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Research Article

Antimicrobial Resistance Profile of MDR & Non-MDR Meropenem-Resistant *Pseudomonas aeruginosa* Isolates of Patients in Intensive Care Unit of Tertiary Hospital

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ABSTRACT

Pseudomonas aeruginosa is one of the Gram-negative bacteria that frequently causes infection of patients in the Intensive Care Unit (ICU) which is easily resistant to antimicrobial drugs. Patients infected with carbapenem-resistant *P. aeruginosa* are predicted to have a poor prognosis. This study aims to know the resistance profile of meropenem-resistant *P. aeruginosa* of patients in the ICU. The results of this study can be used as a measure on the success of antimicrobial resistance control, infection control programs and become a reference for empirical therapy in the ICU. This study used descriptive research and was carried out at the Clinical Microbiology Laboratory of Sanglah Hospital Denpasar for three years, from 2018 to 2020. The results showed 38 of the 93 isolates of *P. aeruginosa* in the ICU were resistant to meropenem and were derived from sputum and urine. The percentage of meropenem-resistant *P. aeruginosa* isolates was higher in the multi-drug-resistant group and mostly came from sputum specimens. In 2018, Non-MDR meropenem-resistant *P. aeruginosa* isolates was that 100% sensitive to all other antibiotics used to treat *P. aeruginosa* infections, including; ceftazidime, cefepime, ciprofloxacin, gentamicin, amikacin, and piperacillin-tazobactam. In 2019 no meropenem-resistant *P. aeruginosa* isolates were found. In 2020, its sensitivity to antibiotics ceftazidime and piperacillin-tazobactam was 20.0%, ciprofloxacin 60.0% and to antibiotics gentamicin and amikacin 100%. MDR meropenem-resistant *P. aeruginosa* isolates in 2018 were still sensitive to ceftazidime (15.4%) and amikacin (69.2%) antibiotics, while in 2019 they were only sensitive to amikacin (37.5%). In 2020, *P. aeruginosa* isolates were sensitive to the antibiotics ceftazidime and cefepime (11.1%), piperacillin-tazobactam (22.2%), and amikacin (88.9%). Amikacin may be the choice of treatment for MDR meropenem-resistant *P. aeruginosa*.

Keywords: Resistance Profile; *Pseudomonas aeruginosa*; ICU; Meropenem; Resistance

ABSTRAK

Pseudomonas aeruginosa merupakan salah satu bakteri Gram negatif penyebab infeksi pada pasien di Intensive care unit (ICU) yang mudah resisten. Pasien terinfeksi *P. aeruginosa* yang resisten karbapenem diindikasikan memiliki prognosis yang buruk. pengendalian infeksi dan menjadi acuan pemberian terapi empiris di ICU. Penelitian ini menggunakan metode penelitian deskriptif dan dilakukan di Instalasi Mikrobiologi Klinik Rumah Sakit Sanglah Denpasar selama tiga tahun, dari 2018 hingga 2020. Hasil penelitian menunjukkan 38 dari 93 isolat *P. aeruginosa* di ICU resisten terhadap meropenem dan berasal dari spesimen sputum dan urine. Presentasi isolat *P. aeruginosa* yang resisten meropenem lebih tinggi pada kelompok multi-drug resisten dan sebagian besar berasal dari spesimen sputum. Pada tahun 2018, isolat *P. aeruginosa* Non-MDR yang resisten meropenem, 100% sensitif terhadap semua antibiotik lainnya yang digunakan untuk terapi infeksi *P. aeruginosa*, antara lain ; ceftazidime, cefepime, ciprofloxacin, gentamicin, amikacin, dan piperacillin-tazobaktam. Pada tahun 2019 tidak ditemukan isolat *P. aeruginosa* Non-MDR resisten meropenem. Pada tahun 2020, sensitifitasnya terhadap antibiotik ceftazidime dan piperacillin-tazobactam 20,0%, ciprofloxacin 60,0% dan terhadap antibiotik gentamicin serta amikacin 100%. Isolat *P. aeruginosa* MDR resisten meropenem pada tahun 2018 masih sensitif terhadap antibiotik ceftazidime (15,4%) dan amikacin (69,2%), sedangkan pada tahun 2019 hanya sensitif terhadap antibiotik amikacin (37,5%). Pada

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(15,4%) dan amikacin (69,2%), sedangkan pada tahun 2019 hanya sensitif terhadap antibiotik amikacin (37,5%). Pada

tahun 2020, isolat *P. aeruginosa* sensitif terhadap antibiotik ceftazidime dan cefepime (11,1%), piperacillin-tazobactam (22,2%), serta amikacin (88,9%). Amikacin dapat menjadi pilihan terapi *P. aeruginosa* MDR resistan meropenem.

Kata kunci: Profil Resistansi; *Pseudomonas aeruginosa*; ICU; Meropenem; Resistansi

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INTRODUCTION

Pseudomonas aeruginosa is one of the gram-negative bacteria that is often found as a contaminant in hospitals.^{1,2} This bacterium can be an opportunistic pathogen causing nosocomial infections in the blood, lungs, and other body parts after surgery, especially in immunocompromised patients, patient received appropriate medical procedure, invasive, surgical wound or burns.^{2,3} Nosocomial infections are estimated to occur annually in 1.75 million hospitalized patients worldwide and result in 175,000 deaths.⁴ *P. aeruginosa* accounts for 10%-20% of Hospital Acquired Infections in Europe.⁵ The National Healthcare Safety Network (NHSN) reported, *P. aeruginosa* as the third most common gram-negative bacteria causing nosocomial infections during 2011-2014.^{6,7}

Research by Ribeiro et al. from January 2010 to December 2013 found that *P. aeruginosa* was the second most common bacterium in the ICU Sao Paulo Hospital Brazil (14.5%), of which 48.7% was multi-resistant drug organism.⁸ At Sanglah Hospital itself in the second half of 2020, *P. aeruginosa* ranked third highest bacteria that cause infection in the Intensive Care Unit (ICU) and High Care Unit (HCU).⁹ Patients admitted to the ICU have a five to ten times higher risk of developing *P. aeruginosa* infection compared to patients admitted to other inpatients.¹⁰ High frequency infection in the ICU is associated with a decrease in the patient's immunity due to the disease and the use of invasive devices such as catheters, nasogastric tubes, and ventilators.^{3,10} *P. aeruginosa* has quorum sensing ability which is associated with the occurrence of biofilms on invasive medical devices in patients in the ICU.^{1,2} The spread of *P. aeruginosa* infection through person-to-person contact is also more prone to

occur in the ICU due to several factors a patient is combined in one relatively small room.¹⁰

In the management of infection therapy, the selection of empiric antibiotics in the ICU is not easy.⁴ According to *Performance Standard for Antimicrobial Susceptibility Testing on Clinical and Laboratory Standard Institute* (2021), *P. aeruginosa* sensitive to antibiotics, beta-lactam combinations such as piperacillin tazobactam, 3rd generation cephalosporins especially ceftazidime, 4th generation cephalosporins (cefepime), aminoglycosides (gentamicin, amikacin), monobactams (aztreonam), carbapenems (except ertapenem) and fluoroquinolones (ciprofloxacin).¹¹ The aztreonam group often becomes resistant.¹ Treatment of infectious diseases caused by *P. aeruginosa* becomes difficult because *P. aeruginosa* is easily resistant to various types of antibiotics. The prevalence of *P. aeruginosa* resistance to antibiotics is higher in ICU patient isolates compared to non ICU patients.^{10,12}

The irresponsible use of an antibiotic widely, repeatedly, and over a long period of time can lead to the emergence of antibiotic resistance.¹⁰ The increase in treatment costs in cases of infection due to resistant bacteria is caused by various factors, including; patients get longer treatment, longer hospital stays, more intensive attention from health professionals such as doctors and nurses, or the use of newer antibiotics. Newer antibiotics generally cost more than older antibiotics. The potential for increased costs in overcoming cases of infection by resistant bacteria needs attention because it can increase the financial burden that must be borne by the state in the era of implementing the National Health Insurance program (JKN).¹⁴

Carbapenem is a type of beta-lactam antibiotic which has a broad spectrum of antibacterial

activity.¹⁴ Carbapenems such as meropenem and imipenem are potential antimicrobial agents that also used to treat Multi-Drug Resistant *Pseudomonas aeruginosa* (MDRPA) infections.^{14,15} Increasing resistance to carbapenem antibiotics is one of the phenomena that must be watched out for at this time. Patients infected with carbapenem-resistant *P. aeruginosa* are indicated to have a poor prognosis.¹⁶

This study aims to know the resistance profile of meropenem-resistant *P. aeruginosa* in the ICU. The results of this study can be used as a measure on the implementation of antimicrobial resistance control, infection control programs and become a reference for empirical therapy in the ICU.

MATERIAL AND METHODS

This study used a descriptive research and was conducted at the Clinical Microbiology Laboratory of Sanglah Hospital Denpasar for three years, from 2018 to 2020. Sanglah Hospital Denpasar is a tertiary referral hospital and the main health care center for the eastern part of Indonesia with facilities of 710 beds. The sample was clinical isolates of meropenem-resistant *P. aeruginosa* from patients admitted to ICU. All type of specimens were included in this study. Identification and antimicrobial susceptibility testing were conducted using the VITEK 2 automated system with GN card for identification and AST GN 93 for antimicrobial susceptibility testing, according to the 2020 Clinical Laboratory Standard Institute (CLSI) standard.^{11,17} Data of antibiotic susceptibility test were collected and resistance profile was analyzed. Meropenem-resistant *P. aeruginosa* is a *P. aeruginosa* isolate with a minimum inhibitory concentration of ≥ 8 g/mL based on a dosage regimen of 1 gram every 8 hours.¹¹ The antibiotics assessed in this study were the antibiotics of choice for *P. aeruginosa* that were available and included in the Sanglah Hospital formulary, including piperacillin tazobactam, ceftazidime, cefepime, gentamicin, amikacin, and ciprofloxacin.¹⁸ Multidrug-resistant (MDR) is a condition in which bacteria are resistant to

at least one type of antibiotic from 3 antibiotic groups.¹³ MDR *P. aeruginosa* is a *P. aeruginosa* isolate that is resistant to at least one of three or more classes of antibiotics of choice for this bacterium, including: quinolones (ciprofloxacin), extended-spectrum cephalosporins (ceftazidime, cefepime), penicillin (piperacillin tazobactam), aminoglycosides (gentamicin or amikacin) and carbapenems (meropenem).^{11,13} The exclusion criteria were incomplete data on meropenem-resistant *P. aeruginosa* isolates from the ICU including the results of antibiotic sensitivity tests as well as data from other treatment rooms including the COVID-19 special ICU.

RESULTS

This study observe the sensitivity pattern of meropenem-resistant *P. aeruginosa* in 3 consecutive years, from 2018 to 2020. In general, from 2018 to 2020, 93 *P. aeruginosa* bacteria were isolated in the ICU Sanglah Hospital Denpasar. The number of non-multidrug-resistant (Non-MDR) *P. aeruginosa* isolates in the ICU showed an increasing number but the MDR isolates showed a decreasing number (Figure 1).

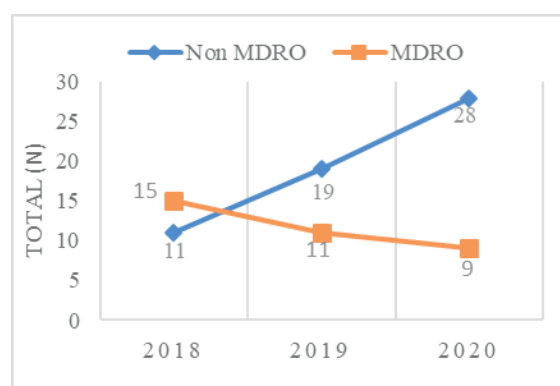


Figure 1. *Pseudomonas aeruginosa* in ICU during the period of 2018-2020

Most of the *P. aeruginosa* isolates came from sputum specimens, both Non-MDR and MDR, followed by urine and blood specimens. MDR *P. aeruginosa* isolates in 2018, 100% came from sputum specimens, while in 2019 and 2020, specimens came from sputum and urine specimens (Table I).

Table I. *Pseudomonas aeruginosa* in ICU during the period of 2018-2020 based on specimen

Specimen	2018 (%)		2019 (%)		2020 (%)	
	Non-MDR	MDR	Non-MDR	MDR	Non-MDR	MDR
Sputum	9(81.8)	15(100)	19(100)	9(81.8)	25(89.3)	8(88.9)
Blood	2(18.2)	0(0)	0(0)	0(0)	0(0)	0(0)
Urine	0(0)	0(0)	0(0)	2(18.2)	3(10.7)	1(11.1)
Total	11(100)	15(100)	19(100)	11(100)	28(100)	9(100)

Of the 93 isolates of *P. aeruginosa* in the ICU, 38 (40.9%) isolates had developed resistance to meropenem. The meropenem-resistant isolates were obtained from sputum and urine specimens. There were no meropenem-resistant isolates from blood. In 2018, 16 isolates were found from sputum, of which 3 of 9 (33.3%) were Non-MDR and 13 of 15 (86.7%) MDR. In 2019, 8 of 11 MDR isolates were resistant against meropenem, which was 66.7% in sputum and 100% in urine. In the Non-MDR group, no meropenem-resistant isolates were found. In 2020, the number of meropenem-resistant isolates were 14 isolates, 5 Non-MDR isolates came from sputum (20.0%) and 9 isolates from MDR, of which 8 isolates from sputum (100%) and 1 isolate from urine (100%). The percentage of meropenem-resistant *P. aeruginosa* isolates was higher in the MDR group (Figure 2).

Based on table II, in 2018, Non-MDR meropenem-resistant *P. aeruginosa* isolates was 100% sensitive to all other antibiotics used to treat *P. aeruginosa* infections, including; ceftazidime, cefepime, ciprofloxacin, gentamicin, amikacin, and piperacillin-tazobactam. In 2019 no meropenem-resistant *P. aeruginosa* isolates were found. In 2020, the percentage of sensitivity of other antibiotics used to treat *P. aeruginosa*

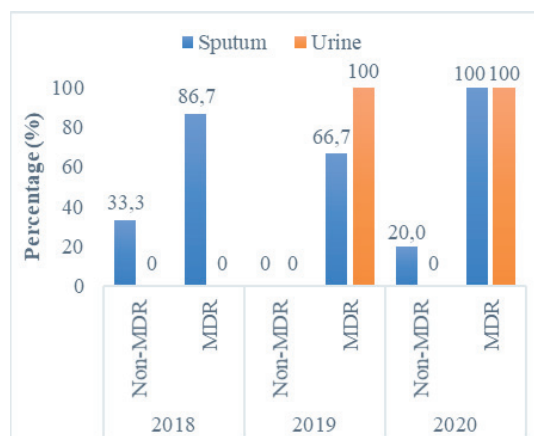


Figure 2. Meropenem-resistant *Pseudomonas aeruginosa* in ICU (N=38 isolates)

infection decreased dramatically compared to 2018, especially ceftazidime and piperacillin-tazobactam (20.0%), followed by ciprofloxacin (60.0%) while the sensitivity to gentamicin and amikacin was still 100%. MDR meropenem-resistant *P. aeruginosa* isolates in 2018 were still sensitive to ceftazidime (15.4%) and amikacin (69.2%). In 2019, MDR meropenem-resistant isolates of *P. aeruginosa* were only 37.5% sensitive to amikacin. The percentage was decreasing compared to 2018 and other antibiotics were already resistant. However, in 2020 the

Table II. Results of antibiotic susceptibility test of meropenem-resistant *P. aeruginosa* isolates in 2018-2020

No	Antibiotics	Non-MDR(%S)			MDR(%S)		
		2018(N=3)	2019(N=0)	2020(N=5)	2018(N=13)	2019(N=8)	2020(N=9)
1	Ceftazidime	3/3 (100)	0/0	1/5 (20.0)	2/13 (15.4)	0/8 (0.0)	1/9 (11.1)
2	Cefepime	3/3 (100)	0/0	1/5 (100)	0/13 (0.0)	0/8 (0.0)	1/9 (11.1)
3	Ciprofloxacin	3/3 (100)	0/0	3/5 (60.0)	0/13 (0.0)	0/8 (0.0)	0/9 (0.0)
4	Gentamicin	3/3 (100)	0/0	5/5 (100)	0/13 (0.0)	0/8 (0.0)	0/9 (0.0)
5	Amikacin	3/3 (100)	0/0	5/5 (100)	9/13 (69.2)	3/8 (37.5)	8/9 (88.9)
6	Piperacilin tazobactam	3/3 (100)	0/0	1/5 (20.0)	0/13 (0.0)	0/8 (0.0)	2/9 (22.2)

sensitivity of meropenem-resistant *P. aeruginosa* isolates to antibiotics improved, including to the ceftazidime and cefepime (11.1%), piperacillin-tazobactam (22.2%), and amikacin (88.9%).

The sensitivity pattern of MDR meropenem-resistant *P. aeruginosa* isolates (Table 3) showed that there was a pattern of MDR meropenem-resistant *P. aeruginosa* isolates that were also resistant to all antibiotics in the hospital. This pattern always exists every year with a fluctuating percentage and a significant decline in 2021. The pattern of MDR meropenem-resistant *P. aeruginosa* isolates sensitive to ceftazidime and amikacin antibiotics was only found in 2018. In 2021, the pattern of antibiotic sensitivity was more diverse. Most of them were resistant to various antibiotics, but each of these sensitivity patterns was still sensitive to amikacin antibiotics and one isolate of MDR *P. aeruginosa* was meropenem-resistant, besides being sensitive to amikacin, they were also sensitive to the ceftazidime, cefepime, piperacilin, tazobactam antibiotics. The Non-MDR meropenem-resistant *P. aeruginosa* isolate in 2018, the sensitivity pattern of 100% showed sensitivity to all anti-pseudomonal antibiotics

available at Sanglah Hospital Denpasar. However, in 2020, the pattern of sensitivity to antibiotics varied because some antibiotics were already resistant.

DISCUSSION

Pseudomonas aeruginosa is one of the environmental bacteria that is often found in hospitals.^{1,2} These bacteria can be opportunistic pathogens that cause nosocomial infections, including pneumonia, urinary tract infections, sepsis, osteomyelitis and skin infections including wounds and burns.² *P. aeruginosa* can grow in a variety of environmental conditions. Incidence of infection and resistance is common in the ICU. The bacteria found were often resistant to antibiotics.^{10,19} Based on data from the antibiogram of Sanglah Hospital for the July–December 2020 period, *P. aeruginosa* was the third highest bacteria in the ICU and HCU.⁹ The high rate of frequency of *P. aeruginosa* in the ICU is related to the decreased immunity itself, as well as the use of invasive devices such as catheters, nasogastric tubes and ventilators.^{3,10}

Table III. Resistance profile of MDR and Non-MDR meropenem-resistant *P. aeruginosa* isolates

No	Ceftazidime	Cefepime	Piperazilin tazobactam	Ciprofloxacin	Gentamicin	Amikacin	2018	2019	2020
							MDR(%)	MDR(%)	MDR(%)
Meropenem-Resistant <i>Pseudomonas aeruginosa</i>									
1	S	R	R	R	R	S	2/13 (15.4)	0/8 (0.0)	0/9 (0.0)
2	R	R	R	R	R	S	5/13 (58.8)	3/8(37.5)	6/9 (66.7)
3	R	R	R	R	R	R	4/13 (30.8)	5/8 (62.5)	1/9 (11.1)
4	R	R	S	R	R	S	0/13 (0.0)	0/8 (0.0)	1/9 (11.1)
5	S	S	S	R	R	S	0/13 (0.0)	0/8 (0.0)	1/9 (11.1)
Meropenem-Resistant <i>Pseudomonas aeruginosa</i>									
No							Non-MDR (%)	Non-MDR (%)	Non-MDR (%)
1	S	S	S	S	S	S	3/3 (100)	0/0	1/5 (20.0)
2	R	R	R	R	S	S	0/3 (0.0)	0/0	2/5 (40.0)
3	R	R	R	S	S	S	0/3 (0.0)	0/0	2/5 (40.0)

According to the Performance Standard for Antimicrobial Susceptibility Testing at the 2020 edition of the Clinical and Laboratory Standard Institute, *P. aeruginosa* is sensitive to beta lactam combination antibiotics such as piperacillin tazobactam, 3rd generation cephalosporins especially ceftazidime, 4th generation cephalosporin (cefepime), aminoglycosides (gentamicin, amikacin), monobactam (aztreonam), carbapenems (except ertapenem) and fluoroquinolones.¹¹ The aztreonam group often becomes resistant.¹ Widespread, repeated, and long-term use of an antibacterial agent can lead to the emergence of antibacterial resistance.¹⁵

P. aeruginosa is intrinsically resistant to several antibiotics and has the ability to rapidly generate resistance to new antimicrobials. *P. aeruginosa* was the first bacterium to show an MDR phenotype.⁸ Carbapenem antibiotics have become important in clinical management.^{8,20} Carbapenem-resistant *P. aeruginosa* infections are common.²¹ In February 2017, the World Health Organization made a priority list of pathogenic bacteria in the development of new antibiotics. Carbapenem-resistant *P. aeruginosa* is second ranked in the group of top priority (critical) bacteria because of its high resistance to most antibiotics including carbapenems and third-generation cephalosporins which are the best choices in the treatment of MDR bacteria.²² In the United States, 10%–20 % of clinical isolates of *P. aeruginosa* identified in health facilities, resistant to at least one carbapenem group antibiotic.²³ *P. aeruginosa* became meropenem-resistant due to upregulation of the efflux pump.²⁴

In this study, the percentage of meropenem-resistant *P. aeruginosa* isolates was higher in the multidrug-resistant group and most of them came from sputum specimens. Most of the sputum specimens collected in this study were from endotracheal tube secretions. *P. aeruginosa* has the ability of a bacterial cell-cell communication mechanism, known as quorum sensing (QS) which plays a role in gene expression and biofilm formation. The results of this study also support research in New York by Walter *et al.*, that during July-October 2015 carbapenem-resistant

P. aeruginosa was most commonly found in sputum specimens followed by urine.¹⁸ Research by Asempta TE *et al.*, in 2017-2018 also showed that 89% meropenem-resistant *P. aeruginosa* was found in respiratory specimens.²⁵

The sensitivity of meropenem-resistant *P. aeruginosa* isolates varied to various antibiotics. Research carried out by Vitkauskienė A *et al.*, in 2003 and 2008, isolates of *P. aeruginosa* that were resistant to carbapenems were more often resistant to ciprofloxacin and gentamicin than isolates sensitive to carbapenems. In 2008, isolates that were carbapenem-resistant were also more frequently resistant to ceftazidime, cefepime, aztreonam, piperacillin, and amikacin.²⁶ Results from the study by Asempta TE *et al.* in July-October 2017 showed that most of the carbapenem-resistant *P. aeruginosa* isolates had lower resistance to ceftazidime.²⁵ Research by Garcinuno *et al.* The data from 2009-2013 found that most of the meropenem-resistant *P. aeruginosa* isolates were also resistant to fluoroquinolones. Administration of amikacin therapy resulted in a more than threefold reduction in the risk of resistance.²⁷ Overuse of fluoroquinolones in the treatment of *P. aeruginosa* infections increased bacterial resistance to fluoroquinolones in recent years. Resistance to fluoroquinolones is mainly due to: (1) point mutations in the DNA gyrase (*gyrA* and *gyrB*) and topoisomerase IV (*parC* and *parE*) genes, (2) the presence of transferable plasmid-mediated quinolone resistance (PMQR), and (3) mutations in genes that regulate efflux expression and decreased expression of outer membrane porins.²⁸ From the results of this study, in 2018 Non-MDR meropenem-resistant *P. aeruginosa* isolates were still sensitive to all antibiotics but in 2020 most of the sensitivity patterns showed sensitivity to gentamicin and amikacin. Although the MDR meropenem-resistant isolates of *P. aeruginosa* showed less sensitivity to various antibiotics, in 2020 the percentage of sensitivity to antibiotics except ceftazidime increased. Sanglah Hospital published Guidelines for the Use of Prophylactic and Therapeutic Antibiotics in 2019, ceftazidime is included in the Watch group of antibiotics. Ceftazidime not recommended as empiric

antibiotic therapy but should be based on the results of bacterial culture (definitive therapy) to *P. aeruginosa*, so its use restricted, in which allows the sensitivity *P. aeruginosa* to the ceftazidime increased in Sanglah hospital. This can be seen in the pattern of sensitivity, where although there is a pattern that is already resistant to all antibiotics every year, the percentage shows a fluctuating picture and significantly decreases in 2020. In addition, there were various other sensitivity patterns that showed MDR meropenem-resistant *P. aeruginosa* isolates were still sensitive to amikacin. The results of this study support the statement of Baseti et al. in 2018 which stated that all antipseudomonal antibiotics except amikacin were associated with the emergence of resistance in *P. aeruginosa*. Aminoglycosides modifying enzymes (AME) inactivate aminoglycosides by attaching acetyl, phosphate or adenylyl groups to the amino and hydroxyl substituents on the antibiotic molecule. This modification significantly reduced the affinity of the aminoglycoside for the target of the 30S ribosomal subunit and blocks the activity of the aminoglycoside. However, compared to other aminoglycosides, amikacin is usually a poor substrate for this enzyme and is known to provide better antibiotic activity against *P. aeruginosa*.²⁸ The results of this study also support the study carried out by Khan F et al. in 2012-2013 regarding the Prevalence and Susceptibility Pattern of Multi Drug Resistant Clinical Isolates of *Pseudomonas aeruginosa* in Karachi and research by Anggraini D et al., regarding the Prevalence and Sensitivity Pattern of Multidrug Resistant Antimicrobial *Pseudomonas aeruginosa* in Arifin Achmad Pekanbaru Hospital in 2015 that amikacin is a therapeutic option for MDR *P. aeruginosa*.^{29,30}

CONCLUSION

The resistance profile of meropenem-resistant *P. aeruginosa* in the ICU varies. Meropenem-resistant *P. aeruginosa* isolates that were Non-MDR for 3 years were still mostly sensitive to gentamicin and amikacin, while in multi-drug resistant isolates, amikacin was the choice of treatment.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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