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ORIGINAL ARTICLE

Detection of plasmid-mediated quinolone resistance in clinical isolates of *Enterobacteriaceae* strains in Hamadan, West of Iran

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Abstract Plasmid mediated quinolone resistance (PMQR) determinants have arisen as a significant concern in recent years. The aim of this study was screening of resistant-clinical isolates to fluoroquinolone antibiotics and detection of *qnr* and *aac(6′)-Ib-cr* genes.

For this purpose we collected 100 fluoroquinolone-resistant *Enterobacteriaceae* which were from 3 hospitals in Hamadan, west provinces of Iran, between October 2012 and June 2013. The all samples were identified by biochemical tests and confirmed by PCR method. Antimicrobial susceptibility to 14 antimicrobial agents including levofloxacin and ciprofloxacin were determined by disk diffusion methods and ciprofloxacin MIC was obtained by broth microdilution method as Clinical Laboratory Standards Institute (CLSI) recommendations. The isolates were screened for the presence of *qnrA*, *qnrB*, *qnrS* and *aac(6′)-Ib-cr* genes using PCR assay. Among the screened isolates, 64 strains (64%) of *Escherichia coli*, 23 strains (23%) of *Klebsiella pneumoniae*, 13 strains (13%) of *Proteus mirabilis* were collected as quinolone-resistant isolates. out of 100 isolates, two (2%) were positive for *qnrS*, seventeen (17%) isolates were positive for *qnrB* and we did not find *qnrA* gene in any of the isolates. There were also 32 positive isolates for *aac(6′)-Ib-cr* determinant. We described the

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prevalence of *qnr* and *aac(6′)-Ib-cr* genes in fluoroquinolone-resistant *Enterobacteriaceae* in Hamadan city. The carriage rate of multidrug-resistant *Enterobacteriaceae* in healthy people in Hamadan City is extremely high. Moreover, genes encoding transferable quinolones, in particular *aac(6′)-Ib-cr*, are highly prevalent in these strains.

1. Introduction

Enterobacteriaceae is a rod-shaped Gram-negative bacteria, many members of which are a normal part of the flora. They are considered as one of the most common human pathogens and frequently cause several diseases such as urinary tract, cystitis, pyelonephritis, septicemia, pneumonia, peritonitis, meningitis and infections associated with prosthetic devices such as catheters (Aslani and Alikhani, 2009; Haghighatpanah et al., 2016; Nordmann et al., 2011; Patel et al., 2009; Paterson and Bonomo, 2005; Sedighi et al., 2016). Quinolone antibiotics are broad-spectrum antibiotics and very important in the treatment of a wide range of diseases, especially urinary tract infections. Large range of activities, and the low side effects, as well as acceptable oral absorption, made these antibiotics as the first-line drugs to treat a variety of infections. The most common quinolone family is ciprofloxacin (Mandell, 2005; Shahcheraghi et al., 2013). These antibiotics tend to bind tightly to the bacterial enzymes (DNA gyrase or topoisomerase IV), and inhibit the bacterial growth. Aminoglycoside and quinolone antibiotics are used to treat infections caused by many genera and species of *Enterobacteriaceae* family. Over the past three decades, resistance to quinolones and aminoglycosides among *Enterobacteriaceae* family has increased significantly. One of the most reasons which has been reported worldwide is the incidence of plasmid-mediated resistance genes (Briales et al., 2012; Alikhani et al., 2013).

Fluoroquinolone resistance is mainly caused by mutations in chromosomal genes encoding the quinolone targets, such as DNA gyrase and topoisomerase IV, but in the past few decades, plasmid-mediated quinolone resistance (PMQR), has been increasingly reported in most parts of the world (Briales et al., 2012; Hooper and Rubinstein, 2003). Generally, three mechanisms of plasmid-mediated quinolone resistance have been described: (i) *qnr* proteins that protect the quinolone targets, (ii) *aac(6′)-Ib-cr* enzyme that acetylate aminoglycosides, ciprofloxacin and norfloxacin, (iii) Efflux pumps associated with QepA which excretes hydrophobic fluoroquinolones (Amin and Wareham, 2009; Yamane et al., 2008; Strahilevitz et al., 2009; Robicsek et al., 2006a).

In the present study, we investigated the prevalence of the PMQR determinants including *qnrA*, *qnrB*, *qnrS* and *aac (6′)-Ib-cr* in fluoroquinolone-resistant *Enterobacteriaceae* isolates that were obtained from clinical specimens. However, No previous survey has considered clinical isolates in our area for the presence of *aac(6′)-Ib-cr* determinant.

2. Materials and methods

2.1. Bacterial isolates

In total, 100 clinical isolates of non-replicate *Enterobacteriaceae* strains collected between October 2012 and June 2013 were selected for the study based on resistance to ciprofloxacin (zone diameter $\leqslant$15 mm) and/or reduced susceptibility/resistance to levofloxacin (zone diameter $\leqslant$13 mm). Specimens included in the study were from inpatients admitted at hospitals and from outpatients. All collected isolates were non-susceptible to ciprofloxacin. Samples were cultured on MacConkey agar. Then isolates were recognized by biochemical tests like: TSI, KIA, SIM, Simon citrate, MR-VP (Mahon et al., 2011). Our detection was confirmed by the presence of *rpoB* gene in all isolates by PCR. Previous studies showed that the *rpoB* gene can be used as the most promising target for detection of *Enterobacteriaceae* by PCR amplification (Fazzeli et al., 2012).

2.2. Antimicrobial susceptibility testing

Antimicrobial susceptibility was determined by the broth microdilution and disk diffusion methods following Clinical and Laboratory Standards Institute (CLSI) recommendations (CLSI, 2013; Safari et al., 2015). The tested antimicrobial agents were: ciprofloxacin (Sigma, Steinheim, Germany) by broth microdilution; and cefepime (30 μg), cefotaxime (30 μg), ceftazidim (30 μg), aztreonam (30 μg), ertapenem (10 μg), imipenem (10 μg), meropenem (10 μg), amikacin (30 μg), kanamycin (30 μg), doxycyclin (30 μg), ciprofloxacin (5 μg), levofloxacin (5 μg), tigecycline (15 μg), trimethoprim/-sulfamethoxazole (25 μg) (MAST, UK) using the disk diffusion method.

2.3. Screening for qnr and aac (6′)-Ib-Ir genes

All clinical isolates were grown for 18 h at 37 °C in MacConkey agar and DNA was extracted by SDS-Proteinase K phenol chloroform method as described (Farajnia et al., 2013). The *qnrA*, *qnrB* and *qnrS* genes were screened using a multiplex PCR-based technique (Yang et al., 2013) and the presence of *aac(6′)-Ib-cr* was detected using single PCR, producing a 482-bp product (Park et al., 2006) (Table 1). The Comparison of *aac(6′)-Ib-cr*-positive and *aac(6′)-Ib-cr*-negative isolates with antibiotics resistant were shown in Table 5.

2.4. Statistical analysis

Statistical analysis was performed using chi-square test with SPSS software (version 16). A P value of $\leqslant$0.05 was considered to indicate statistical significance.

3. Results

Among the screened isolates, 64 strains of *Escherichia coli* (64%), 23 strains of *Klebsiella pneumoniae* (23%), and 13 strains of *Proteus mirabilis* (13%) were collected as fluoroquinolone-resistant isolates. Most of quinolone-

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Table 1 PCR primers used in this study.

Primer	Primers	Size bp	References
rpoB-F	CAGGTCGTCACGGTAACAAG	512 bp	Fazzeli et al. (2012)
rpoB-R	GTGGTTCAGTTTCAGCATGTAC		
aac(6′)-Ib-cr F	TTGCGATGCTCTATGAGTGGCTA	482 bp	Park et al. (2006)
aac(6′)-Ib-cr R	CTCGAATGCCTGGCGTGTTT		
qnrA-F	AGAGGATTTCTCACGCCAGG	580 bp	Yang et al. (2013)
qnrA-R	TGCCAGGCACAGATCTTGAC		
qnrB-F	GGMATHGAAATTCGCCACTG	264 bp	Yang et al. (2013)
qnrB-R	TTTGCYGYYCGCCAGTCGAA		
qnrS-F	GCAAGTTCATTGAACAGGGT	428 bp	Yang et al. (2013)
qnrS-R	*TCTAAACCGTCGAGTTCGGCG*		

resistant strains were obtained from urine and tracheal samples with 48% and 36%, respectively. The other samples were collected from blood culture (4%), bed sore (2%), stool culture (1%), wound culture (8%) and throat culture (1%).

3.1. Antimicrobial susceptibility

Antibiotic susceptibility testing by disk diffusion showed that the 100 isolates were all susceptible to meropenem (100%). The highest sensitivity after meropenem was obtained with imipenem (92%) and ertapenem (82%). Resistance was most often observed with cefotaxime (97%), trimethoprim/sulfamethoxazole (90%), ceftazidime (89%), aztreonam (84%), doxycycline (77%), kanamycin (75%) and cefepime (61%) (Table 2). The ciprofloxacin minimum inhibitory concentrations (MIC) of 100 isolates were tested by broth microdilution (Table 3). Among the isolates, 9 strains were intermediate to ciprofloxacin but all of the *qnr* and *aac(6′)-Ib-cr* positive isolates were resistance to ciprofloxacin.

Table 2 The antibiotic resistance patterns of clinical isolates.

Antibiotic	Resistance No (%)	Intermediate No (%)	Sensitive No (%)
Aztreonam	84 (84)	8 (8)	8 (8)
Amikacin	33 (33)	11 (11)	56 (56)
Ceftazidime	89 (89)	4 (4)	7 (7)
Cefotaxime	97 (97)	1 (1)	2 (2)
Ciprofloxacin	97 (97)	0 (0)	3 (3)
Cefepime	61 (61)	21 (21)	18 (18)
Doxycycline	77 (77)	11 (11)	12 (12)
Kanamycin	75 (75)	6 (6)	19 (19)
Trimethoprim-sulfamethoxazole	90 (90)	0 (0)	10 (10)
Levofloxacin	85 (85)	6 (6)	9 (9)
Imipenem	0 (0)	8 (8)	92 (92)
Meropenem	0 (0)	0 (0)	100 (100)
Ertapenem	7 (7)	11 (11)	82 (82)

3.2. Screening for the qnr and aac(6′)-Ib-cr genes

The *qnr* genes were detected in 19/100 (19%) of fluoroquinolone resistance-*Enterobacteriaceae* by PCR. The *qnrB* gene were present in 11 (47.8%) of *K. pneumoniae*, 4(6.25%) of *E. coli* and 2 (15.38%) of *P. mirabilis*. The *qnrS* gene was present in 1 (4.34%) of *K. pneumoniae* and 1 (7.69%) of *P. mirabilis*. We did not find *qnrA* gene in any of the isolates (Table 4).

The *aac(6′)-Ib-cr* gene was detected in 32 (32%) of isolates. We found 13 (56.5%) of *K. Pneumoniae*, 11 (17.18%) of *E. coli* and 8 (61.53%) of *P. mirabilis* positive for this gene (Table 4).

4. Discussion

Over three past decades, bacterial resistance to quinolones has increased in clinical isolates. According to our results, fluoroquinolone-resistant isolates showed multidrug resistance to other antimicrobial agents like ceftazidime, cefotaxime, cefepime, kanamycin, amikacin, aztreonam, doxycycline and trimethoprim/sulfamethoxazole, that it may involve other

Table 4 Prevalence of *qnr* and *aac(6′)-Ib-cr* genes among *Enterobacteriaceae* spp.

Genes	*K. pneumoniae* No (%)	*E. coli* No (%)	*P. mirabilis* No (%)
aac(6′)-Ib-cr	13 (56.5)	11 (17.2)	8 (61.5)
qnrA	0 (0)	0 (0)	0 (0)
qnrB	11 (47.8)	4 (6.25)	2 (15.4)
qnrS	1 (4.34)	0 (0)	1 (7.7)

Table 3 Ciprofloxacin MIC of isolated bacteria.

Break point	Resistance (⩾1 μg/ml)					Intermediate (0.12–0.5 μg/ml)			Sensitive (⩽0.06 μg/ml)
MIC (μg/ml)	1	2	4	8	⩾16	0.125	0.25	0.5	⩽0.06
Isolates (no)	0	2	0	0	89	0	3	6	0
Total (%)	91					9			0

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Table 5 Comparison of *aac(6′)-Ib-cr*-positive and *aac(6′)-Ib-cr*-negative isolates with antibiotics resistant.

		aac(6′)-Ib-Ir gene		Total	*P value*
		Negative No (%)	Positive No (%)		
Kanamycin	R	45 (66.2)	30 (93.8)	75 (75)	0.716
	I	6 (8.8)	0 (0)	6 (6)	
	S	17 (25)	2 (6.3)	19 (19)	
Ciprofloxacin	R	65 (95.6)	32 (100)	97 (97)	0.079
	S	3 (4.4)	0 (0)	3 (3)	
Levofloxacin	R	57 (83.8)	28 (87.5)	85 (85)	0.573
	I	4 (5.9)	2 (6.3)	6 (6)	
	S	7 (10.3)	2 (6.3)	9 (9)	

mechanisms, such as chromosomal mutation in genes encoding for DNA gyrase (Yang et al., 2013; Shaheen et al., 2013), efflux pumps and producing AmpC β-lactamases (Gu et al., 2004) but these isolates still are susceptible to carbapenem antibiotics.

Previous studies suggested that the quinolone resistance rates in uropathogenic *E. coli* (UPEC) were high (84.2% antimicrobial resistance against nalidixic acid) because quinolones are the first choice of urinary tract infection (Muhammad et al., 2011), but in this study, *K. pneumoniae* had the highest fluoroquinolone resistance rates among *Enterobacteriaceae* spp. In the present study, 100 fluoroquinolone-resistant strains were examined for the presence of genes that naturally increases resistance to quinolones. In this study, we detected 17 *qnr*B and 2 *qnrS* genes but we did not find *qnrA* gene in any of the isolates and it is probably associated with the geographical distribution of *qnr* genes. The *qnr* genes were more prevalent among *Klebsiella* spp. (12/23, 52.2%) than among *E. coli* (4/64, 6.25%), as previously described in other studies conducted in France (Poirel et al., 2006), the United States (Robicsek et al., 2006b), Spain (Lavilla et al., 2008), China (Jiang et al., 2008) and Norway and Sweden (Karah et al., 2010). In previous study, the prevalence of *qnr* genes was much lower in *E. coli* isolates (4.8%) than in other species of clinical isolates of the *Enterobacteriaceae* in China, however, the prevalence of *aac(6′)-Ib-cr* appeared to be lower in *Enterobacter cloacae* isolates (9.3%) than in isolates of the other species tested. *qnr*A gene was not found in any of isolates (Yang et al., 2008).

To our best knowledge, this is the first study on the prevalence of *aac(6′)-Ib-cr* plasmid-mediated quinolone resistance in Hamadan city, and present findings suggest that *aac(6′)-Ib-cr* gene was more prevalent than *qnr* genes. *The aac(6′)-Ib-cr* gene was detected most often in *Klebsiella* spp. (13/23, 56.5%) than among *E. coli* (11/64, 17.2%). In the present study, there is no isolates which carried 2 types of *qnr* genes but 15 isolates with *aac(6′)-Ib-cr* carried *qnr*S (one strain of *Klebsiella* and one strain of *Proteus*) and *qnrB* (seven isolates of *Klebsiella*, four isolates of *E. coli* and two isolates of *Proteus*), simultaneously. There was a relationship between the presence of *qnr*A, -B, or -S genes and *aac(6′)-Ib-cr*. *aac(6′)-Ib-cr* was detected only in 15/19 (78.9%) of *qnr*-positive isolates but in 17/81 (20.9%) of the *qnr*-negative isolates (P 0.0001 by a two-tailed Fisher's exact test), indicating that the *qnr* genes and *aac(6′)-Ib-cr* can circulate dependently. A comparable prevalence was reported from China where the prevalence of the *aac(6′)-Ib-cr* variant among *E. coli* and *K. pneumoniae* isolates was 55.2% among *qnr*-positive isolates but only 6% among *qnr*-negative isolates (Jiang et al., 2008). The reason is not understood yet, but it is known that some plasmids can carry both *aac(6′)-Ib-cr* and *qnr* genes (Robicsek et al., 2006b). According to previous studies, the *cr* variant of *aac(6′)-Ib-cr* encodes an enzyme that had slightly reduced efficiency in acetylation of kanamycin (Robicsek et al., 2006c). *aac(6′)-Ib-cr* confers resistance to kanamycin but not to gentamicin (Robicsek et al., 2006b). So we analyzed the relationship between *aac(6′)-Ib-cr* and susceptibility to ciprofloxacin, levofloxacin and kanamycin (Table 2). The results of this study confirmed that there is no relationship between *aac(6′)-Ib-cr* and susceptibility to ciprofloxacin, levofloxacin and kanamycin ($P \geqslant 0.05$).

This study showed that the prevalence of plasmid-mediated quinolone resistance due to the *qnr* and *aac(6′)-Ib-cr* genes was high among fluoroquinolone-resistant clinical isolates of *Enterobacteriaceae* in Hamadan. Fluoroquinolone resistance is mainly caused by mutations in chromosomal genes encoding the quinolone targets, such as DNA gyrase and topoisomerase IV. So PMQR is not the only resistant mechanism to quinolone. In our study, 41 fluoroquinolone-resistant clinical isolates (41%) were positive for plasmid-mediated quinolone resistance genes and the other strains (59 isolates) had probably the other resistant mechanisms that are not investigated in this study. Among 3 important species (*E. coli*, *Klebsiella* and *Proteus* spp.), the prevalence of *qnr* appeared to be much lower in *E. coli* isolates (6.25%) than in other species of clinical isolates of the *Enterobacteriaceae*. However, the prevalence of *aac(6′)-Ib-cr* appeared to be lower to (17.2%) in *E. coli* isolates. *qnrA* gene was not found in large numbers of resistant clinical isolates of *Enterobacteriaceae* spp. Infections caused by *qnr*-positive isolates might subsequently enhance the selection of resistant mutants and increase the risk of therapeutic failure.

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