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The Frequency and Antibiotic Resistance Pattern of the blaOXA-48 beta-Lactamase Gene in Escherichia coli Strains Isolated from Urinary Tract Infections

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ABSTRACT

Aims Escherichia coli, a gram-negative bacterium, is a predominant pathogen causing urinary tract infections, responsible for approximately 90% of cases in young women. This study aimed to investigate the frequency of the blaOXA-48 gene in carbapenem-resistant uropathogenic Escherichia coli.

Materials & Methods This cross-sectional descriptive study was conducted from July to November 2022 using 320 urine samples from hospitals and healthcare centers in Yasuj City, Iran. The antibiotic resistance of the isolates was assessed through the disk diffusion method. The presence of the blaOXA-48 gene was investigated using the polymerase chain reaction with specific primers. Data was analyzed using SPSS 24 software.

Findings Escherichia coli showed varying degrees of resistance to different antibiotics. The highest resistance was against doripenem (96.6%), while the lowest was against tetracycline (22.5%). The PCR method revealed 55 (36.7%) positive (24 males and 31 females) and 95 (63.3%) negative (39 males and 56 females) cases of blaOXA-48 gene in the studied Escherichia coli samples.

Conclusion The most effective antibiotic for treating urinary tract infections caused by Escherichia coli is tetracycline.

Keywords Urinary Tract Infection; Escherichia coli; Antibiotic Resistance; blaOXA-48

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Introduction

Urinary tract infection (UTI) refers to microbial colonization or inflammation of the urinary system, including cystitis (bladder inflammation), urethritis, or infections of the kidneys and renal pelvis (pyelonephritis) [1]. UTI is the most common infectious disease after respiratory infections worldwide [2]. Urinary tract infections have a significant impact on the physical, mental, and well-being of patients. More than half of the patients experience depression, and 38.5% suffer from anxiety, with appropriate treatment improving their quality of life [2]. However, microbial resistance in these infections is common, necessitating the identification of the microbial agent for prescribing suitable antibiotics [3, 4]. Urinary tract infections are caused by the growth of microorganisms in the urinary system. In a study involving women, *Escherichia coli*, followed by Klebsiella and Enterococcus, were identified as the predominant agents causing urinary tract infections [2].

Escherichia coli, commonly known as *E. coli*, is one of the most prevalent members of the Enterobacteriaceae family [5]. This bacterium is a Gram-negative bacillus, motile, equipped with flagella, with many of its strains possessing pili [6]. Among Gram-negative bacteria that develop drug resistance, *E. coli* is the most common cause of urinary tract infections and bloodstream infections. One of the significant public health challenges is antimicrobial resistance [7]. Due to the widespread use of antibiotics, carbapenem-resistant strains have become a serious global public health concern. Over the past ten years, there has been an increasing report of carbapenem-producing strains within the Enterobacteriaceae family [8]. Consequently, the production of β-lactamases with a broad spectrum and resistance to carbapenems in *Escherichia coli* has escalated in the last decade [9]. *Escherichia coli* inherently exhibits resistance to many types of β-lactamases. Carbapenems are among the most effective agents for treating severe infections caused by *Escherichia coli*. Resistance to carbapenems occurs due to the production of carbapenemases (a class of enzymes capable of hydrolyzing carbapenems and other beta-lactams). Other resistance mechanisms include weak binding of carbapenems to bacterial penicillin-binding proteins, purine deficiency in the bacterial cell membrane, and the bacterium overexpression of multidrug efflux pumps [10].

One of the most common mechanisms in Gram-negative bacteria resistant to carbapenems is the acquisition of carbapenemase genes. Three categories of carbapenemases have been identified, including Class A carbapenemases (KPC), Class B metalloenzymes, and Class D enzymes (OXA-48 type) [8]. Class D enzymes are a group of serine beta-lactamases known as oxacillinases or (OXA) OXAcilin-hydrolyzing enzymes [11]. Pseudo-enzymes like OXA-48 (OXA-48, OXA-162, OXA-163, OXA-181, OXA-204, OXA-232) represent one of the major families responsible for a wide spectrum of beta-lactam/carbapenem resistance in Enterobacteriaceae. The production of beta-lactamase enzymes by these bacteria is among the most significant factors contributing to resistance against antibiotics [12].

The emergence of antibiotic resistance has made the treatment of infections caused by drug-resistant pathogens, particularly Gram-negative bacteria, more complex [13]. Gram-negative bacteria-producing carbapenemases can be the causative agents of a wide spectrum of infections, including bacteremia, endocarditis, wound infections, urinary tract infections, and hospital-acquired pneumonia. These infections are often associated with high mortality rates, treatment failure, and prolonged hospitalization. Therefore, accurate and rapid diagnosis of patients in the clinical microbiology laboratory is crucial for selecting antibiotic treatment regimens and implementing infection control measures.

Diagnosing these microorganisms comes with challenges, as the methods for identifying carbapenemases have not been well standardized [14]. Additionally, numerous genes play a role in carbapenem resistance, and their prevalence varies in different regions. This leads to changes in the drug resistance pattern in different areas, emphasizing the need to investigate the nature of antibiotic resistance and examine the frequency of effective genes in resistance development in various regions [15].

Considering the importance of the issues mentioned, this study aimed to determine the antibiotic resistance pattern and investigate the frequency of the blaOXA-48 gene in carbapenem-resistant uropathogenic *Escherichia coli*.

Materials and Methods

Sample Collection

This cross-sectional descriptive study was conducted from July to November 2022. Considering a 40% prevalence of the oxa48 gene, a 95% confidence interval, and a precision of 5%, a total of 320 urine samples were collected from hospitals and healthcare centers in Yasuj City, Iran, along with personal information such as age, gender, and urban or rural residence. From this total, 150 isolates were obtained using microbiological methods, Gram staining, and standard biochemical techniques (TSI tests, Simon's citrate, urea test, SIM, and MR/VP tests) for identification and characterization [16-18].

Determination of antibiotic resistance

Isolates of *Escherichia coli* were evaluated for antibiotic resistance using the disk diffusion method and following the CLSI 2018 guidelines (Clinical & Laboratory Standards Institute) [8, 19]. For this purpose, *Escherichia coli* bacteria were cultured on

specific media and incubated. After incubation, one colony from each isolate was selected and transferred to the Muller-Hinton broth medium. After obtaining turbidity equivalent to 0.5 McFarland standard, a loopful of the liquid medium was aseptically taken and streaked onto Muller-Hinton agar. After placing antibiotic disks, including meropenem, imipenem, ertapenem, ciprofloxacin, cefixime, cotrimoxazole, ceftriaxone, ceftazidime, norfloxacin, colistin, amikacin, gentamicin, tetracycline, and doxycycline (Padtan Teb; Iran), on the medium with sterile forceps at appropriate intervals, it was incubated at 37 degrees Celsius for 24 hours.

Following incubation, the sensitivity or resistance was determined based on the size of the growth inhibition zone, and the results were further verified using the CLSI table [19]. Specifically, the antibiotic disks were assessed for meropenem, imipenem, ertapenem, ciprofloxacin, cefixime, cotrimoxazole, ceftriaxone, ceftazidime, norfloxacin, colistin, amikacin, gentamicin, tetracycline, and doxycycline, and the zones of inhibition were measured to determine the susceptibility or resistance of the isolates.

Identification of carbapenemase phenotype

Isolates resistant to carbapenems were examined for carbapenemase production using the Modified Hodge Test (MHT) phenotype method. A 0.5 McFarland turbidity of the *E. coli* standard strain ETCC25922 was prepared in 5 milliliters of saline for this test. This suspension was then diluted 1:10, uniformly streaked onto Muller-Hinton agar medium, and a carbapenem disk was placed at the center of the plate. The test organism was streaked in a straight line from the edge of the disk to the edges of the plate. After performing this procedure, the plate was incubated at 37 degrees Celsius. After 24 hours, a positive MHT strain produces a cloverleaf-shaped indentation around the growth inhibition zone of the carbapenem disk, extending from the disk edge into the area where the test strain was streaked [20, 21]. Carbapenem-resistant isolates were stored in TSB medium enriched with 10% glycerol at -70 degrees Celsius for further stages [22].

DNA extraction

DNA extraction was performed using the boiling (heat) method [19]. The frequency of the blaOXA-48 gene in carbapenem-resistant *Escherichia coli* isolates was evaluated using specific primers for the blaOXA-48 gene and the polymerase chain reaction (PCR) molecular method. The desired primers were designed using the Runner Gene software (744 bp), confirmed through the NCBI database, validated by Blast, and manufactured by Macrogene, Korea (Reverse: 5'GAGCACTTCTTTTGTGATGGC3'; Forward: 5'TTGGTGGCATCGATTATCGG3').

Amplification reactions were carried out in a 25-microliter volume using a thermocycler device (Eppendorf, Germany; Table 1). The mixture consisted of 2 microliters of DNA template, 1× buffer, 5pmol of primers, 100 mM dNTP, and 0.5 U of Taq DNA Polymerase. Subsequently, PCR amplification was performed, and the PCR products were electrophoresed on a 2% agarose gel (CinnaGene; Iran). Staining was done with ethidium bromide, and the gel was photographed and identified under UV light using a gel documentation system (Optigo ISOGENE) [8].

Data analysis

Data was analyzed using SPSS 24 software. The data were initially examined for normal distribution using the Chromatography-Smirnoff test. Descriptive statistics, including mean, standard deviation, and frequency distribution table, were utilized for statistical analysis.

Table 1. Temperature, time, and cycling program for the thermocycler in the PCR reaction for the identification of blaOXA-48 genes

Cycle	Initial Denaturation	Denaturation	Primer Annealing	DNA Extension	Final Extension	Number of Cycles
Temperature	94	94	65	72	72	30
Time	10 minutes	40 seconds	40 seconds	10 minutes	10 minutes	

Findings

Out of 150 collected samples of *Escherichia coli* bacteria from urine samples of patients visiting laboratories and hospitals in Yasuj, 87 (58%) were from women, and 63 (42%) were from men.

According to morphological characteristics and biochemical tests, all isolated urine samples were *Escherichia coli* (Table 2).

Antibiotic susceptibility test

Escherichia coli showed varying degrees of resistance to different antibiotics.

The highest resistance was against doripenem (96.6%), while the lowest was against tetracycline (22.5%; Figure 1).

blaOXA-48 gene frequency

The PCR method revealed 55 (36.7%) positive (24 males and 31 females) and 95 (63.3%) negative (39 males and 56 females) cases of blaOXA-48 gene in the studied *Escherichia coli* samples.

Table 2. Biochemical test results

Test	Result
Tsi	A/A , g+ , H_2S -
MR	+
VP	-
SIM	Motile, Indole +
Citrate	-
EMB agar	+
Nutrient agar	+

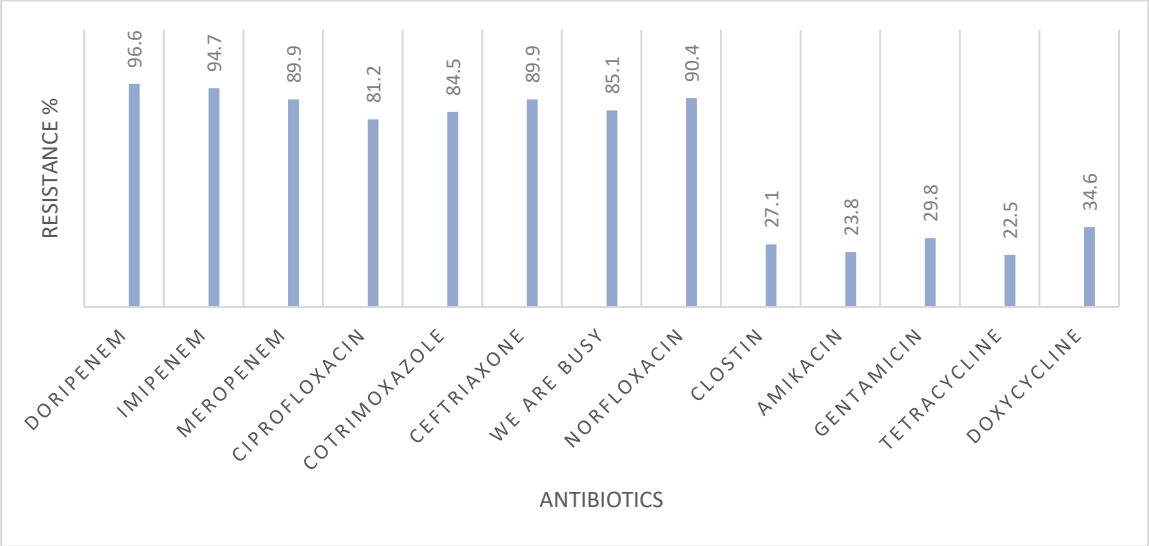

Figure 1. Frequency of antibiotic resistance in isolated *Escherichia coli* from patients referring to healthcare centers

Discussion

The present study aimed to determine the antibiotic resistance pattern and investigate the prevalence of the blaOXA-48 gene in carbapenem-resistant uropathogenic *Escherichia coli*.

Urinary tract infections are prevalent, ranking second in frequency after respiratory diseases. They are among the major and significant bacterial infections in industrialized countries, constituting 80% of hospital-acquired infections [23]. *Escherichia coli*, as one of the key contributors to urinary tract infections, exhibits varying resistance to different antibiotics [24]. The highest resistance was against doripenem (96.6%), while the lowest was against tetracycline (22.5%). Molaabaszadeh *et al*. in Tabriz have reported the highest antibiotic resistance rates against ampicillin (83.95%), gentamicin (43.11%), cotrimoxazole (63.92%), amikacin (31.96%), and ceftriaxone (31.01%) [25]. These results differ from the findings of this study, suggesting that the variation may be due to excessive use of antibiotics. In Haghighatpanah *et al*., the highest antibiotic resistance was related to amoxicillin and the highest sensitivity was reported for imipenem [26]. In contrast, in this study, a high percentage of samples showed resistance to imipenem (94%). Comparing the results of this study with other studies indicates the prevalence of antibiotic resistance within the beta-lactam family in bacteria isolated from clinical samples. Considering that environmental factors and different patterns of antimicrobial use play a role in the emergence and spread of these strains worldwide, the differences in antibiotic resistance results between this study and others can be justified. In Kiakha *et al*., 87 *Escherichia coli* isolates from patients with urinary tract infections were examined, and the resistance results against cotrimoxazole (66.6%), ceftazidime (44.8%), amikacin (19.5%), gentamicin (13.8%), and imipenem (4.5%) were reported [27]. The current study showed higher antibiotic resistance in all cases, which may be attributed to the irrational use of these antibiotics, the development of antibiotic resistance genes, and the transfer of these genes in *Escherichia coli* bacteria. The dissemination of resistance genes through horizontal gene transfer leads to the rapid spread of antibiotic resistance among clinical bacteria isolates. This difference may also indicate a lack of public awareness about the importance of completing the course of treatment for infectious diseases. In Mohamadimehr, the resistance to ciprofloxacin and gentamicin was reported at 58.3% and 27.7%, respectively [28], while the current study results showed a similar rate for gentamicin (29%), but a noticeable difference for ciprofloxacin (81%).

Candan & Aksöz investigated the resistance characteristics to carbapenems and related factors in *Escherichia coli*. In their study, 50 *Escherichia coli* strains were assessed using multiplex PCR. The findings revealed that OXA-48 carbapenemase was identified in 22% of all strains [29].

Additionally, Zhao *et al*. examined the characteristics of *Escherichia coli*, Enterobacter cloacae, and Klebsiella oxytoca-producing OXA-48 from a hospital in China. In their results, several Enterobacterial isolates producing OXA-48, including 3 strains of *Escherichia coli*, three strains of Enterobacter cloacae, and one strain of *Klebsiella oxytoca*, were collected. All isolates showed low resistance to carbapenems or were even sensitive to imipenem and meropenem. Moreover, all isolates carried a plasmid harboring blaOXA-48 [30].

Dagher *et al*. investigated the characteristics of carbapenem-resistant *Escherichia coli* in Lebanon. Their findings indicated that 27 isolates were resistant to carbapenems, and 20 isolates harbored a broad-spectrum beta-lactamase gene. Furthermore, they identified 13 isolates carrying blaOXA-48 [9].

During 2008-2010, the prevalence of carbapenem-resistant Enterobacteriaceae increased from 0.4% to 1.6% in 2012, predominantly associated with OXA-48-producing *Escherichia coli* [31]. This trend agreed with this study's findings, where carbapenem resistance, linked to OXA-48 production, was observed in 67.36% of the isolates. Additionally, the higher frequency of this gene in the present study compared to the studies by Kandan & Aksoz and Daqour *et al*. may be attributed to the larger sample size in the current study.

Gurung *et al*. conducted a study to identify the OXA-48 gene in carbapenem-resistant Klebsiella pneumoniae and *Escherichia coli* isolated from urine samples using PCR. Among the isolates, *Escherichia coli* was the most common, with 52 out of 121 bacterial isolates (97 *Escherichia coli* and 24 *Klebsiella pneumoniae* isolates) being multidrug-resistant. Furthermore, 11 out of 121 isolates (97 *Escherichia coli* and 24 *Klebsiella pneumoniae*) were resistant to carbapenems (both imipenem and meropenem). Of these 11 carbapenem-resistant isolates, only 7 were carbapenemase producers, including 28% *Escherichia coli* and 72% *Klebsiella pneumoniae*, with 42% carrying the blaOXA-48 gene [20]. The results of this study regarding the prevalence of the blaOXA-48 gene are similar to the current study.

One limitation of this study is the lack of investigation into other antibiotic resistance mechanisms. The results of this study indicate a relatively high resistance of the isolated samples to various antibiotics. This resistance may be a consequence of the extensive use of these antibiotics, either in pure form or in combination, for the treatment of patients, leading to an increase in antibiotic resistance in these isolates. Moreover, blaOXA-48 is a potential tool for gene dissemination among clinical isolates. Although costly, molecular diagnostic techniques such as PCR are far more prevalent than other protocols, assisting healthcare professionals in coping with the growing challenges of antibiotic resistance. Rapid identification of the blaOXA-48 gene can play a crucial role in controlling and treating urinary tract infections. Furthermore, the increased resistance of the bacteria isolated in the current study to antibiotics may be attributed to the indiscriminate use of antibiotics, highlighting the importance of physicians paying attention to the indications, risks, and unnecessary prescriptions of antibiotics. It is also a warning for pharmacies to refrain from providing antibiotics without a prescription from a physician. Considering the mobile nature of the transferable elements of this type of resistance, and given that organisms containing this gene demonstrate extensive drug resistance patterns, it is recommended that studies be conducted on the mobile genes and their frequencies in other Gram-negative bacteria as well. This would aid in making preventive decisions to prevent the spread of such strains and in choosing suitable treatment protocols.

Conclusion

The most effective antibiotic for treating urinary tract infections caused by *Escherichia coli* is tetracycline.

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