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"Synergistic Activity of Ceftazidime-Avibactam and Aztreonam Against MBL-Producing *Pseudomonas aeruginosa*: A Molecular Study"

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ABSTRACT

Objectives: *Pseudomonas aeruginosa* causes infections in immunocompromised patients and demonstrates high rates of multidrug resistance (MDR). Combining Ceftazidime-avibactam with aztreonam is effective against MBL-producing organisms. This study aimed to isolate *P. aeruginosa* from clinical samples, identify MBL production, and assess the efficacy of CZA alone and in combination with aztreonam against MDR strains. **Materials and Methods:** Non-repetitive clinical isolates of *P. aeruginosa* was identified using conventional methods or MALDI-TOF. Antimicrobial susceptibility testing performed as per CLSI guidelines. MBL production was assessed using the imipenem-EDTA combined disc method, and the blaNDM-1 gene was identified by PCR. Synergy between CZA and aztreonam was evaluated via the Double Disc Synergy Test and Disc Stacking methods. **Results:** Among 100 isolates, 62% were hospital-acquired, with a high prevalence in ICU samples. MBL production was phenotypically confirmed in 11 isolates and by PCR in 13 isolates. Resistance to CZA and aztreonam was observed in 20% and 24% of isolates, respectively, with 98% exhibiting synergy between CZA and aztreonam. Synergy was noted in 92.3% of blaNDM-1-positive strains. Resistance to ceftazidime and colistin was 37% and 2%, respectively. The synergism observed between Ceftazidime-Avibactam and Aztreonam in NDM-1 positive isolates was statistically significant with p-value 0.0023 (Chi square test). **Conclusion:** The CZA-aztreonam combination demonstrates high efficacy against MDR *P. aeruginosa*, including MBL-producing strains resistant to colistin. Routine resistance screening and incorporation of combination therapy could improve outcomes and mitigate resistance spread.

INTRODUCTION:

Non-fermentative Gram-negative bacilli (NFGNB) are widely present in various environments. These aerobic, non-spore-forming organisms do not metabolize carbohydrates via fermentation pathways[1]. Previously regarded as mere contaminants, NFGNB have now emerged as significant pathogens in hospital settings, particularly affecting immunocompromised patients. Hospital equipment, such as humidifiers, ventilators, dialysate fluids, and catheters, has

Journal of Molecular Science
Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 485-490
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facilitated the entry and colonization of NFGNB, leading to infections such as urinary tract infections, wound infections, sepsis, pneumonia, osteomyelitis, and meningitis[2]. Factors like prolonged hospital stays, chronic illnesses, and extended antibiotic use further predispose patients to NFGNB infections. Key genera within this group include *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia*, *Alcaligenes*, and *Weeksella*[3,4,5,6].

Antibiotic resistance is notably prevalent among hospital-acquired NFGNB isolates, with resistance documented against many commonly used antimicrobials. Ceftazidime-avibactam, a recently introduced β-lactamase inhibitor combination, has shown effectiveness against several β-lactamase enzymes, including extended-spectrum β-lactamases (ESBLs), class A and D β-lactamases, and AmpC, though not against Metallo-β-lactamases (MBLs) [7]. In clinical practice, NFGNB infections are often treated with antibiotics such as third- and fourth-generation cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones. Given the frequent multi-drug resistance (MDR) exhibited by NFGNB, combination therapy is commonly employed. β-lactamase-producing NFGNB are often treated with β-lactam/β-lactamase inhibitor (BL-BLI) combinations like piperacillin-tazobactam, cefoperazone-sulbactam, and ticarcillin-clavulanate. Recently, ceftazidime-avibactam has been added to this regimen for MDR gram-negative bacilli. Avibactam, a novel β-lactamase inhibitor, targets class A and C enzymes, and some class D enzymes, but lacks activity against class B enzymes (MBLs)[8,9]. A combination of aztreonam with ceftazidime-avibactam has demonstrated efficacy against MBL-producing pathogens[10].

This study aimed to isolate *Pseudomonas aeruginosa* from clinical samples, determine MBL production, and evaluate the effectiveness of ceftazidime-avibactam alone and in combination with aztreonam.

MATERIALS AND METHODS:

Study Setting: This cross-sectional study was approved by the Institutional Ethics Committee (IEC No. CSP-MED/21/NOV/72/142) and conducted from December 2021 to April 2022 at the Clinical Microbiology Department of Sri Ramachandra Hospital-SRIHER, a tertiary care centre.

Inclusion Criteria: The study included non-repetitive *Pseudomonas aeruginosa* isolates from blood, urine, exudates, and respiratory specimens collected from patients. A total of 100 clinically significant isolates were identified using conventional techniques or automated systems such as MALDI-TOF. The clinical relevance of the isolates was determined based on clinical history, Gram stain results, and colony count from non-sterile sites.

Laboratory Procedures: Collected specimens underwent Gram staining and were cultured on 5% sheep blood agar and MacConkey agar. Urine samples were inoculated on CLED agar, and sterile fluids, exudates, and tissue samples were additionally inoculated in thioglycolate broth. Oxidase-positive, non-lactose-fermenting colonies were identified as NFGNB based on colony morphology, pigment production, and biochemical tests, including motility, indole, citrate utilization, urease production, nitrate reduction, and growth at 42°C and 44°C.

Antimicrobial Susceptibility Testing: Susceptibility to various antibiotics was tested using the disc diffusion method per Clinical Laboratory Standards Institute (CLSI) guidelines [11]. Antibiotics tested included amikacin, ciprofloxacin, ceftazidime, aztreonam, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, and colistin.

Phenotypic Detection of NDM: MBL production was screened using the imipenem-EDTA combined disc (IPM-EDTA) method. A ≥7 mm increase in the inhibition zone around the IPM-EDTA disc compared to the IPM disc alone was considered positive for MBL production[12]. **[Figure 1]**

Figure-1: IMIPENEM-EDTA method- Increase in zone diameter of ≥7 mm around the IPM-EDTA disk compared to that of the IPM disk alone was considered positive for MBL.

Synergy Testing (CZA-AT Synergy): Synergy between ceftazidime-avibactam (CZA) and aztreonam (AT) was assessed using the Double Disc Synergy Test (DDST) **[Figure 2]** and Disc Stacking (DS) method. A CZA disc and an aztreonam disc are placed 20–25 mm apart on a Mueller–Hinton agar plate inoculated with the test organism. Synergy is indicated by distortion or expansion of the zone of inhibition between the two-disc compared to individual agents.[13,14] **[Figure 3]**

Journal of Molecular Science
Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 485-490
DoI-10.004687/1000-9035.2025.068

Figure-2: An increase in the zone diameter of around 2 mm in comparison to the single antimicrobial agent or distortion of the inhibitory zone are signs of synergy.

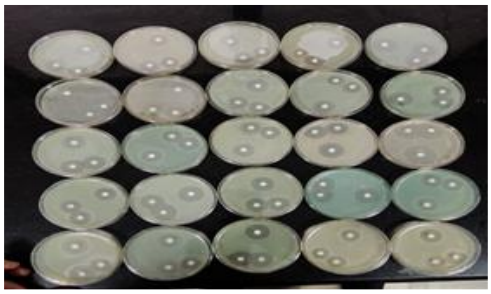

Figure-3: Synergy testing by Disc Stacking Method

PCR for blaNDM-1: PCR was conducted on all isolates using primers for the blaNDM-1 gene. **[Table 1]** PCR conditions included an initial denaturation at 94°C, followed by 35 cycles at 95°C, annealing at 58°C, and extension at 72°C. Amplified segments were visualized under UV light, with controls in place for validation.[15] **[Figure 4]**

Table-1: Conventional PCR configuration

Gene	Primer	Amplified segment(bp)	Annealing temperature
bla$_{NDM-1}$	F: GGCGGAATGGCTCATCACGA	287	58˚c
	R: CGCAACACAGCCTGACTTTC		

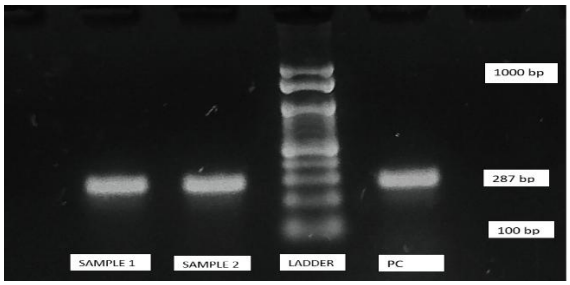

Figure-4: Agarose gel showing the PCR-amplified product of the *bla*NDM-1 gene.

RESULTS:

Out of 100 isolates, 62 were hospital-acquired and 38 were community-acquired. Sample sources included pus, urine, respiratory samples, ear swabs, blood, tissue, and wound swabs. Approximately 20% of isolates were resistant to ceftazidime-avibactam, and 34% were resistant to aztreonam. MBL production was detected in 11 isolates by phenotypic methods and in 13 isolates by PCR (The Bio edit sequence programme was used to analyze the aligned sequences. The *BLA*ST programme was used to compare the nucleotide sequences, and the sequences were then submitted to GENBANK for accession numbers) **[Table 2]**, with a high presence of blaNDM-1 in ICU samples. In the total sample, nearly all isolates (98%) showed positive synergism for Ceftazidime-Avibactam with Aztreonam, indicating high effectiveness of this combination in the tested sample. Among the 13 NDM1 positive isolates, the majority (92.3%) showed synergism with Ceftazidime-Avibactam and Aztreonam across both testing methods, with only one isolate (7.7%) showing no synergism. **[Table 3]** The data indicates a significant prevalence of the **blaNDM1** gene in *Pseudomonas aeruginosa* isolates, particularly from urine samples **[Figure 5]**, with a high correlation between conventional PCR results and phenotypic detection methods in most cases.

Table-2: Genbank Accession Numbers

GenBank Accession Numbers for the Nucleotide Sequences	
BankIt2672344 Seq1	OQ428193
BankIt2672413 Seq2	OQ428194
BankIt2672423 Seq3	OQ428195
BankIt2672427 Seq4	OQ428196

Table-3: CZA-AT synergism by Disc Stacking method and Double Disc Synergy Test

CZA-AT Synergism (n=13)	Disc Stacking Method	Double Disc Synergy Test
POSITIVE	12(92.3%)	12(92.3%)
NEGATIVE	1(7.7%)	1(7.7%)

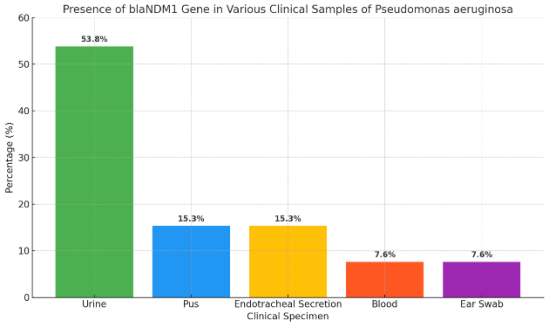

Figure-5: Presence of *bla*NDM1 among the various clinical samples of *Pseudomonas aeruginosa.*

Drug Resistance Patterns: Resistance was highest against ceftazidime (37%), with colistin resistance in 2%. **[Table 4]** Among carbapenem-resistant isolates, 61.9% harboured the blaNDM-1 gene, showing high prevalence rates for this gene in

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 485-490
DoI-10.004687/1000-9035.2025.068

carbapenem-resistant strains.

The mean resistance rate is 22.9% this rate provides an average level of resistance across all antibiotics tested, giving an overall sense of the resistance level among *Pseudomonas aeruginosa* samples. The median resistance rate is 21% it is the middle value when the resistance percentages are ordered from lowest to highest, which helps us understand the central point without being skewed by extreme values. Range of resistance rates is 35% (from 2% to 37%) (The range shows the difference between the highest and lowest resistance rates, which helps capture the spread of resistance rates across different antibiotics.) This indicates that, on average, about 22.91% of *Pseudomonas aeruginosa* samples are resistant to the antibiotics tested, with a median resistance rate of 21%. The wide range (35%) shows considerable variability in resistance, with some antibiotics showing much lower resistance levels (e.g., Colistin at 2%) and others significantly higher (e.g., Ceftazidime at 37%). The identical results between the Disc Stacking Method and the Double Disc Synergy Test provide robust evidence for the synergism of Ceftazidime-Avibactam (CZA) with Aztreonam (AT) in NDM-1 positive isolates.

Table-4: Anti-microbial resistance pattern among *Pseudomonas aeruginosa*

Antibiotics	Resistant	Susceptible
Cefoperazone/sulbactam	22%	78%
Piperacillin / Tazobactam	22%	78%
Ceftazidime	37%	63%
Cefepime	31%	69%
Aztreonam	34%	66%
Imipenem	21%	79%
Meropenem	21%	79%
Colistin	2%	98%
Ciprofloxacin	21%	79%
Amikacin	21%	79%
Ceftazidime-Avibactam	20%	80%

DISCUSSION:

Pseudomonas aeruginosa is one of the most common and challenging pathogens in healthcare, known for causing a wide array of infections and exhibiting resistance to multiple antibiotic classes. The bacterium's intrinsic resistance mechanisms and capacity to acquire additional resistance genes complicate treatment, often necessitating the use of carbapenems as a first-line defence[16]. However, the emergence of carbapenemase-producing strains, particularly those harbouring Metallo-β-lactamase (MBL) genes like blaNDM-1, has greatly limited effective therapeutic options, presenting a significant public health concern. In our study carbapenem-resistant *P. aeruginosa* was accounted in 21% of the clinical isolates, with 61.9% of these carbapenem-resistant strains carrying the blaNDM-1 gene. This aligns with findings from prior studies, including a systematic review by Bea Jorelli U. Fernando et al., which reported a 54.55% prevalence of blaNDM-1 among carbapenem-resistant *P. aeruginosa* in cross-sectional studies [17]. In our study 11 of the *P. aeruginosa* isolates were phenotypically positive for MBL where as 13 of them were positive for blaNDM- gene by PCR. Similar findings were also observed in other studies also[18,19].

In our study *P. aeruginosa* isolates were susceptible to ceftazidime-avibactam (CZA), reflecting similar findings by Patricia García, V. Adámková, and James A. Karlowsky,[20,21] who noted significant activity of CZA against multidrug-resistant *P. aeruginosa* in previous research. The high susceptibility for CZA can be utilized as an effective treatment option for managing *P. aeruginosa* infections, especially in carbapenem-resistant cases. Furthermore, aztreonam was found to be effective in 66% of our isolates. This rate is comparable with the study by C L Terrier who has reported 53.8% aztreonam susceptibility among the *Pseudomonas spp*[22]. still demonstrates its utility as part of combination therapy for multidrug-resistant strains.

Combination therapy of ceftazidime and aztreonam (CZA-AT) showed synergistic effects against most of our isolates, with a 98% synergy rate observed by both Disc Stacking (DS) and Double Disc Synergy Test (DDST) methods. Synergistic effects were particularly evident among isolates positive for the blaNDM-1 gene, with 92.3% of NDM-1-producing strains showing synergistic inhibition. This high synergy rate is comparable to studies like that of Priya Sreenivasan et al.,[23] which documented an 86% synergy rate between CZA and aztreonam among resistant isolates. The use of CZA-AT against NDM-1 producers was also supported from K Lee et al.,[24] who reported an 80% synergy rate with this combination.

The global prevalence of the *bla*NDM-1 gene among carbapenem-resistant *Pseudomonas aeruginosa* varies significantly, influenced by regional antimicrobial practices and infection control policies. For instance, studies from India, such as those by Vijeta Bajpai et al[25]. in 2019 and Lavanya Mohanam et al[26]. in 2017, have reported *bla*NDM-1 as the predominant carbapenemase gene, with a prevalence as high as 54.55% in some hospital settings. Our study showed a relatively lower incidence, with 13% of isolates harbouring *bla*NDM-1 confirmed by conventional PCR, while 11% demonstrated phenotypic evidence of NDM-1 production using the I-EDTA method. The presence of blaNDM-1 is particularly concerning due to its transmissibility and ability to rearrange extensively within bacterial plasmids, making it a high-risk factor for rapid dissemination within healthcare settings[27].

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 485-490
DoI-10.004687/1000-9035.2025.068

Our study's antibiogram analysis showed the highest resistance rates against third-generation cephalosporins, particularly ceftazidime (37%), with varying resistance levels against other antibiotic classes. Notably, colistin resistance was observed in 2% of the isolates, highlighting the limited options remaining for last-resort antibiotics. Narimisa N in his systematic review and meta-analysis has observed a rising trend in colistin resistance among *P. aeruginosa* isolates with prevalence increasing from 2% in 2006–2010 to 5% between 2020 and 2023[28]. Interestingly, both colistin-resistant strains showed synergism towards CZA-AT, suggesting a promising alternative for treating colistin-resistant, carbapenemase-producing *P. aeruginosa*.

CONCLUSION:

P. aeruginosa remains a significant nosocomial pathogen with high multidrug resistance, particularly among ICU patients and those undergoing invasive procedures. The high prevalence of MBL-producing isolates, especially those with blaNDM-1, underscores the need for continuous surveillance, early detection, and stringent infection control practices to mitigate spread. The synergistic effect of CZA-AT presents a potential treatment alternative, particularly for infections involving NDM-1 producers. Clinical microbiologists should incorporate routine resistance screening for optimal antibiotic selection and to minimize the need for toxic alternatives like colistin and polymyxin B. Future studies, encompassing other non-fermenting gram-negative bacteria, could further validate CZA-AT as an effective regimen against a broader range of multidrug-resistant organisms.

Limitations of the study: During our study only 13 of our *P. aeruginosa* carried blaNDM-1 gene thus limiting the statistical significance is one of the limitations of this study. Clinical outcome data of these patients would have strengthened the study, but since the primary aim was to study the *in-vitro* synergy we could not investigate it.

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CONFLICTION OF INTEREST: Nil

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REFERENCES:

1. Koneman EW, Allen SD, Jande WM, et al. *Color Atlas and Textbook of Diagnostic Microbiology*. 5th ed. Philadelphia: Lippincott; 1997. p. 286-7.
2. Vijaya D, Bavani SK, Veena M. Prevalence of nonfermenters in clinical specimens. *Indian J Med Sci*. 2000;54(3):87-91.
3. Walkty A, DeCorby M, Nichol K, Mulvey MR, Hoban D, Zhanel G. Antimicrobial susceptibility of *Pseudomonas aeruginosa* isolates obtained from patients in Canadian intensive care units as part of the Canadian National Intensive Care Unit study. *Diagn Microbiol Infect Dis*. 2008;61(2):217–21.
4. Murray PR, Baron EJ, Jorgensen JH, et al. *Manual of Clinical Microbiology*. Washington, DC: ASM Press; 2007. p. 749-69.
5. Singhal R, Mohanty S, Sood S, et al. *Indian J Med Res*. 2005;121:63-4.
6. Cohen J, Powderly WG. *Infectious Diseases*. 2nd ed. London: Mosby Publications; 2004.
7. El Chakhtoura NG, Saade E, Iovleva A, Yasmin M, Wilson B, Perez F, et al. Therapies for multidrug-resistant and extensively drug-resistant non-fermenting gram-negative bacteria causing nosocomial infections: a perilous journey toward 'molecularly targeted' therapy. *Expert Rev Anti Infect Ther*. 2018;16(2):89-110.
8. Ehmann DE, Jahić H, Ross PL, Gu RF, Hu J, Kern G, et al. Avibactam is a covalent, reversible, non–β-lactam β-lactamase inhibitor. *Proc Natl Acad Sci USA*. 2012;109(29):11663–8.
9. Lahiri SD, Johnstone MR, Ross PL, McLaughlin RE, Olivier NB, Alm RA. Avibactam and Class C β-Lactamases: Mechanism of Inhibition, Conservation of the Binding Pocket, and Implications for Resistance. *Antimicrob Agents Chemother*. 2014;58(10):5704-13.
10. Marshall S, Hujer AM, Rojas LJ, Papp-Wallace KM, Humphries RM, Spellberg B, et al. Can ceftazidime-avibactam and aztreonam overcome β-lactam resistance conferred by metallo-β-lactamases in Enterobacteriaceae? *Antimicrob Agents Chemother*. 2017;61(4)
11. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. 31st ed. CLSI supplement M100. Wayne, PA: CLSI; 2021.
12. Thapa P, Bhandari D, Shrestha D, Parajuli H, Chaudhary P, Amatya J, et al. A hospital-based surveillance of metallo-beta-lactamase producing gram-negative bacteria in Nepal by imipenem-EDTA disk method. *BMC Res Notes*. 2017;10(1):322.
13. Mayer I, Nagy E. Investigation of the synergic effects of aminoglycoside-fluoroquinolone and third-generation cephalosporin combinations against clinical isolates of *Pseudomonas* spp. *J Antimicrob Chemother*. 1999;43(5):651-7.
14. Altoparlak U, Aktas F, Celebi D, Ozkurt Z, Akcay MN. Prevalence of metallo-beta-lactamase among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolated from burn wounds and in vitro activities of antibiotic combinations against these isolates. *Burns*. 2005;31(6):707-10.
15. Elmonir W, Shalaan S, Tahoun A, Mahmoud SF, Remela EMA, Eissa R, et al. Prevalence, antimicrobial resistance, and genotyping of Shiga toxin-producing *Escherichia coli* in foods of cattle origin, diarrheic cattle, and diarrheic humans in Egypt. *Gut Pathog*. 2021;13(1):8.
16. Souza GH de A de, Rossato L, Brito GT, Bet GMDS, Simionatto S. Carbapenem-resistant *Pseudomonas aeruginosa* strains: a worrying health problem in intensive care units. *Rev Inst Med Trop Sao Paulo*. 2021;63
17. Fernando BJU, Antonio MOB, Guzman KMAD, Gatbonton JCY, Vendivil ST, Tiongco REG, et al. The prevalence of blaNDM-1 in clinical isolates of carbapenem-resistant *Pseudomonas aeruginosa*: a systematic review. *SciMedicine J*. 2021;3(4):387-98.
18. Aggarwal A, Bhalla M, Fatima KH. Detection of New Delhi metallo-β-lactamase enzyme gene *blaNDM-1* associated with the *Int-1* gene in Gram-negative bacteria collected from the effluent treatment plant of a tuberculosis care hospital in Delhi, India. *Access Microbiol*.

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 485-490
DoI-10.004687/1000-9035.2025.068

2020;2(2):000125. doi:10.1099/acmi.0.000125.
19. Shenoy KA, Jyothi EK, Ravikumar R. Phenotypic identification & molecular detection of bla (ndm-1) gene in multidrug resistant Gram-negative bacilli in a tertiary care centre. Indian J Med Res. 2014 Apr;139(4):625-31. PMID: 24927351; PMCID: PMC4078503.
20. Adámková V, Mareković I, Szabó J, Pojnar L, Billová S, Horvat Herceg S, et al. Antimicrobial activity of ceftazidime-avibactam and comparators against *Pseudomonas aeruginosa* and *Enterobacterales* collected in Croatia, Czech Republic, Hungary, Poland, Latvia, and Lithuania: ATLAS Surveillance Program, 2019. *Eur J Clin Microbiol Infect Dis*. 2022;41(6):989-96.
21. Karlowsky JA, Kazmierczak KM, Valente MLN de F, Luengas EL, Baudrit M, Quintana A, et al. In vitro activity of ceftazidime-avibactam against *Enterobacterales* and *Pseudomonas aeruginosa* isolates collected in Latin America as part of the ATLAS global surveillance program, 2017–2019. *Braz J Infect Dis*. 2021;25(6):101647.
22. Le Terrier C, Nordmann P, Poirel L. In vitro activity of aztreonam in combination with newly developed β-lactamase inhibitors against MDR Enterobacterales and Pseudomonas aeruginosa producing metallo-β-lactamases. J Antimicrob Chemother. 2022 Dec 23;78(1):101-107. doi: 10.1093/jac/dkac360. PMID: 36308322.
23. Sreenivasan P, Sharma B, Kaur S, Rana S, Biswal M, Ray P, et al. In vitro susceptibility testing methods for the combination of ceftazidime-avibactam with aztreonam in metallo-beta-lactamase producing organisms: role of combination drugs in antibiotic resistance era. *J Antibiot (Tokyo)*. 2022;75(8):454-62.
24. Lee K, Lim YS, Yong D, Yum JH, Chong Y. Evaluation of the Hodge test and the imipenem-EDTA double-disk synergy test for differentiating metallo-beta-lactamase-producing isolates of *Pseudomonas* spp. and *Acinetobacter* spp. *J Clin Microbiol*. 2003;41(10):4623-9.
25. Bajpai V, Govindaswamy A, Khurana S, Batra P, Aravinda A, Katoch O, Hasan F, Malhotra R, Mathur P. Phenotypic & genotypic profile of antimicrobial resistance in *Pseudomonas* species in hospitalized patients. Indian J Med Res. 2019 Feb;149(2):216-221. doi: 10.4103/ijmr.IJMR_1_18. PMID: 31219086; PMCID: PMC6563739.
26. Mohanam L, Menon T. Coexistence of metallo-beta-lactamase-encoding genes in *Pseudomonas aeruginosa*. *Indian J Med Res*. 2017;146(Suppl)
27. Li, Y., Yang, Y., Wang, Y. *et al.* Molecular characterization of bla_{NDM}-harboring plasmids reveal its rapid adaptation and evolution in the Enterobacteriaceae. *One Health Adv.* **1**, 30 (2023). https://doi.org/10.1186/s44280-023-00033-9
28. Narimisa N, Keshtkar A, Dadgar-Zankbar L, Bostanghadiri N, Far YR, Shahroodian S, Zahedi Bialvaei A, Razavi S. Prevalence of colistin resistance in clinical isolates of *Pseudomonas aeruginosa*: a systematic review and meta-analysis. Front Microbiol. 2024 Oct 9;15:1477836. doi: 10.3389/fmicb.2024.1477836. PMID: 39473844; PMCID: PMC11520190.