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THE ANTIBIOTIC RESISTANCE AND THE ABILITY OF BACTERIATO PRODUCE β-LACTAMASES

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ABSTRACT

Background : Accessibility of bacterial patterns and their sensitivity to pus can be utilized as a thought in giving anti-microbials observationally. Vale Sorowako Inco Hospital was located in mining region where health services were not as enormous as in huge cities but can still carry out free sensitivity tests without send them to a referral hospital. *Methods*: Antibiotics (Penicillin, cefuroxime, Ceftriaxone, and meropenem) were tried by dise diffusion. The suspension of the test microscopic organisms was included with NaCL 0.85% until it reaches turbidity, at that point a stick sterile cotton swab of bacterial suspension on the MHA (Muller Hinton Agar) media, paper disks containing the antibiotics were put on the media and incubated for 24 hours. *Results*: *Staphylococcus aureus, Enterobacter cloacae, Enterobacter aerogenes, Acinetobacter baumannii, Pseudomonas aeruginosa, Serratia odorifera,* and *Aeromonas hidropila* were bacteria isolated from pus. *S. aureus* and *E. cloacae* were the most (25%). Meropenen is the most sensitive antibiotics (90%), Penicillin and Cefuroxime are the most resistance (45%). *Conclusions* : The resistance that happens at Vale Sorowako Inco Hospital is not due to a prescription without a culture test ask, since antibiotics given by clinicians are continuously based on a culture test, but since of the capacity of bacteria to produce β-lactamases and the the presence of genes that can code for β-lactamases which moreover cause bacteria to resistant to antibiotics.

Keywords : Antibiotic, Resistance, Pus β-Lactamases

A. INTRODUCTION

Infection is the presence of a microorganism in tissues or body fluids which is accompanied by a clinical symptom both local and systemic (Leaper D, et al. 2015). Infectious diseases can be caused by four major groups of pests, namely : bacteria, fungi, viruses and parasites (Shen SS, et al. 2019) . One of the body's responses to infection is characterized by its formation of pus, where the pus is a protein-rich fluid resulting from the inflammatory process formed from dead cells of leukocytes, necrotic tissue, and cellular debris (Trojan R, et al. 2016) . The presence of pus which lasts a long time in an infected wound indicates that there are bacteria that continue to thrive in the area (Gupta M. et al. 2019.) So it is necessary to do culture testing, and resistance testing know the type of infectious bacteria to be given appropriate therapy illness (Tängdén T. et al. 2015)

In Indonesia 90%-100% of pharmacies fulfilled antimicrobial requests without a prescription (Zellweger RM. et al. 2016) The increasing use of antibiotics is giving rise problems and global threats to health will especially cause bacterial resistance to antibiotics (Hernando-Amado S, et al. 2019). The number of resistant bacteria is increasing quickly and some pathogenic bacteria have resistance to some antibiotics (Martens E. et al. 2015). Infectious diseases caused by bacteria failed to respond to treatment resulting in prolongation disease (prolonged illness) and an increased risk of death (greater risk of death) and the length of stay in the hospital (length of stay) (Mahmoud E, et al. 2021). So, when the response to treatment becomes slow, even will experience failure, the patient becomes infectious for a long time (carrier), thus this will provide more significant opportunities for resistant lines to spread to others (Sims N. et al. 2020)

One of the ways to reduce the resistance level is by choose the type of antibiotic based on information about the spectrum of bacteria cause the infection, and the susceptibility pattern of bacteria to antibiotics (Tacconelli E. dkk. 2018). One of the ways to determine the spectrum of bacteria and the
Availability of bacterial patterns and their resistance and sensitivity to pus specimens can be used as a consideration in giving antibiotics empirically (Rai S, et al. 2017). Vale Sorowako Inco Hospital is Remote mining hospital, which serves a small number of residents of the mining area, where health services are not as big as in big cities but can still carry out independent sensitivity tests without having to send them to a referral hospital.

B. RESEACH METHOD

Preparation of Antibiotics

Four types of antibiotics (Penicillin, cefuroxime, Ceftriaxone, and meropenem) were tested by dise diffusion. Resistance and sensitivity are based on the size of the bacteria halo zone in the around the antibiotic disc by referring to the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2010).

Sensitivity Test

The sensitivity test used is the Kirby-Bauer diffusion method with how to take the test bacterial colonies that have been grown for 24 hours previously and suspended in 0.5 ml of liquid medium and then incubation for 5-8 hours. The suspension of the test

bacteria was added with NaCL 0.85% until it reaches turbidity, then using a stick sterile cotton swab of bacterial suspension on the MHA (Muller Hinton Agar) media, then a paper disk containing the antibiotic agent is placed on the media and incubated for 24 hours. Observations are made by looking at whether there is an inhibition zone around the paper disk where there is a zone Inhibitory showed the presence of antibacterial activity against the test bacteria.

C. FINDING AND DISCUSSION

Table 1
Distribution of bacteria isolated from pus

Species	Abundance (%)
Staphylococcus aureus	(25)
Enterobacter cloacae	(25)
Enterobacter aerogenes	(15)
Acinetobacter baumannii	(10)
Pseudomonas aeruginosa	(10)
Serratia odorifera	(10)
Aeromonas hidropila	(5)

Table 2

All types of bacteria to antibiotics

No.	Species	Gram +	Gram -	Antibiotic			
				Penicillin	**Cefuroxime**	**Ceftriaxone**	**Meropenen**
1.	*Acinetobacter baumannii*	x	√	R	R	S	S
2.	*Staphylococcus aureus*	√	x	R	S	S	S
3.	*Aeromonas hidropila*	x	√	S	S	R	S
4.	*Serratia odorifera*	x	√	R	S	S	S
5.	*Staphylococcus aureus*	√	x	S	R	S	S
6.	*Staphylococcus aureus*	√	x	S	R	S	R
7.	*Enterobacter cloacae*	x	√	S	R	S	S
8.	*Enterobacter aerogenes*	x	√	S	S	R	S
9.	*Enterobacter cloacae*	x	√	S	R	S	S
10.	*Enterobacter aerogenes*	x	√	S	S	S	S
11.	*Acinetobacter baumannii*	x	√	S	S	R	S
12.	*Pseudomonas aeruginosa*	x	√	R	R	R	S
13.	*Enterobacter cloacae*	x	√	R	S	S	S
14.	*Enterobacter cloacae*	x	√	R	R	R	S
15.	*Enterobacter cloacae*	x	√	S	R	S	S
16.	*Pseudomonas aeruginosa*	x	√	R	R	S	S
17.	*Serratia odorifera*	x	√	R	R	S	R
18.	*Enterobacter aerogenes*	x	√	R	R	R	S
19.	*Staphylococcus aureus*	√	x	S	S	S	S
20.	*Staphylococcus aureus*	√	x	S	S	R	S

R = Resistant

S = Sensitive

Fig. 1. Resistence pattern against various antibiotics

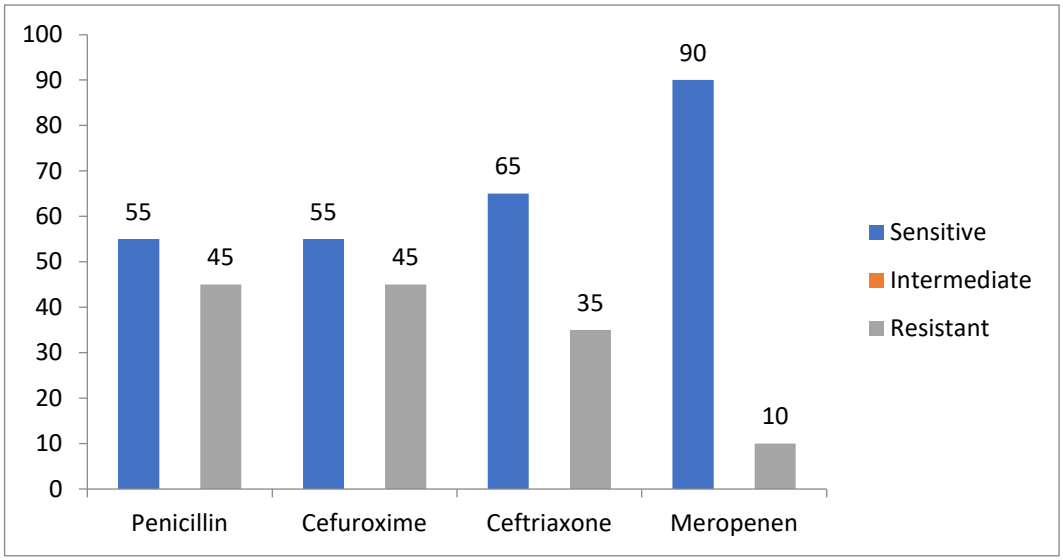

Fig. 2. Diagram of pus percentage

Antibiotic sensitivity test is a test used to test sensitivity of a bacterium to antibiotics, Sensitivity test aims to determine the working power/effectiveness of an antibiotic in killing bacteria (Akbari R, et al, 2018). The sample used in the form of wound infection (pus) from several patients at Vale Sorowako Inco Hospital, using several types of Antibiotics that are often used, especially to treat wound infections, are from: penicillin group, 2nd generation cephalosporin group, namely cefuroxime and Meropenem (Fig. 1).

Pus is the result of a bacterial infection process that occurs due to the accumulation of neutrophilic tissue, necrotic tissue, cellular debris, dead leucocytes (Scalise A, et al 2015). After the infection process is suppressed, the pus will gradually autolysis within a few days, then the final product will be absorbed into the surrounding tissue (Scalise A, et al. 2015), but in some cases the infection process is difficult to suppress, resulting in the production of pus, this can be due to the infecting bacteria being resistant to antibiotics (Serra, et al. 2015). In this study, samples were taken from infections that produce pus for a long period of time (Fig. 2), so it is necessary to do a culture examination and test for resistance to pus for appropriate therapy (Tängdén T.a et al. 2015)

Gupta et al (2019) reported on antimicrobial resistance patterns of burn wound infections found *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii* and *E. coli* were the foremost common living beings in patients, isolated bacteria were least resistant to antibiotics Tigecycline and Colistin. *K. pneumoniae* from the pus sample of hospitalized patients had antibiotic resistance (Balasubramanian B, et al. 2021). *A. baumannii* and *P. aeruginosa* are the foremost predominant microbes in burn contaminations (Akbari R, et al. 2019). Serra et al (2015) reported *Staphylococcus aureus* and *P. aeruginosa* are the most bacteria isolated from chronic wounds. *Enterobacter cloacae* was bacteria that caused wound infection in cardiac surgery patients(Breathnach AS (Breathnach AS, et al. 2006). *E. cloacae* and *E.*

aerogenes were bacteria found after Spine surgery (Nelson K, et al. 2020).Related with this research which found *S. aureus, E. cloacae, E. aerogenes, A. baumannii, P. aeruginosa, Serratia odorifera,* and *Aeromonas Hidropila* (Table 1).

The basis for classifying antibiotics that are sensitive, intermediate or resistant is based on antibiotics that have gone through laboratory testing and are adjusted to the standard standard criteria of each type of antibiotic. The standard of each antibiotic is different for a particular bacteria being tested. The test results are then marked with the letters "S" and "I" (intermediate) while resistant antibiotics are marked with the letter "R". Sensitivity indicates that the antibiotic has a greater inhibitory power than the required criteria, the intermediate is in the lowest minimum range until it reaches sensitivity, and resistance indicates the inhibition formed is far below the predetermined criteria (Ministry of Health, 2011).

Based on the frequency distribution of bacterial susceptibility patterns to penicillin, cefuroxime and meropenem antibiotics, the results showed that the antibiotic with the highest sensitivity was meropenem by 90% (table 3 and fig. 3), because meropenem is a β-lactam antibiotic from the carbapenem group (Nelson K, et al. 2020) [25] with a broad spectrum (Raza A, et al. 2020). Meropenem could be a secure antibiotic and has been more than 25 years commercially accessible (Tattersall T, et al, 2018).

Meropenem is a third-line antibiotic for severe bacterial infections (Tattersall T, et al, 2018) steady to most β-lactamases, other than the carbapenem grup (Tattersall T, et al, 2018), and a carbapenem group that is active against Gram –positive and Gram-negative bacteria (Torfoss D, et al, 2019). *S. aureus* is Gram-positive bacteria, *E. cloacae, E. aerogenes, A. baumannii, P. aeruginosa, S. odorifera, A. hidropila* are Gram-negative bacteria in this research (table 2). In line with this research, Lakshmaiah found 78.26% sensitivity of meropenem in 72 patients with hematologic malignancies (Lakshmaiah KC, et al. 2015)

Meropenem is an anti microbial that is exceedingly vulnerable toward degradation through hydrolysis of the amide bond within the β-lactam ring indeed at relatively moo temperatures (i.e., room temperature and above) and mugginess in both solubilized and unadulterated strong states. The heat and stickiness cause corruption of the β-lactam ring, which is the key component of the anti microbial required for its antibacterial activity (Mitragotri S, et al. 2014. Upon hydrolysis, meropenem debases into meropenemic corrosive as a β-lactam hydrolyzed item and oligomeric pollutions (dimers and trimers), which are related with expanded anaphylactic response (Raza A, et al. 2020).

The mechanism of action of meropenem is to disrupt the bacterial cell wall, thereby inhibiting bacterial growth and causing cell death, meropenem penetrates rapidly into the bacterial cell wall and binds to penicillin-binding proteins (PBP) with high affinity, hindering peptidoglycan crosslinking associated with cell wall synthesis, thereby inactivating bacteria (O. Gutkind G, et al. 2012).

Meanwhile, the highest resistance rates were cefuroxime and penicillin, which were 50% (table 3 and fig. 3). This shows that the antibiotic meropenem can still be used as a treatment for pus wound infections based on sensitivity testing and bacterial culture examination.

The results showed that the penicillin and the cephalosporin group (cefuroxime) had the same sensitivity level, 50% (table 3 and fig. 3). Cefuroxime should have a higher sensitivity level than the penicillin group, because cefuroxime have a spectrum of action, broad range, clinically active against gram-positive and negative bacteria, resistant to β-lactamase enzymes, and safer than penicillin drugs (Jobanputra AH, et al. 2015). Based on the data, it can be said that cephalosporin antibiotics have decreased sensitivity levels at Vale Sorowako Inco Hospital.

Resistance to Cefuroxime antibiotics occurs due to mutations that result in the production of different penicillin binding protein (PBP) so that Cefuroxime cannot inhibit PBP anymore (Zhao H, et al. 2018). In addition, resistance can also occur due to mutations that change the porin involved in transport across the outer membrane, this results in the Cefuroxime being unable to reach the cytoplasmic membrane (site of PBP) (Zhanel GG, et al. 2018). The ability of bacteria to produce β-lactamases and the presence of genes that can code for β-lactamases also make bacteria resistant to antibiotics due to hydrolysis of the β-lactam ring bond which results in inactivation of antibiotics (Zhao H, et al. 2018).

Bacteria that are resistant to β-lactam antibiotics have 3 resistance mechanisms, namely the destruction of antibiotics with β-lactamases (Lingzhi L, et al. 2018), decreasing the penetration of antibiotics to bind to transpeptidase proteins, and decreasing the binding affinity between these binding proteins and antibiotic compounds (Jose M, et al. 2017). Some bacteria such as *staphylococcus*, and most of the enteric rod-shaped bacteria have β-lactamase enzymes that can break down the β-lactam ring on the antibiotic and make it inactive (Andersen JL. Et al 2015) In detail, the mechanism that occurs begins with a protein transpepdase so that it loses its ability to inhibit the formation of the bacterial cell wall. Several studies state that in addition to being naturally found in gram-positive and negative bacteria, the gene encoding the enzyme β-lactamase is also found in plasmids and transposons so that it can be transferred between bacterial species (Jose M, et al. 2017). This will cause the ability of resistance to β-lactam antibiotics to spread quickly. The diffusion of β-lactam antibiotics into bacterial cells occurs through the mediation of a transmembrane protein called porins and the ability to diffuse is influenced by the size, charge, and hydrophilic nature of an antibiotic (Masi M, et al. 2019) (Vergalli J, et al 2020).

The resistance that occurs at Vale Sorowako Inco Hospital is not due to a prescription without a culture test request, because antibiotics given by clinicians are always based on a culture test, but because of the ability of bacteria to produce β-lactamases and the presence of genes that can code for β-lactamases which also cause bacteria to become resistant to antibiotics.

The study was approved by Medical laboratory service and operation guide Vale Sorowako Inco Hospital South Sulawesi Indonesia 2016, and Regulation of The Minister of Health of The Republic of Indonesia, number 43 year 2013. Written informed consent was waived by Medical laboratory service and operation guide Vale Sorowako Inco Hospital South Sulawesi Indonesia 2016. The study complied with the

Declaration of Helsinki, concerning maintaining the confidentiality of the patient's data as the data were anonymized.

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