# Study of metallo β lactamase producing pseudomonas aeruginosa and antimicrobial resistance pattern isolated from various clinical specimens at a tertiary care Hospitals Udaipur, Rajasthan

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**Abstract**

**Background:** The most prevalent mechanism of carbapenem resistance is the development of metallo-β lactamase. Metallo- β lactamase is an Ambler class B zinc-dependent enzyme that can hydrolyze all β lactam antibiotics, including carbapenem.

**Objective:** The purpose of this study was to identify metallo β lactamase producing pseudomonas aeruginosa and antimicrobial resistance pattern isolated from various clinical specimens at a tertiary care hospital in Udaipur, Rajasthan.

**Methodology:** In this study we have analyzed 1000 samples from various clinical samples (Urine, Endrotracheal, Tracheostomy, Pus, Sputum, and C.S.F) and isolate 625 samples of pseudomonas species. Out of 625 samples 506 samples are of *Pseudomonas aeruginosa*. These 506 samples were further processed for detection of extended spectrum beta lactamase, metallo beta lactamase and AMPc beta lactamase.

**Result:** Out of total 506 samples, we found 151 (29.84%) samples were positive for the extended spectrum beta lactamase (ESBL), 61 (12.05%) samples were positive for metallo beta lactamase (MBL) formation and 125 (24.70%) samples were positive for AMPc beta lactamase. Highest resistance were observed against gefotaxime (55.53%), tigycycline (54.94%) and ceftazidime (51.97%).

**Conclusion:** A routine MBL production test and further research for new antimicrobial drug (which should be less harmful) are needed.

**Keywords:** Metallo beta lactamase, carbapenem resistance, antimicrobial resistance

## 1. Introduction

Pseudomonas are gram-negative bacilli that are stringent aerobes, motile with one or two flagella, oxidatively use glucose, and are oxidase positive. It is a member of the Pseudomonadaceae family and belongs to the fluorescence group of r RNA group I in molecular taxonomy. [1] Pseudomonas fluorescence and Pseudomonas putida are also

members of this Fluorescent group, however they are seldom associated in clinical illnesses in humans. These bacteria are responsible for 10% of all infections in hospitals, including community-based infections like otitis externa, keratitis, and varicose vein ulcers. They also cause hospital-acquired infections like catheter-associated urinary tract infections (CAUTI), ventilator-associated pneumonia (VAP), burn infections, bedsore, septicaemia, and necrotising pneumonia in cystic fibrosis patients. Their sophisticated Quorum sensing system enables them to rapidly build biofilm and avoid antibiotic attack. Their ability to withstand or use disinfectants/antiseptics like cetrimide for nutrition makes them a prominent presence in the hospital environment and ICU. [2]

Pseudomonas aeruginosa is a bacteria that has been linked to a number of illnesses, including septicemia [3, 4], chronic suppurative otitis media [5, 6], cystic fibrosis [7, 8] and pneumonia [9]. P. aeruginosa infections have been treated with aminoglycosides, fluroquinolones, cephalosporins and carbapenems [3, 7, 8]. However, *P. aeruginosa* susceptibility to β-lactams, carbapenems, quinolones and aminoglycosides has been observed to be lower in several countries [4, 9]. Because of its particular anti-pseudomonal effect, ceftazidime is the most commonly recommended cephalosporin in the treatment of pseudomonal infections. However, resistance to ceftazidime has been steadily growing in recent years [5, 10].

Resistance to several medicines is typically caused by the combination of various mechanisms in a single isolate [11]. Overexpression of efflux pump [12], acquisition of Extended-Spectrum β-Lactamases (ESBLs) and Metallo-β-Lactamases (MBLs) [13], and target site or outer membrane alteration [11] are among the processes implicated in *P. aeruginosa* resistance.

The most prevalent mechanism of carbapenem resistance is the development of metallo-β lactamase. Metallo-β lactamase is an Ambler class B zinc-dependent enzyme that can hydrolyze all β lactam antibiotics, including carbapenem8. Ambler class A,C,D β lactamases employ serine as an active site, making them easily destroyed by β lactamase inhibitors such as clavulanic acid or sulbactam. However, because clavulanic acid and sulbactum do not block metallo-β lactamase, MBL generating Pseudomonas has emerged as a nightmare for treating physicians. Furthermore, the MBL resistance determinant is found in a highly mobile genetic region, allowing for simple transmission from patient to patient or even from patient to health care provider. As a result, prevention is always preferable to treatment of MBL Pseudomonas infection. [14]

IMP, VIM, SPM, GIM and SIM are five separate forms of MBLs whose prevalence is quickly growing. The most common of them are IMP and VIM. With the global growth in the prevalence and varieties of MBLs, early diagnosis is critical, with the benefits of prompt application of strong infection control practises and treatment with alternative antimicrobials. MBL producers can be identified using molecular methods. These, however, are not accessible in smaller centres. [15]

Clinicians in every hospital should be aware of the local incidence of MBL generating Pseudomonas in order to develop an appropriate antibiotic policy and infection control plan to avoid the spread of this hazardous superbug. With this in mind, we

undertook a study of metallo β lactamase producing pseudomonas aeruginosa and antimicrobial resistance pattern isolated from various clinical specimens at a tertiary care hospital in Udaipur, Rajasthan.

## 2. Material and Methods

**Study design:** The study was conducted from May 2020 to December 2022, in the department of Microbiology, Pacific Medical College and Hospital, Udaipur. It was done on various clinical samples of IPD and OPD patients. Complete data about the patients such as name, age, sex, date, time of collection, source of specimen and details about the clinical history was recorded. Various clinical samples like Urine, Endotracheal, Blood, Pus, Sputum, and CSF were collected by aseptic technique in sterile container except blood which is collected in blood culture bottle.

**Sample size:** In our research study we have analyzed 1000 samples from various clinical samples (Urine, Endrotracheal, Tracheostomy, Pus, Sputum, and C.S.F) and isolate 625 samples of pseudomonas species. Out of 625 samples 506 samples are of *Pseudomonas aeruginosa*. These 506 samples were further processed for detection of extended spectrum beta lactamase, metallo beta lactamase and AMPc beta lactamase.

**Inclusion criteria:** Pseudomonas species were isolated from clinical samples according to CLSI guidelines for detection of antimicrobial resistance in Pseudomonas species.

**Exclusion criteria:** Those samples which contents contamination and environmental flora which were excluded from study plan and do not process further for detection.

**Identification:** Isolated bacterial strains were identified on the basis of their morphological and biochemical characteristics.

Morphological identifications were done on the basis of following criteria:

1. Shape of the colony
2. Size of the colony
3. Hemolysis
4. Color
5. Transparency

Biochemical characterizations were based on following observations:

1. Gram staining
2. Catalase test
3. Oxidase test
4. Triple Sugar Iron test
5. Motility indole urease test
6. Nitrate Reduction test
7. Simmons Citrate test
8. MRVP test

9. Hemolysis test

**Antimicrobial susceptibility testing:** Antimicrobial susceptibility testing was done on Mueller Hinton agar (MHA) according to CLSI guidelines for Kirby Buer disc diffusion test. After 24 hours of incubation zone of inhibition were measured.

**Detection of metallo-β-lactamase in pseudomonas species**

**ESBL detection:** ESBL was detected by application of 3$^{rd}$ generation Cephalosporin alone and with combination with beta lactamase inhibiter such as clavulanic acid.

**Procedure:** 2-3 well isolated colonies were suspended in 0.5 ml of sterile broth and the turbidity matched to 0.5 McFarland standards. Using a sterile cotton swab, the broth culture was uniformly spread on the sterility checked Mueller Hinton Agar plate. Ceftazidime alone and in combination with Clavulanic acid was placed at a distance of 20 mm from center to center. Plates were incubated at 37 $^{o}$C overnight. A measurement of ≥ 5mm increase in zone diameter for Ceftazidime with Clavulanic acid versus Ceftazidime zone when tested alone, confirms an ESBL producing organism.

**AMPc detection:** AMPc resistance was detected as per CLSI guidelines of antimicrobial application alone and with EDTA.

**MBL detection:** Metallo-beta lactamase was detected on MHA with Carbapenem alone and with carbapenem with EDTA. Their zone difference is more or equal to 5mm.

**Procedure:** The test organism was inoculated on to Mueller-Hinton agar plate as recommended by the CLSI. Two imipenem (10 µg) discs were placed at a distance of 20 mm center to center on the plate. 10 µL of 0.5M EDTA (750 µg) solution was added to one of imipenem disc and incubated overnight at 37 $^{o}$C. Enhancement of the zone of inhibition of imipenem-EDTA disc compared to that of imipenem disc alone by ≥ 7mm was considered positive for MBL production.

## 3. Result

Out of total 506 *Pseudomonas aeruginosa* isolates were found in study in which 371 samples were isolated from males which make 73.32% percentage. Females were 135 which were 26.67% samples of Pseudomonas aeruginosa patients.

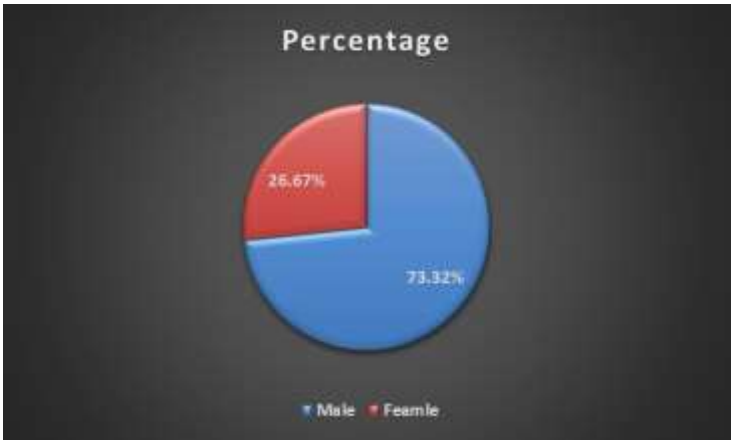


**Fig 1:** Sex wise distribution of Pseudomonas aeruginosa species

Out of total 506 samples, we found 151 (29.84%) samples were positive for the extended spectrum beta lactamase (ESBL), 61 (12.05%) samples were positive for metallo beta lactamase (MBL) formation and 125 (24.70%) samples were positive for AMPc beta lactamase.

**Table 1:** ESBL, MBL and AMPc production of Pseudomonas aeruginosa

| S.N. | Types of resistant | Sample | Percentage |
|---|---|---|---|
| **1** | ESBL | 151 | 29.84% |
| **2** | MBL | 61 | 12.05% |
| **3** | AMPc | 125 | 24.70% |

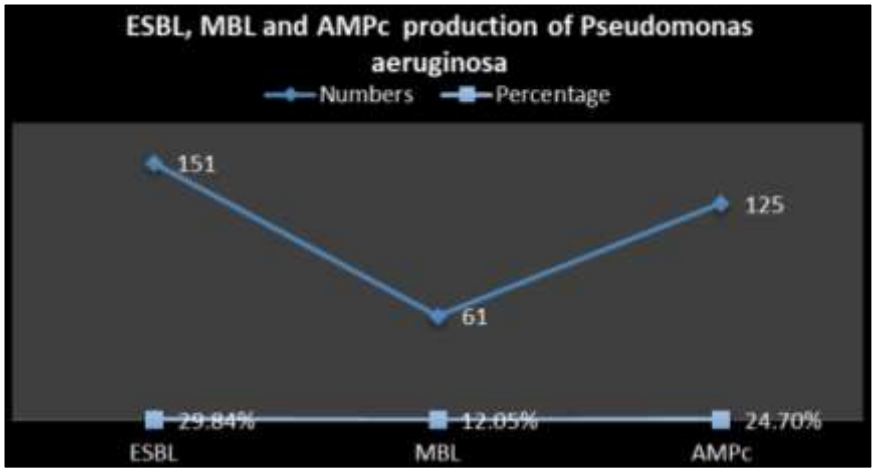


**Fig 2:** ESBL, MBL and AMPc production of Pseudomonas aeruginosa

Our study found that the age group between 0-10 years contains 11(2.17%) samples positive for *P. aeruginosa*. In the age group between 11-20 years 13 (2.56%) samples were positive for *P. aeruginosa*. In the age group 21-30 years, 60 (11.85%) samples were positive for *P. aeruginosa*. In the age group between 31-40 years, 65 (12.84%) samples were positive for *P. aeruginosa.* In the age group between 41-50 years, 66

(13.04%) samples were positive for *P. aeruginosa*. In the age group between 51-60 years, 69 (13.63%) samples were positive for *P. aeruginosa*. In the age group between 61-70 years, 113 (22.33%) samples were positive for *P. aeruginosa*. In the age group between 71-80 years, 67 (13.24%) samples were positive for *P. aeruginosa*. In the age group between 81-90 years, 42 (8.30%) samples were positive for *P. aeruginosa.* In the age group between 91-100 years, 0 (0%) sample was positive for *P. aeruginosa*.

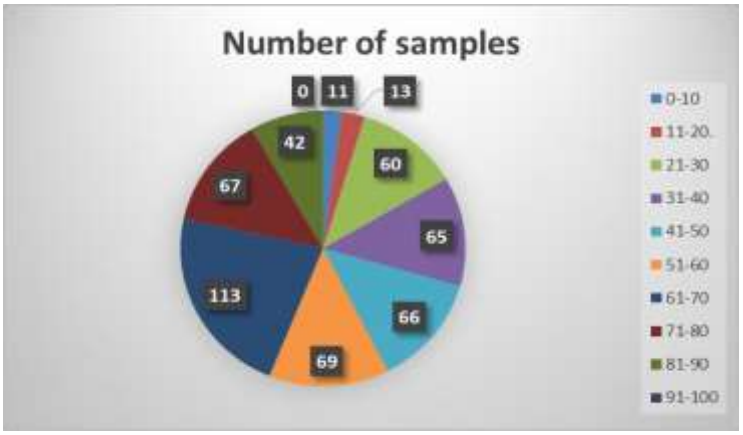


**Fig 3:** Age wise distribution of Pseudomonas aeruginosa samples

In our research study we found 440 samples which belong from indoor department that forms 86.95% percentages of sample and outpatients department contains 66 samples which form 13.04% percentage of total sample that includes IPD and OPD. IPD patients contains major portion of isolates.

**Antibiotic resistance and sensitivity pattern:** In our study, we found that Amikacin showed resistance in 163 (32.21%) samples and sensitivity in 339 (66.99%) samples out of 506 total *P. aeruginosa* positive samples. Gentamicin showed resistance in 158 (31.22%) and sensitivity in 347 (68.57%) samples out of 506 samples. Ciprofloxacin showed resistance in 183 (36.16%) samples and sensitivity in 309 (61.06%) samples out of 506 samples. Ofloxacin showed resistance in 188 (37.15%) samples and sensitivity in 291 (57.50%) samples out of 506 samples. Levofloxacin showed resistance in 170 (33.59%) samples and sensitivity in 315 (62.25%) samples out of 506 samples. Moxifloxacin showed resistance in 151 (29.84%) samples and sensitivity in 341 (67.39%) out of 506 samples. Norfloxacin showed resistance in 120 (23.71%) samples and sensitivity in 126 (24.90%) samples out of 506 samples. Cefepime showed resistance in 221 (43.67%) samples and sensitivity in 274 (54.15%) samples out of 506 samples. Erythromycin showed resistance in 169 (33.39%) samples and sensitivity in 163 (32.21%) samples out of 506 samples. Clindamicin showed resistance in 183 (36.16%) samples and sensitivity in 145 (28.65%) samples out of 506 samples. Cefotaxime showed resistance in 281 (55.53%) samples and sensitivity in 219 (43.28%) samples out of 506 samples. Ceftazidime showed resistance in 263 (51.97%) samples and sensitivity in 239 (47.23%) samples out of 506 samples. Ceftazidime with Clavulanic acid showed resistance in 175 (34.58%)

samples and sensitivity in 323 (63.83%) samples out of 506 samples. Tigycycline showed resistance in 278 (54.94%) samples and sensitivity in 224 (44.26%) samples out of 506 samples. Polymyxin B showed resistance in 88 (17.39%) samples and sensitivity in 411 (81.22%) samples out of 506 samples. Colistin showed resistance in 107 (21.14%) samples and sensitivity in 395 (78.06%) samples out of 506 samples. *Ticarcillin clavulanic* acid showed resistance in 185 (36.56%) samples and sensitivity in 317 (62.64%) samples out of 506 samples. *Piperacillin tazobactam* showed resistance in 88 (17.39%) samples and sensitivity in 117 (23.12%) samples out of 506 samples.

**Table 2:** Resistance and sensitivity Patterns of Antibiotics

| S.N. | Antibiotics | Code | Resistance | Percentage | Sensitive | Percentage |
|---|---|---|---|---|---|---|
| 1 | AMIKACIN | AMK | 163 | 32.21% | 339 | 66.99% |
| 2 | GENTAMICIN | GNT | 158 | 31.22% | 347 | 68.57% |
| 3 | CIPROFLOXACIN | CIPRO | 183 | 36.16% | 309 | 61.06% |
| 4 | OFLOXACIN | OFL | 188 | 37.15% | 291 | 57.50% |
| 5 | LEVOFLOXACIN | LEV | 170 | 33.59% | 315 | 62.25% |
| 6 | MOXIFLOXACIN | MOX | 151 | 29.84% | 341 | 67.39% |
| 7 | NORFLOXACIN | NOR | 120 | 23.71% | 126 | 24.90% |
| 8 | CEFEPIME | CEF | 221 | 43.67% | 274 | 54.15% |
| 9 | ERYTHROMYCIN | ERY | 169 | 33.39% | 163 | 32.21% |
| 10 | CLINDAMYCIN | CLIN | 183 | 36.16% | 145 | 28.65% |
| 11 | CEFOTAXIME | CEFO | 281 | 55.53% | 219 | 43.28% |
| 12 | CEFTAZIDIME | CTZ | 263 | 51.97% | 239 | 47.23% |
| 13 | TIGYCYCLINE | TIGY | 278 | 54.94% | 224 | 44.26% |
| 14 | POLYMYXIN B | POL | 88 | 17.39% | 411 | 81.22% |
| 15 | COLISTIN | COL | 107 | 21.14% | 395 | 78.06% |
| 16 | CEFTAZIDIME CLAVULANIC ACID | CCA | 175 | 34.58% | 323 | 63.83% |
| 17 | TICARCILLIN CLAVULANIC ACID | TCA | 185 | 36.56% | 317 | 62.64% |
| 18 | PIPERACILLIN TAZOBACTAM | PTZ | 87 | 17.19% | 117 | 23.12% |
| 19 | MEROPENEM | MRP | 102 | 20.19% | 421 | 83.20% |
| 20 | ERTEPENEM | ERT | 178 | 35.17% | 408 | 80.63% |
| 21 | AZTREONAM | AZT | 88 | 17.39% | 302 | 59.68% |
| 22 | COTRIMOXAZOLE | COT | 257 | 50.79% | 418 | 82.60% |
| 23 | NITROFURANTION | NIT | 99 | 19.56% | 237 | 46.83% |
| 24 | IMIPENEM | IMI | 164 | 32.41% | 113 | 22.33% |
| 25 | IMIPENEM EDTA | IMEDTA | 72 | 14.22% | 164 | 32.41% |
| 26 | CEFOXITIN | CXT | 164 | 32.41% | 164 | 32.41% |
| 27 | CEFOXITIN EDTA | CXTEDTA | 96 | 18.97% | 164 | 32.41% |
| 28 | TOBRAMYCIN | TOB | 145 | 28.65% | 363 | 71.73% |

Meropenem showed resistance in 102 (20.19%) samples and sensitivity in 421 (83.20%) samples out of 506 samples. Ertepenem showed resistance in 178 (35.17%) samples and sensitivity in 408 (80.63%) samples out of 506 samples. Aztreonam showed resistance in 88 (17.39%) samples and sensitivity in 302 (59.68%) samples out of 506 samples. Cotrimoxazole showed resistance in 257 (50.79%) samples and sensitivity in 418 (82.60%) samples out of 506 samples. Nitrofurantoin showed resistance in 99 (19.56%) samples and sensitivity in 237 (46.83%) samples out of 506 samples. Imipenem showed resistance in 164 (32.41%) samples and sensitivity in 354 (69.96%) samples out of 506 samples. Imipenem EDTA showed resistance in 72 (14.22%) samples and sensitivity in 472 (93.28%) samples out of 506 samples. Cefoxitin showed resistance and sensitivity in 164 (32.41%) samples respectively, out of 506 samples.

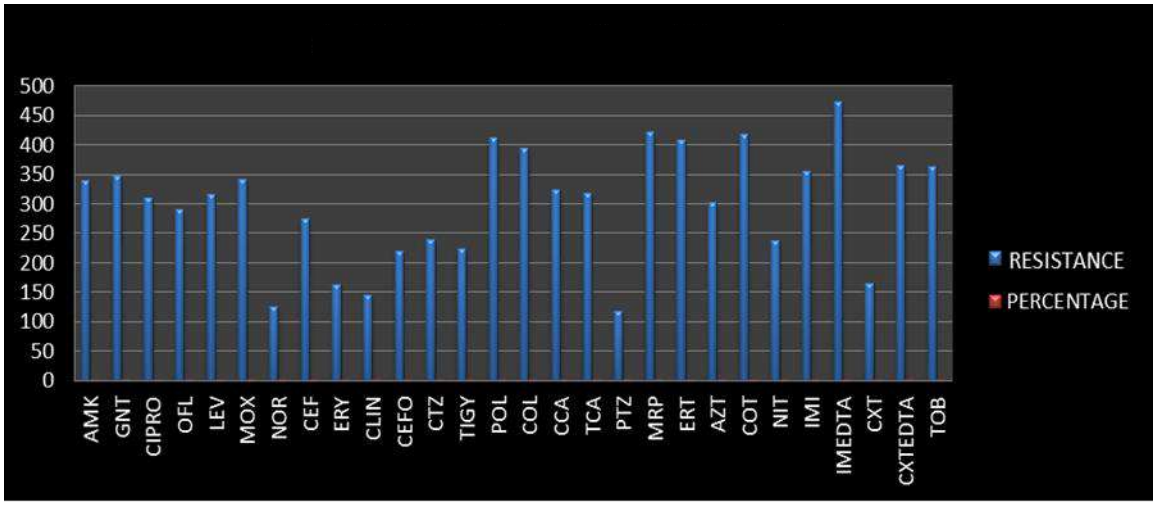


**Fig 4:** Antibiotic resistance pattern of *P. aeruginosa*

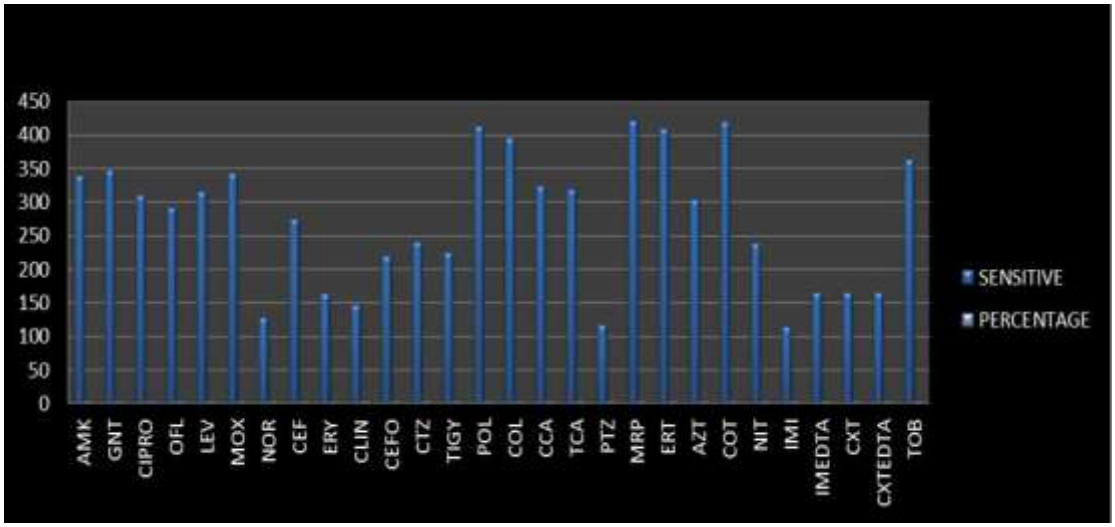


**Fig 5:** Antibiotic sensitivity pattern of *P. aeruginos*

Cefoxitin EDTA showed resistance in 96 (18.97%) samples and sensitivity in 164 (32.41%) samples out of 506 samples. Tobramycin showed resistance in 145 (28.65%) samples and sensitivity in 363 (71.73%) samples out of 506 samples.

## 4. Discussion

The rise of multi-drug resistant Pseudomonas aeruginosa has confounded treatment decisions and may result in treatment failures. In the current study, 506 clinical isolates of *P. aerugionsa* were obtained from diverse clinical specimens and screened for ESBLs and MBLs. According to the findings of this investigation, 29.84% of the isolates were ESBL positive, in contrast to an earlier study that indicated 20.27% of ESBL production in *P. aeruginosa* [16]. Furthermore, 12.05% of the isolates were MBL producers, according to our findings. Several studies [17, 18] found that the frequency of MBLs in *P. aeruginosa* ranged from 7.5 to 20.8%. Our findings clearly suggest that the prevalence of ESBL and MBL in P. aeruginosa has been rising, resulting in a higher risk of infection.

MBL is particularly common in ICU settings, as well as in immunocompromised patients and infants, whereas it is less common in OPD samples. In comparison to other research, like Navaneeth BV *et al*. [19] (12%), Shashikala *et al*. [20] (10.9%, ami varaiya *et al*. [16] (20.8%), Deeba bhashir *et al*. [22] (11.66%) and choudhary *et al*. [23] (12.05%), the proportion of MBL Pseudomonas aeruginosa in total samples from ICU patients was lower (5.21%). The reason for this was that the incidence was measured as a proportion of total Non-fermenting Gram negative bacilli rather than total *P. aeruginosa* strains.

Carbapenem hydrolyzing MBLs have emerged as the most important mechanism for carbapenem resistance, as recently reported globally. The creation of MBL by Pseudomonas aeruginosa has enormous therapeutic repercussions, resulting in no other alternative for therapy other than some antibiotics with severe side effects and no magic bullet. Other gram negative bacteria are resistant to carbapenems because they have other antibiotic resistance genes, and the only treatment options available are potentially hazardous medicines such as Polymyxin B and Colistin. When compared to a research done by Varaiya A *et al*., [21] the piperacillin/tazobactam combination had the highest sensitivity (53%) across MBL positive and negative isolates.

Among the other medicines, piperacillin/tazobactum exhibited the highest in vitro susceptibility. In reality, combining antibiotics may lead to overuse and the establishment of drug resistance. Combination treatment should adequately cover relevant infections for maximum impact while minimising the potential for drug resistance.

## 5. Conclusion

Our findings show that the prevalence of ESBL and MBL mediated resistance among P. aeruginosa is growing, and that the medications widely used to treat *P. aeruginosa* infections are becoming resistant. Piperacillin/tazobactum has the highest *in vitro* susceptibility, but combining antibiotics may lead to overuse and drug resistance. So

that a routine MBL production test and further research for new antibiotics (which should be less harmful) are needed.

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