Original Article

Molecular Analysis of the Antiseptic Resistance Genes among Multidrug-Resistant *Pseudomonas aeruginosa* Isolated from Burn Patients

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Abstract

Background: *Pseudomonas aeruginosa* is known to be susceptible to a variety of antibiotics and disinfectants, and this resistance has become a major problem, particularly among hospitalized patients. **Objectives:** The present study aims to determine the association between class 1 integrons (*intI1*) and genes responsible for antiseptic resistance (*fabV, qacΔE1*, and *qacE*) among multidrug-resistant (MDR) *P. aeruginosa* from burn patients. **Materials and Methods:** Sixty-four isolates from burns were identified using both standard approaches and the VITEK 2 system. Disc diffusion antimicrobial susceptibility testing was performed. Polymerase chain reaction (PCR) was utilized to identify class 1 integrons and antiseptic resistance genes using specific primers for *intI1, fabV, qacE1, and qacE.* **Results:** 64 MDR *P. aeruginosa* isolates were obtained from burn patients during the research period. The antibiotic susceptibility of all 64 *P. aeruginosa* isolates was examined. MDR resistance to at least three antibiotic classes were found in all of the isolates. The PCR results revealed that 100% of the isolates tested positive for the class 1 integron gene. According to the current findings, all isolates possessed the *qacΔE1* and *fabV* genes. While the *qacE* results were being processed, 87.50% of the isolates tested positive. There was no correlation between the presence of antiseptic resistance genes and antibiotic resistance ($P > 0.05$). **Conclusion:** our data suggest that *P. aeruginosa* isolates have profound antibiotic resistance and an antiseptic resistance gene. The integron was mostly found in all isolates, indicating that the Antiseptic resistance gene corresponds to the integron class 1.

Keywords: Antibiotic resistance, antiseptic resistance gene, *Pseudomonas aeruginosa*

Introduction

The Center for Disease Control and Prevention (CDC) reports that each year, nosocomial infections cause around two million new cases of infection worldwide and about 90,000 deaths.[1,2] WHO predicts that a sizable proportion of preventable deaths will result from microbiological diseases caused by bacteria resistant to antibiotics.[3] The development of many virulence factors and the appearance of additional antibiotic-resistance genes are thought to be the causes of *Pseudomonas aeruginosa* pathogenicity.[4] Antibiotic and disinfectant resistance in different bacterial strains is currently a significant public health issue, and it is spreading globally.[5] Disinfectant activity, temperature, and the type of surface all affect how well biofilms tolerate disinfectants.[6] In hospitals and other medical facilities, numerous antiseptic and disinfectant types are employed, and multiple cases of bacteria with antiseptic resistance have been documented. Small multidrug resistance genes (*smr)* and quaternary ammonium compound resistance genes (*qac*) were classified as the resistance determinants; Hence, it was deduced that the resistance mechanisms encoded by the genes *qacA*, *smr*, and *qacE* included efflux systems.[7] On plasmids and

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integrons of numerous drug-resistant Gram-negative and Gram-positive bacteria, the genes *qacE* and *qacΔE1* have been found. A mutation of the *qacE* gene is known as *qacΔE1*.[8] Given that these genes are present in class 1 integrons, which are commonly found in Gram-negative bacteria and comprise *qacΔE1* which acts as a multidrug transfer gene, the *qacE* gene (attenuated form *qacΔE1*) is widely distributed in these bacteria, particularly in Enterobacteriaceae and *Pseudomonas* species.[9,10] In both mammals and microbes, fatty acid synthesis is a crucial metabolic route. As a result of the difference between the mammalian and bacterial fatty acid synthesis pathways, bacterial fatty acid synthesis is a promising target for the development of new antimicrobial medicines.[11] The final stage of the elongation cycle in the production of fatty acids is catalyzed by enoyl-acyl carrier protein reductases (ENRs). Four unique ENR isozymes, *fabI, fabL, fabK*, and *fabV* were identified based on the varying sensitivity of bacteria to the biocide triclosan, which is present in hand soaps and a wide range of other items used on a daily basis.[12] It has been established that *P. aeruginosa fabV* is responsible for the innate triclosan resistance of this organism by complementing the known triclosan-resistant ENR-producing gene.[13] *fabV* has been proposed as the cause of *P. aeruginosa's* innate triclosan resistance.[14] Therefore, the purpose of this research is to determine the distribution of antiseptic resistance genes *qacE, qacΔE1,* and *fabV* genes among multidrug-resistant (MDR) *P. aeruginosa* isolated from burn cases and their relative with presence integron class I.

Materials and Methods

Subjects of study

In 2022, many hospitals in Babylon, Iraq provided 103 clinical samples of patients with burns. The 64 *P. aeruginosa* isolates recovered from the study were identified using standard biochemical assays and the VITEK 2 system.

Susceptibility testing for antimicrobials

As per reference,[15] the disk diffusion test was employed to ascertain antibiotic susceptibility. *Pseudomonas aeruginosa* ATCC 27853 (ATCC/USA) was assessed as a reference strain for antibiotic resistance as a control positive. However, isolates with multiple drug resistance may be recognized since they are resistant to at least three separate antibiotic classes.[16]

Extraction of genomic DNA

To extract genomic DNA, *P. aeruginosa* isolates were employed (Favorgen DNA Extraction KIT, Ping Tung, Taiwan) provides the extraction process for genomic DNA. Nano-drop (Analytik Jena, Jena, Germany) was used to determine the DNA content and purity of the samples.

Detection of integron class1 and antiseptic resistance genes

In all isolates, the presence of *intI1, qacΔE1, qacE*, and *fabV* was determined. Specific primers were designed for each gene [Table 1]. In a final amount of 25 µL, the polymerase chain reaction (PCR) was performed. The following steps were taken: PCR amplification was performed as previously[8,17] to identify *intI1, qacΔE1, qacE, and fabV*; PCR products were separated according to.[18]

Statistical analysis

Chi-square at a probability of 0.05 was applied to assess the differences of tested variables using the Statistical Package for the Social Sciences.

Ethical approval

This research was performed abiding the ethical principles set by the University of Babylon according to document number *B220128* (including the number and the date in May 15, 2022) to get this approval.

Results

Identification of isolates

Sixty-four isolates of MDR *P. aeruginosa* were obtained from burn patients during the course of the investigation. There were at least three classes to which any of the chosen isolates were resistant.

There were 64 confirmed *P. aeruginosa* isolates identified among 103 burn samples collected from various hospitals in the Babylon. Total *P. aeruginosa* isolates were uncovered in hospitalized patients who were 37 (57.81%) female and 27 (42.19%) male.

Table 1: Primers for PCR amplification for integron class I and antiseptic resistance genes in *P. aeruginosa* isolates

Gene	Sequence	Product size (bp)	Reference
Int1*: F*	5'- GCA TCC TCG GTT TTC TGG -3'	457	[17]
Int1: R	5'- GGT GTG GCG GGC TTC GTG -3'		
qacΔE1: F	5'- TAG CGA GGG CTT TAC TAA GC -3'	335	[18]
qacΔE1: R	5'- ATT CGA AAT GCC GAA CAC CG -3'		
qacE: F	5'- ATG AAA GGC TGG CTT -3'	300	
qacE: R	5'- TCA CCA TGG CGTC GG -3'		
fabV: F	5'- TCGACCTGGTGGTCTACAGC -3'	530	
fabV: R	5'- GACCTGCTCGATGCAACC -3		

For the primary identification tests, the morphological characteristics of bacterial growth on previously inoculated medium, such as MacConkey agar and Cetrimide agar, at 37°C for 18–24 h, were utilized. The automated VITEK 2 compact system with GN-ID cards (bioMerieux, Marcy-l'Étoile, France) was used to identify each *P. aeruginosa* isolate in accordance with the manufacturer's instructions.

Resistances patterns

The sensitivity of each of the 64 *P. aeruginosa* isolates to 16 antibiotics was examined (Bioanalyse/Turkey). The results indicated that it could be possible to observe the rates of antibiotic susceptibility of distinct isolates. According to [Table 2], 100% of the *P. aeruginosa* isolates were resistant to CTX. In contrast, CZX (98.44%), *Cefepime (96.88%), Tetracycline (96.44%)*, *Piperacillin and* Ticarcillin *clavulanic* for each one (*93.75%), Cefoperazone (92.19%), Piperacillin-tazobactam, Gentamicin and Meropenem (90.62%), Amikacin and Aztreonam (89.06%), Imipenem (85.94%), Ciprofloxacin (82.81%), Doripenem (81.25%)* and the most sensitive antibiotic was *azithromycin (65.62%). Notably, 100% of the isolates exhibited MDR resistance to at least three categories of antibiotics*. To check for patterns of antibiotic resistance, *P. aeruginosa* ATCC 27853 was also examined as a positive control strain.

Molecular profiles of integron class I and antiseptic resistance genes

The result of the PCR findings revealed that 100% of the isolates showed positive for class 1 integron gene [Figure 1].

The current findings show that all isolates had the *qacΔE1* and *fabV* genes, with molecular sizes of about (335 and 530) bp, respectively as demonstrated in Figures 2 and 3.

While the *qacE* findings were in, 87.50% of the isolates that tested positive were about 300 bp length as demonstrated in Figure 4.

Figure 5 summarizes all of the above findings and displays different percentages of antiseptic resistance genes.

Relationship between antibiotic resistance and antiseptic resistance genes

Antibiotic resistance and genes encoding antiseptic resistance were not found to be associated, as Table 3 shows ($P > 0.05$).

Discussion

During the laboratory diagnosis, 103 samples (62.13%) from burns obtained 64 isolates of *P. aeruginosa.* Every isolate was tested to determine their susceptibility to 16 different antibiotics. Resistance to Beta-lactams, Tetracyclines, and Aminoglycosides was highest in antibiotic susceptibility, followed by the other two groups studied [Figure 1].

The current findings were relative agreement with previous findings,[19] and as explained by Azimi *et al*.[20] the 160 isolates of *P. aeruginosa* were 100% resistant to amoxicillin clavulanate, ciprofloxacin, and cefoxitin, 99.4% resistant to gentamicin, amikacin, cefepime, and aztreonam, 98.8% resistant to imipenem, 98.1% resistant to meropenem, 84.4% resistant to piperacillin/tazobactam, and 80% resistant to ceftazidime. Furthermore, all 160 isolates were designated as MDR. Global expansion of *P. aeruginosa* MDR isolates has resulted in serious problems that might complicate the selection of empirical medications. It is a major pathogen that causes a range of infections in hospitals and healthcare settings.[21,22]

Table 2: Antibiotics susceptibility of *P. aeruginosa* isolates (No. 64)

Antibiotic	Resistant no. (%)	Sensitive no. (%)
Piperacillin (PRL)	60 (93.75%)	4 (6.25%)
Piperacillin-tazobactam (PIT)	58 (90.62%)	6 (9.38%)
Ticarcillin clavulanic (TCC)	60 (93.75%)	4 (6.25%)
Ceftizoxime (CZX)	63 (98.44%)	1 (1.56%)
Cefotaxime (CTX)	64 (100%)	0
Cefepime (FEP)	62 (96.88%)	2 (3.12%)
Cefoperazone (CFP)	59 (92.19%)	5 (7.81%)
Amikacin (AK)	57 (89.06%)	7 (10.93%)
Gentamicin (CN)	58 (90.62%)	6 (9.38%)
Ciprofloxacin (CIP)	53 (82.81%)	11 (17.19%)
Tetracycline (TE)	63 (98.44%)	1 (1.56%)
Imipenem (IPM)	55 (85.94%)	9 (14.06%)
Meropenem (MEM)	58 (90.62%)	6 (9.38%)
Doripenem (DOR)	52 (81.25%)	12 (18.75%)
Azithromycin (AZM)	22 (34.38%)	42 (65.62%)
Aztreonam (ATM)	57 (89.06%)	7 (10.93%)

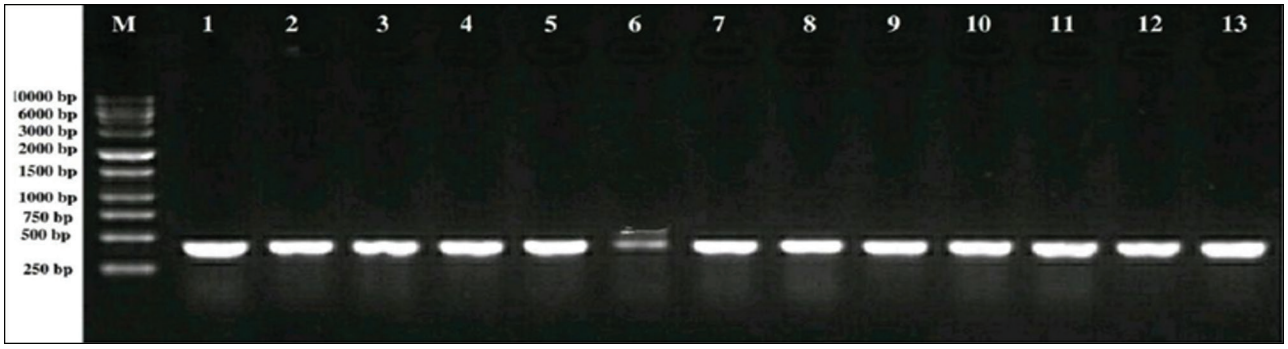

Figure 1: PCR amplification with specific primers for *intI1* gene (457 bp), on 1.5 % agarose at 70 volts for 2 hrs. Lane M, 100-bp DNA marker. Lane (1-13) positive cases

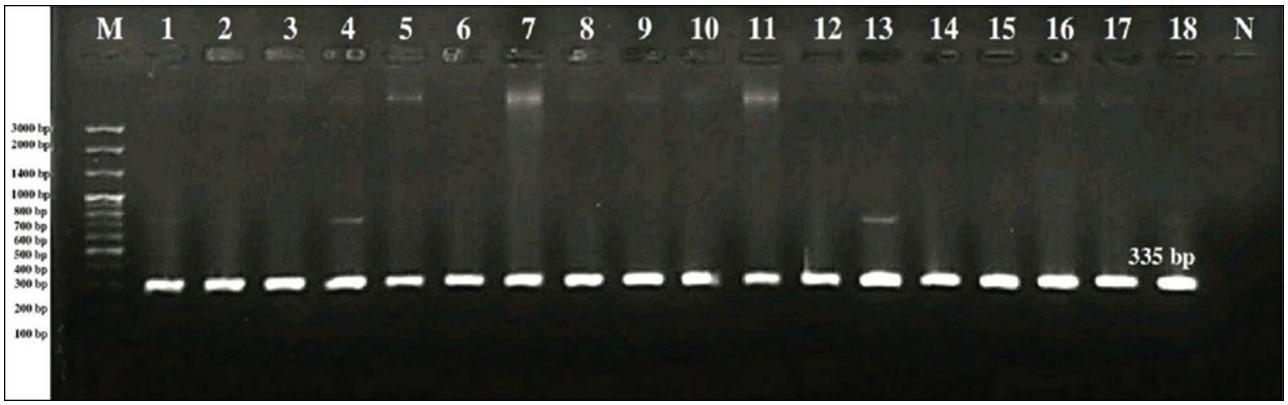

Figure 2: PCR amplification with specific primers for *qacΔE1* gene (335 bp), on 1.5 % agarose at 70 volts for 2 hrs. Lane M, 100-bp DNA marker. Lane N: negative control. Lane (1-18) positive cases

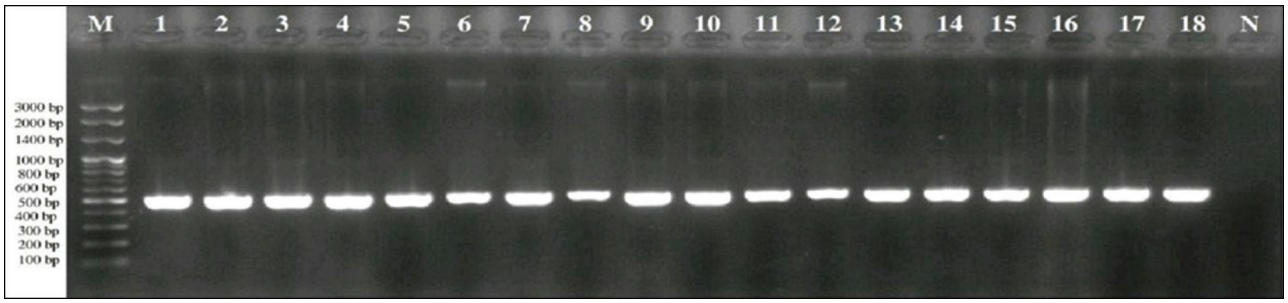

Figure 3: PCR amplification with specific primers for *fabV* gene (530 bp), on 1.5 % agarose at 70 volts for 2 hrs. Lane M, 100-bp DNA marker. Lane N: negative control. Lane (1-18) positive cases

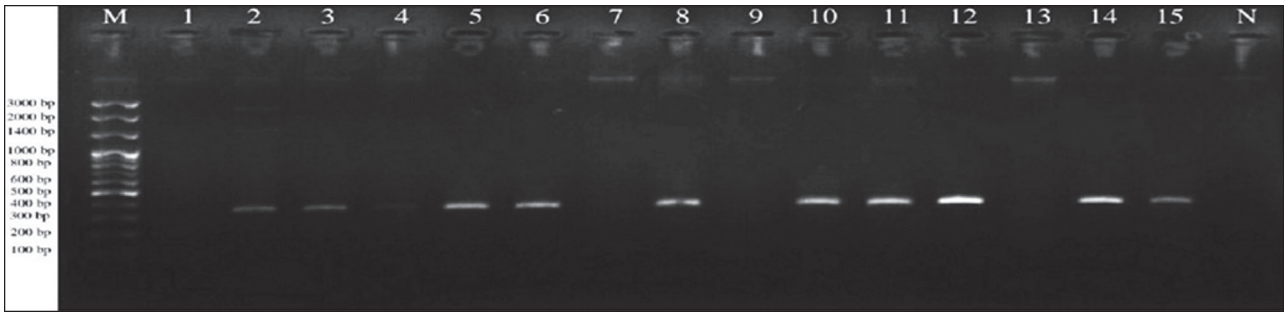

Figure 4: PCR amplification with specific primers for *qacE* gene (300 bp), on 1.5 % agarose at 70 volts for 2 hrs. Lane M, 100-bp DNA marker. Lane (2,3,4,5,6,8,10-12,14 and 15) positive cases. Lane (1,7,9, and 13) negative cases. N: negative control

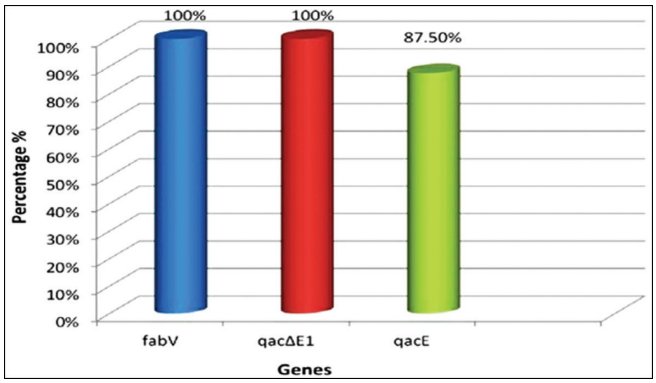

Figure 5: Distribution of antiseptic resistance genes in *P. aeruginosa* isolates

Table 3: Association of occurrence of Antiseptic Resistance Genes among antibiotic resistance

AB	*fabV*	*qacΔE1*	*qacE*	*p*-value
Piperacillin PRL	60(93.75%)	60(93.75%)	56(87.50%)	0.913
Piperacillin-tazobactam PIT	58(90.62%)	58(90.62%)	54(84.38%)	0.910
Ticarcillin clavulanic TCC	60(93.75%)	60(93.75%)	55(85.94%)	0.867
Ceftizoxime CZX	63(98.44%)	63(98.44%)	56(87.50%)	0.764
Cefotaxime CTX	64(100%)	64(100%)	56(87.50%)	0.705
Cefepime FEP	62(96.88%)	62(96.88%)	54(84.38%)	0.698
CefoperazoneCFP	59(92.19%)	59(92.19%)	53(82.81%)	0.810
AmikacinAK	57(89.06%)	57(89.06%)	53(82.81%)	0.909
GentamicinCN	58(90.62%)	58(90.62%)	54(84.38%)	0.910
CiprofloxacinCIP	53(82.81%)	53(82.81%)	52(81.25%)	0.994
TetracyclineTE	63(98.44%)	63(98.44%)	55(85.94%)	0.702
ImipenemIPM	55(85.94%)	55(85.94%)	49(76.56%)	0.797
MeropenemMEM	58(90.62%)	58(90.62%)	54(84.38%)	0.910
Doripenem DOR	52(81.25%)	52(81.25%)	50(78.12%)	0.974
AzithromycinAZM	22(34.38%)	22(34.38%)	18(28.12%)	0.773
AztreonamATM	57(89.06%)	57(89.06%)	51(79.69%)	0.804

Antimicrobial resistant strains have caused MDR *P. aeruginosa* to become resistant to a variety of pharmacological classes, such as carbapenems, fluoroquinolones, cephalosporins, and aminoglycosides.[1] Even though chromosomal abnormalities are often the means of acquisition and transmission. These consist of several mobile DNA segments, such as integrons, transposons, and plasmids.[23] Integrons were discovered to be to function as antimicrobial resistance gene repositories in microbial communities and as a primary source of resistance genes. Antibiotic resistance mediated by integrons was reported in *P. aeruginosa* isolates.[24,25] The integron is a genetic component that can play a significant part in the spread of multidrug resistance in Gram-negative bacteria, particularly in *Pseudomonas*.[24]

The significance of classes 1 integrons in highly antibiotic resistant *P. aeruginosa* isolates was demonstrated in this study and concurred with,[26] which also emphasized their occurrence and significance.

In the present investigation, *qacΔE1* was detected in 100% of *P. aeruginosa* isolates, indicating a greater frequency than that reported by Helal and Khan[27] (57.8%). and Kadry *et al*.[28] (30.5%), and similar to findings reported by.[29,30] However, the *qacE* of 87.50% in this investigation differs from that of 92.5% in another study conducted by[31] involving 120 isolates of *P. aeruginosa*. The gene's existence *fabV* was found to be 100% greater in the current investigation than in the previous study (84.2%) out of 76 *P. aeruginosa* isolates.[32]

In hospitals and other healthcare settings, antiseptics and disinfectants are frequently used to prevent infection and lower the risk of illness and outbreaks. Despite the widespread use of disinfectants, microbial contamination has lately been found to be significantly more common. Due to its ability to adapt to the random delivery of almost deadly disinfectant dosages, this may be connected to antimicrobial and disinfection resistance, as well as the development of several virulence factors.[33]

Genes known as *Qac* genes confer reduced susceptibility to quaternary ammonium compounds (QACs). Thus far, a number of *qac* genes have been identified; these genes are broadly distributed in both ambient and clinical bacteria.[34,35]

The *qacΔE1* gene, which was initially characterized as a variation of the *qacE* gene, is located in the conserved 3' region of the class I integron.[36] The *qacE* gene (including the attenuated variation *qacE1*) is extensively distributed in Gram-negative bacteria such as enterobacteria and *P. aeruginosa*. Other species, including *Aeromonas spp*., and *Acinetobacter spp*., also include these genes.[37] This is brought on by the high frequency of class I integrons, which are frequently found in the *qacE1* gene of Gram-negative bacteria.[38] *P. aeruginosa* becomes resistant to triclosan biocide due to the *FabV* isozyme, which is also concerned with energy consumption, protein synthesis, adhesion, and swimming motility.[39]

Conclusion

Antiseptics and disinfectants of various sorts are used in hospitals and medical institutions. It confers resistance to disinfection and sterilization agents, particularly QACs. As a result, maximizing antimicrobial use, antiseptics, and disinfectants, as well as infection control, are recommended techniques to preventing the spread of drug-resistant microorganisms.

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Conflicts of interest
There are no conflicts of interest.

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