


Mutations in *gyrA* and *parC* Genes in Quinolone-Resistant *Klebsiella pneumoniae* Isolates from Borujerd Hospitals

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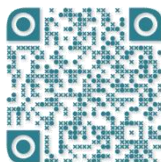
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ABSTRACT

Background & Objective: Quinolones are the antibiotics used to treat infections. Several reports have indicated the increased resistance to quinolone in *Klebsiella pneumoniae* strains all over the world. The aim of this study was to investigate amino acid substitutions in GyrA and ParC proteins among quinolone-resistant isolates of *K. pneumoniae* in Borujerd (west of Iran) hospitals.

Materials & Methods: Totally, 100 isolates of *K. pneumoniae* were collected. After validating the isolates by conventional laboratory methods, an antimicrobial susceptibility test was carried out for some antibiotics from the quinolones family. Quinolone resistance and Minimum Inhibitory Concentration (MIC) of Ciprofloxacin were detected by disk diffusion and E-test methods, respectively. The amplification of *gyrA* and *parC* genes in quinolone-resistant strains was performed by PCR using specific primers. PCR products were sequenced in order to detect the mutations in *gyrA* and *parC* genes.

Results: Generally, 38% of all the collected isolates were resistant to Nalidixic acid and Ciprofloxacin, 18% were resistant to Ofloxacin, and 15% were resistant to Norfloxacin. Concurrent resistance to Nalidixic acid, Ciprofloxacin, Ofloxacin, and Norfloxacin was determined in 15% of the cases. In 86% (n=20) of Ciprofloxacin-resistant strains, MIC was measured 128 µg/mL. The mutation rate was 40% (n=9) in *gyrA* gene in quinolone-resistant strains and 35% (n=8) in *parC* gene.

Conclusion: Briefly, our research findings revealed that a relatively high resistance to quinolones as well as fluoroquinolone was observed among *K. pneumoniae* isolates in Borujerd hospitals. It is likely that mutation occurrence in certain positions of *gyrA* and *parC* genes has a significant effect on developing high-level resistance to quinolone in *K. pneumoniae*.

Keywords: *Klebsiella pneumoniae*, *gyrA* and *parC* mutations, Quinolone resistance



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Introduction

Klebsiella pneumoniae is a kind of intestinal gram-negative bacterium causing a broad range of diseases, including bacteremia, pneumonia, and urinary tract infections. The importance of this opportunist bacterium has been determined in recent years. As a result of excessive consumption of antibiotics, some drug-resistant strains of this bacterium have emerged and spread (1).

Due to the overuse of antibiotics, for instance, cephalosporins, in recent years, the prevalence of infections by *K. pneumoniae* isolates producing broad-spectrum beta-lactamases has been significantly reported worldwide (2). Fluoroquinolones are often used as an empirical treatment for many nosocomial and non-hospital infections resulted from multidrug-resistant gram-negative pathogens (3).

Quinolones were introduced as a Nalidixic acid for the first time in 1962. For five decades, different types of quinolones have been prescribed for clinical use (4, 5).

Fluoroquinolones are fluorinated quinolone derivatives such as Ciprofloxacin and Levofloxacin carrying a similar mechanism of action. These drugs were initially introduced because of their activity against aerobic gram-negative bacteria such as *K. pneumoniae*. They have a high antibacterial effect and a small amount of toxicity. They also reach appropriate therapeutic levels in tissues and blood. Due to the fact that *K. pneumoniae* is a leading cause of urinary tract infections, fluoroquinolones can be the most appropriate antibiotic for this bacterium. Ciprofloxacin is an oral or intravenous antibiotic widely used for treating urinary tract infections due to its rapid effect. Quinolone compounds cause their antibacterial activity through their inhibitory effect on certain known topoisomerase enzymes called DNA gyrase (Topoisomerase II) and Topoisomerase IV which are coded by *gyrA* and *parC* genes. Heterothermic proteins consist of two Subunits A and B of the two enzymes mentioned earlier (6, 7).

Resistance to fluoroquinolones in gram-negative bacteria is often due to chromosomal mutations, the displacement of specific amino acids in the quinolone-resistant domain (QRD) of *gyrA* and *gyrB* genes (7). Also, mutations decreasing the drug accumulation and plasmids protecting the bacteria from the killing effects of quinolones have an important role in resistance to quinolones (8). At first, mutations diminish the susceptibility of the gyrase enzyme in the bacteria, then others in *gyrA* or *parC* can increase resistance to these antibiotics. A region of DNA known as “quinolone resistance-determining region” (QRDR) can affect the resistance of bacteria against these antibiotics via the amino acid substitution in this region (8).

Considering the importance of controlling *K. pneumoniae* infections in hospitals and decreasing the antibiotic resistance such as resistance to quinolones, no studies have been conducted on mutations in *gyrA* and *parC* genes in Borujerd hospitals. The present study aimed to investigate the amino acid substitutions of GyrA and ParC proteins in the clinical isolates of *K. pneumoniae* with high-level quinolone resistance in Borujerd hospitals.

Materials and Methods

Klebsiella pneumoniae Isolates

In a cross-sectional study, in total, 100 *K. pneumoniae* isolates were randomly isolated from clinical samples, including wounds (4%), blood (3%), trachea (15%), and urine (78%) samples of patients hospitalized in different (ICU, pediatric, emergency, and internal) wards in three hospitals of Borujerd, in the west of Iran.

Antimicrobial Susceptibility Test

The antibiotic susceptibility of isolated *K. pneumoniae* to quinolone antibiotics, including Ciprofloxacin (30 µg), Norfloxacin (30 µg), Nalidixic acid (10 µg), and Ofloxacin (5 µg) was tested using a standard disk diffusion method. Then the determination of Ciprofloxacin MICs by E-test was carried out according to CLSI criteria. Standard strain *K. pneumoniae* ATCC 12022 was considered as a control.

E-test Procedure

To change the susceptibility or resistance of the isolated bacteria from Enterobacteriaceae family to Ciprofloxacin based on CLSI criteria for MIC, values of 1 µg/mL were considered as sensitive while the values of 2 µg/mL and ≥4 µg/mL were considered as semi-susceptible and resistant, respectively.

DNA Extraction and PCR Assay

PCR and sequencing were performed to amplify and detect mutations in *gyrA* and *parC* genes in quinolone and also fluoroquinolone-resistant *K. pneumoniae* isolates. Generally, the genomic DNAs of the mentioned isolates were extracted by a commercial DNA extraction kit (Cinapure DNA, CinaClon, Iran) according to the manufacturer's instructions and were amplified by PCR assay. The oligonucleotide primers used in the PCR

reactions were *gyrA*-F (5'-CGACCTTGCAGAGAAAT-3'); *gyrA*-R (5'-GTTCCATCAGCCCTTCAA-3'), and primer *parC*-F (5'-TACGTCATCATGGACAGG-3'); *parC*-R (5'-GCCACTTCACGCAGGTTG-3') (Metabion, Germany). For all amplification reactions, a PCR mixture was used which contained 12.5 µL of 2X Master Mix (Ampliqon, Denmark) in the total volume of 50 µL. DNA amplification was performed in a thermocycler (PEQ STAR, Germany). For *gyrA*, the PCR program was: an initial denaturation at 98°C for 5 minutes, 35 cycles of denaturation at 94°C for 1 minute, 1 minute of annealing at 64°C, and 2 minutes of extension at 72°C, and final extension at 72°C for 5 minutes. The temperature profile for *parC* gene was comprised of 95°C for 2 minutes, followed by 35 cycles of 1 minute at 95°C, 1 min of annealing at 60°C, 2 minutes of extension at 72°C, and final extension of 10 minutes at 72°C. DNA fragments were analyzed by agarose gel electrophoresis (1%, wt/vol) containing 0.5 mg of ethidium bromide per liter and visualized by ultraviolet illumination.

The sequencing of PCR products was carried out using the Applied Biosystems DNA analyzers sequencing system (Bioneer Co., Korea). To detect the mutation in *gyrA* and *parC* genes, the sequences of these genes in Ciprofloxacin-resistant strains were copied in FASTA format in online pairwise alignment tools (Emboss/needle), then they were aligned with the sequences of *gyrA* and *parC* genes of the wild-type strain of *K. pneumoniae*.

Statistical Analysis

SPSS version 21 (SPSS Inc., Chicago, IL., USA) was employed for statistical analysis. Descriptive statistics and Pearson's chi-square tests were used to evaluate the correlation between the mutation and Ciprofloxacin resistance. P-values less than 0.05 were considered as statistically significant.

Results

Resistance to Fluoroquinolones

The results demonstrated that among 100 *K. pneumoniae* isolates, 38 of them were resistant to Nalidixic acid and Ciprofloxacin, simultaneously, while 18 and 15 isolates were resistant to Ofloxacin and Norfloxacin, respectively. Furthermore, 15 isolates were resistant to Nalidixic acid, Ciprofloxacin, Ofloxacin, and Norfloxacin, simultaneously. The presence of mutations in *gyrA* and *gyrB* genes was evaluated in 38 quinolone-resistant isolates (Figure 1). Mutations were detected in 37% (n=14) of them. The frequencies of mutations in *gyrA*, *parC*, and both *gyrA* and *parC* were 64% (n=9), 57% (n=8), and 21% (n=3) in strains with point mutations (Figure 2). In 63% (n=24) of quinolone-resistant strains, no mutations were detected at all. According to the results of our E-test, MIC values ranged from 2 µg/mL to 128 µg/mL, whereas 20 isolates (86%) resistant to Ciprofloxacin with MIC= 128 µg/mL were determined. The MIC values including 64 µg/mL and 2 µg/mL were detected in one (4.5%) and two (8.5%) of the Ciprofloxacin-resistant isolates, respectively.

Sequencing of the *parC* and *gyrA* QRD:

The results of sequencing data were acquired and analyzed using Chromas software. Then the nucleotide sequences were compared and the protein sequences of the mutations created in the *gyrA* and *parC* genes were evaluated. The results are presented in Table 1. Data sequences were examined to detect the presence of amino acid substitution in certain positions. Fourteen amino acid substitutions in *GyrA* and 16 amino acid substitutions in *ParC* proteins were observed in quinolone-resistant isolates. These results are presented in Table 1 and Figure 2.

In the case of *GyrA* protein, 14 point mutations were detected at position numbers: Arg232 →Gln, Val437→Ala, His194 →Gln, Ala204→Ser, Arg207→Trp, Leu210→Tyr, and Arg214 →Cys, Pro216 →Ser and Ser83, 217, 21→Phe,

Asp232 →Ala, Arg502 →Met. Five- and two-point mutations in *GyrA* were detected in two isolates by number 7 and 11, respectively (Table 1). In the case of *ParC* protein, 16 amino acid substitutions were detected at position numbers: Trp10, 208 →Arg, Trp11→Cys, Met46→Thr, Ser141, 143 and 80 →Ile, 139 and Gln149 →His, Lys155 →Glu, Ser196→Pro, Gly205→Trp, Ser211→Ala, Leu245 →Ser. Two-point mutations in *ParC* were detected in 4 isolates (isolates by numbers 8, 11, 29, 61) and five-point mutations were detected in one isolate (by number 90). Also, a double mutation in *gyrA* and *parC* genes was identified in 3 strains (strains number 6, 8, and 11) and most of the quinolone-resistant strains exhibited a high MIC value (128µg/mL).

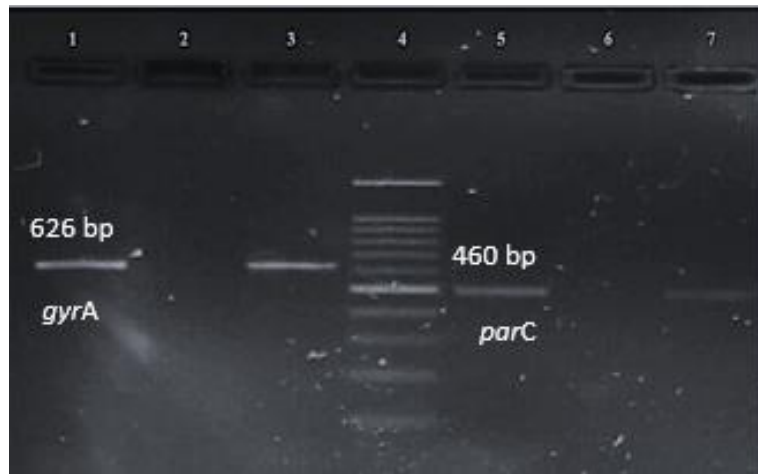


Figure 1. Gel electrophoresis of PCR products for *gyrA* and *parC* genes. The 1st lane represents the positive control for *gyrA*, the 2nd lane shows the negative control, the 3rd lane is a sample containing *gyrA* and lane 4 represents a 100 bp DNA size marker; the 5th and 6th lanes show the positive and negative controls of *parC* gene, respectively; the 7th lane shows the *parC* sample.

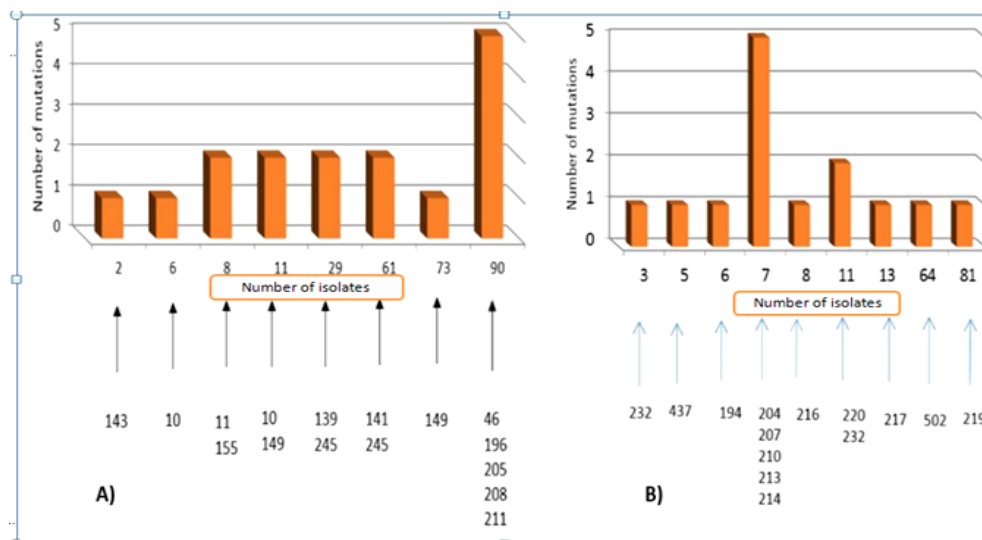


Figure 2. Substitution of amino acids and number of mutations in *parC* gene (A) and *gyrA* gene (B) in *K. pneumoniae* isolates.

Table 1. Substitution of amino acids in GyrA and ParC proteins in *K. pneumoniae* isolates

Number Strain	Codon & Amino acid substitution		MIC μg/mL	Isolated
	<i>gyrA</i>	<i>parC</i>		
2	-	AGC → ATC	128	Urine
	-	Ser80 → Ile		
3	CGA → CAA	-	128	Urine
	Arg 232 → Gln	-		
5	GTC → GCC	-	2	Urine
	Val437 → Ala	-		
6	CAT → CAG	TGG → ACG	2	Urine
	His194 → Gln	Trp10 → Arg		
7	GCA → TCA	-	128	Trachea
	Ala 204 → Ser	-		
	CGG → TGG	-		
	Arg 207 → Trp	-		
	CTC → TAC	-		
	Leu210 → Tyr	-		
	CGC → TGC	-		
	Arg 213 → CyS	-		
	CGC → TGC	-		
8	Arg214 → Cys	-	128	Trachea
	CCG → TCG	TGG → TGT		
	Pro216 → Ser	Trp11 → Cys		
11	-	AAA → GAA	128	Urine
	-	Lys155 → Glu		
	TCC → TTC	TGG → GGG		
	Ser83 → phe	Trp10 → Gly		
13	GAC → GCC	CAG → CAT	128	Urine
	Asp87 → Ala	Gln149 → His		
29	TCC → TTC	-	128	Urine
	Ser83 → phe	-		
	-	CAG → CAT		
	-	Gln139 → His		
61	-	TTG → TCG	128	Urine
	-	leu245 → Ser		
	-	AGC → ATC		
64	-	Ser80 → Ile	128	Urine
	-	ATC → AGC		
73	-	Ile245 → Ser	128	Urine
	AGG → ATG	-		
81	Arg502 → Met	-	128	Urine
	-	AGC → ATG		
90	-	Ser80 → Ile	64	Urine
	-	-		
	TCC → TTC	-		
	Ser83 → Phe	-		
	-	ATG → ACG		
	-	Met46 → Thr		
	-	TCC → CCC		
	-	Ser196 → Pro		
	-	GGA → AGA		
-	Cly205 → Trp			
-	TGG → CGG			
-	Trp208 → Arg			
-	TCA → GCA			
-	Ser211 → A19			

Discussion

In this study, a relatively high resistance (38%) to fluoroquinolones including Ciprofloxacin was observed among *K. pneumoniae* isolates in Borujurd hospitals. In general, the findings of this study indicate that mutations in certain positions of *gyrA* and *parC* genes may have a profound impact on developing a high-level resistance to quinolone in *K. pneumoniae*. However, other mechanisms of resistance to quinolones should be considered. According to the results, the frequency of point mutations in *gyrA* and *parC* genes was 37% in quinolone-resistant strains. This suggests that other mechanisms can have a role in resistance to quinolone, along with the mutations in *gyrA* and *parC* genes. Bacteria gain resistance to quinolones in several ways such as changes in target enzymes including DNA gyrase and topoisomerase IV, changes in the endocytic pathways like penetrating the antimicrobial agent, increasing efflux pumps, and decreasing porin-expressions (9-11), and obtaining Qnr plasmids (2, 3). In addition to the plasmid-mediated efflux systems, chromosomal multidrug efflux pumps are able to actively remove fluoroquinolones and other agents from the bacterial cell (6). It has been proved that the main mechanism for resistance (which is dependent on the chromosome) to quinolones is the mutations in the genes encoding subunits A and B in DNA gyrase and topoisomerase IV. These enzymes are the main targets of quinolones.

The permeability of cell membrane and the ability of antibiotics in penetrating into the cell are key indexes in the efficacy of antibiotics such as fluoroquinolones with intracellular targets (12). The inner and outer membranes in the cell walls of gram-negative bacteria are considered as a particular barrier. Mutations created in down-regulation of these proteins could increase the MIC of fluoroquinolones (13).

The real contribution of plasmid mediated quinolone resistance to the MIC of Ciprofloxacin is not obvious in Ciprofloxacin-resistant isolates. Thus, there is not a significant difference between the MICs of Ciprofloxacin-resistant isolates with or without *qnrB* genes (6). A study showed that among the *K. pneumoniae* strains producing ESBL, resistance to Ciprofloxacin is higher. Resistant strains that have mutations in the *gyrA* and *parC* genes, or the plasmid *aac (6') -Ib-cr* gene, along with the *qnr* genes reveal a high resistance to Ciprofloxacin (14).

Compared to our research, some studies have reported a lower resistance to quinolones as well as mutation rates in *K. pneumoniae*. In 2018, Mirzaii et al. reported that 15 (6.8%) of the 220 *K. pneumoniae* isolates were resistant to at least one of the quinolones and only 1 (6.7%) of the

15 *K. pneumoniae* isolates was found to carry Ser83Leu substitution in *gyrA* protein in Tehran (15). In a study by Alijani et al. it was revealed that the Ciprofloxacin resistance rate was lower than that of our study (16). However, Huang reported much more resistance to Ciprofloxacin (more than 60%) and also point mutations in *gyrA* (more than 95%) in China hospitals (17). Thus, based on the results, the double mutation Ser83→Leu + Asp87→Asn was the most prevalent type of *gyrA* changes in antimicrobial-resistant isolates (15-18). In 2014, Norouzi et al. reported some *K. pneumoniae* strains substituting Ser 83 →Ile and Ser 83 →Phe in *gyrA* gene (8). Marquz et al. reported a resistance rate (37%) to Ciprofloxacin (similar to our study) in Malaysia's hospitals (6). However, they reported that 33 isolates had multiple mutations either in *gyrA* alone (n=1) or in both *gyrA* and *parC* regions (n=32). There are some differences among reports because the pattern of antibiotic resistance is different in various regions and this resistance profile is constantly changing in time with the increasing use of antibiotics.

According to the results of our study and others in Iran and Asian countries (Malaysia, Taiwan, Japan, and Singapore), the most similar findings in amino acid substitutions Ser 83→ Phe in *gyrA* region and ser80→Ile in *parC* region were those regarding *K. pneumoniae* isolates reported from Malaysia (6).

Some researchers believe that at least 3 mutations in the *gyrA* gene are required to produce a high level of resistance to Ciprofloxacin (18). Fu et al. identified 7 mutation patterns without any effects on drug resistance in the isolates including the mutations outside the QRDR region and the conversion of alanine 171 to serine and valine 198 to isoleucine (19).

Generally, the present study reveals that regardless of mutation position, several types of mutations in *gyrA* and *parC* genes may result in resistant strains. In 2014, Farah al-Marzooq reported that the rise of Ciprofloxacin MICs strongly correlates with the rise in the total number of mutations in *gyrA* and/or *parC* genes (6). On the other hand, our findings are in contrast with those of Fu. Y et al. (20) and indicate that only one mutation could cause a high rate of resistance with MIC 128 µg/mL.

In our study, quinolone-resistant strains did not show any significant mutations on specific positions of the chromosome which suggests that other mechanisms such as plasmid resistance or alteration in the efflux pumps (21) may create quinolone resistance in these strains while chromosomal resistance is not involved. In the relation between *gyrA* gene mutations and fluoroquinolones

resistance, various results have been obtained. In a study in Brazil in which gene mutations in *gyrA* and *parC* genes were investigated in intestinal bacteria isolated from patients, 33% of resistant isolates had mutations in codons 21 or 23 or both, and none of the isolates susceptible to Ciprofloxacin had gene mutation in topoisomerase (3).

In general, there are some suggestions to increase knowledge about resistance to fluoroquinolones including investigating the mechanism of resistance to quinolones especially Ciprofloxacin using molecular methods and the evaluation of resistance profile to quinolones especially in hospitals. Complete antibiotic treatment can be effective in preventing microbial resistance and in implementing care plans. These inhibitive measures can also reduce antibiotic resistance. Moreover, periodic and systematic studies on resistance patterns are necessary in order to obtain an appropriate treatment regimen for patients (22, 23).

Conclusion

Based on our findings, the relatively high resistance to fluoroquinolones including Ciprofloxacin is significant particularly in hospitalized patients. The same amount of fluoroquinolone resistance is vital for treating patients especially for those who are hospitalized or have a weakened immune system because they should be treated by antibiotics for a long time. Resistance to Ciprofloxacin is significant in *K. pneumoniae* and it is feared that it will increase. Hence, it is better to use more effective quinolone antibiotics or a drug with effects similar to Ciprofloxacin such as Levofloxacin. The concomitant mutations in the QRD regions are estimated to contribute meaningfully to high-level fluoroquinolone resistance and to the presence of different substitutions at amino acids in GyrA and ParC proteins. This suggests that different sites have noticeable roles in resistance to quinolones. However, the mutations in *gyrA* and *gyrB* genes, other mechanisms of resistance to quinolones, their effects on resistance, and MIC changes should be investigated. Further investigations of molecular techniques so as to fully examine the genetic pattern of resistance, the existence of precise care, monitoring programs, and serious preventive measures are recommended.

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Conflict of Interest

Authors declared no conflict of interests.

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