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Antimicrobial Sensitivity Pattern of Pseudomonas Aeruginosa in Healthcare-Associated Infections: Hospital-Based Study

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ABSTRACT

Pseudomonas aeruginosa, especially a multi drug-resistant strain is an important pathogen responsible for the healthcare-associated infection. Multi drug-resistant Pseudomonas aeruginosa is increasingly encountered in healthcare settings, leaving clinicians with limited effective anti pseudo monal drugs for treatment. Thus, it presents a serious therapeutic challenge associated with increased morbidity and mortality. Identification of multi drug-resistant strains and their antimicrobial sensitivity pattern is essential to develop proper antibiotic policy and effective antimicrobial stewardship program. This study aimed to determine antibiotic sensitivity profiles with the minimum inhibitory concentration of commonly used anti pseudo monal antibiotics against Pseudomonas aeruginosa associated with healthcare-associated infections in a tertiary care hospital. One hundred and sixty consecutive, non-repeat isolates of Pseudomonas aeruginosa were collected from various clinical samples. Susceptibility studies were performed, using E-strips and minimum inhibitory concentrations of ceftazidime, cefepime, piperacillin/tazobactam, imipenem, meropenem, amikacin, gentamicin and colistin were tested and interpreted as per clinical laboratory standard institute guidelines. The only antibiotic with 100% susceptibility rates were colistin. The rate of susceptibility pattern was Imipenem 59.38%, Meropenem 55%, Piperacillin/Tazobactam 50.63%, Cefepime 36.25%, Ceftazidime 34.38%, Amikacin 38.13% and Gentamicin 20%. The results highlight the challenge of optimizing empirical antimicrobial therapy for Pseudomonas aeruginosa infections. It will be useful for clinicians to treat patients effectively, thus saving the cost and duration of patient care. It will also help the Infection Control Team in the selection of proper anti pseudo monal antibiotic policy and set an effective antimicrobial stewardship program.

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Key Words
Pseudomonas aeruginosa, healthcare-associated infection, minimum inhibitory concentration, E-strip

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INTRODUCTION

Pseudomonas aeruginosa is an important pathogen responsible for healthcare-associated infections and associated with inconvenience to patients, prolonged hospital stays and an economic burden on the healthcare system[1]. It is also an important independent risk factor for increased morbidity and mortality. *P. aeruginosa* is a frequently recovered species from various clinical specimens. *P. aeruginosa* is intrinsically resistant to many commonly used antibiotics and develops resistance to anti pseudo monal antibiotics by various mechanisms[2,3]. A highly impermeable outer membrane, the expression of numerous non-specific efflux pumps and phenotypic variations like biofilm formation, small-colony variant (SCV) cells, or persisters are important intrinsic properties responsible for antibiotic resistance[4]. These resistance mechanisms with other acquired antibiotic resistance mechanisms found on mobile genetic elements such as plasmids or transposons encoding drug-specific efflux pumps, target modifiers, or inactivating enzymes, make the bacterium resistant to virtually all the available anti pseudo monal agents[5]. The important anti pseudo monal agents are some ß-lactams like piperacillin, ticarcillin, ureidopenicillins, ceftazidime, cefepime, imipenem, meropenem and aztreonam, aminoglycosides (amikacin, gentamicin, tobramycin and netilmicin) and fluoroquinolone (ciprofloxacin, levofloxacin). Amino glycosides are the most effective and commonly used antibiotics in the empirical treatment of infections caused by or suspected to be caused by *P. aeruginosa*, especially suspected multi drug-resistant (MDR) strains. An amino glycoside with anti-pseudo monal penicillin (eg. piperacillin or piperacillin/tazobactam or ticarcillin or ticarcillin/clavulanate) or anti pseudo monal cephalosporin (e.g. cefepime or ceftazidime) is the recommended treatment option for *P. aeruginosa* infection[6]. Meta-analysis on the effectiveness of beta-lactam with aminoglycoside or fluoroquinolones showed a higher clinical cure rate for patients receiving empirical treatment with combination therapy[7]. The emergence of resistance to the currently available anti pseudo monal drugs has become a serious threat in treatment, especially if the isolates are multi drug-resistant. In the United States, almost 50000 healthcare-associated *P. aeruginosa* infections are reported annually with 13% being due to MDR isolates[8]. The treatment of MDR isolates in critically ill patients is becoming more challenging and stresses the importance of preparing proper anti bio grams to help clinicians with accurate information regarding the sensitivity patterns and help them in selecting appropriate anti pseudo monal antibiotics to treat the patients. Indirectly this will also help to reduce the burden and spread of MDR isolates in the healthcare setting. This study aimed to determine antibiotic sensitivity profiles with the minimum inhibitory concentration of commonly used anti pseudo monal antibiotics against *P. aeruginosa* isolated from healthcare-associated infections in a tertiary care hospital.

MATERIALS AND METHODS

Isolation and Identification: This prospective study was carried out from August 2021 to July 2022. One hundred and sixty consecutive, non-repeat clinical isolates of P. aeruginosa were collected from various clinical samples from hospitalized patients at a tertiary care hospital and were identified by conventional phenotypic methods.

Minimum Inhibitory Concentration: Minimum Inhibitory Concentration (MIC) for piperacillin/ tazobactam, ceftazidime, cefepime, imipenem, meropenem, amikacin, gentamicin and colistin were determined against all isolates by E-test method. Results were interpreted according to CLSI, 2021[9]. E-Test strips containing ceftazidime, cefepime, amikacin, gentamicin, piperacillin-tazobactam, imipenem, meropenem and colistin (AB Biodisk North America Inc., Culver City, Calif.) were tested. 100 mm-diameter Mueller-Hinton agar plates (Becton Dickinson, Cockeysville, Md.) were inoculated with swabs saturated with suspensions of the study isolates equivalent to a 0.5 McFarlane standard. The antimicrobial agent-coated test strips were placed on each plate in accordance with the manufacturer's instructions. The results were read after 18-24 h of incubation in ambient air at 35°C.

RESULTS AND DISCUSSIONS

MIC was determined for all isolates (n=160). Sensitivity to different anti pseudo monal antibiotics are as follows: Amikacin 61 (38.13%), Gentamicin 32 (20%), Ceftazidime 55 (34.38%), Cefepime 58 (36.25%), Imipenem 95 (59.38%), Meropenem 88 (55%), Piperacillin-Tazobactam 81 (50.63%) and all isolates are sensitive to Colistin. MIC range, MIC50 and MIC 90 values of sensitive and resistant isolates to different antibiotics tested. A total of 93 (58.12%) isolates were resistant to amikacin with 78 (48.75%) isolates having MIC90 of $\geq$256µg/mL. Similarly, 122 (76.25%) isolates were resistant to gentamicin of which 65 (40.63%) isolates had MIC90 of $\geq$64 µg/mL. A total of 104 (65%) isolates were resistant to ceftazidime and 97 (60.62%) to cefepime of which 89 (55.63%) and 83 (51.88%) were showing MIC90 of $\geq$128µg/mL. Out of 160 isolates, 65 (40.62%) were resistant to imipenem and 67 (42.87%) were resistant to meropenem, of which 27 (16.88%) and 24 (15%) showed high-level resistance (MIC90 $\geq$32µg/mL) to imipenem and meropenem respectively. On the other hand, 70 (43.75%) isolates were resistant to piperacillin-tazobactam with a MIC90

Table 1: MIC Interpretation

Drugs	MIC Interpretive Criteria (n=160)			Resistant Isolates			Sensitive Isolates		
				RANGE	MIC50	MIC90	RANGE	MIC50	MIC90
Amikacin	≤16 61 (38.13%)	32 6 (3.75%)	≥64 93 (58.12%)	64 -256	256	256	4-16	4	8
Gentamicin	≤4 32 (20%)	8 6 (3.75%)	>16 122(76.25%)	16-64	64	64	1-4	2	2
Ceftazidime	≤8 55 (34.38%)	16 1 (0.63%	>32 104 (65%)	32-128	128	128	2-8	4	8
Cefepime	≤8 58 (36.25%)	16 5 (3.13%)	>32 97 (60.62%)	32-128	128	128	2-8	4	8
Imipenem	≤2 95 (59.38%)	4 0	>8 65 (40.62%)	8-32	16	32	0.5-2	0.5	1
Meropenem	≤2 88 (55%)	4 5 (3.13%)	>8 67 (42.87%)	8-32	16	32	0.5-2	1	2
PIP-TAZ	≤16/4 81 (50.63%)	32/2-64/2 9 (5.63%)	>128/4 70 (43.75%)	128/4-256/4	256/4	256/4	4/4-16/4	16/4	16/4
Colistin	≤2 160 (100%)	4 0	>8 0	8-256	0	0	0.5 - 2	0.5	0.75

Fig. 1: Growth of *P. Aeruginosa* with Blue Green Diffusible Pigment

Fig. 2: Hugh-Leifson Oxidation-Fermentation Test (Tube A and B: *P. Aeruginosa* Showing no Fermentation in Tube A, Oxidation in Tube B Tube C and D: E. Coli Showing Oxidation in Tube C, Fermentation in Tube D)

Fig. 3: E Stripe for MIC Detection: Piperacillin-Tazobactam Resistant Strain (MIC≥256µg/mL)

Fig. 4: E Stripe for MIC Detection: Meropenem Resistant Strain (MIC≥32µg/mL)

Fig. 5: E Stripe for MIC Detection: Imipenem Resistant Strain (MIC≥32µg/mL)

Fig. 6: E Stripe for MIC Detection: Colistin Sensitive Strain (MIC≥1.5µg/mL)

of ≥256/4. All isolates were sensitive to colistin. Multi drug-resistant *P. aeruginosa* is a serious threat to patients attending healthcare facilities, especially critical care units, burn units, dialysis units and long-term care facilities. It is one of the important causes of infection in immune-compromised patients or patients on higher antibiotics or immunomodulating drugs. To reduce the risk of drug resistance and synergistic activity, combination therapy is recommended for the treatment of multidrug-resistant *P. aeruginosa*. Anti pseudo monal ß-lactam and amino glycoside combinations are frequently used for the treatment of MDR P. aeruginosa due to their synergistic activity, concentration-dependent killing, and post-antibiotic effect of amino glycosides. In our study, we detected the antibiotic sensitivity profiles with the minimum inhibitory concentration of commonly used anti pseudo monal antibiotics against *P. aeruginosa* isolated from healthcare-associated infections in a tertiary care hospital. In the study, the antimicrobial susceptibility patterns, the highest resistance was found in gentamicin, followed by ceftazidime, cefepime, amikacin, piperacillin-tazobactam, meropenem and imipenem. The study conducted by MM Gill *et al.* showed a similar pattern of antibiotic susceptibility in MDR *P aeruginosa*[10]. Ceftazidime was one of the most effective antipseudomonal antibiotics among the cephalosporin group, especially for the treatment of pneumonia[11]. However, the drug showed low activity against the isolates in the present study. In this current study, 65% of isolated *P. aeruginosa* were resistant to ceftazidime. A high rate of ceftazidime resistance was also reported in India by Prashant *et al.* (53%), DiSwedi *et al.* (63%), and Arumugam *et al.* (55.6%)[12-14]. Cefepime has had a constant antipseudomonal activity over the years, but the susceptibility to the drug is gradually decreasing in recent years. Increasing resistance to *P. aeruginosa* to cefepime was also detected in the present study. Piperacillin has the broadest spectrum of activity against *P. aeruginosa*, especially the combination of therapy of piperacillin with tazobactam, a ß-lactamase inhibitor to improve its effectiveness. But the studies showed reduced susceptibility to the combination due to the emergence of MDR strains. Past studies also found a similar higher resistance to the combination to the present study[15,16]. However, a few studies from India also showed higher susceptibility to the piperacillin-tazobactam combination[14,17,18]. Due to the very broad spectrum of activity, carbapenems are the last resort of treatment for *P. aeruginosa*, especially for MDR strains. Metallo-ß-lactamase is the enzyme that hydrolyzes the carbapenems quite effectively, therefore early detection of carbapenem resistance or Metallo-ß-lactamase is very essential for the accurate treatment of infection-caused *P. aeruginosa*[19]. In this current study, we observed that *P. aeruginosa* was highly susceptible to meropenem (58.13%) and imipenem (59.38%). The study by Wright *et al.* reported 77.4% of susceptibility to meropenem and a similar study by Viren et al showed a susceptibility of 69.6%[20,21]. The MIC90 values for most of the antibiotics were higher than the maximum tested concentration except imipenem and meropenem, which were lower than other tested concentrations indicating that most of the isolates were susceptible to these two antibiotics. Amino glycosides are commonly used antibiotics to treat different gram-negative bacteria. It is also effective against *P. aeruginosa*[20-24]. Amikacin or gentamicin is often used clinically in combination with ß-lactam antibiotics or cephalosporins for the treatment of infection caused by *P. aeruginosa*. Despite the anti pseudo monal effectiveness of amikacin or gentamicin, an increased resistance was evident in the present study. Colistin is the third level of treatment and is not very commonly prescribed, except for severe cases or critically ill patients with healthcare-associated infections. In the present study, we found all isolates were sensitive to colistin. However, Arumugam *et al.* observed a sensitivity of 69.2% to colistin and 74.6% to polymyxin B. They also found that among the susceptible strains, 17% and 11% are resistant to colistin and polymyxin B respectively, which indicates the emergence of MDR *P. aeruginosa*[14]. Continuous and injudicious use of antibiotics against MDR stains might lead to the development of resistance to commonly used anti pseudo monal drugs, drugs that have broader spectrum and reserve drugs for drug-resistant strains. Antibiogram with MIC value if carried out properly every year, might show an increase of MIC50 and MIC90 value for these anti pseudo monal antibiotics. Though there was a decrease in morbidity with combination therapy like anti pseudo monal penicillin or cephalosporin or carbapenem with a second agent, the combination failed to exhibit a significant benefit in terms of the emergence of resistance. The selection of empirical antibiotics or drug combinations for presumed infection before culture and sensitivity report without hospital-based guidelines or antibiogram is worsening the condition. The combination should be selected after considering the hospital-based surveillance data with organisms and their susceptibility pattern of that hospital along with patients' data like comorbidities and previous antibiotic history. Clinicians should work in

collaboration with the microbiology laboratory and hospital infection control committee to understand the organisms and their resistant patterns in the hospital before starting any antimicrobial therapy or combination therapy or broad-spectrum antibiotics.

CONCLUSION

The study illustrates the potential value and necessity of close monitoring of multi drug-resistant pathogens and their susceptibility patterns in any healthcare setting. Clinicians should choose their therapeutic drugs with a reserve and consult with a clinical microbiologist on a regular basis before treating *P. aeruginosa* infections, especially MDR strains. The emergence and continuous increase of MDR *P. aeruginosa* with a lack of newer anti pseudo monal antibiotics on the horizon demand a newer approach to prevent healthcare-associated infections. Hospital Infection Control Committee and Infection control team should monitor the exact prevalence of MDR strains and their susceptibility pattern and develop proper antibiotic policies. Clinicians should remain adherent to the policies and other healthcare workers should follow the infection control practices. Better healthcare administration of the existing antibiotics policies, antimicrobial stewardship programs and infection control practices is the key to winning the combat against healthcare-associated MDR *P. aeruginosa* infections.

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