

Antibiotic Susceptibility Pattern and Clinical Profile of *Pseudomonas aeruginosa* Isolated from Lower Respiratory Tract Samples: A Cross-sectional Study

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ABSTRACT

Introduction: *Pseudomonas aeruginosa* can cause respiratory tract infections, skin infections in burns and blood stream infections. Respiratory tract infections, skin infections in burns and blood stream infections by *P. aeruginosa* are major causes of morbidity and mortality in immunocompromised patients. Emerging resistance to different drugs is becoming a major problem worldwide.

Aim: To assess about the pattern of antibiotic susceptibility of *P. aeruginosa* isolated from lower respiratory tract.

Materials and Methods: The present cross-sectional study was conducted in Amala Institute of Medical Sciences Thrissur, Kerala, India, a tertiary care centre for a period of six months, from December 2022 to May 2023 after obtaining ethical clearance. Out of 2236 lower respiratory tract samples, 71 *P. aeruginosa* isolates cultured from sputum and bronchial wash from inpatients of General Medicine, Respiratory Medicine and Pulmonary Medicine who were included in the study by consecutive sampling method. *Pseudomonas aeruginosa* were isolated from lower respiratory tract samples, identified and antibiotic susceptibility testing was done by manual and automated methods. History and clinical details of patients were collected from wards and Intensive Care Unit (ICUs) by using a

proforma after getting informed consent from them. Descriptive statistics were used to determine the antibiotic susceptibility pattern of the isolates and to analyse the clinical profile of the patients. Similar study of this kind has not been published from Central Kerala recently.

Results: In a six month period, out of 2236 lower respiratory tract samples, 71 *Pseudomonas aeruginosa* were included in the study. Mean age was 64 years. A total of 29 (40%) patients had the habit of smoking, 25 (35%) had Chronic Obstructive Pulmonary Disease (COPD), 16 (23%) had bronchiectasis. One patient had cystic fibrosis, 29 (41%) had a clinical diagnosis of pneumonia. Susceptibility of different antibiotics was as follows: Meropenem-89%, Imipenem-80%, Ciprofloxacin-85%, Ceftazidime-37% Piperacillin tazobactam and Cefaperozone sulbactam-39%. Multidrug Resistant (MDR) strains were 14 (20%).

Conclusion: This study revealed that, three fourths of the patients had chronic respiratory illness. Meropenem and Amikacin were the most susceptible drugs. Several treatment options are now available for difficult to treat *Pseudomonas*, but the increasing rates of resistance is a major concern to be addressed.

Keywords: Antibiotic resistance, Bronchiectasis, Pneumonia

INTRODUCTION

Pseudomonas is a predominant inhabitant of soil and aquatic environments. Different species of *Pseudomonas* are there like *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Pseudomonas fluorescens*, and *Pseudomonas stutzeri*. *Pseudomonas aeruginosa* (*P. aeruginosa*) is an aerobic Gram negative motile bacilli capable of infecting any system. Respiratory tract infections, skin infections in burns and blood stream infections by *P. aeruginosa* are major causes of morbidity and mortality in immunocompromised patients. Since this organism prefers moist atmosphere, it is present in hospital environments like sinks, showers and respiratory equipments and can cause healthcare associated infections.

The prevalence of *P. aeruginosa* isolated from respiratory samples among patients with Community Acquired Pneumonia (CAP) ranges from 3.8 to 5.5% in different parts of the world [1]. *P. aeruginosa* has a prevalence rate of 7.1-7.3% amongst all healthcare associated infections like pneumonia, surgical site infections, urinary tract infections [2]. *P. aeruginosa* can act like a commensal or pathogen in patients with chronic lung diseases like bronchiectasis and Chronic Obstructive Pulmonary Disease (COPD). It can also cause pneumonia in previously healthy individuals. As per the local hospital antibiogram,

P. aeruginosa is a leading microorganism isolated from the respiratory samples of outpatient, inpatient and ICU patients with pulmonary pathology. A large international study conducted by Vincent JL et al., about aetiology of infections in ICU patients found that *P. aeruginosa* was the cause of 23% of all infections acquired from ICU. Most common site of *P. aeruginosa* infections was respiratory tract [3]. A prospective observational study conducted in 28 ICUs in the USA found that *P. aeruginosa* was the cause of 11% of all healthcare associated pneumonia or ventilator associated pneumonia in ICU patients second only to *Staphylococcus aureus* [4].

Strains of *P. aeruginosa* can be resistant to many drugs because of its different virulence factors like pili, flagella, secretion systems, endotoxin (lipopolysaccharide) and alginate [5]. *P. aeruginosa* is known to produce biofilms which causes difficulty in treatment of the infections caused by this organism. Biofilm formation is an intricate process which involves many chemicals. Biofilm increases bacterial tolerance to environmental threats, by forming microcolonies and also promotes the transfer of antibiotic resistance genes between bacterial species [6].

The aim of the study was to assess the pattern of antibiotic susceptibility of *P. aeruginosa* isolated from lower respiratory tract.

The primary objective of the study was to analyse the antibiotic susceptibility pattern of *P. aeruginosa* isolates. The secondary objective of the study was to study the clinical profile of those patients from whom *P. aeruginosa* were isolated.

MATERIALS AND METHODS

The present cross-sectional study was conducted at Amala Institute of Medical Sciences, Thrissur, Kerala, India for a period of six months from December 2022 to May 2023, after obtaining ethical clearance. (No.17/EC/22/AIMS - 02 dated 31-10-2022 Date of Ethical Board review: 29-10-2022). Informed consent was taken from patients before collecting data from them.

Sample size calculation:

$$n = \frac{(Z_{1-\alpha/2})^2 p.q}{d^2}$$

p = Proportion sensitivity to Piperacillin – Tazobactam (58%)

(Resistance of Piperacillin – Tazobactam is 42%, so sensitivity is 100-42=58) [7]

q = 1-p

d = Relative precision (20%)

1- $\alpha/2$ = Desired confidence interval 95%

n = 70

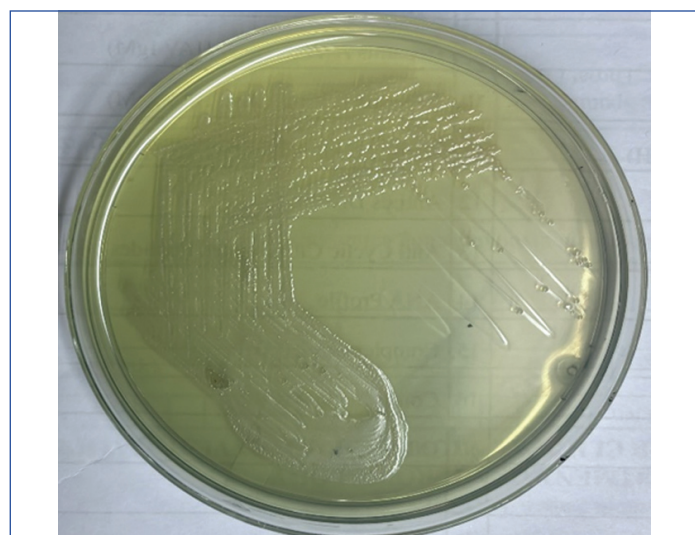
Inclusion criteria: *P. aeruginosa* isolates cultured from sputum and bronchial wash samples over the six month period from December 2022 to May 2023 from inpatients of General Medicine, Respiratory Medicine and Pulmonary Medicine.

Exclusion criteria: Patients who were not able to give adequate data like history of smoking, hospitalisation, respiratory illness, use of inhalers, dialysis etc.,

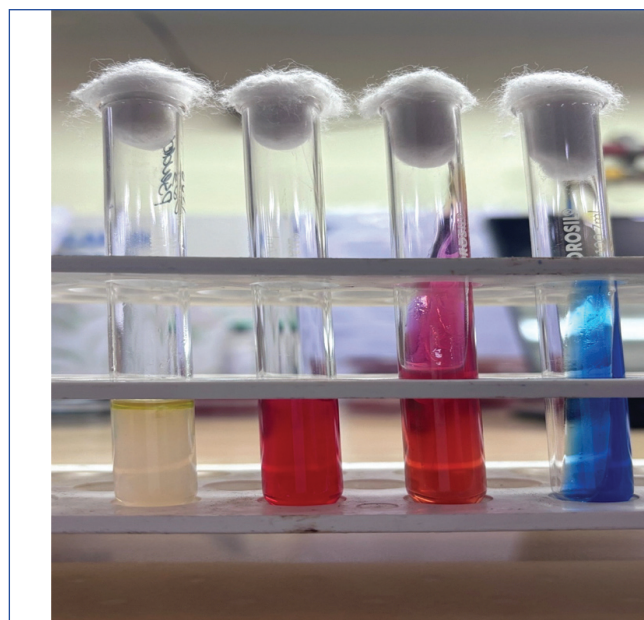
Only one isolate per patient was included in the study. Informed consent was taken from the patients before proceeding with the isolates.

Study Procedure

Lower respiratory tract samples, which included bronchial wash samples collected by flexible bronchoscopy under aseptic precautions and sputum samples received in the Microbiology Lab were processed according to the lab Standard Operating Procedure (SOP). *P. aeruginosa* was identified by standard methods like colony morphology, characteristic pyocyanin production [Table/Fig-1] and odour, biochemical reactions like positive oxidase reaction and citrate utilisation. Indole was not produced, mannitol was usually not fermented, there was lack of acid production in Triple Sugar Iron Agar (TSI) [Table/Fig-2] [8].

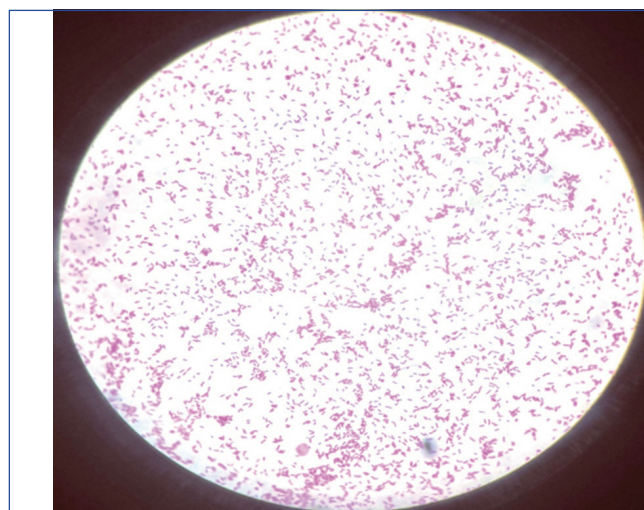


[Table/Fig-1]: *P. aeruginosa* on nutrient agar plate showing greenish colour due to Pyocyanin pigment.



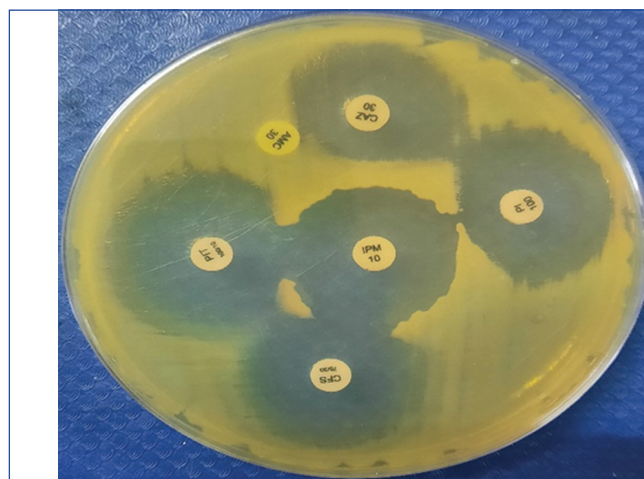
[Table/Fig-2]: Biochemical reactions of *P. aeruginosa*: Indole negative, Mannitol not fermented, Triple Sugar Iron Agar (TSI) with alkaline slant/alkaline butt with no gas and no H₂S.

The colonies were subjected to Gram staining which showed the morphology of Gram negative bacilli [Table/Fig-3] [8].



[Table/Fig-3]: Gram stain picture of *P. aeruginosa* showing Gram negative bacilli (Magnification 100x).

Antibiotic susceptibility testing was done using Kirby Bauer disc diffusion method [Table/Fig-4] quality control for disc diffusion was done by *P. aeruginosa* 27853 [9].



[Table/Fig-4]: Antibiotic susceptibility test done by disc diffusion method. Induced Amp C can be seen by flattened zone near ceftazidime, piperacillin, piperacillin tazobactam and cefepime sulbactam discs.

For MDR organisms, sensitivity using Vitek 2 was also done. To know the Minimum Inhibitory Concentration (MIC) values of different antibiotics as well as susceptibility to ceftazidime - avibactam [9]. Different characteristics of the isolates like mucoid type colony morphology and induced Amp C were also studied. Induced Amp C resistance was detected using Imipenem disc which is a potent inducer and by checking for flattened zone near Ceftazidime disc [Table/Fig-4] [10]. History and clinical details of patients were collected from wards and ICUs by using a proforma after getting informed consent from them. Several parameters like recent hospitalisation, co-existing respiratory illness, use of inhalers etc., were studied.

STATISTICAL ANALYSIS

Data was analysed using the IBM Statistical Package for Social Sciences (SPSS) version 23. Descriptive statistics were used to determine the antibiotic susceptibility pattern of the isolates and to analyse the clinical profile of the patients.

RESULTS

In a six month period, a total of 2236 lower respiratory tract samples (1793 sputum and 443 bronchial wash samples) apart from endotracheal aspiration samples were received in Microbiology lab for culture and sensitivity. Out of 1793 sputum samples, 410 cultures showed positive growth (23%) and 1383 samples were normal flora. Out of total 443 bronchial wash samples, 100 cultures showed positive growth (22%). Number of *P. aeruginosa* isolates were 72 in sputum (17% of sputum isolates) and 25 in bronchial wash (25 % of bronchial wash isolates), making a total of 97. According to the exclusion criteria, 26 isolates were excluded from the study. Finally, 71 *P. aeruginosa* isolates (51 from sputum samples and 20 from bronchial wash) were included in the study.

Out of 71 isolates, 46 (65%) were from males and 25 (35%) were from females. Maximum number of patients was in the age group 61-70 years, i.e., 24 (33.8%). Mean age was 64 years [Table/Fig-5].

Age group (in years)	Male	Female	Total
11-20	2 (4.3%)	0	2 (2.8%)
21-30	1 (2.2%)	0	1 (1.4%)
31-40	2 (4.3%)	0	2 (2.8%)
41-50	2 (4.3%)	3 (12%)	5 (7%)
51-60	7 (15.2%)	6 (24%)	13 (18.3%)
61-70	18 (39.1%)	6 (24%)	24 (33.8%)
71-80	9 (19.6%)	10 (40%)	19 (26.8%)
81-90	5 (10.9%)	0	5 (7%)
Total	46 (100%)	25 (100%)	71 (100%)

[Table/Fig-5]: Distribution of subjects based on gender.

A total of 54 (76%) isolates were from patients admitted to wards and 17 (24%) isolates were from patients admitted to various ICU s like respiratory ICU, critical ICU, medical ICU and cardiac ICU. Seven (9%) patients were active smokers, while 21 (30%) patients were ex-smokers. A total of 1 (1%) patient gave the history of passive smoking and 42 (60%) patients were non-smokers. Three (4%) cases were referred from other hospitals.

Regarding respiratory diseases, 6 (8%) patients had asthma, 16 (23%) patients had bronchiectasis, 1 (1.4%) patient had Kartagener's syndrome, 25 (35%) patients had COPD, 1 (1.4%) patient had Obstructive Sleep Apnoea (OSA), 1(1.4%) patient had cystic fibrosis, 3 (4%) patients had Interstitial Lung Disease (ILD), 1 (1.4%) case of old pulmonary tuberculosis. No chronic lung diseases were there for 24 (34%) people [Table/Fig-6].

A total of 38 (53%) patients were using inhalers for respiratory illness. A total of 21(30%) patients had history of hospitalisation in last two years. Out of 21, 6 (8%) patients had ICU admission.

Respiratory disease	No. of patients	Percentage (%)
Asthma	4	5.6%
Bronchiectasis only	10	14.1%
Bronchiectasis + Asthma only	2	2.8%
Bronchiectasis + Kartagener's syndrome	1	1.4%
COPD only	21	29.6%
COPD + bronchiectasis	3	4.2%
COPD + OSA	1	1.4%
Cystic fibrosis	1	1.4%
ILD	3	4.2%
Old pulmonary TB	1	1.4%
No respiratory disease	24	33.8%
Total	71	100.0%

[Table/Fig-6]: Distribution of subjects based on combination of respiratory diseases.

Patients were stratified according to their final diagnosis. There were seven distinct diagnoses. The commonest was pneumonia followed by acute exacerbation of COPD. The rarest were cystic fibrosis and lung abscess [Table/Fig-7].

Final diagnosis	No. of subjects	Percentage (%)
Bronchogenic carcinoma	3	4.2%
COPD acute exacerbation	22	31.0%
Asthma acute exacerbation	2	2.8%
Bronchiectasis	13	18.3%
Pneumonia	29	40.8%
Cystic fibrosis	1	1.4%
Lung abscess	1	1.4%
Total	71	100.0%

[Table/Fig-7]: Distribution of subjects based on final clinical diagnosis.

Out of the *P. aeruginosa* isolates, 13 isolates (18%) were of mucoid strain.

MDR strains were 14 in number (20 %). Polymixin B and colistin were tested in 15 out of 71 isolates. Of intermediate sensitivity in Vitek 2. Ceftazidime-Avibactam was tested in 14 MDR isolates out of total 71 by Vitek 2. Seven isolates (50%) were susceptible. Induced AmpC resistance was seen in 28 isolates (39%) [Table/Fig-8].

Name of antibiotics	Susceptible isolates	Percentage (n=71)
Ceftazidime	26	37%
Gentamycin	67	94%
Amikacin	65	92%
Piperacillin - tazobactam	28	39%
Cefoperazone - Sulbactam	28	39%
Imipenem	57	80%
Meropenem	63	89%
Ciprofloxacin	60	85%

[Table/Fig-8]: Susceptibility to different antibiotics.

DISCUSSION

Out of the total 71 *P. aeruginosa* isolates, 65% were isolated from males. This is in accordance with the study conducted by Samad A et al., [11].

A total of 76% patients were from wards. A total of 40% patients were smokers. *P. aeruginosa* is known to colonise the airways of smokers and patients with chronic lung disease. They can cause pneumonia and trigger exacerbations of lung diseases. It is found that cigarette smoke exposure increases resistance of *Pseudomonas* to neutrophil killing [12].

A total of 25 patients (35 %) had COPD. *P. aeruginosa* is known to act like a coloniser in lungs in a significant number of adults with COPD. It can also cause acute exacerbations of asthma, bronchiectasis and COPD in predisposed individuals [13].

Sixteen (23%) patients had Bronchiectasis. *P. aeruginosa* is found to be one of the most common organisms isolated from lower respiratory tract samples in patients with bronchiectasis. It can be isolated when the patient is clinically stable as well as during exacerbations. Many studies have found that this organism was associated with increased frequency of exacerbations in patients with bronchiectasis along with severe radiologic parameters and worse lung function [14].

A 34% of isolates were from patients without any pre-existing chronic respiratory illnesses. A total of 29 patients (41 %) had a final diagnosis of pneumonia during the current hospital admission in which *P. aeruginosa* was isolated from respiratory samples. In this study, one patient was found to have cystic fibrosis. *P. aeruginosa* can cause chronic lung infections in cystic fibrosis patients which can significantly reduce quality of life and increase morbidity and mortality [15,16].

Among the *P. aeruginosa* strains isolated, there were 13 mucoid strains. All the patients had chronic lung conditions like bronchiectasis, asthma or COPD. It is found that in patients with chronic lung pathology, *P. aeruginosa* can change to a highly mucoid phenotype from non mucoid type which is indicative of the over production of alginate, a capsular exopolysaccharide. Alginate can inhibit the clearance of organisms by alveolar macrophages thus contributing to the persistence of infection [17].

Though Gentamicin and Amikacin are found to be the most susceptible antibiotics in the present study, both these antibiotics have been removed from the reporting panel of respiratory samples for *P. aeruginosa* as per Clinical and Laboratory Standards Institute (CLSI) 2023 [9]. Amikacin sensitivity of 92% and meropenem sensitivity of 89% is in accordance with the study conducted by Samad A et al., [11]. Among carbapenems, meropenem was found to be more sensitive (89%) than imipenem (80%). Imipenem sensitivity of 65.2% in pseudomonas has been reported [18]. In the present study, the sensitivity to ciprofloxacin was found to be 85 %. This data is in accordance with the study conducted by Lubega G et al., in Uganda where the sensitivity of Ciprofloxacin was found to be 80% [19]. Antipseudomonal Cephalosporin, Ceftazidime had only 37% susceptibility in the present study. This is in accordance with 34% susceptibility of *P. aeruginosa* to ceftazidime in sputum samples as per the study by Anvari M et al., [20].

Combination of beta lactam and beta lactamase inhibitors used for antibiotic susceptibility in the lab are piperacillin - tazobactam and cefoperazone - sulbactam. They were also having a low susceptibility of 39%. According to a study by Pokharel K et al., the susceptibility of *P. aeruginosa* to piperacillin tazobactam was 76% [18]. The antibiotic susceptibility of *P. aeruginosa* clinical isolates to Piperacillin Tazobactam was 77% according to the study by Sader HS et al., [21]. Here, we had checked the presence of inducible Amp C genes in all isolates, which was very high in number (28 isolates, 39 %) [10]. According to a study by Muddassir M et al., 15% of *P. aeruginosa* isolates were detected as inducible Amp C producers [22] and it was 47.5% according to an Indian study [23].

The increasing trend of different resistance mechanisms can pose serious threat to patients. In the present study, the MDR strains were 14 in number (20%). Isolates which are non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories are called MDR organisms [24]. An increasing prevalence of MDR and XDR *P. aeruginosa* strains, are found in many geographical areas with rates ranging from 15 to 30% [25]. Another study from Peshawar shows that the MDR isolates were 28 (39.44%) out of total 71 *P. aeruginosa* isolates [11].

Ceftazidime - avibactam is a new drug effective for *P. aeruginosa*. It is a treatment option for resistance mechanisms due to KPC and Oxa 48. In the present study, out of MDR strains, only 50% were susceptible to this drug. A study conducted by O'Neill D et al., showed 67% susceptibility to ceftazidime avibactam [26] Resistance to this drug has been reported in many parts of the world. It can be either intrinsic resistance mechanisms like NDM or acquired resistance mechanisms. For NDM, VIM and IMP type of resistances, ceftazidime - avibactam should be combined with Aztreonam as aztreonam is effective against metallo-beta lactamases [27].

Other treatment options for MDR *P. aeruginosa* include Fosfomycin which is not routinely tested and reported in our lab. Intravenous Fosfomycin should always be administered along with another antibiotic in combination for *Pseudomonas* infections since heteroresistance is extremely common [28]. Changes in outer membrane porins, efflux pumps, and novel PBP3 insertions are other mechanisms of resistance apart from enzymatic mechanisms [25,27].

According to Infectious Diseases Society of America (IDSA) guidelines, treatment options for "difficult to treat *P. aeruginosa*" (DTRPA) include ceftolozane-tazobactam, imipenem-cilastatin-relebactam, and cefiderocol apart from ceftazidime-avibactam [29].

Limitation(s)

Conventional methods of antibiotic susceptibility testing were done. Only the MDR isolates were subjected to further antibiotic susceptibility testing by Vitek 2.

CONCLUSION(S)

P. aeruginosa is a major pathogen causing infections in hospitals. Out of the total 71 *P. aeruginosa* included in the study, three fourth patients were from ward. Majority of the patients admitted had a final diagnosis of pneumonia followed by COPD and bronchiectasis. Among the different antibiotics tested, meropenem and amikacin were the most susceptible drugs. Ceftazidime, the antipseudomonal cephalosporin and beta lactam beta lactamase inhibitors had a low susceptibility rate. A 20% isolates were MDR, out of which only half of the isolates were susceptible to ceftazidime-avibactam which is a very alarming situation. Several treatment options are now available for difficult to treat *Pseudomonas*, but the increasing rates of resistance is a major concern to be addressed.

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