Empirical Antibiotic for Diabetic Foot Infection in Indonesian Tertiary Hospital, Is It Time to Rethink the Options?

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ABSTRACT

Background: *The choice of empiric antibiotics in Diabetic Foot Infection (DFI) is a key to successful therapy. Meanwhile, the management of DFI in Indonesia is based on guideline originating from western countries which have different bacteriological patterns. Therefore, this study aimed to describe the bacterial and antibiotic susceptibility pattern on DFI which potentially contribute to better antibiotics selection guidelines.* ***Methods:*** *This was a cross-sectional descriptive study conducted using consecutive sampling with DFI patients admitted in the emergency room and wards of Hasan Sadikin Hospital between February and July 2020. Tissue samples were obtained from all wounds, while antibiotic susceptibility tests were carried out on the culture results.* ***Results:*** *A total of 65 bacterial growths were obtained from 45 enrolled patients. Gram-negative bacteria dominated with 54 growths (83.07%) including Klebsiela pneumonia 13 (20%) as the most common. Furthermore, antibiotics with good susceptible (> 80%) against Gram-negative bacteria are the carbapenemes (meropenem and ertapenem) and amikacin. The multi drug resistant bacteria were found in 18 growths (27.7%), which include ESBL, Carbapenemase producing bacteria, and MRSA. However, there were no susceptibility pattern differences between patients with ulcer duration above or below 2 months, higher grade wound (Wagner 4 and 5) and lower, as well as patients with previous or no antibiotic history.* ***Conclusion:*** *The growth of Gram-negative bacteria dominated DFI with limited susceptibility to the empirical first-line antibiotics in the known international guidelines. Therefore, there is a need to reconsider the algorithm for selecting empirical antibiotics and management of DFI which is appropriate in our current condition.*

Keywords*: diabetic foot infection, antibiotic susceptibility, bacterial pattern.*

INTRODUCTION

The main problem in the management of diabetic foot infection (DFI) is chronic ulcers which are often difficult to heal. This is mostly caused by impaired wound healing due to immunopathy and peripheral arterial disease. Besides, inappropriate use of antibiotics also interferes with the wound healing process due to unresolved infection. Consequently, the choice of empirical therapy is important because antibiotiçs need to be given immediately before culture results are available.[1]

Currently, Indonesia does not have a personal guideline for the management of DFI. The country still uses the international guidelines issued by the Infectious Disease Society of America (IDSA) and the International Working Group of Diabetic Foot (IWGDF) for the choices of empiric antibiotic therapy. Meanwhile, the guidelines were developed based on bacterial patterns different from the types found in Asia. This indicates there is a need to study the bacterial type and local susceptibility pattern in Indonesia.[2-4]

The bacterial pattern and antibiotic susceptibility continuously change over time due to a long-term history of antibiotic use and hospitalization, duration, as well as wound grade.[2, 5] Therefore, this study aims to determine the pattern of bacteria and antibiotic susceptibility test on DFI in Hasan Sadikin General Hospital Bandung, a tertiary referral hospital in Indonesia. The results are expected to help clinicians with rational empiric antibiotic use and determining the factors that guide the selection.

METHODS

The subject of this study is patients with diabetes mellitus aged >18 years with diabetic foot infection, namely wounds under the malleolus with more than 2 signs of inflammation: redness, pus secretions, warmth, and swelling, were admitted to the ER and wards of Hasan Sadikin General Hospital Bandung from February to July 2020. Baseline data collection and scraping samples were conducted immediately in the ER or in the ward, with the following procedure: the ulcers were cleaned by Nacl 0,9% using a sterile syringe with a minimum pressure of 15 Psi, samples were taken aseptically from the base or edge of the ulcer by the curettage method with a scalpel. The sample was placed into Amies transport medium/sterile tube and immediately sent to the Microbiology and Clinical Pathology Laboratory. Furthermore, inoculation to culture media was carried out less than 30 minutes from the time of sample collection into blood agar and Mc.Conkey agar, then incubated for 24 hours at 35.6 ° C. The initial identification of the isolates on the growing medium was carried out by the analyst, then, further analysis was carried out for identification of bacteria and automatic bacterial susceptibility test by the Vitek2 Compact tool. The susceptibility test results were obtained in the form of Minimum Inhibitory Concentration (MIC) and divided into 3 categories namely resistant, intermediate, and sensitive.[6]

Ethical Approval

This study has approved by the Ethical Committee of Hasan Sadikin Hospital on February 3, 2020 (Reference number LB.02.01/X.6.5/27/2020).

RESULTS

The 45 subjects consist of 19 patients (42.2%) with polymicrobial bacterial growth, hence, a total of 65 bacterial growth were obtained. The grade of ulcer found was Wagner 2 (8.9%), 3 (42.2%), 4 (26.7%), and 5 (22.2%), while the predominant bacteria are Gram-negative with a total of 54 growths (83.07%). Furthermore, patients with Gram-negative growth had history of antibiotic use (30.6%) compared to others with Gram-positive growth (22.2%). The subjects had normal ABI values (0.9-1.3) on average, but 66.7% (2/3) of patients with combined Gram-positive and negative bacterial growths had values above 1.3 which indicate arterial calcification. Additionally, polymicrobial growth was found in 18 patients (50%) with Gram-negative bacteria cultures, while 3 cultures showed the growth of both Gram-positive and negative bacteria (**Table 1**).

The direct Gram staining examination results were compared with the growth of bacteria on the culture. The Gram-negative reading detected 10/20 (50.0%) of Gram-negative bacterial

growth, then combined with the mix result, a total of 17/27 Gram-negative growth with a sensitivity of 63.0% were detected. Gram negative result shows Gram-negative bacterial growth in 10/11 giving a specificity of 87.5%. Meanwhile, Gram-positive microscopy reading was sensitive at 7/8 (87.5%) with a specificity of 10/20 (50.0%) without the mix reading and 17/27 (63.0%) with the mix Gram-positive/negative findings. All the reading of mix Gram-positive and negative shows growth of Gram-negative bacterial group (**Table 1**).

Based on the results, a total of 15 bacterial species were found in the culture, the 5 most commonly found were *Klebsiella pneumonia* (20%), *Acinetobacter baumanii* (12.3%), *Escherichia coli* (10.8%), *Pseudomonas aeruginosa* (9.2%) and *Staphylococcus aureus* (9,2%) as shown in **Table 2**. Antibiotics with a good susceptibility (>80%) to all bacterial growth were carbapenems (meropenem and ertapenem) and amikacin. The results also showed that the antibiotics with good susceptibility against all Gram-negative bacteria was amikacin (96.2%), while meropenem and ertapenem have good susceptibility to almost all Gram-negatives except for *A. baumanii*. Moreover, cefepime is the only cephalosporin with good susceptibility

Table 1. Characteristics of Research Subjects.

Variables	Bacteri classification		
	Gram (-) N=34	Gram (+) N=8	Mixed Gram (+) and (-) N=3
Age (year)			
Median (IQR)	58 (12.2)	57.5 (10.5)	43.0 (-)
Sex			
Female	18 (52.9)	3 (37.5)	1 (33.3)
Male	16 (47.1)	5 (62.5)	2 (66.7)
ABI			
0.60 – 0.89	11 (32,4)	2 (25.0)	1 (33.0)
0.90 – 1.30	22 (64.7)	6 (75.0)	-
>1.30	1 (0.02)	0 (0)	2 (66.7)
Laboratorium			
RPG, Median (range)	231 (80 – 589)	219 (96 – 469)	259 (244 – 275)
FPG, Median (range)*	211 (107 – 492)	264 (148 – 567)	310 (286 – 334)
2hPG, Median (range)	225 (94 – 341)	344 (162 – 704)	338 (316 – 361)
Bacteria, n (%)*			
>1	15 (44.1)	-	3 (100)
1	19 (55.9)	8 (100)	-
Initial test	(N=27)		
Gram (-)	10 (37.0)	1 (12.5)	1 (50.0)
Gram (+)	10 (37.0)	7 (87.5)	1 (50.0)
Mixed Gram (+) and (-)	7 (25.9)	-	-
MDR, n (%)			
Yes	21 (61.8)	7 (87.5)	2 (66.7)
No	13 (38.2)	1 (12.5)	1 (33.3)
Wagner classification			
2 and 3	18 (52.9)	4 (50.0)	1 (33.3)
4 and 5	16 (47.1)	4 (50.0)	2 (66.7)
Wound duration			
<2 months	22 (64,7)	3 (37,5)	3 (100)
≥2 months	12 (35,3)	5 (62,5)	0 (0.0)

Notes : ABI : Ankle Brachial Index, RPG : Random plasma glucose, FPG : Fasting plasma glucose, 2hPG : 2 hour post prandial plasma glucose, MDR : Multi Drug Resistance.

*P value ≤ 0,05

Table 2. Types of Bacterial Growth

Pathogen	Gram	n=65	
		Total	%
Gram-Negative			
Klebsiella pneumonia	Negative	13	20,0
Acinetobacter baumanii	Negative	8	12,3
Escherichia coli	Negative	7	10,8
Pseudomonas aeruginosa	Negative	6	9,2
Proteus mirabilis	Negative	5	7,7
Morganella morganii	Negative	5	7,7
Citrobacter freundii	Negative	4	6,2
Enterobacter cloacae	Negative	2	3,1
Pantoea agglomerans	Negative	1	1,5
Proteus hauseri	Negative	1	1,5
Serratia marcescens	Negative	1	1,5
Gram-Positive			
Staphylococcus aureus	Positive	6	9,2
Enterococcus faecalis	Positive	2	3,1
Staphylococcus haemolyticus	Positive	2	3,1
Staphylococcus hominis	Positive	1	1,5

Table 3. Frequency Distribution of Antibiotic Susceptibility Based on Gram Classification.

Antibiotic	Total test	Susceptible result n, (%)	Gram			
			Gram Negative (N=54)		Gram Positive (N=11)	
			Total test	Susceptible result, n (%)	Total test	Susceptible result, n (%)
Cephalosporin						
Ceftriaxone	56	26 (46.4)	47	21 (44.7)	9	5 (55.6)
Cefotaxime	47	25 (53.2)	38	20 (52.6)	9	5 (55.6)
Ceftazidime	62	30 (48.4)	53	25 (47.2)	9	5 (55.6)
Cefepime	63	41 (65.1)	54	33 (66.7)	9	5 (55.6)
Cefeporazone	9	5 (55.6)	-	-	9	5 (55.6)
Penicilin						
Ampicillin sulbactam	57	21 (36.8)	46	14 (30.4)	11	7 (63.6)
Amoxicillin clavulanat	12	7 (58.3)	1	0 (0)	11	7 (63.6)
Piperacilin tazobactam	64	39 (60.9)	53	32 (60.4)	11	7 (63.6)
Ampicillin*	41	6 (14.6)	39	4 (10.3)	2	2 (100)
Florokuinolon						
Ciprofloxacin	63	28 (44.4)	54	23 (42.6)	9	5 (55.6)
Levofloxacin	11	6 (54.5)	1	0 (0)	10	6 (60.0)
Moxifloxacin	8	4 (50.0)	0	0 (0)	8	4 (50.0)
Karbapenem						
Meropenem	58	52 (89.7)	53	47 (88.7)	5	5 (100)
Ertapenem	44	40 (90.9)	39	35 (89.7)	5	5 (100)
Aminoglikosida						
Amikacin	53	51 (96.2)	53	51 (96.2)	-	-
Gentamycin*	65	38 (58.5)	54	30 (55.6)	11	10 (90.9)
Others						
Tigecycline*	63	43 (68.3)	53	33 (62.3)	10	10 (100)
Vancomycin	12	11 (91.7)	1	0 (0)	11	11 (100)
Aztreonam	46	24 (52.2)	46	24 (52.2)	-	-
Clindamycin	9	5 (55.6)	1	0 (0)	8	5 (62.5)
Cotrimoxazol	55	33 (60.0)	47	27 (57.4)	8	6 (75.0)

Note : *P value ≤ 0,05

Table 4. Frequency Distribution of Antibiotic Susceptibility in Most Bacteria.

	Gram (-)														Gram (+)	
	AB		CF		EC		KP		MM		PA		PM		SA	
	n=8		n=4		n=7		n=13		n=5		n=6		n=5		n=6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AN	6	75	4	100	7	100	13	100	5	100	5	83	5	100	-	-
SAM	3	37,5	0	0	0	0	6	46,2	0	0	-	-	4	80	5	83,3
AM	-	-	0	0	0	0	0	0	0	0	-	-	4	80		
ATM	-	-	2	50	2	28,6	6	46,2	4	80	4	67	4	80		
CZ	0	0	0	0	0	0	-	-	0	0	0	0	-	-	5	83,3
FEP	1	12,5	4	100	5	71,4	11	84,6	5	100	3	50	5	100	5	83,3
CTX	-	-	2	50	2	28,6	6	46,2	4	80	-	-	4	80	5	83,3
CAZ	1	12,5	2	50	3	42,9	6	46,2	3	60	3	50	5	100	5	83,3
CRO	1	12,5	2	50	2	28,6	6	46,2	4	80	-	-	4	80	5	83,3
CIP	1	12,5	2	50	1	14,3	6	46,2	4	80	3	50	4	80	4	66,7
SXT	5	62,5	2	50	2	28,6	6	46,2	4	100	-	-	4	80	5	100
ETP	-	-	4	100	7	100	13	100	5	100	-	-	4	80	5	100
GM	2	25	3	75	2	28,6	7	53,8	5	100	4	67	4	80	5	83,3
MEM	3	37,5	4	100	7	100	13	100	5	100	5	83	5	100	5	100
TZP	1	12,5	2	50	6	85,7	10	76,9	4	80	3	60	4	80	5	83,3
TGC	7	87,5	4	100	7	100	12	92,3	0	0	0	0	-	-	6	100
VA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	100
AMC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	83,3
MXF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	66,7
LFX	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	66,7
E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	80
CC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	80

Note: AB *: Acinetobacter baumanii,* CF *: Citrobacter freundii,* Ecl *: Enterobacter cloacae,* EC *: Escherichia coli,* KP *: Klebsiella pneumonia,* MM *: Morganella morganii,* PA *: Pantoea agglomerans*, PM *: Proteus mirabiis*, SA : Staphylococcus aureus, AN : Amikacin, AMC : amoxicillin clavulanat, SAM : ampicilin sulbactam, AM: ampicilin, ATM : aztreonam, PEN : benzylpenicillin , CZ : cefazolin, CC : clindamycin, CF : cephalotin, CXM : cefuroxime, CFP : cefoperazone, CFR : cefadroxil, E : erythromycin, FEP : cefepime, CTX : cefotaxime, CAZ : ceftazidime, CRO : ceftriaxone, CIP : ciprofloxacin, SXT : cotrimoxazol, ETP : ertapenem, GM: gentamycin, LFX : levofloxacin, LNZ : linezolide, MEM: meropenem, TZP: piperacillin tazobactam, TGC: tigecycline, MXF : moxifloxacin, STR : streptomycin, TE : tetracycline, VA : vancomycin.

against Gram-negative bacteria except for *A. baumanii* and *P. aeruginosa* (**Table 3**).

Staphylococcus aureus, the most common Gram-positive bacteria has good susceptibility to many of the antibiotics tested, which are penicillin with beta-lactamase inhibitors, the cephalosporin group namely ceftriaxone, ceftazidime, cefotaxime and cefepime, as well as other antibiotics such as cotrimoxazole, erythromycin, gentamycin and the carbapenem group (**Table 4**). The growth of MDR bacteria was found in approximately 18 growths (27.7%), including 11 ESBL-producing Enterobacteriaceae, and 6 carbapenemase-producing bacteria with 5 growths of *A. baumanii* and 1 growth of *P. aeruginosa*, as well as 1 growth of *Methicillin*

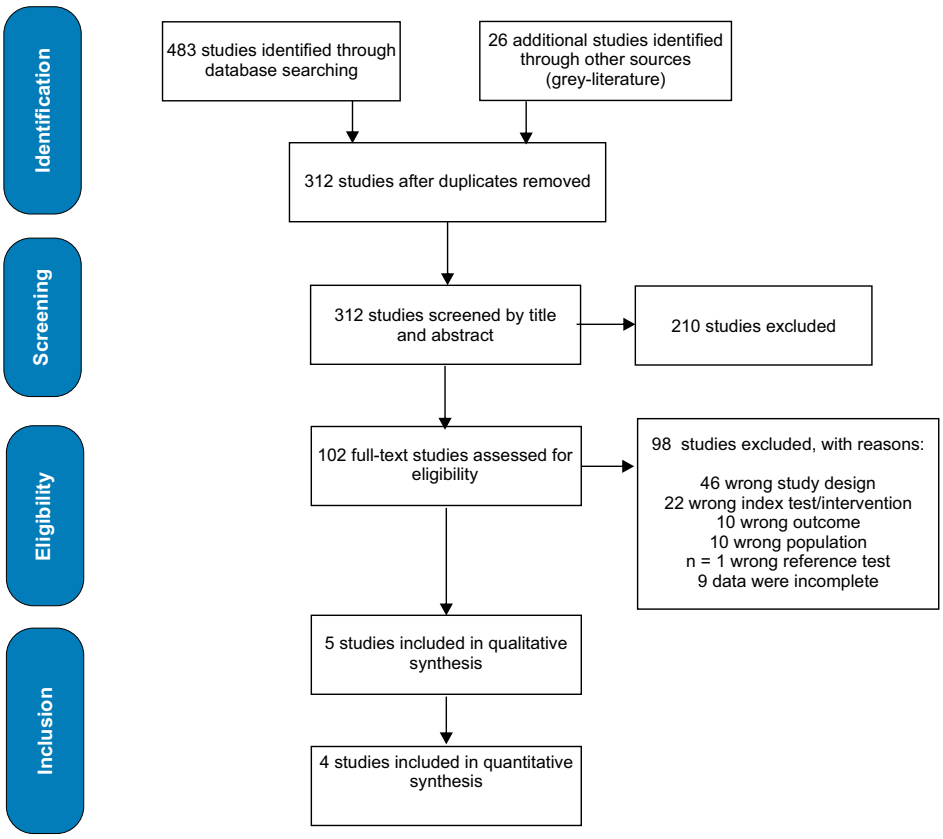

Figure 1.

Resistance Staphylococcus aureus (MRSA).

Several antibiotics have better susceptibility in patients without a history of previous hospitalization, including amoxicillin clavulanate, piperacilin tazobactam, levofloxacin, moxifloxacin, and clindamycin with susceptibility of 40%, 46.4%, 20%, 25% and 40% and higher susceptibility in patients without history, which were 71.4%, 72.2%, 83.3%, 75% and 75%, respectively, but among these antibiotics only ampicillin and piperacillin tazobactam have a p-value of ≤0.05 (**Figure 1**). There were no significant differences in the susceptibility pattern among patients with or without a previous history of antibiotics, and in the group of patients with moderate (Wagner 2-3) or severe ulcer grade (Wagner 4-5).

DISCUSSION

Based on the results, Gram-negative bacteria were the most dominant in bacterial growth. This is consistent with previous studies which stated that the growth of Gram-negative bacteria dominates diabetic foot infections in Asia. [7,8] In contrast, Gram-positive bacteria are more often found in western countries. The cause of this difference is still not clearly known, but several reports suggest differences in environmental factors, use of footwear, personal hygiene, and history of antibiotics.[7-10]

The direct Gram examination results did not correctly correlate with the characterization of bacteria based on isolation. The gram-negative in microscopy show modest sensitivity to detect true culture result but with good specificity (87.5%). However, when the microscopic finding is Gram-positive, the sensitivity was 87.5%, but the specificity was low. Therefore, when the microscopy smear finding is gram-negative, it indicates the presence of gram-negative bacteria. Previous studies found that Gram and culture results were inconsistent.[11, 12]

Based on the results, the antibiotics with good susceptibility (above 80%) for Gram-negative bacteria were the carbapenems (meropenem and ertapenem) and amikacin.

This pattern has changed compared to previous study by Astawa (1996) conducted at the same hospital which reported that ciprofloxacin was the best antibiotic for Gram negative bacteria.[13] Antibiotics for Gram-negative bacteria recommended by international guidelines are ceftriaxone, ampicillin sulbactam, ciprofloxacin and tigecycline.[4] However, these antibiotics have poor susceptibility to Gram-negative bacteria in this study.

Antibiotics with good susceptibility for Gram-positive bacteria in this study were carbapenems, gentamicin, tigecycline and vancomycin. This is in line with Wu (2018) which stated that tigecycline and vancomycin were the best antibiotics for Gram-positive bacteria. Antibiotics recommended for moderate-to-severe DFI by Gram-positive bacteria include quinolones, cephalosporins and beta-lactam antibiotics,[4, 14, 15] but, these antibiotics have poor susceptibility in this study.

Furthermore, multidrug resistance (MDR) bacteria were found in this study including ESBL, Carbapenem Resistance *A. baumanii* and *P. aeruginosa,* as well as MRSA. The prevalence of MDR bacteria and ESBL bacteria is increasing worldwide. MDR bacterial infection is commonly found in severe and chronic ulcers, as well as patients with a history of antibiotics and previous hospitalization.[5, 8] In this study, MDR bacteria were more commonly found in patients with a history of previous hospitalization.

Several studies reported that certain antibiotics had better susceptibility in a group of patients without previous hospitalization history and low grade Wagner group.[5] In this study, only ampicillin and piperacillin tazobactam had a higher susceptibility level in the patient without previous hospitalization history. However, the susceptibility difference between the moderate (Wagner 2 and 3) and the severe ulcer group (Wagner 4 and 5) was not statistically significant.[5]

This study has several limitations, first, the sample size was small, hence, an association analysis was not performed. Second, the culture facility in the laboratory did not accommodate the isolation of anaerobic bacteria. Meanwhile, anaerobic bacteria species might also participate in the pathology of DFI. [8]

CONCLUSION

The growth of Gram-negative bacteria dominates diabetic foot infection in RSHS Hospital Indonesia. Some antibiotics had a lower susceptibility level compared to previous studies conducted in the same setting. This indicates that the choice of antibiotics with good susceptibility toward Gram-positive and negative bacteria is limited. Therefore, international guidelines used for antibiotics selection are no longer applicable because the recommended antibiotics have poor susceptibility in this study.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests concerning the publication of this paper.

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