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Original Article *Özgün Araştırma*

PEDIATRIC URINARY TRACT INFECTION MANAGEMENT IN THE ERA OF RISING ANTIBIOTIC RESISTANCE: INSIGHTS FROM A SINGLE-CENTER COHORT

Artan Antimikrobiyal Direnç Döneminde Pediatrik İdrar Yolu Enfeksiyonu Yönetimi: Tek Merkezli Bir Kohort Çalışması Bulguları

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ABSTRACT

Objective: Urinary tract infections (UTIs) are one of the most common bacterial infections in children and can lead to serious complications. This study aimed to investigate the clinical and microbiological characteristics of pediatric UTIs, identify factors associated with renal scarring, analyze trends in antibiotic resistance, and evaluate the impact of urinary anomalies and vesicoureteral reflux (VUR) on recurrence of infection and long-term outcomes.

Material and Methods: In this retrospective study, 699 children followed up for UTI were evaluated. Clinical features, laboratory and imaging findings (Ultrasound, voiding cystourethrogram, DMSA renal scan), microbiological data, antibiotic resistance patterns and long-term complications were analyzed. Risk factors for renal scarring were assessed using multivariate logistic regression.

Results: Out of the 699 patients followed for UTIs, 530 were female. The median age at the first UTI was 12 months. Renal ultrasonography was performed on all patients. Anomalies were detected in 15.7% of patients. *E. coli* was the predominant pathogen (82.6%). Renal scarring was detected in 15.7% of patients and was significantly associated with high-grade VUR, recurrent UTI, abnormal US findings, and fever≥38°C. The prevalence of ESBL-producing bacteria was 2.4%, with ubstantialtly higher ciprofloxacin resistance (28%) compared to non-ESBL bacteria (7.5%). Over time, E. coli resistance to TMP-SMX and amoxicillin-clavulanate declined, whereas cefixime resistance slightly increased.

Conclusion: Renal scarring in pediatric UTI is strongly associated with VUR severity, recurrent infections, and urinary tract anomalies. Antibiotic resistance remains a growing concern, particularly among ESBL-producing pathogens. Rational use of antibiotics and individualized risk-based prophylactic strategies are critical to minimizing long-term complications and resistance.

Keywords: *Pediatric urinary tract infection, vesicoureteral reflux, renal scarring, antibiotic resistance, extended-spectrum beta-lactamase*

ÖZ

Amaç: İdrar yolu enfeksiyonları (İYE), çocuklarda en sık görülen bakteriyel enfeksiyonlar arasında yer almakta olup ciddi uzun dönem komplikasyonlara yol açabilmektedir. Bu çalışmanın amacı, pediatrik İYE'lerin klinik ve mikrobiyolojik özelliklerini değerlendirmek, renal skar oluşumu ile ilişkili risk faktörlerini belirlemek, antibiyotik direnç eğilimlerini incelemek ve üriner sistem anomalileri ile vezikoüreteral reflünün (VUR) enfeksiyon nüksü ve uzun dönem sonuçlar üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmada, İYE nedeniyle izlenen 699 çocuk değerlendirildi. Klinik özellikler, laboratuvar sonuçları, görüntüleme bulguları (ultrasonografi, işeme sistoüretrografisi ve DMSA sintigrafisi), mikrobiyolojik veriler, antibiyotik direnç profilleri ve uzun dönem komplikasyonlar analiz edildi. Renal skar ile ilişkili risk faktörleri çok değişkenli lojistik regresyon analizi ile belirlendi.

Bulgular: Çalışmaya dâhil edilen 699 hastanın 530'u kız olup, ilk İYE geçirme medyan yaşı 12 ay idi. Tüm hastalara renal ultrasonografi uygulanmış olup, olguların %15,7'sinde üriner anomaliler saptandı. Başlıca etken mikroorganizma *Escherichia coli* idi (%82,6). Renal skar %15,7 oranında tespit edildi ve yüksek dereceli VUR, tekrarlayan İYE, anormal ultrason bulguları ve ≥38°C ateş ile anlamlı ilişki gösterdi. Geniş spektrumlu beta-laktamaz (GSBL) üreten suş oranı %2,4 olup, bu suşlarda siprofloksasin direnci (%28), GSBL-negatiflere kıyasla (%7,5) belirgin derecede yüksekti. Zaman içinde *E. coli*'nin trimetoprim-sülfametoksazol ve amoksisilin-klavulanat direncinde azalma görülürken, sefiksim direncinde hafif bir artış izlendi.

Sonuç: Pediatrik İYE'de renal skar gelişimi, VUR derecesi, tekrarlayan enfeksiyonlar ve üriner sistem anomalileri ile güçlü şekilde ilişkilidir. Zaman içinde direnç paternleri değişmekle birlikte, GSBL üreten patojenler önemli bir sorun olmaya devam etmektedir. Uzun dönem komplikasyonları ve antimikrobiyal direnç gelişimini azaltmak için antibiyotiklerin akılcı kullanımı ve bireyselleştirilmiş, risk temelli profilaktik yaklaşımlar büyük önem taşımaktadır.

Anahtar Kelimeler: *Pediatrik idrar yolu enfeksiyonu, vezikoüreteral reflü, böbrek skarlaşması, antibiyotik direnci, geniş spektrumlu beta-laktamaz,*

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INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections in children.[1] Recurrent UTIs can lead to serious long-term consequences, such as renal scarring, hypertension, and chronic renal disease.[2,3] A multicenter study conducted in our country has demonstrated that the leading cause of chronic renal failure in childhood is pyelonephritis that develops based on vesicoureteral reflux (VUR).[4]

The prevalence and incidence of UTIs significantly vary with age, sex, and circumcision status, highlighting a critical public health concern. Overall, the prevalence of UTI in febrile infants is approximately 7%, which is highest in uncircumcised males, especially those younger than three months. The risk of UTI in pre-pubertal girls is 3-5% and in boys is 1-2%.[5,6]

UTIs in children are predominantly caused by *Escherichia coli (E. coli)*, accounting for approximately 60-90% of cases.[7,8] Other gram-negative bacteria that cause UTIs are species of *Klebsiella, Proteus, Enterobacter, and Citrobacter.*[8] Among Gram-positive organisms *Staphylococcus saprophyticus* and *Enterococci* spp. are occasionally implicated, while *Staphylococcus aureus* is a rare etiological agent in this population.

Antibiotic resistance has become an increasing concern in recent years.[9] Particularly, the prevalence of extended-spectrum beta-lactamase (ESBL) producing gram-negative bacilli has risen significantly.[10]

Recent studies indicate that the prevalence of ESBL-producing pathogens causing UTIs has reached 7.4% in North America, 18.8% in Europe, 27.7% in South Asia, and a concerning 60% in India.[11-13] Several factors have been associated with the emergence and spread of antibiotic resistance including a history of prior hospitalizations, recurrent UTIs, and the use of broad-spectrum antibiotics without clear clinical indications.[14]

In children, UTIs are associated with a concerning recurrence rate of 30-40%, with most recurrences occurring within the first year after the initial episode.[15,16] In particular, recurrent episodes of pyelonephritis increase the risk of renal scarring, which may lead to chronic kidney disease (CKD).[17]

We sought to identify the most common clinical symptoms and findings associated with UTIs, along with the etiological factors and trends of antibiotic susceptibility over time. Additionally, the study aimed to identify the most prevalent urinary anomalies. Finally, we aimed to determine the frequency of renal scarring and and explore the factors contributing to its development, given its critical role in the pathogenesis of CKD.

MATERIALS AND METHODS

This retrospective study involved 699 patients aged 1 month to 18 years who were followed for UTI at Gazi University's Faculty of Medicine, Department of Pediatric Nephrology, between March 2007 and March 2012. Newborns (0-1 month), those who did not meet the diagnostic criteria and those with incomplete data were excluded from the study. The patients' age at first UTI, gender, circumcision status in male patients, and accompanying symptoms such as fever, vomiting, and dysuria were evaluated.[18] A positive urine culture was defined as the growth of one urinary tract pathogen >100.000 colony-forming units per milliliter (CFU/ml) for specimens obtained by the mid stream urine or ≥50.000 CFU/ml urine obtained through urethral catheterization.[19,20] A diagnosis of UTI was established based on the presence of more than 5 leukocytes in high-power field in a centrifuged urine (pyuria), along with a positive culture. In urine dipstick analysis, leukocyte esterase and nitrite positivity were examined, the presence of bacteria was also noted. White blood cell (WBC) and C-reactive protein (CRP) levels were measured in all patients. A CRP level of 0-6 mg/L was considered normal. Values higher than normal were categorized into two groups: 6-20 mg/L and greater than 20 mg/L. Some patients were tested for CRP, while others were tested for high-sensitivity CRP (hsCRP). A normal hsCRP level was defined as 0-0.05 mg/dL, and levels of ≥0.05 mg/dL and above were considered positive.

Renal ultrasonography (US) was performed on all patients, and the most common anomalies were recorded. Voiding cystourethrography (VCUG) was performed in patients with abnormalities on renal US or those with recurrent febrile UTI. Both VCUG and dimercaptosuccinic acid (DMSA) scans were performed on patients according to the American Academy of Pediatrics (AAP) guidelines.[19] We assessed the frequency and severity of VUR, its spontaneous resolution rate, the association with recurrent UTIs, and the prevalence of renal scarring on DMSA scans. The effects of associated urinary tract anomalies, presence of VUR, high fever, and infection recurrence on scar formation were evaluated. Additionally, the impact of VUR and prophylactic antibiotics on the recurrence of UTI was assessed. Complications such as proteinuria, hypertension, and CKD were documented. Urine culture result, along with their patterns of antibiotic resistance, were analyzed. The study period was divided into two, and it was examined whether there was a difference in terms of microorganisms and antibiotic resistance patterns between 2007-2010 and 2010-2012. This study has been approved by the local ethics committee (approval date: 22.02.2012, number:058).

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Statistical analysis

Descriptive statistics are presented as either mean ± standard deviation or median (min-max) for continuous variables or as the numbers and percentages for categorical variables, due to normality. For comparisons between two independent groups, the Student's *t*-test was used for normally distributed variables, while the Mann-Whitney *U* test was applied for non-normally distributed data. Categorical variables were analyzed using Pearson's Chi-square test or Fisher's exact test, as appropriate based on expected cell counts. Additionally, multivariate logistic regression analysis was conducted to identify the risk factors that had the greatest impact on scar development. Odds ratios (OR) and 95% confidence intervals for each variable were calculated. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Out of the 699 patients followed for UTIs, 530 were female (75.8%). The median age of the patients was 36 months, with girls being significantly older than boys (p<0.001). The median age at the first UTI among all patients was 12 months, and boys tended to have their first UTI at a younger age compared to girls (p<0.001). Remarkably, only 23.0% of girls (122 patients) had their first UTI before the age of 6 months. The distribution of age at first UTI by gender is shown in the Table 1.

Table 1: Distribution of age at first UTI by gender

	Girls (n: 530, 75.8%)	***Boys (n: 169, 24.2%)***	***p-value***	***Total (n=699)***
Age (months)	60 (1-204)	9 (1-168)	<0.001	36 (1-204)
Age at first UTI (month)	18 (1-180)	6 (1-168)	<0.001	12 (1-180)
Age at first UTI				
0-6 months	122 (23%)	81 (47.9%)	<0.001	203 (29%)
6-12 months	98 (18.5%)	43 (25.4%)	0.050	141 (20.2%)
12-24 months	58 (10.9%)	20 (11.8%)	0.749	78 (11.2%)
2-5 years	159 (30%)	20 (11.8%)	<0.001	179 (25.6%)
>5 years	93 (17.5%)	5 (3%)	<0.001	98 (14%)

UTI: Urinary tract infection

Fever was the most common symptom and seen in 58.9% of patients (n= 412). Loss of appetite was found in 58.4% (n= 408), dysuria in 46.9% (n= 328), and abdominal pain in 41.1% (n= 287). Other symptoms were vomiting (24.3%), pollakuria (19.3%), and diarrhea (3.1%). All patients had pyuria. Leukocyte esterase (LE) was positive in 90.8% of the patients, nitrite in 26.0%, while bacteria were seen in only 4.1% in microscopic examination.

The association between the degree of fever and laboratory findings was assessed to determine whether higher fever levels correlated with more pronounced changes in inflammatory or infection-related markers (Table 2). LE was positive in 93.2% of patients with fever ≥*38°C* compared to those with <*38°C* (p=0.01). WBC levels are significantly higher in patients with fever ≥*38°C* compared to those with <*38°C* (respectively 12000 vs 7300, p<0.001). Among patients with fever ≥38°C, 88% had elevated Hs-CRP levels, compared to only 28% in those with fever <38°C (p<0.001). Similarly, while the vast majority of patients with lower fever (<38°C) had CRP levels ≤6 mg/L (89.3%), this proportion was markedly lower (42.1%) in those with higher fever (≥38°C) (p<0.001). Furthermore, moderate CRP elevation (6-20 mg/L) was more common in the high-fever group (38.5% vs. 9.2%), and markedly elevated CRP levels (>20 mg/L) were significantly more frequent in patients with fever ≥38°C (19.4% vs. 1.5%) (all p < 0.001).

Table 2: The association between the degree of fever and laboratory findings

	Fever <38°C (n=287)	**Fever ≥38°C (n=412)**	**p-value**
WBC /mm^3	7300 (3760-26000)	12000 (4110-32900)	<0.001
CRP (mg/L)	2 (0.2-61)	8 (0-336)	<0.001
Patients with positive LE (n/%)	251 (87.5%)	384 (93.2%)	0.010
Patients with high Hs-CRP (mg/dl) (n/%)	7 (2.4%)	72 (17.4%)	<0.001
	Fever <38°C (n=261)	**Fever ≥38°C (n=330)**	**p-value**
Patients with CRP (0-6) (n/%)	233 (89.3%)	139 (42.1%)	<0.001
Patients with CRP (6-20) (n/%)	24 (9.2%)	127 (38.5%)	<0.001
Patients with CRP (>20) (n/%)	4 (1.5%)	64 (19.4%)	<0.001

WBC: White blood cell, CRP: C-reactive protein, LE: Leukocyte esterase

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Renal US was performed on all patients. Anomalies were detected in 15.7% of patients. Among patients with abnormal US findings, 49.6% had hydronephrosis, 27.5% had urinary stones, 10.0% had morphological or positional abnormalities and 12.8% had hypoplasia or dysplasia. VCUG was performed on 75.0% of the patients, revealing vesicoureteral reflux (VUR) in 21.0%. Among patients with VUR, 81.0% had low-grade reflux (grade I-III), 19.0% had high-grade reflux (grade IV, V). Additionally, VUR was bilateral in 40.5% of the patients and unilateral in 59.5%.

Of the 148 patients with VUR, 25.3% had spontaneous resolution. The median age of resolution was 28 months (17-156 months). Notably, 92.1% of the patients with spontaneous resolution had low-grade VUR (grades I-III).

DMSA scans were performed on 80% of the patients. Renal scarring was identified in 15.7% of the 559 patients who underwent the DMSA procedure. Renal scarring was observed in 52.7% of patients with ultrasonographic anomalies, compared to 13.1% of those without anomalies, demonstrating a statistically significant difference (p<0.001).

Analysis of factors influencing renal scarring revealed that the presence of fever, elevated CRP levels, abnormal ultrasonographic findings, and VUR were all significantly associated with an increased risk of scarring (Table 3).

Table 3: Factors affecting the presence of renal scarring in DMSA scans

	With Scar	Without Scar	p-value
Fever			
<38°C	35 14.7%)	203 (5.3%)	0.032
≥38°C	72 (23%)	246 (77%)	
CRP (mg/L)			
0-6	51 (16.2%)[a]	264 (83.8%)[a]	<0.001
6-20	25 (21.2)[b]	93 (78.8%)[b]	
>20	22(42.3%)[a,b]	30 (57.7%)[a,b]	
US			
Normal	61 (13.1%)	405 (86.9%)	<0.001
Abnormal	49(52.7%)	44 (47.3%)	
VCUG			
Normal	34 (10.5%)	290 (89.5%)	<0.001
Abnormal	66 (46.8%)	75 (53.2%)	
VUR grade			
I-II-III	43 (38.1%)	70 (61.9%)	<0.001
IV-V	23 (82%)	5 (18%)	
VCUG grade			
Normal	34 (10.5%)	290 (89.5%)	<0.001
I-II-III	43 (38.1%)	70 (61.9%)	

CRP: C-reactive protein, US: Ultrasonography, VCUG: Voiding cystourethrography, VUR: vesicoureteral reflux
a: The difference between the patient group with CRP levels of 0-6 and the patient group with CRP levels greater than 20 is statistically significant (p<0.001).
b: The difference between the patient group with CRP levels of 6-20 and the group with CRP levels greater than 20 is also statistically significant (p<0.005).

Table 4: Risk factors that affect scar development: Multivariate logistic regression analysis

	Odds ratio	95% confidence interval		Wald	p-value
		Lower limit	Upper limit		
Fever	2.02	1.03	3.96	4.25	0,039
Abnormalities in US	4.16	2.03	8.48	15.33	<0,001
CRP>6	1.26	0.66	2.41	0.51	0,475
VUR grade I-III	5.35	2.95	9.71	30.49	<0,001
VUR grade IV-V	10.85	3.33	35.30	15.78	<0,001
Recurrent UTI	6.60	2.37	18.32	13.12	<0,001

US: ultrasonography, VUR: Vesicoureteral reflux, UTI: urinary tract infection

A multivariate logistic regression analysis revealed that the most significant factor affecting scar development was the grade of VUR. It was found that the scarring increased 5.35 times (95% Confidence Interval: 2.952-9.713, p<0.001) in the grade I-III group and 10.85 times (95% Confidence Interval: 3.338-35.308, p<0.001) in the grade IV, V group compared to the group without VUR The other factors that most increase the risk of scar formation were recurrence of infection, abnormality in US and high fever (Table 4).

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A total of 1066 urine cultures were screened from 699 patients. *E. coli* was found to be the most frequently grown microorganism with a rate of 82.6%. Distribution of microorganisms was shown in Figure 1.

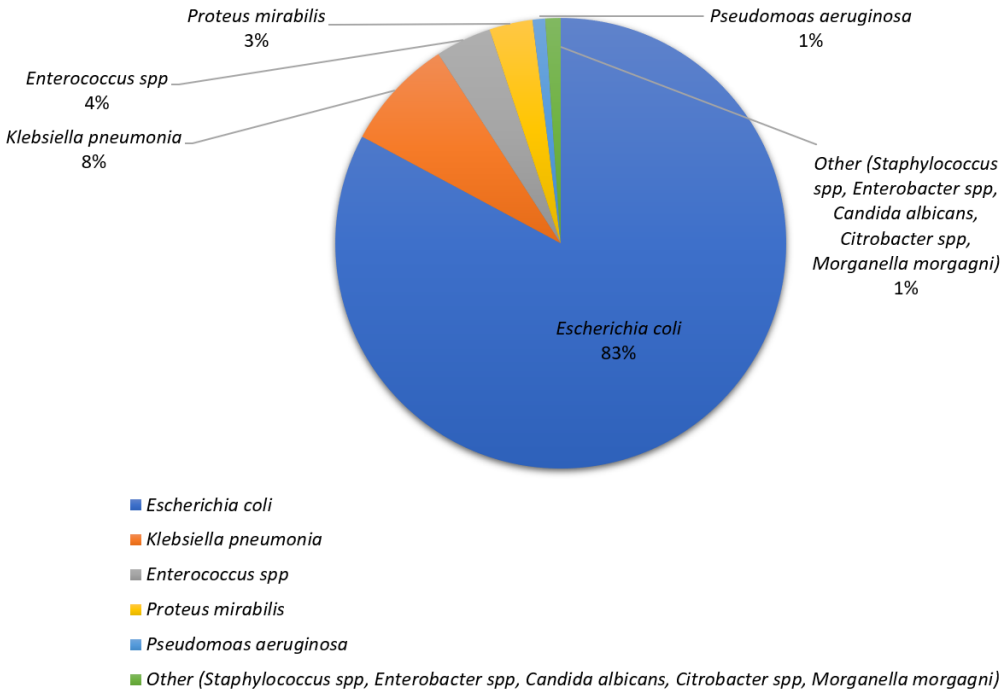


Figure 1: Distribution of microorganisms causing UTIs

Imipenem and meropenem resistance was determined as 3.9% in patients with all of the ESBL (+) bacteria. The difference was not statistically significant when compared to those with ESBL (-). Resistance to aminoglycoside antibiotics, including amikacin and gentamicin, was not significantly higher in ESBL (+) bacteria compared to ESBL (-) ($p>0.05$). The resistance to ciprofloxacin in ESBL (-) bacteria was recorded at 7.5%, whereas it rose to 28% in ESBL (+) ones ($p<0.001$). However, there was no significant difference in resistance to piperacillin-tazobactam between ESBL (+) and ESBL (-) bacteria ($p=0.23$) (Figure 2).

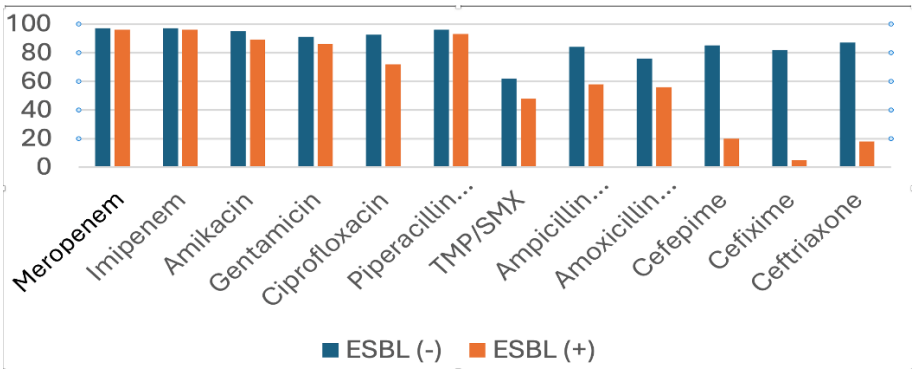


Figure 2: Antibiotic susceptibility rates for ESBL (+) and ESBL (-) bacteria

Antibiotic susceptibilities of microorganisms causing UTI are shown in Table 5 and 6. Analysis of antibiotic susceptibility trends revealed a significant increase in *E. coli* susceptibility to trimethoprim-sulfamethoxazole (TMP-SMX) from 47.1% to 62.1%, and to amoxicillin-clavulanate from 67.8% to 81.5% between 2007-2010 and 2010-2012 ($p<0.001$). Similarly significant increase in *Klebsiella pneumonia* susceptibility to amoxicillin-clavulanate between 2007-2010 and 2010-2012 (51.6.% to 90.6%, $p<0.001$). No significant differences were observed for other antibiotics in the rest of the microorganisms.

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Table 5: Antibiotic susceptibility of microorganisms

	E-coli	*Klebsiella pneumonia*	*Enterococcus spp*	*Proteus mirabilis*	*Pseudomonas aeruginosa*	*Staphylococcus spp.*	*Enterobacter spp.*	*Citrobacter spp*	*Morganella morgagni*
TMP-SMX	54.4%	51.8%	38.9%	51.5%	30.0%	50.0%	0.0%	0.0%	0.0%
Ampicillin/Sulbactam	81.5%	80.7%	71.1%	93.8%	33.3%	-	0.0%	100.0%	50.0%
Amoxicillin/Clavulanate	74.5%	76.2%	-	83.9%	16.7%	-	0.0%	100.0%	0.0%
Nitrofurantoin	87.2%	66.7%	66.7%	80.0%	-	-	-	-	-
Cefepime	82.3%	80.0%	-	84.8%	50.0%	-	33.3%	50.0%	50.0%
Cefixime	79.3%	79.7%	-	87.0%	50.0%	-	0.0%	50.0%	0.0%
Cefuroxime	78.1%	50.0%	-	75.0%	-	-	-	-	-
Azithromycin	-	-	100.0%	-	-	80.0%	-	-	-
Ceftriaxone	82.1%	79.8%	45.5%	84.8%	50.0%	-	33.3%	50.0%	50.0%
Ceftazidime	53.8%	100.0%	-	-	66.7%	-	0.0%	-	-
Cefoperazone	93.7%	91.7%	-	93.5%	80.0%	-	66.7%	100.0%	50.0%
Ciprofloxacin	91.1%	90.6%	73.0%	93.9%	77.8%	100.0%	50.0%	100.0%	50.0%
Amikacin	94.7%	92.9%	-	96.9%	77.8%	-	100.0%	50.0%	50.0%
Gentamicin	91.0%	87.1%	50.0%	89.7%	70.0%	50.0%	100.0%	100.0%	50.0%
Meropenem	95.8%	95.3%	-	100.0%	70.0%	-	100.0%	100.0%	50.0%
Imipenem	95.7%	95.2%	-	100.0%	70.0%	-	100.0%	100.0%	50.0%
Piperacillin/Tazobactam	95.4%	96.4%	-	90.0%	90.0%	-	100.0%	100.0%	50.0%
Penicillin	-	-	60.6%	-	-	40.0%	-	-	-
Erythromycin	-	-	35.7%	-	-	100.0%	-	-	-
Vancomycin	-	-	91.4%	-	-	80.0%	-	-	-
Teicoplanin	-	-	91.4%	-	-	100.0%	-	-	-

Table 6: Distribution of UTI microorganisms based on antibiotic susceptibility in the periods of 2007-2010 and 2010-2012

	E. coli		***Klebsiella pneumonia***		***Enterococcus spp***		***Proteus mirabilis***		***Pseudomonas aeruginosa***		***Staphylococcus spp.***	
	2007-2010	2010-2012	2007-2010	2010-2012	2007-2010	2010-2012	2007-2010	2010-2012	2007-2010	2010-2012	2007-2010	2010-2012
TMP-SMX	47.1%	62.1%	46.7%	54.7%	33.3%	41.7%	50%	53.3%	25%	33.3%	0%	100%
Ampicillin/Sulbactam	78.1%	85%	76.7%	83%	66.7%	75%	94.4%	92.9%	50%	25%	-	-
Amoxicillin/Clavulanate	67.8%	81.5%	51.6%	90.6%	-	-	82.4%	85.7%	33.3%	0%	-	-
Nitrofurantoin	76.9%	92.3%	50%	75.5%	-	66.7%	100%	66.7%	-	-	-	-
Cefepime	83.1%	81.5%	74.2%	83.3%	-	-	88.9%	80%	75%	33.3%	-	-
Cefixime	83%	77.5%	75%	80.4%	-	-	100%	75%	100%	33.3%	-	-
Cefuroxime	87.5%	50%	50%	48%	-	-	100%	0%	-	-	-	-
Azithromycin	-	-	-	-	100%	100%	-	-	-	-	66.7%	100%
Ceftriaxone	82.6%	81.6%	74.2%	83%	50%	40%	88.9%	80%	75%	33.3%	-	-
Ceftazidime	66.7%	25%	-	100%	-	-	-	-	100%	50%	-	-
Cefoperazone	92.4%	95%	90.3%	92.5%	-	-	94.1%	92.9%	100%	66.7%	-	-
Ciprofloxacin	90.1%	92.2%	87.1%	92.6%	72.2%	73.7%	100%	86.7%	75%	80%	100%	100%
Amikacin	93.1%	96.5%	90.3%	94.4%	-	-	94.4%	%100	75%	80%	-	
Gentamicin	88.3%	93.9%	83.9%	88.9%	58.8%	42.9%	87.5%	92.3%	75%	66.7%	0%	100%
Meropenem	94.2%	97.4%	93.5%	96.3%	-	-	100%	100%	75%	66.7%	-	-
Imipenem	94.2%	97.4%	93.5%	96.2%	-	-	100%	100%	75%	66.7%	-	-
Piperacillin/Tazobactam	94%	96.9%	93.5%	98.1%	-	-	93.8%	85.7%	100%	83.3%	-	-
Penicillin	-	-	-	-	71.4%	52.6%	-	-	-	-	33.3%	50%
Erythromycin	-	-	-	-	61.5%	13.3%	-	-	-	-	100%	100%
Vancomycin	-	-	-	-	93.3%	90%	-	-	-	-	66.7%	100%
Teicoplanin	-	-	-	-	93.3%	90%	-	-	-	-	100%	100%

TMP-SMZ: Trimethoprim-sulfamethoxazole.

Recurrent UTIs were diagnosed in 63.8% (n=442) of patients. Among them, 66.3% experienced fewer than three recurrences annually, 32.4% had three to six, and 1.4% had more than six. Recurrences occurred within six months in 55.2% of cases, between six and twelve months in 33.8%, and after twelve months in 11.0%. Recurrence of UTI was found in 79.7% and 66.2% of patients with and without VUR and the likelihood of UTI recurrence increased with the severity of VUR. UTI recurrence was observed in 73.4% of patients with ultrasound-detected anomalies versus 62.0% without anomalies (p=0.02). Among patients with renal scars on

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DMSA, only 8.2% had no recurrence. Recurrence rates were significantly higher in those with scars (91.2%) compared to those without (72.5%) (p<0.001).

During follow-up, proteinuria was detected in 3.4% (n=24), hypertension in 0.7% (n=5), and elevated creatinine in 0.7% (n=5) of patients. Proteinuria, elevated creatinine, and hypertension were significantly more frequent in patients with VUR or renal scarring (p<0.001). All patients with hypertension and elevated creatinine had recurrent UTIs and scarring. Recurrent UTIs were also significantly associated with increased proteinuria (p=0.013).

DISCUSSION

This study provides valuable insights about UTIs in children, by not only evaluating infection rates but also exploring underlying etiological factors and antibiotic susceptibility patterns. Moreover, it critically assesses the key determinants of renal scarring in a large pediatric cohort over five-year follow-up period.

UTIs are one of the most common bacterial infections in childhood. Before age seven, approximately 8.0% of girls and 2.0% of boys experience at least one UTI.[21] Incidence in the first year is 0.7% for girls and 2.7% for boys, with UTIs more common in girls thereafter.[22] In our study, 75.8% of UTI patients were girls and 24.2% boys. Boys most frequently had their first UTI within six months, while in girls it occurred mostly between ages 2-5 (30%). This aligns with literature showing higher UTI rates in boys during infancy, and increased prevalence in girls after age two, likely due to neonatal foreskin colonization in boys and shorter urethra and the development of voiding dysfunction during toilet training in girls.

Although it has been shown that UTIs recur in 30-40% of children [15,16], a higher rate of recurrence was detected in our study (63.8%). The elevated recurrence rate is likely due to our nephrology department serving as a referral center, where the majority of patients are referred specifically for recurrent UTIs.

Our findings indicate that UTIs predominantly recur within the first year, with the highest recurrence rate (55.1%) in the initial six months. Beyond this period, recurrence rates decline to approximately one-fifth. Therefore, the decision to continue prophylaxis after the first year should be carefully individualized based on each patient's risk factors and recurrence history. These results are consistent with existing literature that most recurrences occur within 12 months of the initial infection.[15,16]

Imaging methods are primarily used in the management and follow-up of UTI rather than its diagnosis. In our study, 15.7% of patients had anomalies on US, while VUR was detected in 21.2% (148 patients) of those who underwent VCUG. VUR was found in 40.7% (22 patients) of patients with hydronephrosis detected on US. However, these patients constitute only 14.8% of all reflux cases. This suggests that while the presence of hydronephrosis on US may indicate VUR, its absence does not exclude VUR.

In our study, the anomaly detected on US, the presence of VUR, and the increase in its grade were predictors of scar development. The most influential factor on scar development was the grade of VUR. Similarly, in the literature, it was found that the incidence of scarring was higher in children with VUR than in those without.[23-25] Additionally, it is widely recognized that recurrent UTIs play a pivotal role in renal scar formation.[17] Our research aligns with the literature, revealing that patients with recurrent UTIs-especially those with more than 3 recurrences-face a dramatically elevated risk of developing renal scars compared to those without recurrent UTIs.

In recent years, the rise of antibiotic resistance has posed significant challenges in treatment. Our study revealed a high rate of *E. coli* resistance to TMP/SMX, reaching 45.6%, likely due to its widespread use in prophylactic regimens. However, a statistically significant decline in resistance was observed over time, decreasing from 52.9% to 37.9%. This trend may reflect a shift in clinical practice toward reduced use of TMP/SMX, with broader-spectrum agents such as cefixime being more frequently preferred in UTI prophylaxis or being more selective in the patients who will receive prophylaxis in recent years.

Resistance of *E. coli* to amoxicillin-clavulanate and ampicillin-sulbactam was found to be 25% and 18.5%, respectively. A statistically significant decline in amoxicillin-clavulanate resistance was observed in *E. coli* and *Klebsiella* isolates, possibly due to its limited use in empirical treatment of gram-negative infections and UTIs in our clinic. Conversely, cefixime resistance increased from 17.0% to 22.5%, although this change was not statistically significant. Therefore, cefixime remains a viable option for oral treatment of community-acquired UTIs.

The overall amikacin resistance in *E. coli* was 5.3%, while gentamicin resistance was 9%. Additionally, no increase in resistance to aminoglycosides was noted over the years. Furthermore, carbapenem resistance in *E. coli* was approximately 4%, with no noticeable increase in resistance over time. Ayata et al. evaluated antibiotic resistance in *E. coli* from 1995 to 1996 and found TMP/SMX resistance to be similar to our study at 57.1%.[26] However, they reported higher resistance rates for ampicillin sulbactam and amoxicillin clavulanate at 59.2% and 42.3%, respectively. Aminoglycoside resistance in their study was similarly detected at 10% or below. In a study published by Çetin et al. in 2006, resistance rates for TMP/SMX, ampicillin sulbactam,

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and amoxicillin clavulanate were found to be higher than our findings, at 82%, 63%, and 55%, respectively.[27] Additionally, a previous study comparing resistance patterns between 2000 and 2006 identified a statistically significant increase in imipenem resistance for *E. coli*, from 0% to 9%, which contrasts with our findings.

The antibiotic susceptibility of gram-negative bacilli differs over time, and the prevalence of ESBL producing species rises.[6,20] Indeed, the prevalence of ESBL-producing UTIs in children and adults has increased to 7.4% in North America, 18.8% in Europe, 27.7% in South Asia, and 60% in India according to the recent literatüre.[28-31] In our study, the prevalence of ESBL (+) bacteria was identified as 2.4%. We observed that ESBL (+) bacteria exhibited slightly higher resistance to amikacin (11% vs. 4.2%) which was not statistically significant but a marked and significantly higher resistance to ciprofloxacin (28% vs 7.5%) compared to ESBL (-) ones. Piperacillin-tazobactam exhibited one of the lowest resistance patterns among ESBL (+) bacteria and showed minimal resistance difference compared to ESBL (-) bacteria, underscoring its potential as a valuable therapeutic option. Similarly, imipenem and meropenem, both with resistance rates of 4% in ESBL (+) bacteria were effective options. Nevertheless, the use of these broad-spectrum antibiotics should be approached with caution to prevent the emergence of further resistance.

In a study conducted by Bours et al., the resistance to ciprofloxacin in ESBL (+) bacteria was found to be high (62%).[32] Grandesso et al. reported that all ESBL (+) microorganisms were sensitive to imipenem and meropenem, with 95% sensitivity to amikacin which aligns with our findings.[33] Interestingly, despite the low resistance to piperacillin-tazobactam reported in our study, they found a significantly higher resistance rate of 40%.[33] The higher levels of ciprofloxacin resistance observed in ESBL-positive microorganisms at our center represent an important finding that warrants further investigation through prospective studies. Since there is resistance to many antibiotics, it would be wise to reduce the risk factors that increase the growth of ESBL (+) microorganisms as much as possible, paying attention to rational antibiotic applications. The risk group should be well determined and treatment should be planned by taking into consideration the hospital's own antibiotic resistance.

To prevent antibiotic resistance, unnecessary use should be avoided. When indicated, the narrowest effective spectrum should be chosen, with appropriate dosing and treatment duration. Antibiotic prophylaxis is commonly employed to prevent recurrent UTIs, especially in children with VUR and urinary tract anomalies. However, its effectiveness and routine use remain controversial. Concerns regarding the contribution of prophylaxis to antibiotic resistance have been raised. [34] The RIVUR trial's extended follow-up demonstrated that prophylaxis with TMP-SMX significantly reduces UTI recurrence risk, particularly in patients with high-grade VUR, but does not significantly prevent renal scarring over the long term.[35] Similarly, the PRIVENT trial showed limited benefit of prophylaxis in preventing recurrent UTIs in the general pediatric population, alongside concerns for resistance development.[36] In our study, only 5.9% of patients did not receive prophylaxis. Recurrence rates were higher among patients on prophylaxis (66% vs. 19%), likely reflecting a selection bias, as prophylaxis is typically reserved for those with severe or recurrent infections. Furthermore, high-grade VUR remains a strong independent risk factor for recurrence regardless of prophylaxis use. No significant difference in renal scarring was observed between prophylaxis and non-prophylaxis groups, aligning with existing literature and underscoring the need for individualized prophylactic decisions.

The AAP guideline, examining the relationship between recurrent UTI and prophylaxis in VUR, reports no statistically significant difference in the number of recurrences between the groups receiving and not receiving prophylaxis in those without reflux and those with grade I-IV reflux.[19] Our findings also suggest that antibiotic prophylaxis does not effectively prevent UTI recurrence and highlight the need to address underlying risk factors. Given its widespread use, reducing unnecessary and prolonged prophylaxis is essential to minimize antibiotic resistance and side effects. Current evidence supports a more selective approach to prophylaxis.

The retrospective nature of the study is a limitation of the study. In addition, as a single center study from a tertiary health center, the data may not be sufficient to generalize the antibiotic susceptibility profile. Moreover, we did not perform molecular tests to correlate the findings with antibiotic resistance patterns. In our study, it was shown that the presence of anomalies on US, the presence of VUR and its increase in severity, and recurrence of UTI are risk factors for scar development, and the presence of scars is also associated with long-term complications. In addition, the higher level of ciprofloxacin resistance observed in ESBL (+) bacteria at our center represent an important finding. In order to prevent the development of antibiotic resistance, it is recommended to choose the narrowest possible spectrum antibiotic, taking into account local and global susceptibility test results. This data is important for the continued use of this antibiotic in empirical treatment and warrants further investigation through prospective studies. Since there is resistance to many antibiotics, it would be wise to reduce the risk

factors that increase the growth of ESBL (+) bacteria as much as possible.

Conflict of interest: There is no conflict of interest between the authors.

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