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Evaluation of Antibiotic Resistance Patterns of *Escherichia coli* Isolated from Patients at a Hospital in Kerman city

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Abstract
Background: Antibiotic resistance is a worldwide concern that decreases the beneficial effects of antibiotics. *Escherichia coli* is a prevalent etiological agent of infections, particularly within hospital intensive care units. Therefore, comprehending the antibiotic resistance profile of *E. coli* is essential for effective treatment. This study evaluated the antibiotic resistance characteristics of *E. coli* collected from patients admitted to Afzalipour hospital in Kerman, Iran.
Methods: This retrospective study examined 139 patients hospitalized at Afzalipour hospital between September 2017 and August 2019. *E. coli* isolates from clinical specimens were evaluated for antibiotic susceptibility using disk diffusion and agar dilution techniques. The data were analyzed with a chi-square test in SPSS.
Results: Cefazolin and cefotaxime were the most resistant drugs within the examined population. In contrast, gentamicin and amikacin demonstrated reduced resistance rates. The resistance level varied based on the sample type and the department where the patients were admitted.
Conclusion: Excessive and wrong uses of antibiotics develop antibiotic resistance in *E. coli*. Therefore, gentamicin and amikacin can be considered to reduce antibiotic resistance challenges.
Keywords: Antibiotic resistance, Antibacterial drug resistance, Urinary tract infections, *Escherichia coli* infection

Introduction

Today, antibiotic resistance is an important global concern, which enhances the ability of bacteria to survive and thrive even in the presence of antibiotics. This problem poses a serious threat to both human and animal populations worldwide (1). Although antibiotics initially reduced infection deaths, bacterial evolution has led to increased resistance. Therefore, the improper use and indiscriminate use of antibiotics (2,3) and the increase in drug-resistant pathogenic bacteria (4) are the primary causes of antibiotic resistance. Moreover, antibiotic resistance can occur due to various reasons, including the indiscriminate use of β-lactams (a class of antibiotics), long-term hospitalization of patients, and the use of intravenous and urinary catheters (5).

Escherichia coli is an extensively studied gram-negative bacterium in various fields, including genetics, biotechnology, and microbiology (6). *E. coli* demonstrates both probiotic and pathogenic characteristics (7). Non-pathogenic strains are part of the normal gut flora, but pathogenic variants cause urinary tract infections, meningitis, and gastrointestinal disorders (8-10). *E. coli* is the second most prevalent cause of infections in hospitals, after Staphylococcus aureus (11). Hospital-acquired infections are an important problem, resulting in prolonged hospitalizations, higher medical costs, and sometimes mortality.

Several mechanisms are involved in antibiotic resistance development in bacteria. These mechanisms can act separately or together, which leads to different levels and

forms of resistance (12,13). For example, *E. coli* employs multiple genetic mechanisms to acquire resistance to antimicrobial drugs. These strategies include point mutations, insertions and deletions of genetic material, conjugation, transformation, transduction, β-lactamase production, and altered membrane permeability (14). Thus, understanding and addressing these mechanisms is crucial to prevent antibiotic resistance and maintain antibiotic efficacy in treating bacterial infections.

Considering the importance of antibiotic resistance in *E. coli* and the influence of area epidemiology, it is essential to investigate the drug resistance patterns in hospitals. Therefore, the present study aimed to investigate the antibiotic resistance patterns of *E. coli* in different hospital departments and sample types at Afzalipour hospital, Kerman City. This was necessary to understand the prevalence and distribution of drug resistance within this hospital, which could improve infection control and antibiotic treatment.

Methods
This study was a retrospective descriptive-analytical research performed at Afzalipour hospital in Kerman, Iran, from September 2018 to August 2020. All protocols were approved by the Ethics Committee of Kerman University of Medical Sciences (Ethical code: IR.KMU.AH.REC.1399.123).

Study population
The research population included 139 male and female patients hospitalized in different departments of the hospital.

Sample collection
The *E. coli* isolates were collected from various hospital wards. Trained nurses employed standard aseptic techniques to collect urine, tracheal and bronchial secretions, feces, wound swabs, ascites fluid, abscesses, and cerebrospinal fluid samples. The samples were sent to the laboratory under sterile conditions following standard protocols.

Bacterial identification and cultivation
Escherichia coli isolates were identified using standard biochemical tests (24). Patients showing signs of antibiotic resistance received further testing, and those who tested positive were included in the study.

Disk diffusion test
All specimens were cultured on Mueller-Hinton agar. Antibiotic-containing discs were placed on the culture media, which were then incubated at 35 °C for 24 hours. Then, the diameter of the inhibition zones around the discs was measured and interpreted according to the Clinical and Laboratory Standards Institute (CLSI)

guidelines (15). The antibiotics tested were ofloxacin (5 µg), gentamicin (10 µg), amikacin (30 µg), ceftriaxone (30 µg), imipenem (10 µg), ciprofloxacin (5 µg), cefotaxime (30 µg), cotrimoxazole (25 µg), erythromycin (15 µg), clindamycin (2 µg), cefazolin (30 µg), and doxycycline (30 µg). *E. coli* ATCC 25922 (American Type Culture Collection) was used for quality control.

Statistical analysis
Data analysis was conducted using SPSS version 22 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test assessed data normality. In addition, the chi-square test was used to examine the association between antibiotic resistance patterns and categorical variables, including patient characteristics, hospital departments, or infection sources. P values < 0.05 were considered statistically significant.

Results
Descriptive results
The results showed that 61.2% of the samples were from females. Most samples were collected from the urinary tract (59%), followed by the bronchi and trachea (20.9%). The highest numbers of samples were collected from the emergency ward (13.7%) and the general internal department (12.9%). Refer to Table 1 for more details.

Table 1. Descriptive findings of the study

Variable	Variable	Frequency (%)	P value
Gender	Male	54 (38.8 %)	0.080
	Female	85 (61.2%)	
Samples	Urinary tract	82 (59%)	0.060
	Bronchus and trachea	29 (20.9%)	
	Abscesses and ulcers	14 (10.1%)	
	CSF	8 (5.8%)	
	Ascites	3 (2.1%)	
	Stool	3 (2.1%)	
Inpatient wards	Emergency	19 (13.7%)	0.055
	Internal general	18 (12.9%)	
	ICU	16 (11.5%)	
	Children	15 (10.8%)	
	Surgery	13 (9.35%)	
	Women	11 (7.9%)	
	Digestion	10 (7.2%)	
	Glands	8 (5.7%)	
	Lung infectious	7 (5%)	
	Liver and bone marrow transplantation	7 (5%)	
	CCU	6 (4.3%)	
	Skin	5 (3.6%)	
	Oncology	4 (2.87%)	

*Statistical data using the chi-square test show no statistically significant relationship between patient gender and the type of samples selected from various hospital departments.

Figure 1 illustrates that ciprofloxacin (75%) and cefotaxime (62.6%) were the most frequently administered antibiotics.

The resistance rates of *E. coli* bacteria were highest for cefazolin (78.4%), cefotaxime (66%), and clindamycin (64.3%), whereas the lowest resistance rates were observed for amikacin (45%), imipenem (42%), and gentamicin (18.3%) (Table 2).

Analytical results
Antibiotic resistance based on gender
This study examined bacterial resistance to several common antibiotics in both males and females. In summary, antibiotic resistance exhibited no significant variation between males and females, indicating that gender is not a significant factor. Resistance to cefazolin, clindamycin, and ceftriaxone was increased, although aminoglycosides such as amikacin and gentamicin exhibited reduced resistance. Table 3 presents data on *E. coli* responses to several antibiotics, classified by gender.

Figure 2 illustrates the antibiotic resistance patterns of *E. coli* obtained from hospital patient samples. Figure 2A shows that urine samples had significantly more resistance to cefotaxime than other samples ($P=0.04$) (Figure 2A).
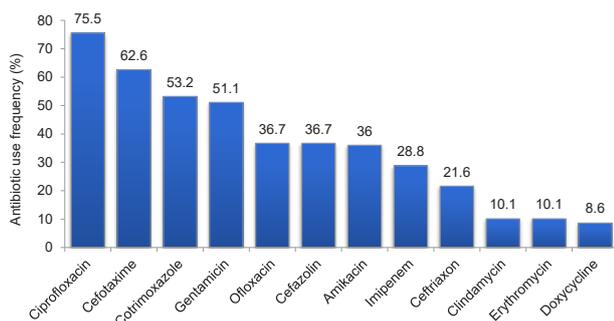

Figure 1. Frequency of antibiotic prescriptions

Table 2. Antibiotic resistance of *Escherichia coli* by class of antibiotic

Antibiotics	Patients (N)	Resistance (%)	P value
Ciprofloxacin	105	59 (56.2)	<0.0001
Cefotaxime	87	58 (66)	<0.0001
Cotrimoxazole	74	44 (59.5)	<0.0001
Gentamicin	71	13 (18.3)	<0.0001
Ofloxacin	51	22 (43.1)	<0.0001
Cefazolin	51	40 (78.4)	<0.0001
Amikacin	50	21 (42)	<0.0001
Imipenem	40	18 (45)	<0.0001
Ceftriaxon	30	19 (63.3)	<0.0001
Clindamycin	14	9 (64.3)	<0.0001
Erythromycin	14	8 (57.1)	<0.0001
Doxycycline	12	7 (58.3)	<0.0001

*Chi-square test results for antibiotic resistance distribution indicate that the difference in resistance between antibiotics is statistically significant ($P<0.0001$).

Furthermore, the majority of cotrimoxazole-resistant samples were from urine (41 cases, 93.2%); however, the sample type did not exhibit a significant correlation with cotrimoxazole resistance ($P=0.65$) (Figure 2B). The prevalence of cefazolin resistance was higher in urinary tract samples (56.4%, 22 instances); nevertheless, the type of sample did not exhibit a significant correlation with cefazolin resistance ($P=0.20$) (Figure 2C).

E. coli showed more than 50% resistance to doxycycline in patient samples who had received the antibiotic. Moreover, all wound and abscess samples exhibited resistance to doxycycline, indicating a statistically significant difference compared to other samples ($P=0.04$). This confirms more resistant bacteria in these samples. In contrast, samples from the bronchus and trachea had the lowest resistance, suggesting that the majority of bacteria in these regions are susceptible to doxycycline. The urine and cerebral fluid samples had modest resistance (Figure 2D).

E. coli had a high resistance to erythromycin in ascitic fluid, wound, cerebrospinal fluid, and abscess samples. This indicates an increased resistance in these samples. No statistically significant correlation was found between sample type and antibiotic resistance ($P=0.52$) (Figure 2E).

Table 3. *E. coli* antibiotic responses by gender

| Antibiotics	Resistance pattern	Gender Male	Gender Female	P value
Ceftriaxone	Resistant (%)	11 (61.1)	8 (66.7)	1
	Sensitive (%)	7 (38.9)	4 (33.3)	
Ofloxacin	Resistant (%)	10 (58.8)	12 (35.3)	0.11
	Sensitive (%)	7 (41.2)	22 (64.7)	
Ciprofloxacin	Resistant (%)	26 (60.5)	33 (53.2)	0.46
	Sensitive (%)	17 (39.5)	29 (46.8)	
Gentamicin	Resistant (%)	1 (4.8)	12 (24)	0.09
	Sensitive (%)	20 (95.2)	38 (76)	
Amikacin	Resistant (%)	11 (42.3)	10 (41.7)	0.9
	Sensitive (%)	15 (57.7)	14 (58.3)	
Cefazolin	Resistant (%)	15 (78.9)	25 (78.1)	0.1
	Sensitive (%)	4 (21.1)	7 (21.9)	
Clindamycin	Resistant (%)	5 (83.3)	4 (50)	0.3
	Sensitive (%)	1 (16.7)	4 (50)	
Erythromycin	Resistant (%)	5 (71.4)	3 (42.9)	0.59
	Sensitive (%)	2 (28.6)	4 (57.1)	
Doxycycline	Resistant (%)	3 (50)	4 (66.7)	1
	Sensitive (%)	3 (50)	2 (3.33)	
Imipenem	Resistant (%)	12 (52.2)	6 (35.3)	0.28
	Sensitive (%)	11 (47.8)	11 (64.7)	
Cotrimoxazole	Resistant (%)	13 (61.9)	31 (58.5)	0.78
	Sensitive (%)	8 (38.1)	22 (41.5)	
Cefotaxime	Resistant (%)	18 (60)	40 (70.2)	0.33
	Sensitive (%)	12 (40)	17 (29.8)	
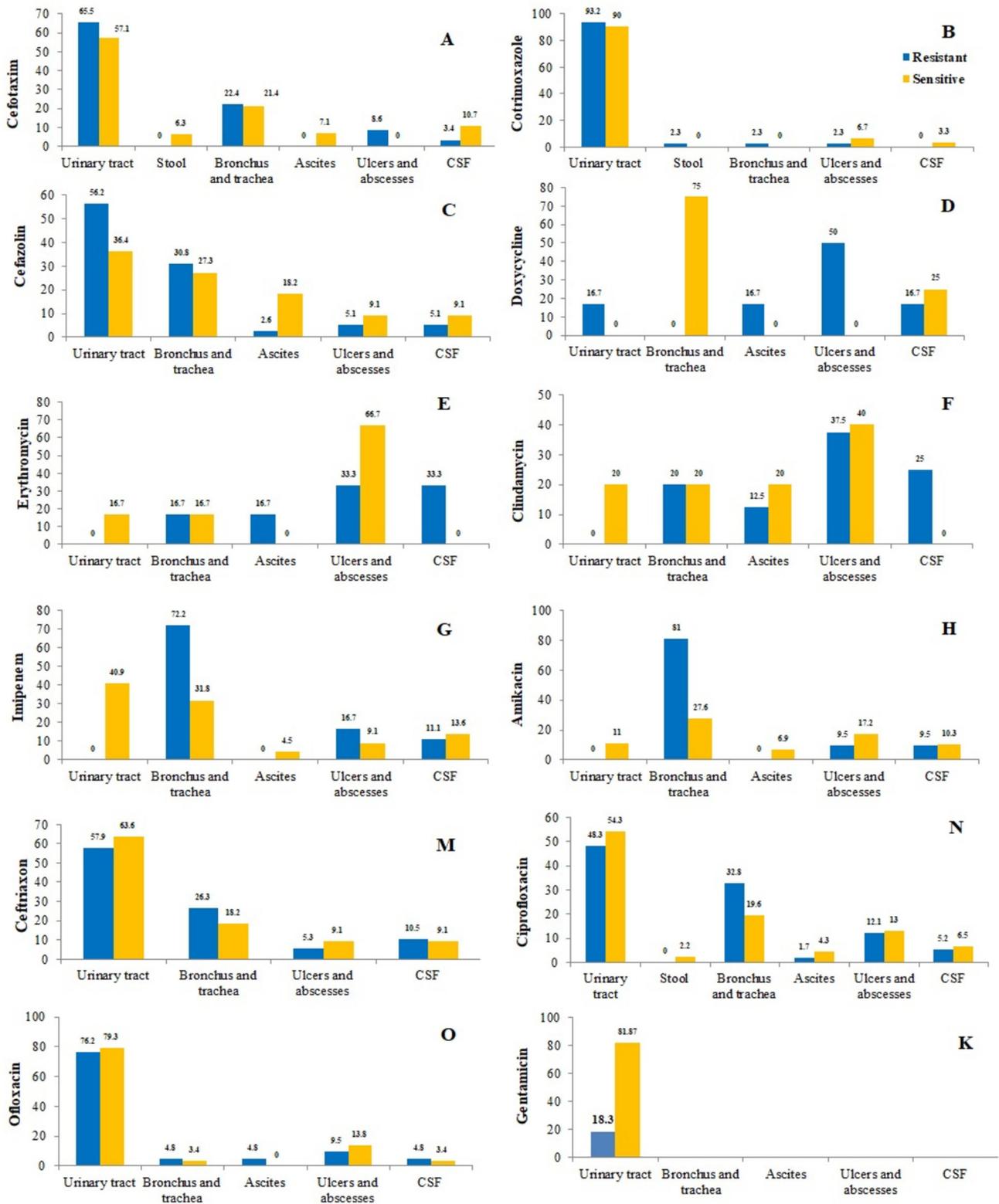
Figure 2. The antibiotic resistance pattern of *E. coli* based on the samples

In clindamycin-resistant samples, the highest resistance was observed in bronchial, tracheal, ulcer, and cerebrospinal fluid samples, whereas urinary tract and ascitic samples exhibited the lowest rate. No statistically significant correlation was observed between the antibiotic resistance pattern and the sample type ($P = 0.90$)

(Figure 2F).

The majority of the total samples were susceptible to imipenem. However, over 72% of imipenem-resistant samples were from bronchial and tracheal specimens, which demonstrated much higher resistance to imipenem compared to other sample types ($P = 0.005$) (Figure 2G).

Most of the samples showed susceptibility to Amikacin. Bronchial and tracheal samples demonstrated significantly higher resistance compared to other samples ($P = 0.0001$) (Figure 2H). These samples exhibited increased resistance to Amikacin (81%) and Imipenem (72%) antibiotics than other samples, indicating a higher capacity for *E. coli* bacteria in the respiratory system to develop resistance to these antibiotics.

Figure 2M shows that urine samples exhibit the highest resistance to ceftriaxone among the analyzed antibiotic resistances. This indicates that several bacteria in urinary tract infections have resisted this drug. In contrast, the lowest resistance to ceftriaxone is observed in ulcers and abscesses samples. *E. coli* samples suggest that the sample type did not influence the resistance pattern ($P = 1$) (Figure 2M). Similarly, urine samples exhibit the highest resistance to ciprofloxacin, although resistance to ciprofloxacin appears increased in certain specimens (e.g., ulcers and bronchus) compared to ceftriaxone. The sample type showed no significant correlation with the antibiotic resistance pattern ($P = 0.58$) (Figure 2N). Both drugs exhibit significant resistance to urinary infections. This result emphasizes that the widespread use of these antibiotics for urinary infections has resulted in increased bacterial resistance.

In 29 samples, *E. coli* bacteria showed Ofloxacin resistance, with the majority (76.2%, 16 cases) from urinary tract specimens. However, there was no significant correlation between sample type and antibiotic resistance patterns ($P = 0.91$) (Figure 2O). The study found that 13 of 71 (18.3%) urine samples exhibited resistance to gentamicin. These findings indicate that a large proportion of urine-derived bacteria were sensitive to this antibiotic (Figure 2K).

Discussion

The study investigated antibiotic resistance patterns of *E. coli* isolates from patients at Afzalipour hospital in Kerman, Iran. *E. coli* has shown significant resistance to cefazolin, clindamycin, cefotaxime, ceftriaxone, cotrimoxazole, and ciprofloxacin. In contrast, gentamicin, amikacin had significant sensitivity, suggesting their potential effectiveness, especially for urinary tract infections. There was no significant correlation between patient gender and antibiotic resistance.

The present findings confirm previous studies and indicate a similar pattern of antibiotic resistance in *E. coli*. Baghbani et al. showed that 52.7% of the 256 analyzed samples were from females, while 40.3% were from males. Furthermore, *E. coli*, the main urinary pathogen, exhibited the highest resistance to ampicillin and the lowest resistance to imipenem. Studies suggest that females demonstrate a greater susceptibility to urinary tract infections than males. It appears that a few variances in the results could result from regional differences,

sample types, and anatomical variations between genders.

Studies on antibiotic resistance have demonstrated significant resistance to first-line antibiotics, including ampicillin and sulfamethoxazole-trimethoprim. Conversely, amikacin and imipenem have shown the highest sensitivity (15,16). Further studies analyzing urine samples confirmed significant resistance to Ampicillin, with sensitivity to imipenem and amikacin. This suggests that these antibiotics may represent the most effective treatments for *E. coli*-induced urinary tract infections (17-19). In addition, research on isolated *E. coli* strains from private medical diagnostic laboratories showed a high susceptibility to amikacin (98%), imipenem (90.95%), nitrofurantoin (85.97%), and cefotaxime (71.02%). On the other hand, significant resistance was observed against Ampicillin (83.95%), tetracycline (80.97%), cotrimoxazole (63.92%), and nalidixic acid (52%) (20, 21). Razzaghi et al documented the highest resistance to ampicillin (66.6%) and the lowest one to imipenem (1%), cefoxitin (1.2%), and gentamicin (1.7%) in *Escherichia coli* strains from patients (22). Therefore, our findings, along with the findings of other researchers, support the effectiveness of amikacin and imipenem in the treatment of *E. coli* infections.

It has been documented that *Escherichia coli* has several major genetic pathways for resistance to antimicrobial drugs. *E. coli* exhibits resistance to ceftriaxone, clindamycin, cotrimoxazole, and ciprofloxacin through complex mechanisms such as enzymatic degradation, target alteration, and genetic adaptations. Resistance to cefazolin and cefotaxime primarily comes from the production of extended-spectrum beta-lactamases (ESBLs), which activate these antibiotics. Beta-lactamases catalyze the hydrolysis of the beta-lactam ring, thereby decreasing the effectiveness of antibiotics. Resistance to Ceftriaxone is attributed to the synthesis of CTX-M type beta-lactamase by *E. coli* (23). Resistance strategies to clindamycin involve the methylation of ribosomal target sites, therefore blocking antibiotic binding. Genetic mutations in ribosomal protein-encoding genes can reduce sensitivity to clindamycin (24). The resistance to cotrimoxazole is due to the acquisition of genes that encode dihydropteroate synthase, an enzyme important to folate production (25). Integrons, also in *E. coli*, are related to increased antibiotic resistance since these genetic elements can simultaneously acquire and express several resistance genes (25). Resistance to ciprofloxacin in *E. coli* is predominantly attributed to mutations in the genes encoding DNA gyrase (gyrA) and topoisomerase IV (parC) (26). Mutations change the target sites of fluoroquinolones, significantly reducing the drug's binding affinity and leading to increased resistance levels. Studies demonstrate that specific mutations in these genes are associated with increased minimum inhibitory concentrations (MICs) for Ciprofloxacin, establishing a clear relationship between genetic modifications and

antibiotic efficacy (26).

On the other hand, gentamicin and amikacin, classified as aminoglycosides, exhibit lower resistance rates. It is attributed to their distinct mechanisms of action and the relative stability of their target sites. Resistance to these drugs often involves aminoglycoside-modifying enzymes, which are less common than β-lactamases (27). Antibiotic-modifying enzymes alter the antibiotic drug, inhibiting its binding to the ribosome (28). Gentamicin and amikacin exhibit a comparable mechanism of action by binding to the 30S ribosomal subunit of bacteria, thereby inhibiting protein synthesis, a critical process for bacterial growth and replication (29). Research indicates that the effectiveness of amikacin and gentamicin is due to their capacity to penetrate bacterial cell membranes and their antimicrobial activity against resistant strains (29, 30). Studies indicate that the prevalence of resistance genes for gentamicin is lower than that for beta-lactams, suggesting that although resistance exists, it is not as extensive (31). The diversity of these mechanisms in *E. coli* strains reduces resistance rates in certain populations.

Conclusion

The study found that while gentamicin and amikacin were highly effective, their usefulness may diminish over time due to increasing antibiotic resistance. A significant proportion of bacteria isolated from urine samples showed resistance to multiple antibiotics. However, susceptibility patterns varied across different specimen types. This research highlights the increasing challenges of antibiotic resistance in *E. coli*. Although some treatments have been effective, we need a comprehensive strategy including appropriate antibiotic use, infection prevention, and the development of new antimicrobial agents. To deal with this growing threat, it is important to understand the phenotypic and genotypic characteristics of these resistant strains.

Authors' Contribution
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Formal analysis: Shahrzad Sadat Eftekhar Vaghefi, Fatemeh Shahsavari.
Investigation: Mohammad Akbarpour.
Methodology: Mohammad Ehsan Khani.
Project administration: Reza Malekpoor Afshar, Mohammad Akbarpour.
Resources: Reza Bahramabadi.
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Supervision: Reza Malekpoor Afshar.
Validation: Maryam Iranpour.
Visualization: Shahrzad Sadat Eftekhar Vaghefi, Fatemeh Shahsavari.
Writing–original draft: Fatemeh Shahsavari.

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