

Original Research Article

Analysis of antibiotics administration in diabetic ulcer patients at Panembahan Senopati regional hospital Bantul

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ABSTRACT

Background: This study provides an overview of diabetic ulcer infection, antibiotic susceptibility patterns, the most common types of antibiotics, factors influence in antibiotics administrations, and verifying the guideline used of antibiotics.

Methods: The research used descriptive analysis combined with interviews. The study was starting from February-March 2021. Eighty-six diabetic ulcer patients were selected considering the inclusion and exclusion criteria. We interviewed seven doctors.

Results: 71 bacterias were found with a gram-negative bacteria count of 80.3%- higher than gram-positive bacteria (19.7%). The most common gram-negative bacteria found are *Escherichia coli* (12.7%) and show the most heightened sensitivity with imipenem (80.7%), while cefuroxime and trimethoprim-sulfamethoxazole show the highest resistance (64.9%). The most common gram-positive bacteria found are *Staphylococcus aureus* (14.1%), and vancomycin shows the most heightened sensitivity (100%), while penicillin shows the highest resistance (71.4%). The most common single antibiotic administration was ceftriaxone, as well as a combination of two antibiotics, namely ceftriaxone and metronidazole.

Conclusions: *Escherichia coli* was the most gram-negative bacteria, which has the highest sensitivity with imipenem, while *Staphylococcus aureus* was the most gram-positive bacteria, which has the most heightened sensitivity with vancomycin. The most common single antibiotic administration was ceftriaxone, as well as a combination of two antibiotics, ceftriaxone and metronidazole. Factors that influence antibiotics administration are patient condition, susceptibility testing, training, and advice from colleagues. Every doctor uses different guidelines for diabetic foot ulcer.

Keywords: Diabetic ulcers, Antibiotics, Antibiotic guidelines

INTRODUCTION

Diabetes Mellitus (DM), primarily type 2 diabetes mellitus, is a chronic disease that affects almost the entire world population globally and is a significant problem in healthcare.¹ The prevalence of DM in Indonesia in 1983 was 1.63%, which increased to 5.7% in 2017 and is estimated to grow to 6.0% in 2030.² Based on Basic Health

Research (Riskesdas) results in 2018, the prevalence of DM increased from 6.9% in 2013 to 8.5% in 2018.³

Diabetes Mellitus can cause various microvascular and macrovascular complications. DM complications can include retinopathy, neuropathy, atherosclerosis, nephropathy, and foot ulcers. These various complications can arise due to defects in the vascular system, which results in circulatory disorders.⁴ For instance, diabetic foot

ulcer cases in Dr. Cipto Mangunkusumo Central Hospital are recorded at around 8.7%.³ Diabetic foot ulcers result from complications from various risk factors such as peripheral neuropathy, peripheral artery disease, leg deformities, arterial insufficiency, trauma, and associated infection.⁴

Antibiotics contribute significantly to reducing morbidity and mortality due to infection. The doctor's choice of antibiotics is influenced by several factors, including the severity and duration of the infection, patients' recovery expectation, fear of disease complications, unclear disease diagnosis, and the influence of drug companies.⁵ The management of diabetic foot ulcers is divided based on the severity of the wound. Uninfected wounds, for example, do not require systemic antibiotics for both wound healing and prevention.⁶ Infection in diabetic foot ulcers requires a variety of management to produce good results. Antibiotics are needed in case of infection and combined with debridement, pressure reduction, and surgical procedures. Surgery is performed by cleaning the necrosis and callus tissue as well as drainage of the pus. Edema should be treated by leg elevation and compresses.⁶

Irrational use of antibiotics can lead to resistance, increased costs, and patient morbidity.⁷ Antibiotic resistance can occur through bacteria damaging antibiotics with the enzymes they produce, changing the antibiotic catch point receptors, shifting the antibiotic targets on bacterial cells, and modifying the nature of the bacterial cell walls so that antibiotics cannot penetrate the walls.⁸ Antibiotics used in diabetic ulcer infections should be administered based on bacterial culture and antibiotic susceptibility testing. Indonesian Ministry of Health issued a regulation on antibiotic resistance control. The Minister of Health Regulation No.8 of 2015 states that each hospital must optimally implement an antibiotic resistance control program and use general guidelines for antibiotics administration, using the Minister of Health Regulation No. 2406 of 2011 as a reference for antibiotic policy formulation in hospitals.⁹ The Indonesian Society of Internal Medicine officially published the clinical practice guideline for infection control of diabetic ulcer treatment. As a type B hospital, Panembahan Senopati Regional Hospital, Bantul, has an Antimicrobial Resistance Control Program team that understands the quality indicators of the antimicrobial resistance control program. The success of the program has never been previously studied. This study aims to provide an overview of the microbial and antibiotics patterns and evaluate the administration of antibiotics in diabetic ulcer cases during inpatient's hospitalization.

METHODS

This study was conducted with a mixed method. The quantitative design in this study was descriptive analysis, while the qualitative design was a case study, and the strategic methods used is embedded design. The study population included inpatient diabetic foot ulcer medical

records and doctors from the internal medicine unit and surgery unit at Panembahan Senopati Regional Hospital. This study was conducted at Panembahan Senopati Regional Hospital from February until March 2021. Determination of quantitative sample based on inclusion criteria, namely patients who received antibiotic therapy had susceptibility testing done to their pus specimen and identifying the bacteria causing the infection. In contrast, the exclusion criteria were patients with diabetes mellitus without ulcers and patient ulcers without diabetes mellitus. The sampling technique in this study was purposive sampling. Samples were taken by entering the entire population that met the inclusion criteria. All samples that meet the criteria are taken data according to the time of the study. The quantitative data collection used documentation of microorganism culture, antibiotic susceptibility testing, and antibiotic administration data of inpatient diabetic foot ulcers from January 2019 until December 2020 of the medical record. The qualitative data collection used an interview with five doctors from the internal medicine unit and two from the surgery unit to get information about factors that influence the administration of antibiotics and the guideline used in administering antibiotics. The quantitative data is first done, and then the qualitative data. The data then analyze together. All statistical data analyses were performed with Statistical package for social sciences (SPSS) programs, and qualitative data analyzed using content analysis. This study was conducted according to ethical guidelines approved by the Ethics Commission of Aisyiyah University Yogyakarta.

RESULTS

A total of 86 research subjects were involved in this study. Among them, 64 samples (74.4%) met the inclusion criteria. The data were obtained through the medical record department by taking the results of bacterial susceptibility testings in January 2019 - December 2020. Qualitative data were obtained through interviews with respondents, namely 5 Functional Medical Doctors from the Internal Medicine unit and 2 Functional Medical Doctors from the General Surgery unit.

Patient demographic characteristics

Based on table 1, about sex differences, more than half—34 patients (53.1%)—are women, while as many as 30 patients are male (46.9%). The patient's average age in this study is 56.6 years. Based on the procedures performed, as many as eight patients (12.5%) received amputation, 37 patients (57.8%) received debridement in the operating room, and the remaining 19 patients (29.7%) received necrotomy.

Bacterial characteristics

In this study, based on table 2, from subjects where bacterial growth is evident in the culture, a total of 71 types of bacteria were obtained, with 57 (80.3%) gram-negative bacteria and 14 gram-positive bacteria (19.7%). Most of

the infections in this study are caused by monomicrobial, as many as 57 (89.9%) compared to only 7 (10.9%) polymicrobial.

Table 1: Patient demographic characteristics.

Characteristics		Total (n=64)	%
Sex	Female	34	53.1
	Male	30	46.9
Age (years), average and range		56.61 (29-75)	
Procedures	Amputation	8	12.5
	Debridement	37	57.8
	Necrotomy	19	29.7

Table 2: Characteristics of bacteria.

Characteristics of bacteria	Number (n)	%
Gram-negative bacteria	57	80.3
Gram-positive bacteria	14	19.7
Monomicrobes	57	89.9
Polymicrobes	6	10.9

Bacterial pattern and antibiotics testing

This study concluded that the most common gram-negative bacteria found are *Escherichia coli* (12.7%), followed by *Proteus mirabilis* and *Proteus vulgaris* (8.5%), and *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* (7.0%). Meanwhile, the most common gram-positive bacteria found are *Staphylococcus aureus* (14.1%), followed by *Staphylococcus epidermidis* (4.1%), and *Hemolytic alpha streptococcus* (1.4%). The microbial pattern in ulcer patients can be seen in Table 3.

Based on the antibiotic sensitivity testing against gram-negative bacteria, we discovered that imipenem has the highest sensitivity value at 80.7%, followed by amikacin (77.2%) and meropenem (75.4%). The antibiotics with the highest resistance to gram-negative are cefuroxime and trimethoprim-sulfamethoxazole (64.9%), followed by fosfomycin (47.4%) and chloramphenicol (43.9%). The results of the antibiotic sensitivity testing against gram-negative bacteria can be seen in Table 4.

Based on the antibiotic sensitivity test results against gram-positive bacteria in Table 5, we observed that vancomycin possesses the highest sensitivity level at 100%, followed by imipenem and cefuroxime at 85.7%. In contrast, antibiotics with the highest resistance value against gram-positive bacteria are penicillin (71.4%), followed by erythromycin (42.9%).

Before susceptibility testing in diabetic ulcer patients, antibiotics can be administered alone or through a combination of 2 or 3 antibiotics. The 3rd generation

cephalosporin group, ceftriaxone, is the single most commonly administered antibiotic at 15.6%. Meanwhile, the most common combination of 2 antibiotics is ceftriaxone and metronidazole, which are included in the nitroimidazole group (18.8%). In addition, the combined administration of 3 antibiotics is between cefotaxime, metronidazole, and amikacin (1.6%). The pattern of antibiotic use before bacterial culture and susceptibility testing can be seen in Table 6.

Table 3: Pattern of microbes causing diabetic ulcer infection.

Bacteria	Number (n=71)	Percentage
<i>Escherichia coli</i>	9	12.7
<i>Proteus mirabilis</i>	6	8.5
<i>Proteus vulgaris</i>	6	8.5
<i>Enterobacter cloacae</i>	5	7.0
<i>Pseudomonas aeruginosa</i>	5	7.0
<i>Acinetobacter baumannii</i>	4	5.6
<i>Serratia marcescens</i>	4	5.6
<i>Klebsiella oxytosa</i>	3	4.2
<i>Pseudomonas luteola</i>	3	4.2
<i>Pseudomonas oryzae</i>	3	4.2
<i>Enterobacter aerogenes</i>	2	2.8
<i>Klebsiella</i>	1	1.4
<i>Pseudomonas</i>	1	1.4
<i>Staphylococcus aureus</i>	10	14.1
<i>Staphylococcus epidermidis</i>	3	4.1
<i>Streptococcus alfa hemolitik</i>	1	1.4

Following susceptibility testing, antibiotics can be administered in diabetic ulcer patients alone or through a combination of 2 or 3 antibiotics. Ceftriaxone was the single most commonly administered antibiotic at 15.6%. The most common combination of 2 antibiotics is ceftriaxone and metronidazole at 14.1%. Meanwhile, the combined administration of 3 antibiotics is between cefotaxime, metronidazole, and meropenem at 1.6%. The pattern of antibiotic administration after bacterial culture and antibiotic susceptibility testings can be seen in Table 7.

Guidelines used in administering antibiotics

Interviews were conducted with five doctors from the internal medicine unit and two from the general surgery unit. We obtained three themes. Theme 1 about guidelines

used in administering antibiotics consists of 3 categories the Indonesian Society of Internal Medicine, Ministry of Health regulations, and susceptibility testing experience. Theme 2, about factors that influence antibiotics administration, consists of four category seminar or

training activities, advice from a colleague, patients condition, and susceptibility testing. Theme 3 about reducing the incidence of resistance in practice consists of 3 categories patient condition and symptom, follow the protocol, and other antibiotics.

Table 4: Results of antibiotic sensitivity testing against gram-negative bacteria.

No	Type of antibiotic	Sensitive		Resistance		Intermediate		Negative	
		N	%	N	%	N	%	N	%
1	Amikacin	44	77.2	6	10.5	6	10.5	1	1.8
2	Amoxicillin-clavulanic acid	11	78.6	2	14.3	0	0	1	7.1
3	Ampicillin sulbactam	10	71.4	1	7.1	0	0	3	21.4
4	Cefepime	28	49.1	12	21.1	2	3.5	15	26.3
5	Cefotaxime	27	47.4	10	35.1	5	8.8	5	8.8
6	Cefpirome	6	10.5	9	15.8	0	0	42	73.7
7	Ceftazidime	32	56.1	13	22.8	6	10.5	6	10.5
8	Ceftriaxone	25	43.9	18	31.6	10	17.5	4	7
9	Cefuroxime	18	31.6	37	64.9	1	1.8	1	1.8
10	Chloramphenicol	25	43.9	25	43.9	7	12.3	0	0
11	Ciprofloxacin	33	57.9	19	33.3	3	5.3	2	3.5
12	Fosfomycin	22	38.6	27	47.4	2	3.5	6	10.5
13	Gentamicin	34	59.6	19	33.3	1	1.8	3	5.3
14	Imipenem	46	80.7	3	5.3	3	5.3	5	8.8
15	Meropenem	43	75.4	2	3.5	1	1.8	11	19.3
16	Sulfa-TMP	12	21.1	37	64.9	8	14	0	0
17	Tobramycin	40	70.2	15	26.3	2	3.5	0	0

Table 5: Results of antibiotic sensitivity testing against gram-positive bacteria.

No	Type of antibiotic	Sensitive		Resistance		Intermediate		Negative	
		N	%	N	%	N	%	N	%
1	Amikacin	11	78.6	2	14.3	1	7.1	0	0
2	Amoxicillin-clavulanic acid	11	78.6	2	14.3	0	0	1	7.1
3	Ampicillin sulbactam	10	71.4	1	7.1	0	0	3	21.4
4	Cefepime	5	35.7	3	21.4	1	7.1	5	35.7
5	Cefotaxime	7	50	1	7.1	5	35.7	1	7.1
6	Cefoksitin	8	57.1	2	14.3	3	21.4	1	7.1
7	Cefpirome	2	14.3	1	7.1	0	0	1	78.6
8	Ceftazidime	7	50	2	14.3	4	28.6	1	7.1
9	Ceftriaxone	7	50	2	14.3	4	28.6	1	7.1
10	Cefuroxime	12	85.7	1	7.1	1	7.1	0	0
11	Ciprofloxacin	8	57.1	4	28.6	1	7.1	1	7.1
12	Clindamycin	9	64.3	4	28.6	0	0	1	7.1
13	Erythromycin	4	28.6	6	42.9	2	14.3	2	14.3
14	Imipenem	12	85.7	1	7.1	0	0	1	7.1
15	Meropenem	8	57.1	1	7.1	1	7.1	4	28.6
16	Oxacillin	8	57.1	1	7.1	1	7.1	0	0
17	Penicillin	3	21.4	10	71.4	0	0	1	7.1
18	Sulfa-TMP	9	64.3	4	28.6	1	7.1	0	0
19	Vancomycin	14	100	0	0	0	0	0	0

Table 6: The pattern of antibiotic use before bacterial culture and susceptibility testing.

No	Antibiotic administration	Name of antibiotic	Number (N)	Percentage
1	Single antibiotic	Ceftriaxone	10	15.6
		Ceftazidime	4	6.3
		Cefotaxime	3	4.7
		Meropenem	2	3.1
		Ampicillin Sulbactam	1	1.6
		Ciprofloxacin	1	1.6
2	Combination of 2 antibiotics	Ceftriaxone, metronidazole	12	18.8
		Ceftazidime, metronidazole	10	15.6
		Meropenem, metronidazole	5	7.8
		Cefotaxime, metronidazole	3	4.7
		Ampicillin sulbactam, clindamycin	2	3.1
		Ceftriaxone, clindamycin	1	1.6
		Ceftriaxone, fosmycin	1	1.6
		Ceftriaxone, amikacin	1	1.6
		Cefotaxime, clindamycin	1	1.6
		Ceftazidime, moxifloxacin	1	1.6
		Ceftazidime, amikacin	1	1.6
		Moxifloxacin, metronidazole	1	1.6
		Imipenem, metronidazole	1	1.6
		Ciprofloxacin, clindamycin	1	1.6
		Ciprofloxacin, metronidazole	1	1.6
3	Combination of 3 antibiotics	Cefotaxime, amikacin, metronidazole	1	1.6

Table 7: The pattern of antibiotic use after bacterial culture and susceptibility testing.

No	Antibiotic administration	Name of antibiotic	Number (N)	Percentage
1	Single antibiotic	Ceftriaxone	10	15.6
		Meropenem	7	10.9
		Ceftazidime	5	7.8
		Ampicillin Sulbactam	3	4.7
		Vancomycin	1	1.6
		Imipenem	1	1.6
		Cefotaxime	1	1.6
2	Combination of 2 antibiotics	Ceftriaxone, metronidazole	9	14.1
		Ceftazidime, metronidazole	6	9.4
		Ciprofloxacin, metronidazole	3	4.7
		Meropenem, clindamycin	2	3.1
		Meropenem, metronidazole	2	3.1
		Amoxicillin-clavulanic acid, metronidazole	1	1.6
		Ceftriaxone, fosmycin	1	1.6
		Ceftriaxone, amikacin	1	1.6
		Meropenem, ciprofloxacin	1	1.6
		Cefuroxime amikacin	1	1.6
		Cefuroxime, amoxicillin-clavulanic acid	1	1.6
		Ampisilin subactam, clindamycin	1	1.6
		Cefotaxime, ciprofloxacin	1	1.6
3	Combination of 3 antibiotics	Cefotaxime, metronidazole, meropenem	1	1.6
		Ceftazidime, metronidazole, moxifloxacin	1	1.6

From theme 1, four doctors from internal medicine used the Indonesian Society of Internal Medicine guideline. One general surgery was used the Ministry of Health regulation, and another two doctors from the internal and general surgery unit use susceptibility testing experience. Information obtained from interview results as follows:

"Well, we don't have a Clinical Practice Guide. During antibiotic administration, we use the guidelines from the Indonesian Society of Internal Medicine or PAPDI; we have the Clinical Practice Guide from PAPDI. So, PAPDI issued existing clinical practice guidelines regarding ulcer DM. However, it only mentions the broad spectrum and does not specify which antibiotics to use." (R5, interview on March 17, 2021).

"For the guidance, we continue to use what was issued by PAPDI. For the treatment of diabetic ulcers, we also combine the patterns found in the hospital and take the existing literature into account." (R2, interview, March 13, 2021).

"For antibiotics administration, we already have the clinical practice guidelines for ulcer cases—we usually stick to it. The hospital's standard operating procedures are also based on the clinical pathway from our association. Usually, in the beginning, we administer antibiotics from the Cephalosporin class, and then we can add metronidazole when anaerobes are discovered." (R6, interview, March 18, 2021)

"Organizational guidelines. Was Issued organizational, clinical practice guidelines" (R3, interview on March 17, 2021).

"The guidelines are from the Ministry of Health—the one concerning antibiotic administration. I use it because it has been legally recognized throughout Indonesia. Later, we will adjust it to our respective region or hospital, based on the conclusion of the Antimicrobial Resistance Control Program." (R7, interview on March 24, 2021).

"Personally, I learned from my school days at Sardjito. There used to be a team that worked on the hospital microbial pattern. Well, for DM ulcers, it was first determined what germs are the most typical, and the administration of antibiotics would follow that. As for this current hospital, it doesn't exist yet, so I adopted the pattern from my school days. There are guidelines from the PAPDI, but I use one from my school years because they are more in line." (R4, interview on March 17, 2021).

"Usually, we base it from experience. Everything goes back to the susceptibility testing. So, here we use Cipro because it works well or is considered sensitive." (R1, interview, March 13, 2021).

Factors influence in antibiotics administration

Theme 2 is about factors that influence antibiotics administration. From this theme, there are seminars and training activities. Five respondents attend training, while two respondents did not yet attend training. Here information obtained as follow:

"For training, the administration of antibiotics has become one. I often take diabetic foot care, the last time before the pandemic was about five years ago in Jakarta. That's about diabetic foot care until the discussion." (R2, Interview on March 13, 2021).

"In terms of special antibiotic training, not yet. For ulcers, there is special training for the metabolic endocrine organization, apart from giving insulin, there is also training for diabetic ulcers" (R6, Interview on March 18, 2021).

From category advice from a colleague, four doctors chose to discuss with other colleagues in administering antibiotics, while three others never asked for advice from colleagues. The interview as follow:

"We discussed with friends, especially patients with culture-resistant, multi-drug resistant cultures" (R5, interview on March 17, 2021)

"Never, according to the existing results, because all is standards" (R2, interview on March 13, 2021).

In category patient condition, respondents in this study gave antibiotics to patients based on the degree of injury, signs of infection, and the patient's comorbidities. The interview as follow:

"Apart from the patient's condition—whether the type of wound is minor or severe, there is a grading system. Secondly, we usually use broad antibiotics first, which correspond to the possibility of most specific microbes present in the skin. Well, for me personally, the use of a broad spectrum is still allowed as long as susceptibility testing has not been carried out. For wounds, after the first antibiotic is given, we should first test the susceptibility. We also observe the use of broad antibiotics in patients whose susceptibility is not clear by looking at the site of infection. So, evident-based considerations regarding the types of microbes that are mostly found there are still used—or, based on the hospital pattern if it already exists." (R5, interview, March 17, 2021).

"First, we assess the clinical condition of the ulcers. So, there are five degrees of DM ulcers. If, for example, it is a mild degree of one to two, I will administer oral antibiotics. We already have guidelines that we adhere to. For the selection of DM ulcer antibiotics, if the results of susceptibility testing have not come out, I will follow the Clinical Practice Guidelines." (R4, interview on March 17, 2021).

"It depends. If they have not been through susceptibility testing, we will administer empirical antibiotics, which are still considered highly sensitive at this hospital. Only later, if there are susceptibility testing results, will it be adjusted to the results of these tests. In addition, not all DM patients are given antibiotics, depending on the type and severity of the wound and its systemic. With certain antibiotics, we may stop within a few weeks as well; maybe it is no longer needed even though the wound is still not completely healed, so we stop or switch to another antibiotic. Well, the choice is between stopping or replacing it with another one so that antibiotic resistance does not occur." (R7, interview on March 24, 2021).

From the susceptibility testing category, some respondents in this study used culture experience, empirical antibiotics that are still sensitive, and provide a broad spectrum in selecting antibiotics. Here the interview as follow:

"... is based on empiric therapy. We also make adjustments based on the previous examinations carried out at the hospital. Here, an Infection Prevention and Control Unit (IPC) takes samples to measure patterns in the hospital; this pattern is considered. For diabetic ulcers, we usually give a broad spectrum—including the use against anaerobic microbes. But if there are specific conclusions from the PPI, we will also consider them." (R3, Interview on March 13, 2021).

"Usually, I administer Ciprofloxacin. It is because it leans towards gram-negative bacteria too, and still produces good susceptibility testing results. So, the use of Ciprofloxacin depends on the case. If there is an improvement, the treatment continues. However, if there is no improvement within ten days or two weeks, susceptibility testing is carried out, and then observations are conducted. Usually, we will observe the patient in three days, then again, in five days. If the condition improves, the administration is continued; if there is no progress, we will test why it is not getting better with Ciprofloxacin." (R1, Interview on March 17, 2021).

Reducing the incidence of resistance in practice

Respondent in theme three about reducing the incidence of resistance in practice by assessing whether or not antibiotics are needed and the conditions that exist in the patient. Some statements are as follows:

"To be clear is that first, we assess whether the patient needs antibiotics first. Then the second we give the right dose, on time. Yes, but the use of antibiotics has many factors yes. And I try not to change antibiotics as much as possible" (R4, interview on March 17, 2021).

"If there is resistance, we will closely monitor the ulcer. Suppose it is stated that the ulcer does not need antibiotics. In that case, it is marked by repeated examinations of infection markers such as stable leukocytes and no signs of infection, the use of antibiotics should be stopped. If the

infection markers are still high, we need to think that there is resistance or change the drug." (R2, interview on March 13, 2021).

Category follows the protocol, respondents in this study used antibiotics that were still sensitive in the hospital and were used according to sensitivity culture. Here's the statement:

"The antibiotics were replaced with sensitive ones, based on the susceptibility testing earlier. We obey the protocol that we will do the culture within a few days if there is no improvement—controlling the patient in taking medication, for example, 2 or 3 times" (R1, interview on March 13, 2021).

"First of all, we use antibiotics according to the culture. Yes, as soon as possible, we use the right antibiotics" (R3, interview on March 17, 2021).

Using another antibiotics category, respondents in this study selected rolling and alternative antibiotics that were most suitable, trying to provide antibiotics outside of the culture to reduce the incidence of resistance. Here are some of his statements:

"It is rolling with alternative antibiotics. Choose another alternative antibiotic that is most suitable, safest. The second is by rolling antibiotics, so we don't use certain antibiotics for a long period. So later, there will be a cycle, a variety of antibiotics. The cycle may be every a week or a month if we need to change it" (R7, interview on March 24, 2021).

"If all of them are resistant, we will try to give antibiotics outside of culture" (R5, interview on March 17, 2021).

DISCUSSION

Based on table 1, about sex differences, more than half—34 patients (53.1%)—are women, while as many as 30 patients are male (46.9%). These results are similar to a study conducted by Fitria et al in dr. Zainal Abidin Regional Hospital and Meuraxa Regional Hospital, Banda Aceh, in November-December 2015, reported that 31 women suffered from diabetic ulcers (54.4%).¹⁰ Women are more at risk of developing type 2 diabetes mellitus because their body mass index values are commonly not ideal.¹¹ Hormones in women can also become a determinant: women who experience menopause will experience an accelerated decrease in estrogen and increase insulin resistance so that they are at increased risk of type 2 diabetes, cardiovascular disease, and malignancy.¹² The patient's average age in this study is 56.6 years. The result of this study corresponds to previous research conducted at Dr. Mintohardjo Marine Hospital (RSAL), Jakarta, in 2012, which reported that the most significant percentage of diabetic ulcers is found in patients aged 51-60 years.⁶ Diabetic ulcers are more common in people aged 50 years and over due to decreased

physiological functions of the body. They experience a decrease in blood glucose control function, such as reduced secretion and insulin resistance.¹¹

The study showed that gram-negative bacteria (80.3%) higher than gram-positive bacteria (19.7%) and monomicrobial, as many as (89.9%) compared to (10.9%) polymicrobial. The results are similar to those conducted by Rahmawati et al at Abdul Wahab Sjahranie Hospital, Samarinda, in the January-December 2017 period, which confirmed that the most common bacteria found in diabetic ulcers are gram-negative (54%) while gram-positive bacteria are only at 46%.¹³ Acute diabetic ulcer infection is dominated by aerobic gram-positive bacteria, with *Staphylococcus aureus* being the most typical. Meanwhile, chronic ulcers are dominated by aerobic gram-negative bacteria and obligate anaerobic bacteria.⁶ Infections of severe nature in the hospital are usually produced by 3 to 5 types of bacteria, including aerobes and anaerobes.¹⁴

This study concluded that the most common gram-negative bacteria are *Escherichia coli* (12.7%), while the most common gram-positive bacteria is *Staphylococcus aureus* (14.1%). Research conducted by Sulistianingsih et al in June 2013-February 2014 at Abepura Regional Hospital, Jayapura, discovered that *Escherichia coli* (38%) infects many cases of diabetic ulcers.¹⁵ Infection by *E. coli* bacteria can be influenced by several factors, such as cleaning up wounds with non-sterile medical devices, poor water sanitation, and cuts left open for a long time while cleaning, so they are easily exposed to bacteria. *E. coli* can be found in water reservoirs and the air. If these bacteria exceed the microbial limit, they can be pathogenic in the air and penetrate the body's tissues and cause infection.¹⁵

The study discovered that imipenem has the highest sensitivity value at 80.7% against gram-negative bacteria, while the highest resistance to gram-negative is cefuroxime and trimethoprim-sulfamethoxazole at 64.9%. Research conducted by Al Benwan et al in Kuwait in 2012 also reported that imipenem, amikacin, and piperacillin/tazobactam effectively against gram-negative bacteria.¹⁶ The carbapenem, aminoglycoside, and piperacillin/tazobactam class antibiotics also still display high sensitivity to bacteria caused by *E. Coli* in Asia.¹⁷ Meropenem and imipenem act via a beta-lactam-resistant monocyclic ring. Meropenem is shown to be active against gram-negative organisms but not gram-positive, while imipenem has a broader working spectrum to work against gram-positive and anaerobes.¹⁸ Production of ESBL can explain the resistance in the isolate. Other enzymes production such as AmpC β -lactamases, capable of hydrolyzing the extended-spectrum cephalosporins, example- cefuroxime, cefotaxime, ceftriaxone, ceftazidime, could be the reason for resistance in non-ESBL producing isolate.¹⁹

This study showed that vancomycin possesses the highest sensitivity level at 100% against gram-positive bacteria, while penicillin was the highest resistance antibiotic at

71.4%. Vancomycin belongs to the tricyclic glycopeptide class. Vancomycin has bactericidal properties against aerobic and anaerobic gram-positive bacteria, including multi-resistant *staphylococcus*. Research conducted by Al Benwan et al. in Kuwait in 2012 reported that vancomycin is the most effective antibiotic against gram-positive bacteria.¹⁶ Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterial problem of concern in diabetic ulcer cases for two decades. Al Benwan, in his research, found that MRSA was higher than previous studies in Kuwait and Saudi Arabia. The high MRSA can be influenced by several factors, including the absence of strict regulations regarding the administration of antibiotics, the lack of compliance with infection control in hospitals, and the increased prevalence of MRSA in the community. An increase in MRSA, if it continues to occur, can affect the administration of empiric antibiotic therapy.¹⁶

These study findings also revealed that the 3rd generation cephalosporin group, ceftriaxone is the single most commonly administered antibiotic before susceptibility testing at 15.6%, and the most common combination of 2 antibiotics with metronidazole 18.8%. Following susceptibility testing, ceftriaxone was the most commonly administered antibiotic at 15.6%, and the most combination of 2 antibiotics with 14.1%. This study found no noticeable changes in the most common administration of antibiotics, either alone or in combination. If it produces an excellent clinical response, the administration of empiric antibiotics is continued; if the patient is in bad condition, then the antibiotic treatment must be comprehensive for all types of isolated bacteria.¹⁴ The use of a combined cephalosporin and nitroimidazole as empirical therapy is more effective in lower leg infections as it expands the spectrum activity to fight gram-positive and gram-negative bacteria and obligates anaerobic bacteria.²¹

Indonesian Society of Internal Medicine clinical practice guideline stated that the control of infection in the diabetic foot with wounds is divided into two. Superficial diabetic foot wounds can be treated with antibiotics for gram-positive bacteria. In contrast, deeper wounds are given antibiotics for gram-negative bacteria plus metronidazole if there is suspicion of anaerobic bacterial infection. Wounds that are deep and extensive and accompanied by symptoms of systemic infection that require hospital treatment, broad-spectrum antibiotics can be given, which can include gram-positive, gram-negative, and anaerobic bacteria so that we can use 2 or 3 classes of antibiotics in their administration. Ceftriaxone—a third-generation cephalosporin—produces an excellent activity against *Enterobacteriaceae*, including beta-lactamase-producing strains. However, its action against gram-positive coccus is less active than first cephalosporin generation, which is effective against gram-positive and has moderate activity against gram-negative bacteria. Meanwhile, metronidazole can be administered if it's suspected of involving anaerobic bacteria.⁹

The importance of setting General Guidelines for the Use of Antibiotics aims to provide a reference for health workers to use antibiotics in the provision of health services, health care facilities in the use of antibiotics. Antibiotics have a significant contribution in reducing morbidity and mortality due to infection. The ability of antibiotics to treat or prevent infectious diseases has led to a tremendous increase in their use. Indonesian Minister of Health Regulation Number 8 of 2015 states that every hospital must carry out an optimal antibiotic resistance control program and in the reference for formulating antibiotic policies in hospitals using general guidelines for the use of antibiotics following Indonesian Minister of Health Regulation Number 2406 of 2011. For the specific infection control treatment, the Indonesian Society of Internal Medicine has officially published clinical practice guidelines for diabetic foot ulcers.²⁸

The choice of antibiotics by a doctor is influenced by several factors, including the severity and duration of the infection, the hope for the patient's recovery, the fear of complications, the diagnosis of the disease is not precise, and the influence of drug companies.²² Antibiotic administration in this study was influenced by several factors such as training activities or seminars, input from colleagues, patient conditions, and sensitivity culture.

Research by Zubair et al concluded that the selection of empiric antibiotics is carried out by considering the severity of the ulcer/gangrene, microbiological data (results of bacterial culture and antibiotic susceptibility testing), previous antibiotics used, history of ulcers/gangrene, and other factors related to the patients.²³ Rodrigues et al in their systematic review study in 2013, also found that intrinsic factors influence antibiotic administration in the form of doctor's attitude, satisfaction, and fear of the patient's possible condition—such as complications and death.²⁴ Meanwhile, extrinsic factors are influenced by patients in the form of signs and symptoms of the illness and health facility factors, namely the policy system and applicable guidelines. In addition to antibiotics administration guidelines, level of training, daily practice, length of work, and access to diagnostic tests are factors that influence antibiotic prescription.²⁵

Antibiotics are widely used in various therapies caused by infections. Irrational use of antibiotics can lead to resistance, increased costs, and patient morbidity.⁷ Antibiotics used in cases of diabetic ulcer infection should be given based on the results of bacterial culture and antibiotic sensitivity tests. Hospitals can use the results of most bacterial culture and sensitivity examinations as primary data in empirical antibiotic selection. Appropriate use of empiric antibiotics is expected to reduce unnecessary costs and length of treatment and prevent further complications.

We can prevent antibiotic resistance by implementing an antibiotic control program. This program aims to ensure

the effective treatment of patients with infections while minimizing the damage caused by antibiotics. This is done by optimizing the selection of antibiotics, dosage, route of administration, and duration of therapy while limiting undesirable things such as the emergence of resistance, costs, and adverse patient events.²⁶ Education, audits, rules, and policies, intravenous to oral switching are interventions that can reduce excessive antibiotic prescribing in hospitalized patients, reduce the incidence of antibiotic resistance, infection from the hospital, and increase patient outcomes.²⁷ Antibiotics with rotational administration also have advantages. The antibiotic rotation aims to reduce antibiotic resistance through future changes in antibiotic selection to prevent specific resistance mechanisms.²⁷ This study still has many weaknesses, including lack of exploration of the conducted interviews, and researchers have limited references in antibiotic sensitivity data and patterns of microorganisms that already exist in hospitals.

CONCLUSION

Based on the study conducted at Panembahan Senopati Regional Hospital, Bantul, we can conclude that the most common bacteria found in diabetic ulcer cases are gram-negative (80.3%) compared to gram-positive bacteria (19.7%). The most common gram-negative bacteria found in diabetic ulcer cases are *Escherichia coli* (12.7%). Meanwhile, the most common gram-positive bacteria found are *Staphylococcus aureus* (14.1%). Imipenem has the highest sensitivity value against gram-negative bacteria at 80.7%, while the highest resistance to gram-negative is displayed by cefuroxime and trimethoprim-sulfamethoxazole (64.9%). Vancomycin possesses the highest sensitivity level against gram-positive bacteria at 100%, while penicillin shows the highest resistance against gram-positive bacteria at 71.4%. The most common single antibiotics administration was ceftriaxone, as well as combination of 2 antibiotics, namely ceftriaxone and metronidazole. The factors influencing the choice of antibiotics in diabetes ulcer cases are microbiological data (bacterial culture and antibiotic susceptibility testing), the clinical condition of the ulcers, and other factors related to the patients. Every doctor uses different guidelines for antibiotics administration in diabetes ulcer cases—some use guidelines from the Indonesian Society of Internal Medicine, the Ministry of Health, and or based on susceptibility testing experiences.

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