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Antibiotic Resistance Patterns and Distribution of Extended-Spectrum Beta-Lactamases and Different Classes of Integrons Among *Pseudomonas aeruginosa* Strains Recovered from Various Clinical Samples

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Abstract

Background: Treatment of infections caused by *Pseudomonas aeruginosa* (*P. aeruginosa*) is becoming more difficult with each passing year. Class A extended-spectrum beta-lactamases (ESBLs) and integrons play a vital role in antibiotic treatment failure and ensuing poor patient outcomes. We aimed to determine the prevalence of antibiotic resistance patterns, class A ESBLs genes, as well as different classes of integrons among *P. aeruginosa* strains obtained from clinical specimens.

Materials and methods: In total, 90 non-repetitive isolates of *P. aeruginosa* were collected from clinical specimens. Standard microbiology laboratory tests were used to identify *P. aeruginosa*. Antibiotic resistance patterns were ascertained using the disc diffusion method based on clinical and laboratory standard institute guidelines. The PCR (polymerase chain reaction) was applied to detect ESBLs (bla_{CTXM}, bla_{SHV}, and bla_{TEM}) genes and different classes of integrons (I, II, and III).

Results: In this study, isolates were mostly resistant to ceftazidime 41 (45.6%) and gentamicin 39 (43.3%). Out of 90 investigated isolates, 25 (27.8%) were multi-drug resistant (MDR). ESBLs genes including bla_{CTXM}, bla_{TEM}, and bla_{SHV} were detected in 22.2% (20 of 90), 28.9% (26 of 90), and 31.1% (28 of 90) of the isolates, respectively. The prevalence of class I and II integrons was 61.1% and 4.4%, respectively. Class III integrons were not detected.

Conclusion: Based on this study's results, the prescription of ceftazidime and gentamicin should be restricted. In addition, ESBLs genes and integrons seem to play a significant role in the emergence and spread of MDR infections. It is of pivotal importance that microbiology laboratory remains vigilant about identifying ESBLs and integrons-positive isolates through surveillance systems.

Keywords: *Pseudomonas aeruginosa*, class A ESBL, multi-drug resistant, integrons.

INTRODUCTION

Pseudomonas aeruginosa (*P. aeruginosa*) is a widespread opportunistic pathogen that frequently infects patients with burn wounds, cystic fibrosis, cancer, pulmonary, and underlying diseases [1]. In addition, *P. aeruginosa* infections, a leading global pathogen, due to the existence of multiple antibiotic resistance genes and mechanisms are significantly correlated with high mortality, morbidity, and poor patient outcomes [2]. Restricted antibiotics are available to treat multi-drug-resistant (MDR) *P. aeruginosa* infections because they are resistant to at least one antibiotic belonging to three antibiotic categories, especially beta-lactams, aminoglycosides, and fluoroquinolones [3,4]. World Health Organization (WHO) designated *P. aeruginosa* as one of the most important pathogens with critical priority [4].

It has been reported that several resistance mechanisms including efflux pumps overexpression, target modifying enzymes, mutations, porin loss, and expression of antibiotic structure destroying enzymes are responsible for the emergence of MDR-*P. aeruginosa* and ensuing treatment failure [5,6]. Among the mechanisms mentioned, extended-spectrum-beta-lactamases (ESBLs) genes and different classes of integrons are known to be the most important mechanisms [5,6].

Based on molecular structure, four classes of ESBLs enzymes have been identified (A-D). Class A beta-lactamases including *bla*$_{CTXM}$, *bla*$_{TEM}$, and *bla*$_{SHV}$ are clavulanic-acid-sensitive proteins and responsible for resistance against penicillins and cephalosporins [7].

Integrons, due to the ability of capturing exogenous resistance gene cassettes from different microorganisms and transferring them to others, play a significant role in increasing antibiotic-resistant infections [8]. Due to the captured multiple antibiotic resistance genes, the ability to move, and horizontal gene transfer (HGT), integrons play an important role in the emergence of MDR isolates and failure of antimicrobial treatment [8].

Thus, we aimed to determine the prevalence of antibiotic resistance profiles, class A ESBLs (*bla*$_{CTXM}$, *bla*$_{SHV}$, and *bla*$_{TEM}$), as well as different classes of integrons (I, II, and III) among *P. aeruginosa* isolates obtained from clinical specimens.

MATERIALS AND METHODS

Bacterial isolates and identification

In this cross-sectional descriptive study, from February 2019 to November 2022, 90 non-repetitive clinical isolates of *P. aeruginosa* were collected from patients referred to an educational hospital in Zabol Province, Southeast Iran. Based on clinical and laboratory criteria and guidelines, isolates were collected from patients suspected of having infections. Identification of *P. aeruginosa* was carried out based on the following tests: growth on Cetrimide agar medium (HiMedia, India), TSI (triple sugar iron agar test, Alkali/Alkali), Gram staining (Gram-negative), oxidase (positive), motility (positive), citrate (positive), indole (negative), grapelike odor, sugar oxidation, growth at 42 °C and pigment production [9]. Obtained isolates were stored at -20 °C using cryovials containing trypticase soy broth (HiMedia, India) and 20% glycerol.

Antibiotic susceptibility testing

Antibiotic susceptibility patterns were ascertained according to CLSI (Clinical and Laboratory Standards Institute) recommendations [10]. The following antibiotics were applied, ofloxacin (5 µg), imipenem (10 µg), ceftazidime (30 µg),

meropenem (10 µg), gentamicin (10 µg), amikacin (30 µg), piperacillin (100 µg), tobramycin (10 µg), ciprofloxacin (5 µg), cefepime (30 µg) and levofloxacin (5 µg). Phenotypic detection of the class A ESBLs enzymes was carried out using ceftazidime and cefotaxime disks alone and in combination with clavulanic acid [10]. MDR isolates were resistant to at least one antibiotic in three different categories [3]. For quality controls, *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922 were used.

DNA extraction and detection of ESBLs and integrons

Bacterial genomic DNA was extracted using the boiling method [11]. Briefly, three colonies of fresh culture of *P. aeruginosa* were completely dissolved in 300 µL nuclease-free water. The provided suspension was boiled at 95 °C for 12 min. The supernatant, after centrifugation, was used for PCR assay.

Each PCR reaction assay (Eppendorf thermal cycler, Hamburg, Germany) was carried out in a final volume of 20 µL of ready-to-use master mix (Ampliqon, Denmark) consisting of 15 µL ready-to-use master mix (1.5 mM $mgcl_2$), 1 µL of forward and reverse primers (100 pmol) and 3 µL of DNA template (Table1). The following PCR programs were used: denaturation at 95 °C for 5 min, 30 cycles of denaturation at 94 °C for 55 s, annealing at 55 °C for *bla*$_{CTXM}$, 56 °C for *bla*$_{SHV}$, 54 °C for *bla*$_{TEM}$, and55-57 °C for integrons, for 45 s, extension at 72 °C for 60 s, as well as a final extension step at 72 °C for 12 min [11-13]. In PCR product separation, agarose gel electrophoresis 1% (w/v) was performed using the voltage of 8 V/cm for 20 minutes.

Table 1. PCR primer sets used to detect integrons and ESBLs in this study

Gene	Sequence (5…..3)	Ref.
IntI	F. CCTCCCGCACGATGATC R. TCCACGCAT CGTCAGGC	11
IntII	F. TTATTGCTGGGATTAGGC R. ACG GCTACC CTCTGTTAT C	11
IntIII	F. AGT GGG TGG CGA ATG AGT G R. TGT TCT TGT ATC GGC AGG TG	11
bla$_{CTXM}$	F. TCTTCCAGAATAAGGAATCCC R. CCGTTTCCGCTATTACAAAC	12
bla$_{TEM}$	F. ATCAGCAATAAACCAGC R. CCCCGAAGAACGTTTTC	13
bla$_{SHV}$	F. TGGTTATGCGTTATATTCGCC R. GGTTAGCGTTGCCAGTGCT	12

Association between antibiotic resistance and genes

The association between variables (antibiotic resistance patterns, resistance genes, and samples) was analyzed by Chi-square and Fisher's exact tests. SPSS software (V16, Chicago) was used, and a *P* value <.05 was considered statistically significant.

RESULTS

Samples

Out of 90 patients, 37 (41.1%) were male and 53 (58.9%) were female. Ninety *P. aeruginosa* strains were recovered from clinical specimens including sputum (n=34, 37.8%), urine (n=40, 44.4%), stool (n=7, 7.8%), blood (n=5, 5.6%), and wound (n=4, 4.4%).

Antibiotic susceptibility patterns

The isolates were mostly resistant against ceftazidime 41 (45.6%) and gentamicin 39 (43.3%) (Table 2). Out of 90 investigated isolates, 25 (27.8%) were found to be MDR. The isolates were mostly susceptible to imipenem (81%). A statistically significant relationship was not observed between antibiotic resistance and gender ($P>.05$), except for ofloxacin ($P<.05$).

Table 2. Antibiotic resistance patterns in ESBL-positive and ESBLs-negative isolates (based on phenotypic test) of *P. aeruginosa*

Antibiotics	ESBLs-Positive (n=42)	ESBLs-Negative (n=48)	Total Resistance (n=90)	*P* Value
Ceftazidime	40 (95.2%)	1 (2.1%)	41 (45.6%)	≤0.01
Amikacin	18 (42.9%)	0 (0%)	18 (20%)	≤0.01
Piperacillin	28 (66.7%)	3 (6.3%)	31 (34.4%)	≤0.01
Tobramycin	19 (45.2%)	8 (16.7%)	27 (30%)	≤0.01
Ciprofloxacin	28 (66.7%)	3 (6.3%)	31 (34.4%)	≤0.01
Cefepime	22 (52.4%)	6 (12.5%)	28 (31.1%)	≤0.01
Levofloxacin	24 (57.1%)	3 (6.3%)	27 (30%)	≤0.01
Ofloxacin	28 (66.7%)	8 (16.7%)	36 (40%)	≤0.01
Meropenem	16 (38.1%)	3 (6.3%)	19 (21.1%)	≤0.01
Imipenem	15 (35.7%)	2 (4.2%)	17 (18.9%)	≤0.01
Gentamicin	30 (71.4%)	9 (18.8%)	39 (43.3%)	≤0.01

Distribution of ESBLs and Integrons

Based on phenotypic tests 46.7% (42 of 90) of isolates were found to be ESBLs-producing strains. The ESBLs genes including *bla*$_{CTXM}$, *bla*$_{TEM}$, and *bla*$_{SHV}$ were detected in 22.2% (20 of 90), 28.9% (26 of 90), and 31.1% (28 of 90) of the isolates, respectively. Out of 90 isolates, thirty-nine isolates (43.3%) were positive for at least one investigated ESBLs genes. In addition, the combination of ESBLs genes was as follows; *bla*$_{SHV}$+*bla*$_{CTXM}$ (2.2%), *bla*$_{TEM}$+*bla*$_{SHV}$ (21.1%), *bla*$_{CTXM}$+*bla*$_{TEM}$+*bla*$_{SHV}$ (7.8%). Resistance to antibiotics in these isolates was significantly high ($P\leq.01$). In this study, the prevalence of class I (*INTI*) and II (*INTII*) integrons was 61.1% and 4.4% respectively. Class III integron was not detected. Prevalence of investigated genes (*bla*$_{CTXM}$, *bla*$_{TEM}$, *bla*$_{SHV}$, and *INTI*) among MDR isolates was higher than non-MDR isolates ($P<.05$).

Association between antibiotic resistance and genes

There was a significant relationship between ESBLs and resistance against antibiotics (Table 2). In addition, as Table 3 shows, the distribution of ESBLs genes among MDR and integron-positive isolates was significantly higher than other isolates ($P\leq.01$). Considering the positive value of *Phi* (0.48, 0.49, and 0.44) for *bla*$_{TEM}$, *bla*$_{SHV}$, and *bla*$_{CTXM}$, respectively, it can be concluded that there was a positive association between ESBLs and MDR. Also, correlation analysis between Integrons and ESBLs genes disclosed a positive relationship between *bla*$_{CTXM}$ and class I integron (*Phi* = 0.31, *P-value* ≤0.01). The significant relationship between samples, sex, and investigated genes was not observed (Table 4).

Table 3. Distribution of ESBLs genes among class I integron positive and MDR-*P. aeruginosa* isolates

Genes	*INTI* Positive (n=55)	*INTI* Negative (n=35)	*P* Value	MDR (n=25)	Non-MDR (n=65)	*P* Value
bla$_{CTXM}$	18 (32.7%)	2 (5.7%)	≤.01	13 (52%)	7 (10.8%)	≤0.01
bla$_{SHV}$	21 (38.2%)	7 (20%)	0.06	17 (68%)	11 (16.9%)	≤0.01
bla$_{TEM}$	19 (34.5%)	7 (20%)	0.1	16 (64%)	10 (15.4%)	≤0.01

Table 4. Distribution of ESBLs-, MDR- and class I integron-positive *P. aeruginosa* based on sex and specimen type

Genes	*bla*$_{CTXM}$ (n=20)	*P* Value	*bla*$_{SHV}$ (n=28)	*P* Value	*bla*$_{TEM}$ (n=26)	*P* value	*INTI* (n=55)	*P* Value
Sex								
Male (n=37)	8 (40%)	0.90	11 (39.3%)	0.81	9 (34.6%)	0.42	25 (45.5%)	0.29
Female (n=53)	12 (60%)		17 (60.7%)		17 (65.4%)		30 (54.5%)	
Specimen								
Sputum (n=34)	6 (30%)		12 (42.9%)		12 (46.2%)		22 (40%)	
Urine (n=40)	12 (60%)		11 (39.3%)		11 (42.3%)		21 (38.2%)	
Stool (n=7)	0 (0%)	0.42	0 (0%)	0.17	0 (0%)	0.42	6 (10.9%)	0.38
Blood (n=5)	1 (5%)		3 (10.7%)		2 (7.7%)		4 (7.3%)	
Wound (n=4)	1 (5%)		2 (7.1%)		1 (3.8%)		2 (3.6%)	

DISCUSSION

P. aeruginosa is a well-known opportunistic pathogen and is documented as one of the most important etiological agents of different infections including, but not limited to, respiratory infection, urinary tract infection, blood infection, and wound infection [14]. Due to the remarkable capacity of *P. aeruginosa* to resist antimicrobial compounds, its eradication has become more difficult with each passing year [15]. In this study, the prevalence of antibiotic resistance patterns, class A ESBLs (*bla*$_{CTXM}$, *bla*$_{TEM}$, and *bla*$_{SHV}$), as well as class I, II, and III integrons were investigated.

Based on this study's findings, the isolates were mostly resistant against ceftazidime (45.6%) and gentamicin (43.3%). In addition, the most effective antibiotics were imipenem and meropenem, with 81.1% and 78.9% of all isolates being susceptible, respectively. These results are similar to other findings reported from different provinces of Iran. For instance, results of a comprehensive meta-analysis study conducted in Iran revealed that collected *P. aeruginosa* in different provinces of Iran were mostly resistant against ceftazidime, gentamicin, and ciprofloxacin, with 50.4%, 46.9%, and 47% of isolates being resistant, respectively [16].

In this study, as shown in Table 2, 18.9% and 21.1% of *P. aeruginosa* isolates were resistant against imipenem and meropenem, respectively, which is similar to other studies conducted in Iran and European countries. For example, in Gilan province (north of Iran) and Zahedan province (southeast of Iran), resistance against imipenem was

reported to be 23.3% and 17.2%, respectively [16]. Also, in some European countries such as Spain (18.6%) and Lithuania (21.8%), the prevalence of resistance agreed with our findings [17].

It has been reported that different factors such as extensive use of antibiotics, unrestricted access to antibiotics, indiscriminate use of antibiotics in veterinary medicine, as well as non-adherence to the guidelines of infection prevention and control procedures in healthcare settings contribute to the prevalence of antibiotic resistance [18].

Results of this study revealed that, based on the phenotypic test, 46.7% of investigated isolates were ESBLs-positive. This prevalence was higher than those reported from other parts of Iran, including Shiraz (12.7%), Ardabil 8.3% and Tehran (31.9%) [19-21], however, was lower than those reported from Ethiopia (78%) and Burkina Faso (58%) [22,23].

In this study, based on genotypic and phenotypic tests, 39 isolates (43.3%) and 42 isolates (46.7%) were ESBLs positive, respectively. This difference may be attributed to different sensitivity and susceptibility of the test, mutations in ESBLs, or other class A ESBLs genes, which have not been evaluated in the present study [22-25].

Globally, ESBLs-producing Gram-negative bacteria, *P. aeruginosa* in particular, have been responsible for numerous infection outbreaks and due to simultaneous resistance against different antibiotics contributed to poor patient outcomes. Therefore, it is essential to identify ESBLs-producing isolates in hospitals as a routine test [24,25].

Based on the results of this study, as Table 3 shows, most MDR isolates were ESBLs- and integron-positive. Also, the ESBLs genes including *bla*$_{CTXM}$, *bla*$_{TEM}$, and *bla*$_{SHV}$ were detected in 22.2% (20 of 90), 28.9% (26 of 90), and 31.1% (28 of 90) of the isolates, respectively. On the other hand, the most prevalent investigated ESBLs was *bla*$_{SHV}$. These findings are in agreement with Imani Fooladi et al. Rezai and Nazari Alam et al., reported *bla*$_{SHV}$ in *P. aeruginosa* as the most prevalent ESBLs genes, ranging from 37.5% to 86% [19,20,26]. Nevertheless, results of independent studies in different cities of Iran and different parts of the world disclosed that these genes are widely distributed and are responsible for antibiotic treatment failure [27,28].

Integrons are mobile genetic elements that harbor various genes responsible for drug resistance and owing to their easily transmissible capacity, they play an important role in the spread of drug resistance infections. It has been demonstrated that more than 40 genes associated with conferring resistance against disinfectants, antiseptics, and antibiotics such as beta-lactams, aminoglycosides, and sulfonamides, are located in integrons [29]. Therefore, their detection is of utmost importance.

Results of this study indicate that class I integron is the most prevalent gene, with 61.4% of all isolates being positive. The prevalence of class I integron in this study was similar to Ardabil (58.3%) and Hamadan (55%), however, was lower than Shiraz, Ahvaz, and Kerman (95%) [30,31].

P. aeruginosa, is recognized for its substantial ability to survive under a spectrum of environmental conditions and its resistance to available drugs. Previous studies have revealed that the presence of some risk factors including ICU hospitalization, underlying diseases, previous antibiotics consumption, source of samples, various drug resistance mechanisms, particularly, mutation, AmpC overproduction, and efflux pump overexpression are associated with high

mortality rates in case of patients infected with *P. aeruginosa*. Therefore, for successful infection control and prevention, these risk factors must be considered [32-34].

This study faces some limitations that should be considered; first, other class A ESBLs genes such as *PER, GES, VEB, PSE,* and *BEL,* as well as other classes of beta-lactamase genes such as class D and class B beta-lactamase were not investigated; second, other resistance mechanisms including efflux pumps overexpression, AmpC beta-lactamases and porin loss, as well as clonal relatedness of isolates and nucleotide sequence of genes were not evaluated.

CONCLUSION

Based on the findings of this study, the prevalence of resistance against ceftazidime, gentamicin, and ofloxacin is high; therefore, restricted use of them is recommended. In addition, the results of this study show that *bla*$_{CTXM}$, *bla*$_{SHV}$, *bla*$_{TEM}$, and class I integrons can play an important role in treatment failure.

Declarations

Ethical Approval: This study was approved by the Ethics Committee of ZBMU (IR.ZBMU.REC.1401.032 and IR.ZBMU.REC.1401.048)

Consent for publication

Not applicable.

Competing interests: There is no conflict of interest.

Authors' contributions: Study design: HV. Data collection and laboratory procedures: ZY, MKH, MB, and HV. Analysis of data: HV and SHSH. Manuscript preparation: HV

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Availability of data: All data supporting the findings of the study were included in the article.

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أنماط مقاومة المضادات الحيوية وتوزيع البيتا–لاكتامازات الواسعة الطيف من الفئة A والفئات المختلفة من الإنتغرونات بين سلالات بكتيريا الزائفة الزنجارية المستخلصة من عينات سريرية متنوعة

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الملخص

الخلفية والاهداف: أصبح علاج العدوى التي تسببها بكتيريا الزائفة الزنجارية (Pseudomonas aeruginosa) أكثر صعوبة مع مرور كل عام. تلعب البيتا–لاكتامازات الواسعة الطيف من الفئة A والإنتغرونات دورًا حيويًا في فشل العلاج بالمضادات الحيوية وما يترتب عليه من نتائج سيئة للمرضى. هدفنا هو تحديد مدى انتشار أنماط مقاومة المضادات الحيوية، جينات البيتا–لاكتامازات الواسعة الطيف من الفئة A، بالإضافة إلى الفئات المختلفة من الإنتغرونات بين سلالات الزائفة الزنجارية التي تم الحصول عليها من العينات السريرية.

منهجية الدراسة: تم جمع ما مجموعه 90 عزلة غير مكررة من بكتيريا الزائفة الزنجارية من العينات السريرية. تم استخدام اختبارات مختبرية ميكروبيولوجية قياسية لتحديد بكتيريا الزائفة الزنجارية. تم تحديد أنماط مقاومة المضادات الحيوية باستخدام طريقة انتشار الأقراص بناءً على إرشادات معهد المعايير السريرية والمختبرية. تم استخدام تفاعل البلمرة المتسلسل (PCR) للكشف عن جينات البيتا–لاكتامازات الواسعة الطيف (blaCTXM, blaSHV, و blaTEM) والفئات المختلفة من الإنتغرونات (I, II, و III).

النتائج: في هذه الدراسة، كانت العزلات مقاومة في الغالب للسيفتازيديم 41 (45.6%) والجنتاميسين 39 (43.3%). من بين 90 عزلة التي تم فحصها، كانت 25 (27.8%) متعددة المقاومة للأدوية (MDR). تم الكشف عن جينات البيتا–لاكتامازات الواسعة الطيف بما في ذلك blaCTXM, blaTEM, و blaSHV في 22.2% (20 من 90)، 28.9% (26 من 90)، و31.1% (28 من 90) من العزلات على التوالي. كان انتشار الإنتغرونات من الفئة I و II بنسبة 61.1% و 4.4% على التوالي. لم يتم الكشف عن الإنتغرونات من الفئة III.

الاستنتاج: بناءً على نتائج هذه الدراسة، يجب تقييد وصف السيفتازيديم والجنتاميسين. بالإضافة إلى ذلك، يبدو أن جينات البيتا–لاكتامازات الواسعة الطيف والإنتغرونات تلعب دورًا مهمًا في ظهور وانتشار العدوى متعددة المقاومة للأدوية. من الأهمية بمكان أن يبقى مختبر الميكروبيولوجيا يقظًا في التعرف على العزلات الإيجابية للبيتا–لاكتامازات والإنتغرونات من خلال أنظمة المراقبة.

الكلمات الدالة: الزائفة الزنجارية، البيتا–لاكتامازات الواسعة الطيف من الفئة A، متعددة المقاومة للأدوية، الإنتغرونات.