

The Effectiveness of Empiric Antibiotic in Patients With Diabetic Foot Infection

Bambang Arianto^{a*}, EEn Hendarsih^a, Brenda P^b, Dewi Masyithah^{a,b}

^{a,b}Department of Surgery Haji Surabaya General Hospital Faculty of Medicine,
University of Muhammadiyah Malang, Malang, East Java, Indonesia. 65145.

*Email: dr.bambangRSHaji@gmail.com

Abstract

Objective: Diabetic foot is one of the most dreaded chronic complications of Diabetes Mellitus since it can potentially lead to disability and even death. This study aims to identify empiric antibiotics for initial treatment in patients with a diabetic foot infection.

Material and Method: This study is retrospective research with a *cross-sectional study* approach. The sample in this study was 332 people with a diabetic foot infection who were tested for culture and antibiotic sensitivity in 2015-2020 at Haji General Hospital Surabaya.

Results: The distribution of respondents based on the history of antibiotic use mainly was Ceftriaxone and Metronidazole, as many as 78 (34.8%), rather than using Amikacin, Metronidazole as many as 4 (1.7%). While the use of no antibiotics was 108 (32.5%).

Conclusion: Antibiotic sensitivity, particularly in the two most common types of germs, Clindamycin, Fosfomycin, Cefepime, and Gentamycin, can be considered as empirical antibiotics while waiting for the results of germ culture and antibiotic sensitivity.

Keywords: diabetic foot ulcer; diabetes mellitus; empiric antibiotics.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease characterized by elevated blood glucose levels. Diabetes mellitus is a disease due to metabolic disorders of carbohydrates, fats, and proteins caused by a relative or absolute lack of insulin hormone. These uncontrolled conditions may lead to acute metabolic and long-term vascular complications^{1,2}.

Diabetes mellitus is one of the global health concerns, with the number of sufferers increasing yearly. Recorded WHO (World Health Organization) data predicted an increasing number of DM sufferers in Indonesia, from 8.4 million in 2000 to around 21.3 million in 2030³. According to the Baseline Health Research (Riskesdas) results, DM increased in Indonesia, from 5.7% in 2007 to 6.9% in 2013. According to Riskesdas 2013, most of diabetes in Jambi province was 6.9% in 2013 and 8.5% in 2018.

Diabetic foot is one of the chronic complications of Diabetes Mellitus that people with Diabetes Mellitus most dread as it causes disability and even the possibility of death. Almost a third of the 5 cases of Diabetes Mellitus treated have problems with their feet. Consequently, the medical treatments take a long time to be cured and cost high expenses. Furthermore, decreased laborers due to disability and absenteeism at work resulted in enormous costs incurred⁵.

The incidence of diabetic patients is high and continues to increase. One-third have ulcers, and 50% of them are infected. People with diabetes are prone to causing wounds that are difficult to heal. If the damage becomes infected, it may worsen and lead to sepsis. Infectious diabetic foot wounds may necessitate amputation. Moreover, severe sepsis may result in death. Therefore, rapid treatment with debridement and empiric antibiotics is needed to prevent wound aggravation, risk of amputation, sepsis, and death.

Many cases of diabetic foot ulcers come to the hospital for treatment. Some of them come either with severe infection or with sepsis. The cause is microorganisms in diabetic foot ulcers. As a result, it is necessary to examine the types of microorganisms that infect diabetic foot ulcers and the empirical antibiotics that should be

used before the effects of germ culture and antibiotic sensitivity.

MATERIAL AND METHOD

This type of study is a retrospective study with a cross-sectional study approach. The population in this study were all patients diagnosed with diabetes mellitus with diabetic foot infection in 2015-2020 at the General Hospital of Haji Surabaya, obtaining 332 respondents. The sample of this study were patients with a diabetic foot infection who were tested for culture and antibiotic sensitivity in 2015-2020 at the General Hospital of Haji Surabaya. This research was conducted at the microbiology laboratory of Haji Surabaya Hospital.

The sampling technique This type of study is a retrospective study with a *cross-sectional study* approach. The population in this study were all patients diagnosed with diabetes mellitus with diabetic foot infection in 2015-2020 at the general hospital of Haji Surabaya, obtaining 332 respondents.

RESULTS

Three hundred thirty-two respondents diagnosed with diabetic foot infection were tested for culture and antibiotic sensitivity at Haji Surabaya Hospital.

Sex	n	%
Sex	156	46.9 %
Female	176	53.0 %
Total	332	100 %

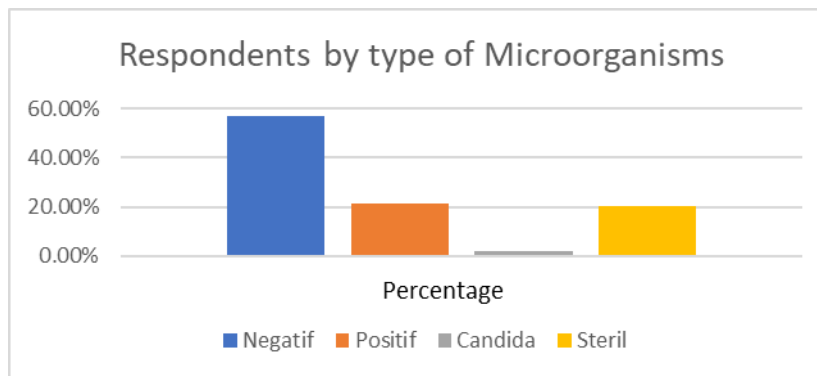
Table 1. Distribution of Sex

The distribution of respondents based on gender was mainly female, with as many as 176 people (53.0%) than male.

No.	History of Antibiotic Utilization	Amount	Percentage
1	No Antibiotic	108	32.5%
1	Ceftriaxone dan Metronidazole	78	34.8%
2	Ceftriaxone	74	33.0%
3	Ampicillin Sulbactam dan Metronidazole	13	5.8%
4	Ampicillin Sulbactam	11	4.9%
5	Amikacin	10	4.4%
6	Metronidazole	7	3.1%
7	Meropenem	6	2.6%
8	Amikacin, Metronidazole	4	1.7%

Table 2. Distribution of Respondents Based on History of Antibiotic Utilization

The distribution of respondents based on the history of antibiotic use mainly was Ceftriaxone and Metronidazole, as many as 78 (34.8%), rather than using Amikacin, Metronidazole in 4 (1.7%). At the same time, the use of no antibiotics was 108 (32.5%).



Resource: Clinical Microbiology Laboratory at Haji General Hospital East Java Province

Figure 1. Respondents by Type of Microorganisms

No.	Gram	Amount	Percentage
1	Negative	183	55.1%
2	Positive	76	22.8%
3	Candida	6	1.8%
4	Sterile	67	20.1%
Total		332	100.0%

Table 3. Examination results based on microorganism type

The distribution of respondents based on the type of microorganism was primarily negative, with as many as 183 (55.1%), rather than Candida in 6 (1.8%).

No	Organisma	AMP	SAM	TZP	CZO	CAZ	CRO	FEP	ATM	MEM	AMG	GEN	CIP	TGC	FOSS	XT	CTX	OXAL	VX	MX	ERY	CLI	NZ	ANT	CTY	RIF	FOX	AMC	ETP	
Gram Positif																														
1	Staphylococcus aureus	20	41.2				42.9	100		42.9	0	57.4	48.5	95.8	92.5	81.8		43.3	51.5	52.9	57.6	1.4	100	80	18.2	91.7	43.8	11.8		
2	Enterococcus faecalis	90	100	100		100	0	23		40		50	54.5	100	50	100	0	33.3	85.7	100	16.7	0	18.9	6.7	33.3	0				
3	Staphylococcus haemolyticus	0	0			100	0			0		50	25	100	66	62.5		0	25	14.4	33	317	5100	71	44.4	100	33	3	50	
4	Streptococcus agalactiae	100	100				66.7			50		33	33.3	100	66	7100		33.3	100	75	100	100	100	100	0		100	100		
5	Staphylococcus xylosus	0	50				0			0		50	50		0	50		0	50	50	0	50	100	50	0		0	0		
6	Staphylococcus epidermidis	0	0				0					0	0	100	0	100		0	0	0	0	100	100	0	0		0	0		
7	Corynebacterium ulcerans	0					0			0	100	0	0					0	0			0	0	0	0		0	0		
8	Kocuria kristinae					100	100	100										100	100	100	100	100	100	100						
9	Micrococcus sp.		0									0	0	0		0		0	0	0	0	0	0	0	0		0			
10	Streptococcus porcinus					0	100	100										0	100		100	100	100	100						
11	Streptococcus uberis	100	100			0	0	0					0						100		0	0	100	0						
Gram Negatif																														
1	Escherichia coli	3.4	24.4	79.5	2.4	39.5	34.9	52.5	39.5	97.7	92	66	21.4	76.7	80	39	37.1		33.3	28.6		100		3.9		36.7	52.4	100		
2	Pseudomonas aeruginosa	0	22.2	70	7.1	64.5	18.2	81.5	37.9	89.7	100	81	83.3	11.4	50	20	100		63.2	100	0	37.1		16.7		0	33.3	100		
3	Klebsiella pneumoniae	3.7	33.3	77.8	14.3	46.4	44.4	59.3	42.9	85.7	88	93.7	33.3	71.4	38	50	7.75	100	36.4	29	100	6	7100	100	50		100	38.5	100	
4	Proteus mirabilis	1.3	28	91.7	12.3	65.4	48.1	52.2	65.4	92.3	83	3	44	14	17.6	9	34	5	46.2	0					10		18.1	75		
5	Acinetobacter baumannii	0	17.3	0	0	0	0	0	0	16.7	62.5	9	0	36.4	16	40	50		50			50		16	100	0	0			
6	Klebsiella aerogenes	20	36.4	91.7	18.2	50	58.3	22.2	30	75	91	3	80	63.6	57.1		63.6	50		81.8	33.3				50		50	100		
7	Classtromonas luteola		100	75	100	50	50	50	75	50	66	75	100	100			33.3		100	100	0			0						
8	Providencia	0	0	50	0	0	0	50	0	50	75	33	33.3	33.3	0	33.3		0						0			0			

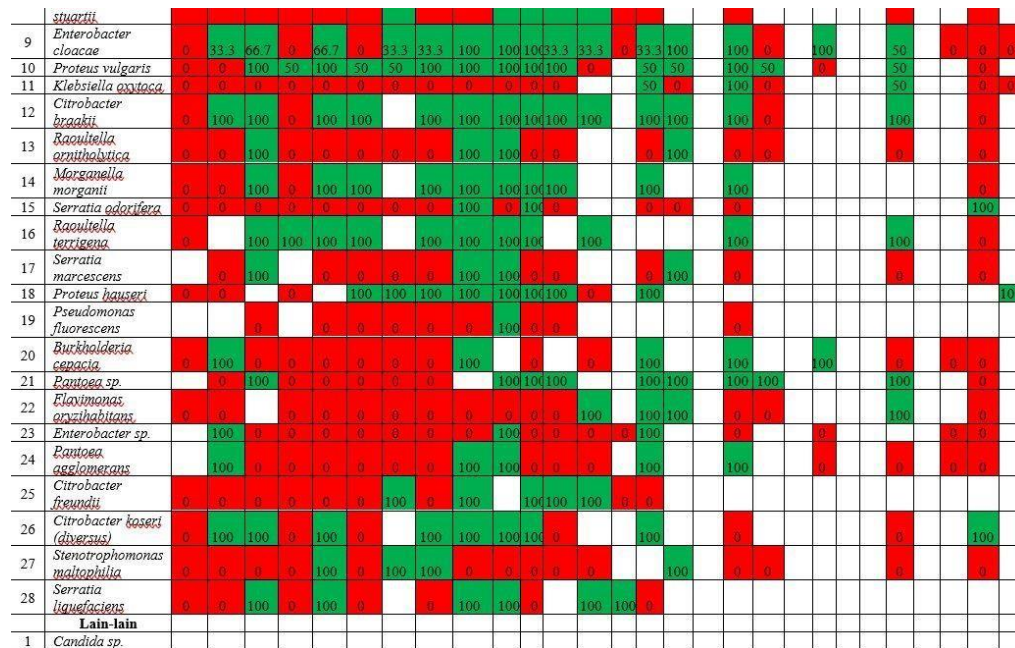


Figure 2. Table of Bacterial Sensitivity Pattern of Pus/Soils specimens with a diagnosis of DM Gangrene

Desc: ■ < 30%: Not recommended for use; ■ 30-60%: May be considered with consideration; ■ >60% : Recommended for use

MC/LC	: Macrolides/Lincosamides	AG	: Aminoglikosides	T/C	: Tetracycline dan Chloramphenicol
AMC	: Amoxicillin/Clavulanic acid	CIP	: Ciprofloxacin	CZO	: Cefazolin
AMK	: Amikacin	CLI	: Clindamycin	DOX	: Doxycyclin
ATM	: Astreonom	CPD	: Cefpodoxime	ERY	: Erytromicin
AMP	: Ampicillin	CRO	: Ceftriaxone	FEP	: Cefepime
CAZ	: Ceftazidime	COL	: Colistin	FOX	: Cefoxitin
CFM	: Cefixime	CTX	: Cefotaxime	FOS	: Fosfomicin
CHL	: Chloramphenicol	CXM	: Cefuroxime	GEN	: Gentamicin
GP	: Glycopeptides	SN	: Sulfonamide	Q	: Quinolone
LNZ	: Linezolid	OFX	: Ofloxacin	TOB	: Tobramicycn
L VX	: Levofloxacin	PIP	: Piperacillin	TCY	: Tetracycline
MEM	: Meropenem	PEN	: Penicillin G	TCC	: Ticarcillin
MNO	: Minocyclin	RIF	: Rifampicin	TCY	: Tetracicl yn
MFX	: Moxifloxacin	SAM	: Ampicillin/Sulbactam	TZP	: Pipperacillin /
NIT	: Nitrofurantoin	SXT	: Trimethoprim e /		Tazobactam
NOR	: Norfloxacin		Sulfamethoxazole	VAN	: Vancomicin

DISCUSSION

An ulcer can be defined as a wound or damage to the skin barrier to the dermis's entire layer (*full thickness*)⁶. The presence of open wounds on the skin will facilitate the invasion of bacteria. Some studies show that about 40-80% of diabetic ulcers experience infection⁷. Infection is often described as a disease caused by pathogenic microbes that occur when microorganism replication occurs in tissues, causing an inflammatory response and is associated with tissue damage⁸.

Identifying infection is one part of assessing diabetic foot wounds, which can be done by examining risk factors for disease and paying attention to signs and symptoms⁹. The Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF) have developed clinical criteria to recognize and classify LKD infections. The microorganisms that often cause diabetic foot infections are staphylococcus aureus and Pseudomonas pyogenes. They are normal skin flora, but since the skin barrier is compromised, they enter and cause disease. Along the way, nosocomial germs also cause infections, resulting in multi-organisms' conditions.

Infections are a frequent complication of ulcers typically caused by organisms around the skin. Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus are three common pathogenic aerobic gram-positive bacteria that cause infection. While gram-negative bacteria are Escherichia coli, Klebsiella sp, Enterobacter sp, Citrobacter sp, Proteus vulgaris, Proteus mirabilis, Pseudomonas aeruginosa. Aerobic and anaerobic gram-negative bacteria thrive in deeply located infections. Aerobic bacteria rapidly infect the bloodstream, which can lead to bacteremia. Infections in superficial ulcer areas are most commonly caused by gram-positive aerobes, while gram-negative aerobes and anaerobes are rare¹⁰.

Laboratory tests have a role in detecting infections, especially the microbial etiology of the infection. Microbial etiology can be determined by examining biopsies or purulent secretions¹¹. For example, in a pilot study, biopsy results showed $\geq 10^5$ CFU/gram/tissue in 28 wound biopsies, and 79% of wounds were infected¹².

However, the problem often occurs when the ulcer is covered with necrotic tissue or thick slough, making it challenging to take specimens at the wound base before debridement. Due to the patient's severe condition, it is necessary to stabilize the general need for debridement. LKD fluid specimens are taken by a swabbing technique using Tube and Medium Transport (Eurotubo) to examine bacterial colonization¹³.

The distribution of the number of examinations per year is rising, indicating that more clinicians are using microbiological analysis to diagnose diabetic foot ulcers and that microbiological examination facilities are improving in the examination of diabetic foot ulcer microorganisms.

Antibiotics are needed to treat diabetic foot infections. Broad-spectrum antibiotics are used because the germs that cause diabetic foot ulcer infections are multi-germ. Then when the results of germ culture and antibiotic susceptibility have been determined, antibiotics are given a narrow spectrum according to the results of the microbiological examination. In addition, the antibiotic regimen must adjust to the severity and infecting bacteria

Empirical antibiotics are given to patients individually or in combination with two antibiotics. The empirical antibiotic is used as an initial treatment for patients with a bacterial infection, but the causative bacteria are not yet known. Based on the results obtained from this study, the use of single antibiotics was more widely used than the use of combined antibiotics. Fluoroquinolone class antibiotics have a mechanism that inhibits topoisomerase II (DNA gyrase) and topoisomerase IV, which are needed by bacteria for DNA

replication. These antibiotics are widely used for patients with moderate to severe diabetic ulcers. This antibiotic has a broad spectrum because it can work on gram-positive and gram-negative bacteria. Fluoroquinolone antibiotics are used for infections caused by *Gonococcus*, *Shigella*, *Escherichia coli*, *Salmonella*, *Hemophilus*, *Moraxella catarrhalis*, and *Enterobacteriaceae* and *Pseudomonas aeruginosa*, which are groups of infecting bacteria in patients with diabetic ulcers⁴.

Respondents were sampled for microbiological examination after the provision of antibiotics. This happened because the patient came to the emergency department with severe infection or sepsis, so antibiotics were needed according to the patient's condition. At that time, debridement and microbiological examination sampling could not be done, so waiting for the general situation to improve and can be done debridement surgery in the operating room. The most widely used antibiotic type is a broad-spectrum combination of ceftriaxone and metronidazole.

Microbiological examination revealed gram-negative germs, gram-positive germs and *Candida*. There was no germ growth; however, an anaerobic germ examination was not conducted due to the unavailability of facilities.

The most common gram-negative microbes were *Escherichia coli* and *pseudomonas aeruginosa*. *Escherichia coli* is a fecal germ that contaminates diabetic foot ulcers. This can happen because of the patient's poor general condition, poor hygiene and immunocompromise due to diabetes. *Pseudomonas aeruginosa* is contaminated by hospital germs due to the patient's poor general condition and prolonged treatment.

In the gram-negative microbial examination, the most common is *Staphylococcus aureus*. *Staphylococcus aureus* germs are skin germs that infect diabetic foot ulcers because the patient's condition is poor and immunocompromised due to diabetes.

A sensitivity test to an antimicrobial can indicate the appropriate conditions with its inhibitory effect on bacteria. The use of antibiotics in Diabetes Mellitus patients with ulcers is generally given empirically. However, the empirical antibiotic selection is based on the type of bacteria most often causes diabetic ulcers.

An antibiotic sensitivity test examines a bacterium's sensitivity to an antibiotic. The sensitivity test aims to determine the effectiveness of an antibiotic¹⁴. The trial of bacterial sensitivity to antibiotics can be carried out by testing, namely by using the agar diffusion method and dissolved Kirby-Bauer method (standard single disk method): making a suspension of bacterial culture and then adjusting to the standard turbidity with McFarland 0.5 standard.

Antibiotics that inhibit bacterial growth are recommended to treat ulcers with bacterial infections. However, antibiotics may not always be effective in wound healing, or the damage may be difficult to cure because antibiotics can cause resistance over time. Therefore, evaluating the total resistance of empirical antibiotic utilization is accomplished by looking at the type of bacteria in diabetic ulcers against several antibiotics¹⁵.

In the microbial map of bacterial sensitivity patterns to antibiotics, by paying attention to the most gram-positive and gram-negative germ types, the most sensitive antibiotics are clindamycin, Fosfomycin, cefepime and gentamycin. These medicines can be treated as empirical antibiotics while waiting for germ culture and antibiotic sensitivity results. This is an important consideration considering using ceftriaxone combined with metronidazole for empirical therapy when the patient arrives for the first time at the emergency room unit of Haji Surabaya Hospital.

CONCLUSION

Research on the microbial map of diabetic foot ulcers at Haji Surabaya Hospital, East Java, found that most patients with diabetic foot ulcers were female. The most common microbes were gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus*. Based on antibiotic sentence, especially in the two most common types of germs, clindamycin, Fosfomycin, cefepime and gentamycin, can be considered as empirical antibiotics while waiting for the results of germ culture and antibiotic sensitivity.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

ETHICAL CLEARANCE

This study received ethical approval from the Health Research Ethics Committee, General Hospital of Haji Surabaya.

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