Published Online: 2025 March 16 **Research Article**

Investigating the Frequency of Genotypic and Phenotypic Resistance to Plasmid-Mediated Ciprofloxacin in Clinical Isolates of *Klebsiella pneumoniae* in Ardabil

Malek Namaki Kheljan [1], Maliheh Hasanzadeh [2], Zohreh Neyestani [3], Mohammad Ali Jafarizare [4], Kazem Nejati-Koshki [5], Mehdi Asghari Vostakoli [5,*]

[1] Department of Microbiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Department of Biology, Ardabil Branch, Islamic Azad University, Ardabil, Iran
[3] Department of Microbiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4] Department of Orthopedics, Fatemi Hospital, Ardabil University of Medical Science, Ardabil, Iran
[5] Pharmaceutical Sciences Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

[*] ***Corresponding Author:*** Pharmaceutical Sciences Research Center, Ardabil University of Medical Sciences, Ardabil, Iran. Email: mehdibiochemist@gmail.com

Received: 2 June, 2024; **Revised:** 8 February, 2025; **Accepted:** 17 February, 2025

Abstract

Background: A total of 186 *Klebsiella pneumoniae* isolates collected from clinical samples were included in this study to investigate plasmid-mediated resistance to ciprofloxacin.

Objectives: Additionally, the frequency of plasmid-mediated quinolone resistance (PMQR) genes, including *qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *oqxA*, and *oqxB*, was examined.

Methods: The minimum inhibitory concentration (MIC) of ciprofloxacin was determined using the agar dilution method. The presence of PMQR genes was identified using a PCR assay.

Results: Among the 186 *K. pneumoniae* clinical isolates, 51.61% (n = 96) were resistant, 11.29% (n = 21) exhibited intermediate resistance, and 37.09% (n = 69) were susceptible to ciprofloxacin. The prevalence of *qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *oqxA*, and *oqxB* genes in *K. pneumoniae* clinical isolates was 33.33% (n = 39), 78.63% (n = 92), 0% (n = 0), 0% (n = 0), 82.05% (n = 96), 76.06% (n = 89), and 75.21% (n = 88), respectively.

Conclusions: This study found a significant association between ciprofloxacin resistance in *K. pneumoniae* and the presence of *qnrA*, *qnrB*, *qnrS*, *oqxA*, and *oqxB* genes.

Keywords: *Klebsiella pneumoniae*, Ciprofloxacin, Plasmid-Mediated Quinolone Resistance, Minimum Inhibitory Concentration

1. Background

Ciprofloxacin, a quinolone antibiotic, is a broad-spectrum antimicrobial agent widely used in humans. This class of antibiotics was introduced into clinical practice in the 1960s. However, resistance rates to these agents in *Enterobacteriaceae* have increased globally in recent years (1). Resistance to this broad-spectrum antibiotic, which is used to treat systemic infections and chronic urinary infections caused by gram-negative bacteria such as *Klebsiella pneumoniae* and gram-positive bacteria, is a significant concern in the discussion of microbial drug resistance (2).

Ciprofloxacin resistance generally results from mutations in the quinolone resistance-determining region (QRDR), which encodes genes for topoisomerase IV (*parC*, *parE*) and DNA gyrase (*gyrA*, *gyrB*) (1, 3). A plasmid-mediated quinolone resistance (PMQR) mechanism was later identified as an alternative resistance mechanism. The PMQR was first described in 1998 in an isolate of *K. pneumoniae* (4). The PMQR mechanisms are classified into three types: (1) Proteins and enzymes that protect bacterial topoisomerases

How to Cite: Namaki Kheljan M, Hasanzadeh M, Neyestani Z, Jafarizare M A, Nejati-Koshki K, et al. Investigating the Frequency of Genotypic and Phenotypic Resistance to Plasmid-Mediated Ciprofloxacin in Clinical Isolates of *Klebsiella pneumoniae* in Ardabil. Arch Clin Infect Dis. 2025; 20 (3): e148969. https://doi.org/10.5812/archcid-148969.

from quinolones (*qnrA*, *qnrB*, *qnrC*, *qnrD*, and *qnrS*), (2) acetylation enzymes such as *aac(6)-Ib*, which increase resistance to aminoglycosides, and (3) multidrug efflux pumps (*qepA* and *oqxAB*), which expel antibiotics from bacterial cells. These factors collectively contribute to bacterial drug resistance (4, 5).

Mobile genetic elements, typically carried by plasmids and transferred through conjugation, play a crucial role in the dissemination of antibiotic resistance genes and the development of multidrug resistance (MDR) in bacteria. This poses significant challenges in infectious disease management and public health. Additionally, integrons can capture gene cassettes containing PMQR genes from other bacteria or environmental sources and incorporate them into their genetic structure, enabling bacteria to acquire quinolone resistance genes. The horizontal transfer of integrons carrying PMQR gene cassettes facilitates the spread of quinolone resistance among bacterial populations (6).

To date, no comprehensive study has examined the prevalence of PMQR determinants in *K. pneumoniae* clinical isolates from Ardabil, Iran. *K. pneumoniae* is a major cause of infections, including urinary tract infections (UTIs), pneumonia, sepsis, and bloodstream infections. Ciprofloxacin is commonly used as an effective antibiotic for treating recurrent infections caused by this pathogen (7). As a leading cause of healthcare-associated infections worldwide, MDR *K. pneumoniae* presents significant treatment challenges due to its resistance to antibiotics, chemical disinfectants, and human defense mechanisms such as phagocytosis (8).

Infections caused by *K. pneumoniae* are associated with high morbidity and mortality rates. Recent epidemiological studies have identified specific genetic characteristics in *K. pneumoniae* strains linked to hypervirulence. Additionally, *Klebsiella* species are known to harbor a vast array of antibiotic resistance genes and have played a critical role in the spread of resistance to other gram-negative bacteria. Many of the antibiotic resistance genes now commonly found in multidrug-resistant organisms were first identified in *Klebsiella* (9).

2. Objectives

Therefore, this study aimed to evaluate the presence of PMQR genes (*qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *oqxA*, and *oqxB*) in clinical samples of *K. pneumoniae* in Ardabil.

3. Methods

3.1. Bacterial Isolation

From June 2020 to July 2022, 186 *K. pneumoniae* isolates were collected from clinical specimens of patients admitted to hospitals affiliated with Ardabil University of Medical Sciences, Iran. The isolates were accurately identified using standard microbiological and biochemical tests before being stored in trypticase soy broth (TSB) containing 20% glycerol at -70°C for long-term preservation.

3.2. Ciprofloxacin Susceptibility Tests

The minimum inhibitory concentration (MIC) of ciprofloxacin (Sigma-Aldrich, USA) for *K. pneumoniae* strains was determined using the standard agar dilution method following the Clinical and Laboratory Standards Institute (CLSI M100-2022) guidelines. *Escherichia coli* ATCC 25922 and ATCC 35218 were used as quality control standard strains.

3.3. Detection of Plasmid-Mediated Quinolone Resistance Genes by PCR

The entire plasmid was extracted following the method described by Heringa et al. (10). The quantity and quality of the extracted DNA were assessed using a NanoDrop^{TM} 2000/2000c Spectrophotometer (Thermo Fisher Scientific, USA). The extracted DNA was stored at -20°C until further use for gene detection. All collected isolates were screened for the presence of PMQR genes, including *qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *oqxA*, and *oqxB*, using PCR with specific primers (Table 1). The amplification conditions for PCR are detailed in Table 2.

The PCR protocol was conducted in a total volume of 25 µL using Ampliqon master mix (Denmark). Each primer was included at a concentration of 10 µmol/L, and 3 µL of extracted DNA was used as the template for amplification. The PCR reaction was performed in a thermal cycler, which amplified the target DNA sequences through different temperature stages according to the specified protocol. Following PCR, the amplified products were separated on a 1% agarose gel in 0.5x TBE buffer and visualized based on fragment size. The PCR products were subsequently confirmed by sequencing to ensure the correct DNA sequence had been amplified.

3.4. Data Analysis

In this study, the researchers collected data on the MICs of ciprofloxacin against *K. pneumoniae* strains harboring PMQR genes. The data were analyzed using SPSS software version 16. The chi-square test was applied

Table 1. Primer Sequences and PCR Program

Genes and Primer Sequence (5′ - 3′)	Annealing (°C)	Product Size (bp)	Ref
qnrA	58	516	1
F: ATTTCTCACGCCAGGATTTG			
R: GATCGGCAAAGGTTAGGTCA			
qnrB	53	469	1
F: GATCGTGAAAGCCAGAAAG			
R: ACGATGCCTGGTAGTTGTCC			
qnrC	50	447	4
F: GGGTTGTACATTTATTGAATC			
R: TCCACTTTACGAGGTTCT			
qnrD	60	636	1
F: ATGGAAAAGCACTTTATCAATGA			
R: AACAATAACACCTAAACTCTCAACAA			
qnrS	60	255	2
F: TCGGCACCACAACTTTTCAC			
R: TCACACGCACGGAACTCTAT			
oqxA	64	489	2
F: CTCTCCTTTCTGCTCGTCGG			
R: AATAGGGGCGGTCACTTTGG			
oqxB	60	240	3
F: CGAAGAAAGACCTCCCTACCC			
R: CGCCGCCAATGAGATACA			

Table 2. The Amplification Program for PCR

Step	Temperatures and Times	Cycles
Initial denaturation	4 min at 94°C	1
Denaturation	1 min at 94°C	30
Annealing	1 min (temperatures are shown for each primer in Table 1)	
Extension	1 min at 72°C	
Final extension	1 min at 72°C	1

to assess the correlation between the presence of PMQR genes and the MICs of ciprofloxacin. A P-value of < 0.05 was considered statistically significant, indicating a significant association between the presence of PMQR genes and the level of resistance to ciprofloxacin in *K. pneumoniae* strains.

3.5. Ethics Statement

The study adhered to the ethical principles outlined in the 1975 Declaration of Helsinki and received approval from the Ethics Committee of Ardabil University of Medical Sciences under the ethical code IR.ARUMS.REC.1402.136. Written informed consent was obtained from all participants included in the study.

4. Results

In the present study, among 186 *K. pneumoniae* clinical isolates, 51.6% (n = 96) were resistant, 11.29% (n = 21) were intermediate, and 37.09% (n = 69) were susceptible to ciprofloxacin. The prevalence of the *qnrA*, *qnrB*, *qnrS*, *oqxA*, and *oqxB* genes in *K. pneumoniae* clinical isolates was 20.9% (n = 39), 49.4% (n = 92), 51.6% (n = 96), 47.8% (n = 89), and 47.3% (n = 88), respectively. The *qnrC* and *qnrD* genes were not detected in any of the isolates. Additionally, the prevalence of *qnrA*, *qnrB*, *qnrS*, *oqxA*, and *oqxB* genes in ciprofloxacin-resistant *K. pneumoniae* isolates was 40.6% (n = 39), 80.2% (n = 77), 90.6% (n = 87), 82.3% (n = 79), and 82.3% (n = 79), whereas in the other isolates, the prevalence was 0% (n = 0), 16.6% (n = 15), 10% (n = 9), 11.1% (n = 10), and 10% (n = 9), respectively.

As shown in Table 3, the presence of *qnrA*, *qnrB*, *qnrS*, *oqxA*, and *oqxB* genes was significantly associated with

Table 3. Association Between Ciprofloxacin Resistance and Plasmid-Mediated Quinolone Resistance Genes in Clinical Isolates of *Klebsiella pneumonia* [a]

Gene	Ciprofloxacin (MIC)	
	≤ 0.5	1 ≤
qnrA +	0	39
qnrA -	90	57
qnrB +	15	77
qnrB -	75	19
qnrS +	9	87
qnrS -	81	9
oqxA +	10	79
oqxA -	80	17
oqxB +	9	79
oqxB -	81	17

Abbreviation: MIC, minimum inhibitory concentration.

[a] P-value < 0.01.

Table 4. Association Between Ciprofloxacin MIC_{90} and Genomic Profile of *Klebsiella pneumoniae* Isolates [a]

Genomic Profile	N = 186	MIC_{90}
qnrA + ***qnrB*** + ***qnrS*** + ***oqxA*** + ***oqxB***	31 (16.66)	16
qnrB + ***qnrS*** + ***oqxA*** + ***oqxB***	27 (14.51)	2
qnrA + ***qnrB*** + ***oqxA*** + ***oqxB***	2 (1.07)	8
qnrA + ***qnrB*** + ***qnrS*** + ***oqxB***	1 (0.53)	2
qnrA + ***qnrB*** + ***oqxB***	2 (1.07)	4
qnrA + ***qnrS*** + ***oqxA***	2 (1.07)	16
qnrB + ***qnrS*** + ***oqxB***	9 (4.83)	4
qnrB + ***oqxA*** + ***oqxB***	4 (2.15)	4
qnrA + ***qnrS***	2 (1.07)	2
qnrB + ***oqxB***	5 (2.68)	4
qnrS + ***oqxA***	13 (6.98)	4
qnrS	11 (5.91)	0.5
oqxB	6 (3.22)	0.5
qnrB	11 (5.91)	0.5
oqxA	8 (4.3)	0.5
No gene	52 (27.95)	0.25

Abbreviation: MIC, minimum inhibitory concentration.

[a] Values are expressed as No. (%).

increased MIC values and resistance to ciprofloxacin in *K. pneumoniae* isolates ($P < 0.05$).

The MIC range for ciprofloxacin was 0.125 - 16 µg/mL. The analysis of ciprofloxacin-resistant genes in *K. pneumoniae* isolates resistant to ciprofloxacin revealed 15 gene patterns. An increase in the MIC level of ciprofloxacin was observed in isolates harboring multiple PMQR genes. The most frequent genomic profiles were *qnrA*+ *qnrB*+ *qnrS*+ *oqxA*+ *oqxB* and *qnrB*+ *qnrS*+ *oqxA*+ *oqxB*. Isolates that simultaneously carried the *qnrA*, *qnrS*, and *oqxA* genes exhibited the highest MIC values against ciprofloxacin (Table 4).

5. Discussion

In recent years, numerous cases of pathogenic drug-resistant bacteria have emerged due to the indiscriminate and arbitrary use of antibiotics. This has led to treatment failures, increased complications, and high healthcare costs. In this context, resistance to quinolone antibiotics, including ciprofloxacin, has risen

significantly over the years (11). Resistance to ciprofloxacin in *K. pneumoniae* infections, a common cause of hospital-acquired infections, poses serious clinical implications, including limited treatment options (12). As a result, the growing prevalence of ciprofloxacin-resistant infections is particularly concerning, especially during antibiotic therapy in hospitalized patients. Resistant strains often require more complex and costly treatment regimens, leading to prolonged hospital stays and increased healthcare expenses (13). Furthermore, these resistant strains can spread within healthcare settings, potentially causing outbreaks in at-risk populations. Patients with ciprofloxacin-resistant *K. pneumoniae* infections may experience increased morbidity and mortality, as they often present with more severe clinical conditions and require intensive treatment (14). Overall, resistance patterns to ciprofloxacin in *K. pneumoniae* significantly impact treatment strategies and clinical outcomes, emphasizing the need for careful monitoring and reassessment of treatment protocols to combat antibiotic resistance effectively.

In the present study, the resistance rate to ciprofloxacin among *K. pneumoniae* clinical isolates was found to be 51.6%. In comparison, Yuan et al. reported a resistance rate of 66% to ciprofloxacin (15), while Saadatian et al. observed a resistance rate of 68.7% in *K. pneumoniae* isolates (16), which aligns with our findings. Variations in geographical regions may contribute to slight differences in resistance rates.

Studies indicate that *qnr* genes play a crucial role in the development of resistance to quinolones, including ciprofloxacin. In this study, the prevalence rates of *qnrA*, *qnrB*, and *qnrS* genes in *K. pneumoniae* clinical isolates were 20.9%, 49.4%, and 51.6%, respectively. According to our findings, a study conducted by Abosadegh et al. in Tehran in 2019 reported the *qnrS* gene as the most prevalent (35%), followed by *qnrB* (31%) and *qnrA* (13%) (17). Similarly, a study conducted in Iraq in 2020 identified *qnrS* and *qnrB* genes in 76% and 36% of isolates, respectively, while *qnrA*, *qnrC*, and *qnrD* genes were absent in all isolates (18). Differences in the prevalence of resistance genes across various regions in Iran and worldwide are likely influenced by factors such as geographical variations, sample types, antibiotic usage patterns, accessibility to broad-spectrum and newer antibiotics, genetic variations in bacterial strains, and disparities in antibiotic prescribing practices based on regional healthcare policies.

The *oqxAB* efflux pumps, associated with the *oqxA* and *oqxB* genes and located on the PolA52 plasmid, are among the primary factors contributing to antibiotic resistance in bacteria, particularly resistance to ciprofloxacin (19). In the present study, the prevalence rates of the *oqxA* and *oqxB* genes were 47.8% and 47.3%, respectively, which are somewhat lower than those reported in a study by Zomorrodi et al., where the *oqxA* and *oqxB* genes were detected in 69.7% and 72.1% of isolates, respectively (20). Rodriguez-Martinez et al. identified concurrent signals of *oqxA* and *oqxB* in both chromosomal locations and large plasmids (21). Other studies have reported *oqxAB* gene prevalence rates ranging from 74% to 100%. Thus, the approximate 47% prevalence of *oqxAB* genes identified in this study, similar to the findings of Yang et al., is relatively low (1). This discrepancy may be attributed to the fact that, in this study, as in the study by Yang et al., only plasmid DNA was purified, whereas other studies analyzed the whole genome to identify the *oqxAB* gene. Additionally, this difference may indicate variations in the prevalence of efflux pump-encoding genes among hospital strains due to epidemiological factors (1).

It is important to acknowledge the limitations of this study. Conducted in a single hospital, the isolates examined may not fully represent the broader clinical population, potentially limiting the generalizability of the findings. Furthermore, the study did not analyze the clonal relationships among *PMQR*-positive isolates. The co-location of the *qnr* gene with other *PMQR* genes also requires confirmation through PCR or Southern blot hybridization using specific DNA probes from a single plasmid.

To validate these results, nationwide epidemiological surveys and additional molecular studies are necessary to investigate the potential horizontal transfer of *PMQR* genes. Other limitations include insufficient coordination among hospitals for sample collection and the relatively small sample size from Ardabil, Iran. Future studies should aim to increase the sample size to enhance the robustness and generalizability of the findings.

5.1. Conclusions

Understanding the frequency of *qnr* genes and efflux pumps in clinical samples is crucial for selecting appropriate treatment regimens and mitigating the increasing trend of antibiotic resistance. Consequently, the findings of this study can assist healthcare providers in making informed treatment decisions and in preventing the inappropriate prescription of antibiotics.

Acknowledgements

The authors would like to thank the staff of Imam Khomeini Hospital of Ardabil for providing us with clinical *K. pneumoniae* isolates.

Footnotes

Authors' Contribution: M. N. K.: Conceptualization, methodology, investigation, writing-original draft, visualization; V. A.: Methodology, investigation, writing-original draft; Z. N.: Writing-original draft, methodology; M. A. J.: Validation, data curation, supervision; K. N. K.: Validation, data curation, supervision; M. A. V.: Conceptualization, validation, data curation, supervision, project administration, funding acquisition.

Conflict of Interests Statement: The authors declared no conflict of interest.

Data Availability: AThe dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: The study was approved by the Ethics Committee of the Ardabil University of Medical Sciences, Iran (registration No. IR.ARUMS.REC.1402.136).

Funding/Support: This study was financially supported by Ardabil University of Medical Sciences, Iran (grant No 401000347).

Informed Consent: Written informed consent was obtained from all participants included in the study.

References

1. Yang HY, Nam YS, Lee HJ. Prevalence of plasmid-mediated quinolone resistance genes among ciprofloxacin-nonsusceptible Escherichia coli and Klebsiella pneumoniae isolated from blood cultures in Korea. *Can J Infect Dis Med Microbiol*. 2014;**25**(3):163-9. [PubMed ID: 25285114]. [PubMed Central ID: PMC4173980]. https://doi.org/10.1155/2014/329541.
2. Campoli-Richards DM, Monk JP, Price A, Benfield P, Todd PA, Ward A. Ciprofloxacin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs*. 1988;**35**(4):373-447. [PubMed ID: 3292209]. https://doi.org/10.2165/00003495-198835040-00003.
3. Lin B, Lin Z, Xie B, Weng H, Wang X, Cheng L, et al. [Detection of Quinolone Resistance Genes and QRDR Mutation in Riemerella anatipestifer Found in Putian, Fujian]. *Fujian J Agricul Sci*. 2022;**37**(11):1400-6. ZH.
4. Hansen LH, Jensen LB, Sorensen HI, Sorensen SJ. Substrate specificity of the OqxAB multidrug resistance pump in Escherichia coli and selected enteric bacteria. *J Antimicrob Chemother*. 2007;**60**(1):145-7. [PubMed ID: 17526501]. https://doi.org/10.1093/jac/dkm167.
5. Jacoby GA, Strahilevitz J, Hooper DC. Plasmid-mediated quinolone resistance. In: Tolmasky ME, Alonso JC, editors. *Plasmids: Biology and Impact in Biotechnology and Discovery*. New Jersey: Wiley; 2015. p. 475-503. https://doi.org/10.1128/9781555818982.ch25.
6. Yang L, Yang L, Lu DH, Zhang WH, Ren SQ, Liu YH, et al. Co-prevalance of PMQR and 16S rRNA methylase genes in clinical Escherichia coli isolates with high diversity of CTX-M from diseased farmed pigeons. *Vet Microbiol*. 2015;**178**(3-4):238-45. [PubMed ID: 26013416]. https://doi.org/10.1016/j.vetmic.2015.05.009.
7. Kareem SM, Al-Kadmy IMS, Kazaal SS, Mohammed Ali AN, Aziz SN, Makharita RR, et al. Detection of gyrA and parC Mutations and Prevalence of Plasmid-Mediated Quinolone Resistance Genes in Klebsiella pneumoniae. *Infect Drug Resist*. 2021;**14**:555-63. [PubMed ID: 33603418]. [PubMed Central ID: PMC7886241]. https://doi.org/10.2147/IDR.S275852.
8. Mohamed SH, Mohamed MSM, Khalil MS, Azmy M, Mabrouk MI. Combination of essential oil and ciprofloxacin to inhibit/eradicate biofilms in multidrug-resistant Klebsiella pneumoniae. *J Appl Microbiol*. 2018;**125**(1):84-95. [PubMed ID: 29517825]. https://doi.org/10.1111/jam.13755.
9. Bengoechea JA, Sa Pessoa J. Klebsiella pneumoniae infection biology: living to counteract host defences. *FEMS Microbiol Rev*. 2019;**43**(2):123-44. [PubMed ID: 30452654]. [PubMed Central ID: PMC6435446]. https://doi.org/10.1093/femsre/fuy043.
10. Heringa S, Monroe J, Herrick J. A simple, rapid method for extracting large plasmid DNA from bacteria. *Nature Precedings*. 2007;**1**. https://doi.org/10.1038/npre.2007.1249.1.
11. Bagheri-Nesami M, Rafiei A, Eslami G, Ahangarkani F, Rezai MS, Nikkhah A, et al. Assessment of extended-spectrum beta-lactamases and integrons among Enterobacteriaceae in device-associated infections: multicenter study in north of Iran. *Antimicrob Resist Infect Control*. 2016;**5**:52. [PubMed ID: 27980729]. [PubMed Central ID: PMC5134273]. https://doi.org/10.1186/s13756-016-0143-2.
12. Khairy RMM, Mahmoud MS, Shady RR, Esmail MAM. Multidrug-resistant Klebsiella pneumoniae in hospital-acquired infections: Concomitant analysis of antimicrobial resistant strains. *Int J Clin Pract*. 2020;**74**(4). e13463. [PubMed ID: 31830351]. https://doi.org/10.1111/ijcp.13463.
13. Caneiras C, Lito L, Melo-Cristino J, Duarte A. Community- and Hospital-Acquired Klebsiella pneumoniae Urinary Tract Infections in Portugal: Virulence and Antibiotic Resistance. *Microorganisms*. 2019;**7**(5). [PubMed ID: 31100810]. [PubMed Central ID: PMC6560439]. https://doi.org/10.3390/microorganisms7050138.
14. Campos AC, Albiero J, Ecker AB, Kuroda CM, Meirelles LE, Polato A, et al. Outbreak of Klebsiella pneumoniae carbapenemase-producing K pneumoniae: A systematic review. *Am J Infect Control*. 2016;**44**(11):1374-80. [PubMed ID: 27156198]. https://doi.org/10.1016/j.ajic.2016.03.022.
15. Yuan J, Xu X, Guo Q, Zhao X, Ye X, Guo Y, et al. Prevalence of the oqxAB gene complex in Klebsiella pneumoniae and Escherichia coli clinical isolates. *J Antimicrob Chemother*. 2012;**67**(7):1655-9. [PubMed ID: 22438434]. https://doi.org/10.1093/jac/dks086.
16. Saadatian FA, Nowroozi J, Eslami G, Sabokbar A, Hashemi A. [The study of antibiotic resistance among Klebsiella pneumoniae and expression level of oqxA and acrA genes by using real-time PCR]. *Res Med*. 2016;**40**(1):42-8. FA.
17. Abosadegh R, Ghane M, Babaeekhou L. High Frequency of qnr Genes in Urinary Isolates of Extended-Spectrum β-Lactamase (ESBL)-producing Klebsiella pneumoniae in Tehran, Iran. *Shiraz E-Med J*. 2019;**21**(3). https://doi.org/10.5812/semj.92032.
18. Mustafa MS, Abdullah RM. Prevalence of Quinolones Resistance Proteins Encoding Genes (qnr genes) and Co-Resistance with β-lactams among Klebsiella pneumoniae Isolates from Iraqi Patients. *Baghdad Sci J*. 2020;**17**(2). https://doi.org/10.21123/bsj.2020.17.2.0406.
19. Kumar S, Varela MF. Biochemistry of bacterial multidrug efflux pumps. *Int J Mol Sci*. 2012;**13**(4):4484-95. [PubMed ID: 22605991]. [PubMed Central ID: PMC3344227]. https://doi.org/10.3390/ijms13044484.

20. Zomorrodi A, Zargar M, Noroozi J. [Evaluation of antibiotic resistance associated with ophthalmic oqxAB pumps in Klebsiella pneumoniae causing urinary tract infection]. *Med Sci J*. 2019;**29**(2):163-70. FA. https://doi.org/10.29252/iau.29.2.163.

21. Rodriguez-Martinez JM, Diaz de Alba P, Briales A, Machuca J, Lossa M, Fernandez-Cuenca F, et al. Contribution of OqxAB efflux pumps to quinolone resistance in extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae. *J Antimicrob Chemother*. 2013;**68**(1):68-73. [PubMed ID: 23011289]. https://doi.org/10.1093/jac/dks377.