ORIGINAL ARTICLE

Occurrence of aac(6')-Ib-cr and Qnr Genes among Quinolone-Resistance Enterobacteriaceae Isolated from Patients with Urinary Tract Infection in Najaf, Iraq

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ABSTRACT

INTRODUCTION: The *aac(6')-Ib-cr* gene is one of the most common genes among plasmids and has dual activity against both aminoglycoside and quinolone antibiotics, making it among the most important plasmid-mediated quinolone resistance genes. This research aimed to confirm the frequency of *aac(6')-Ib-cr* and *qnr* genes in quinolone-resistant *Enterobacteriaceae* isolates obtained from patients with urinary tract infection in Najaf, Iraq. **MATERIALS AND METHODS:** Quinolone resistance was examined in 318 urine samples taken from individuals who had suspected urinary tract infections (135 *Klebsiella pneumonia* cases, 75 *Proteus mirabilis* cases, and 108 *Escherichia coli* cases). Using PCR, antibiotic susceptibility patterns were assessed for quinolone resistance isolates and the presence of the *aac(6')-Ib-cr, qnrA*, *qnrB*, and *qnrS* were looked into. **RESULTS:** Quinolone-resistant isolates totaling 176 were identified. *aac(6')-Ib-cr* was detected in 93 (52.8%) cases, 50 of which were *E. coli*, 39 were *K. pneumoniae*, and 4 were *P. mirabilis*, according to PCR analysis data. *qnrA* 6 (3.4%), *qnrB* 22 (12.5%), and *qnrS* 5 (2.8%) isolates were identified to have the following *qnr* genes. *P. mirabilis* did not have the *qnrS* gene, which was absent from all analyzed genes detected in bacterial isolates. **CONCLUSION:** It was shown that of the plasmid-mediated quinolone resistance genes, the *aac(6')-Ib-cr* gene was the most common. Every gene analyzed was present in both *K. pneumoniae* and *E. coli*.

Keywords
Plasmid-mediated quinolone resistance, *qnr* genes, PMQR, *qnrA*, *aac(6')-Ib-cr*

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INTRODUCTION

Many resistance mechanisms against quinolones have been established by *Enterobacteriaceae*. The mechanisms mostly entail a mutation in the chromosomal genes (DNA gyrase then topoisomerase IV), which encode quinolone targets, and/or decreased drug permeability.[1,2] Genes on plasmids, such as *Qnr, QepA* and *Oqx*AB (plasmid-mediated efflux pump), and an aminoglycoside acetyltransferase *aac(6')-Ib-cr* gene variation, can also cause quinolone resistance.[3]

It becomes more difficult to treat quinolone-resistance *Enterobacteriaceae* infections when plasmid-mediated quinolone resistance (PMQR) is prevalent, because it promotes the spread of resistance.[4] The presence of *qnr* genes in *Enterobacteriaceae* species that are less sensitive to fluoroquinolones.[5]

Aminoglycosides have been a mainstay in treating infections produced by *Enterobacteriaceae*. In contrast, aminoglycoside-resistant strains of these bacteria have emerged in recent years.[6] Nosocomial infections produced by *Enterobacteriaceae* are particularly difficult to treat because of three processes that reduce the efficiency of aminoglycosides. These consist of altered ribosome binding sites, the emergence of enzymes that modify aminoglycosides, and decreased cell permeability or absorption.[7]

Aminoglycoside-modifying enzymes are the chief machine of aminoglycoside resistance in *Enterobacteriaceae*.[8] The structural disintegration of aminoglycosides by acetyltransferases and other enzymes is a possibility, as phosphotransferases, and adenyltransferases.[9] The aminoglycoside acetyltransferase *aac(6')-Ib* mainly encodes resistance to specific aminoglycoside antibiotics

(kanamycin, tobramycin, and amikacin).[10] This gene may have another function in a variation of the 6'-N-aminoglycoside acetyltransferase (*aac(6')-Ib*-cr) gene, to acetylate quinolones with piperazinyl subunit (for example ciprofloxacin and norfloxacin) only.[1] This gene may present in a multidrug-resistant plasmid within the cassette of the class one integron, which can carry many other quinolone resistance genes.[1,10]

Given that there are no clear indications of, the *aac(6')-Ib-cr* gene's existence in Al-Najaf, Iraq. Finding out how common the *aac(6')-Ib-cr* and plasmid-mediated quinolone resistance (PMQR) genes are in clinical isolates of *Enterobacteriaceae* resistant toward quinolones in Al-Najaf, Iraq, is the goal of this study.

MATERIAL AND METHODS

Bacterial isolation

Al-Zahra Education Hospital for Parenthood and Pediatrics, Al-Sader Medical City, and Al-Hakeem Overall Hospital remained the three hospitals in Al-Najaf city midpoint from which 318 midstream urine samples were collected from patient roles who presented with urinary tract infections between January 2020 and December 2022. The VITEK 2 system and VITEK 2 GN ID Card (Biomerieux, France) were used to authenticate each strain of bacteria.

Antimicrobial susceptibility testing and detection of quinolone resistance isolates

The antibiotic sensitivity tests were achieved in compliance with the Clinical Laboratory Standard Institute (CLSI) standard. [11] To identify isolates resistant to quinolones, all isolates were tested against ciprofloxacin (CIP, 5 μg) and nalidixic acid (ND, 5 μg) (Cypress, Belgium). The results were verified using MIC strips (Liofilchem, Italy).

Antibiotic resistance patterns were conducted according CLSI guidelines.[11] Ampicillin (AM, 10 μg), amoxicillin (AX, 25 μg), cefotaxime (CTX, 30 μg), ceftazidime (CAZ, 30 μg), ceftriaxone (CTR, 30 μg), cefoxitin (FOX, 30 μg), aztreonam (ATM, 30 μg), imipenem (IPM, 10 μg), meropenem (MEM, 10μg), levofloxacin (LEV, 5 μg), lomefloxacin (LOM, 10 μg), norfloxacin (NOR, 10 μg), ofloxacin (OFX, 5 μg), amikacin (AK, 30 μg), tobramycin (TOB, 10 μg), gentamycin (CN, 10 μg), netilmicin (NET, 30 μg), sulphamethazole (SMZ, 250 μg), trimethoprim (TMP, 5 μg).

Detection of plasmid-mediated quinolone resistance (PMQR) genes

The cells underwent a previously described analysis to detect the presence of the *aac(6')-Ib* gene. Using previously described primers to amplify every known variant of the target gene, the primers were selected.[12] PCR amplification conditions were 95˚C for 3 minutes, followed by 94˚C for 45 seconds, 55˚C for 45 seconds, 72˚C for 45 seconds for 34 cycles, and 72˚C for 5 minutes as the final extension. The amplification yielded 482 bp. The PCR results were given to a gel documentation system (Biometra, Germany) for visualization, and they were electrophoresed. After restriction, *aac(6')-Ib* showed 272 bp and 210 bp fragments, but *aac(6')-Ib-cr* did not exhibit a restriction site. These PCR-positive isolates were then subjected to additional analysis using the BtsCl enzyme. Using primer sets, monoplex PCR was used to screen for *qnrA*, *qnrB*, and *qnrS*. PCR amplification conditions previously described, the 512 bp, 417 bp, and 469 bp PCR products were obtained accordingly.[13] The agarose was stained with ethidium bromide; the electrophoresis was performed at 70 volts for 90 minutes.

RESULTS

The present study revealed that out of the 318 clinical isolates, *Enterobacteriaceae* strains were found in the midstream urine samples collected where *Escherichia coli*) ,(%34 ,108 *Klebsiella pneumoniae* (135, 42.5%), and *Proteus mirabilis* (75, 23.5%).

In the current investigation, 176 isolates (60 *E. coli*, 74 *K. pneumoniae*, and 42 *P. mirabilis*) were shown to be resistant to quinolones based on CLSI standards. The pattern of antimicrobial resistance against quinolone resistance found in 176 isolates is displayed in Table I. According to An analysis of the design for resistance to antibiotics, the majority of quinolone-resistant bacteria in this study were resistant to penicillin (99.3%) and amoxicillin (98.8%).

There were followed by sulphamethazole (82.9%), trimethoprim (80.1%), cefotaxime (79.5%), ceftazidime (76.1%), ceftriaxone (74.4%), and aztreonam (63.6). We can observe that the fluoroquinolone group had a high level of resistance to lomefloxacin (66.4%), although the other fluoroquinolones, levofloxacin (36.9%), norfloxacin (48.2%), and ofloxacin (50.5%), had intermediate resistance. Amikacin (21.5%), tobramycin (69.3%), gentamycin (58.5%), and netilmicin (26.1%) were also found in this investigation

Table I: Antibiotic susceptibility pattern of 176 quinolone-resistance *Enterobacteriaceae* clinical isolates

Antibiotics	E. coli (60 isolates) n. (%)	K. pneumoniae (74 isolates) n. (%)	Proteus spp (42 isolates) n. (%)	Total (176 isolates) n. (%)
Ampicillin	59 (98.3)	74 (100)	42 (100)	175 (99.3)
Amoxicillin	58 (96.7)	74 (100)	42 (100)	174 (98.8)
Cefotaxime	51 (85)	64 (86.5)	25 (59.5)	140 (79.5)
Ceftazidime	50 (83.3)	63 (85.1)	21 (50)	134 (76.1)
Ceftriaxone	48 (80)	61 (82.4)	22 (52.4)	131 (74.4)
Cefoxitin	11 (18.3)	39 (52.7)	21 (50)	71 (40.3)
Aztreonam	42 (70)	59 (79.7)	11(26.2)	112 (63.6)
Imipenem	6 (10)	23 (31.1)	0 (0)	29 (16.4)
Meropenem	15 (25)	25 (33.8)	0 (0)	40 (22.7)
Levofloxacin	28 (46.7)	24 (32.4)	13 (31)	65 (36.9)
Lomefloxacin	41 (68.3)	56 (75.7)	20 (47.6)	117 (66.4)
Norfloxacin	33 (55)	35 (47.3)	17 (40.5)	85 (48.2)
Ofloxacin	34 (56.7)	36 (48.6)	19 (45.2)	89 (50.5)
Amikacin	2 (3.3)	26 (35.1)	10 (23.8)	38 (21.5)
Tobramycin	40 (66.7)	52 (70.3)	30 (71.4)	122 (69.3)
Gentamycin	37 (61.7)	39 (52.7)	27 (64.3)	103 (58.5)
Netilmicin	4 (6.7)	29 (39.2)	13 (31)	46 (26.1)
Sulphamethazole	54 (90)	62 (83.8)	30 (71.4)	146 (82.9)
Trimethoprim	47 (78.3)	66 (89.2)	28 (66.7)	141 (80.1)

All 176 quinolone resistance isolates investigated through PCR for the existence of *aac(6')-Ib*, *qnrA*, *qnrB*, *qnrS* genes. A total of 131 (74.4%) were demonstrated that harbored *aac(6')-Ib* gene, the most common gene found in *E. coli* 54 (90%) followed by *K. pneumoniae* 57 (77%) and *P. mirabilis* 20 (47.6%) (Figure .(1 In the same manner, the present study confirmed that the *aac(6')-Ib-cr* gene 93 (52.8%) of isolates *E. coli* 50 (83%) followed by *K. pneumoniae* 39 (52.7%) and *P. mirabilis* 4 (9.5%) The *qnrA* was found most frequently in *P. mirabilis* 3 (7.1%), followed by *K. pneumoniae* 2 (2.7%), and *E. coli* 1 (1.6%) (Figure 2). A total of 17 (23%) *K. pneumonia* isolates carried *qnrB* gene (Figure 3), while only 1 (14%) carried *qnrS* (Figure 4). In *E. coli*, both qnrB and qnrS were detected in 4 (6.6%) isolates while in *P. mirabilis* harbor only *qnrB* gene. Table II demonstrated the frequency of the plasmid-mediated quinolone resistance (PMQR) gene among 176 quinolone resistance isolates.

Table II: Frequency of plasmid-mediated quinolone resistance (PMQR) gene among 176 quinolone resistance isolates

Gene	E. coli n=60	K. pneumonia n=74	Proteus spp n=42	Total n=176
aac(6')-Ib	54 (90%)	57 (77%)	20 (47.6%)	131 (74.4%)
aac(6')-Ib-cr	50 (83.3%)	39 (52.7%)	4 (9.5%)	93 (52.8%)
qnrA	1 (1.7%)	2 (2.7%)	3 (7.1%)	6 (3.4%)
qnrB	4 (6.7%)	17 (23%)	0	21 (11.9%)
qnrS	4 (6.7%)	1 (1.4%)	0	5 (2.8%)

DISCUSSION

Quinolone antibiotic was first discovered in the sixties in the last century and used to treat urinary tract infections in adult patients, then it developed to treat other sites of infection over time.[14] However, an expansion in the use of quinolone and fluoroquinolone group classes of antibiotics led to the appearance of resistance against this group.[15] Quinolone resistance mediated by plasmids was initially recognized in the members of the *Enterobacteriaceae* family. Over time, many of the genes that produce quinolone resistance within this category have been identified.[16] The prevalence of PMQR genes in Al-Najaf city was fairly assessed.[17] Therefore, in this study, we investigated the presence of these genes among three members of the *Enterobacteriaceae* family (*E. coli, K. pneumoniae*, and *P. mirabilis*) and understood their antibiotic susceptibility background.

In our study, the results show 52.8% of collected quinolone-resistance *Enterobacteriaceae* clinical isolates harbor at least one PMQR gene. These results were significantly high, several studies accomplished worldwide revealed a lower rate. In Algeria,[18] Europe, Spain,[19] and Mexico,[15] rates are 13.5%, 20%, 31.8%, and 32.1% respectively. The *aac(6')-Ib-cr* gene causes resistance to quinolone as well as aminoglycoside, especially it is responsible for reducing susceptibility to ciprofloxacin in vivo[1]. In this study, the prevalence of *aac(6')-Ib-cr* gene was 52.8%, and this finding may explain the high level of resistance to ciprofloxacin and norfloxacin, especially when combined with chromosomal mutation.[3] The rate

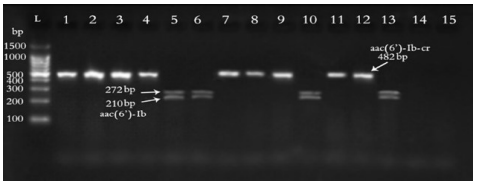

Figure 1: Agarose gel of PCR amplification products of *K. pneumoniae*. isolates amplified with primer targeting the *aac(6')-Ib* genes after digested with BstCI. Lane (L), molecular size marker (100 bp), lane (1,2,3,4,7,8,9,11,12) display positive results with *aac(6')-Ib-cr*, lane (5, 6, 10, 13) display *aac(6')-Ib* wild-type genes.

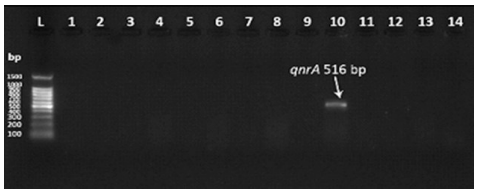

Figure 2: Agarose gel of PCR amplification products of *Proteus spp.* isolates amplified with primer targeting the *qnrA* genes. Lane (L), molecular size marker (100 bp), lane (10) displays positive results with *qnrA*, lane (1,2,3,4,5,6,7,8,9,11,12,13,14) displays negative results with *qnrA* genes.

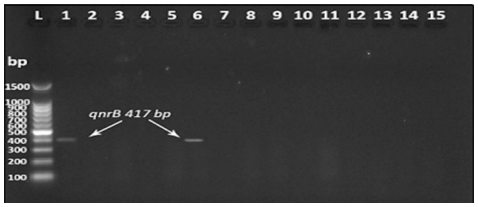

Figure 3: Agarose gel of PCR amplification products of *E. coli.* isolates amplified with primer targeting the *qnrB* genes. Lane (L), molecular size marker (100 bp), lane (1,6) displays positive results with *qnrB*, lane (2,3,4,5,7,8,9,10,11,12,13,14) displays negative results with *qnrB* genes.

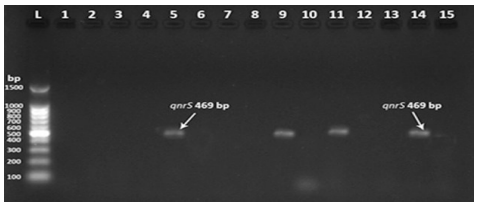

Figure 4: Agarose gel of PCR amplification products of *E. coli* isolates amplified with primer targeting the *qnrS* genes. Lane (L), molecular size marker (100 bp), lane (5,9,11,14) displays positive results with *qnrS*, lane (1,2,3,4,6,7,8,10,12,13) displays negative results with *qnrS* genes.

of *aac(6')-Ib-cr* gene in the present study was similar to the study conducted in Iran 68.6%[25], and higher than a study conducted in Brazil 40.8%26, Mexico 15.1%20. The *aac (6')-Ib-cr* gene was present more frequently in *E. coli* 83% followed by *K. pneumoniae* 52.7%, and less frequently in *P. mirabilis* 9.5%, in agreement with other studies.[18,20] The high frequency of *aac(6')-Ib-cr* gene puts the therapeutic options in the narrow circle where it is expressed as resistant to both quinolone and aminoglycoside drugs in the future.

In this study, the prevalence of Qnr determinants was found in 23.8% of *Enterobacteriaceae* quinolone resistance isolates. The *qnr* gene was strongly associated with various species of *Enterobacteriaceae* worldwide.[21] A previous study has reported that *qnr* genes represent 5.7% in China,[22] 15.1% in Tunisia,[23] and 28.7% in Spain,[18] of quinolone-resistance *Enterobacteriaceae* clinical isolates. Among the 176 quinolone-resistance *Enterobacteriaceae* clinical isolates, the frequency of *qnrA* was 6 (3.4%), three of them found in *P. mirabilis*. This finding was close to results accomplished in India,[23] and Iran,[24] while another study conducted in Europe and Brazil didn't record this gene in *Enterobacteriaceae* isolates.[25,26] The *qnrB* in the present study was found in 21 (11.9%) *Enterobacteriaceae* quinolone resistance isolates, 17 located in *K. pneumonia*. This result was higher than recorded in Qatar,[27] Sweden.[29] The *qnrB* gene was the most prevalent *qnr* resistance gene, not only in this study but also recorded by studies conducted in Morocco,[28] Iran,[24] Austria,[29] and Turkey.[4] Five isolates carried the *qnrS* gene, mostly in *E. coli*, this result was similar to that recorded in Eurpe.[30]

Unfortunately, there is no clear strategy in our country to control the administration and use of antibiotics, as they are given without a prescription in pharmacies, and therefore it is difficult to reduce the spread of antibiotic resistance genes among bacteria, which in turn reduces the effect and treatment options for infected patients, which leads to aggravating the health condition. The limitation of this study is that no equal number of isolates from each bacterium selected from the *Enterobacteriaceae* family. Not all PMQR genes were screened, which gives incomplete information about resistance genes.

CONCLUSIONS

Isolates with elevated quinolone resistance, particularly to cephalosporins and penicillins, were detected. *aac(6')-Ib-cr* was the most common PMQR gene among the isolates, with a widespread frequency of these genes observed. Every gene that was checked turned up in *K. pneumoniae* and *E. coli*. Investigation of quinolone resistance genes in Al-Najaf necessitates more research, in Iraq, since the limitation of data in this area.

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CONFLICT OF INTEREST

Researchers don't have any conflicts of interest.

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