How to Cite:
Vigiawati, K. A., Budayanti, N. N. S., & Iswari, I. S. (2022). The presence of the vim-2 gene of Pseudomonas aeruginosa carbapenem resistance. *International Journal of Health Sciences*, *6*(S10), 1093–1101. https://doi.org/10.53730/ijhs.v6nS10.13809

The presence of the *vim-2* gene of *Pseudomonas aeruginosa* carbapenem resistance

Kadek Ayu Vigiawati
Clinical Microbiology Study Program Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah Central General Hospital Denpasar, Bali, Indonesia, 80114
Email: kadekayu061184@gmail.com

Ni Nyoman Sri Budayanti
Clinical Microbiology Study Program Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah Central General Hospital Denpasar, Bali, Indonesia, 80114
Corresponding author email: budayantinns@unud.ac.id

Ida Sri Iswari
Clinical Microbiology Study Program Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah Central General Hospital Denpasar, Bali, Indonesia, 80114
Email: idasriiswari@yahoo.co.id

Abstract---*Pseudomonas aeruginosa* is an opportunistic pathogen that causes infection in immunocompromised patients. *Pseudomonas aeruginosa* can cause severe acute and chronic infections in patients on ventilators and patients with burns, surgery, diabetic foot ulcers, and catheterization. *vim*-2 gene distributes metallo-β-lactamase with a broad spectrum of substrates against penicillins, cephalosporins, cefamycins, and carbapenems. Therefore, an attractive drug target for the treatment of β-lactam-resistant infections. This study aims to know the presence of *the vim*-2 *P. aeruginosa* carbapenem resistance gene. *Pseudomonas aeruginosa* is the most common microorganism that causes infection in the community and hospitals. Resistance of *P. aeruginosa* to various antibiotics is an increasingly common overuse or inappropriate use. *vim*-2 gene is of high clinical relevance due to its wide distribution and broad substrate range and therefore represents an important drug target for treating antibiotic-resistant infections. Based on the literature review, a molecular examination of the *vim-2* gene is critical to be a reference in selecting appropriate antibiotics in addition to phenotypic study.

Manuscript submitted: 5 Dec 2022, Manuscript revised: 14 Dec 2022, Accepted for publication: 30 Dec 2022

Keywords---antibiotics, carbapenem resistance, *Pseudomonas aeruginosa*, *vim*-2 genes.

Introduction

Pseudomonas aeruginosa (*P. aeruginosa*) is an opportunistic pathogen that causes infection in immunocompromised patients (Zafer *et al.*, 2015; CDC, 2019). *P. aeruginosa* can cause severe acute and chronic infections in patients on ventilators and patients with burns, surgery, diabetic foot ulcers, and catheterization (Crone *et al.*, 2020). Various clinical diseases caused by *P. aeruginosa* are bacteremia, ektima gangrenosum, wound infection, lung disease, especially in individuals with Cystic Fibrosis (CF), nosocomial Urinary Tract Infection (UTI), endocarditis, bone infection, eye infection, including keratitis. Ulcers, endophthalmitis, infections after burns or trauma, and in rare cases, central nervous system infections, including meningitis (Mahon, 2019). *P. aeruginosa* accounts for up to 6% of all bacteremia and as much as 75% of nosocomial bacteremia and is the third most common cause of gram-negative rod bacteremia, after *Escherichia coli* and *Klebsiella pneumonia* (Mahon, 2019).

Acute infection with antibiotic-resistant *P. aeruginosa* causes thousands of deaths worldwide (CDC, 2019). The increasing resistance and Multidrug Resistant (MDR) of *P. aeruginosa* in hospitalized patients is a significant public health threat (Nathwani *et al.*, 2014). In 2018, the CDC Antibiotic Resistance Laboratory Network identified an outbreak of carbapenem-resistant *P. aeruginosa* with an unusual form of resistance (CDC, 2019). Multidrug Resistant bacteria tremendously impact human health, causing more than 670.000 infections and 33.000 deaths yearly in the European Union (EU). MDR *P. aeruginosa* is responsible for more than 72.000 infections and more than 4.800 deaths in the EU annually. 61.892 cases and 4.155 deaths were attributed to carbapenem-resistant strains. Internationally, 10% to 50% of *P. aeruginosa* isolates are resistant to carbapenem (Kakoullis, 2021).

P. aeruginosa infections are difficult to treat the cause of intrinsic resistance and many commonly used antimicrobial drugs, making carbapenem an important antimicrobial for the clinical management of severe *P. aeruginosa* infections (Walters *et al.*, 2019). Beta-lactam antibiotics, including penicillins, cephalosporins, monobactams, and carbapenems, play a crucial role in treating *P. aeruginosa* infections. Today, however, resistance to beta-lactam antibiotics has drastically increased and resulted in poorer patient outcomes (Glen & Lamont, 2021). Carbapenems are a potent antibiotic used to treat infections caused by MDR gram negative bacteria; however, the effectiveness of these antibiotics is currently being the emergence of carbapenem-resistant bacteria (Kateete *et al.*, 2016). *P. aeruginosa* to carbapenem resistance is one of the main concerns in antimicrobial therapy for patients with infection (Yoon & Jeong, 2021).

Some MDR strains of *P. aeruginosa* are resistant to almost all antibiotics, including carbapenem. Two to 3% of carbapenem-resistant *P. aeruginosa* carry a Mobile Genetic Element (MGE) that makes the enzyme carbapenemase, which makes the antibiotic carbapenem ineffective (CDC, 2019). This mechanism is

associated with significant morbidity and mortality, as more than 85% of the estimated MDR-associated *P. aeruginosa* infections and deaths are associated with carbapenem-resistant strains (Kakoullis, 2021). Through intrinsic, acquired, and adaptive mechanisms, *P. aeruginosa* can develop resistance against beta-lactams. All three strategies for developing drug resistance can severely limit therapeutic options for treating severe infections (Lister, Wolter, and Hanson, 2009).

β-lactamase enzymes consist of Ambler classes A, B, C, and D β-lactamases. This classification structure of the enzyme protein is Class A, C, and D enzymes containing serine residues. In contrast, class B enzymes require an ion cofactor Zn^{2+}, metallo-β-lactamase, to hydrolyze the beta-lactam ring (Ruppé, Woerther and Barbier, 2015). *P. aeruginosa* strains producing Verona integron mediated (*vim*) were first isolated in Verona, Italy. *vim*-2 was first identified in France in 1996 (Poirel *et al.*, 2000). In the United States, Carbapenem-Resistant *Pseudomonas aeruginosa* Carbapenemase-producing (CP-CRPA) was first reported in 2001 in isolates producing metallo-β-lactamase *vim* from cancer patients in Texas (Walters *et al.*, 2019). *vim*-2 is a widely distributed metallo-β-lactamase with a broad spectrum of substrates against penicillins, cephalosporins, cefamycins, and carbapenems and is, therefore, an attractive drug target for the treatment of beta-lactam-resistant infections

Method

Literature Search Design in the form of journals and textbooks using google chrome on the NCBI Pubmed site (https://pubmed.ncbi.nlm.nih.gov/), Cochrane, and using Google Scholar (https://scholar.google.co.id/). The keywords used include antibiotics, carbapenem resistance, *Pseudomonas aeruginosa*, and Verona Integron Mediated 2 (*vim-2*) genes. The limitations of journals are those published 2000-2021, and according to the topics raised, those meet criteria such as being indexed by Scopus, ISSN, national journals, or international journals. Based on the literature search design, 24 journals and textbooks were obtained with details of 14 Q1 indexed journals, 6 Q2 indexed journals, 1 Copernicus Value indexed journal, 1 S1 indexed journal at Sinta Indonesia, and two textbooks that became the basis for writing.

Result and Discussion

In Prof I.G.N.G. Ngoerah Hospital Denpasar *P. aeruginos*a, one of the four bacteria most common, 27.3% are carbapenem-resistant. In 2018-2020 *P. aeruginosa* isolates were mainly found in sputum, urine, and blood specimens, where as many as 40.9% of isolates had developed resistance to meropenem (Sanglah, 2021; Lameng *et al.*, 2021). *P. aeruginos*a is the species most frequently isolated in clinical specimens. In hospitals, these bacteria can find of in humid environments, swimming pools, hot tubs, catheters, and humidifiers. Reservoirs include plants, soil, and tap water. These bacteria can cause mild illness in healthy people and severe infections in people with weakened immune systems (Mahon et al., 2019).

Pseudomonas infection is a strain of bacteria commonly found in the environment. Like on the ground and in the water. The most common type causing infection in humans is *P. aeruginosa*, which can cause infection in the blood, lungs, or other body parts after surgery (Centers for Disease Control and Prevention, 2019). Urinary tract infections (UTIs) can cause *P. aeruginosa,* especially in people who use catheters, leading to pyelonephritis. In comparison, some subgroups, such as the elderly and women, appear more susceptible to infection. Complicated UTIs are more commonly caused by uropathogenic *P. aeruginosa*, which shows a higher prevalence of antimicrobial resistance and a greater tendency to form biofilms in medical devices (Newman, Floyd, and Fothergill, 2017).

Many antimicrobial agents are resistant, and *P. aeruginos*us and other *pseudomonas* are important when bacteria more sensitive than the normal microbiota are suppressed. Clinical findings *P. aeruginosa* causes wound infection and burns, producing blue-green pus; meningitis when a lumbar puncture or during a neurosurgical procedure; and urinary tract infections when inserted through catheters and instruments or in irrigating solutions. Respiratory tract involvement, especially from contaminated respirators, causes necrotizing pneumonia. These bacteria are often found in mild otitis externa in swimmers and can cause invasive (malignant) otitis externa in patients with diabetes. An eye infection can cause rapid eye damage following an injury or surgical procedure. In infants or debilitated persons, *P. aeruginosa* can invade the bloodstream and cause fatal sepsis; this usually occurs in leukemia or lymphoma patients who have received antineoplastic drugs or radiation therapy and in patients with severe burns. In most *P. aeruginosa* infections, the symptoms and signs are non-specific and are related to the organ involved. Occasionally, ultraviolet fluorescence can detect verdoglobin (a breakdown product of hemoglobin) or fluorescent pigment in wounds, burns, or urine. Symptoms and signs are non-specific and are related to the organ involved. Occasionally, ultraviolet fluorescence can detect verdoglobin (a breakdown product of hemoglobin) or fluorescent pigment in wounds, burns, or urine. Symptoms and signs are non-specific and are related to the organ involved. Occasionally, ultraviolet fluorescence can detect verdoglobin (a breakdown product of hemoglobin) or fluorescent pigment in wounds, burns, or urine.

Bacteria *P. aeruginosa* is constantly finding new ways to avoid the effects of antibiotics used to treat the infections they cause. Antibiotic resistance occurs when germs no longer respond to the antibiotics designed to kill them. If these bacteria resist several antibiotics, they can become resistant to many drugs (Centers for Disease Control and Prevention, 2019). *Carbapenem* is an antibiotic belonging to the beta-lactam group. Beta-lactam antibiotics have four beta-lactam rings containing nitrogen structures (Mahon, 2019). *Carbapenem*s are often the last option for effective therapy, available for treating severe infections caused by MDR bacteria(Matsumura *et al.*, 2017).

The broadest spectrum of activity in the beta-lactam class, the carbapenems, have a high affinity for PBP and are stable to most Ambler classes A, C, and D β-lactamase (Mahon, 2019)**.** This fact seems to be due to the easy penetration of gram-negative and gram-positive bacterial cells and the high resistance to β-

lactamases. In addition, carbapenems are equal to or more active than third-generation cephalosporins against gram-negative rods. And very effective against obligate anaerobes such as *Bacteroides fragilis*. Meropenem was not significantly affected by dehydropeptidase-1 and did not require concomitant cilastatin administration. Carbapenem preparations are rarely administered orally (Ryan, 2019).

*P. aeruginos*a produces metallo-β-lactamase-producing (MPPA), an important nosocomial pathogen showing resistance to all-lactam antibiotics except monobactam. Each metallo-β-lactamases gene is located on a specific MGE, including integrons, transposons, plasmids, or on chromosomes, where they carry genes encoding the determinants of resistance to carbapenems and other antibiotics, conferring multidrug resistance against *P. aeruginosa*. In addition, these genetic elements can be transferred to other gram-negative species, increasing the rate of antimicrobial resistance and complicating the treatment of infected patients (Hong *et al.*, 2015). Class B β-lactamases are also known as "Metallo" because they require a divalent cation, namely Zn2+ ion, as a metal cofactor to hydrolyze beta-lactams. Metallo-β-lactamases is the most common type of carbapenemase produced by clinical isolates of *P. aeruginosa*, where the *vim* gene is the most widespread, followed by *imp* gene (Yoon & Jeong, 2021).

The acquired metallo-β-lactamases genes, mostly located in class 1 integrons as gene cassettes, have been found in various bacterial species, including *P. aeruginosa.* Metallo-β-lactamases is the most common type of carbapenemase produced by clinical isolates of *P. aeruginosa*. *vim*-1-producing *P. aeruginosa* strain was first isolated in Verona, Italy (Poirel *et al.*, 2000). Together with the *vim*-2 subtype, the first two *vim* enzymes were originally discovered in *P. aeruginosa* as a class 1 integron gene cassette. Notably, *vim*-2 has a 10-fold more efficient hydrolytic activity for imipenem and meropenem than *vim*-1, and in most countries, *vim*-2 is a carbapenemase. *P. aeruginosa* dominantly produces them. So far, 66 *vim* variants have been identified, and subtype 2-producing *P. aeruginosa* has been widely distributed, with some regional exceptions by specific outbreaks. *Vim*-producing *P. aeruginosa* clinical strains have been identified in almost all countries reporting surveillance data on six European continents.(Zafer *et al.*, 2015).

Gene metallo-β-lactamases in *vim*-1 was first identified in *P. aeruginosa* in Verona, Italy, and has since been reported in other gram-negative species from several countries. Whereas metallo-β-lactamases bla *vim*-2 was first reported in *P. aeruginosa* in Marseilles, France, in 1996, isolated from a 39-year-old French woman who was treated with Chronic Myelogenous Leukemia (Poirel *et al.*, 2000). *vim*-2 has emerged as the dominant metallo-β-lactamases variant worldwide. Multilocus sequence typing (MLST) has identified *international Clonal Complexes* (CCs) responsible for the spread of metallo-β-lactamases producing *P. aeruginosa*, especially in European countries (Zafer *et al.*, 2015). In the United States, Carbapenem-Resistant *Pseudomonas aeruginosa* Carbapenemase-producing (CP-CRPA) was first reported in 2001 in isolates producing metallo-β-lactamases *vim* from cancer patients in Texas (Walters *et al.*, 2019). The first metallo-β-lactamases reported in Korea was *vim*-2-producing *P. aeruginosa* isolated in 2002. Since then, many metallo-β-lactamases enzymes, including *vim*-2, have been

detected in isolates of *P. aeruginosa, Acinetobacter spp*, and *Enterobacteriaceae* (Hong *et al.*, 2015).

In addition to being detected in bacteria, *P. aeruginos*us *vim*-2 was also isolated from the bacterium *Acinetobacter baumanni* (*A. baumanni*). Of the 100 isolates of *A. baumanni* studied in Iran, 7% carried the bla-*vim*1 gene, and 6% carried the bla-*vim*2 gene where the *vim*-2 isolate was isolated on tracheal aspirate specimens (n=4), cerebrospinal fluid (n=1), and blood (N=1). Several metallo-β-lactamases genes were identified in *A. baumanii*: *imp*, *spm*, *vim*, *gim*, and *ndm*. Resistance to carbapenem in *A. baumanni* bacteria has increased due to the production of β-lactamases, including Ambler class A, D, and B enzymes, and also mainly due to gene transfer via MGEs such as plasmids or transposons (Rezaei *et al.*, 2018).

Verona integron mediated 2 is a widely distributed metallo-β-lactamases with a broad spectrum of substrates, including penicillins, cephalosporins, cefamycins, and carbapenems, and is, therefore, an attractive drug target for the treatment of beta-lactam resistant infections. The primary mechanism by which bacteria develop resistance to beta-lactam antibiotics is the expression of β-lactamases, enzymes capable of hydrolyzing the β-lactam ring and rendering antibiotics ineffective. In its mature form, *vim*-2 is a monomeric enzyme consisting of 240 amino acids with a molecular mass of 25 kDa. The structure of *vim*-2 is seen as the enzyme folded in the α/β sandwich; the two zinc ions are connected, and there is a hydroxide in the active site. *vim-2* has high clinical relevance due to its wide distribution and substrate range (Christopeit *et al.*, 2016). Enzymes share the same hydrolytic spectrum as *imp*-type enzymes are *vim*, with an amino acid identity of less than 40%. *vim*-2 is the most widespread metallo-β-lactamases in *P. aeruginosa* and has been the source of various outbreaks.*vim* hydrolyzes all classes-of lactams except monobactam and cefiderocol, making therapeutic options very limited in cases of infection (Christopeit *et al.*, 2016).

Conclusion

*Pseudomonas aeruginos*a is the most common microorganism that causes infection in the community and hospitals. Resistance of *P. aeruginosa* to various antibiotics is increasingly common and often caused by overuse or inappropriate use of antibiotics. The increasing prevalence of CRPA causes the most commonly prescribed beta-lactam antibiotics to become ineffective. Many antimicrobial agents *of P. aeruginosa* are intrinsically resistant, including penicillins, ampicillin, first and second-generation cephalosporins, trimethoprim-sulfamethoxazole, chloramphenicol, and tetracyclines. *P. aeruginosa* is usually sensitive to aminoglycosides, semisynthetic penicillins such as piperacillin and ticarcillin, third and fourth-generation cephalosporins (ceftazidime and cefepime, respectively), carbapenems (except ertapenem), and fluoroquinolones.

It is believed to originate from mutation points in the β-lactamase coding gene (bla), namely *imp*, *vim*, *spm*, *gim*, and *ndm*, where *vim* is most often found among them. These five genes play a role in the occurrence of *P. aeruginosa* resistance to beta-lactam antibiotics, one of which is carbapenem, a therapy option in cases of infection caused by *P. aeruginosa* bacteria. Resistance to any of these agents may develop while the patient is receiving therapy. The incidence of resistance was

much higher in the nosocomial strains of *P. aeruginosa*. Treating severe *P. aeruginosa* infection usually requires combination therapy, often with ceftazidime, cefepime, piperacillin, or a carbapenem (imipenem or meropenem) with an aminoglycoside (tobramycin or amikacin). Multidrug-resistant *P. aeruginosa* infection can be fatal in critically ill patients.

We need to understand how pathogens acquire resistance determinants to fight drug-resistant pathogens. Molecular examination of the *vim* gene is critical to be a reference in guidelines for selecting the right antibiotic in addition to phenotypic examination. Taking advantage of the latest techniques, the bacterial genome should be assessed for mobile genetic elements carrying carbapenemase encoding genes and for genomic islands. Furthermore, the mobile genetic elements should be investigated extensively through such techniques, enabling a comprehensive understanding of the spread of Antibiotic resistance.

Acknowledgments

All authors and I are grateful to two anonymous reviewers for their valuable comments on the earlier version of this paper.

References

CDC (2019) Antibiotic Resistance Threats In The United States 2019, Cdc. Available at: https://doi.org/10.1186/s13756-020-00872-w.

Centers for Disease Control and Prevention (2019) Pseudomonas aeruginosa in Healthcare Settings.

Christopeit, T., Yang, K.W., Yang, S.K. and Leiros, H.K.S. (2016) 'The structure of the metallo-β-lactamase VIM-2 in complex with a triazolylthioacetamide inhibitor', Acta Crystallographica Section:F Structural Biology Communications, 72(11), pp. 813–819. Available at: https://doi.org/10.1107/S2053230X16016113.

Crone, S., Vives-Flórez, M., Kvich, L., Saunders, A.M., Malone, M., Nicolaisen, M.H., Martínez-García, E., Rojas-Acosta, C., Catalina Gomez-Puerto, M., Calum, H., Whiteley, M., Kolter, R. and Bjarnsholt, T. (2020) 'The environmental occurrence of Pseudomonas aeruginosa', Apmis, 128(3), pp. 220–231. Available at: https://doi.org/10.1111/apm.13010.

Glen, K.A. and Lamont, I.L. (2021) 'β-lactam Resistance in Pseudomonas aeruginosa: Current Status, Future Prospects', Pathogens, 10(12). Available at: https://doi.org/10.3390/pathogens10121638.

Hong, D.J., Bae, I.K., Jang, I.H., Jeong, S.H., Kang, H.K. and Lee, K. (2015) 'Epidemiology and characteristics of metallo-ß-lactamase-producing Pseudomonas aeruginosa', Infection and Chemotherapy, 47(2), pp. 81–97. Available at: https://doi.org/10.3947/ic.2015.47.2.81.

Kakoullis, L. (2021) 'Mechanisms of Antibiotic Resistance in Important Gram-Positive and Gram-Negative Pathogens and Novel Antibiotic Solutions', Antibiotic Resistance, pp. 263–276. Available at: https://doi.org/10.3390/ antibiotics10040415 Academic10.1128/9781555815554.ch14.

Kateete, D.P., Nakanjako, R., Namugenyi, J., Erume, J., Joloba, M.L. and Najjuka, C.F. (2016) 'Carbapenem resistant Pseudomonas aeruginosa and Acinetobacter baumannii at Mulago Hospital in Kampala, Uganda (2007–

2009)', SpringerPlus, 5(1). Available at: https://doi.org/10.1186/s40064-016-2986-7.

Lameng, I.S.V., Budayanti, N.N.S., Prilandari, L.I. and Adhiputra, I.K.A.I. (2021) 'Antimicrobial Resistance Profile of MDR & Non-MDR Meropenem-Resistant Pseudomonas aeruginosa Isolates of Patients in Intensive Care Unit of Tertiary Hospital', Indonesian Journal of Tropical and Infectious Disease, 9(3), p. 152. Available at: https://doi.org/10.20473/ijtid.v9i3.30000.

Lister, P.D., Wolter, D.J. and Hanson, N.D. (2009) 'Antibacterial-resistant Pseudomonas aeruginosa: Clinical impact and complex regulation of chromosomally encoded resistance mechanisms', Clinical Microbiology Reviews, 22(4), pp. 582–610. Available at: https://doi.org/10.1128/CMR.00040-09.

Mahon, C.R. (2019) media: Textbook of Diagnostic Microbiology, Laboratory Medicine. Available at: https://doi.org/10.1309/u0mb-0p7r-rrwf-4bth.

Mahon, C.R. and Lehman, D.C. (2016) Textbook of diagnostic microbiology.

Matsumura, Y., Peirano, G., Devinney, R., Bradford, P.A., Motyl, M.R., Adams, M.D., Chen, L., Kreiswirth, B. and Pitout, J.D.D. (2017) 'Genomic epidemiology of global VIM-producing Enterobacteriaceae', Journal of Antimicrobial Chemotherapy, 72(8), pp. 2249–2258. Available at: https://doi.org/10.1093/jac/dkx148.

Nathwani, D., Raman, G., Sulham, K., Gavaghan, M. and Menon, V. (2014) 'Clinical and economic consequences of hospital-acquired resistant and multidrug-resistant Pseudomonas aeruginosa infections: A systematic review and meta-analysis, Antimicrobial Resistance and Infection Control, 3(1). Available at: https://doi.org/10.1186/2047-2994-3-32.

Newman, J.W., Floyd, R. V. and Fothergill, J.L. (2017) 'The contribution of Pseudomonas aeruginosa virulence factors and host factors in the establishment of urinary tract infections, FEMS Microbiology Letters, 364(15), pp. 1–11. Available at: https://doi.org/10.1093/femsle/fnx124.

Poirel, L., Naas, T., Nicolas, D., Collet, L., Bellais, S., Cavallo, J.D. and Nordmann, P. (2000) 'Characterization of VIM-2, a carbapenem-hydrolyzing Metallo-β-lactamase and its plasmid- and integron-borne gene from a Pseudomonas aeruginosa clinical isolate in France', Antimicrobial Agents and Chemotherapy, 44(4), pp. 891–897. Available at: https://doi.org/10.1128/AAC.44.4.891-897.2000.

Rezaei, A., Fazeli, H., Balaji, M., Moghadampour, M. and Faghri, J. (2018) 'Prevalence of Metallo-beta-lactamase producing Acinetobacter baumannii isolated from intensive care unit in tertiary care hospitals, Annali di Igiene Medicina Preventiva e di Comunita, 30(4), pp. 330–336. Available at: https://doi.org/10.7416/ai.2018.2224.

Ruppé, É., Woerther, P.L. and Barbier, F. (2015) 'Mechanisms of antimicrobial resistance in Gram-negative bacilli', Annals of Intensive Care, 5(1). Available at: https://doi.org/10.1186/s13613-015-0061-0.

Ryan, K.J. (2019) Antibacterial Agents and Drug Resistance, Sherris Medical MicrobiologyI. Available at: https://doi.org/10.1007/978-3-319-99921-0_4.

Sanglah, R. (2021) Pola Kepekaan Mikroorganisme RSUP Sanglah Tahun 2021.

Tille, P. (2013) Bailey & Scott's Diagnostic Microbiology.

Walters, M.S., Grass, J.E., Bulens, S.N., Hancock, E.B., Phipps, E.C., Muleta, D., Mounsey, J., Kainer, M.A., Concannon, C., Dumyati, G., Bower, C., Jacob, J., Cassidy, P.M., Beldavs, Z., Culbreath, K., Phillips., W.E., Hardy, D.J., Vargas,

R.L., Oettinger, M., Ansari, U., Stanton, R., Albrecht, V., Halpin, A.L., Karlsson, M., Rasheed, J.K. and Kallen, A. (2019) 'Carbapenem-resistant pseudomonas aeruginosa at us emerging infections program sites, 2015', Emerging Infectious Diseases, 25(7), pp. 1281–1288. Available at: https://doi.org/10.3201/eid2507.181200.

Yoon, E.J. and Jeong, S.H. (2021) 'Mobile Carbapenemase Genes in Pseudomonas aeruginosa', Frontiers in Microbiology, 12(February). Available at: https://doi.org/10.3389/fmicb.2021.614058.

Zafer, M.M., Al-Agamy, M.H., El-Mahallawy, H.A., Amin, M.A. and El Din Ashour, S. (2015) 'Dissemination of VIM-2 producing Pseudomonas aeruginosa ST233 at tertiary care hospitals in Egypt', BMC Infectious Diseases, 15(1), pp. 1–7. Available at: https://doi.org/10.1186/s12879-015-0861-8.