



Literature review

The relationship between bacterial characteristics and mortality in diabetic foot ulcers' patients admitted to Dr. H. Abdul Moeloek General Hospital, Lampung

Iswandi Darwis^{1*}, Gusti Ngurah P Pradnya Wisnu², Sekar Mentari²

1) Internal Medicine Department, Faculty of Medicine, Universitas Lampung/ Dr. Hi. Abdul Moeloek General Hospital, Lampung Province

2) Research Assistant at Internal Medicine Department, Faculty of Medicine, Universitas Lampung/ Dr. Hi. Abdul Moeloek General Hospital, Lampung Province

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*Correspondence:

iswandi.darwis@gmail.com

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ABSTRACT

Around 25% of people with diabetes experience diabetic foot ulcers in their lives, accompanied by infections due to various types of bacteria. Infection due to Gram-negative and Gram-positive bacteria are reported to have different inflammation patterns, where the latter being reported to have a higher mortality rate. This study was an analytic observational study with a cross-sectional design to determine the relationship between bacterial characteristics and mortality in diabetic foot ulcers. Data were obtained from medical records of diabetic ulcer patients admitted to Dr. H. Abdul Moeloek General Hospital, Lampung, in 2017–2020. There were 131 diabetic foot ulcers patients identified, with the median age of the subjects was 53 years, 43.5% of the subject were male, and 56.5% were female. The mean hemoglobin was 9.3 g/dl, WBCs were $19.0 \times 10^3/\text{ml}$, and platelets were $422.1 \times 10^3/\text{ml}$. The mean length of stay in the hospital was 10.7 days. Eighteen subjects died during the hospital stay, with 15 of them were from the Gram-negative monomicrobial group. The results of the Fischer Exact test on mortality and bacterial characteristics among monomicrobial infections ($p=0.688$) indicate no relationship between the characteristics of the infectious pathogen and mortality in diabetic foot ulcers.



INTRODUCTION

A diabetic foot ulcer is the most common complication of diabetes mellitus. Around 25% of patients with DM will develop a diabetic foot ulcer in their lifetime (Jeyaraman *et al.*, 2019). This condition occurs due to a combination of neuropathy, lower leg biomechanical disorders, peripheral artery disease, and poor wound healing due to diabetes (Powers, 2015). A diabetic foot ulcer can be accompanied by infections, ranging from simple superficial cellulitis to chronic osteomyelitis (Amin and Doupis, 2016).

Infection in diabetic foot ulcers is caused by various types of bacteria, whose characteristics depend on the disease's severity and geographic location. In North America and Europe, the main bacteria causing infection in diabetic foot ulcers are aerobic Gram-positive cocci, especially *S. aureus* and *Streptococcus*, and coagulase-negative *Staphylococcus*. Meanwhile, the leading cause of diabetic foot ulcers in tropical/subtropical regions is aerobic Gram-negative bacilli, both as monomicrobial or polymicrobial infection (Lipsky *et al.*, 2020). Mild infection in diabetic ulcers is usually caused by Gram-positive bacteria, while more severe infections usually involve anaerobic and Gram-negative bacteria (Goh *et al.*, 2020).

Infection with Gram-negative and Gram-positive bacteria are reported to have different mechanisms in causing clinical manifestations. Lipoteichoic acid in Gram-positive bacteria and lipopolysaccharides in Gram-negative bacteria cause different host responses, which will result in a different inflammation pattern (Surbatovic *et al.*, 2015). Infection by Gram-negative bacteria has been associated with high morbidity and mortality rates (Blot, 2019; Maskarinec *et al.*, 2020). This study was conducted to determine the relationship between bacterial characteristics

and mortality in diabetic foot ulcers based on that analysis.

METHODS

This study was an observational analytic study with a cross-sectional design to determine the relationship between bacterial characteristics and mortality in diabetic foot ulcers. This research was conducted at Dr. H. Abdul Moeloek General Hospital, Lampung Province. The data were obtained from the medical records of diabetic foot ulcers patients admitted to the internal medicine ward of Dr. H. Abdul Moeloek General Hospital, Lampung Province, in 2017–2020. Ethical clearance was obtained from the Medical Faculty of Lampung University and the hospital authority before this study's commencement (Ethical clearance number: 1379/UN26.18/PP.05.02/00/2020).

The subjects of this study were 131 patients meeting the inclusion criteria. The inclusion criteria are the completeness of medical record data, which includes including demographic data (gender and age), laboratory tests (complete blood count, blood chemistry, and pus culture results taken prior to the administration of empirical antibiotics on admission), and clinical outcomes (length of hospital stay and in-hospital mortality). Subjects receiving antibiotics therapy within 72 hours prior to the collection of the pus sample were excluded from this study. The data obtained were analyzed with univariate and bivariate analysis, performed with the Fisher's Exact test. Data were processed with SPSS Statistics v22.0. The test result was considered to be significant if the *p-value* is less than 0.05.

RESULTS

The subjects of this study were 131 patients with diabetic foot ulcers. The characteristics of research subjects are presented in **Table 1**. The median age of the study subjects was 53



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years. The subjects in this study consisted of 57 (43.5%) males and 74 (56.5%) females. Among patients with diabetic foot ulcers, 111 subjects had a monomicrobial infection, and ten subjects had a polymicrobial infection. Gram-negative bacteria were identified in 114 subjects, while Gram-positive bacteria were found in 17 subjects. *Enterobacter spp.* and *Staphylococcus*

spp. were the most common Gram-negative and Gram-positive microorganisms found, respectively (shown in **Table 2**). The subjects' median in-hospital length of stay was 10.7 (5.9) days, and 18 (13.7%) subjects died during the hospital stay. The median hemoglobin test result was 9.3 (2.0) g/dl, the median WBC count was 19.0 (7.8) $\times 10^3$ /ml, and the median platelet count was 422.1 (170.2) $\times 10^3$ /ml.

Table 1. Characteristics of the subjects (N=131)

Characteristics	n (%)	Median (SD)
Median age (years)		53 (31-87)
Sex		
Male	57 (43.5%)	
Female	74 (56.5%)	
Pus culture result		
Gram-positive bacteria	17 (12.9%)	
Gram-negative bacteria	114 (87.1%)	
Length of hospital stay (days)		10.7 (5.9)
In-hospital Mortality	18 (13.7%)	
Hemoglobin (g/dL)		9.3 (2.0)
WBC count ($\times 10^3$ /mm ³)		19.0 (7.8)
Platelet count ($\times 10^6$ /mm ³)		422.1 (170.2)

Table 2. Bacteria Found in the Diabetic Ulcers based on Microbial Culture (N=131)

Bacteria	Frequency (n)	Percentage (%)
Gram-negative		
<i>Enterobacter spp.</i>	33	25.2
<i>Klebsiella spp.</i>	27	20.6
<i>Proteus spp.</i>	21	16
<i>Pseudomonas spp.</i>	17	12.9
Others	16	12.2
Gram-positive		
<i>Staphylococcus spp.</i>	14	10.7
<i>Streptococcus spp.</i>	3	2.3

Table 3. Relationship Between Bacterial Characteristics and Mortality

	Mortality		p-value
	+	-	
Gram-negative	15 (15.3%)	83 (84.7%)	0.688 ^a
Gram-positive	1 (7.7%)	12 (92.3%)	

^aFischer's Exact test was applied



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The relationship between mortality and bacterial characteristics among diabetic foot ulcers patients with monomicrobial infection was analyzed and is presented in **Table 3**. Based on statistical analysis, it was found that there was no significant relationship between bacterial characteristics and mortality in diabetic foot ulcers patients.

DISCUSSION

The characteristics of an infectious pathogen are reported to influence the mechanism of the host's immunological reaction and the response to therapy (Xu *et al.*, 2013). The microbial infection triggers complex interactions between the pathogen and the host through the introduction of pathogen-associated molecular patterns (PAMP) to the innate immune system. Toll-like receptors (TLR) of the innate immune system are dedicated to the identification of various bacterial components. Lipopolysaccharides, a component of Gram-negative bacteria's outer membrane, will be recognized by TLR-4, while TLR-2 will recognize lipoteichoic acid, a major constituent of the cell wall of Gram-positive bacteria. Depending on the receptors involved, this process leads to the activation of a transcription response program that includes nuclear factor κ B (NF- κ B), followed by the production and secretion of cytokines, chemokines, and nitrogen monoxide (NO) (Wen *et al.*, 2016). This different mechanism elicited during this process leads to a different pattern of inflammation between Gram-positive and Gram-negative bacterial infections (Surbatovic *et al.*, 2015).

Dysregulated inflammatory response and the production of cytokines have an important role in the development of multiple organ dysfunction in sepsis (Wen *et al.*, 2016). Several studies have shown an association of levels of several cytokines with the severity and outcome of patients with sepsis. Surbatovic *et*

al. reported that the levels of TNF- α , IL-8, IL-1ra, and IL-10 were higher in septic patients who died than those who did not (Surbatovic *et al.*, 2015). The cytokine production pattern and initial mediators of inflammation are also believed to depend on the characteristics of the infectious pathogen and the host response. The gram-negative infection has been reported to produce higher levels of TNF- α , IL-6, IL-8, and IL-10, thus higher risk of more severe disease and mortality than Gram-positive infections (Xu *et al.*, 2013).

Our findings showed no relationship between the characteristic of pathogens and mortality in diabetic foot ulcers (p -value = 0.688). These findings differ from several other studies that report that the infecting pathogen's characteristics can influence mortality. Pachori *et al.* reported that Gram-negative infections, especially *Pseudomonas spp.*, were associated with a significantly higher mortality rate (Pachori *et al.*, 2019). Another study reported that skin and soft tissue infections in DM patients caused by Gram-negative bacteria had a higher mortality rate than infections caused by Gram-positive bacteria (Benavent *et al.*, 2019). Similar results were also reported by Phua *et al.*, who reported mortality in severe sepsis subjects (Phua *et al.*, 2013). Surbatovic *et al.* and Tabah *et al.* reported higher mortality in sepsis due to infection with Gram-negative bacteria (Tabah *et al.*, 2012; Surbatovic *et al.*, 2015). Meanwhile, our findings were supported by Zahar *et al.*, which reported that the type of infectious pathogen did not affect severe sepsis and septic shock mortality (Zahar *et al.*, 2011). Chotirmall *et al.* and Kushwaha *et al.* also reported that although a positive culture showed a higher mortality rate than a negative culture, the isolated organism's characteristic had little impact on it (Chotirmall *et al.*, 2016; Kushwaha *et al.*, 2020).

One of the essential parts of diabetic ulcers management is antibiotic administration



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(Frykberg and Banks, 2016). Before a culture and antibiotic susceptibility results can be obtained, it is recommended to administer an empiric antibiotic regimen. This empiric antibiotic regimen should cover the most frequently isolated Gram-positive, Gram-negative, and obligate anaerobic bacteria in a local setting (Lipsky *et al.*, 2020). The usage of appropriate empiric antibiotics have been reported to reduce mortality in bacteremia (Gradel *et al.*, 2017; Disselkamp, Coz Yataco, and Simpson, 2019). The implementation of this recommendation could be the reason for the nonsignificant difference in mortality rate between Gram-positive and Gram-negative infections in diabetic foot ulcers. Furthermore, although not significantly different, there was a percentage difference between mortality in Gram-negative (15.3%) and Gram-positive (7.7%)

CONCLUSION

No relationship between the characteristics of the infectious pathogen and mortality in patients with diabetic foot ulcers was found in this study. Further research in multiple centers with a larger sample size should be carried out to confirm the relationship between the two.

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