

Prevalence of *bla*_{Oxacillinase-23-} and *bla*_{Oxacillinase-24/40-} type Carbapenemases in *Pseudomonas aeruginosa* Species Isolated From Patients With Nosocomial and Non-nosocomial Infections in the West of Iran

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KEYWORDS

Carbapenemase genes, Metallo-beta-lactamases, OXA-carbapenemases, *Pseudomonas aeruginosa*

ABSTRACT

Background and Objective: *Pseudomonas aeruginosa* (*P. aeruginosa*) cause serious nosocomial and non-nosocomial infections. The *bla*_{Oxacillinases (OXA)-23} and *bla*_{OXA24/40} induce resistance to carbapenems. The current study aimed at detecting blaOXA-23 and blaOXA-24/40 in *P. aeruginosa* strains isolated from patients with nosocomial and non-nosocomial infections.

Methods: The current descriptive cross sectional study was conducted in Sanandaj, Iran (Kurdistan Province) from December 2015 to August 2017, on 146 strains of *Pseudomonas* spp. isolated from patients' specimens. Microbiological methods and polymerase chain reaction (PCR) for *gyrB* were applied to detect *P. aeruginosa*. Imipenem (IMP)-disk diffusion method and OXA-23-/OXA-24/40-multiplex PCR were used to identify resistant strains. Stata 12 using Fisher exact test and logistic regression were employed to analyze the data ($P \leq 0.05$).

Results: The *gyrB*-PCR results showed that 91.78% of isolates were *P. aeruginosa*. Nosocomial infection caused by *P. aeruginosa* was observed in 41.79% of the studied patients; however, 27.61% of *P. aeruginosa* strains were resistant to IMP; *bla*_{OXA-23} and *bla*_{OXA24/40} were detected in 11.19% and 2.24% of the strains, respectively; a co-existence of *bla*_{OXA-23} and *bla*_{OXA24/40} was also observed in 2.23% of *P. aeruginosa* strains. There were no significant relationships between antibiotic resistance and harboring resistance genes; in addition, between IMP resistance and age, gender, place of residence, inpatient/outpatient, and type of specimen no association was found ($P \geq 0.05$).

Conclusion: Resistance to IMP and the detection of resistant genes in the current study were observed in the clinical samples. Antibiotics should be prescribed more cautiously in order to prevent antibiotic resistance in pathogens.

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Introduction

Pseudomonas aeruginosa (*P. aeruginosa*) is the most common bacterial pathogen found in serious nosocomial and also non-nosocomial infections. Some of the infections caused by these bacteria are pneumonia, urinary tract infection (UTI), surgical

site infections, and sepsis (1, 2). These bacteria are often associated with multi-drug resistance (MDR) and extensively drug resistance (XDR). Thus, different infections caused by *P. aeruginosa* are difficult to treat and lead to morbidity, mortality, and also high economic burden on the patients (1). *P. aeruginosa*

strains are the common extended-spectrum beta-lactamase (ESBL) producers among pathogenic bacteria (3). According to Ambler Classification, beta-lactamases are classified into four groups of A, B, C, and D. Different genes encode class D beta-lactamases; in addition, they are poorly inhibited by clavulanic and ethylenediaminetetraacetic acids (EDTA), and have many differences in the amino acid sequences (4). The following types are examples of this enzyme: *OXA* (Oxacillinase)-1, 2, 10, 13, and 17 that are the prototype gene and cause resistance to oxacillin and cephalosporin (2). On the other hand, carbapenem-hydrolyzing class D beta-lactamases such as *OXA-23* and *-24/40* induce resistance to carbapenems such as imipenem (IMP), meropenem (MEM), and doripenem (DRP). Hydrophobic bridge formed by *Tyr112* and *Met223* plays an important role in carbapenemase activity of this enzyme (5). *OXA-23* was firstly reported in 1995 and *OXA-24/40* was identified in Spain in 2000 (6, 7). Epidemiology of carbapenem-resistant *P. aeruginosa* (CRPA) is studied in different geographical parts of the world and ranges from 10% to 50%. The lowest rates of CRPA are reported in Canada (3.3%) and the Dominican Republic (8%), and higher rates are observed in Brazil, Peru, Costa Rica, Russia, Greece, Poland, Iran, and Saudi Arabia (above 50%). The geographical distribution of CRPA is gradually increasing (8). Molecular and phenotypic techniques such as polymerase chain reaction (PCR) and disk diffusion method are used to study antibiotic resistant *P. aeruginosa* (9-11). According to the above mentioned contents, treatment of infections caused by *P. aeruginosa* harboring *bla*_{OXA-23} and *bla*_{OXA24/40} is very difficult. No study is conducted so far on the distribution of these genes in *P. aeruginosa* in Kurdistan Province, Iran. According to the increasing resistance, and failure of antibiotics to remove *P. aeruginosa*, the current study was conducted to investigate *P. aeruginosa* strains harboring *bla*_{OXA-23} and *bla*_{OXA24/40} and evaluate their characteristics. Such information can be used in healthcare centers and the hospital infection control practices advisory committees in order to make better decisions regarding the control and prevention of infectious diseases caused

by these bacteria, which in turn can help to properly prescribe antibiotics. Therefore, the current study aimed at investigating the phenotypic and molecular detections of *bla*_{OXA-23} and *bla*_{OXA24/40} among *P. aeruginosa* strains isolated from patients with nosocomial and non-nosocomial infections in different tertiary hospitals in Kurdistan Province, Iran.

Materials and methods

The current descriptive cross sectional study was conducted at the Cellular and Molecular Research Center of Kurdistan University of Medical Sciences, Sanandaj, Iran from December 2015 to August 2017. All *Pseudomonas* spp. isolated from 49 females and 97 males admitted to tertiary hospitals were collected (Table 2). Inclusion criteria of the current study were admission to tertiary hospitals; having infections caused by *P. aeruginosa*, and isolation of *P. aeruginosa* from their clinical specimens. Strains that were not identified in molecular and phenotypic tests as *P. aeruginosa* and those that did not grow on bacterial cultures were excluded from the study. The study protocol was also approved by the Ethics Committee of the local university (ethical code: MUK.REC.1394/337). Overall, 146 strains of *Pseudomonas* spp. were isolated. Patients' demographic information was collected from the hospital information system (HIS). Nosocomial and non-nosocomial *P. aeruginosa* infections were also detected according to the definition of centers for disease control and prevention (CDC) (12). For *P. aeruginosa* species, phenotypic features were detected using microbiological methods (13). To extract DNA for PCR, single and pure colonies of overnight culture on Mueller-Hinton agar (MHA) (Merck, Germany) were dissolved in 500 µL of sterile deionized water in a 1.5-mL tube; then, powdered glass was added to them slightly; 500 µL of Tris-EDTA (ethylenediaminetetraacetic acid) (10 mM Tris, 1 mM EDTA, pH 8.0) was also added to them. After centrifugation (7000 rpm, five minutes), 3 µL of supernatant was used for PCR as DNA template. For *P. aeruginosa* molecular detection by PCR, *gyrB* (*gyrase B*) forward (F) and reverse (R) primers (SinaClon, Iran) in a final volume of 25 µL (7.5 µL

deionized water, 3 μ L DNA template, 1 μ L each F and R primers, and 12.5 μ L Master mix) were used. *P. aeruginosa* ATCC 25922 (Darvash, Iran) and deionized water were applied as positive and negative controls, respectively (Table 1) (14). For antibiotic sensitivity testing, a suspension of *P. aeruginosa* adjusted to 0.5 McFarland turbidity standard was prepared, and then, was cultured on MHA. Kirby-Bauer disk diffusion method was applied according to Clinical and Laboratory Standards Institute (CLSI) guidelines with IMP (10 μ g) (Rosco, Denmark) (12). Multiplex PCR for

*bla*_{OXA-23} and *bla*_{OXA-24/40} using F- and R-primers (Sina-Clon, Iran) were performed. Acinetobacter baumannii strains harboring *bla*_{OXA-23} and *bla*_{OXA-24/40} and distilled water were respectively used as positive and negative controls in this assay (Table 1) (15). The PCR was amplified with the final volume of 21 μ L (8 μ L deionized water, 2 μ L DNA template, 0.2 μ L of each F and R primers for *bla*_{OXA-23} and *bla*_{OXA-24/40}, and 10 μ L Master mix) (7). Stata software version 12 using Fisher exact test and logistic regression analysis were used to analyze the data ($P \leq 0.05$).

Table 1. Primers Sequences and PCR Conditions in the Current Study

Primer and Gens Name	Sequence	Product Size (bp)	PCR Condition
<i>gyr B</i>	5'-CCTGACCATCCGTCGCCACAAC-3'	222	Initial denaturation at 95°C for 5 min 1 cycle followed by 35 cycles; denaturation at 94°C for 45 s, annealing at 66°C for 45 s, extension at 72°C for 1 min, and final extension at 72°C for 10 min 1 cycle
	5'-CGCAGCAGGATGCCGACGCC-3'		
<i>bla</i> _{OXA-23}	5-GAT CGG ATT GGA GAA CCAGA-3'	501	Initial denaturation at 94°C for 5 min 30 cycles, 94°C for 25 s, 52°C for 40 s, 72°C for 50 s, and a final extension at 72°C for 6 min
	5'-ATT TCT GAC CGC ATT TCC AT-3'		
<i>bla</i> _{OXA-24/40}	5'-GGT TAG TTG GCC CCC TTA AA-3'	246	
	5'-AGT TGA GCG AAA AGG GGA TT-3'		

Results

According to microbiological test results, 146 *Pseudomonas* spp. were detected. Phenotypic test showed 133 (91.09%) *P. aeruginosa* strains. But *gyrB*-PCR with 222 bp DNA fragments on gel electrophoresis determined 134 (91.78%) *P. aeruginosa* strains isolated from different hospitals (47 from females (35.07%) and 87 (64.93%) from males with the mean age of 50.35 \pm 20.19 years) (Figure1; Table 2). Nosocomial infection with *P. aeruginosa* was observed in 56 (41.79%) in-patients [14 (25%) females and 42 males (75%)] (Table 3). Results of the antibiotic sensitivity test showed IMP resistance in *P. aeruginosa* (Table 4)

strains. Gel electrophoresis detected DNA fragments of *bla*_{OXA-23} on 501 bp and *bla*_{OXA-24/40} on 246 bp in 15 (11.19%) and three (2.24%) strains, respectively (Figure 2). Three (0.45%) of the 15 IMP-resistant isolates carried the *bla*_{OXA-23} and non-resistant isolates were the carriers of *bla*_{OXA-24/40}. In addition, three (2.23%) strains of *P. aeruginosa* showed a co-existence of *bla*_{OXA-23} and *bla*_{OXA-24/40}. Four (7.14%) *P. aeruginosa* strains isolated from nosocomial infections carried *bla*_{OXA-23}, but none of them carried *bla*_{OXA-24/40}. There was no significant relationship between antibiotic resistance and presence of genes, and between IMP-resistance and age, gender, place of residence, inpatient/outpatient, and type of specimen ($P \geq 0.05$).

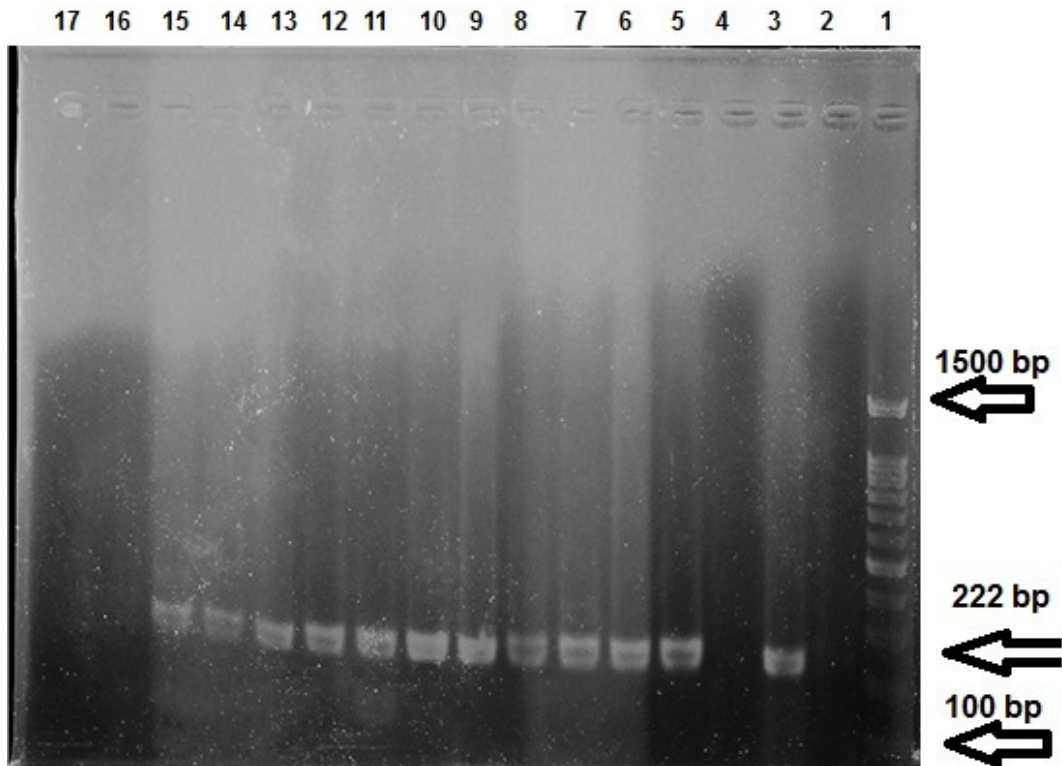


Figure 1. Gel electrophoresis of *gyrB*-PCR products; Line 1: marker, molecular weight 100–1500 bp; Line 2: negative control; Line 3: positive control; Lines 3, 16, 17: negative examples of *gyrB*; Line 5 to 15: positive examples of *gyrB* (222 bp length)

Table 2. The Source of *Pseudomonas aeruginosa* in Hospitals

Hospital	Outpatient, N (%)	Inpatient, N (%)	Death, N (%)	Number of Isolates (%)
Toohid	9 (69.23)	85 (71.42)	1 (50)	95 (70.89)
Besat	3 (23.07)	29 (24.36)	1 (50)	33 (24.62)
Imam Hossein	1 (7.69)	3 (2.52)	0	4 (2.98)
Imam Khomeini	0	1 (0.84)	0	1 (0.74)
Fajr	0	1 (0.84)	0	1 (0.74)
Kowsar	0	0	0	0
Total	13	119	2	134

Table 3. Source of *Pseudomonas aeruginosa* in Clinical Samples

Source	No. (%) of Strains	No. (%) of Strains related with Nosocomial infection
Wards		
Intensive Care Unit (ICU)	40 (29.85)	39 (69.64)
Women's Internal	13 (9.70)	02
Men's Internal	8 (5.97)	1 (1.78)
Men's Ward	1 (0.75)	0
Women Heart	3 (2.24)	0
Infectious	15 (11.19)	0
Emergency	12 (8.96)	1(1.78)
Laboratory	10 (7.46)	0
Men's Surgery	8 (5.97)	4 (2.98)
Neurology	7 (5.22)	6 (4.47)
Respiratory	4 (2.99)	0
Burn	4 (2.98)	2 (1.49)
Oncology	3 (2.24)	1 (1.78)
Women's heart	3 (2.23)	1 (1.78)
Digestion	2 (1.49)	0
Women's Surgery	1 (0.75)	0
Heart Surgery	1 (0.75)	0
General Surgery	1 (0.75)	1 (1.78)
Orthopedic	1 (0.75)	0
Total	134	56
Specimens		
Urea	61 (45.52)	12 (21.42)
Tracheal	29 (21.64)	29 (51.78)
Wound	15 (11.19)	5 (8.92)
Blood	16 (11.94)	3 (5.35)
Lung Secretions	4 (2.99)	3 (5.35)
Pleural Fluid	4 (2.98)	2 (3.57)
Sputum	2 (1.49)	1 (1.78)
Intestines Biopsy	1 (0.75)	0
Stool	1 (0.75)	0
Abdominal Fluid	1 (0.70)	1 (1.78)
Total	134	56

* Men's internal ward was related to patients with internal diseases such as Endocrine disorders, liver disorders and rheumatism or diseases, Men's surgery ward was related to patients with surgery such as general medical surgery, urinary system, orthopedic surgery and neurosurgery

Table 4. Results of IMP Sensitivity Testing for *Pseudomonas aeruginosa*

Infection Type	Infection Type		
	Sensitive, N (%)	Intermediate, N (%)	Resistant, N (%)
Nosocomial	33 (36.66)	2(2.22)	21 (22.22)
Non-nosocomial	57 (63.33)	5(5.55)	16 (18.88%)
Total(134)	90 (67.16)	7(5.22)	37 (27.61)

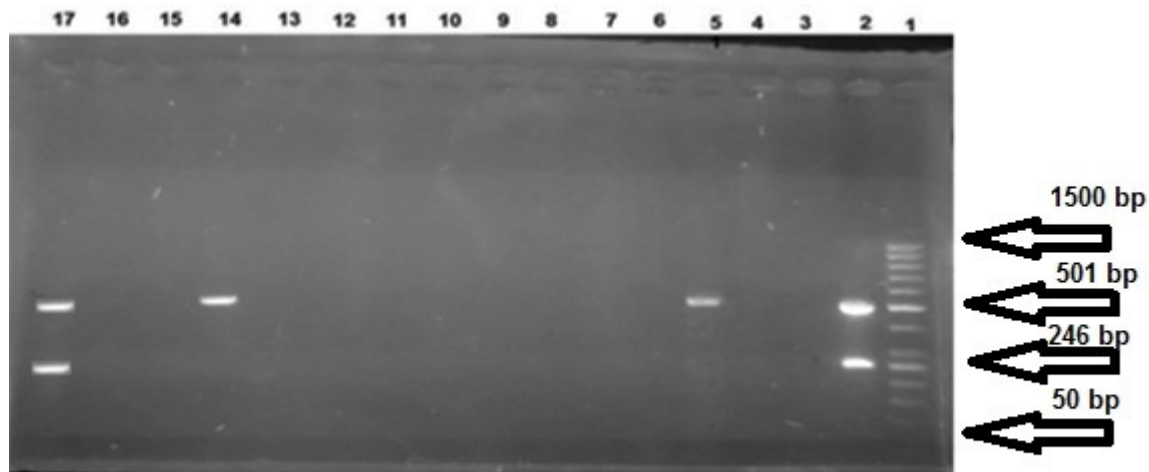


Figure 2. Gel electrophoresis of multiplex PCR products of *bla*_{OXA-23} and *bla*_{OXA-24/40}; Line 1: marker, molecular weight 50–1500 bp; Line 2: positive control; Line 3: negative control; Lines 4, 6–13, 15, 16: negative samples for *bla*_{OXA-23} and *bla*_{OXA-24/40}; Line 17: positive samples for *bla*_{OXA-24/40} (246 bp length); Lines 5, 14, 17: positive samples for *bla*_{OXA-23} (501 bp length)

Discussion

P. aeruginosa cause infection in different hospital wards (2, 16). In the current study, among 146 *Pseudomonas* spp., 91.09% using phenotypic test and 91.78% using *gyrB*-PCR were identified as *P. aeruginosa*. Based on the results of phenotypic test and *gyrB*-PCR for *P. aeruginosa*, Farajzadeh Sheikh et al., reported all the 223 isolates as *P. aeruginosa* (17). PCR is a rapid technique; it is a gold standard with high sensitivity and specificity, and it is reliable to identify microbial pathogens (17, 18). In the current study, most *P. aeruginosa* strains were isolated from Toohid Hospital (70.89%), followed by Besat Hospital (24.62%). Since Toohid and Besat hospitals are the tertiary referral centers in Sanandaj, the center of Kurdistan Province, Iran, and most of the patients are referred to them from surrounding cities, the highest rates of infection were reported from these hospitals. Nosocomial infection caused by *P. aeruginosa* was observed in 41.79% of inpatients. The majority of *P. aeruginosa* strains were isolated from intensive care units (ICUs) (29.85%) of which 69.64% were related to nosocomial infections. Verma et al., in India reported 24% and 18% prevalence of *P. aeruginosa* respectively from burn ward and ICU in patients with nosocomial infection. In addition, resistance to antibiotics in these wards were high (19). Due to the fact that *P. aeruginosa* is an MDR and opportunistic pathogen;

it can cause nosocomial infection, especially among inpatients admitted to ICU. Moreover, personal underlying risk factors such as nature and duration of invasive procedures used, length of ICU and hospital stay, and antibiotic treatment can affect the different rates of nosocomial infections in ICUs (19, 20). Results of the antibiotic sensitivity testing against IMP showed that bacteria isolated from nosocomial infections were more resistant to IMP (22.22%). Mohsenpour et al., reported that 134 isolates out of 374 were IMP-resistant, while 240 were IMP-sensitive; the resistance rates were higher in ICU and patients with nosocomial infections, which was similar to the results of the current study (21). Major factors leading to carbapenem-resistance are metallo-beta-lactamases (class D MBLs) and carbapenem-hydrolyzing oxacillinases (15). However, rates of antibiotic resistance in a study tend to differ according to certain factors such as type of antibiotics, genetic variations of bacteria and resistant strains, and differences in antibiotic consumption pattern at different locations (22). In the current study, *bla*_{OXA-23} and *bla*_{OXA-24/40} were detected in 11.19% and 2.23% of the isolates, respectively. In addition, *bla*_{OXA-23} was detected in 7.14% of the patients with nosocomial infections. By performing multiplex PCR, Esenkaya Taşbent and Özdemir showed that of 184 IMP- and/or MEM-resistant *Pseudomonas* spp. strains isolated from different clinical samples, 6.5%

and 0.54% were positive for *bla*_{OXA-23} and *bla*_{OXA-24/40}, respectively (23). In the current study, 0.45% of 15 IMP-resistant isolates were the *bla*_{OXA-23} carriers, but none of the resistant isolates were *bla*_{OXA-24/40} carriers. To justify this matter, the environment and/or genetic context can modify the phenotypic expression of resistant genes and thus, genotype does not always result in the expected phenotype (24). The results were similar to those of the current study. Based on the results of PCR, Odumosu et al., showed that the prevalence of *bla*_{OXA-10} in *P. aeruginosa* strains was 80% (10). Multiplex PCR results in a study by Farsiani et al., showed harboring *bla*_{OXA-23} in all 36 isolates of *A. baumannii* and accordingly, the prevalence of *bla*_{OXA-24/40} was 64% (15). These rates in the study by Odumosu were higher than those of the current study about *bla*_{OXA} genes. According to the results of PCR, Aghazadeh et al., detected *OXA I, II, and III* in *P. aeruginosa* species, and enterobacterial repetitive intergenic consensus-PCR (ERIC-PCR) proved high genetic diversity among these isolates (2). In a study by Saderi et al., 39.06% of 94 *P. aeruginosa* isolates were MBLs producers. They used the combination disk diffusion method to detect MBL-producing *P. aeruginosa* (25). Different mechanisms of gene transfer such as horizontal gene transfer (including transposable elements) can be the cause of transmission of class D carbapenem-hydrolyzing beta-lactamases genes among different bacterial strains; it is a global concern threatening all the countries and communities (9, 15, 26, 27). Finally, the following can be considered as the strength points of the current study: clinical samples were gathered in the span of three years, employment of CLSI guidelines to diagnose

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and determine resistance patterns of bacteria, the employment of PCR method, and using easy-to-access and cost-effective methods. However, weaknesses and limitations of the current study were possible contamination of the laboratory environment, which may lead to false results and lack of access to the medical history and specimens of all the patients.

Conclusion

In the current study, IMP-resistant *P. aeruginosa* strains were detected in different clinical samples taken from patients with nosocomial and non-nosocomial infections. Some of the isolates carried *OXA* genes. Carbapenems are still the most important and effective antibiotics against different infections caused by *P. aeruginosa*; therefore, according to the current study results, more effective planning and measures should be taken in order to determine the resistance and prevalence of such genes in the studied strains, and control and prevent the spread of these bacteria in hospital wards.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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