MICROBIAL DRUG RESISTANCE
Volume 31, Number 2, 2025

DOI: 10.1089/mdr.2024.0191

Influential Factors in the Treatment of *Pseudomonas aeruginosa* Infections at a Tertiary Hospital in Vietnam

Tiep Khac Nguyen,[1,2] Ngoc Khanh Le,[1] Pham Hong Nhung,[3,4] Thao Thi Huong Bui,[5] Gang Wang,[2] Françoise Van Bambeke,[2] and Phung Thanh Huong[1]

As an opportunistic pathogen, *Pseudomonas aeruginosa* is often associated with severe respiratory infections. A study conducted in an ICU of a tertiary hospital in Vietnam, where infection management is relatively good, yielded only 18 clinical isolates of *P. aeruginosa* over 6 months. Though the number is small, treating *P. aeruginosa* infections is highly complicated. Out of 18 patients, 15 showed no improvement after treatment, leading to worsening conditions or death, possibly due to various factors. High rates of mechanical ventilation (83.3%) may be a contributing factor, suggesting a certain correlation between ventilation and treatment failure. The antibiotic resistance rate in these isolates is relatively high, with a multidrug-resistant rate of 44.4%, resulting in treatment failures when empirical antibiotics are used without susceptibility testing. All isolates have the ability to form biofilms. Moreover, bacteria in stationary phase or within biofilms exhibited poor responses to meropenem and amikacin (about 10% of bacteria survive after antibiotic exposure). Conversely, ciprofloxacin shows much better efficacy, indicating that fluoroquinolones should be used in combination therapy for *P. aeruginosa* infection to eliminate persistent cells and biofilm-embedded microorganisms, thus enhancing treatment effectiveness.

Keywords: *Pseudomonas aeruginosa*, resistance, persistence, biofilm, amikacin, meropenem, ciprofloxacin

Introduction

The Gram-negative opportunistic pathogen *Pseudomonas aeruginosa*, widely distributed in many places, as well as in the human body and animals,[1] causes various types of infections.[2] These infections are particularly severe in patients with lung-related conditions such as chronic obstructive pulmonary disease or those on mechanical ventilation, with mortality rates ranging from 18% to 61%.[3]

To treat infections caused by *P. aeruginosa*, various classes of antibiotics are commonly utilized, including β-lactams, aminoglycosides, quinolones, and more recently, polymyxins.[3] However, treatment remains complicated with failure rates ranging from approximately 10% to 30%, and may be higher in cases of multidrug-resistant (MDR) isolates or in immunocompromised individuals.[4]

Treatment responses are influenced by a multitude of factors.[5] Among these factors, antibiotic resistance stands out as an extensively studied phenomenon, marked by an elevation in minimum inhibitory concentration (MIC) values compared to susceptible microorganisms.[4] Contrarily, the concept of "antibiotic persistence" has only recently gained formal recognition, and still receive less attention both in research and clinical practice. Persistent phenotype does not exhibit elevated MIC but highly heterogeneity within the microbial population. The majority of microorganisms respond to antibiotics as a sensitive population, being swiftly eradicated, whereas a small subset exhibits minimal or no response.[6] However, this phenomenon may be linked to treatment failures, particularly in cases of persistent, recurrent, and chronic infections. Additionally, it serves as a precursor to the emergence of antibiotic resistance.[7] Recently, the persistence phenotype has been

[1]Faculty of Biotechnology, Hanoi University of Pharmacy, Hanoi, Vietnam.
[2]Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium.
[3]Department Microbiology, Hanoi Medical University, Hanoi, Vietnam.
[4]Department of Microbiology, Bach Mai Hospital, Hanoi, Vietnam.
[5]Department of Pharmacology, Hanoi Medical University, Hanoi, Vietnam.

Table 1. Clinical Characteristics of Patients

No	*Isolates*	*Gender*	*Age*	*Infection*	*On ventilator*	*Nosocomial*	*Immunodeficiency factor*	*Information of treatment*[a]	*Improvement after treatment*[b]
1	47866	M	55	Pulmonary	X		Smoke	**COL, TZP, >10 days**	No
2	48293	F	25	Pulmonary	X	X		COL (9 MIU), 3 days	No (died)
3	53603	F	78	Pulmonary	X	X	Aged patient, cancer	**COL (6 MIU), >15 days TPZ (4 g/0.5 g), 2 days**	No
4	48515	M	75	Pulmonary	X	X	Guillain Barré syndrome, elder	**TZP (12 g/1.5 g), 4 days**	No
5	48757	M	60	Pulmonary	X	X	Aged patient, smoke, alcoholism	**COL (9 MIU), 12 days, TZP (12 g/1.5 g), 6 days**	No
6	48825	M	56	Pulmonary	X	X	Tuberculosis since 30 years, diabetic	**CAZ, 4 days**	No
7	49115	M	75	Pulmonary	X	X	Aged patient	CAZ, 6 days	No
8	49326	F	85	Pulmonary	X		Aged patient	**MEM, >20 days**	No
9	49364	M	20	Pulmonary				COL (9 MIU), IPM (3 g), AMK (1 g), 10 days	**Yes**
10	49360	F	54	Pulmonary	X	X	Cancer	Refused treatment	No
11	53976	M	55	Pulmonary	X	X	After surgery	**COL, 14 days**	No
12	49631	M	65	Pulmonary	X	X	Diabetic, hypertension, COPD	CAZ (1 g), 6 days	**Yes**
13	24386	M	75	Sepsis		X	Aged patient	Refused treatment	No
14	50323	F	26	Pulmonary	X	X		**TZP (16/2 g), 12 days**	No
15	50388	M	61	Pulmonary	X	X	Diabetic	**COL, 24 days**	No
16	36791	M	44	Pulmonary	X	X	After surgery	**COL (6 MIU), 9 days**	No
17	50350	F	41	Pulmonary	X	X	Myasthenia gravis	**COL (6 MIU), 6 days**	No
18	49787	M	55	Pulmonary			Myasthenia gravis	CAZ (4 g), 7 days	**Yes**

[a]Information of treatment: Treated with susceptible antibiotics for >4 days but shown no improvement is in bold. Treated with resistance antibiotic is underlined.
[b]Improvement after treatment: Based on clinical progress or microbiology negative confirmation.
AMK, amikacin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; COL, colistin; COPD, chronic obstructive pulmonary disease; FEP, cefepime; GEN, gentamicin; IMP, imipenem; MER, meropenem; TOB, Tobramycin; TZP, piperacillin/tazobactam.

reported in various species, including *P. aeruginosa*, posing an emerging challenge to infection treatment.[8,9] Furthermore, the association between persistence phenotype and the biofilm-forming ability of some bacteria has been reported,[10–12] and may contribute to the failure of antibiotic treatment.

In this study, we evaluated the treatment response in *P. aeruginosa* infection with clinical isolates at the ICU of one of the largest tertiary hospitals in Vietnam. Additionally, we investigated several factors influencing treatment effectiveness, including antibiotic resistance and persistence, biofilm-forming capability, as well as clinical factors.

Material and Methods

Clinical data

The study complied with the Declaration of Helsinki and was approved by Bachmai Hospital Ethics Committee (approval number: 1789/QD-BM) and conducted during June–December 2015. Clinical characteristics including isolates number, gender, age, infection type, using ventilator or not, nosocomial or not, immunodeficiency factor, treatment information, and status after treatment were obtained from the 18 medical records (Table 1).

Isolates and antibiotics

From patients admitted to the ICU at Bach Mai Hospital, Vietnam, 18 isolates of *P. aeruginosa* were collected, including 17 isolates from the respiratory tract and one from blood (24386). All isolates were identified using colony morphology, Gram stain, and MALDI Biotyper (Germany). Only non-duplicate isolates, which means no more than one isolate from the same sample, were included in the study.

P. aeruginosa ATCC 27853 is a reference strain from the American Type Culture Collection (ATCC) (USA). Antibiotics were obtained as microbiological standard from Bayer (Germany) (ciprofloxacin—CIP) or Bristol-Myers Squibb (Belgium) (amikacin—AMK) or Hospira UK Ltd. (United Kingdom) (meropenem—MER).

Antibiotic susceptibility testing

Antibiogram was obtained from medical records.

P. aeruginosa isolates that showed resistance to at least one antibiotic in three or more antimicrobial categories were identified as MDR.[13]

MICs of selected antibiotics were determined using the microdilution method in cation-adjusted Muller-Hinton II broth (USA), following the instructions of the Clinical and Laboratory Standards Institute (CLSI),[14] with classification as susceptible (S), intermediate (I), and resistant (R) based on CLSI criteria.[14] MIC_{50} and MIC_{90} were calculated from MIC values, corresponding to the antibiotic concentrations inhibiting 50% and 90% of the microbial population.[10]

Quantification of persisters

Bacteria were grown until they reached the stationary phase after undergoing two subcultures (overnight and 24 hours) at 37°C in MHB. Subsequently, they were treated with AMK, MER, or CIP at 50× MIC for 5 hours, 37°C, and 130 rpm. The colony-forming unit (CFU) was enumerated following dilution in phosphate-buffered saline, spreading on tryptic soy agar, and overnight incubation. The percentage of persistence was determined by the following formula[15,16]:

$$\text{Percentage of persistence} = \frac{\text{CFUs after 5 hours treatment}}{\text{Initial inoculum}} \times 100\%$$

Biofilm formation

Overnight bacterial cultures were diluted in tryptic soy broth supplemented with 2% glucose and 1% sodium chloride

Table 2. Analysis of the Association Between Clinical Factors and the Efficacy of Antibiotic Treatment

				Association analysis		
Clinical factor	*No improvement* (n = *15)*	*Improvement* (n = *3)*	p	*OR*	*95% CI*	p
Sex						
Female	6 (40%)	0 (0%)	0.52	4.79	0.21–109.19	0.33
Male	9 (60%)	3 (100%)				
Age						
≥60	8 (53.3%)	1 (33.3%)	1.0	2.29	0.17–30.96	0.53
18–59	7 (46.7%)	2 (66.7%)				
Infection origin						
Nosocomial	13 (86.67%)	1 (33.3%)	0.11	13	0.77–219.11	0.08
Non-nosocomial	2 (13.3.%)	2 (66.6%)				
Mechanical ventilation						
Yes	14 (93.3%)	1 (66.7%)	0.06	28	1.21–648.81	0.04
No	1 (6.7.%)	2 (33.314.3%)				
Immunodeficiency factors						
Yes	15 (100%)	2 (66.7%)	0.17	18.6	0.58–596.66	0.1
No	0 (0%)	1 (33.3%)				
MDR						
Yes	8 (53.3%)	0 (0%)	0.22	7.93	0.35–179.96	0.19
No	7 (46.6%)	3 (100%)				

CI, confidence interval; MDR, multidrug-resistant; OR, odds ratio.

(TGN) to reach an OD_{620} of 0.05. In total, 200 µL of this suspension were distributed in 96-well plates and incubated at 37°C for 24 hours to obtain mature biofilms. Mature biofilms were then incubated with 200 µL fresh TGN containing CIP, MER, and AMK at their Cmax (3 mg/L for CIP[17]; 30 mg/L for MER[18]; 70 mg/L for AMK[19]) during 24 hours, after which the medium was removed and the biofilm was washed with 200 µL MOPS sodium salt buffer at pH 7 (Sigma, USA).

CFU counting, metabolic assay by fluorescein diacetate (FDA), and biomass quantification by crystal violet were performed according to previously described methods, with quantification of fluorescence or absorbance measured with a SpectraMax M3 plate reader (Avantor®, USA).[10,12,20]

Statistical analysis

The association between clinical factors and antibiotic treatment efficacy was evaluated using odds ratios (OR) with a 95% confidence interval (CI). Haldane's adjustment was utilized in cases where variables had a value of zero. Statistical significance was determined when the two-tailed p value was <0.05. All tests were conducted using the statistical software SPSS 20 (IBM, USA).

Between-group comparisons of percentage of persistence or control vs. antibiotic-treated biofilms were conducted utilizing one-way ANOVA with Tukey's post hoc test. A statistically significant p value of <0.05 was considered. The data were analyzed using GraphPad Prism (GraphPad 4.0, USA).

Results

Over a 6-month period, only 18 cases of *P. aeruginosa* infection were documented, predominantly with pulmonary infection, among those, 14 were nosocomial. All hospital-acquired infections in this study were associated with ventilator usage (Table 1).

Most of these patients exhibited poor responses to the used antibiotics, with up to 15 out of 18 patients showing no improvement. Even when treated with susceptible antibiotics, 11 patients did not show improvement. The correlation between clinical factors and treatment response in infection is depicted in Table 2.

Among the aforementioned clinical factors, mechanical ventilation status showed a significant association with an OR of 28.1 (95% CI: 1.21–648.81, $p = 0.04$). However, the Fisher test did not reveal a statistically significant difference between the two groups (Table 2).

To further elucidate the factors influencing the effectiveness of infection treatment, we found that the resistance rate within this collection was relatively high with 50%; 44.4%; and 11% of the isolates resistant to aztreonam, imipenem, and meropenem; ceftazidime, cefepime, tobramycin, gentamicin,

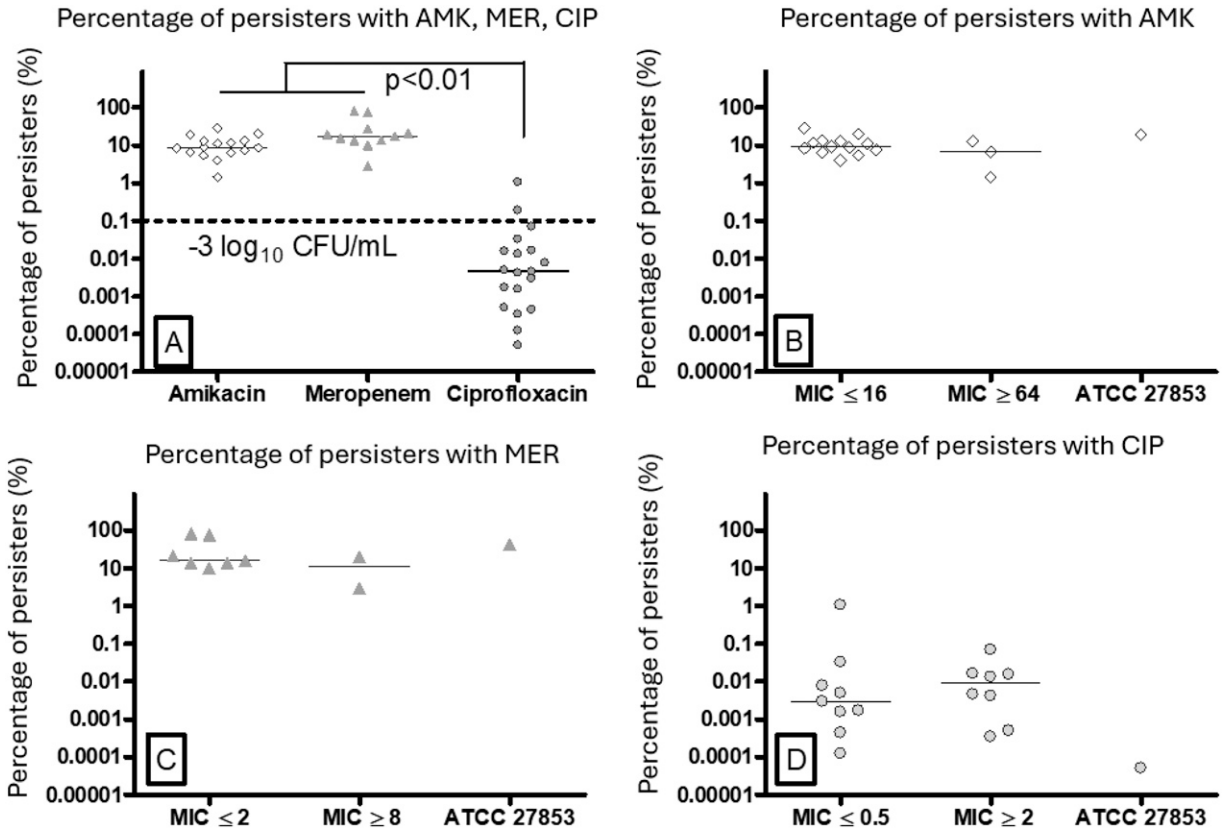

FIG. 1. Characterization of persistence phenotype of the clinical isolates. **(A)** Percentage of persisters in 18 clinical isolates after 5 hours antibiotic exposure to amikacin (AMK), meropenem (MER), or ciprofloxacin (CIP) at 50 times their MIC. **(B–D)** Same data, stratified according to the susceptibility or resistance of each isolate to the considered antibiotic, and including the reference strain ATCC27953 as a comparator. The dotted line corresponds to a reduction of 99.9% of the bacterial counts as compared to the initial inoculum. Data are shown as mean of three independent experiments for each isolate.

and ciprofloxacin; and amikacin, relatively. The rate of MDR isolates is 44.4% (Supplementary Table S1). The resistance pattern from antibiogram was coherent to MIC value of three important antibiotic classes in *P. aeruginosa* treatment, including meropenem, amikacin, and ciprofloxacin (Supplementary Table S2).

In the next step, the persistence characteristics of the isolates were tested for three representative antibiotics. After 5 hours of exposure at the 50× MIC, both amikacin (Fig. 1A) and meropenem showed limited bactericidal efficacy, causing a reduction of only approximately 1 $\log_{10}$ CFU/mL. Conversely, ciprofloxacin was bactericidal toward most of the isolates, causing a reduction of more than 3 $\log_{10}$ CFU/mL (Fig. 1A). When stratifying isolates based on their MIC, no difference in the persistence percentages was noticed between susceptible and resistant isolates, as well as reference strain ATCC27853 regardless of the tested antibiotic (Fig. 1B–D).

Further, we evaluated the biofilm-forming activity of the *P. aeruginosa* isolates and found that all of them produced biofilm. In untreated control, the CFU number and biomass were similar in all biofilms, whereas some variation was noticed in their metabolic activity (Fig. 2A–C). We then examined the activity of representative antibiotics used at their Cmax after 24 hours of exposure. Ciprofloxacin demonstrated excellent bactericidal activity in 9 of 18 isolates that were susceptible to ciprofloxacin (Fig. 2A, B) and exhibited a reduction of more than 3 $\log_{10}$ CFU/mL and 90% of FDA value (Fig. 2D, E). Conversely, ciprofloxacin was inactive on resistant isolates, the MIC of which was approximately equal to or greater than the Cmax (Supplementary Table S2). Meropenem exhibited poor bacterial eradication within the biofilm. Even on susceptible isolates, this antibiotic led to less than 1 $\log_{10}$ CFU/mL and 60% FDA value reduction (Fig. 2D, E). Amikacin performed slightly better than meropenem in eradicating bacteria but was less effective than ciprofloxacin. On susceptible isolates, amikacin could reduce bacterial counts by 1–2 $\log_{10}$ CFU/mL and 80% FDA value; however, for resistant isolates, amikacin was nearly inactive (Fig. 2D, E). All three antibiotics failed to significantly impact the total biomass in the biofilm (Fig. 2C, F).

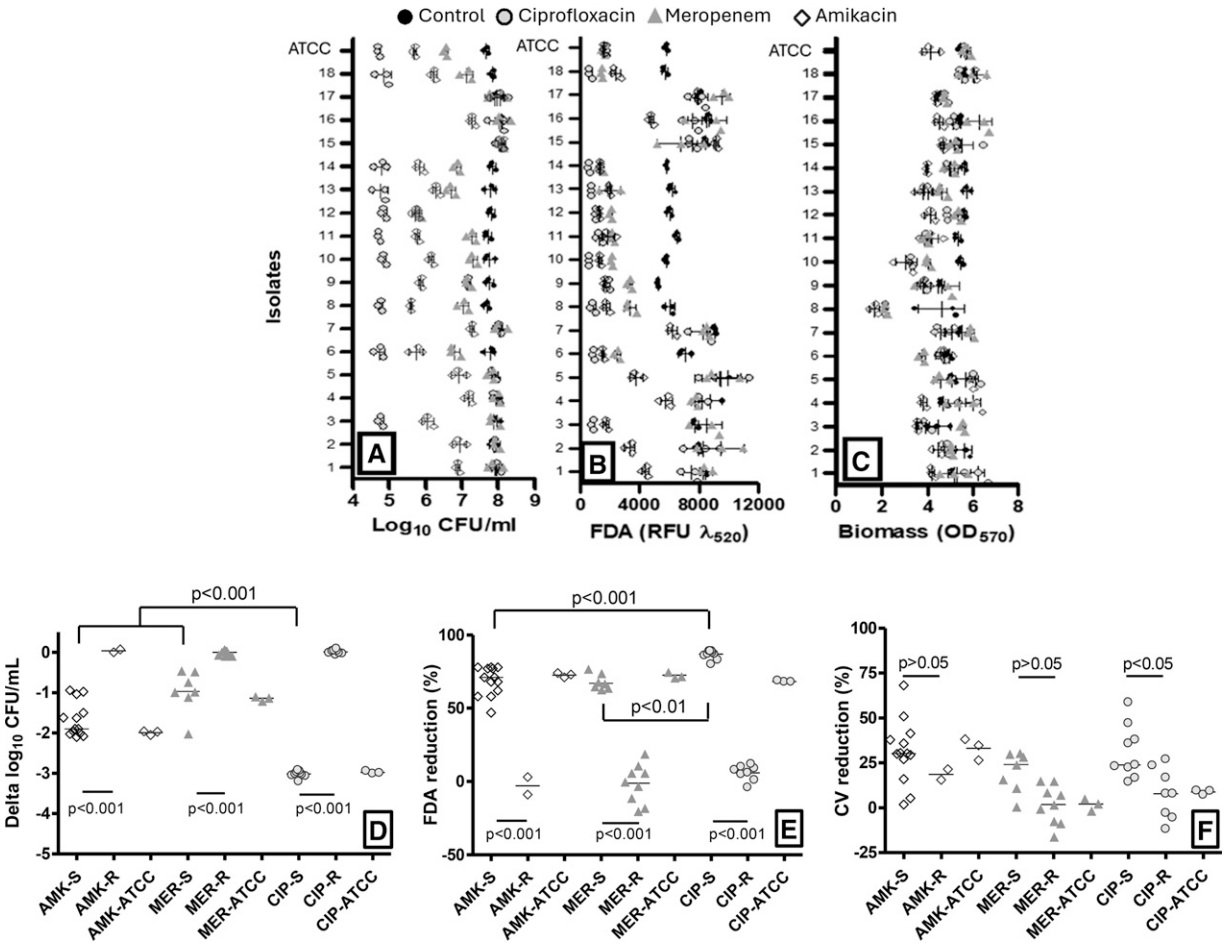

FIG. 2. Activity of selected antibiotics on bacteria in biofilm. CFU counts **(A)**, metabolic activity assessed by the fluorescence of FDA **(B)**, and biomass assessed by CV staining **(C)** for 18 clinical isolates and ATCC 27953 (isolate 0) strains exposed to amikacin, meropenem, and ciprofloxacin at concentrations equivalent to Cmax during 24 hours. **(D–E)** Effects of the three antibiotics (AMK, MER, CIP) on biofilms, expressed as change in CFU counts or in percentage reduction in FDA value and in biomass as compared to the untreated control. Clinical isolates stratified according to their susceptibility to the tested antibiotics (susceptible [**S**] or resistant [**R**]). Data are shown as the mean of three independent experiments for each isolate. CFU, colony-forming unit; CV, crystal violet; FDA, fluorescein diacetate.

Discussion

Although *P. aeruginosa* infections are not numerous, 15 of 18 cases showing no improvement posttreatment highlights the need to investigate treatment efficacy. Statistical analysis revealed only mechanical ventilation significantly increased odds (OR = 28.1), though without Fisher test significance. Ventilation-associated pneumonia (VAP) remains prevalent in critically ill patients, driving extensive ICU antibiotic use globally, with a 15.6% incidence rate.[21] Notably, *P. aeruginosa*, along with *Staphylococcus aureus*, emerges as the primary bacterial agent responsible for VAP, with an associated mortality rate of 13.5%, despite appropriate antibiotic therapy.[22] *P. aeruginosa* and *S. aureus* are leading VAP agents, with 13.5% mortality despite proper therapy. Unsurprisingly, 14 of 15 unimproved cases here involved ventilation. Limited statistical significance likely reflects the small sample size.

To further elucidate the factors influencing the effectiveness of infection treatment, we evaluated the characteristics of the isolates and found that the resistance rate within this collection is relatively high. Amikacin was the most active antibiotic with 11% of resistance. This result is consistent with a multicenter study in Vietnam, where amikacin was reported to be the most susceptible antibiotic for *P. aeruginosa.*[23]

Although the antibiotic resistance rate was quite high, it is not the sole determinant of the poor treatment response. Some previous studies identified that factors including patient immunosuppression and the antibiotic persistence phenotype are also influential in antibiotic nonresponders.[16,24] In the current study, 100% of the nonresponsive patients were related to immunodeficiency. We also found a high rate of antibiotic persistence in all isolates after amikacin treatment at around 10%, and over 10% with meropenem. This is especially dangerous for patients with immunocompromising factors, who are unable to completely eradicate the remaining persister after treatment. Therefore, the use of these two antibiotic groups as the first-line treatment for *P. aeruginosa* respiratory infections needs careful consideration. The correlation between antibiotic persistence phenotypes and persistent infections has been demonstrated across numerous species such as *Klebsiella pneumoniae*,[12] *S. aureus*,[10,11] and *P. aeruginosa.*[24] Intriguingly, although ciprofloxacin is not the first-line indication for treating *P. aeruginosa* infections, this study has demonstrated a very low rate of bacterial persistence with ciprofloxacin. Similarly, other studies on quinolone antibiotics have shown that the rate of bacterial persistence with fluoroquinolones is typically less than 0.1%.[11,16] Therefore, fluoroquinolones should be considered to combine with a first-line antibiotics in treating *P. aeruginosa* infections to better eradicate any remaining persistent bacteria, thus enhancing treatment effectiveness.

One of the key factors contributing to antibiotic tolerance and persistence in bacteria is their capability to establish biofilms. Therefore, we continued to evaluate the biofilm-forming activity of *P. aeruginosa* isolates and found that all of the tested isolates, including reference strains, could form biofilms. Among the three antibiotics studied, ciprofloxacin exhibited the highest ability in eradicating bacteria within biofilms, achieving a remarkable reduction of 99.9% after 24 hours of exposure. In contrast, amikacin and meropenem demonstrated limited or no efficacy. This outcome raises significant concerns regarding the suitability of the current treatment regimen for *P. aeruginosa* infections.

Despite disadvantages related to the limited number of isolates in the study, our research has partly shown the factors contributing to the treatment nonresponse of *P. aeruginosa* infections in an ICU of a tertiary hospital in Vietnam. Additionally, these data can be referred to antibiotic selection in *P. aeruginosa* surveillance and control in such a tropical country with limited resources and high prevalence of AMR.

Authors' Contributions

T.K.N. and P.T.H.: Conceptualization and writing, reviewing and editing, and supervision. T.K.N., N.K.L., P.T.H., P.H.N., F.V.B., and G.W.: Methodology. T.K.N., N.K.L., G.W., P.T.H., and T.T.H.B.: Investigation. T.K.N., N.K.L., P.H.N., P.T.H., W.G., and T.T.H.B.: Formal analysis. P.H.N.: Resources. All authors contributed to the article and approved the submitted version.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author Disclosure Statement

The authors declare no conflicts of interest.

Funding Information

Not funded by any research funds.

Supplementary Material

Supplementary Table S1
Supplementary Table S2

References

1. Crone S, Vives-Flórez M, Kvich L, et al. The environmental occurrence of *Pseudomonas aeruginosa*. Apmis 2020;128(3): 220–231; doi: 10.1111/apm.13010
2. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: Summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2011–2014. Infect Control Hosp Epidemiol 2016;37(11):1288–1301; doi: 10.1017/ice.2016.174
3. Pachori P, Gothalwal R, Gandhi P. Emergence of antibiotic resistance *Pseudomonas aeruginosa* in intensive care unit; A critical review. Genes Dis 2019;6(2):109–119; doi: 10 .1016/j.gendis.2019.04.001
4. Reynolds D, Kollef M. The epidemiology and pathogenesis and treatment of *Pseudomonas aeruginosa* infections: An update. Drugs 2021;81(18):2117–2131; doi: 10.1007/ s40265-021-01635-6
5. Yoshida S, Suzuki K, Suzuki A, et al. Risk factors for the failure of treatment of *Pseudomonas aeruginosa* bacteremia in critically ill patients. Pharmazie 2017;72(7):428–432; doi: 10.1691/ph.2017.7453
6. Balaban NQ, Helaine S, Lewis K, et al. Definitions and guidelines for research on antibiotic persistence. Nat Rev Microbiol 2019;17(7):441–448; doi: 10.1038/s41579-019-0196-3

7. Van Den Bergh B, Fauvart M, Michiels J. Formation, physiology, ecology, evolution and clinical importance of bacterial persisters. FEMS Microbiol Rev 2017;41(3):219–251; doi: 10.1093/femsre/fux001
8. Soares A, Alexandre K, Etienne M. Tolerance and persistence of *Pseudomonas aeruginosa* in biofilms exposed to antibiotics: Molecular mechanisms, antibiotic strategies and therapeutic perspectives. Front Microbiol 2020;11:2057; doi: 10.3389/fmicb.2020.02057
9. Patel H, Buchad H, Gajjar D. *Pseudomonas aeruginosa* persister cell formation upon antibiotic exposure in planktonic and biofilm state. Sci Rep 2022;12(1):16151; doi: 10.1038/s41598-022-20323-3
10. Nguyen TK, Argudín MA, Deplano A, et al. Antibiotic resistance, biofilm formation, and intracellular survival as possible determinants of persistent or recurrent infections by *Staphylococcus aureus* in a vietnamese tertiary hospital: Focus on bacterial response to moxifloxacin. Microb Drug Resist 2020;26(6):537–544; doi: 10.1089/mdr.2019.0282
11. Nguyen TK, Peyrusson F, Siala W, et al. Activity of moxifloxacin against biofilms formed by clinical isolates of *Staphylococcus aureus* differing by their resistant or persister character to fluoroquinolones. Front Microbiol 2021; 12:785573; doi: 10.3389/fmicb.2021.785573
12. Pham HN, Than TDN, Nguyen HA, et al. Antibiotic resistance, biofilm formation, and persistent phenotype of *Klebsiella pneumoniae* in a Vietnamese tertiary hospital: A focus on amikacin. Microb Drug Resist 2024;30(5):203–209; doi: 10.1089/mdr.2023.0267
13. Magiorakos A-P, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268–281; doi: 10.1111/j.1469-0691.2011.03570.x
14. Clinical and Laboratory Standards Institute (CLSI). M100 Performance Standards for Antimicrobial Susceptibility Testing, 33rd Edition. Clinical and Laboratory Standards Institute (CLSI); 2023.
15. De Groote VN, Fauvart M, Kint CI, et al. *Pseudomonas aeruginosa* fosfomycin resistance mechanisms affect non-inherited fluoroquinolone tolerance. J Med Microbiol 2011; 60(Pt 3):329–336; doi: 10.1099/jmm.0.019703-0
16. Nguyen TK, Peyrusson F, Dodémont M, et al. The persister character of clinical isolates of *Staphylococcus aureus* contributes to faster evolution to resistance and higher survival in THP-1 monocytes: A study with moxifloxacin. Front Microbiol 2020;11:587364; doi: 10.3389/fmicb.2020.587364
17. Owens RC, Patel KB, Banevicius MA, et al. Oral bioavailability and pharmacokinetics of ciprofloxacin in patients with AIDS. Antimicrob Agents Chemother 1997;41(7): 1508–1511; doi: 10.1128/aac.41.7.1508
18. Mouton JW, van den Anker JN. Meropenem clinical pharmacokinetics. Clin Pharmacokinet 1995;28(4):275–286; doi: 10.2165/00003088-199528040-00002
19. Logre E, Enser M, Tanaka S, et al. Amikacin pharmacokinetic/pharmacodynamic in intensive care unit: A prospective database. Ann Intensive Care 2020;10(1):75; doi: 10 .1186/s13613-020-00685-5
20. Diaz Iglesias Y, Van Bambeke F. Activity of antibiotics against *Pseudomonas aeruginosa* in an *in vitro* model of biofilms in the context of cystic fibrosis: Influence of the culture medium. Antimicrob Agents Chemother 2020;64(4); doi: 10.1128/aac.02204-19
21. Ramírez-Estrada S, Borgatta B, Rello J. *Pseudomonas aeruginosa* ventilator-associated pneumonia management. Infect Drug Resist 2016;9:7–18; doi: 10.2147/IDR.S50669
22. Migiyama Y, Sakata S, Iyama S, et al. Airway *Pseudomonas aeruginosa* density in mechanically ventilated patients: Clinical impact and relation to therapeutic efficacy of antibiotics. Crit Care 2021;25(1):59; doi: 10.1186/s13054-021-03488-7
23. Tran GM, Ho-Le TP, Ha DT, et al. Patterns of antimicrobial resistance in intensive care unit patients: A study in Vietnam. BMC Infect Dis 2017;17(1):429; doi: 10.1186/s12879-017-2529-z
24. Mulcahy LR, Burns JL, Lory S, et al. Emergence of *Pseudomonas aeruginosa* strains producing high levels of persister cells in patients with cystic fibrosis. J Bacteriol 2010;192(23):6191–6199; doi: 10.1128/JB.01651-09

Address correspondence to:
Phung Thanh Huong, PhD
Faculty of Biotechnology
Hanoi University of Pharmacy
13-15 Le Thanh Tong
Hanoi
Vietnam

E-mail: huongpt@hup.edu.vn