study, the rate of girls diagnosed with UTI was 60.6%, which was consistent with the studies in the literature. We found that the rate of UTI in girls increased with age.

UTI increases especially in three periods of childhood. Infancy, when the child starts walking, and adolescence (20). There are several studies in the literature that focused on the age groups of patients. Although these studies investigated different age intervals and age groups, they all reported that UTI was particularly common in the first two years of life and adolescence (3,17,21,22). In our study, as in other studies in the literature, 58.5% of the patients were in the 0-2 years age group.

The diagnosis of UTI is most difficult in children younger than two years of age because patients in this age group cannot talk about their complaints. They usually present to the hospital with complaints such as fever, irritability, vomiting, and loss of appetite. On the other hand, older children can localize their complaints and describe them much better. Children in this age group may present to the hospital with complaints like fever, vomiting, abdominal pain, flank pain, dysuria, pollakiuria, urinary incontinence, blood in the urine, and etc. In adolescence, lower urinary system findings are more common (23). In the study conducted by Hameed et al., fever and vomiting have been found in 84.2% and 51.5% of the patients respectively (24). Shaikh et al. have conducted a study on 1.214 patients and found fever≥ 39°C in 49% of patients (25). In our study, the most common findings were fever (65.2%) and vomiting (20.5%). Considering the studies in the literature, the most common complaint at admission was fever and our study supported this finding. The rate of fever in the group with *E. coli* growth in urine culture (74.2%) was significantly higher than in the group with non-*E. coli* growth in urine culture (56.1%) (p< 0.05). In our study, a fever≥ 38°C with tympanic measurement was considered a high fever and was the most common symptom among participants (26).

Anatomical, structural, and functional differences in the urinary system and lesions like stones and masses are risk

factors for UTI. Since these anomalies can cause obstruction, impaired urine flow and consequent retention, uropathogens cannot be effectively cleared from the system, allowing them to multiply and cause infections following the incubation period (27). The relationship between urinary system anomalies and particularly non-*E. coli* pathogens has been reported in several publications in the literature. According to the Italian Society of Pediatric Nephrology (ISPN), the following should be investigated considering the presence of urinary anomalies. Family history, abnormal US findings, children younger than six months, detection of pathogens other than *E. coli*, renal failure, and micturition disorders (28-30). Like ISPN, National Institute for Health and Care Excellence (NICE) has stated that urinary anomalies should be suspected in the presence of non-*E. coli* pathogens (28). Yılmaz et al. have conducted a study with 300 patients and demonstrated a relationship between the presence of VUR and the first UTI (31). In another study, Ristola et al. have investigated 282 patients and showed the relationship of non-*E. coli* UTI with urinary anomaly, VUR, recurrent UTI (32). In our study, we found urinary anomalies in 47% of children and VUR was the most common finding in this group (45%). We also determined that the incidence of underlying risk factors was significantly higher in the non-*E. coli* group.

Urinary US is the most common imaging method used to study the urinary system in children. It is used for diagnosis and follow-up of UTI. Studies have suggested that anomalies found on US examination were more common in *E. coli* infections than in non-*E. coli* infections (29,33). Several studies have attempted to demonstrate the relationship between non-*E. coli* UTI and urinary system anomalies (30,32). In our study, the rate of urinary anomalies was 31.8% and 62.1% in *E. coli* and non-*E. coli* groups respectively and the difference was statistically significant, which was consistent with the findings in the literature. This finding suggested that the subjects with urinary anomalies might be more susceptible to bacteria other than *E. coli* (34).

Complete urinalysis is one of the main methods used to diagnose UTI. According to the literature, pyuria and positive leukocyte esterase test rates were higher in the *E. coli* group than in the non-*E. coli* group (35,36). In our study, the comparison of pyuria and leukocyte esterase positivity did not show any significant difference, which may be related to the small size of the groups in our study. Erythrocyte and bacterial counts in urine and the positive urine nitrite test rate were significantly higher in the *E. coli* group. It should be noted that urinary nitrite level is not a sensitive marker for UTI in childhood, especially in infants due to frequent voiding. In addition, many non-*E. coli* pathogens do not reduce nitrates to nitrites (37).

In addition to urinalysis and clinical findings, laboratory tests related to kidney functions and the inflammatory process should be considered in the evaluation of UTI. An increase in inflammatory markers is expected in UTI (38). In our study, in addition to CRP (an inflammatory marker), neutrophil/lymphocyte ratio (NLR) and mean platelet volume (MPV), which have been increasingly investigated in recent studies, were also included in the evaluation. Regarding the literature, there are not many studies comparing *E. coli* and non-*E. coli* groups for laboratory parameters like in our study. On the other hand, in our study, there was no statistically significant difference between the groups for NLR, platelets, MPV, urea, creatinine, and BUN values. In our study, we also compared the laboratory parameters in the groups with and without urinary anomalies and found that neutrophil/lymphocyte ratio, CRP, urea, and creatinine values were significantly higher in the group with urinary anomalies than in group without anomalies. This finding can be explained by a weaker defense system in the host with urinary anomaly and consequently a more severe infection profile (34,39-41).

Antibiotic resistance in *E. coli* and non-*E. coli* groups has been investigated and compared in several studies in the literature (4,7,36,42). In different European countries, the resistance rate of *E. coli* strains isolated from pediatric patients with UTIs to amoxacillin/cavulanic acid varies between 12% and 32% and these resistance rates have increased by approximately 2% each year (42-46). Nowadays, cephalosporin group antibiotics have an important place in empirical antibiotic treatment of UTIs and in several European studies, resistance to second generation cephalosporins in UTIs caused by *E. coli* was found to be below 50% (42,47,48). When antibiotic resistances in the *E. coli* group were analyzed in our study, 72% resistance to amoxacillin-clavulanate and 59% resistance to cefuroxime, which is a second generation cephalosporin, were found. The frequent prescription of these antibiotics, especially in children with upper respiratory tract infections in primary and secondary health care settings, may have led to the emergence of high resistance.

In various studies conducted in UTIs in Türkiye, TMP-SMX resistance varies between 20-60% (49). In our study, this rate was found to be 54.5% and is compatible with the data from Türkiye. According to a meta-analysis in which countries were classified on the basis of Organisation for Economic Cooperation and Development (OECD) status, ampicillin resistance of *E. coli* bacteria in children with UTI was found to be 53.4% in OECD countries and 79.4% in non-OECD countries, and in Türkiye, which is an OECD country, ampicillin resistance was found to be 67% (50). In our study, ampicillin resistance of the *E. coli* group was found to be 84%, which was quite high.

The results of our study are alarming. The antibiotic resistance rate found in our study was much higher than that reported in other studies and the incidence of extended-spectrum beta-lactamase-producing *E. coli*, especially in the *E. coli* group was striking. Our country is one of the most antibiotics-using countries in the world, which increases the incidence

of resistant microorganisms (51). At the same time, the fact that our center is a tertiary hospital and complicated cases in our region are more often referred to our hospital has made this situation more pronounced.

Limitations

The retrospective study design is the most important limitation of our study. In addition, the single-center design and limited sample size are other limitations of our study. The ratio of males was higher in the non-*E. coli* group. Uncircumcised boys are at risk for urinary tract infection. It is easier for bacteria to accumulate under the foreskin (or prepuce) and in the urethra in uncircumcised boys, but circumcision is unclear in our study (52). Therefore, we had to have information about circumcision status in order to explain this high rate of male in the non-*E. coli* group. Although it is known that male children are circumcised in our region, where the population mostly consists of Muslims, circumcision can be performed at any period of childhood.

Another limitation of our study was the lack of information in the patient records about whether it was the first UTI or recurrent UTI. All health data of citizens of the Republic of Türkiye are recorded from birth by the Ministry of Health on a digital platform. However, in our region, where the refugee population is high, this information can only be obtained from the patients' relatives. This information was not included in our study due to low reliability.

Conclusion

In our study, we found that the underlying risk factors and urinary anomalies were more common in patients with non-*E. coli* infections. This should always be kept in mind and especially in patients, who are followed due to UTI caused by non-*E. coli* pathogens. Urinary system imaging should be performed, and relatively longer follow-up periods should be planned. In addition, antibiotic resistance was remarkably high in our study. In our country, awareness of this problem has increased, and the rates of antibiotic use have decreased in recent years. When treating patients, antibiotics should be chosen appropriately, and the public and healthcare personnel should be educated about this issue.

Ethics Committe Approval: This study approval was obtained from İstanbul Medipol University non-Invasive Clinical Research Ethics Committee (Decision no: 27, Date: 06.01.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - SA, AÖ, AT; Design - AÖ, ME, ÖBG; Supervision - AÖ, ME, ÖBG; Resource - SA, AÖ, AT; Data Collection and/or Processing - SA, AÖ, AT; Analysis and/or Interpretation - SA, AÖ, ME; Literature Search - SA, AÖ, ÖBG; Writing - SA, AÖ, ME; Critical Review- AÖ, AT, ME.

Conflict of Interest: All authors declare that they have no conflicts of interest or funding to disclose.

Financial Disclosure: The authors declared that this study has received no financial support.

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