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Frequency of Plasmid-Mediated Quinolone Resistance Genes *qnr* A, *qnr* B and *qnr* S Among Clinical Isolates of *Klebsiella pneumoniae*

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Abstract

Introduction: Plasmid-mediated quinolone resistance (PMQR) is a growing clinical concern throughout the world. The purpose of this study was to detect *qnr*-encoding genes and to evaluate the clonal relatedness of *qnr*-positive *Klebsiella pneumoniae* isolates.

Materials and Methods: A total of 88 *K. pneumoniae* isolates assessed to quinolone which were obtained from Tehran hospital in Tehran, Iran. Bacterial identification was administrated using standard laboratory methods. Quinolone resistance was determined using the Kirby-Bauer disk diffusion method according to the Clinical Laboratory Standards Institute (CLSI) guidelines. The PCR was employed to detect *qnr*A, *qnr*B and *qnr*S genes.

Results: The results of disk diffusion showed that 39.3%, 32.1%, 27.4%, 27.1%, 22.6% of strains were fully resistant to nalidixic, norfloxacin, *ofloxacin,* ciprofloxacin *and levofloxacin,* respectively. The *qnrB* (43% isolates) was the most commonly detected gene, followed by *qnrS* (34% isolates) and *qnr*A (23 % isolates) either alone or in combination with other genes.

Conclusions: This study describes the high prevalence of the *qnrB*, *qnr*S, and *qnr*A genes among *K. pneumoniae* isolates in Iran. The detection of *qnr* genes accentuate the need for organizing tactful policies associated with infection control measures in hospital settings in Iran.

Keywords: *Klebsiella pneumoniae*, PCR, Plasmid-Mediated Quinolone Resistance

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Introduction

Klebsiella pneumoniae is an opportunistic pathogen that frequently causes severe nosocomial infections such as pneumonia, urinary tract infections, soft tissue infections and septicemia.[1,2] This organism is also known as a community-acquired pathogen.[3] Over the last few years, infections by carbapenem-resistant *Klebsiella pneumoniae* have caused high rates of mortality and morbidity.[4,5]

Quinolones were introduced for the treatment of bacterial infections in the 1960s.[6] In the 1980s, more systemically active drugs became available.[7] Quinolone agents inhibit DNA gyrase as their target site. In recent decades, fluoroquinolone resistance among Enterobacteriaceae has been increased. The primary mechanism of fluoroquinolone resistance in the family of Enterobacteriaceae is related to the mutation of chromosomal genes encoding topoisomerase IV, DNA gyrase, efflux pumps and porins. The recent reports demonstrate that quinolone resistance may also be mediated by plasmid-mediated quinolone resistance (PMQR) genes including *qnrA, qnrB, qnrC, qnrD, qnrS, qnrVC, aac(6')-Ib-cr,* qepAB and oqxAB.[8,9] Quinolone resistance genes code the pentapeptide repeat family proteins interacting with DNA gyrase and topoisomerase IV enzymes to hinder quinolone inhibition.[10]

The first PMQR (*qnr*) gene was detected in a *K. pneumoniae* isolate from Birmingham, Alabama, in 1994.[11] It occurred in an integron-like structure near Orf513 in pMG252 plasmid.[12] The second PMQR mechanism involves the acetylation of the drug by a variant of the gene encoding aminoglycoside acetyltransferase AAC (6')-Ib.[13] The third mechanism of PMQR were the transporters, known as quinolone efflux pumps (*QepAB and OqxAB*), which exhibit resistance to the hydrophilic quinolones, especially to ciprofloxacin, enrofloxacin, and norfloxacin.[9] The relationship between quinolone resistance and resistance to other antimicrobial agents, particularly aminoglycosides and β-lactams, is a serious problem in managing these infections. In-vitro studies have shown that after exposure to antibiotics, high levels of resistance can occur in isolates carrying the PMQR genes.[14,15]

Therefore, monitoring and the surveillance of PMQR genes among Enterobacteriaceae are required. The disk diffusion test, could not detect PMQR positive isolates because of the low-level resistance. Molecular techniques such as PCR assays are required as confirmatory tests for PMQR detection in epidemiological studies. Data on the frequency of *qnrA*, *qnrB*,

and *qnrS* genes is limited in *K. pneumoniae* isolates collected from clinical samples from humans in Iran. Accordingly, the aim of this study was to determine the prevalence of *qnrA*, *qnrB*, and *qnrS* genes in *K. pneumoniae* isolated from clinical specimens of patients who had referred to a hospital in Tehran, Iran.

Materials and Methods

Bacterial Isolation From Clinical Samples

In the present cross-sectional study, 88 non-repetitive *K. pneumoniae* isolates were collected from the clinical samples of patients admitted to the Tehran hospital from 21 September 2018 to 24 September 2019. Various clinical specimens including; sputum, blood, and urine were assayed. Identification of bacteria was performed by gram stain, culture characteristic and biochemical methods. For the preservation of bacteria at -70°C, trypticase soy broth containing 20% glycerol was used.

Antimicrobial Susceptibility Testing

Antibiotic susceptibility to detection of quinolone resistance against nalidixic acid (30 µg), norfloxacin (10 µg), ofloxacin (5 µg), levofloxacin (5 µg) and ciprofloxacin (5 µg) was used by Kirby-Bauer disk diffusion testing according to the Clinical Laboratory Standards Institute (CLSI) guidelines.[16] The antibiotic disks were purchased from the Rosco. If isolates resistance to two of the quinolone antibiotics were classified as high-level quinolone resistance and resistance to nalidixic acid were classified as intermediate isolates and ciprofloxacin-susceptible isolates were classified as low-level quinolone resistance.[17] For quality control in antibiotic susceptibility, the *Escherichia coli* American Type Culture Collection (ATCC) 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used.

DNA Extraction and PCR Assay

The DNA of every isolate was extracted using fresh overnight culture in TSB by Favorgen; Taiwan Kit. Extracted DNA was subjected to PCR assay targeting three genes of *qnrA*, *qnrB* and *qnrS* using specific primers (Table 1). The reaction mixtures were prepared in a total volume of 20 µL containing 10 µL of PCR master mix plus, 1 µL of template DNA and 5ng of genomic DNA, 0.5 µL of each primer (0.5 µM) and 8 µL water. The QnrA, QnrB and Qnrs producing *K. pneumoniae* strains and *E. coli* ATCC25922 were used as positive and negative quality controls for the PCR test respectively.

The PCR amplifications were performed in a thermocycler as follows: 95°C for 5 minutes and 30 cycles of 45 seconds at 95°C, 45 seconds at a specific annealing temperature for each primer and 45 seconds at 72°C. A final extension step of 10 minutes at 72°C was performed. Analysis of PCR products were checked on 1.5% gel electrophoresis containing safe DNA stain and results were visualized under gel document system.

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

In the present study, 88 *K. pneumoniae* isolates were obtained from different clinical specimens including 93.5% from urine specimens, 5.2% from blood specimens and 1.3% from sputum specimens. The isolates were collected from 67.5% patients admitted to intensive care units and 32.5% from those admitted to the outpatient. The mean age of the patients was 39.4 years (range: 1-90 years); 22.5% patients were male and 77.5% were female. The findings of the disk diffusion test revealed that 39.3%, 32.1%, 27.4%, 27.1%, 22.6% isolates were resistant to nalidixic, norfloxacin, ofloxacin, ciprofloxacin and levofloxacin, respectively (Figures 1-3).

The PCR assay for *qnr*-encoding genes described that from among the 88 *K. pneumoniae* isolates, *qnrB, qnrS* and *qnrA* were present in 43%, 34% and 23% of isolates respectively. In total, 50% of the isolates showed high-level quinolone resistance and *qnr*-positive isolates were mostly (80%) observed in urine samples (Table 2).

Among the 88 cases, 41 *K. pneumoniae* isolates were at least resistant to an antibiotic and 26 isolates showed resistance genes. Among the PMQR-positive isolates, 73% (19 of 26 isolates) carried two different PMQR genes and 7.6% (2 isolates) carried three different PMQR genes (Table 2).

Discussion

The prevalence of *qnrA, qnrB and qnr S* genes in quinolone – non-susceptible *K. pneumoniae* isolated was investigated from different samples in Iran. Quinolones are among the most commonly prescribed antimicrobial agents for the treatment of major infections caused by the Enterobacteriaceae family.[14] Also, resistance development to these antibiotics in bacteria complicates treatments and may sometimes lead to treatment defeat.[14,15] Recently, PMQRs have been reported in various studies, especially among enterobacteria.[15] However, there are few data on the prevalence of *qnr* genes among Enterobacteriaceae isolates in Iran.[18] The high resistance rate observed among urine isolates (93.5%) in this study emphasizes the need of a local and national antimicrobial

Table 1. Primers Used for the Detection of *qnr* Genes in *Klebsiella pneumoniae* Isolates

Target Genes	Primer Sequence (5'-3')	Annealing Temperature (°C)	Size (bp)	Reference
qnrA	Forward: ATTTCTCACGCCAGGATTTG Reverse: GATCGGCAAAGGTTAGGTCA	54	516	17
qnrB	Forward: GATCGTGAAAGCCAGAAAGG Reverse: ACGATGCCTAGTAGTTGTCC	53	469	17
qnrS	Forward: ACGACATTCGTCAACTGCAA Reverse: TAAATTGGCACCCTGTAGGC	53	417	17

qnr: quinolone resistance.

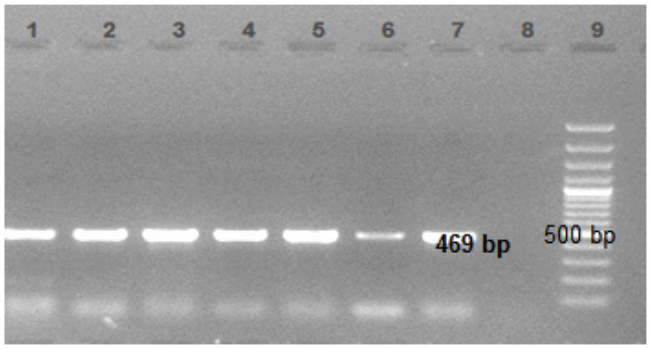

Figure 1. Analysis of PCR Product of *qnrB* Gene. Lanes 1-6: Positive results for *qnrB*, lane 7: Positive control, lane 8: Negative control, lane 9: Lader (100 bp).

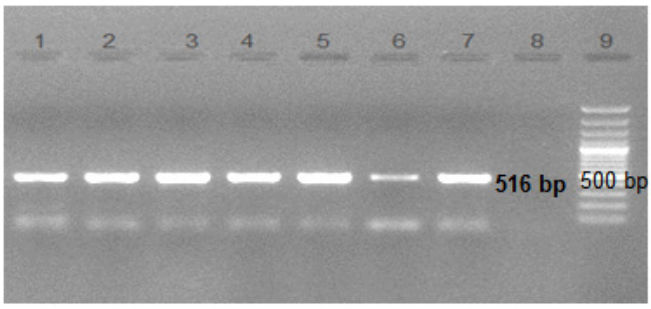

Figure 2. Analysis of PCR Product of *qnrA* Gene. Lanes 1-6: Positive results for *qnrB*, lane 7: Positive control, lane 8: Negative control, lane 9: Lader (100 bp).

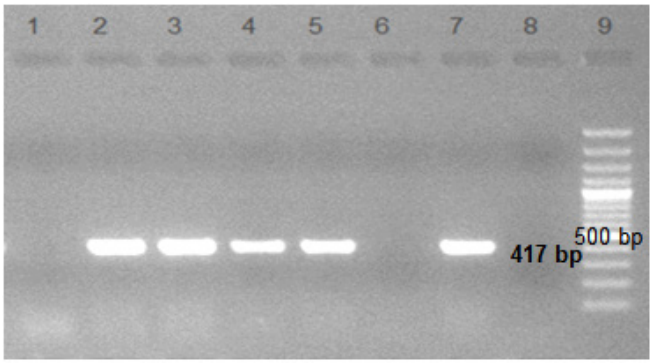

Figure 3. Analysis of PCR Product of *qnrS* Gene. Lane 1: Negative control, lanes 2-5: Positive results for *qnrS*, lane 6: Negative results for qnrS, lane 7: Positive control, lane 8: Negative control, lane 9: Lader (100 bp).

resistance surveillance system for monitoring the operation of antimicrobials and outward of antibiotic resistance in bacterial isolates present in hospital settings.

The present study demonstrated a high (50%) prevalence of PMQR determinants between quinolone resistant *K. pneumoniae* isolates collected from a hospital in Iran. The PMQR genes reported in our hospital were similar to those reported from many countries, particularly in China.[19] However, the frequency of the genes found in our study was higher than that reported by Rodríguez-Martínez et al from Spain (1.8%).[20] Totally, the prevalence of the *qnr* genes in bacterial isolates vary in the range of 1% to 50% in various studies,[19-23] depending on the selection criteria and study period for bacterial isolates. Moreover, this may indicate that the rate of PMQR is increasing among enterobacteria.

Briales et al reported that the prevalence of *qnr* genes has increased to 3.7%. Despite the fact that the prevalence of *qnr* genes in Spain continues to be low, it can be concluded that the wide geographical distribution of PMQR genes and their association with ESBL-producing plasmids should be taken into account as an extra factor that could compromise the therapeutic usefulness of quinolones.[23]

Yang et al[19] also reported the presence of different PMQR genes in clinical isolates of *K. pneumoniae*, indicating the wide spread of *qnr* genes among clinical isolates of enterobacteriaceae. Wang et al reported that *qnrA*, *qnrB* and *qnrS* were detected either alone or in combination in 3.8%, 4.7% and 3.8% of these isolates, respectively which had a much lower resistance rate compared to the present study.[24] In another study in Korea, Shin et al[22] reported that 55.9% of *K. pneumoniae* ciprofloxacin-resistant isolates only contained *qnrB* (*qnrB2*, *qnrB4* and/or *qnrB6*). These data suggest that inappropriate and extensive use of broad-spectrum antibiotics has resulted in the emergence of resistant isolates in hospital settings.

Purified qnrB, like qnrA, protected DNA gyrase from quinolone action. It seems to be even more potent than QnrA in blocking the action of ciprofloxacin.[25] In the present study, qnrB had the highest frequency of resistance**.** India and the

Table 2. Distribution of the *qnrA*, *qnrB* and *qnrS* Genes Among 80 *qnr*-Positive *Klebsiella pneumoniae* Isolates

qnr-Encoding Genes	Pattern Antibiotic Resistance	N (Isolate)
qnrB		
	NA	1
	OFLOX-NA	1
	OFLOX-NA-NOR-CP	1
	OFLOX-NA-NOR-CP-LVX	2
qnrA- qnrB		
	NA-CP	1
	NA	3
	CP	2
	NA-NOR	2
qnrB- qnrS		
	NA-CP	1
	OFLOX-NA-NOR	1
	OFLOX-NA-NOR-CP	1
	OFLOX-NA-NOR-LVX	2
	OFLOX-NA-NOR-CP-LVX	6
qnrA-qnrB- qnrS		
	NA	1
	OFLOX-NA-NOR-CP-LVX	1
Total		26

NA= Nalidixic acid, OFlOX= Ofloxacin, NOR= Norfloxacin, CP=Ciprofloxacin, LVX= Levofloxacin.

United States suggest that this resistance mechanism has been present long enough to disseminate widely. Preliminary surveys indicate that in ceftazidime-resistant *Enterobacter* and *Klebsiella* isolates from the United States *qnrB* is as common as *qnrA*.[26]

It has been stated that *qnrB2* has been found on plasmids collected in 1996, and the association of *qnrB* with *SHV-12* on plasmids found in both India and the United States suggests that this resistance mechanism has been present long enough to disseminate widely.

Previous studies indicate that in ceftazidime-resistant *Enterobacter* and *Klebsiella* isolates from the United States, *qnrB* is as common as *qnrA*.[26] It would not be surprising if even more members of the *qnr* family were discovered.

The frequency of the *qnrB* and *qnrs* genes in antibiotic resistance against nalidixic acid and norfloxacin has been observed. This may be due to the change in the presence of plasmid. Resistance to quinolones is associated with porin loss, defined efflux pump or DNA gyrase alterations and increase expression four- to eight folds.[27]

According to study results of Taha et al,[28] the frequency of *qnrA* and *qnrB* genes in NA-resistant isolates was 7 (12.5%) and 6 (10.7%), respectively. These findings showed that some *qnrA*-and *qnrB*-negative isolates were also resistant to NA and fluoroquinolones signifies that other *qnr* genes or resistance mechanisms, such as mutations in the target enzyme (e.g., DNA gyrase and topoisomerase IV) and/or activation of efflux pumps, may be involved.

Conclusions

It has been found in this study that the prevalence of *qnr* genes has increased to 50%. Despite the fact that the prevalence of *qnr* genes is warning us that transferable resistance determinants continue to emerge and could seriously undermine therapeutic regimens with β-lactams, fluoroquinolones, and aminoglycosides. The possibility of *K. pneumoniae* transferring these resistant plasmids to other *Enterobacteriaceae* and non-fermenting gram-negative bacilli is a serious consideration in the care of hospitalized patients.

Authors' Contributions

MN and SM participated in the research design and contributed to different parts of the research.

Conflicts of Interest Disclosure

There are no conflicts of interest in the present study.

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