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Detection of β-lactamase genes and characterization of class 1 integrons in multidrug-resistant *Pseudomonas aeruginosa* strains in Guilan, Iran

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Abstract

Background: Infections caused by extended-spectrum β-lactamase (ESBL)-producing *Pseudomonas aeruginosa* (*P. aeruginosa*) are a serious concern in hospitals around the world. Many β-lactamase genes are carried by integrons. This study was conducted to investigate the frequency of β-lactamase genes and characterize class 1 integrons in multidrug-resistant *P. aeruginosa* strains in Guilan, northern Iran.

Methods: A total of 110 *P. aeruginosa* isolates were collected from different hospitals in 2021 and identified using standard microbiological methods. The isolates were studied for their antibacterial susceptibility and ESBL-producing ability by disk diffusion. All ESBL-producing isolates were investigated for the presence of β-lactamase resistance and integron genes by polymerase chain reaction (PCR). Gene cassette screening was done based on sequence analysis of class 1 integrons.

Results: Based on antibiotic susceptibility testing, 40 isolates (37.4%) were ESBL producers. The frequency of β-lactamase genes, including *VIM, SIM, IMP, SPM*, and *OXA2*, was 10.3%, 1.9%, 20.6%, 14%, and 4%, respectively. *GIM* and *OXA* 10 genes were not found in any of the strains. Furthermore, the *int1* gene was identified among 37 isolates (34.6%). The sequencing results of *int1* showed 12 different types of gene cassettes among 13 strains. In this assay, *blaOXA-2* was the only bla gene identified in *int1*.

Conclusion: The integrons carrying multidrug resistance genes are highly prevalent in *P. aeruginosa* isolates, and ESBL genes were also observed in these strains. Therefore, constant monitoring of drug resistance, especially ESBL producers, is critical to disease management in clinical settings.

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Introduction

Pseudomonas aeruginosa (P. aeruginosa) is a Gram-negative bacterium responsible for a wide variety of infections, including urinary tract infection, pneumonia, septicemia, wound infection, meningitis, and many life-threatening infections (1). Various mechanisms, such as β-lactamase production, target mutation, overexpression of output pumps, and reduced outer membrane permeability, are believed to be involved in the resistance of *P. aeruginosa* to antimicrobial agents (2). Due to the significance of β-lactam antibiotics in hospital use, various forms of β-lactamases, e.g., extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, and metallo-β-lactamases (MBL), have evolved. ESBLs are the major enzymes in bacteria that are resistant to various β-lactam antibiotics, including penicillins, cephalosporins, and carbapenems. However, they are inhibited by β-lactam inhibitors, such as clavulanic acid, sulbactam, and tazobactam (3,4). These enzymes break down the amide bond of the β-lactam ring and inactivate antimicrobial agents. ESBL genes, including *blaSHV*, *blaTEM,* and *blaCTX-M,* are encoded by plasmids and can transfer between bacterial species (5,6). These enzymes are highly prevalent in *Enterobacteriaceae* and *P. aeruginosa* strains. Mutations in genes encoding TEM and SHV enzymes lead to the production of ESBLs with an extended substrate catalytic activity, allowing for the breakdown of all cephalosporins, penicillins, and aztreonam (7). An increase in the frequency of ESBLs has been reported in recent years, but it varies in different geographical locations. Overall, clinical treatment failure occurs when inappropriate antimicrobial therapy is used to treat infections caused by ESBL-producing *P. aeruginosa* strains. Therefore, enabling laboratory technicians to correctly identify ESBL-producing *P. aeruginosa* isolates would lead to a better selection of antibiotics and improved infection outcomes (8,9). The growing resistance of *P. aeruginosa* to several antibiotics, as a result of excessive antibiotic administration, has resulted in high levels of antibiotic resistance and cross-resistance between antibiotics and the emergence of multidrug-resistant (MDR) forms of *P. aeruginosa* (10). Integrons are genetic elements that can carry multiple antibiotic resistance genes.

To date, four classes of integrons have been described in Gram-negative bacterial isolates. Three main classes of integrons have a 5′ conserved segment, including an *intI* gene encoding an integrase and an *attI* recombination site, but have distinct 3′ conserved segments (6). In class 1 integrons, the 3′ conserved segment includes three open reading frames (ORFs)-qacEΔ1, a deletion derivative of the antiseptic resistance gene *qacE*, the sul1 sulfonamide resistance gene, and ORF5 (Of unknown function), or *int* genes, as in Tn402. Gene cassettes are randomly integrated with the region between 3' and 5' of integrons. These cassettes are mobile gene elements that encode one or more antibiotic resistance genes and do not have a promoter sequence in their structure; thus, the expression of gene cassettes depends on the expression of integrons. Therefore, integrons act both as a gene expression vector and a natural cloning system (7). More than 80 different gene cassettes of class 1 integrons have been described and shown to confer resistance to a wide range of antiseptics, disinfectants, and antibiotics, such as β-lactams, fluoroquinolones, aminoglycosides, chloramphenicol, trimethoprim, streptothricin, rifampin, erythromycin, fosfomycin, and lincomycin (11).

Few studies have been conducted to investigate the prevalence of MDR strains of *P. aeruginosa* producing ESBL in Guilan province, northern Iran. A previous study in Guilan Province investigated the antimicrobial resistance, biofilm-forming ability, and virulence potential of *P. aeruginosa* isolated from burn patients, and the results showed that 72.2% (65/90) of *P. aeruginosa* isolates were MDR, and 55.5% (50/90) and 35.6% (32/90) were positive for ESBL and MBL production, respectively (12). The present study was conducted to investigate the frequency of antibiotic resistance, detection of β-lactamase, and characterization of gene cassettes carried by integrons in MDR *P. aeruginosa* strains in Guilan Province.

Methods

Bacterial isolates

This descriptive cross-sectional study was performed in 2021. A total of 110 *P. aeruginosa* isolates were collected from different hospitals in Rasht, northern Iran, and identified using standard microbiological methods. All clinical samples were inoculated on *eosin methylene blue* (EMB), MacConkey, and blood agar, and incubated at 37°C for 24 hours. *P. aeruginosa* colonies were identified using microbiological methods.

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed by the Kirby-Bauer disc diffusion method according to the instructions of the Clinical and Laboratory Standards Institute (CLSI, 2020). Antimicrobial discs, including gentamicin (30 µg), amikacin (30 µg), ciprofloxacin (5 µg), co-trimoxazole (25 µg), piperacillin (100 µg), ceftazidime (30 µg), meropenem (10 µg), imipenem (10 µg), colistin (10 µg), azithromycin (30 µg), kanamycin (30 µg), erythromycin (30 µg), ceftriaxone (30 µg), and cefotaxime (30 µg) were used for initial screening of *P. aeruginosa* strains. The ATCC 27853 standard strain of *P. aeruginosa* was used as a control. ESBL production was determined by the double disk diffusion method using disks of ceftazidime (30 µg) and cefotaxime (30 µg) alone and in combination with clavulanic acid (10 µg) on Muller Hinton agar. A positive test result was defined as a ≥5 mm increase in the zone diameter compared to a disk without clavulanic acid. Moreover, an imipenem-EDTA double-disk synergy test was used for MBL enzyme production assay. Enhancements in the diameter of the zone of inhibition in IMP+EDTA in comparison with the IMP-only disks were considered to be MBL producers.

Detection of β-lactamase and integron genes

The DNA of *P. aeruginosa* isolates positive in the DDST was extracted using a DNA extraction kit as instructed by the manufacturer (Sigma-Aldrich, St Louis, MO). Subsequently, the frequency of β-lactamase genes (*bla-VIM, IMP, AMPC, SIM, GIM, SPM, OXA10,* and *OXA2*) and *int1* and *Int2* integron genes was determined in strains using PCR with specific primers as shown in Table 1. PCR was carried out in 25 µl PCR volumes containing 10 ng template DNA, 0.5 mM of dNTPs, 10 pm of each primer, and 1 µl of Taq DNA polymerase in 1x PCR buffer. DNA amplification was performed in a Mastercycler Personal thermal cycler (Eppendorf, Germany) based on cycling parameters described in Table 1. PCR products were analyzed in 1% agarose gel containing 25 µg of ethidium bromide in tris-ethylenediaminetetraacetic acid (EDTA) buffer, and the gel was photographed under an ultraviolet illuminator using a gel documentation system and confirmed by sequencing.

Detection of gene cassettes in *int1*

Gene cassettes within class 1 integrons were amplified using 5'-CS and 3'-CS primer pairs (Table 1). The PCR products were then sequenced and identified using the basic local alignment search tool (BLAST) for the gene cassette screening strategy. For PCR products longer than 700 bp, internal primers were designed based on the obtained sequences, and the internal parts of the integrons were amplified and subsequently sequenced.

Table 1. Nucleotide sequences of primers used in this study

Gene	Primer sequence (5′-3′)	Annealing temperature (°C)	Ref.
VIM	F: GTGTTTGGTCGCATATCGC R: CGCAGCACCAGGATAGAAG	53	13
IMP	F: GGAATAGAGTGGCTTAATTC R: GCCAAGCTTCTATATTTGCG	55	13
SIM	F: TACAAGGGATTCGGCATCC R: TAATGGCCTGTTCCCATG	52	14
GIM	F: TCGACACACCTTGGTCTG R: AACTTCCAACTTTGCCAT	52	14
SPM	F: CCTACAATCTAACGGCGACC R: TCGCCGTGTCCAGGTATAAC	53	14
OXA2	F: ATGGCAATCCGAATCTTCGC R:TTATCGCGCAGCGTCCGAGT	55	13
Int1	F: CAGTGGACATAAGCCTGTTC R:CCGAGGCATAGACTGTA	55	9
In-(5'CS)	F: GGCATCCAAGCAGCAAGC R: AAGCAGACTTGACCTGAT	52	9

Results

Antibiotic resistance profile of *P. aeruginosa* strains

A total of 110 *P. aeruginosa* isolates were recovered during the study period. Based on antibiotic susceptibility testing, the highest phenotypic resistance was against cefoxitin and ceftazidime. Meanwhile, colistin and piperacillin were the most effective antibiotics. More than 85% of the isolates (n = 90) exhibited an MDR phenotype (Resistant to three classes of antibiotics), while 37% were classified as extensively drug-resistant (XDR) phenotype (Resistant to three classes of antibiotics plus imipenem). Seven isolates were resistant to all evaluated antibiotics. Moreover, according to the DDST, 40 isolates (37.4%) were ESBL-positive and 28 isolates (25.45%) were MBL-positive. The results of antibacterial resistance are presented in Table 2.

Table 2. Antimicrobial resistance properties in *pseudomonas aeruginosa* strains

Antibiotic	Resistant isolates
Amikacin	56 (52.33%)
Gentamycin	49 (45.7%)
Ceftazidime	62 (58%)
Cefotaxime	36 (33.6%)
Ceftriaxone	41 (38.3%)
Cefoxitin	87 (81.3%)
Imipenem	45 (42.0%)
Meropenem	36 (33.6%)
Piperacillin	16 (15.0%)
Co-Trimoxazole	25 (23.3%)
Erythromycin	40 (37.4%)
Azithromycin	29 (27.1%)
Enrofloxacin	49 (45.8%)
Ciprofloxacin	55 (51.4%)

Frequency of *β-lactamase* and class I integron genes

β-lactamase genes, including *bla-VIM*, *IMP*, *SIM*, *GIM*, *SPM*, *OXA10*, and *OXA2,* were detected in ESBL- and MBL-positive strains. Based on the results of PCR, the frequency of *VIM*, *SIM*, *IMP*, *SPM*, and *OXA2* genes was 10.3%, 14%, 20.6%, 1.9%, and 4%, respectively. *OXA 10*, *SPM*, and *GIM* genes were not detected in any of the isolates. Furthermore, the *int1* gene was identified in 37 isolates (34.6%). *Int2* gene was not detected in any of the isolates.

Characterization of the *int1* gene

Primers related to conserved regions of *int1* were used for the detection of *int1* polymorphism in *P. aeruginosa* strains. PCR results showed bands with lengths between 700 and 3000 bp (Figure 1).

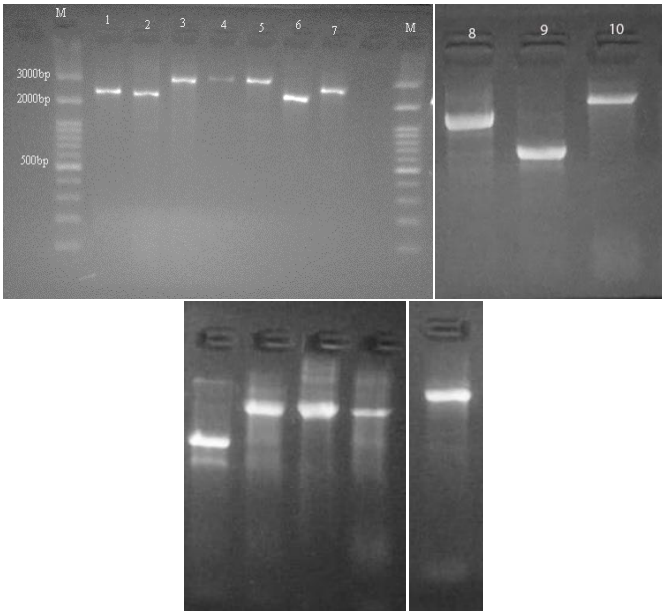

Figure 1. Size polymorphism in class 1 integron gene amplicons. Lanes M; 100bp molecular marker, Lanes 1-10; Size polymorphism in class 1 integron gene amplicons in tested isolates.

Identification of *int1* gene cassettes

Among 13 selected isolates, 12 different types of gene cassettes in class 1 integrons and 18 different genes were identified in the sequence analysis of the *int1* gene. The most frequent genes were *dfrA1* (n = 5), *aadA2* (n = 4), and *aacA4* (n = 4). The class D β-lactamase gene, *blaOXA-2,* was the only *bla* gene identified in the examined isolates. The number of gene cassettes in tested isolates varied between 1 and 4. The type of gene cassettes identified in class 1 integrons among *P. aeruginosa* isolates is shown in Table 3.

Table 3. Class 1 integron associated gene cassettes identified in *pseudomonas aeruginosa* strains

Type of gene cassette	Number of isolates
dfrA17	1
aadA1	1
aadB	2
aacA4	1
dfrA1	1
aacA4, dfrA1	1
aadB, dfrA1	1
dfrA32, aadA2, ereA	1
aadA2, aadA, ereA	1
aadA, ereA, aadA2	1
aacA4, dfrA1, aadA2	1
aacA8, blaOXA-2, aacA7, aadA6	1

Discussion

P. aeruginosa, one of the most common nosocomial infectious agents, has led to the death of a large number of hospitalized patients (15). ESBL antibiotics are commonly used for the treatment of diseases caused by these Gram-negative bacteria. However, some bacteria are resistant to β-lactam antibiotics due to ESBL production (16). In the current study, the rate of MDR *P. aeruginosa* was 85%. *P. aeruginosa*, especially its MDR strains, is very common in Iranian hospitals. Similar resistance rates were reported in other studies in Iran. For instance, Nikokar et al. documented a rate of 45.3% MDR among burn patients in Guilan in 2012 (17). In 2017, Fazeli et al. evaluated patients admitted to a teaching hospital and reported a rate of 73% MDR (18). In 2015, Ghanbarzadeh et al. conducted a single-center study on burn patients in Tehran and estimated the MDR rate at 93.1% (19). In our study, the highest and lowest rates of resistance belonged to cefoxitin (81.3%) and piperacillin (15%), respectively. Rates of resistance to ceftazidime and ceftriaxone were 62% and 56%, respectively. Moreover, our results suggested high resistance to imipenem at 42.05%, and the rate of resistance to cefotaxime was 33.6%. The increase in resistance to cephalosporins and imipenem is concerning. This might be due to selective pressure on these antibiotics, and it is highly important to monitor the prescription of these antibiotics. Following present results, Ameen et al. investigated the antibiotic resistance profile in *P. aeruginosa* strains and reported that among 230 strains of *P. aeruginosa*, 49.5% were resistant to imipenem (20).

In the present study, 37% of the isolates showed XDR phenotype, 37.4% of isolates were ESBL-positive, and 25.45% were MBL-positive based on DDST. The emergence of ESBL-producing *P. aeruginosa* is increasingly reported as a major cause of healthcare-associated infections (3). Overuse of antibiotics can lead to more resistant strains, resulting in gene and horizontal diffusion. High frequencies of ESBL production in *P. aeruginosa* isolates from burn patients in Iran were previously reported by Rafiee et al. (39.2% ESBL and 37.3% MBL production among 51 *P. aeruginosa* isolates) (21). This study demonstrated that the most prevalent genotype for MBL production was *blaIMP,* which was detected in 20.6% of isolates, followed by *SIM* (14%), *VIM* (10.3%), *SPM* (1.9%), and *OXA2* (4%). *OXA 10* and *GIM* were not observed in any of the strains. The *blaVIM* and *blaIMP* genes were common in MDR isolates of *P. aeruginosa* in previous studies in Iran (22,23).

On the other hand, a similar study in South Africa reported low frequency of *blaIMP,* while *blaVIM* was not detected among *P. aeruginosa* isolates (3). Moreover, in accordance with our results, *bla*IMP was the most frequently detected metallo-β-lactamase gene in a study conducted by Haghi et al. (9). The prevalence of class 1 integrons in this study was 34.6%, which is similar to the findings of Khosravi et al. in Ahvaz (24). The gene cassettes identified in 13 selected isolates included 1-4 different genes in a class 1 integron. A class 1 integron carrying the carbapenem resistance gene (*aacA8-blaOxa-2-aadA7-aadA6)* was also identified in meropenem-resistant *P. aeruginosa*. A high frequency of aminoglycoside resistance gene cassettes, including *aadA* family, which induce streptomycin and spectinomycin resistance, was identified in this assay. Gene cassettes *dfrA1*, *aad8*, *dfrA17*, *dfrA32*, and *aacA8* were identified for the first time in this study.

The high frequency of aminoglycoside resistance gene cassettes in class 1 integrons has been reported in several studies. In a previous report, different aminoglycoside resistance genes, including *aadA1*, *aadA2*, *aadA5*, *aadA6*, *aadB*, *accA4*, and *aac(6)-IIa*, and three *bla* genes *blaOXA10*, *blaP1*, and *blaCARB-8* were identified in integrons structure (25).

In a study conducted by Ahmadian et al. in northern Iran, the resistance genes identified in class I integrons included *aadA6-orfD* (35.71%), *aacA4-blaOXA-10* (21.42%), *aadB-aacA4-blaOXA-10* (19.04%), *blaOXA-10-aacA4-VIM1* (11.9%), *aacA4-catB10* (7.14%), *aacA5-aadA1-cmlA5* (7.14%), *blaOXA31-aadA2* (4.76%), and *aac(3)-Ic-aacA5-cmlA5* (4.76%). The *blaOXA-10-aacA4-VIM1* cassette array and aminoglycoside resistance genes were predominant (26). The highest frequency belonged to aadA2, which is similar to our findings. In another study from Iran, the analysis of integron cassette sequences indicated the presence of *dfrA17, dfrA7, aadB, aadA1, and dhfr1-sat2* resistance gene cassettes among the isolates (9).

The predominant cassette arrangement described by Hsiao et al. among 11 different types of gene cassette arrays in *P. aeruginosa* isolates in southern Taiwan included *aac(6')-II-catB2-aadA2*, *aac(6')-II-aadA2*, *aac(6')-II-catB2*, *aacA4-aadA15*, *aacC1-orfA-orfB-aadA1*, *cm1A-aadA1*, *catB3-blaOxA-10-aadA15*, *aacA4-catB8-aadA1*, *aadB-orfF1-aadA11*, *dfrB1*, and *dfrB4a-aacA4-aacA4-aadA1* (27). In 2018, Chowdhury et al. examined *P. aeruginosa* isolates with widespread antibiotic resistance in Australia and identified two genomic islands that carried transposons Tn6161 and Tn6163, respectively. A genomic island *GI1* gene cassette *blaGES-5-aacA4-gcuE15-aphA15* was also found in a class 1 integron, which confirms resistance to carbapenems and aminoglycosides (28). The presence of the *aacA4* gene cassette in our study was similar to the findings of Chowdhury et al. (28). In addition, a high prevalence of *aadA* gene, which shows resistance to streptomycin/spectinomycin, was observed in a study conducted by Odumosu et al. Gene cassette identification showed the presence of *aadA6-orfD* and *aadA13*, respectively (29).

In the present study, the investigated class 1 integrons included 12 gene cassettes: *aadA2*, *aadA6*, *era*, *aacA4*, *dfrA1*, *aad8*, *aacA8*, *blaoxa2*, *aacA7*, *dfrA17*, *dfrA32*, and *aadB*. Gene cassettes *dfrA1*, *aad8*, *dfrA17*, *dfrA32*, and *aacA8* were first identified in this study. In a study in China, many genes, including *aadA1*, *aadA2*, *aadA5*, *aadA6*, *aadB*, *accA4*, and *aac(6')-IIa* in integron structures were associated with aminoglycoside resistance. Resistance genes that are often identified (*aadA* family) are adenyl transferase aminoglycoside genes that cause resistance to streptomycin and spectinomycin. In addition, three genes, i.e., *blaOXA10*, *blaP1*, and *blaCARB-8*, were identified within integrons (25). Gene cassettes *aadB*, *accA4*, *aadA1*, and *aadA2* in the mentioned study are similar to those found in our study.

Conclusion

The high prevalence of class 1 integrons and resistance genes is a serious concern. It may jeopardize the control and treatment of Pseudomonas infections, increase the length of hospital stays, and raise mortality rates. Appropriate measures must therefore be taken to ensure the proper use of antibiotics in clinical and agricultural settings. In general, the results of the present study showed that class I integrons are widely distributed among *P. aeruginosa* strains isolated from hospitals in Guilan. They can be considered carriers of gene cassettes and can play an important role in the acquisition of MDR in this bacterium.

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None.

Ethical statement

Since we did not use any animal models or patients and only used isolates that were previously obtained from clinical samples in laboratories, we did not require ethical approval for this study; however, we confirm that the study complies with all regulations.

Conflicts of interest

All contributing authors declared no conflicts of interest.

Author contributions

Tahereh Panahi: Data curation, writing-original draft. Leila Asadpour: Writing, review and editing, supervision, and methodology. Najmeh Ranji: Methodology.

Data availability statement

The data utilized and analyzed in this study can be obtained from the corresponding author upon request.

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