Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20250103 • *J Pediatr Inf 2025;19(1):e13-e23*

Insights into Extended-Spectrum Beta-Lactamase Producing Bacteria Related Urinary Tract Infections in Children: A Single Center Experience

Çocuklarda Genişlemiş Spektrumlu Beta-Laktamaz Üreten Bakteriler ile İlişkili Üriner Sistem Enfeksiyonlarına Dair Bulgular: Tek Merkez Deneyimi

Burcu Bursal[1](İD), Abdurrahman Avar Özdemir[2](İD), Neval Topal[2](İD), Rıdvan Bal[2](İD), Şule Çelik[3](İD)

[1] *Clinic of Pediatric Infectious Diseases, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye*
[2] *Clinic of Pediatrics, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye*
[3] *Clinic of Microbiology, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye*

Cite this article as: Bursal B, Özdemir AA, Topal N, Bal R, Çelik Ş. Insights into extended-spectrum beta-lactamase producing bacteria related urinary tract infections in children: A single center experience. J Pediatr Inf 2025;19(1):e13-e23.

Abstract

Objective: Urinary tract infections (UTIs) are prevalent bacterial diseases frequently observed in primary care settings. The prevailing approach in managing children with suspected UTI is to administer an antibiotic treatment without delay, pending the findings of culture and sensitivity tests. This study aimed to examine the risk variables associated with antibiotic resistance in children who have UTIs caused by bacteria that produce extended-spectrum beta-lactamase (ESBL).

Material and Methods: This study retrospectively analyzed a cohort of 162 pediatric patients who were diagnosed with community-acquired UTIs over the period from June 2021 to March 2024. ESBL-producing bacteria were the causative microorganisms in 92 patients, while non-ESBL-producing bacteria were the causative microorganisms in 70 cases. There were no notable disparities between the two groups in terms of age, gender, and first presentation.

Results: *Escherichia coli* was the most common cause of the cases, accounting for 86.4% of them, with 41.4% of those instances being caused by ESBL-producing strains. Out of the *Klebsiella* species, 53.2% were found to produce ESBL. Antibiotic resistance rates of ESBL-producing bacteria were 43.5% for trimethoprim/sulfamethoxazole, 5.6% for nitrofurantoin, 55.4% for quinolones, and 12.3% for aminoglycosides. Resistance rates for non-ESBL-producing bacteria were 31.9% for trimethoprim/sulfamethoxazole, 3% for nitrofurantoin, 17.4% for quinolones, and 9.7% for aminoglycosides. Blood in the urine, high white blood cell counts, and elevated procalcitonin and C-reactive protein levels were all

Öz

Giriş: İdrar yolu enfeksiyonları (İYE), birinci basamak sağlık hizmetlerinde sıklıkla görülen yaygın bakteriyel hastalıklardır. İdrar yolu enfeksiyonu şüphesi olan çocukların yönetiminde hakim yaklaşım, kültür ve duyarlılık testlerinin sonuçlarını beklemeksizin antibiyotik tedavisi uygulamaktır. Bu çalışmada, genişlemiş spektrumlu beta-laktamaz (GSBL) üreten bakterilerin neden olduğu İYE geçiren çocuklarda antibiyotik direnci ile ilişkili risk değişkenlerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada, Haziran 2021 ile Mart 2024 tarihleri arasında toplum kaynaklı İYE tanısı almış 162 çocuk hastadan oluşan bir kohort, retrospektif olarak analiz edilmiştir. Genişlemiş spektrumlu beta-laktamaz üreten bakteriler 92 hastada etken mikroorganizma iken, GSBL üretmeyen bakteriler 70 vakada etken mikroorganizma olmuştur. İki grup arasında yaş, cinsiyet ve ilk başvuru açısından kayda değer bir farklılık bulunmamıştır.

Bulgular: *Escherichia coli*, vakaların %86.4'ünü oluşturarak en yaygın neden olmuştur ve bu vakaların %41.4'üne GSBL üreten suşlar neden olmuştur. *Klebsiella* türlerinin %53.2'sinin GSBL ürettiği tespit edilmiştir. Genişlemiş spektrumlu beta-laktamaz üreten bakterilerin antibiyotik direnç oranları trimetoprim/sülfametoksazol için %43.5, nitrofurantoin için %5.6, kinolonlar için %55.4 ve aminoglikozidler için %12.3'tür. Genişlemiş spektrumlu beta-laktamaz üretmeyen bakteriler için direnç oranları trimetoprim/sülfametoksazol için %31.9, nitrofurantoin için %3, kinolonlar için %17.4 ve aminoglikozidler için %9.7'dir. İdrarda kan görülmesi, yüksek beyaz kan hücresi sayısı ve yüksek prokalsitonin ve C-reak-

Correspondence Address/Yazışma Adresi

Burcu Bursal

Clinic of Pediatric Infectious Diseases,
Kanuni Sultan Süleyman Training and Research Hospital,
İstanbul, Türkiye

E-mail: burcubursal@hotmail.com

Received: 05.08.2024 **Accepted:** 14.10.2024
Available Online Date: 12.03.2025

significant risk factors for ESBL-producing bacteria. Amikacin was used as the final treatment in 40% of the cases with ESBL-producing bacteria.

Conclusion: Identifying the risk factors for ESBL-producing bacteria is crucial for developing new management strategies for UTIs. In patients with underlying risk factors, it is important to target the treatment to the specific pathogen and prevent recurrence. To ensure effective treatment and lower the likelihood of generating resistant bacterial strains, empirical antibiotic selection should be based on local resistance patterns. Amikacin used once a day can be beneficial as a first treatment before the results of culture susceptibility are known, and it helps with the treatment of patients who are hospitalized. Additionally, we believe that prospective observational studies are needed on this topic.

Keywords: Antimicrobial resistance, ESBL-producing bacteria, risk factors

tif protein seviyeleri GSBL üreten bakterileri için önemli risk faktörleridir. Genişlemiş spektrumlu beta-laktamaz üreten bakterilerin bulunduğu vakaların %40'ında nihai tedavi olarak amikasin kullanılmıştır.

Sonuç: Genişlemiş spektrumlu beta-laktamaz üreten bakteriler için risk faktörlerinin belirlenmesi, İYE'ler için yeni yönetim stratejilerinin geliştirilmesi açısından çok önemlidir. Altta yatan risk faktörleri olan hastalarda, tedaviyi spesifik patojene hedeflemek ve nüksü önlemek önemlidir. Etkili tedaviyi sağlamak ve dirençli bakteri suşları üretme olasılığını azaltmak için, ampirik antibiyotik seçimi yerel direnç modellerine dayanmalıdır. Günde bir kez kullanılan amikasin, kültür duyarlılığı sonuçları bilinmeden önce ilk tedavi olarak faydalı olabilir ve hastaneye yatırılan hastaların tedavisine yardımcı olur. Ayrıca, bu konuda ileriye dönük gözlemsel çalışmalara ihtiyaç olduğuna inanıyoruz.

Anahtar Kelimeler: Antimikrobiyal direnç, GSBL üreten bakteriler, risk faktörleri

Introduction

Urinary tract infections (UTIs) are common and important clinical concern in children. It ranks as the second most prevalent category of illnesses in kids, following upper respiratory tract infections (1). UTIs during childhood can lead to serious health issues, including hypertension and chronic renal failure. These complications arise due to ongoing kidney damage that occurs when UTIs are not promptly diagnosed and treated in early infancy (2). Children frequently have UTIs, with different incidence rates depending on their age and sex. Girls are more susceptible due to their shorter urethral length, which facilitates bacterial ascent (3). Uncircumcised boys under one year old also exhibit a slightly higher risk (4). Approximately 80% of pediatric UTIs are attributed to the primary pathogenic bacterium, *Escherichia coli* (5). In the treatment of UTI, cephalosporins are typically suggested as the initial choice for both oral and injectable medications (6). Community-acquired UTIs have been developing resistance to commonly used antibiotics over the years. Several types of gram-negative bacteria, such as *Enterobacteriaceae* spp., *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*, often produce extended-spectrum beta-lactamase (ESBL) enzymes. These enzymes make the bacteria resistant to beta-lactam antibiotics, including third and fourth-generation cephalosporins and monobactams. ESBL-producing *Enterobacteriaceae* spp., which are acquired in both community and hospital settings, are widespread globally (7). Recent research conducted post-2020 indicate a substantial rise in the prevalence of ESBL-producing bacteria worldwide. Specifically, *E. coli* and *Klebsiella pneumoniae* from the *Enterobacteriaceae* family have shown significant rises in ESBL production rates. The study Antimicrobial Resistance Surveillance in Europe 2023 indicates that the prevalence of ESBL-producing *E. coli* may reach up to 50%, while *K. pneumoniae* may reach 70% in Türkiye, highlighting the significant antimicrobial resistance burden in the region (8).

The efficacy of standard empirical antibiotic regimens frequently wanes against ESBL-producing strains, leading to treatment failure. Due to this, antibiotic therapy must be adjusted gradually based on the findings of culture and susceptibility. UTIs caused by ESBL-producing bacteria have a greater likelihood of leading to serious consequences such as sepsis, kidney scarring, and extended hospital stays, compared to UTIs caused by non-ESBL-producing bacteria. The purpose of this study was to investigate the risk factors and antibiotic resistance in pediatric patients who have been diagnosed with community-acquired UTIs caused by bacteria that produce ESBL.

Materials and Methods

Electronic medical records of children hospitalized with UTIs in the pediatric infectious disease department's inpatient wards were reviewed in this retrospective analysis. The study encompassed individuals with community-acquired UTIs who were admitted to the hospital between June 2021 and March 2024. The participants ranged in age from 1 month to 18 years. Data collected from the medical records database encompassed demographics (age, sex), past medical history (UTI episodes, hospitalizations), prior antibiotic use (prophylaxis and within one month of admission), diagnostic tests [blood culture, laboratory results like complete blood count, urinalysis, C-reactive protein (CRP), abdominal ultrasound, voiding cystourethrogram (VCUG)], and initial and definitive antimicrobial therapy and duration of therapy.

The investigation specifically targeted UTIs caused by strains of *E. coli* and *Klebsiella* spp. After collecting the data, patients were divided into two groups: ESBL-producing and non-ESBL-producing, based on the results of culture susceptibility tests. Subsequently, a comparison study was performed to identify potential risk variables linked to UTIs caused by ESBL-producing bacteria.

Leukocytosis is characterized by a leukocyte count that exceeds the normal value based on age, while a positive CRP is defined as a level greater than 5 mg/L (9).

Urine samples for culture were collected either through clean-catch midstream voiding or bladder catheterization, depending on the patient's age and level of toilet training. The diagnosis of UTI was confirmed based on microbiological criteria. Patients having a catheterized specimen were diagnosed with severe bacteriuria if there was a proliferation of ≥5 x 10^4 CFU/mL. However, in the case of clean-catch midstream specimens, the presence of a single uropathogen at a concentration of at least 1 x 10^5 CFU/mL is considered as confirmation of a UTI. In the case of individuals with suspected febrile UTI, which is characterized by a fever of 38°C or higher, the presence of a single uropathogen identified using catheterized or clean-catch specimens at specific thresholds was thought to be diagnostic.

The urine samples were placed on culture plates containing 5% blood agar and eosin-methylene blue agar for microbiological examination. After incubating overnight at a temperature of 35°C, the bacterial growth was assessed. A threshold of ≥5 x 10^4 CFU/mL was used to determine if the presence of uropathogens was significant.

For bacterial identification, classical microbiological techniques and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) were employed. MALDI-TOF MS is an advanced method that uses laser energy to ionize bacterial proteins, allowing rapid and precise identification by analyzing their mass-to-charge ratios. This technique has become a standard in clinical microbiology laboratories for its efficiency and accuracy in identifying a wide range of bacterial species based on unique protein fingerprints (10).

Antibiotic susceptibility testing and ESBL detection were performed using the VITEK® 2 automated system (Biomerieux), following the standards set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The VITEK® 2 system automates the interpretation of susceptibility results by measuring bacterial growth responses to various antibiotics, providing reliable data for clinical treatment decisions. EUCAST guidelines ensure that the testing is standardized across laboratories, enhancing the comparability and accuracy of the results (11).

The statistics utilized in defining the data included average, standard deviation, median, minimum, maximum, frequency, and ratio values. The variables were assessed for their distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was employed to analyze non-normally distributed independent quantitative data. The chi-square test was employed for the analysis of qualitative-independent data, and the Fisher's exact test was used when the requirements for the chi-square test were not met. The degree of influence was analyzed using both univariate and multivariate logistic regression. The analysis was conducted using SPSS 28.0.

This study was conducted following ethical standards, and ethics approval was obtained from the local ethics committee (2024.04.79) prior to initiation.

Results

A three-year investigation was carried out, focusing on pediatric patients who were admitted to the hospital with fever and had confirmed positive urine cultures. The study cohort comprised 162 individuals, who were separated into two groups: 92 patients with ESBL-producing bacteria and 70 patients with non-ESBL-producing bacteria. The ESBL group had a median age of 11 months (with an interquartile range of 36.1 ± 44.8), while the non-ESBL group had a median age of 5.5 months (with an interquartile range of 26.6 ± 34.8). There was a numerical difference; however, statistical significance was not observed between the two groups (p= 0.131). Out of the entire patient population, 71 individuals (43.2%) were males. Among them, 40 individuals (43.5%) belonged to the ESBL group, whereas 31 individuals (44.3%) belonged to the non-ESBL group.

The bacterium *E. coli* was shown to be the most common cause of UTIs, present in 86.4% of all patients, while *Klebsiella* spp. was responsible for the remaining 13.6%. *E. coli* was the most commonly identified pathogen in both the group of bacteria producing ESBL (n= 79) and the group of bacteria not producing ESBL (n= 61). Table 1 provides a thorough comparison of the clinical and demographic characteristics of the ESBL and non-ESBL groups.

There were no notable disparities detected between the ESBL-producing and non-ESBL-producing groups in terms of sex, average age, risk factors, presenting symptoms, and antibiotic usage prior to admission (Table 1). Urinalysis results showed that 27.2% of the samples tested positive for nitrite, 52.5% had bacteria in the urine, and 93.2% had white blood cells (WBC) in the urine. Leukocyte count in the urine was considerably elevated in the ESBL group as compared to the non-ESBL group (p< 0.05). There were no notable distinctions observed between the groups in terms of leukocyte esterase positive, nitrite positivity, erythrocyte count, bacterial presence in urine, urine density, urine pH, and proteinuria (p> 0.05) (Table 2).

The ESBL group had a significantly greater prevalence of renal ultrasound abnormalities compared to the non-ESBL group (p< 0.05) (Table 2). In addition, the ESBL group had a significantly greater proportion of patients who received ceftazidime, gentamicin, cefuroxime, piperacillin-tazobactam, amoxicillin-clavulanic acid, ceftriaxone, cefepime, amikacin, cefoxitin, and cefotaxime compared to the non-ESBL group (p< 0.05). Ceftriaxone resistance was seen in 90% of the ESBL isolates, and all of them exhibited consistent resistance to cefuroxime, ceftazidime, cefotaxime, and ampicillin. non-ESBL isolates exhibited higher susceptibility to the majority

Table 1. The distribution of demographic characteristics, underlying risk factors, and initial symptoms between the ESBL-producing and non-ESBL-producing groups

		ESBL (-)		ESBL (+)			
		Mean ± SD/n-%	Median	Mean ± SD/n-%	Median	p	
Age (month)		26.6 ± 34.8	5.5	36.1 ± 44.8	11.0	0.131	m
Sex	Boy	31 44.3%		40 43.5%		0.918	X^2
	Girl	39 55.7%		52 56.5%			
Underlying risk factors	(-)	62 88.6%		78 84.8%		0.486	X^2
	(+)	8 11.4%		14 15.2%			
Circumcision	(-)	26 100.0%		33 91.7%		0.258	X^2
	(+)	0 0.0%		3 8.3%			
Initial Symptoms							
Fever		68 97.1%		89 96.7%		0.883	X^2
Vomiting		43 61.4%		56 60.9%		0.942	X^2
Dysuria		13 18.6%		23 25.0%		0.330	X^2
Diarrhea		4 5.7%		11 12.0%		0.175	X^2
Blood in urine		1 1.4%		15 16.3%		**0.002**	X^2
Urine in continence		2 2.9%		7 7.6%		0.191	X^2
Frequent urination		14 20.0%		29 31.5%		0.100	X^2
Loss of appetite		31 44.3%		46 50.0%		0.471	X^2
Abdominal pain		16 22.9%		25 27.2%		0.531	X^2
Antibiotic usage Before admission	(-)	64 91.4%		76 82.6%		0.105	X^2
	(+)	6 8.6%		16 17.4%			

[m] Mann-Whitney U test, X^2 chi-square test (Fischer test).
ESBL: Extended spectrum beta lactamase, SD: Standard deviation.

of tested antimicrobials, with the exception of ampicillin (with a resistance rate of 70.1%) and cefuroxime (with a resistance rate of 66.7%). Table 3 provides a comprehensive breakdown of the frequency of resistance to specific antibiotics in both groups.

Nitrofurantoin exhibited the highest efficacy against ESBL-producing bacteria, with a resistance rate of 5.6% and was followed by meropenem (6.1%), ertapenem (11.5%), and amikacin (12.3%). Within the ESBL-producing group, the rates of resistance were notably high for trimethoprim-sulfamethoxazole (TMP-SMX) (43.5%) and quinolones (55.4%). Among the group that did not produce ESBL, the rates of resistance were 31.9% for TMP-SMX, 3% for nitrofurantoin, 17.4% for quinolones, and 0% for aminoglycosides. The antibiotics most frequently recommended based on empirical treatment were ceftriaxone (87%), cefotaxime (62%), piperacillin-tazobactam (10%), and meropenem (3%).

Treatment was adjusted based on antimicrobial susceptibility results in ESBL patients, while other patients continued with their initial antimicrobials (Table 4). All patients, except three with bacteremia, experienced fever resolution within 48 hours, even before changing antibiotics.

The ESBL group had significantly elevated levels of WBC count, neutrophils, procalcitonin, and CRP in comparison to the non-ESBL group ($p< 0.05$). The ESBL group had a substantially longer hospital stay ($p< 0.05$) compared to the other group. There was no significant difference in recurrence rates between the groups ($p> 0.05$) (Table 4). The univariate model identified several significant variables for differentiating between ESBL and non-ESBL patients, including the presence of hematuria, WBC count, neutrophil count, procalcitonin levels, and CRP levels ($p< 0.05$). The leukocyte count in the urine did not have a significant predictive value in this model ($p> 0.05$). In the multivariate model, the occurrence of blood in the urine was found to be a significant predictor, although the CRP value was not found to be important ($p< 0.05$) (Table 5).

Discussion

Antibiotic resistance in UTIs is becoming more widespread worldwide, presenting serious public health difficulties. The increasing prevalence of antibiotic resistance in children's UTIs is particularly alarming, with *E. coli*, a prominent generator of ESBL, leading the way. UTIs that are accompanied by fever are commonly treated with third-generation cephalosporins.

Table 2. The distribution of laboratory findings and pathogens between the ESBL-producing and non-ESBL-producing groups

		ESBL (-)				ESBL (+)					
		Mean ± SD/n-%			Median	Mean ± SD/n-%			Median	p	
Leukocyte count in urine		202.8	±	449.6	54.0	285.5	±	388.2	120.5	**0.007**	m
Leukocyte esterase	(-)	6		8.6%		5		5.4%		0.432	X^2
	(+)	64		91.4%		87		94.6%			
Nitrit	(-)	51		72.9%		67		72.8%		0.996	X^2
	(+)	19		27.1%		25		27.2%			
Erythrocyte count in urine		26.0	±	61.9	9.5	31.6	±	56.4	14.0	0.240	m
Bacteria	(-)	36		51.4%		41		44.6%		0.386	X^2
	(+)	34		48.6%		51		55.4%			
Urine density		1014.1	±	7.6	1013.5	1014.3	±	7.8	1014.0	0.953	m
Urine pH		6.4	±	0.5	6.5	6.5	±	0.4	6.5	0.556	m
Protein in urine	(-)	57		81.4%		75		81.5%		0.988	X^2
	(+)	13		18.6%		17		18.5%			
Pathogen in Urine											
Escherichia coli		61		87.1%		79		85.9%		0.815	X^2
Klebsiella spp.		9		12.9%		13		14.1%			
Blood culture	(-)	68		97.1%		87		94.6%		0.424	X^2
	(+)	2		2.9%		5		5.4%			
Lumbar puncture	(-)	68		97.1%		90		97.8%		1.000	X^2
	(+)	2		2.9%		2		2.2%			
RUSG	Normal	53		75.7%		47		51.1%		**0.001**	X^2
	Abnormal	17		24.3%		45		48.9%			

[m] Mann-Whitney U test, [X²] chi-square test (Fischer test).
ESBL: Extended spectrum beta lactamase, SD: Standard deviation, RUSG: Renal ultrasonography.

Nevertheless, their efficacy has diminished since ESBL-producing *E. coli* bacteria have developed resistance against them. Multiple studies have examined the prevalence of antibiotic resistance in bacteria obtained from UTIs acquired in the community among children in Türkiye (12-14). This study specifically examined the resistance and symptoms caused by ESBL-producing and non-ESBL-producing groups of *E. coli* and *Klebsiella* spp., which are the most prevalent bacteria in community-acquired pediatric UTIs.

The risk factor identified in our study, using logistic regression analysis, was the presence of hematuria, elevated WBC count, increased neutrophil count, elevated procalcitonin levels, and elevated CRP levels. Multiple studies have repeatedly demonstrated that the occurrence of blood in the urine, known as hematuria, is a significant indicator of ESBL-positive infections. This symptom is often associated with highly resistant bacterial strains, such as ESBL-producing pathogens. It can provide insight into the underlying pathophysiology and severity of the infection. Hernández et al. have found that the presence of blood in the urine is a strong indicator of ESBL-producing *E. coli* bacteremia (15). It has been observed that patients with hematuria have a greater likelihood of ESBL infections when compared to people who do not have blood in their urine. Even after conducting a multivariate analysis, these results remained significant, indicating a strong connection with ESBL positive. A study conducted by Edding et al. has established a connection between hematuria and ESBL infections (16). Their research suggests that the inclusion of hematuria, together with other clinical indicators, might greatly enhance the accuracy of prediction models in identifying patients with ESBL-positive infections.

An elevated WBC count, a common indicator of infection and inflammation, reveals the body's immune response to bacterial invasion. Elevated WBC counts have been commonly found in the context of ESBL infections and are thought to be important predictors. Edding et al. have demonstrated that one of the clinical traits used to create a risk score for ESBL-positive UTI prediction is an elevated WBC count (16). According to the study, those with higher WBC counts had a higher probability of having bacterial infections that produced ESBL, suggesting a strong immune response to a serious infection. Goodman et al. have looked at risk scores and decision trees to figure out how to predict

Table 3. The frequency of resistance to selected antibiotics in both groups

		ESBL (-)		ESBL (+)		p	
		n	%	n	%		
Ceftazidime	Resistant	0	0.0%	81	100.0%	**0.000**	X^2
	Sensitive	33	100.0%	0	0.0%		
Gentamicin	Resistant	1	1.5%	17	18.7%	**0.001**	X^2
	Sensitive	65	98.5%	74	81.3%		
TMP/SMX	Resistant	22	31.9%	40	43.5%	0.135	X^2
	Sensitive	47	68.1%	52	56.5%		
Cefixime	Resistant	1	2.9%	89	100.0%	**0.000**	X^2
	Sensitive	34	97.1%	0	0.0%		
Ertapenem	Resistant	0	0.0%	9	11.5%	0.197	X^2
	Sensitive	20	100.0%	69	88.5%		
Pip/Tazo	Resistant	6	13.6%	35	39.8%	**0.002**	X^2
	Sensitive	38	86.4%	53	60.2%		
Amoxicillin and clavulanate	Resistant	19	34.5%	70	78.7%	**0.000**	X^2
	Sensitive	36	65.5%	19	21.3%		
Ceftriaxone	Resistant	1	1.5%	83	90.2%	**0.000**	X^2
	Sensitive	65	98.5%	9	9.8%		
Cefuroxime axetil	Resistant	5	7.4%	87	100.0%	**0.000**	X^2
	Sensitive	63	92.6%	0	0.0%		
Cefuroxime	Resistant	30	66.7%	89	100.0%	**0.000**	X^2
	Sensitive	15	33.3%	0	0.0%		
Ampicillin	Resistant	47	70.1%	92	100.0%	**0.000**	X^2
	Sensitive	20	29.9%	0	0.0%		
Nitrofurantoin	Resistant	2	3.0%	5	5.6%	0.452	X^2
	Sensitive	64	97.0%	85	94.4%		
Ciprofloxacin	Resistant	8	17.4%	41	55.4%	**0.000**	X^2
	Sensitive	38	82.6%	33	44.6%		
Fosfomycin	Resistant	1	10.0%	0	0.0%	0.400	X^2
	Sensitive	9	90.0%	15	100.0%		
Cefepime	Resistant	1	12.5%	36	80.0%	**0.000**	X^2
	Sensitive	7	87.5%	9	20.0%		
Amikacin	Resistant	0	0.0%	9	12.3%	**0.028**	X^2
	Sensitive	36	100.0%	64	87.7%		
Cefoxitin	Resistant	1	2.4%	36	54.5%	**0.000**	X^2
	Sensitive	40	97.6%	30	45.5%		
Meropenem	Resistant	0	0.0%	2	6.1%	1.000	X^2
	Sensitive	3	100.0%	31	93.9%		
Cefotaxime	Resistant	0	0.0%	15	100.0%	**0.000**	X^2
	Sensitive	28	100.0%	0	0.0%		

[m] Mann-Whitney U test, X^2 chi-square test (Fischer test).
ESBL: Extended spectrum beta lactamase, TMP/SMX: Trimethoprim/sulfamethoxazole, Pip/Tazo: Piperacillin/tazobactam.

Table 4. Initial and final treatment and laboratory findings

		ESBL (-)			ESBL (+)			p	
		Mean ± SD/n-%		Median	Mean ± SD/n-%		Median		
Initial treatment	Meropenem	0	0.0%		3	3.3%		0.259	X^2
	Cefogen	36	51.4%		26	28.3%		**0.003**	X^2
	Ceftriaxone	33	47.1%		54	58.7%		0.144	X^2
	Pip-Tazo	1	1.4%		9	9.8%		**0.029**	X^2
Final treatment	Amikacin	2	2.9%		43	46.7%		**0.000**	X^2
	Ertapenem	0	0.0%		3	3.3%		0.259	X^2
	Gentamicin	1	1.4%		8	8.7%		**0.045**	X^2
	Meropenem	0	0.0%		8	8.7%		**0.011**	X^2
	Cefogen	35	50.0%		2	2.2%		**0.000**	X^2
	Ceftriaxone	30	42.9%		5	5.4%		**0.000**	X^2
	Pip-Tazo	2	2.9%		23	25.0%		**0.000**	X^2
Hemogram WBC		12942.6	± 5698.9	11900.0	15621.0	± 7490.8	15110.0	**0.016**	m
HGB		10.7	± 1.4	11.0	10.9	± 1.6	11.0	0.710	m
HTC		32.9	± 4.4	33.3	32.8	± 4.3	33.0	0.634	m
PLT		381.5	± 155.7	364.0	382.0	± 118.7	371.0	0.625	m
MPV		8.4	± 1.0	8.3	8.4	± 0.9	8.3	0.676	m
Neutrophil		7333.7	± 5140.8	6435.0	10250.7	± 6796.7	9130.0	**0.006**	m
Lymphocyte		4207.1	± 2431.8	3700.0	3687.4	± 2001.1	3300.0	0.272	m
Prokalcitonin		1.7	± 3.3	0.4	3.3	± 4.3	2.0	**0.000**	m
CRP		63.9	± 73.0	33.8	122.4	± 110.8	95.0	**0.000**	m
Urea		22.9	± 13.1	20.6	25.0	± 20.2	22.0	0.503	m
BUN		8.6	± 3.3	8.2	10.2	± 5.3	9.0	0.083	m
Creatinine		0.3	± 0.1	0.3	0.3	± 0.2	0.3	0.239	m
Duration of hospitalization (day)		5.8	± 1.9	5.5	7.6	± 1.8	7.0	**0.000**	m
Recurrent Hospitalization	(-)	51	72.9%		56	60.9%		0.110	X^2
	(+)	19	27.1%		36	39.1%			

[m] Mann-Whitney U test, [X2] chi-square test (Fischer test).
SD: Standard deviation, Pip/Tazo: Piperacillin/tazobactam, WBC: White blood cells, HGB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, MPV: Mean platelet volume, CRP: C-reactive protein, BUN: Blood urea nitrogen.

Table 5. Logistic regression analysis

	Univariate Model			Multivariate Model		
	OR	95% CI	p	OR	95% CI	p
Blood in urine	13.442	1.730-104.428	**0.013**	10.719	1.349-85.189	**0.025**
Leucoyte in urine	1.001	1.000-1.001	0.218			
Hemogram WBC	1.000	1.000-1.000	**0.016**			
Neutrophil	1.000	1.000-1.000	**0.004**			
Prokalcitonin	1.126	1.020-1.243	**0.019**			
CRP	1.007	1.003-1.011	**0.000**	1.007	1.002-1.011	**0.002**

Logistic regression (forward LR).
OR: Odds ratio, CI: Confidence interval, WBC: White blood cells, CRP: C-reactive protein.

ESBL bacteremia and found that a higher WBC count is a strong predictor in both (17). The risk score included several clinical indicators, with the WBC count being one of the main elements influencing the model's prediction ability.

Research has also indicated that having had a UTI in the past, being young, currently using antimicrobial medications, and having underlying conditions such kidney abnormalities and bacteremia increase the risk of developing infections caused by ESBL-producing organisms.

Children with UTIs exhibit a variety of clinical symptoms, which might vary depending on their age, the site of infection, and the severity of the infection (18). Empirical antibiotic treatment is commonly started following a thorough assessment that includes the patient's symptoms, physical examination, and urine test findings to diagnose a UTI. It is important to consider local resistance patterns of the uropathogens when choosing antibiotics for empirical therapy (19). It is crucial to select the correct antibiotic for treating a UTI caused by ESBL-producing bacteria. This decision should be made based on the specific types of bacteria present in the local area and their susceptibility to different antibiotics.

The length of the course of treatment should balance maximizing therapeutic efficacy with reducing the risk of medication resistance developing. The management of UTIs is challenged by the increasing prevalence of ESBL-producing bacteria. Using second- and third-generation cephalosporins as first-line therapies for acute pyelonephritis may cause irreversible kidney damage because ESBL-producing bacteria are resistant to these medications. Appropriate treatment may be delayed until urine culture findings are available. Treatment choices for a confirmed UTI caused by ESBL-producing bacteria are mostly restricted to aminoglycosides and carbapenems, which have resistance rates of 12% and 6%, respectively. Nitrofurantoin is chosen for treating cystitis and for UTI prophylaxis because to its low resistance rates, as oral cephalosporins are ineffective against ESBL strains and TMP-SMX has substantial resistance (43%). Because of its low resistance, nitrofurantoin is a viable substitute for treating lower UTIs in older kids (20). Despite its efficient urine excretion, nitrofurantoin should not be utilized for upper UTIs because it may not reach appropriate tissue concentrations in the renal parenchyma (21).

Ampicillin resistance was found in both ESBL and non-ESBL strains in our patient cohorts, with rates of 70% and 100%, respectively. This suggests that most urinary pathogens in our area would not be sufficiently covered by ampicillin used as a monotherapy for empirical treatment of suspected UTIs.

Our cohorts' ESBL and non-ESBL strains showed consistent susceptibility to gentamicin (81%-98%) and amikacin (87%-100%). Polat et al. have evaluated 53 children with amikacin-sensitive ESBL UTIs, aged 3 to 12 years (22). They have found that a once-daily injectable amikacin regimen over a six-day period resulted in a 96% response rate. Given the dangers of ototoxicity and nephrotoxicity, particularly in patients with impaired renal function, amikacin should only be recommended with caution in patients with amikacin-sensitive infections who cannot be treated with intravenous antibiotics. We adjusted antibiotherapy in our study based on resistance results. After culture results emerged, we changed the initial treatment for ESBL-producing patients (46%), switching to monotherapy with amikacin. We observed no major adverse effects, including clinically evident ototoxicity or significant changes in serum creatinine levels, when we administered amikacin to patients with normal renal function at the prescribed dose and duration.

Park et al. have established the efficacy of aminoglycosides in treating UTIs caused by ESBL-producing bacteria in both children and adults, based on clinical and microbiological evidence (23). Additional evidence further supports the effectiveness of combining aminoglycoside therapy in treating pediatric patients with feverish UTIs caused by bacteria that produce ESBL enzymes (24). Furthermore, an Australian study has suggested gentamicin monotherapy as a safe and effective way to treat UTIs in kids aged one to twelve that need parenteral medication (25). In contrast, our study found that children with ESBL-producing bacteria had an 18% gentamicin resistance rate at all age groups. Since amikacin has a lower resistance rate of 12%, it is a better appropriate aminoglycoside for treating children in our group.

Based on the study by Cho et al., the safety and efficacy of amikacin in treating UTIs due to ESBL-producing *E. coli* were demonstrated effectively. In this study, eight patients with nine episodes of non-bacteremic ESBL-EC UTIs were treated with outpatient parenteral antibiotic therapy (OPAT) using amikacin, as they could not be hospitalized for carbapenem treatment. Symptomatic and laboratory improvements were observed in all cases following amikacin therapy, achieving clinical and microbiological cures in 88.9% of cases. Furthermore, Cho et al. have highlighted that amikacin is well-tolerated, with no significant nephrotoxicity or ototoxicity reported. This suggests that amikacin OPAT is a feasible alternative for managing non-bacteremic UTIs caused by ESBL-EC, particularly in outpatient settings where carbapenem treatment is impractical or costly (26).

Additionally, Ipekci et al. have shown that amikacin demonstrates significant efficacy in treating lower UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae* in adult outpatients. In this study, patients received intramuscular injections of amikacin at 15 mg/kg/day for 10 days. Clinical success, defined as symptom resolution, was achieved in 97.2% of cases, while bacteriological success was observed in

91.7% by day three, 97.1% at the end of treatment, and 94.1% at follow-up 7-10 days later.

The study also reported minimal nephrotoxicity, occurring in only one patient, indicating that amikacin was generally well-tolerated. This suggests that amikacin is an effective and safe alternative for managing ESBL-related lower UTIs, especially for cases where carbapenem use may not be practical or cost-effective (27).

Many children in Türkiye who are suspected of having lower UTIs are first treated with oral cephalosporins or co-trimoxazole. Nonetheless, reports have indicated that co-trimoxazole resistance rates can reach 40% in certain other nations (19). The resistance rates to co-trimoxazole that we found in our study were 43% and 31%, respectively. These results suggest that treating UTIs with this antibiotic as a monotherapy is not recommended.

The use of long-term prophylaxis should be limited due to the substantial risk of antibiotic resistance (28). The European Association of Urology, European Society of Pediatric Urology, and the Swedish and Italian Societies of Pediatric Nephrology suggest a more targeted approach, taking into account the patient's age, the degree of vesicoureteral reflux, and renal scarring (29,30).

To prevent recurring UTIs, it is important to manage constipation and discourage urine withholding practices in children who are already toilet-trained. Our study involved evaluating each patient for these concerns, administering medicine for constipation, and instructing patients and their families on appropriate urination practices. We advise performing a gentle and regular retraction and cleansing of the foreskin for boys who have not undergone circumcision. For instances of phimosis, topical corticosteroids were administered as needed, and the option of circumcision was presented following discussions with a pediatric surgeon and securing the consent of the family.

Our study has limitations. One of the main limitations of this study is the relatively small sample size, which may reduce the statistical power of the findings and limit the generalizability of the results. A small sample size may not capture the full spectrum of clinical presentations and outcomes seen in a larger, more diverse population. Additionally, with a larger cohort, there would be increased ability to detect subtler differences in response to treatment, as well as better insight into the variability of treatment outcomes. Future studies with a larger sample size are recommended to confirm these findings and provide a more robust basis for clinical guidelines. Additionally, the retrospective design limits our ability to control for potential confounding variables, and data from medical records may not capture the complete clinical picture. Our study population was confined to hospitalized patients, potentially introducing selection bias, as these patients often present with more severe symptoms that may not be representative of all children with UTIs. Thus, our findings may not be generalizable to outpatients or those with less severe infections. Third, we could not ascertain whether patients were on prophylactic antibiotics before hospitalization or whether they underwent imaging studies such as VCUG or dimercaptosuccinic acid scans. Another limitation is the lack of long-term follow-up data, which prevents us from evaluating the extended effects and potential recurrence rates of ESBL-related UTIs following amikacin therapy. Long-term follow-up would allow for a more comprehensive understanding of treatment durability and patient outcomes, such as recurrence rates and potential late-onset side effects. Including such data in future studies would provide clinicians with a clearer picture of the long-term safety and efficacy of amikacin in pediatric patients.

Conclusion

In conclusion, our study highlights the challenges in managing UTIs in pediatric inpatients, especially those caused by ESBL-producing *E. coli*. The findings emphasize the need for empirical antibiotic selection based on local bacterial prevalence and resistance patterns rather than universal guidelines. While initial insights into once-daily dosing of amikacin are promising, further research through randomized controlled trials with larger cohorts is necessary to define its safety and effectiveness conclusively. Addressing the study's limitations and incorporating long-term follow-up and comprehensive evaluations will be essential. Improving UTI management in children will require a multifaceted approach, including robust clinical evidence, patient education, and careful monitoring to optimize outcomes and prevent recurrence.

Additionally, our study supports several clinical recommendations. Amikacin serves as an effective and safe alternative for treating UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae*, especially in outpatient settings where carbapenem therapy may be impractical. Regular patient monitoring for nephrotoxicity is recommended, particularly for patients undergoing prolonged treatment. The use of OPAT for amikacin administration is also encouraged in cases where hospitalization is not feasible, reducing healthcare costs and nosocomial infection risks. Furthermore, incorporating amikacin into an antibiotic stewardship strategy can help preserve last-resort antibiotics like carbapenems for more severe infections, contributing to sustainable antimicrobial management.

Ethics Committe Approval: This study was obtained from University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Scientific Research Ethics Committee (Decision no: 79, Date: 24.04.2024).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - BB, AAÖ; Design - BB; Supervision - BB, NT; Resource - BB, ŞÇ, RB; Data Collection and/or processing - BB, RB, NT; Analysis and/or interpretation - BB, AAÖ, NT; Literature search - BB, AAÖ; Writing - BB; Critical review - BB, AAÖ.

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.

References

1. *Hansson S, Jodal U. Urinary tract infection. In: Avner ED, Harmon WE, Niaudet P, (eds). Pediatric Nephrology. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2004:1007-27*
2. *Chang SL, Shortliffe LD. Pediatric urinary tract infections. Pediatr Clin N Am 2006;53:379-400 https://doi.org/10.1016/j.pcl.2006.02.011*
3. *Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: A meta-analysis. Pediatr Infect Dis J 2008;27:302-8 https://doi.org/10.1097/INF.0b013e31815e4122*
4. *Singh-Grewal D, Macdessi J, Craig J. Circumcision for the prevention of urinary tract infection in boys: A systematic review of randomised trials and observational studies. Arch Dis Child 2005;90:853-58 https://doi.org/10.1136/adc.2004.049353*
5. *Sitthisarunkul N, Uthairat M, Dissaneewate P, McNeil E, Vachvanichsanong P. Characteristics and findings of childhood urinary tract infection in the last decade. Urol Int 2019;102:456-61 https://doi.org/10.1159/000497443*
6. *Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev 2014;2014(7):CD003772. https://doi.org/10.1002/14651858.CD003772.pub4*
7. *Ben-Ami R, Rodríguez-Baño J, Arslan H, Pitout JD, Quentin C, Calbo ES, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. Clin Infect Dis 2009;49:682-690 https://doi.org/10.1086/604713*
8. *European Centre for Disease Prevention and Control. Available from: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2023-2021-data*
9. *Pesce MA. Reference ranges for laboratory tests and procedures. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, (eds). Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders, 2007:2943-54*
10. *Patel R. Matrix-assisted laser desorption ionization-time of flight mass spectrometry in clinical microbiology. Clin Infect Dis 2013;57(4):564-72. https://doi.org/10.1093/cid/cit247*
11. *Reller LB, Weinstein M, Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: A review of general principles and contemporary practices. Clin Infect Dis 2009;49:1749-55. https://doi.org/10.1086/647952*
12. *Mir S, Erdoğan H, Güler S, Şengül GN, Koyu A, Aydemir Ş. Resistance to antibiotics of aegeon region in urinary ınfection in pediatric patients. Ege Tıp Derg 2002;41:207-10*
13. *Yüksel S, Oztürk B, Kavaz A, Özçakar ZB, Acar B, Güriz H, et al. Antibiotic resistance of urinary tract pathogens and evaluation of empirical treatment in Turkish children with urinary tract infections. Int J Antimicrob Agents 2006;28:413-6 https://doi.org/10.1016/j.ijantimicag.2006.08.009*
14. *Samancı S, Çelik M, Köşker M. Çocukluk çağı idrar yolu enfeksiyonlarında antibiyotik direnci; tek merkez deneyimi. Türk Pediatr Arş 2020;55:386-92 https://doi.org/10.14744/TurkPediatriArs.2020.22309*
15. *García-Vázquez E, Canteras M, Hernandez-Torres A. Predictive factors of ESBL versus non-ESBL Escherichia coli bacteraemia and influence of resistance on the mortality of the patients. Med Clin (Barc) 2010;136:56-60*
16. *Edding S, Cadeliña J, Leaño DR, Panaligan M, Hufano MC. Clinical risk score model for predicting extended spectrum beta lactamase (ESBL)-positive urinary tract ınfection among hospitalized filipino patients: A retrospective single-center study. Open Forum Infect Dis 2020;7(1):820-1. https://doi.org/10.1093/ofid/ofaa439.1846*
17. *Goodman K, Lessler J, Harris A, Milstone A, Tamma P. A methodological comparison of risk scores versus decision trees for predicting drug-resistant infections: A case study using extended-spectrum beta-lactamase (ESBL) bacteremia. Infect Control Hosp Epidemiol 2019;40:400-7 https://doi.org/10.1017/ice.2019.17*
18. *Jantausch B, Kher K. Urinary tract infection. In: Kher KK, Schnaper HW, Makker SP, (eds). Clinical Pediatric Nephrology. 2nd ed. London: Informa Healthcare, 2006:553-73 https://doi.org/10.3109/9780203482308-44*
19. *Haller M, Brandis M, Berner R. Antibiotic resistance of urinary tract pathogens and rationale for empirical intravenous therapy. Pediatr Nephrol 2004;19:982-6 https://doi.org/10.1007/s00467-004-1528-7*
20. *Abelson Storby K, Osterlund A, Kahlmeter G. Antimicrobial resistance in Escherichia coli in urine samples from children and adults: A 12-year analysis. Acta Paediatr 2004;93:487-91 https://doi.org/10.1080/08035250410023034*
21. *Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. J Urol 2004;172:448-53 https://doi.org/10.1097/01.ju.0000130653.74548.d6*
22. *Polat M, Kara SS. Once-daily intramuscular amikacin for outpatient treatment of lower urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in children. Infect Drug Resist 2017;10:393-9 https://doi.org/10.2147/IDR.S148703*
23. *Park SH, Choi SM, Chang YK, Park SH, Kim YJ, Choi JK, et al. The efficacy of non-carbapenem antibiotics for the treatment of community-onset acute pyelonephritis due to extended-spectrum β-lactamase-producing Escherichia coli. J Antimicrob Chemother 2014;69:2848-56 https://doi.org/10.1093/jac/dku215*
24. *Han SB, Lee SC, Lee SY, Jeong DC, Kang JH. Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae. BMC Infect Dis 2015;15:1-8 https://doi.org/10.1186/s12879-015-1153-z*
25. *Carapetis JR, Jaquiery AL, Buttery JP, Curtis N, Cranswick NE, Garland SM, et al. Randomized, controlled trial comparing once daily and three times daily gentamicin in children with urinary tract infections. Pediatr Infect Dis J 2001;20:240-6 https://doi.org/10.1097/00006454-200103000-00004*
26. *Cho SY, Choi SM, Park SH, Lee DG, Choi JH, Yoo JH. Amikacin therapy for urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli. Korean J Intern Med 2016;31(1):156-61. https://doi.org/10.3904/kjim.2016.31.1.156*
27. *Ipekci T, Seyman D, Berk H, Celik O. Clinical and bacteriological efficacy of amikacin in the treatment of lower urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae. J Infect Chemother 2014;20(12):762-7. https://doi.org/10.1016/j.jiac.2014.08.007*

28. *Selekman RE, Shapiro DJ, Boscardin J, Williams G, Craig JC, Brandström P, et al. Uropathogen resistance and antibiotic prophylaxis: A meta-analysis. Pediatrics 2018;142(1):e20180119. https://doi.org/10.1542/peds.2018-0119*

29. *Stein R, Dogan HS, Hoebeke P, Kocvara R, Nijman RJM, Radmayr C, et al. European Association of Urology; European Society for Pediatric Urology. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol 2015;67:546-58 https://doi.org/10.1016/j.eururo.2014.11.007*

30. *Ammenti A, Cataldi L, Chimenz R, Fanos V, La Manna A, Materassi M, et al. Italian Society of Pediatric Nephrology. Febrile urinary tract infections in young children: Recommendations for the diagnosis, treatment and follow-up. Acta Paediatr 2012;101:451-7 https://doi.org/10.1111/j.1651-2227.2011.02549.x*