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Original Article

Resistance profiles of uropathogenic *E. coli*: ESBL and colistin in focus

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Abstract

Introduction: *Escherichia coli* is among the most common causes of urinary tract infections (UTIs), and the rise in extended-spectrum beta-lactamase (ESBL)-producing isolates is a growing concern because of increasingly limited treatment options. This study aimed to investigate the resistance profiles of ESBL-positive and -negative uropathogenic *E. coli* isolates to antibiotics used in treatment and colistin.

Methodology: Urine samples sent to the Central Laboratory of Istanbul University, Istanbul Faculty of Medicine, for routine examination between September 2023 and January 2024 were included in the study. The presence of ESBL and susceptibility to antibiotics other than colistin were determined by the Vitek2 (bioMérieux, France) automated system, and colistin susceptibility was determined by the reference broth microdilution method.

Results: Of the 80 patients with *E. coli*, 80% were female, and 20% were male; 32.5% were children, and 67.5% were adults. All *E. coli* isolates were susceptible to nitrofurantoin, ertapenem, and meropenem. 40% of the strains were ESBL-positive. In respect of multidrug-resistant bacteria, among ESBL-positive and-negative isolates, 12.5% and 2.1% were resistant to six, 28.1% and 8.3% to five, 34.4% and 6.25% to four, and 18.75% and 16.7% to three different antibiotic groups, respectively. Of 80 *E. coli* strains, 92.5% of which were sensitive to colistin, the MIC_{50} value was 0.5 mg/L, and the MIC_{90} value was 2 mg/L.

Conclusions: Although the colistin resistance rate and minimum inhibitory concentration (MIC) values are not high, it is important to monitor resistance when treating problematic infections with multiple resistance.

Key words: *E. coli;* ESBL; colistin; antimicrobial resistance.

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Introduction

UTIs are among the most common infectious diseases, affecting millions of individuals annually. Uropathogenic *Escherichia coli* (UPEC) is a primary causative agent of both complicated and uncomplicated UTIs. However, the emergence of various antibiotic resistance mechanisms and the increasing prevalence of antimicrobial resistance have rendered the treatment of UTIs progressively more challenging [1–4]. In the first global surveillance report on antimicrobial resistance published by the World Health Organization in 2014, *E. coli* was identified as one of the nine bacteria of international concern due to its resistance to commonly used antibacterial agents [5].

Currently, plasmids encoding various ESBLs—primarily targeting penicillins and cephalosporins, as well as carbapenemases have been identified and can be found in clinical UPEC isolates [3]. Bacteria that acquire these plasmids may become resistant not only to third-generation cephalosporins but also to other antibiotics, thereby developing multidrug-resistant bacteria (MDR) [3,6]. The increase in carbapenem resistance has led to the accelerated clinical use of polymyxins (colistin and polymyxin B), typically as part of combination therapies, as last-resort antimicrobial agents for treating MDR infections [7–9]. However, the increased use of colistin has subsequently resulted in the emergence of colistin-resistant Enterobacterales, including *Acinetobacter* spp., *E. coli*, and *K. pneumoniae* [10–12].

The establishment of antimicrobial stewardship programs is a key strategy in combating antimicrobial resistance. It is recommended that empirical treatment protocols for both community- and hospital-acquired infections be revised based on local, national, and international data on resistance. The enhancement of up-to-date epidemiological data regarding antibiotic resistance is crucial not only for guiding treatment strategies but also for early warning systems and infection control measures [13]. Therefore, awareness of local susceptibility patterns has gained increasing importance.

This study aims to investigate the resistance profiles of ESBL-positive and ESBL-negative UPEC isolates to antibiotics, including colistin, and to determine current data on antimicrobial resistance.

Materials and Methods

Sample Size and Selection of Strains

Urine samples submitted to the Central Laboratory of Istanbul University, Istanbul Faculty of Medicine, for routine examination between September 2023 and January 2024 were included in this study. A total of 80 *E. coli* strains, isolated from urine samples of patients with a preliminary diagnosis of infection UTI in which *E. coli* was considered the causative agent and identified using conventional methods, were analyzed. Only the first specimen obtained from each patient before the initiation of antibiotic therapy was included, while any subsequent samples were excluded from the analysis.

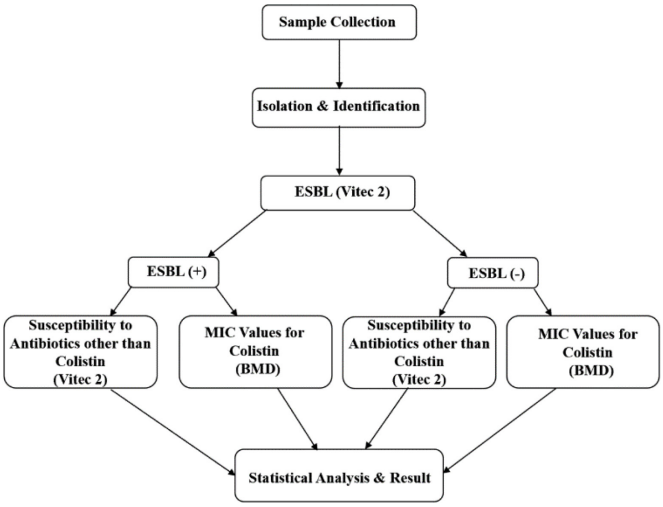
Determination of ESBL Presence and Susceptibility to Antibiotics Other Than Colistin

In our study, the presence of ESBL and susceptibility to antibiotics other than colistin were determined using the Vitek2 automated system. *E. coli* strains were categorized as susceptible or resistant based on the minimum inhibitory concentration (MIC) breakpoints defined for the tested antibiotics [14].

Determination of MIC Values for Colistin

The broth microdilution method (BMD) was employed to determine the MIC values for colistin. For this purpose, a bacterial suspension with turbidity equivalent to 0.5 McFarland standard (approximately 1 × 10^8 CFU/mL) was prepared from fresh bacterial cultures and subsequently diluted 1:20 to obtain a final bacterial concentration of 5 × 10^6 CFU/mL [10]. Two-fold serial dilutions of colistin, ranging from 0.0156 to 8 mg/L, were prepared in a microplate using the standardized bacterial suspension. *E. coli* NCTC 13846 (*mcr*-1 +) and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains. Following incubation at 35 ± 2 °C for 20 hours, the MIC was defined as the lowest concentration of the antibiotic at which no visible bacterial growth was observed [14,15]. The results were interpreted by EUCAST clinical breakpoints: isolates with MIC ≤ 2 mg/L were classified as susceptible, whereas those with MIC > 2 mg/L were considered resistant [14].

Figure 1. Methodological flowchart.



Statistical Analysis and Visualisation

The distribution of the data was assessed using the Shapiro-Wilk. Continuous variables included colistin MIC values. The Mann–Whitney U test was employed to compare the distributions of these continuous variables between two independent groups, particularly to assess differences in median MIC values between our dataset and previously published studies. A two-tailed *p* of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS v.27. Figures and graphs were generated using Python (v.3.11.0) and the Matplotlib (v.3.8.4) and Seaborn (v.0.13.2) libraries. The methodological flowchart is shown in Figure 1.

Figure 2. Demographic distribution of *E. coli* isolates.

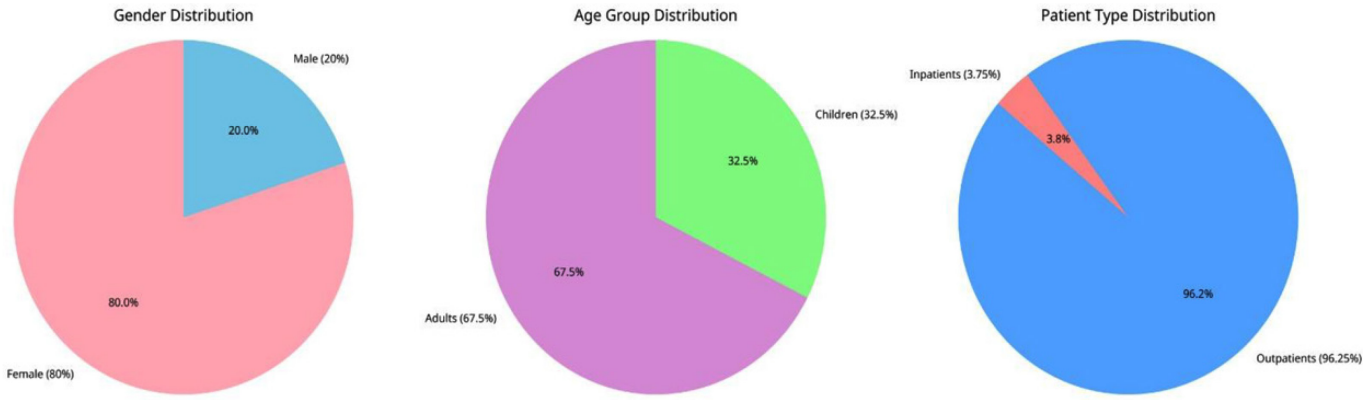
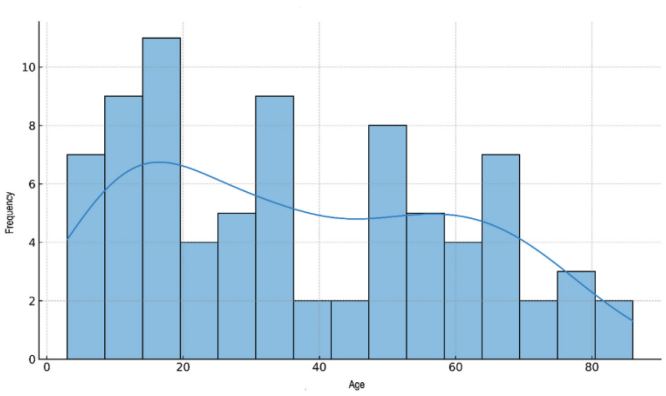


Figure 3. Age histogram of the patients.



Results

Demographic Characteristics of Patients

Of the samples cultured, 20 (25%) were sent from Paediatrics, 20 (25%) from Internal Medicine, 20 (25%) from Urology, 18 (22.5%) from Gynaecology, and 2 (2.5%) from Neurology. Of the 80 patients admitted from different clinical units and from whose urine *E. coli* was isolated, 77 (96.25%) were outpatients and three (3.75%) were inpatients; 64 (80%) were female, 16 (20%) were male, 26 (32.5%) were children, and 54 (67.5%) were adults, with an average age of 37.2 (Figure 2). The age range of paediatric patients was 3-17, while adult patients was 19-86 (Figure 3).

Susceptibility to Antibiotics Other Than Colistin and ESBL Results

All *E. coli* isolates were found to be susceptible to nitrofurantoin, ertapenem, and meropenem. 32 (40%) of the strains were found to be ESBL-positive. In strains that tested positive for ESBL and those that did not, resistance to ampicillin was found in 100% and 45.8% of cases; to cefixime in 100% and 8.3%; to ceftriaxone in 81.25% and 6.25%; to cefepime in 56.25% and 4.2%; to co-amoxiclav in 59.4% and 31.25%; to piperacillin-tazobactam in 28.1% and 18.75%; to co-trimoxazole in 68.75% and 29.2%; to ciprofloxacin in 56.25% and 20.8%; and to amikacin in 0% and 2.1% (Figure 4). In terms of MDR, 12.5% and 2.1% of ESBL-positive and -negative isolates were found to be resistant to six, 28.1% and 8.3% to five, 34.4% and 6.25% to four, and 18.75% and 16.7% to three different antibiotic groups, respectively (Table 1).

Table 1. Antibiotic groups and resistance percentages of all strains.

Class	Antibiotic tested	Resistant (%)
1	**β -Lactam**	
	Ampicillin	67.5%
2	**4th generation cephalosporins**	
	Cefepime	28.7%
3	**3rd generation cephalosporins**	
	Cefixime	30%
	Ceftriaxone	21.2%
4	**Carbapenemes**	
	Ertapenem	0%
	Meropenem	0%
5	**Polypeptide**	
	Colistin	7.5%
6	**Aminoglycosides**	
	Amikacin	2.1%
7	**Combination**	
	Amoxycillin/clavulanicacid	28.7%
	Trimethoprime/sulphametoxazole	45%
	Piperacillin-tazobactam	12.5%
8	**Quinolone**	
	Ciprofloxacin	35%
9	**Nitrofuran**	
	Nitrofurantoin	0%

MIC results of Colistin

According to the MIC values determined for colistin in 80 *E. coli* strains with BMD, 6 (7.5%) of all strains were found to be resistant. Three of the 6 resistant strains were ESBL-positive. Resistance to colistin was detected at a rate of 9.4% and 6.25% in ESBL-positive and -negative strains, respectively. In our study, the MIC values determined for colistin in positive and negative control strains were 4 mg/L for *E. coli* NCTC 13846 (*mcr*-1 +) and 0.5 mg/L for *P. aeruginosa* ATCC 27853, respectively. The numbers of colistin-susceptible and -resistant isolates, MIC distributions, and MIC_{50}-MIC_{90} values are shown in Table 2.

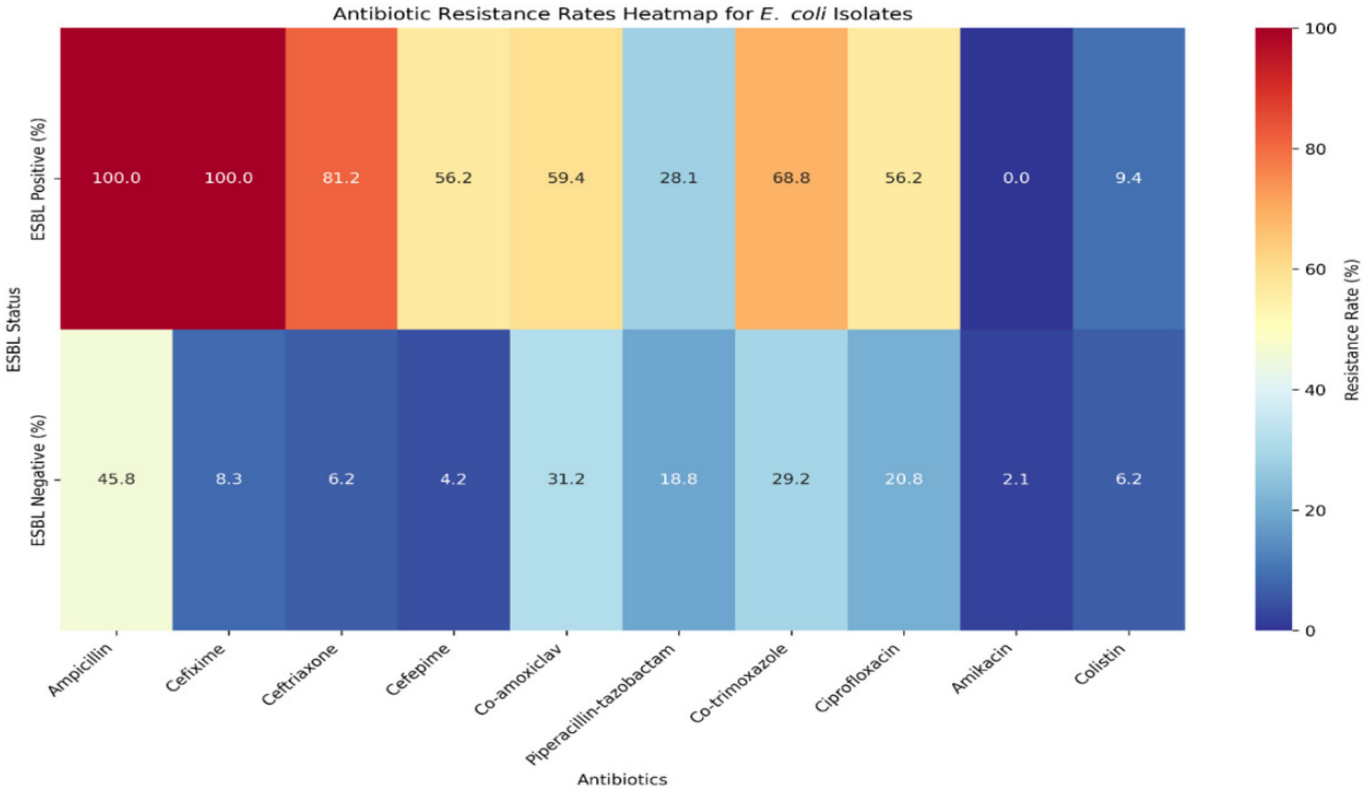
Discussion

UTIs rank among the most common infections requiring antibiotic treatment worldwide [16]. *E. coli* is responsible for approximately 75% of UTIs [1], and nearly half of these infections are known to be recurrent [17]. The European Association of Urology (EAU) guidelines recommend fosfomycin and nitrofurantoin as first-line treatment options for uncomplicated UTIs. Trimethoprim-sulfamethoxazole may be considered an alternative antibiotic if the known resistance rate of *E. coli* is below 20% [18,19]. However, the acquisition of resistance genes through horizontal gene transfer among microorganisms complicates the treatment of

Table 2. Colistin MIC distributions of strains.

			Susceptible			Resistant	MIC_{50}	MIC_{90}
Colistin MIC (mg/L)	0.125	0.25	0.5	1	2	4	0.5	2
Number of Strain (n)	3	15	31	13	12	6		
Total (n)			74 (92.5%)			6 (7.5%)		

Figure 4. Comparative heatmap of antibiotic resistance in ESBL-positive and –negative *E. coli*.



UTIs. Many members of the Enterobacterales producing ESBL can also develop resistance to other antimicrobial agents such as third-generation cephalosporins, aminoglycosides, trimethoprim, quinolones, and carbapenems [7–9,20–23]. In contrast, ESBL-negative *E. coli* strains generally display a lower resistance profile [3,6,20–23]. Consistent with this, in our study, most ESBL-positive strains were found to be resistant to penicillins, cephalosporins, fluoroquinolones, and combination antibiotic groups, while ESBL-negative strains exhibited a lower resistance profile. This resistance is usually caused by the action of β-lactamase enzymes produced by bacteria. These enzymes are usually carried by plasmids, which can lead to rapid spread of resistance mechanisms [3,6]. Antibiotic resistance rates vary across countries and populations [24-26], with contributing factors including educational level and socioeconomic status. An inverse relationship was generally found between education level and misuse of antibiotics. As education increases, the likelihood of misuse decreases. However, there are also regional differences. In Europe, higher education has been associated with some antibiotic misuse [26]. According to the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR), trimethoprim resistance among *E. coli* isolates from patients diagnosed with UTIs was reported as 31.9%, while resistance to nitrofurantoin was 11.7% [24].

In a study by Carter *et al.* [27], the antibiotic susceptibility of 199 *E. coli* isolates from UTI patients was examined, revealing resistance rates of 39.2% for ampicillin, 7.6% for co-amoxiclav, 9% for ciprofloxacin, 25.1% for trimethoprim, and 1% for nitrofurantoin. Muhammad *et al.* [22] collected 804 urine samples from patients suspected of having UTIs, of which 290 showed bacterial growth. Among the isolated strains, 68.9% were *E. coli*, 8.9% were *K. pneumoniae*, and 6.7% were *Staphylococcus aureus*. ESBL positivity was observed in 85.2% of the isolates, with 98.3% classified as MDR. Notably, 97% of the *E. coli* isolates were resistant to more than five antibiotics. In another study, Whelan *et al.* [28] analyzed the antibiotic susceptibilities of 57 UPEC isolates using the BMD, reporting resistance rates of 5.3% to nitrofurantoin, 22.8% to ciprofloxacin, and 38.6% to trimethoprim. Three strains (5.3%) were resistant to all three antibiotics, while 11 strains (19.3%) showed resistance to both ciprofloxacin and trimethoprim, highlighting the prevalence of MDR. These studies support the findings reported by the ESPAUR. Although there is no national surveillance program for

UTIs in our country, several studies have been conducted [20,21,23]. In a study by Süzük Yıldız *et al.* [20], of 509 isolates collected from various hospitals, 127 were identified as *E. coli* and 366 as *K. pneumoniae*. Antibiotic susceptibility testing using the BMD revealed resistance rates among *E. coli* isolates of 78.7% to ampicillin, 59.1% to cefotaxime, 56.7% to trimethoprim/sulfamethoxazole, 51.9% to ceftazidime, ciprofloxacin, and amoxicillin-clavulanate, 50.4% to cefepime, 38.6% to piperacillin-tazobactam, 28.3% to gentamicin, 25.2% to ertapenem, 17.3% to imipenem and meropenem, and 14.9% to amikacin. In the study by Avcıoğlu *et al.* [21], antibiotic susceptibility of 1466 *E. coli* isolates from urine samples was determined using the Vitek 2 automated system. Resistance rates were 81% for ampicillin, 46% for amoxicillin-clavulanate, 42% for cefixime, 41% for ciprofloxacin, and 40% for trimethoprim/sulfamethoxazole. The highest susceptibility was observed for imipenem (98%), nitrofurantoin and fosfomycin (96%), amikacin (95%), and gentamicin (82%). In another study by Teker *et al.* [23], disk diffusion testing of 525 *E. coli* isolates revealed resistance rates of 80% to cephalothin, 69% to ampicillin, and 47.4% to amoxicillin-clavulanate. The least resistance was observed for carbapenems (< 1%), nitrofurantoin (1.7%), fosfomycin (1.8%), and amikacin (2.1%). Additionally, ESBL production was detected in 86 isolates (16.3%). Despite the use of different methods across these studies, the observed resistance rates appear to be comparable and support each other, suggesting a consistent trend in antimicrobial resistance patterns. When compared with the resistance profiles of the 80 ESBL-positive and -negative *E. coli* isolates in our study, the highest susceptibility was observed for nitrofurantoin, meropenem, ertapenem, fosfomycin, and amikacin. The resistance rate of trimethoprim/sulfamethoxazole, considered an alternative when *E. coli* resistance is below 20%, has shown an increasing trend in recent years, which is also supported by our data. A review of the literature suggests that antimicrobial resistance rates in Türkiye are higher than those in many European countries but lower than those reported in Africa [25,29-31]. Such a pattern could be interpreted in light of the findings reported by Mallah *et al.* [26], who highlighted the influence of educational level on antibiotic misuse. With the rise in antibiotic resistance, the clinical use of polymyxins as part of combination therapies for treating MDR infections has increased [7,9]. Therefore, in our study, colistin susceptibility of both ESBL-positive and -negative *E. coli* strains were evaluated using the BMD, which is the standard recommended by EUCAST and the Clinical and Laboratory Standards Institute (CLSI) [7,14]. Due to the large cationic structure and poor agar diffusion properties of polymyxins, diffusion-based tests commonly used in routine laboratories are unreliable for colistin susceptibility testing [31]. Several studies comparing disk diffusion and gradient diffusion methods with the standard BMD have reported inconsistent results [32–34]. Consequently, disk diffusion or gradient diffusion methods are not suitable for detecting colistin resistance in *E. coli,* other Enterobacterales, or non-fermentative bacteria such as *Pseudomonas* spp. and *Acinetobacter* spp. However, in routine laboratory settings, the BMD is rarely used for determining colistin MICs. In cases where no alternative treatment options exist due to resistance, obtaining MIC data for colistin is essential for informed therapeutic decisions [35–37]. In our study, the BMD method, which is the most recommended and the standard for determining colistin susceptibility, was used. Many studies in the literature have determined colistin MICs in *E. coli* isolates by several methods [20,38,39]. In the study by Kawamoto *et al.* [39], a total of 273 strains were isolated, including 180 ESBL-positive strains (81.7% *E. coli*, 15.6% *K. pneumoniae*, and 2.8% *K. oxytoca*) and 93 carbapenem-resistant strains. Among the 147 ESBL-positive *E. coli* isolates, only one (0.68%) was resistant to colistin, and only two (2.2%) were resistant to carbapenems. In the study by Süzük Yıldız *et al.* [20], 11 (8.7%) of 127 *E. coli* strains were resistant to colistin, and 30 (23.6%) showed resistance to any carbapenem. Our findings are consistent with these studies; however, all strains in our study were susceptible to carbapenems. In the study by Arif *et al.* [40], colistin susceptibility of 241 isolates (179 *E. coli*, 42 *P. aeruginosa*, 10 *K. pneumoniae*, and 10 others) obtained from 2000 urine samples was examined using the BMD. Among the *E. coli* isolates, 48 (26.8%) were resistant to colistin. In the study by Mahajan *et al.* [38], colistin resistance was determined using the BMD among 3511 UPEC isolates collected between 2014 and 2023. Only 0.2% of the isolates were resistant. Interestingly, colistin susceptibility was 100% between 2014 and 2018, but resistance increased during the COVID-19 pandemic. Using the BMD, the reference method, we aimed to present the resistance profile of UPEC strains. In our literature review, we identified five studies in which individual MIC values were accessible. In the study conducted by Dortet *et al.* [9], the MIC range of 76 *E. coli* isolates was reported as 0.25–4 mg/L, with three strains found to be colistin-resistant (MIC = 4 mg/L). In the study by Süzük Yıldız

et al. [20], the MIC range of 127 *E. coli* isolates was reported as 0.125–128 mg/L, with six strains identified as colistin-resistant (MIC ≥ 4 mg/L). Although the colistin resistance rates reported in these studies were comparable to our findings, the median MIC values were statistically significantly lower than those in our study (Mann–Whitney U = 1778.5, Z = -4.744, $p < 0.001$; Mann–Whitney U = 2515, Z = -6.268, $p < 0.001$, respectively).

Mirza *et al.* [37] reported colistin resistance in 6 out of 102 *E. coli* isolates, with an MIC range of 0.124–129 mg/L. Arif *et al.* [40] detected colistin resistance in 48 out of 179 *E. coli* isolates, with an MIC range of 0.24–64 mg/L. When compared individually, the median MIC values in both studies were found to be statistically significantly lower than that in our study (Mann–Whitney U = 3136.5, Z = -3.038, $p = 0.002$; Mann–Whitney U = 1199.5, Z = -10.512, $p < 0.001$, respectively).

However, the most significant limitation of our study is the small number of isolates, all obtained from a single center. However, the Central Laboratory of Istanbul University, Istanbul Faculty of Medicine Hospital, is one of the largest laboratories in Turkiye, representing one of the centers with the greatest diversity of clinical isolates. Based on the results from 80 UPEC strains, carbapenems and colistin appear to be viable treatment options for resistant UTIs. Given evolving resistance patterns, empirical first-line treatment recommendations may need to be revised. Although this study did not aim to identify resistance mechanisms, such investigations would be beneficial in elucidating the molecular basis of colistin resistance in *E. coli*. Efflux pump-mediated resistance is one such mechanism, with the *AcrAB-TolC* efflux pump gene known to exist in *E. coli*. Detecting loci such as *mcr, crrA*, and *qseB/qseC* [41], which contribute to colistin resistance, would further support our findings. Moreover, exploring alternative antibiotics and combination therapies is critical for reducing antibiotic use and controlling resistance and is essential for the development of novel treatment strategies.

Acknowledgements

The study was presented at the "1st International Microbiology and Paediatrics Congress" held on 15-18 May 2024 in Bolu, Türkiye.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (protocol code E-29624016-010.06-2754877 and date of approval: 30 July 2024).

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Conflict of interest

No conflict of interest is declared.

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