



ORIGINAL: Antibiotic Resistance and Prevalence of *bla*_{OXA-48} and *bla*_{GES-2} Genes in *Pseudomonas aeruginosa* Isolated from Burn Patients in Tabriz, Iran

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ABSTRACT

Background: *Pseudomonas aeruginosa* is a major cause of hospital-acquired infections in burn units, and its antibiotic resistance presents a significant therapeutic challenge. The emergence of carbapenemase genes, such as *bla*_{OXA-48} and *bla*_{GES-2}, is of particular concern. This study aimed to determine the antibiotic resistance patterns and the prevalence of *bla*_{OXA-48} and *bla*_{GES-2} genes in *P. aeruginosa* isolates from burn patients in Tabriz, Iran.

Methods: In this cross-sectional study, 100 clinical isolates of *P. aeruginosa* were collected from burn patients between June and January 2025. Antibiotic susceptibility testing was performed using the Kirby-Bauer disk diffusion method according to clinical and laboratory standards institute guidelines. Phenotypic detection of extended-spectrum beta-lactamases (ESBL) was conducted using the combined disk test. The presence of *bla*_{OXA-48} and *bla*_{GES-2} genes was confirmed by polymerase chain reaction.

Results: The highest resistance rates were observed against ceftazidime and cefotaxime, each at 96%, followed by imipenem at 91% and meropenem at 90%. Phenotypically, 50% of the isolates were identified as ESBL producers. Genotypic analysis of ESBL-positive isolates revealed that 62% (31/50) carried the *bla*_{GES-2} gene, while 28% (14/50) harbored the *bla*_{OXA-48} gene. Concurrent presence of both genes was detected in 12% (6/50) of the ESBL-positive isolates.

Conclusion: The results demonstrated a high prevalence of antibiotic resistance and a concerning presence of carbapenemase genes *bla*_{GES-2} and *bla*_{OXA-48} in *P. aeruginosa* isolates from burn patients in Tabriz. This highlights the urgent need for continuous surveillance programs and enhanced infection control strategies in burn care centers.

Introduction

Pseudomonas aeruginosa, a member of the Pseudomonadaceae family, is a motile, aerobic, gram-negative, rod-shaped, non-spore-forming, oxidase-positive, and non-lactose-fermenting bacterium[1]. The alarming rise of bacterial resistance worldwide has complicated the treatment of infections caused by *P. aeruginosa*, as this bacterium not only resists antimicrobial agents but also possesses a remarkable ability to adapt to harsh environmental conditions[2-5]. One important characteristic of this bacterium is its ability to form biofilms in specific environments, including burn sites[6]. This ability confers resistance to antibiotics and significantly impacts clinical outcomes; however, biofilm formation may increase bacterial susceptibility to salinity changes, ultraviolet light, and antimicrobial agents[7, 8]. Although *P. aeruginosa* may be part of the normal gut flora, it usually does not adhere to healthy epithelium and does not cause disease in healthy individuals; however, it can cause disease in susceptible individuals and, due to its strong survival and adaptability, persists in the hospital environment[9]. *P. aeruginosa* can chronically colonize, persist, and infect the lower respiratory tract in patients with chronic inflammatory airway diseases such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and bronchiectasis[10]. *P. aeruginosa* is part of the ESKAPE group of pathogens, which have raised the greatest concern due to resistance to new antibiotics[11]. One of the major problems of this bacterium is multidrug resistance, caused by various mechanisms including the production of beta-lactamase and cephalosporinase enzymes encoded by the *AmpC* gene, decreased outer membrane permeability, synthesis of enzymes such as phosphotransferase and acetyltransferase, and alterations in topoisomerase II and IV[12]. Carbapenems are among the last-resort treatments for infections caused by multidrug-resistant (MDR) bacteria; the prevalence of carbapenemases such as *bla*_{GES-2}, a class A carbapenemase, and *bla*_{OXA-48}, a class D

carbapenemase, has attracted attention due to their difficult detection and association with treatment failure[13, 14]. The aim of this study was to determine the prevalence and antibiotic resistance patterns of *bla*_{GES-2} and *bla*_{OXA-48} genes in clinical isolates of *P. aeruginosa* from burn patients in Tabriz. The data obtained from this study will help provide better strategies for infection control and more precise antibiotic prescribing in burn units.

Material and Methods

Isolation and sampling of bacteria

This study was conducted as a multicenter descriptive cross-sectional investigation in hospitals of Tabriz city from June to January 2025, under the ethical approval code IR.IAU.TABRIZ.REC.1403.209. A total of 100 clinical isolates of *P. aeruginosa* were randomly collected from burn patients based on the study objective and distribution of isolates across different wards. To obtain a reliable and representative collection of circulating isolates from the studied centers, this sample size was selected. Initial identification of the isolates was performed using standard biochemical methods, including the oxidase test, growth assessment at 42 and 44°C, cultivation in Oxidation-Fermentation and Kligler Iron Agar (Merck, Germany) media, citrate test, and pigment production evaluation. Patients admitted to burn units of hospitals in northwest Iran, whose *P. aeruginosa* infections were confirmed by microbiological culture and related diagnostic tests, and who provided informed consent to participate in the study, were all considered for inclusion. To maintain scientific validity and data quality, exclusion criteria included patient refusal to continue participation, lack of definitive *P. aeruginosa* diagnosis based on test results, and the presence of serious underlying diseases (e.g., uncontrolled diabetes, metastatic cancer, or advanced autoimmune disorders) that could potentially affect study outcomes.

Using the disk diffusion technique to examine antibiotic susceptibility patterns

Suspensions equivalent to 0.5 McFarland were prepared from each isolate and inoculated onto Mueller-Hinton agar (Merck, Germany) plates to determine the antibiotic susceptibility pattern. Imipenem (10 µg), meropenem (10 µg), ceftazidime (30 µg), ceftriaxone (30 µg), cefepime (30 µg), aztreonam (30 µg), amikacin (30 µg), gentamicin (10 µg), ciprofloxacin (5 µg), and cefotaxime (30 µg) (Padten Teb, Iran) were among the antibiotics used in this study. Antibiotic resistance of the isolates was evaluated using the standard Kirby-Bauer disk diffusion method according to clinical and laboratory standards institute (CLSI) criteria, with *Acinetobacter baumannii* (*A. baumannii*) (ATCC: 27853) as the control strain.

Identification of bacteria that produce beta-lactamases based on phenotype

Beta-lactamase enzymes of the isolates were phenotypically identified using the combined disk [15-17] technique according to CLSI standards. Ceftazidime (30µg) and ceftazidime-clavulanic acid (30µg / 10µg) disks, as well as cefotaxime and cefotaxime-clavulanic acid (30µg / 10µg) (Padten Teb, Iran) disks, were used to assess extended-spectrum beta-lactamase (ESBL) production[18-22]. This approach classifies an isolate as an ESBL producer if the zone diameter difference between the antibiotic disk alone and the antibiotic disk combined with the inhibitor (clavulanic acid) is equal to or greater than 5 mm.

Identification of strains producing *bla*_{OXA-48} and *bla*_{GES-2} genes based on genotype

The prevalence of *bla*_{OXA-48} and *bla*_{GES-2} genes was assessed by polymerase chain reaction (PCR). Bacterial DNA was extracted using a kit from Invitex Stratec Business (Canada). DNA concentration was measured with a Nanodrop device, and purity was

evaluated based on the OD_{260/280} absorbance ratio. The ideal DNA purity was confirmed by OD ratios of 1.8 to 1.9. The PCR reaction contained 12.5 µL of 2x Sinaclon master mix, 1 µL of forward primer (10 pmol), 1 µL of reverse primer (10 pmol), 3 µL of template DNA, and 7.5 µL of nuclease-free distilled water. Table 1 lists the specific primer sequences designed for the amplification of *bla*_{OXA-48} and *bla*_{GES-2} genes. Primers were designed using Allele ID7 software and NCBI nucleotide databases, and the sequence accuracy was confirmed. PCR began with an initial denaturation at 95°C for 10 minutes, followed by 30 amplification cycles consisting of denaturation at 95°C for 30 seconds, primer annealing at 50°C for 60 seconds, and extension at 72°C for 60 seconds. To ensure complete amplification of all PCR products, a final extension was performed at 72°C for five minutes after the cycles. Distilled water was used as a negative control, and *A. baumannii* (ATCC: 19606) served as a positive control. PCR products were then analyzed by electrophoresis on a 1.5% agarose gel. To do this, a 100 base pair (bp) ladder was used as a size marker. DNA bands were visualized and recorded after staining the agarose gel with Safe Stain (V2) using a gel documentation system. Finally, SPSS version 23 and descriptive tests were used to analyze the genotypic and phenotypic data, with a statistical significance threshold of $p < 0.05$.

Informed Consent

All participants were informed about the study and signed written informed consent before enrollment.

Ethical Approval

Ethical approval was obtained from the Clinical Research Ethics Committee of Islamic Azad University, Tabriz Branch by numbered IR.IAU.TABRIZ.REC.1403.209.

Table 1. Specifications of primers used in this study

Primer	Gene sequence	(bp) size
<i>bla</i> _{GES-2} -F <i>bla</i> _{GES-2} -R	GTTTTGCAATGTGCTCAACG TGCCATAGCAATAGGCGTAG	371
<i>bla</i> _{OXA-48} -F <i>bla</i> _{OXA-48} -R	GCGTGGTTAAGGATGAACAC CATCAAGTTCAACCCAACCG	438

Results

The age range of the patients was 20 to 81 years, with a mean age of 48.24 ± 17.08 . Fifty samples (50%) were obtained from females and fifty (50%) from males. The mean age of males and females was 42.26 ± 16.33 and 54.22 ± 15.81 years, respectively. The distribution of *P. aeruginosa* isolates showed no statistically significant variation by gender or age group ($p > 0.05$). Based on antibiogram data, ceftazidime had the lowest resistance (55%), while the highest resistance was to imipenem (91%), meropenem (90%), ceftazidime (96%), and cefotaxime (96%) (Figure 1). Combined disk test results showed that 50 isolates (50%) of 100 *P. aeruginosa* isolates were ESBL-positive. Of the isolates, 22 (44%) ESBL-positive samples were from the male group with a mean age of 49.59 ± 20.42 years, and 28 (56%) ESBL-positive

samples were from the female group with a mean age of 47.64 ± 15.97 years. Demographic factors such as age group and gender showed no significant association with ESBL-positive or ESBL-negative *P. aeruginosa* isolates ($p > 0.05$). The *bla*_{GES-2} gene was detected in 31 (62%) of the 50 ESBL-positive *P. aeruginosa* isolates by PCR, whereas the *bla*_{OXA-48} gene was found in 14 (28%) of the isolates (Figures 2). Six isolates (12%) out of the 50 had both the *bla*_{GES-2} and *bla*_{OXA-48} genes. Neither patient age nor sex was significantly correlated with the presence of the *bla*_{GES-2} and *bla*_{OXA-48} genes ($p < 0.05$). According to these results, the incidence and distribution of these resistance genes in *P. aeruginosa* isolates were not significantly influenced by age or sex. In other words, these genes were present in the isolates regardless of the patient's age or sex.

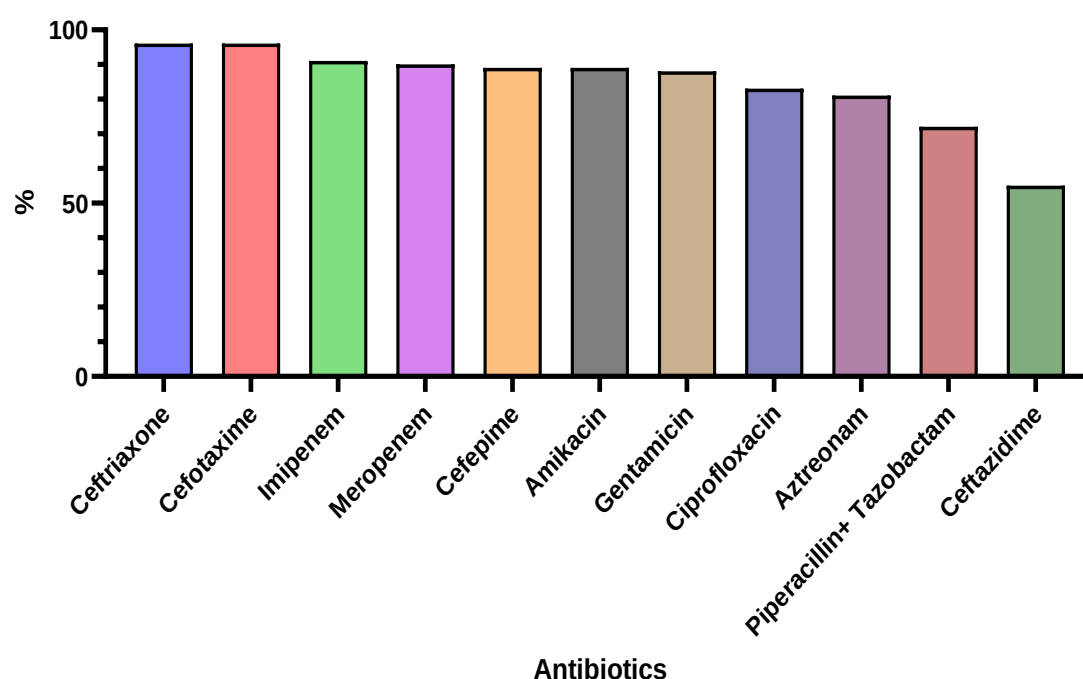


Figure 1. Antibiotic resistance of *P. aeruginosa* isolates isolated from burn patients in Tabriz city

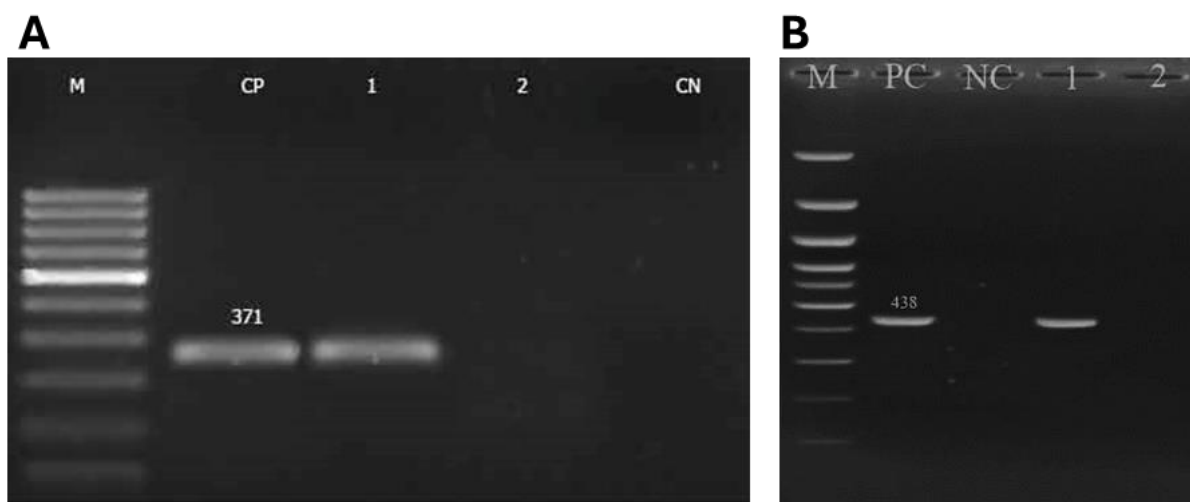


Figure 2. Electrophoresis of PCR product for the(A) *bla*_{GES-2} gene (B) *bla*_{OXA-48} gene

Discussion

This study examines the molecular frequency of the *bla*_{OXA-48} and *bla*_{GES-2} genes and the antibiotic resistance patterns in *P. aeruginosa* strains isolated from burn wound infections in Tabriz, Iran. The results indicate a notable prevalence of the aforementioned genes in these isolates, as well as a high degree of antibiotic resistance. As an opportunistic and MDR organism, *P. aeruginosa* remains a significant cause of infections that can lead to mortality and severe morbidity[23]. Patients hospitalized in intensive care units, immunocompromised individuals, and those with conditions such as cystic fibrosis are at high risk for these infections[24]. Burns are serious injuries that require immediate treatment to prevent complications such as bacterial infections[25]. GES-type ESBLs, first identified in a clinical *Klebsiella pneumonia* (*K. pneumonia*) [26] isolate, have since been detected in other pathogens such as *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii*[27, 28]. However, the development of class D β -lactamases of the OXA (oxacillinase) group has complicated the treatment of infections. For example, *K. pneumoniae*'s *bla*_{OXA-48} gene is essential for both biofilm formation and carbapenem resistance[29, 30]. There are few instances of this gene being widely found in *P. aeruginosa* and *A. baumannii*, despite the fact that it is equally common in *Escherichia coli*. For nosocomial infections to be stopped from

spreading and for treatment to be successful, early detection is crucial[31]. Evaluation of this antibiotic resistance pattern showed that ceftriaxone and cefotaxime had the highest resistance rate (96%). Significant resistance to both imipenem (91%) and meropenem (90%) was also observed. This finding is consistent with the study by Tarafdar et al., which reported the highest resistance to ceftriaxone and cefotaxime and the lowest to ceftazidime[32]. According to another study conducted at Mofid Children's Hospital between 2013 and 2018, *Pseudomonas* isolates exhibited a significant resistance pattern to piperacillin, ciprofloxacin, imipenem, meropenem, gentamicin, and amikacin, respectively[33]. Although the rate of resistance to imipenem and meropenem in our study (90-91%) was slightly lower than that reported by Shariati et al. (95%) [25], it was higher compared to the study by Farhan et al. [34]. Regarding ESBL production, Tarafdar et al. reported a positivity rate of 16.6% (8 out of 48)[32]. The resistance pattern in the current study differed from that of the study by Jafari-Sales et al. which found high resistance to imipenem (98.4%), gentamicin (98%), meropenem (91.8%), amikacin (91.6%), and cefepime (91%)[35]. In terms of gene frequency, the *bla*_{OXA-48} gene was present in 39.16% (121 out of 500) of isolates in the study by Jafari-Sales et al. whereas this rate was 62% (31 out of 50) in the current analysis, suggesting a higher

prevalence of this gene in the population under investigation[35]. On the other hand, *bla*_{GES-2} and *bla*_{OXA-48} frequencies were reported by Tarafdar et al. to be 87.5% and 70.83%, respectively[32]. However, the frequency of these genes in our data were 62% and 50%, respectively, indicating that various bacterial populations or geographic locations had different genetic patterns. Discrepancies can be attributed to factors such as sample size, demographic characteristics, diagnostic methods, and sampling techniques. These factors influence the antibiotic resistance patterns and the distribution of resistance genes. Understanding these reasons not only explains the findings of the present study but also underscores the need for further research to develop infection control strategies tailored to the local epidemiology.

Conclusion

This study reveals a concerning prevalence of antibiotic resistance in *P. aeruginosa* isolates from burn patients in Tabriz. We observed remarkably high resistance rates against cephalosporins and carbapenems, which are critically important last-line treatments. Phenotypic assays confirmed that half of the isolates were ESBL producers. Most importantly, our genetic analysis demonstrated a high prevalence of the carbapenemase genes *bla*_{GES-2} and *bla*_{OXA-48} among the ESBL-positive isolates, with *bla*_{GES-2} being particularly dominant. The co-occurrence of both genes in a subset of isolates underscores a significant risk, as these enzymes can hydrolyze a broad range of β -lactam antibiotics and are frequently associated with treatment failure. The dissemination of these resistance genes highlights the urgent need for burn care centers to implement robust and continuous surveillance protocols. Our findings strongly support the adoption of rigorous antimicrobial stewardship and enhanced infection control measures to curb the spread of these MDR bacteria. Finally, rapid molecular diagnostics for the early detection of these carbapenemase genes are crucial for guiding appropriate therapy and improving patient outcomes.

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Authorship

Concept/Design: A.J.S, M.P; Data acquisition: A.J.S; Data analysis and interpretation: A.G, Z.G; Drafting manuscript: A.G, Z.G, M.F, A.J, Sh.P, G.K.I, M.F.S; Critical revision of manuscript: AJS; Final approval and accountability: MP; Technical or material support: A.J.S, M.P; Supervision: MP; Securing funding (if available): N/A.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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