Original article

Detection of carbapenem-resistant *Pseudomonas aeruginosa* in a tertiary care hospital in Saudi Arabia

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**Background:** *Pseudomonas aeruginosa* is one of the common emerging multidrug-resistant causative bacteria which causes healthcare associated infections that leads to increased morbidity and mortality rates. **Aim:** Detection of resistance pattern of studied isolates to different antipseudomonal drugs and to determine the prevalence of carbapenem resistant *Pseudomonas aeruginosa* and to detect the involved carbapenemases genes among resistant isolates. **Methods:** The study was done from November 2021 to April, 2022 in Al-quwayiyah general hospital. Eighty six *Pseudomonas aeruginosa* isolates were collected. Identification of isolates and antimicrobial susceptibility testing were done using vitek-II machine. Carbapenem resistance was detected by modified Hodge Test then confirmed using multiplex PCR for the detection of *blaVIM, blaKPC, blaIMP, blaNDM-1, blaOXA-48, blaGIM, blaSPM* and *blaSIM* genes. **Results:** Thirty two (37.20%) strains were carbapenem-resistant *Pseudomonas aeruginosa*(CRPA) as detected by multiplex PCR. Among these 32 strains the resistance was 100% to imipenem, meropenem and ciprofloxacin. The isolates had least resistance to aztreonam, 21.88% and colistin, 31.25%. Among 32 CRPA isolates 23 (71.88. %) were multidrug resistant, 19 (59.38%) were Extensively-drug resistant. PCR identified the presence of *blaOXA-48* in 15 (46.88%) isolates, *blaVIM* gene in 10 (31.25%) isolates and *blaNDM* in 12 (37.5%) isolates. On the other hand, *blaGIM, blaIMP* and *blaSIM* were only detected in 2 isolates for each and *blaKPC* detected in one isolate only. **Conclusion:** The prevalence of CRPA was high (37.2%). The appropriate study of the antimicrobial resistance molecular mechanisms will help in management of CRPA patients and implementation of infection control procedures.

**Introduction**

*Pseudomonas aeruginosa* (*P. aeruginosa*) is a major opportunistic bacterium that has been linked to a variety of illnesses in the health care facilitiesand community, including bacteremia, wounds, respiratory tract infections, otitis media, eye infections and other hospital acquired infections [1].

For the management of multi-drug resistant (MDR) *P. aeruginosa* infection, carbapenems have been kept as a last choice. Carbapenem-resistant *P. aeruginosa* (CRPA), on the other hand, may be resistant to other antibiotic classes, and such infections are associated with restricted therapy options and increased rates of death and morbidity, particularly in immunosuppressed and hospitalized patients [2].

The Centers for Disease Control and Prevention (CDC) has classified CRPA as an organism that leads to a serious consequence[3]. Carbapenem resistance in *P. aeruginosa* has been demonstrated to be multifactorial, it may be due to carbapenemase synthesis, efflux pump or gene overexpression[4].
Carbapenemases are classified into three categories: A, D (serine carbapenemases), and B (metallo—lactamases) [5]. Carbapenemases are classified into three categories: A, D (serine carbapenemases), and B (metallo—lactamases) [5]. Class A (blaKPC), class B (blaVIM, blalMP, blaNDM, blaSIM, blaSPMand blaGIM), and class D (blaOXA-48) genes are examples of carbapenemase genes in *P. aeruginosa*.

Carbapenemase genes are frequently found on mobile genetic elements that have the ability to spread quickly. Carbapenems are a type of beta-lactam that inhibits synthesis of cell wall of the bacteria by attaching to penicillin-binding proteins (PBPs). Imipenem, meropenem, ertapenem, and doripenem are some of the carbapenems that are available clinically. All Beta-lactams excluding monobactams, are resistant to metallo-beta lactamases (MBLs) [6].

As carbapenem resistance is difficult to be detected using the standard disc diffusion method, The Clinical and Laboratory Standards Institute (CLSI), 2022 [7] has recommended inhibition-based tests like the double-disk synergy assay, modified Hodge technique (MHT), and combination disk test as comprehensive phenotypic methods for carbapenemase detection. In addition, polymerase chain reaction (PCR) is recommended as a reliable approach for identifying the most common genes in carbapenemase positive clinical samples [8,9].

Aim of this study is the detection of resistance pattern of studied *P. aeruginosa* isolates to different antipseudomonal drugs and to determine the prevalence of carbapenem resistant *P. aeruginosa* among Al-Quwayiyah general hospital admitted patients as well as to detect the prevalence of carbapenemase genes; *blaKPC*, *blaNDM1*, *blalMP*, *blaVIM*, *blaSIM*, *blaSPM*, *blaGIM*, and *blaOXA-48* among *P. aeruginosa*.

**Materials and Methods**

This work was done in Al-Quwayiyah general hospital which is a general hospital in Riyadh, Saudi Arabia which has 250 beds capacity in the period from November 2021 to April, 2022 in the microbiology department. *P. aeruginosa* isolates were collected from ICU, medical, surgical and pediatrics departments from various clinical specimens (blood, urine, sputum, sterile body fluids, pus and others), after receiving ethical approval from the Institutional Ethics Committee. The study included all admitted patients who had isolates of *P. aeruginosa* infections 48 hours after admission.

**Bacterial strains**

Eighty six *P. aeruginosa*strains were isolated and identified by colony shape on MacConkey's and blood agar plates (oxoid, UK), gram staining using the VITEK II machine (bioMérieux, Marcy l’Etoile, France) *P. aeruginosa* quality control ATCC strain 27853 was used.

**Antimicrobial susceptibility testing**

The VITEK 2 system was used to evaluate antimicrobial susceptibility to 10 antimicrobial drugs, including imipenem (IPM), meropenem (MEM), amikacin (AN), tobramycin (TM), ceftazidime (CAZ), cefepim (FEP), ciprofloxacin (CIP), colistin (CS), aztreonam (ATM) and piperacillin-tazobactam (TZP) was done using 291 AST card by VITEK II machine, and the interpretation of data was done according to the CLSI guidelines, 2022 [7].

Both imipenem and meropenem minimum inhibitory concentration (MIC) were done for each strain by the use of an E-test (BioMérieux, France), that were carried out and interpreted as per the manufacturer’s guidelines. *Pseudomonas aeruginosa* carbapenem resistance was defined when imipenem or meropenem MIC was ≥2 mg/L as recommended by CLSI, 2022 guidelines [7]. Moreover, MDR was identified by the presence of resistance to minimally one antimicrobial drug in more than three different groups.*Pseudomonas aeruginosa* strains nonsusceptible to at least one agent in all antibiotic categories but only susceptible to two or less antimicrobial groups was defined as XDR [10,11].

**MBL screening**

All strains were tested for MBL production by a double-disk synergy test using 10 µg of IPM and 2.5 µM ethylenediaminetetraacetic acid as described in CLSI, 2022 guidelines [7]. A positive result was interpreted if there is asynergistic inhibition zone seen between both disks.

**Carbapenem Inactivation Method (CIM)**

Carbapenem Inactivation Method was used to determine carbapenem resistance in *P. aeruginosa* isolates. *Escherichia coli* ATCC 25922 diluted culture (0.5 McFarland standard) was streaked in three different directions on the Mueller-Hinton agar plates, then the Meropenem disk (10 µg) (Oxoid,
Basingstoke, UK) was placed at each plate center. From the edge of the meropenem disk the tested strain was streaked as a thin line to the plate edge. All plates were incubated for 18 hours at 37 °C. A positive MHT was interpreted if there was an indentation in the E. coli inhibition zone or clove growth of E. coli around the meropenem disk [7,12].

Molecular detection of carbapenemase gene

Multiplex polymerase chain reaction (PCR) was done for the detection of blaVIM, blaKPC, blaIMP, blaNDM-1, blaOXA-48, blaGIM, blaSPM and blaSIM was done as described in the technique carried out by Weiß et al. [13] and Hamid et al. [14]. QIAamp DNA Mini kit (QIAGEN, Hilden, Germany) was used to extract DNA from P. aeruginosa strains according to manufacturer's guidelines. Multiplex PCR were carried out in 2 groups using KAPA2G Fast Multiplex PCR Kit (2X) according to manufacturer's guidelines (Kapa Biosystems - Roche diagnostics, Switzerland). The first set of multiplex PCR was done to detect blaVIM, blaIMP, and blaSIM, and the second set of multiplex PCR tested the presence of blaKPC, blaOXA-48, and blaNDM-1. A final reaction volume of 25 μl was prepared in the PCR reactions which contained 12.5 μl of 2X KAPA2G Fast Multiplex Master Mix, 0.5 μl of every oligonucleotide primer and five μl of DNA template. Amplification was carried out by initial denaturation step for 3 min at 95°C, then denaturation for 15 s at 95°C, annealing for 30 s at 60°C, extension for 30 s at 72°C, and finaly extension step for 7 min at 72°C. The products were seen using 1.5% agarose gel electrophoresis which was ethidium bromidestained, and was seen using ultraviolet illumination under automated gel system (Syngene G: Box, Syngene, Cambridge, U.K.). primers were shown in table (1) as carried out by Verma et al. [15]

Statistical analysis

Analysis of the study data was carried out by the use of SPSS version 16 software. Data interpretation was done as percentages and numbers. Z- test was used to compare 2 variables and χ2 (Chi square) test was used to compare between more than two variables. Presence of p value <0.05 was interpreted as statistical significance.

Results

Eighty six P. aeruginosa strains were obtained from 61 (70.93%) males and 25 (29.07%) females. The strains were collected from different clinical samples that included 32 urine samples (37.2%), followed by 26 sputum (30.2%), 22 pus sample (25.6%), 4 blood (4.66%), and 2 other samples (2.33%). Out of these 86 P. aeruginosa strains, 32 (37.20%) were CRPA strains as detected by multiplex PCR. Of these 32 CRPA, 16 were collected from ICUs, 10 were from medical departments, 4 from surgical departments and 2 from pediatric department were from various admitted patients. Of 32 CRPA isolates, MHT was positive in 30 (93.75%). Out of the total 86 isolates there was 39 isolates were resistant to at least one carbapenem either imipenem or meropenem.

Table 2 showed that the antimicrobial susceptibility testing revealed that all 32 CRPA strains showed resistance to imipenem and meropenem, the resistance was also 100% to Ciprofloxacin, followed by amikacin and tobramycin 29 (90.63%), cefazidime 28 (87.5%), piperacillin-tazobactam in 26 (81.25%). The isolates was most susceptible to aztreonam, 21.88% and colistin, 31.25%. Among 32 CRPA isolates 23 (71.88%) were MDR, 19 (59.38%) were XDR.

Table 3 showed that the PCR detected carbapenemases encoding genes in 32 strains of the 39 proved imipenem or meropenem resistant strains. PCR identified the presence of bla OXA-48 in 15 (46.88%), blaVIM gene in 10 isolates (31.25%), blaNDM carbapenemases in 12 (37.5%) isolates, 5 (15.63) P. aeruginosa isolates had blaNDM-1. On the other hand, blaGIM, blaIMP and blaSIM were only detected in 2 isolates for each and blaKPC detected in one isolate only. Some strains had more than one gene as shown.

Figure 1 showed the Multiplex polymerase chain reaction, in Lane 1 100 bp ladder was seen, Lane 5 showed blaSIM, 477 bp, blaVIM, 390 bp and blaSPM 271 bp and Lanes 4, 6, and 8 had blaVIM.
**Table 1.** Primers used for different carbapenemase genes in the multiplex polymerase chain reaction.

<table>
<thead>
<tr>
<th>Primers</th>
<th>Sequence</th>
<th>Productsize</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIM family-F</td>
<td>GAT GGT GTT TGG TCG CATA</td>
<td>390</td>
</tr>
<tr>
<td>VIM family-R</td>
<td>CGA ATG CGC AGC ACCAG</td>
<td></td>
</tr>
<tr>
<td>IMP family-F</td>
<td>GGA ATA GAG TGG CTT AAY TCTC</td>
<td>188</td>
</tr>
<tr>
<td>IMP family-R</td>
<td>CCA AAC YAC TAS GTT ATCT</td>
<td></td>
</tr>
<tr>
<td>GIM-1-F</td>
<td>TCG ACA CAC CTT GGT CTG AA</td>
<td>477</td>
</tr>
<tr>
<td>GIM-1-R</td>
<td>AAC TTCCAA CTT TGC CAT GC</td>
<td></td>
</tr>
<tr>
<td>NDM-1 F</td>
<td>ACC GCC TGG ACC GAT GAC CA</td>
<td>264</td>
</tr>
<tr>
<td>NDM-1 R</td>
<td>GCC AAA GTT GGG CGC GTG TG</td>
<td></td>
</tr>
<tr>
<td>OXA-48-F</td>
<td>TGGTGGGACATCGATTATCGG</td>
<td>744</td>
</tr>
<tr>
<td>OXA-48-R</td>
<td>GAGCACTTCTTTTGTGATG GC</td>
<td></td>
</tr>
<tr>
<td>KPC-F</td>
<td>ATGTCACTGTATCGCGTCT</td>
<td>893</td>
</tr>
<tr>
<td>KPC-R</td>
<td>TTTTCAGAGCGCTTACTGCC</td>
<td></td>
</tr>
<tr>
<td>SPM-1A-F</td>
<td>AAA ATC TGG GTA CGC AAA CG</td>
<td>271</td>
</tr>
<tr>
<td>SPM-1A-R</td>
<td>ACA TTATCC GCT GGA ACA GG</td>
<td></td>
</tr>
<tr>
<td>SIM-1-F</td>
<td>TAC AAG GGA TTC GGC ATC G</td>
<td>571</td>
</tr>
<tr>
<td>SIM-1-R</td>
<td>TAA TGG CCT GTT CCC ATG TG</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Antimicrobial resistance rate among CRPA strains.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>CRPA =32</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Piperacillin-Tazobactam</td>
<td>26</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>29</td>
</tr>
<tr>
<td>Imipenem</td>
<td>32</td>
</tr>
<tr>
<td>Meropenem</td>
<td>32</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>28</td>
</tr>
<tr>
<td>Cefepime</td>
<td>20</td>
</tr>
<tr>
<td>Amikacin</td>
<td>29</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>32</td>
</tr>
<tr>
<td>Colistin</td>
<td>10</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 3. Carbapenem-resistant genes distribution in *P. aeruginosa* strains among studied groups

<table>
<thead>
<tr>
<th>Genes identified</th>
<th>No of isolates = 32</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>bla OXA-48</td>
<td>15</td>
<td>46.88%</td>
</tr>
<tr>
<td>blaVIM</td>
<td>10</td>
<td>31.25%</td>
</tr>
<tr>
<td>blaNDM</td>
<td>5</td>
<td>15.63%</td>
</tr>
<tr>
<td>blaKPC</td>
<td>1</td>
<td>3.13%</td>
</tr>
<tr>
<td>blaGIM</td>
<td>2</td>
<td>6.26%</td>
</tr>
<tr>
<td>blaSIM</td>
<td>2</td>
<td>6.26%</td>
</tr>
<tr>
<td>blaIMIP</td>
<td>2</td>
<td>6.26%</td>
</tr>
<tr>
<td>blaSPM</td>
<td>1</td>
<td>3.13%</td>
</tr>
<tr>
<td>blaVIM+blaNDM-1</td>
<td>2</td>
<td>6.26%</td>
</tr>
<tr>
<td>blaVIM+blaGIM</td>
<td>1</td>
<td>3.13%</td>
</tr>
<tr>
<td>bla OXA +blaNDM-1</td>
<td>1</td>
<td>3.13%</td>
</tr>
<tr>
<td>blaVIM+blaGIM+blaNDM-1</td>
<td>1</td>
<td>3.13%</td>
</tr>
<tr>
<td>bla OXA+blaSPM+blaNDM-1</td>
<td>1</td>
<td>3.13%</td>
</tr>
</tbody>
</table>

Figure 1. Multiplex chain reaction showing blaVIM, blaGIM, blaSPIM.

Discussion

The increase in the use of carbapenems in management of health care associated infections is believed to be associated to the presence of increased carbapenem resistance in *P. aeruginosa* [16].

Eighty six *P. aeruginosa* strains were isolated. Out of these 86 *P. aeruginosa* strains, 32 (37.20%) were CRPA isolates as detected by multiplex PCR. In Saudi Arabia, Al-Agamy et al. [17] noted that the prevalence of carbapenem-resistant *P. aeruginosa* was 34%. Abd alhamid et al. [18] also studied the prevalence of CRPA in two
hospitals among the ICU patients and it was also high as he reported the prevalence of CRPA rate 45.1%. In Egyptian study, which found that 32.3% of strains were MBL-positive [19]. Haji et al. [20] reported 18% in their study and the incidence of prevalence in India varies from 14-69%. The difference in the prevalence of CRPA isolates was mostly due to the number of antibiotics used, infection control practices and infrastructure of hospitals [21].

Multidrug resistant and XDR P. aeruginosa infection is a great medical concern because it is a significant reason of life-threatening healthcare-associated infections such as urinary tract infections, bacteremia, ventilator-associated pneumonia and, as well as tissue and wound soft-infections, which cause high fatality [22].

The strains were collected from various clinical samples that included 32 urine samples (37.2%), followed by 26 sputum (30.2%), 22 pus sample (25.6%), 4 blood (4.66%), and 2 other samples (2.33%). Rabani et al. [23] also reported that P. aeruginosa is a major cause of urinary tract infections, bacteremia, respiratory infections, surgical site infections and many other systemic diseases. He noted in his study that the most common type of specimen from which strains were obtained was urine, that represented about 67%. In Saudi Arabia it was isolated from 88.9% urine samples, thus describing the difficulty in treating urinary tract infections caused by MDR P. aeruginosa [24].

In this study the antimicrobial susceptibility testing revealed that all 32 CRPA strains were resistant to imipenem and meropenem, the resistance was also 100% in Ciprofloxacine, followed by amikacin and tobramycin 29 (90.63%), ceftazidime 28 (87.5%), piperacillin–tazobactam in 26 (81.25%). Similar results were obtained from near countries; in Bahrain, the rate of resistance was 72–100% was reported to ceftazidime, carbapenems, Amikacin, piperacillintazobactam and ciprofloxacine [25]. In an Egyptian research by El Far et al. [26], he showed that the resistance rates of CRPA isolates to fluoroquinolones were from 91–94%, while ceftaziidime resistance was 69.7%, cefepime resistance was 88%, carbapenems resistance was 81.8% and tazobactam–piperacillin resistance was 63.3%. The increased rate of the resistance to anti-pseudomonal drugs, mostly carbapenems, fluoroquinolones and aminoglycosides has been attributed to the emergence of P. aeruginosa MDR/XDR strains, leading to a dangerous and life-threatening medical conditions. [27, 28]

In this study the CRPA isolates was most susceptible to aztreonam, 21.88% and colistin, 31.25%. Basha et al. [29] showed also similar results that aztreonam was the most effective antibiotic and Al Far et al. [26] reported 21% resistance to aztreonam in Saudi Arabia, although 100% susceptibility to colistin in P. aeruginosa strains was revealed by Saeed et al. [30]. Ramadan et al. [31] and Azim et al. [32] revealed that 8% Pseudomonas aeruginosa strains showed resistance to colistin. Moreover, Ibrahim et al. [33] noted that colistin resistance was 30% among P. aeruginosa isolates.

The bacterial phenotypes XDR and MDR P. aeruginosa have led to a lot of attention all over the world; this bacterial phenotype might be the cause of diseases with a high death rate, making treatment challenging [34]. In the current study among 32 CRPA isolates 23 (71.88. %) were MDR, 19 (59.38%) were XDR. El Far et al. [26] reported approximately 79% of the P. aeruginosa strains were MDR and revealed that XDR among carbapenem-resistant isolates was 55%. High MDR detection also found by El Sokkary et al. [35] in Egypt, he reported that 65.2% of the studied P. aeruginosa strains were multidrug resistant. A study from Greece reported high rates of MDR and XDR isolation, that 88.9% and 79% of the P. aeruginosa strains were MDR and XDR respectively, while less strains from Spain (33.3%) and Italy (43.5%) showed antibiotic resistance [36]. The increased rate of MDR and XDR P. aeruginosa strains reported in this study may be caused by the improper use of antibiotics that urge the need for strict monitoring and applying proper antibiotic use strategies [37].

In this study PCR identified the presence of blaOXA-48 in 15 (46.88%), blaVIM gene in 10 isolates (31.25%), blaNDM carbapenemases in 12 (37.5%) isolates, 5 (15.63%) P. aeruginosa isolates had blaNDM-1. On the other hand, blalSIM and blalIMP were only detected in 2 (6.25%) isolates for each and blakPC detected in one isolate only. Jaffar et al. [2022] in Saudi Arabia reported similar results, he noted that P. aeruginosa oxacillinase-48 (OXA-48) was detected in 41.5%, blalNDM genes were found in 22.5%. The other carbapenemases were low detected, blalIMP were
2%, and blaKPC were %. The current results also matched with Zowawi et al. [39] in Saudi Arabia who found that the major determined carbapenemases were OXA-48 (49%) and NDM (23%), while KPC or VIM or IMP not reported in any isolate. One study in Mecca between 2009 and 2010 conducted by Asghar [40] reported high IMP than VIM among MBL-producing P. aeruginosa, IMP genes were detected in 22.6% while VIM genes were detected in 19.4%. However, other reports from Riyadh suggest that VIM is the dominant carbapenemase in P. aeruginosa from that region. AL-Tawfik [41] identified VIM in 42.8% of the isolates. IMP, GIM, SIM, SPM and NDM were not detected which coincides with low incidence described in the current study for same genes. Another study which was done by Tian et al. [42] revealed that the highly detected gene was blaOXA (42%), then blaNDM (37%), followed by blaKPC (17%) and the least was blaIMP (1%). A study carried out in India on CRPA noted that the major detected carbapenemase was blavIM (29%), followed blaNDM (28%) and the least were blaSIM and blaGIM, 5% for each [15].

Conclusion
The prevalence of resistance to carbapenems among P. aeruginosa was increasing (37.2%). The serious condition of decreased carbapenem susceptibility in P. aeruginosa has been recognized throughout the last years in Saudi Arabia and worldwide, indicating the need for proper analysis of the problem. An appropriate study of the antimicrobial resistance molecular mechanisms will help in management of CRPA patients and implementation of infection control procedures.

Ethical approval
Ethical approval was obtained from institutional ethics committee of Al-Quwayiyh General Hospital.

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Conflict of interest
The authors report no conflicts of interest.

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Authorship
Both authors have worked together to complete this research. Author ESK planned and designed the study, prepared the protocol, gathered the samples, contributed in the interpretation and analysis of the findings, drafted and critically revised the paper. Author AAAF was involved in the study's planning and design, sample collection, clinical evaluation of cases and interpretation of the data. The final manuscript was reviewed and approved by both authors.

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