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First Investigation of *OqxAB* and Plasmid-mediated Quinolone Resistance Determinant *Qnr* Genes in *Stenotrophomonas maltophilia* Isolates

Stenotrophomonas maltophilia İzolatlarında *OqxAB*'nin İlk ve Plazmit Aracılı Kinolon Direnç Belirleyicileri-*Qnr* Genlerinin Araştırılması

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Abstract

Introduction: *Stenotrophomonas maltophilia*, a non-fermentative bacterium, predominantly causes opportunistic infections in immunocompromised individuals and those receiving long-term, large-dose, broad spectrum antimicrobial agents. It is inherently resistant to most of the available antimicrobial agents. Trimethoprim-sulfamethoxazole (TMP/SMX), ceftazidime (CAZ), and levofloxacin (LVX) are the drugs of choice used for the infection treatment. The study aims to investigate the presence of plasmid-mediated quinolone resistance determinants of *QnrA*, *QnrB*, *QnrC*, *QnrD*, *QnrS*, and *OqxAB* genes in *S. maltophilia* isolates.

Materials and Methods: A total of 122 *S. maltophilia* isolates from various clinical specimens were tested in the study. The susceptibility of TMP/SMX and LVX was determined by disk diffusion method. The minimum inhibitory concentration value of CAZ was determined by the gradient diffusion test. *Qnr* (A, B, C, S, D) determinants and *OqxAB* were investigated using multiplex polymerase chain reaction. *OqxA* was investigated in the isolates and the presence of *OqxB* in *OqxA*-positive isolates.

Results: Five (4%) of the *S. maltophilia* isolates were resistant to TMP/SMX. Levofloxacin and CAZ resistances were determined as 6.5% and 56.5%, respectively. *QnrS* was detected in two of the isolates, and *OqxA* gene was found in three isolates. However, these isolates were not *OqxB* positive. One of these three positive isolates has been previously found to be *QnrS*-positive.

Conclusion: In our study, *QnrS* was detected in two and *OqxA* gene in three of the *S. maltophilia* isolates.

Keywords: Plasmid-mediated resistance, *Qnr, OqxAB, S. maltophilia*

Öz

Giriş: Non-fermentatif bir bakteri olan *Stenotrophomonas maltophilia*, ağırlıklı olarak bağışıklığı baskılanmış bireylerde ve uzun süreli, geniş spektrumlu antimikrobiyal ajanlar alanlarda fırsatçı enfeksiyonlara neden olur. *S. maltophilia*, mevcut antimikrobiyal ajanların çoğuna doğal olarak dirençlidir. Trimetoprim-sulfametoksazol (TMP/SMX), seftazidim ve levofloksasin (LVX) enfeksiyonların tedavisinde tercih edilen ilaçlardır. Bu çalışmanın amacı, *S. maltophilia* izolatlarında plazmit aracılı kinolon direnç belirleyicileri olan *QnrA, QnrB, QnrC,QnrD, QnrS* ve *OqxAB* genlerinin varlığını ortaya koymaktır.

Gereç ve Yöntem: Çalışmada çeşitli klinik örneklerden toplanan 122 *S. maltophilia* klinik izolatı test edilmiştir. Trimetoprim-sulfametoksazol ve LVX duyarlılığı disk difüzyon yöntemi ile, seftazidim (CAZ) minimum inhibitör konsatrasyon (MİK) değeri ise gradient difüzyon testi ile belirlendi. *Qnr* (A, B, C, S, D) determinantları ve *OqxAB* varlığı multipleks polimeraz zincir reaksiyonu ile araştırıldı. İlk olarak *OqxA* ve *OqxA* pozitif izolatlarda *OqxB* varlığı araştırıldı.

Bulgular: *S. maltophilia* izolatlarının beşi (%4) TMP/SMX'ye dirençliydi. Levofloksasin ve CAZ direnci sırasıyla %6,5 ve %56,5 olarak belirlendi. İki izolatta *QnrS* tespit edildi. Üç izolatta *OqxA* geninin varlığı tespit edildi ancak üç izolatta da *OqxB* tespit edilmedi. Bu üç pozitif izolattan birinin de daha önce *QnrS* pozitif olduğu bulunmuştur.

Sonuç: Çalışmamızda *S. maltophilia* izolatlarında ikisinde *QnrS*, üçünde *OqxA* geninde tespit edildi.

Anahtar Kelimeler: Plazmit aracılı direnç, *Qnr, OqxAB, S. maltophilia*

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Introduction

Stenotrophomonas maltophilia, a non-fermentative Gram-negative bacterium, can cause nosocomial infections and is characterized by intrinsic resistance to several antibiotics[1]. Several mechanisms contribute to its multidrug resistance (MDR), including plasmids, integrons, and transposons[2].

Fluoroquinolones show a good activity against *S. maltophilia*. Nonetheless, in the last years, a considerable increase in the resistance to quinolones has been observed[3,4]. In general, two mechanisms, i.e., target modification (in the DNA gyrase and topoisomerase intravenous) and efflux by MDR pumps, contribute to the resistance to these antimicrobial agents[5]. However, the outer membrane protein changes and the overexpression of efflux systems have been associated with an increased levels of quinolone resistance[6].

The clinical importance of plasmid-mediated quinolone resistance is uncertain, although it is suggested to help stabilize or select for mutations in the quinolone resistance-determining region of DNA gyrase and topoisomerase, which confers high-level quinolone resistance[7]. However, the emergence of plasmid-mediated fluoroquinolone resistance has also been reported; different kind of mechanisms are determined:(1) qnr, (2) aminoglycoside acetyltransferase aac(6')-Ib-cr, (3) *OqxAB* and *QepA*[8,9].The primary structures of *QnrA*, *QnrB*, and *QnrS* are similar: nine pentapeptide repeat units connected by a single glycine, followed by a cysteine, with variable number of units (22 in *QnrS*; 28 in *QnrA*; and 29 in *QnrB*, *QnrC*, and *QnrD*). Two plasmid-mediated quinolone transporters have been found: *OqxAB* and *QepA*[10]. *Qnr* gene exists in several bacterial genera. It is found in the *S. maltophilia* chromosome as *Qnr*, which encoded a protein that contributes to the intrinsic resistance to quinolones[11]. This gene could be plasmid-borne, resulting in high resistance to quinolones in wild-type and mutant bacteria. The first plasmid-mediated quinolone resistance determinant (later termed *QnrA1*) was first reported in 1998 from *Klebsiella pneumoniae*[12-14]. The plasmid-mediated *QnrA* gene source has been identified in the *Shewanella algae* chromosome, while the possible source of plasmid-mediated *QnrS* determinants was identified in the *Vibrio splendidus* chromosome[15,16].

This study aimed to investigate the presence of plasmid-mediated quinolone resistance determinants of *QnrA*, *QnrB*, *QnrC*, *QnrD*, *QnrS*, *OqxA*, and *OqxB* genes in *S. maltophilia* isolates.

Materials and Methods

A total of 122 *S. maltophilia* isolates were collected in January-December 2016, from various clinical specimens. Only one isolate per patient were tested in the study. Bacterial identification was made using standard algorithms (microscopy, culture characteristics, oxidase reaction), followed by an automated system using the Vitek MS (bioMerieux, France). The susceptibility of trimethoprim-sulfamethoxazole (TMP/SMX) and levofloxacin (LVX) were determined using the disk diffusion method, and the minimum inhibitory concentration (MIC) value of ceftazidime (CAZ) was determined using the gradient diffusion test. Levofloxacin and CAZ and TMP/SMX susceptibilities were interpreted according to the Clinical and Laboratory Standards Institute criteria and the European Committee on Antimicrobial Susceptibility Testing, respectively, established for *S. maltophilia*[17,18]. The isolates were stored at -60 °C until the study time.

DNA extraction was performed using a boiling technique for polymerase chain reaction (PCR).

Qnr (A, B, C, S, D) and *OqxAB* determinants were investigated by multiplex PCR using specific primers[19-21]. *OqxA* and the presence of *OqxB* were investigated in the isolates and in *OqxA*-positive isolates. The primers used in the PCR assays were given in Table 1. *QnrA*-, *QnrB*-, *QnrC*-, *QnrS*-, and *OqxAB*-positive strains were used as a positive control and *Escherichia coli* ATCC 25928 as negative control in the PCR assay. The Ethical Committee of the Ondokuz Mayıs University, Faculty of Medicine, approved our study (decision number: B.30.2.ODM.0.20.08/471). The study followed the Declaration of Helsinki principles. Informed parental consent was not obtained due to the nature of the study-only the isolates were tested, and the patients' electronic data were used without ID information.

Statistical Analysis

All data were recorded in Excel spreadsheets, and categorical variables were expressed as numbers and percentages.

Results

The clinical sites of *S. maltophilia* infection were primarily the bloodstream (35.3%) and respiratory tract (33.6%) (Table 2).

Out of 122 *S. maltophilia* isolates, 5 (4%) were resistant to TMP/SMX. Levofloxacin and CAZ resistances were determined as 6.5% and 56.5%, respectively.

QnrS was detected in two isolates (2 and 54). *QnrA*, *QnrB*, *QnrC*, and *QnrD* were not detected. The two *QnrS*-positive isolates were sequenced and confirmed and found that one was susceptible to LVX and the other was resistant to LVX. Both *QnrS*-positive isolates were susceptible to TMP/SMX and CAZ.

The presence of *OqxA* gene was found in three isolates (54, 145, 147) (Figure 1). One of these isolates has been previously found to be *QnrS*-positive (isolate 54). However, the presence of *OqxB* gene was not found. There was no positive isolates for *OqxAB*. One of the *OqxA*-positive isolate was resistant to LVX, and the other two were susceptible.

Table 1. Sequence of primers

Gene	Primer	Sequence	Bp	Ref
QnrA	QnrA-F QnrA-R	ATTTCTCACGCCAGGATTTG GATCGGCAAAGGTTAGGTCA	516	[17]
QnrB	QnrB-F QnrB-R	GATCGTGAAAGCCAGAAAGG ATGAGCAACGATGCCTGGTA	476	[17]
QnrC	QnrC-F QnrC-R	GGGTTGTACATTTATTGAATCG CACCTACCCATTTATTTTC	307	[17]
QnrS	QnrS-F QnrS-R	GCAAGTTCATTGAACAGGGT TCTAAACCGTCGAGTTCGGCG	428	[17]
QnrD	QnrD-F QnrD-R	CGAGATCAATTTACGGGGAATA AACAAGCTGAAGCGCCTG	565	[18]
OqxA	OqxA-F OqxA-R	CTCGGCGCGATGATGCT CCACTCTTCACGGGAGACGA	392	[19]
OqxB	OqxB-F OqxB-R	TTCTCCCCCGGCGGGAAGTAC CTCGGCCATTTTGGCGCGTA	512	[19]

Table 2. Distribution of the clinical specimens and *QnrS*- and *OqxA*-positive isolates

Specimen	Number (%)	*QnrS*-positive n (%)	*OqxA*-positive n (%)
Blood	43 (35.3%)	1 (2.32%)	1 (2.32%)
Tracheal aspirate	23 (18.9%)	-	-
Urine	19 (15.6%)	1 (5.2%)	2 (10.5%)
Sputum	18 (14.8%)	-	-
Wound swab	12 (9.8%)	-	-
Catheter	2 (1.6%)	-	-
Ventriculoperitoneal shunt catheter	2 (1.6%)	-	-
Sterile body fluid	2 (1.6%)	-	-
Bronchoalveolar lavage	1 (0.8%)	-	-
Total	122	2	3

Discussion

S. maltophilia is accepted as a pathogen with gradually increasing importance recently. This could be caused by increasing number of immune-compromised patients, prolonged hospital stay and increasing use of wide spectrum antibiotics like carbapenems. *S. maltophilia* is a bacterium occurring in almost any aquatic or humid environment, including the drinking water supply[22]. Also, it has emerged as an opportunistic pathogen affecting primarily the hospitalized and debilitated host. Nevertheless, the ability of *S. maltophilia* to colonize airway epithelia and plastic surfaces of indwelling medical devices made it a major nosocomial pathogen, especially in the ICU setting[23].

Quinolones are widely used due to their broad spectrum. In a study, it has been stated that ciprofloxacin is the most commonly used antibacterial agent all over the world[24].

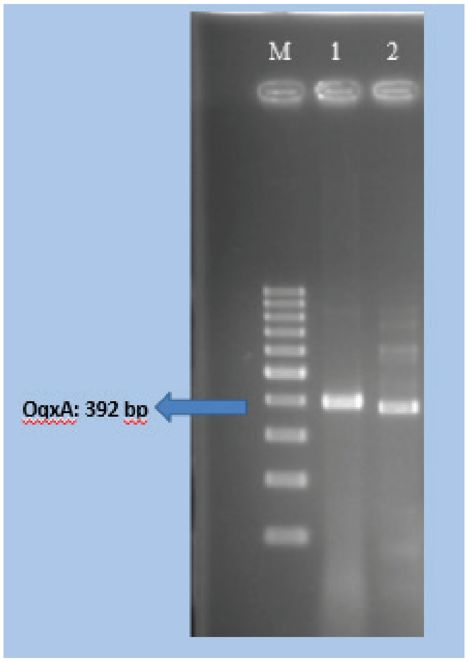

Figure 1. Polymerase chain reaction gel image made with *OqxAB*-positive strain (M, marker; 1, *OqxAB*-positive strain; bp:392 2; one of the clinical strains found to be *OqxA*-positive and detected to be *OqxB*-negative)

Quinolones inhibit topoisomerization by forming drug-enzyme-DNA complexes. By creating a barrier in front of replication-competent RNA polymerase and DNA helicase, they cause events resulting in cell death[25,26].

The quinolone resistance occurs through the three main mechanisms: (i) the changes in the chromosomal targets of the quinolones, (ii) reduced accumulation due to reduced membrane permeability and/or excessive working of the efflux pump systems, and (iii) plasmid-mediated resistance[27].

The first plasmid-mediated quinolone was termed *Qnr* (standing for quinolone resistance). Currently, there are several named and described alleles: *QnrA*, *QnrS*, *QnrB*, *QnrC*, *QnrD*, *QnrE*, and *QnrVC*. The second, *aac(6')-Ib-cr*, is a variant aminoglycoside acetyltransferase, capable of reducing ciprofloxacin activity. Finally, quinolone extrusion, a prevalent chromosomally encoded resistance mechanism, has also been found to be plasmid-borne and mediated by *QepA* or *OqxAB*[28,29].

Qnr determinants isolated from many bacteria belong to *Enterobacteriaceae* family so far, although they are isolated most often from *Klebsiella pneumoniae*, *Enterobacter* spp., *E. coli*, and *Salmonella enterica* isolates[28]. The Qnr determinants were also determined in *Pseudomonas* sp. isolates, with prevalence ranging 0.2-94%[10,28]. *S. maltophilia* spp. contains a chromosomally encoded *Qnr* gene, which confers low-level quinolone resistance upon its expression in a heterologous host. Plasmid-mediated quinolone resistance genes were investigated in *S. maltophilia* isolates in some studies. *Qnr* is identified in the genome of *S. maltophilia* strain R551-3. It codes for a 219 amino acid protein that shares about 60% amino acid identity with qnrB and has two domains of 5 and 28 pentapeptide repeats separated by a glycine[30,31].

Furlan et al.[32] investigated the antimicrobial resistance profile, the presence of mutations in the quinolone resistance-determining region and acquired resistance genes, and the different plasmid families in *S. maltophilia* isolated from Brazilian soils (150 varieties of agricultural soils). Study results showed the presence of *QnrA* and *OqxAB* genes (first time) and *QnrB* and *QnrS* genes (second time) in *S. maltophilia*. Ebrahim-Saraie et al.[33] reported the occurrence of antibiotic resistance and resistance mechanisms among *S. maltophilia* clinical isolates (n=44) from Iranian patients. *Qnr* gene was found in 29 (65.9%) of the isolates.

In a study, the molecular epidemiology of *S. maltophilia* strains associated with an outbreak in the Children's Hospital of México Federico Gómez was investigated. Twenty-one clinical *S. maltophilia* strains were recovered from cultures of blood and urine samples from 10 pediatric patients at the emergency department. Nine environmental *S. maltophilia* strains recovered from faucets in the same area were included. The presence of *sul1*, *qnr*, *intl1*, *pilU*, *hlyIII*, and *rmlA* were investigated by multiplex PCR. *Qnr* genes were detected in 26/30 isolate (86.66%)[34].

The pOLA52 plasmid, causing olaquindox (quinoxaline derivative used in agricultural feeds as growth promoter) antibiotic resistance, was identified from *E. coli* strains isolated from porcine embryos[35]. *OqxAB*, a multidrug efflux pump of resistance-nodulation-division family and recently detected in *E. coli* isolates from humans, was shown as the resistance's reason[36]. It is also found in *K. pneumoniae* chromosome and causes olaquindox resistance according to different expression ratios[21]. The plasmid pOLA52 was detected to cause an 8-16-fold increase in the MIC values of nalidixic acid and ciprofloxacin in *E. coli* strain without the AcrA gene[37].

Among the 556 (1.8%) *E. coli* strains isolated between 1995 and 1998 in Denmark and Sweden, 10 have an MIC of olaquindox of 64 g/ml, of which 9 strains had *oqxA* gene detected in their isolates[36]. Plasmid-mediated *OqxAB* was first detected in a human clinical *E. coli* isolate from South Korea[21].

Fluoroquinolone resistance in *S. maltophilia* isolates occurred by multiple chromosomally encoded resistance determinants, including efflux pumps, plasmid-mediated quinolone resistance determinants, enzymes, and the quinolone resistance protein *SmQnr*[38]. Levofloxacine resistance mechanisms in isolates tested in this study could be other mechanisms than plasmid-mediated. In our study, we determined two *QnrS*-positive isolates. The presence of *OqxA* gene was found in three isolates. However, *OqxB* was not detected. This was the first study that investigated the presence of *OqxAB* in *S. maltophilia* isolates. Our study's limitation is that the number of isolates is limited because *S. maltophilia* was uncommon than the Gram-negative bacteria, Enterobacterales or *P. aeruginosa*.

Conclusion

S. maltophilia is an important opportunistic pathogen and resistant to many antibiotics because the patients' early isolation prevented the clonal spread of *S. maltophilia* clinical isolates. In our study, *QnrS* was detected in two and *OqxA* gene in three *S. maltophilia* isolates. Monitoring *S. maltophilia*'s clinical distribution and antimicrobial resistance is of great significance for the bacterial infection's clinical therapy.

Ethics

Ethics Committee Approval: The Ethical Committee of the Ondokuz Mayıs University, Faculty of Medicine, approved our study (decision number: B.30.2.ODM.0.20.08/471).

Informed Consent: Informed parental consent was not obtained due to the nature of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.T.Ç., A.B., Design: Y.T.Ç., Data Collection or Processing: Y.T.Ç., İ.B., Analysis or Interpretation: Y.T.Ç., İ.B., A.B., Literature Search: İ.B., A.B., Writing: Y.T.Ç., İ.B.

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References

1. Alonso A, Martínez JL. Multiple antibiotic resistance in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 1997;41:1140-2.
2. Barbolla R, Catalano M, Orman BE, Famiglietti A, Vay C, Smayevsky J, Centrón D, Piñeiro SA. Class 1 integrons increase trimethoprim-sulfamethoxazole MICs against epidemiologically unrelated *Stenotrophomonas maltophilia* isolates. Antimicrob Agents Chemother. 2004;48:666-9.
3. Vartivarian S, Anaissie E, Bodey G, Sprigg H, Rolston K. A changing pattern of susceptibility of Xanthomonas maltophilia to antimicrobial agents: implications for therapy. Antimicrob Agents Chemother. 1994;38:624-7.
4. Jia W, Wang J, Xu H, Li G. Resistance of *Stenotrophomonas maltophilia* to Fluoroquinolones: Prevalence in a University Hospital and Possible Mechanisms. Int J Environ Res Public Health. 2015;12:5177-95.
5. Vila J, Ruiz J, Navia MM. Molecular basis of quinolone resistance acquisition in Gram-negative bacteria. Recent Res Devel Antimicrob Agents Chemother. 1999;3:323-44.
6. Alonso A, Martínez JL. Cloning and characterization of SmeDEF, a novel multidrug efflux pump from *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2000;44:3079-86.
7. Poirel L, Cattoir V, Nordmann P. Is plasmid-mediated quinolone resistance a clinically significant problem? Clin Microbiol Infect. 2008;14:295-7.
8. Tran JH, Jacoby GA. Mechanism of plasmid-mediated quinolone resistance. Proc Natl Acad Sci U S A. 2002;99:5638-42.
9. Rodríguez-Martínez JM, Cano ME, Velasco C, Martínez-Martínez L, Pascual A. Plasmid-mediated quinolone resistance: an update. J Infect Chemother. 2011;17:149-82.
10. Strahilevitz J, Jacoby GA, Hooper DC, Robicsek A. Plasmid-mediated quinolone resistance: a multifaceted threat. Clin Microbiol Rev. 2009;22:664-89.
11. Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. Clin Microbiol Rev. 2012;25:2-41.
12. Martínez-Martínez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. Lancet. 1998;351:797-9.
13. Sánchez MB, Hernández A, Rodríguez-Martínez JM, Martínez-Martínez L, Martínez JL. Predictive analysis of transmissible quinolone resistance indicates *Stenotrophomonas maltophilia* as a potential source of a novel family of *Qnr* determinants. BMC Microbiol. 2008;8:148.
14. Wareham DW, Gordon NC, Shimizu K. Two new variants of and creation of a repository for *Stenotrophomonas maltophilia* quinolone protection protein (*SmQnr*) genes. Int J Antimicrob Agents. 2011;37:89-90.
15. Cattoir V, Poirel L, Mazel D, Soussy CJ, Nordmann P. Vibrio splendidus as the source of plasmid-mediated *QnrS*-like quinolone resistance determinants. Antimicrob Agents Chemother. 2007;51:2650-1.
16. Poirel L, Rodriguez-Martinez JM, Mammeri H, Liard A, Nordmann P. Origin of plasmid-mediated quinolone resistance determinant *QnrA*. Antimicrob Agents Chemother. 2005;49:3523-5.
17. Clinical nad Laboratory Standarts Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement. 2014;M100-S24. Available from: file:///Users/galenos/Downloads/CLSIM100-24-2014.pdf
18. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0, 2017. Available from: http://www.eucast.org
19. Kim HB, Park CH, Kim CJ, Kim EC, Jacoby GA, Hooper DC. Prevalence of plasmid-mediated quinolone resistance determinants over a 9-year period. Antimicrob Agents Chemother. 2009;53:639-45.
20. Cavaco LM, Hasman H, Xia S, Aarestrup FM. qnrD, a novel gene conferring transferable quinolone resistance in *Salmonella enterica* serovar Kentucky and Bovismorbificans strains of human origin. Antimicrob Agents Chemother. 2009;53:603-8.
21. Kim HB, Wang M, Park CH, Kim EC, Jacoby GA, Hooper DC. *OqxAB* encoding a multidrug efflux pump in human clinical isolates of *Enterobacteriaceae*. Antimicrob Agents Chemother. 2009;53:3582-4.
22. Cervia JS, Ortolano GA, Canonica FP. Hospital tap water as a source of *Stenotrophomonas maltophilia* infection. Clin Infect Dis. 2008;46:1485-7.
23. Looney WJ, Narita M, Mühlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. Lancet Infect Dis. 2009;9:312-23.
24. Acar JF, Goldstein FW. Trends in bacterial resistance to fluoroquinolones. Clin Infect Dis. 1997;24 (Suppl) 1:S67-73.
25. Andriole VT. The quinolones: past, present, and future. Clin Infect Dis. 2005;41 (Suppl) 2:S113-9.
26. Hooper DC. Mechanisms of action and resistance of older and newer fluoroquinolones. Clin Infect Dis. 2000;31 (Suppl) 2:S24-8.
27. Ruiz J. Mechanisms of resistance to quinolones: target alterations, decreased accumulation and DNA gyrase protection. J Antimicrob Chemother. 2003;51:1109-17.
28. Rodríguez-Martínez JM, Cano ME, Velasco C, Martínez-Martínez L, Pascual A. Plasmid-mediated quinolone resistance: an update. J Infect Chemother. 2011;17:149-82.
29. Albornoz E, Tijet N, De Belder D, Gomez S, Martino F, Corso A, Melano RG, Petroni A. *QnrE1*, a Member of a New Family of Plasmid-Located Quinolone Resistance Genes, Originated from the Chromosome of Enterobacter Species. Antimicrob Agents Chemother. 2017;61:e02555-16.
30. Sánchez MB, Hernández A, Rodríguez-Martínez JM, Martínez-Martínez L, Martínez JL. Predictive analysis of transmissible quinolone resistance indicates *Stenotrophomonas maltophilia* as a potential source of a novel family of Qnr determinants. BMC Microbiol. 2008;8:148.
31. Shimizu K, Kikuchi K, Sasaki T, Takahashi N, Ohtsuka M, Ono Y, Hiramatsu K. *SmQnr*, a new chromosome-carried quinolone resistance gene in *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2008;52:3823-5.
32. Furlan JPR, Sanchez DG, Gallo IFL, Stehling EG. Characterization of Acquired Antimicrobial Resistance Genes in Environmental *Stenotrophomonas maltophilia* Isolates from Brazil. Microb Drug Resist. 2019;25:475-9.
33. Ebrahim-Saraie HS, Heidari H, Soltani B, Mardaneh J, Motamedifar M. Prevalence of antibiotic resistance and integrons, sul and *SmQnr* genes in clinical isolates of *Stenotrophomonas maltophilia* from a tertiary care hospital in Southwest Iran. Iran J Basic Med Sci. 2019;22:872-7.
34. Cruz-Córdova A, Mancilla-Rojano J, Luna-Pineda VM, Escalona-Venegas G, Cázares-Domínguez V, Ormsby C, Franco-Hernández I, Zavala-Vega S, Hernández MA, Medina-Pelcastre M, Parra-Ortega I, la Rosa-Zamboni D, Ochoa SA, Xicohtencatl-Cortes J. Molecular Epidemiology, Antibiotic Resistance, and Virulence Traits of *Stenotrophomonas maltophilia* Strains Associated With an Outbreak in a Mexican Tertiary Care Hospital. Front Cell Infect Microbiol. 2020;10:50.
35. Sørensen AH, Hansen LH, Johannesen E, Sørensen SJ. Conjugative plasmid conferring resistance to olaquindox. Antimicrob Agents Chemother. 2003;47:798-9.
36. Hansen LH, Sørensen SJ, Jørgensen HS, Jensen LB. The prevalence of the *OqxAB* multidrug efflux pump amongst olaquindox-resistant *Escherichia coli* in pigs. Microb Drug Resist. 2005;11:378-82.
37. Hansen LH, Jensen LB, Sørensen HI, Sørensen SJ. Substrate specificity of the *OqxAB* multidrug resistance pump in *Escherichia coli* and selected enteric bacteria. J Antimicrob Chemother. 2007;60:145-7.
38. Azimi A, Rezaei F, Yaseri M, Jafari S, Rahbar M, Douraghi M. Emergence of fluoroquinolone resistance and possible mechanisms in clinical isolates of *Stenotrophomonas maltophilia* from Iran. Sci Rep. 2021;11:9582.