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Antibiotic Evaluation Use towards Diabetic Foot Ulcer Inpatient at Hospital in Surakarta

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Abstracts

A diabetic foot ulcer is one of the diabetes mellitus type 2 complications indicated by open sores. Because it contains bacteria, it is treated with antibiotics. Improper use of antibiotics could harm patients due to the length of wound healing. This study aims to determine the appropriateness of antibiotics in patients with diabetic foot ulcers. This is non-experimental research with a descriptive analysis approach. The medical records of diabetic foot ulcer patients undergoing inpatient and antibiotic prescribing are observed. The data obtained were analyzed by comparing the use of antibiotics based on the National Health Service guidelines, the Indonesian National Drug Information, and the Drug Information Handbook. The results of this study showed antibiotics used are metronidazole (4.8%), vancomycin (4.8%) and antibiotics combination are ceftriaxone-metronidazole (47.6%), ceftriaxone-metronidazole-clindamycin (4,8%), levofloxacin-azithromycin-ceftriaxone (4.8%), cotrimoxazole-ciprofloxacin (4.8%), metronidazole-meropenem (4.8%), ceftriaxone-metronidazole-gentamicin (4.8%), metronidazole-clindamycin-ciprofloxacin (4.8%), ceftriaxone-levofloxacin (4.8%), and ceftriaxone-metronidazole-ciprofloxacin (9.5%). The evaluation results according to criteria appropriate usage of antibiotics that is 100% appropriate indication, 100% for appropriate of patients, 42.3% for appropriate drug, and 61.9% for the appropriate dose.

Keywords: Diabetes mellitus type 2, diabetic foot ulcer, antibiotics.

INTRODUCTION

Diabetic foot ulcers are one of the chronic complications of diabetes mellitus that can have a detrimental impact on increasing health costs that are quite large (Indonesian Endocrinology Doctor Association, 2021). Diabetic foot ulcers are microangiopathic conditions, namely peripheral neuropathy, that can trigger open sores on the skin surface. An open wound can become an infection due to the entry of bacteria and will develop rapidly because it is supported by high blood sugar (Casqueiro et al., 2012). Based on research in China, diabetic foot ulcer sufferers are predicted to experience an increase in number along with the increase in diabetes mellitus patients, especially in developing countries (80% in 2035) (Wu et al., 2017). Nearly 50% of diabetic patients develop foot ulcers. One of the management of foot ulcer infection is by giving antibiotics. The duration of administration of this antibiotic should be based on the severity of the ulcer, namely the absence of infection, mild, moderate, and severe infection based on the size of the wound and the presence or absence of signs of inflammation. Signs of infection are increased white blood cell count, increased erythrocyte sedimentation, and fever (Lepantalo et al., 2011; Lipsky et al., 2016). The most common pathogenic bacteria found in bacterial culture results were gram-positive Staphylococcus aureus, while gram-negative bacteria were Pseudomonas aeruginosa. This is important to know in an effort to determine the appropriate antibiotic for the patient, both in the selection of empirical and definitive antibiotics. Methicillin-susceptible Staphylococcus aureus (MSSA) and Streptococcus agalactiae which are highly resistant to clindamycin are also found frequently in patients with a history of previous antibiotic use (Wu et al., 2017).

Inappropriate prescribing of antibiotics will cause problems including increasing the incidence of resistance, both microbial resistance to single and combined antibiotics, increasing toxicity due to incorrect selection of antibiotics and dosing and frequency and duration, triggering other side effects beyond the patient's illness, and making infection take longer to heal which has an impact on the length of treatment and the cost of patient care which is certainly detrimental (Indonesia Ministri of Health, 2011).

According to some research, the challenges in the treatment of chronic wounds such as diabetic foot ulcers are infection management, ischemic management, and debridement. It is known that various kinds of antibiotics are needed to treat diabetic foot ulcers, and of course antibiotics will have different uses between one patient and another (Frykberg & Banks, 2015; Jeffcoate et al., 2018). There are many guidelines for various diseases, as well as for diabetic foot ulcers. Such as guidelines from IDSA (Infectious Disease Society of America), NICE (The National Institute for Health and Care Excellence), ADA (American Diabetes Association), and others. According to research conducted by Fitriani, 2015, at Klaten Hospital in 2014, the evaluation of antibiotics for diabetic foot ulcer were 100% appropriate indication and patient, 68% correct for the drug, and 76% correct in dosage where the analysis is based on the 2012 IDSA guidelines. By considering the impact that occurs if there is an inappropriate use of antibiotics, this study will try to compare the use of antibiotics in studies of patients with diabetic foot ulcers based on guidelines from IDSA 2012 and NICE 2014 although the most appropriate guideline itself is the selection of follow-up therapy based on on the evidence and adapt to local bacterial patterns present in health care facillities. This study aims to see the description of the use of antibiotics and evaluate the accuracy of diabetic ulcer patients through the appropriate indication, patients, drug of choice, and doses.

RESEARCH METHODOLOGY

Research design

This research is a non-experimental (observational) study with descriptive analysis and retrospective sampling using a purposive sampling method that meets the inclusion criteria. The inclusions criteria are inpatient with diagnosed of diabetic foot ulcer and complete patient medical record data including patient identit, ulcer severity, laboratory data (serum creatinine, white blood cells, and blood sugar levels), and prescribing antibiotics. The potential patient cannot be research subjects when they are pregnant. Patients who were known to have other infections that required antibiotic therapy and had bedsores were also excluded from the group because this would lead to bias in the indications for antibiotic use. The population analyzed was patients suffering from type 2 diabetes mellitus in the inpatient installation of regional public hospital Surakarta in 2015. They were studied retrospectively through their medical record data. This research was approved by the Faculty of Medicine, Sebelas Maret University, with the Ethical Clearance number 609/VII/HREC/2016.

Tools and materials

The tool used in this study was a data collection sheet to record patient medical record data at Hospital X in 2015, National Health Service 2014, IDSA (Infectious Disease Society of America) 2012, Drug Informational Handbook (DIH) guidelines) in 2009, and the British National Formulary in 2016. The research material used in this study

was patient medical records that matched the inclusion criteria in diabetic patients at the regional public hospital.

Data analysis

The results obtained were analyzed using descriptive methods. These data were analyzed to determine the accuracy of antibiotics in patients with diabetic foot ulcer hospitalized at the Surakarta Hospital. The data were analyzed by comparing patient's antibiotic list with the guidelines. For the appropriate category of indication, it compared with the 2014 National Health Service (NHS) Guideline and the 2012 Infectious Disease Society of America (IDSA) Guideline, the right category of patients based on the Drug Informational Handbook (DIH) in 2009, and the appropriate dose category based on the British National Formulary in 2016. A brief statistical data analysis was carried out on ulcer's staging data with the use of drug of choice antibiotics based on the guidelines used. After it was known that the two data were normally distributed, the chi square test was carried out to see the relationship between the ulcer staging and antibiotics.

Table 1. Characteristics of diabetic foot ulcer inpatients

Characteristics	Number of patients	% N=21
Gender		
Male	8	38.1%
Female	13	61.9%
Age		
36-45	4	19.0%
46-55	8	38.1%
56-65	7	33.3%
≥66	2	9.5%
Ulcer staging		
IDSA		
Mild	2	9.5%
Moderate	4	19.0%
Severe (risk of sepsis)	6	28.6%
Wagner	5	23.8%
Grade 1-2	4	19.0%
Grade 3-4		

RESULT AND DISCUSSION

Based on the results of the study, the total population of diabetic foot ulcer patients (Table 1) was 30 medical record data. A total of 21 data were used as samples, while 9 others died due to the diagnosis of infection outside the ulcer and incomplete medical record data. The results showed that women with Diabetic foot ulcers suffered more than 61% of the total diabetic ulcer patients, mostly older people, over 45 years old.

The risk factor of diabetic foot ulcer are elderly, prevalent of neuropathy, poor controlled of blood glucose and blood pressure, male gender, smoking, insulin use, and obesity (Al-Rubeaan et al., 2015). Diagnosis is the first step taken before a patient gets action regarding his illness. The study results at the regional public hospital Surakarta proved that the most diabetic ulcer patients undergoing hospitalization were patients with severe status, which was 28% based on the severity level based on Wagner in 1983 and the Infectious Disease Society of America in 2012. The severity of the ulcer is often cause sepsis. Patients with severe ulcer severity can experience systemic disorders such as fever, vomiting, shock, to severe sepsis that requires further treatment (Selva-Olid et al., 2015).

Injuries that occur in diabetic foot ulcer patients are a sign of continuous tissue healing failure. One of the treatments for Diabetic foot ulcers in regional general hospitals is the administration of antibiotics. The antibiotic regimen given must be adjusted to the severity and the infecting bacteria (Lipsky et al., 2012). In this study, there are seven classes of

Table 2. Distribution of antibiotic use in diabetic foot ulcer

Antibiotic administration pattern	Drug name	cases	% N= 21
Antibiotics			
Cephalosporin	Ceftriaxone	16	76,2%
Quinolone	Ciprofloxacin	4	19,0%
	Levofloxacin	2	9,5%
Macrolide	Azithromycin	1	4,8%
Aminoglycoside	Gentamicin	1	4,8%
Beta lactam	Meropenem	1	4,8%
Sulfonamide and trimethoprim	Cotrimoxazole	1	4,8%
Antibiotic alone	Metronidazole	1	4,8%
	Vancomycin	1	4,8%
Antibiotics combination	Ceftriaxone + metronidazole	10	47,6%
	Ciprofloxacin + metronidazole + clindamycin	1	4,8%
	Levofloxacin + azithromycin + Ceftriaxone	1	4,8%
	Cotrimoxazole + Ciprofloxacin	1	4,8%
	Metronidazole + meropenem	1	4,8%
	Ceftriaxone + metronidazole + gentamycin	1	4,8%
	Metronidazole + clindamycin + Ceftriaxone	1	4,8%
	Ceftriaxone + levofloxacin	1	4,8%
	Ceftriaxone + metronidazole + Ciprofloxacin	2	9,5%

antibiotics used for the treatment of Diabetic foot ulcers, such as cephalosporins (ceftriaxone), quinolones (ciprofloxacin and levofloxacin), macrolides (azithromycin), aminoglycosides (gentamicin), sulfonamides and trimethoprim (cotrimoxazole), and other antibiotics (metronidazole, vancomycin, and clindamycin) (**Table 2**). The most prescribed antibiotics were metronidazole, which was 17 patients out of a total of 21 diabetic foot ulcer patients. Metronidazole is a broad-spectrum antibiotic that has activity against a combination of gram-positive and gram-negative bacteria (National Institute for Health and Care Exellent, 2015), so it can be chosen as an empirical antibiotic before bacterial culture is performed to determine the definitive antibiotic that is suitable for the infecting bacteria (Aliakbar et al., 2019; Susanti et al., 2016).

Appropriate indication criteria is the administration of a drug or therapy that must be adjusted to the disease suffered by the patient, and the disease must be correct following the doctor's diagnosis (Ministry of Health of Republic Indonesia, 2021). Patients who can get a prescription for antibiotics are only patients who have a bacterial infection. In patients with diabetic foot ulcers, the accuracy of indications for antibiotics includes their ability to fight bacteria, especially bacteria whose infection site is on the skin (Indonesian National Drug Information, 2015). From the study results, it is known that the antibiotics used can be said to be 100% accurate. These results are in line with studies showing that antibiotics that can be used for diabetic foot ulcers are anti-pseudomonal penicillins, broad-spectrum penicillins, cephalosporins, carbapenems, and fluoroquinolones (Selva-Olid et al., 2015). However, sometimes the condition of diabetic foot ulcer does not have an infection so it does not need antibiotics. This is a consideration

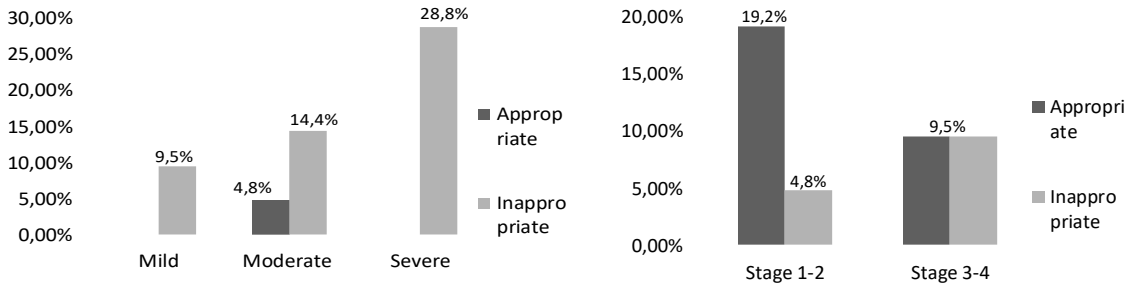
Table 3. Relationship between the degree of ulcer severity and the use of combination antibiotics

Severity	Antibiotic use		Proportion N (%) N=21	P value*
	Single	Combination		
IDSA				
Mild	2		2 (9,5)	0,007
Moderate	1	3	4 (19,1)	0,044
Severe		6	6 (28,5)	0,016
Wagner				
1-2	2	3	5 (23,8)	0,021
3-4		4	4 (19,1)	0,003
Total	5	16	21 (100)	

*chi-square test Asymp. Sig. <0,05

because the use of antibiotics that are not properly indicated will increase antibiotic resistance and the risk of side effects, one of which is diarrhoea associated with Clostridium difficile. Thus, the goal of using antibiotics in foot ulcers is to treat an active infectious process, aiming to tailor therapy to Service guidelines. Antibiotics that were declared the right drug matched the drug of choice in the guidelines.

The results showed (figure 1) that several antibiotic prescriptions did not match the exact criteria for the drug, this was because the antibiotics were not listed in the 2014



(A) (B)

Figure 1. Appropriate drug criteria. (A) Based on Infectious Disease Society of America severity index, (B) based on Wagner classification severity index

the appropriate pathogen (Barwell et al., 2017).

The appropriate drug's criteria is defined as the selection of drugs that must have a therapeutic effect in accordance with the disease. This is often associated with the drug of choice for a disease (Indonesia Ministry of Health, 2011). For example, the accuracy of the drug in diabetic ulcer patients was compared with the 2014 National Health National Health Service guidelines and the 2012 Infectious Disease Society of America guidelines as the drug of choice for Diabetic foot ulcers according to their severity. For example, gentamicin and azithromycin are not the drugs of choice for Diabetic foot ulcers according to the 2014 National Health Service and Infectious Disease Society of America 2012 guidelines, although they are indicated for infections of the skin, skin structures, and

Table 4. Appropriate of indications and appropriate patient's category of various antibiotics used in the treatment of diabetic ulcers

Rationality Category	Cases	% N= 21	Rationality Category	Cases	% N= 21
Appropriate indication	21	100%	Appropriate patient	21	100%
Inappropriate indication	0	0%	Inappropriate patien	0	0%

soft tissues, so they are not appropriate drugs. Based on various studies on therapy for diabetic foot ulcers, factors that can influence the number of cases of inappropriate use of drugs in patients with diabetic foot ulcers include the use of empirical or definitive antibiotics based on bacterial culture, ulcer severity status which causes complications, recurrent ulcers (related to history of use of antibiotics before), and co-morbidities (Awasthi et al., 2020; Hingorani et al., 2016; Jalilian et al., 2020; Yazdanpanah, 2015).

This resulted in the need for consideration of giving antibiotics in addition to the guideline provisions. The degree of ulcer severity itself which was classified by Wagner included an ulcer assessment seen from the depth of the wound and the presence of osteomyelitis or gangrene. Meanwhile, IDSA classifies ulcer severity not only from the appearance of the ulcer but also the presence of symptoms of systemic infection. Some patients receive a combination of antibiotics while others are single. Statistical data processing with chi-square was performed to see the relationship between the degree of ulcer severity and the use of antibiotics. Table 3 shows a relationship between the severity of ulcers (both based on IDSA and Wagner classifications) with the use of combination antibiotics. This is in line with the previous research which shows the more severe the degree of severity of diabetic foot ulcers, the need for aggressive antibiotic therapy, one of which is using a combination. where the use of antibiotic combination therapy can also make the ulcer condition more stable (Barwell et al., 2017; Parizad et al., 2021).

The appropriate patient's criteria can be interpreted as the drug chosen is not contrary to the patient's condition both from the pathophysiological aspect and the clinical condition. It can also be said that it is not contraindicated with the patient. The results showed that 100% of the patients were correct (Table 4).

The criteria for the correct dose are about the amount of dose quantity given. Still, they also the method of administration, the time interval of administration, and the period for administering the drug (Indonesia Ministry of Health, 2011). Determining the dosage of the antibiotics used is adjusted from several considerations, whether or not the given is adjusted to the dose stated in the guidelines, it is also adjusted to the patient's kidney condition by adjusting it to the value of the glomerular filtration rate used for antibiotic drugs. referred if the higher dose for a short duration, otherwise with broad-spectrum antibiotics (Barwell et al., 2017).

In this study, we determine the combination antibiotics are said to be appropriate if neither of those drugs are not right both in terms of dose and frequency (Table 5). In terms of dose adjustment according to the value of the glomerular filtration rate, almost all antibiotics were said to be accurate. Only one was incorrect, the use

Table 5. Percentage of the correct dose of antibiotics used in diabetic ulcer patients

No	Antibiotics	Dose and frequency	Rute	Duration	Standard dose and frequency	Appropriate/ inappropriate	% N=21
1	Metronidazole	500 mg/8 hour	iv	≤ 7 days	500 mg/8 hour (BNF, 2016)	Appropriate	4,8%
2	Vancomycin	500 mg/8 hour	iv	≤ 7 days	1-1,5 mg/12 hour (NHS, 2014)	Inappropriate dose	4,8%
3	Ceftriaxone + Metronidazole	2 g/24 hour	iv	≥ 7 days	2-4 g/24 hour (BNF, 2016)	Appropriate	47,6%
		500 mg/8 hour	iv	≤ 7 days	500 mg/8 hour (BNF, 2016)		
4	Ceftriaxone + Metronidazole	2 g/24 hour	iv	≤ 7 days	2-4 g/24 hour (BNF, 2016)	Appropriate	4,8%
		500 mg/8 hour	iv	≤ 7 days	500 mg/8 hour (BNF, 2016)		
	Clindamycin	300 mg 2x1	po	-	150-300 mg/6 hour (BNF, 2016)	Inappropriate frequency	4,8%
5	Levofloxacin + Ceftriaxone	750 mg/ 24 hour	iv	≤ 7 days	500 mg/24 hour (BNF, 2016)	Inappropriate dose	4,8%
		2 g/24 hour	iv	≤ 7 days	2-4 g/24 hour (BNF, 2016)		
6	Levofloxacin + Ceftriaxone	750 mg/ 24 hour	iv	≤ 7 days	500 mg/24 hour (BNF, 2016)	Inappropriate dose	4,8%
		2 g/24 hour	iv	≤ 7 days	2-4 g/24 hour (BNF, 2016)		
	Azithromycin	500 mg 1x1	po	≤ 7 days	500 mg 1x1 (BNF, 2016)	Appropriate	4,8%
7	Cotrimoxazole + Ciprofloxacin	960 mg 1x1	po	7 days	960 mg 2x1 (NHS, 2014)	Inappropriate dose and frequency	4,8%
		200 mg/12 hour	iv	≤ 7 days	400 mg/12 hour (NHS, 2014)		
8	Metronidazole + Meropenem	500 mg/8 hour	iv	≥ 7 days	500 mg/8 hour (BNF, 2016)	Appropriate	4,8%
		500 mg/8 hour	iv	≥ 7 days	0,5-1g/8 hour (BNF, 2016)		
9	Ceftriaxone + Metronidazole	2 g/24 hour	iv	≤ 7 days	2-4 g/24 hour (BNF, 2016)	Appropriate	4,8%
		500 mg/8 hour	iv	≤ 7 days	500 mg/8 hour (BNF, 2016)		
	Gentamicin	240 mg/24 hour	iv	≤ 7 days	5-7 mg/ kgbb/24 hour (BNF, 2016)		
10	Metronidazole + Clindamycin + Ciprofloxacin	500 mg/12 hour	iv	≤ 7 days	500 mg/8 hour (BNF, 2016)	Inappropriate dose and frequency	4,8%
		300 mg 1x1	po	≤ 7 days	450–600 mg/6 hour (NHS, 2014)		
		400 mg /12 hour	iv	≤ 7 days	400 mg/12 hour (NHS, 2014)		
11	Ceftriaxone + Levofloxacin	2 g/24 hour	iv	≤ 7 days	2-4 g/24 hour (BNF, 2016)	Inappropriate dose	4,8%
		750mg /24 hour	iv	≥ 7 days	500 mg/24 hour (BNF, 2016)		
12	Ceftriaxone + Ciprofloxacin	2 g/24 hour	iv	≥ 7 days	2-4 g/24 hour (BNF, 2016)	Inappropriate dose	9,5%
		800mg/12 hour	iv	≤ 7 days	400 mg/12 hour (NHS, 2014)		
	Metronidazole	500 mg/8 hour	iv	≥ 7 days	500 mg/8 hour (BNF, 2016)	Appropriate	9,5%
		∑			Inapropriate	Appropriate	
		%			38,1%	61,9%	

metronidazole, and ciprofloxacin. The results obtained from the study were 61.9% of the drugs used in the appropriate dose criteria. From this study, it was found that some patients required dose adjustments because the patients had other comorbid diseases such as hypertension and kidney failure. This dosage adjustment has caused several treatment regimens to be inconsistent with the guidelines. This is supported with systematic database review by Selva-Olid et al., 2015 which shows that patients with decreased kidney function require adjustment of antibiotics to be able to treat their diabetic foot ulcers.

The weakness of this study is, the evaluation of the appropriate use of antibiotics was not based on bacterial patterns. Whereas, the pattern of bacterial in each area tends to be different. It's mean that sometimes the hospital have their own guidelines in the use of antibiotics based on the results of research.

CONCLUSION

The research that has been done has resulted in the finding that the antibiotics used in diabetic ulcer patients according to the criteria for the accuracy of the use of antibiotics are 100% correct indication, 43.2% correct drug, 100% correct patient, and 61.9% correct dose. Seeing this fairly high accuracy rate, it is hoped that drug inaccuracies can be minimized so as not to harm the patient and the majority of outcome patients are in a clinical improvement when they leave the hospital.

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