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Original Article

Molecular Monitoring of Fosfomycin Resistance in *Escherichia coli* Strains Isolated from Patients with Urinary Catheters in north-east of Iran

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Introduction: Urinary tract infection is a common nosocomial infection that has recently become difficult to treat because of the increased emergence of multi-drug resistant strains. This study aims to determine the minimum inhibitory concentration, and molecular pattern of resistance to fosfomycin in *Escherichia coli* isolates originated from patients hospitalized with urinary tract infection in the intensive care unit (ICU) and coronary care unit (CCU). **Methods:** Urine samples were obtained from 106 patients in three hospitals of Gorgan, northeast of Iran. After isolation and identification of *E. coli* isolates, the Kirby-Bauer disk diffusion test was performed to evaluate the antibiotic susceptibility pattern. Minimum inhibitory concentrations (MICs) of isolates to fosfomycin were determined using the agar dilution method over a concentration range of 0.5-1024 µg/mL. Also, the presence of *murA* and *glpT* genes were investigated using polymerase chain reaction with specific primers. **Results:** Frequency of *E. coli* isolates was 62.3%, most of which originated from ICU patients (56.5%). The rate of susceptibility to fosfomycin was 85%. Moreover, the MIC of 80.3% of the isolates was less than or equal to 64 µg/mL. We also detected the *murA* and *glpT* genes in 77.8% and 22.2% of fosfomycin-resistant isolates, respectively. **Conclusion:** Our results indicated a high bactericidal activity of fosfomycin against uropathogenic *E. coli* isolates. In agreement with similar studies, we concluded that the presence of *murA* is significantly associated with the development of resistance to fosfomycin. *J Med Microbiol Infec Dis, 2018, 6 (4): 112-117.*

Keywords: Fosfomycin, Uropathogenic *Escherichia coli*, Coronary Care Units, PCR.

INTRODUCTION

Urinary tract infection (UTI) is a common infectious disease that could be either symptomatic or asymptomatic. Urinary catheters and pathogens emanating from the gastrointestinal tract are the leading causes of UTI [1]. Uropathogenic *Escherichia coli* (UPEC) is responsible for 70-90% of UTIs in humans. Therefore, early and accurate diagnosis of UTI is crucial for effective treatment and prevention of infection spread to the upper urinary tract [2]. Prevalence of multi-drug resistant *E. coli* strains that are resistant to beta-lactams, fluoroquinolones, and aminoglycosides have increased dramatically in recent years. As a bactericidal antibiotic, fosfomycin is used with different formulations for the treatment of complicated UTIs. Despite being an old-generation antibiotic, fosfomycin has recently played a significant role in controlling resistant bacteria, particularly *E. coli* [3, 4]. This antibiotic is a phosphoenolpyruvate analog that binds to UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), (an essential enzyme for peptidoglycan biosynthesis) leading to bacterial cell lysis and death [5]. Fosfomycin can also inhibit this enzyme by covalently binding to a key cysteine residue (115 in *E. coli*) in the active site of MurA [6]. The *E. coli* MurA with the Cys115 to Asp mutation exhibits full enzymatic activity and makes the bacteria resistance to fosfomycin, while the gene with the Cys115 to Glu mutation shows no activity [7]. Glucose-6-phosphate (G6P) transporter, UhpT and glycerol-3-phosphate (G3P) transporter (GlpT) facilitate the incorporation of fosfomycin into the bacterial cells [8]. G3P induces expression of GlpT in *E. coli*. In these bacteria, two domains in the GlpT structure are attached to the central loop and act as a secondary active transporter to transfer substrates into the cytoplasm. However, mutations in the *glpT*, GlpT transporter, and *murA* may decrease fosfomycin susceptibility and uptake.

Expression of the GlpT and UhpT transporters is induced by their substrates, G3P and G6P, respectively, and requires the presence of cAMP. Mutations in the structural genes involved in these pathways lower the antibiotic uptake, thereby conferring different levels of fosfomycin resistance [9]. In this study, we aimed to investigate the genetic pattern of fosfomycin resistance in UPEC isolates from patients with UTI.

MATERIAL AND METHODS

Patients and bacterial isolation. Urine samples were collected from 106 patients with UTI in three hospitals of

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Gorgan, northeast of Iran, from Oct. 2017 to Dec. 2018. The patients, either symptomatic or asymptomatic, had a urinary catheter and were hospitalized for more than two weeks. Diagnosis of UTI was made based on positive urine culture, *i.e.*, the presence of 10^5 colonies in asymptomatic patients and 10^4 colonies in symptomatic patients [10]. The specimens were taken from first-morning urine drainage bag and then cultured on blood agar, eosin methylene blue agar, and MacConkey agar. The cultured samples were incubated at 37°C for 18-24 h. The *E. coli* isolates were identified based on Gram staining and biochemical assays including glucose and lactose fermentation, gas production, indole, Voges-Proskauer, Triple Sugar Iron (TSI) agar, sulfide indole motility, and methyl red tests.

Antibiotic susceptibility. From overnight cultures, a suspension of bacteria with a turbidity of 0.5 McFarland was prepared in a physiological serum (NaCl solution 0.9%), and uniformly cultured on Muller Hinton agar (Merck, Germany) using sterilized swabs. Fosfomycin (FOS200 containings 50µg glucose-6-phosphate) (Laboratorios CONDA, Spain), imipenem (IPM10), cefepime (FEP30), gentamicin (GM10), ceftriaxone (CRO30), ciprofloxacin (CP5), colistin (CS10) and gemifloxacin (GEM5) disks were purchased from a commercial company (Padtan Teb Co., Iran). After 18-24 h of incubation at 37°C aerobically, the diameter of growth inhibition zone was measured, and the isolates were defined as resistant, intermediate, and sensitive according to the Clinical and Laboratory Standards Institute guidelines (M100-S25) [11].

Minimum inhibitory concentration (MIC) of fosfomycin was determined using the agar dilution method in an agar enriched with 25 µg/mL of G6P and 2mM cAMP. A stock solution from fosfomycin powder (Sigma-Aldrich, USA) was prepared in sterile distilled water, and a serial dilution was used in Muller Hinton broth. Different antibiotic concentrations ranging from 0.5 to 1024 µg/mL were included in the assay. After inoculation of a 10^5 CFU/mL bacterial suspension and incubation for 16-20 h, the lowest concentration that inhibited the growth of bacteria was defined as the MIC. Finally, the results were compared with the values in tables provided by the CLSI document M100-S25 (2015) [11], and *E. coli* isolates were classified as fosfomycin-susceptible (MIC≤64 µg/mL), fosfomycin-intermediate (MIC=128 µg/mL) and fosfomycin-resistant (MIC≥256 µg/mL). The reference strain *E. coli* ATCC 25922 was used as a positive control.

PCR assay. Genomic DNA was extracted from the isolates using a commercial kit (CinnaGen Alborz, Iran). The presence of the *murA* and *glpT* genes were investigated using polymerase chain reaction (PCR) with specific primers designed by others [12] (Table 1).

The 25 µL PCR reactions contained 1µL of the DNA sample, 1 µL of each forward and reverse primer, 0.5 µL of dNTPs, 2.5 µL of PCR buffer (Sigma-Aldrich, USA), 0.75 µL of magnesium chloride, 1U of *Taq* polymerase enzyme and 18.05 µL of distilled water. Amplification was programmed for an initial denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 1 min, annealing at 63°C for 1 min, extension at 72°C for 1 min, and a final extension at 72°C for 5 min. The PCR products were electrophoresed on 1.5% agarose gel, and the bands were visualized under UV light after staining with ethidium bromide. Detection of the 1785 bp and 1542 bp fragments indicated the presence of the *glpT* and *murA* genes, respectively.

Statistical analysis. Statistical analyses were performed using the software IBM SPSS Statistics 23.0. The chi-squared distribution was used to test for independence using the null-hypothesis (H_0). Data were analyzed using the ANOVA at a significance level of 0.05.

Table 1. The primers used for detection of *murA* and *glpT* genes

Gene/Size	Primer	Primer Sequence
***murA*/1542 bp**	Forward	5' AAACAGCAGACGGTCTATGG 3'
	Reverse	5' CCATGAGTTTATCGACAGAACG 3'
***glpT*/1785 bp**	Forward	5' GCGAGTCGCGAGTTTTCATTG 3'
	Reverse	5' GGCAAATATCCACTGGCACC 3'

RESULTS

Demographic specifications of bacterial isolates. Among the 106 patients with UTI (average age: 44 ±18 years), the individuals ≥ 60 years of age showed the highest rate of infection (36.36%), while 15 and 25-year-old patients had the lowest rate of infection (9.09%). About 62.3% of the isolates were identified as *E. coli*, most of which were isolated from women (62.1%) and ICU patients (56.5%).

Susceptibility to antibiotics. In the Kirby-Bauer test, the highest rates of resistance and susceptibility were observed against imipenem (average=61.8%) and fosfomycin (average=85%), respectively (Table 2).

Minimum Inhibitory Concentration. The effects of different concentrations of fosfomycin (0.5-1024 µg/mL) on the growth of *E. coli* strains showed that 80.3% of the isolates had a MIC of ≤64 µg/mL. The most significant growth changes were observed at concentrations 16 µg/mL and 32 µg/mL, and 44% of the isolates had a MIC of 16 µg/mL (Fig. 1).

***glpT* and *murA* PCR.** Among the fosfomycin-resistant *E. coli* isolates, 22.2% yielded a 1785 bp band indicative of the *glpT* gene (1785 bp band), 77.8% showed a 1542 bp band representative of the *murA* gene. One isolate (11.1%) contained both genes (Figs. 2 and 3).

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Table 2. Distribution of susceptibility to 8 antibiotics in *E. coli* Isolates

Antibiotics		ICU (n=37) N (%)	CCU (n=29) N (%)	*P* value
Fosfomycin	R	7 (18.9)	2 (6.9)	0.36
	I	1 (2.7)	0 (0)	
	S	29 (78.4)	27 (93.1)	
Gentamicin	R	11 (29.7)	6 (20.7)	0.00*
	I	9 (24.3)	2 (6.9)	
	S	17 (46)	21 (72.4)	
Cefepime	R	15 (40.5)	9 (31)	0.00*
	I	7 (19)	0 (0)	
	S	15 (40.5)	20 (69)	
Ceftriaxone	R	11 (29.7)	14 (48.3)	0.04
	I	0 (0)	2 (6.9)	
	S	26 (70.3)	13 (44.8)	
Imipenem	R	24 (64.9)	17 (58.6)	0.04
	I	2 (5.4)	0 (0)	
	S	11 (29.7)	12 (41.4)	
Ciprofloxacin	R	10 (27.1)	7 (24.1)	0.36
	I	12 (32.4)	0 (0)	
	S	15 (40.5)	22 (75.9)	
Gemifloxacin	R	5 (13.5)	2 (6.9)	0.07
	I	6 (16.2)	1 (3.4)	
	S	26 (70.3)	26 (89.7)	
Colistin	R	9 (24.3)	4 (13.8)	0.04
	I	0 (0)	0 (0)	
	S	28 (75.7)	25 (86.2)	

*Significant difference between the study groups based on the one-way ANOVA, R: Resistant, I: Intermediate, S: Susceptible

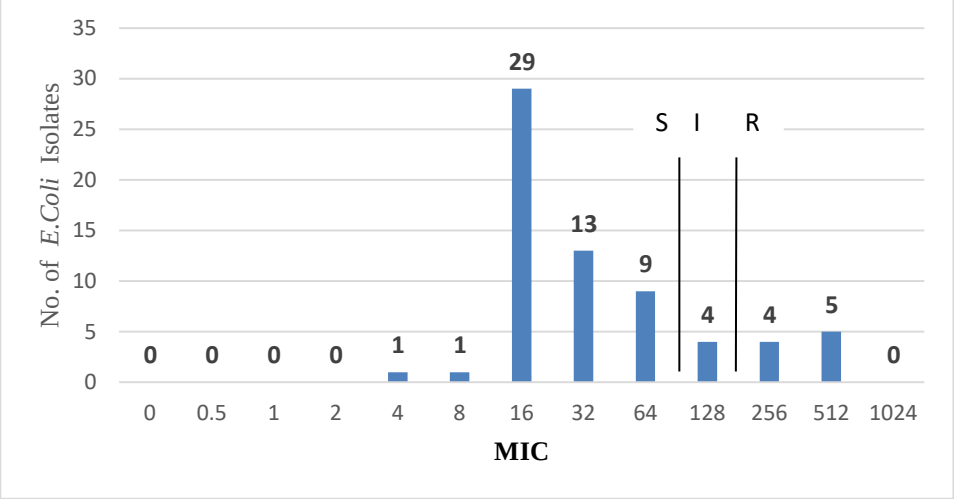


Fig. 1. Absolute Abundance of Fosfomycin MICs of *E. coli* clinical Isolates

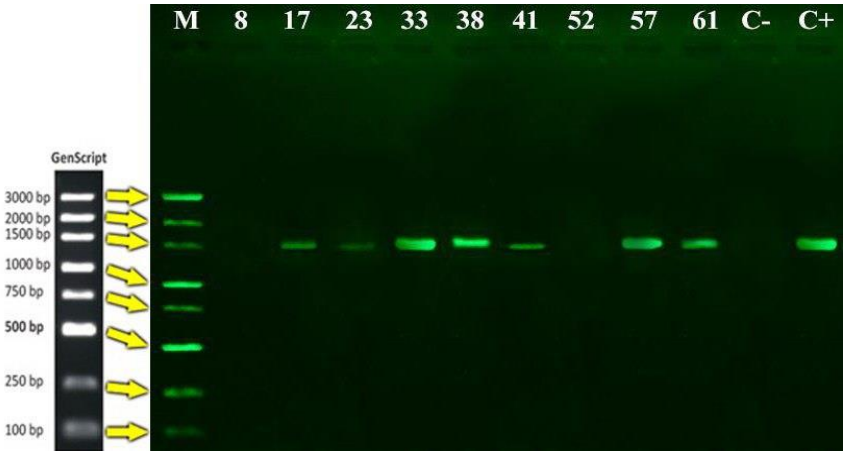


Fig. 2. PCR amplification of of the *murA* gene in *E. coli* isolates. Lanes 17, 23, 33, 38, 41, 57, and 61, *murA*-positive *E. coli* isolates; C^+, positive control; C^-, negative control

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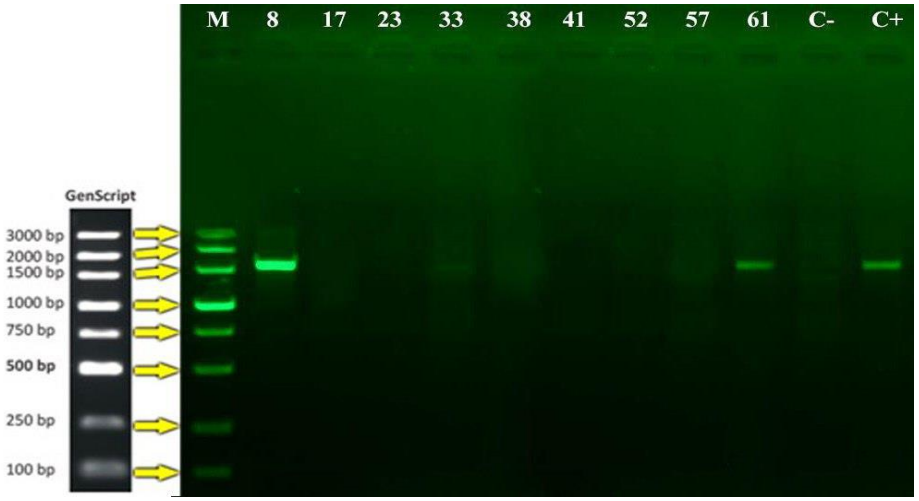


Fig. 3. PCR amplification of *glpT* in *E. coli* isolates. Lanes 8, and 61, *glpT*- Positive isolates; C^+, positive control; C^-, negative control

DISCUSSION

UPEC is a significant cause of UTI in humans, and the pathogenicity of these strains relies on the presence of virulence factors [13]. Given the relatively high frequency of *E. coli* in urine specimens, it is necessary to investigate the virulence factors. With the emergence of multi-drug resistant strains, management of infections caused by *E. coli* strains has become challenging. Therefore, a better understanding of the virulence factors and identification of alternative antibiotics would allow physicians to predict the progression of infection and implement more effective treatment strategies [14].

In our study, out of 106 urine samples, 66 showed infection with *E. coli*. Frequency of isolates was higher in samples collected from women (62.1%). Although, according to the type of patients, it was expected to find more infected men than women. Consistent with this finding, the frequency of *E. coli* isolates in some studies was highest among women [15-17]. In a study, most *E. coli* strains were isolated from subjects aged 12-50 years [14], while in another study, the prevalence of infection was highest among subjects aged 27-39 years and 1-5 years [16]. In line with our findings, researchers observed the highest infection rates in individuals aged 60-80 years [18]. This inconsistency could be related to the difference in characteristics of the study population, including age, ethnicity, and geographical factors. Due to conditions such as weakened immune system, urinary tract obstruction, diabetes mellitus, enlarged prostate, and incomplete bladder emptying, the elderly are more susceptible to develop infections, particularly nosocomial infections caused by opportunistic microorganisms [19].

In the present study, the isolation rate of *E. coli* was the highest in ICU patients (56.5%), which is somewhat consistent with previous findings in Iran [20].

The introduction of new therapies has saved human lives but has also contributed to the emergence of antibiotic resistance and the development of life-threatening nosocomial infections [21]. Such infections not only lower the efficiency of current therapeutic protocols but also increase the duration of hospitalization, amount and frequency of antibiotic administration, and treatment costs [22-24].

In our study, the highest and lowest resistance rates were observed against imipenem (56.1%) and fosfomycin (15%), respectively. Previously, a survey reported a 3% rate of resistance to imipenem in Iran [25], which is much lower than the rate observed in our study. However, the survey included isolates from both blood and urine samples. Another study reported the rate of imipenem resistance around 25% [26], which is also lower than the rate observed in our study. Ciprofloxacin is prescribed as an effective drug for the treatment of various infections caused by gram-negative bacteria. In western Iran, *E. coli* isolates showed a resistance rate of 68% to ciprofloxacin, which is lower than the rate in our study [27]. The resistance to this antibiotic in Canada and Syria were reported 79% and 68%, respectively [28, 29]. The difference in the resistance rates might be due to variations in the patient samples. Nevertheless, the increased rate of resistance to imipenem and ciprofloxacin in our study could be attributed to the origin of isolates, *i.e.*, from ICU and CCU wards.

In the present study, the rate of resistance to cefepime and gentamicin was 42.4% and 34.8%, respectively, which were higher than the rates reported in similar studies in Iran (36% and 19.1%) [26] and (32% and 14%) [30]. The differences might be due to this proven fact that the isolates from ICU and CCU are more resistant than others. However, a study in Pakistan reported an 87% rate of resistance to cefepime [31], which is significantly higher than the rate obtained in our study. The previous study in Iran has also indicated higher rates of antibiotic resistance among *E. coli* isolates from ICU compared to general wards [32], but a study in the USA demonstrated that among Enterobacteriaceae, the highest susceptibility rates were related to ICU isolates compared to the non-ICU organism [33].

We observed the lowest rate of antibiotic resistance against fosfomycin. This antibiotic is less frequently administered in healthcare centers in Iran and is not

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available over the counter. In line with our findings, high rates of fosfomycin susceptibility were reported from Taiwan (94%) [34], Iran (97.3%) [35], and Korea (92.9%) [36]. Despite the favorable therapeutic efficacy of fosfomycin against gram-negative bacterial infections, there have been reports of bacterial resistance to this antibiotic. The bactericidal effects of fosfomycin on various gram-negative and gram-positive bacteria are mainly mediated through inhibition of the MurA enzyme. Resistance to fosfomycin among extended spectrum beta-lactamase-producing *E. coli* isolates is plasmid-mediated [4].

Our results showed that the *glpT* and *murA* genes were present in 22.2% and 77.8% of the *E. coli* isolates, respectively. Moreover, 11.1% of the isolates (one isolate) contained both genes. Similar studies in other countries have shown that most *E. coli* isolates carry at least one virulence gene [37, 38]. Unlike our findings, one study demonstrated that *murA* was not present in fosfomycin-resistant isolates [39]. This disparity between the findings could be due to genetic changes in the sources of antibiotic resistance and geographical factors.

Our results demonstrated a high prevalence rate of antibiotic-resistant among *E. coli* isolates originated from the care units of hospitals of Gorgan, Iran. Such significant resistance rates may contribute to the spread of the antibiotic resistance genes to other *E. coli* communities or similar bacteria. We found that fosfomycin has a favorable effect on clinical isolates of *E. coli*, which necessitate the monitoring of its use to lower the risk of developing resistance to this antibiotic.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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