



## CHARACTERISTICS AND MICROBIOLOGICAL ANALYSIS OF PATIENTS WITH DIABETIC FOOT INFECTION IN JOHOR BAHRU, JOHOR

### Orthopaedics

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### ABSTRACT

Diabetic foot infection (DFI) is one of the major complications of diabetes mellitus which is associated with high morbidity and mortality. It is also a significant risk factor for lower extremity amputation. Providing effective antimicrobial therapy is a key component of treating DFI. This study assesses the microbiological profile of patients with DFI at a tertiary care hospital in southern Malaysia. A retrospective analysis was conducted at Hospital Sultan Ismail, Johor Bahru in Malaysia from 1 January 2023 to 30 June 2024. Patients' demographic data, types of infection, surgical intervention and the microbiological profile were obtained from the medical records. Overall, 170 patients (50%) had infected wound, 5 patients (1.5%) had abscess, 138 patients (40.6%) had necrotizing fasciitis and 27 patients (7.9%) had gangrene. A total of 286 pathogens were isolated from 336 patients. Majority of the pathogens isolated were gram negative pathogens (59%). The most isolated pathogen was *Proteus* sp. (19.6%). This was followed by *Staphylococcus Aureus* (18.5%), *Streptococcus* sp. (16.7%), *Klebsiella* sp. (10.1%), *Pseudomonas* sp. (9.8%) and others. Early initiation of empirical antibiotic(s) is essential to prevent worsening of DFI. This study serves as a guide for clinicians to prescribe the most suitable empirical antibiotic in DFI.

### KEYWORDS

diabetes, diabetic ulcer, diabetic foot infection, microbiology, Malaysia.

### INTRODUCTION

Diabetes mellitus affects approximately 382 million people worldwide, making it a serious health concern. Globally, the prevalence of diabetes is increasing, as estimates put the number of individuals with the disease at over 592 million by 2035, with a global prevalence of 10.1% [1]. In Malaysia, the prevalence of diabetes in the country is on a gradual rise, as it has increased from 11.2% in 2011 to 13.4% in 2015, and to 18.3% in 2019 [2].

Approximately 25% of people with diabetes will get a foot ulcer at some point in their lives. It has been predicted that almost 50% of patients with diabetic foot ulcer suffer from foot infections [3]. Diabetic foot infection (DFI) usually starts with a break in the skin because of trauma or ulceration, which is common in patients with peripheral neuropathy and peripheral artery disease. When DFI goes unnoticed, undetected, and not treated promptly, it can lead to infection of the deep structures, of which osteomyelitis is one of the most common [4]. Unfortunately, osteomyelitis is often associated with high rates of amputation, occurring in 10–15% of patients with mild infections and 50–60% of patients with severe infections [5].

Antibiotics are essential in the treatment of DFI. Empirical antibiotics, that are broad spectrum and cover majority of predicted pathogens in DFI, should be prescribed by clinicians before the results of microbiological culture are available [6-8].

The causative pathogens of DFI vary by geographic, demographic, and clinical situations. In majority of cases, *staphylococcus aureus* is the predominant pathogen, especially in the developed countries. Conversely, studies from countries in Asia, Middle East and Africa have shown predominance of aerobic gram-negative organisms, such as *Pseudomonas* sp., *Klebsiella* sp., *Eschericia Coli* and *Proteus* sp. [9-11]. It is therefore imperative to identify the microbiological profile of DFI in the local setting and prescribe appropriate antimicrobial therapy accordingly.

### MATERIALS AND METHODS

This retrospective study was carried out at the orthopedic department of Hospital Sultan Ismail, Johor Bahru, Malaysia. Electronic medical records from 1 January 2023 to 30 June 2024 (1.5 years) were reviewed. All patients aged 18 years and above with diabetic foot infections who had received surgical interventions were included. For

patients who had multiple surgical procedures, only the first surgery was included. Patients with incomplete data were excluded from the study.

Demographic data such as gender, race, age, types of infection and types of surgical procedure were extracted. The infection types were broadly divided into four categories: infected wound, abscess, necrotizing fasciitis, and gangrene (dry and wet gangrene). The types of surgical procedure performed were categorized as wound debridement, incision and drainage, ray amputation or disarticulation of the toe, mid- or hindfoot amputation, below knee amputation and above knee amputation [6].

The microbiological profile of DFI was also retrieved from the medical records, which includes the causative pathogens and the sensitivity of the pathogens to antibiotics tested. Only deep tissue or bone samples obtained during the surgery were included. The samples were first incubated in the hospital microbiological lab at 37 degrees Celsius in blood agar, MacConkey agar and Chocolate agar for a duration of two days. Conventional method was then done to identify the isolated pathogens. The antibiotic susceptibility test was performed by using the disk diffusion method on Mueller-Hinton agar plates [12]. Descriptive data was used to present the results.

### RESULTS:

Of the total of 340 patients, 197 (57.9%) were male and 143 (42.1%) were female, with male to female ratio of 1.4 to 1. Majority of the patients included in the study was Malay (75.6%), followed by Indian (12%) and Chinese (10%). The age of the patients ranged from 30 to 85 years. The incidence of DFI was found to be highest in the age group of 60-69 years (n=108, 31.8%), followed by 50-59 years (n=98, 28.8%).

Half of the patients were diagnosed to have infected wound (n=170, 50%). This was followed by necrotizing fasciitis (n=138, 40.6%), gangrene (n=27, 7.9%) and abscess (n=5, 1.5%). More than a third of the patients had amputation over the region of the foot, which are ray amputation or toe disarticulation, and mid- or hindfoot amputation (n=120, 35.3%), followed by wound debridement (n=114, 33.5%). Less than a third of the patients (n=101, 29.7%) had undergone major amputation procedures (below knee and above knee amputation).

From the 336 tissue culture samples obtained, nearly half of the samples revealed presence of single microorganism (n=158, 47.0%). It is followed by no growth (n=114, 34.0%) and polymicrobial (n=64, 19.0%). In total, 286 causative pathogens were cultured from 336 tissue samples, with a ratio of 0.85 pathogen per lesion. Gram negative microorganism (n= 170, 59.5%) were found to be more commonly isolated than gram positive microorganism (n=113, 39.5%), with a ratio of 1.5 to 1.

The most common pathogen cultured was *Proteus sp.* (n= 56, 19.6%). This was followed by *Staphylococcus Aureus* (n=53, 18.5%), *Streptococcus sp.* (n=48, 16.8%), *Klebsiella sp.* (n=29, 10.1%), *Pseudomonas sp.* (n=28, 9.8%) and others (table 2). In this study, *Candida sp.* (n=3, 1%) were isolated as well.

The details of antibiotic susceptibility patterns for gram positive and gram negative pathogens are shown in table III and IV. There were fourteen multidrug resistant strain, which consists of ten methicillin-resistant *Staphylococcus Aureus* (MRSA), five extended-spectrum beta-lactamase (ESBL)-producing *Proteus sp.* and three *Acinetobacter sp.* that were multidrug resistant organism (MRO). All MRSA were sensitive towards vancomycin, while all ESBL were sensitive towards ertapenem, meropenem and imipenem.

In this study, in terms of antibiotic treatment for gram positive pathogens, erythromycin (80%) and vancomycin (76.2%) were effective. Gram negative pathogens were susceptible mostly to ceftazidime (100%), cefepime (65.9%) and gentamicin (65%).

## DISCUSSION

Most patients with DFI were Malay ethnicity, in the age group of 60-69 years old and 58% of the patients are male. Similar findings were reported by several studies [6,9]. The male predominance can be explained by gender-related difference in lifestyle, more outdoor work performed by males and poor compliance with foot care [7].

In managing DFIs, current clinical guidelines recommend the use of empirical antibiotic until wound cultures reveal the causative pathogens and their antibiotic susceptibility patterns. Typically, the result of the culture takes two to five days. Poorly obtained specimens may impair the accuracy of the result [13-16]. In order to identify the pathogen more accurately, all samples in the study were taken via deep tissue culture [17,18]. This method of sampling was advocated by The International Working Group on the Diabetic Foot (IWGDF), as studies have shown that sensitivity and specificity of deep tissue specimens for culture results are higher than those of superficial swabs [19-22].

In our study, there was a high percentage of cultures (34%) that had no bacterial growth. This was consistent to studies that were done locally (reported to be ranging from 21-33%), and in our neighboring countries – Thailand (35%) and Indonesia (26%). This could be due to prescription of antibiotic(s) prior to hospitalization and early commencement of antibiotic(s) before the surgery that have reduced the likelihood of obtaining a positive culture [14].

DFIs are commonly due to polymicrobial infection. Previous studies have shown that polymicrobial infection could be as high as 80% to 87.2% [9]. Nonetheless, of those samples that isolated pathogens in our study, monomicrobial culture (47%) had higher percentage than polymicrobial culture (19%). It is similar to studies by Kow and Abd Kadir, which reported monomicrobial culture of 38.1% and 52% [10, 16]. Its high prevalence is likely to be caused by milder infection and low virulence pathogens isolated. According to Raja et al, two-thirds of mild diabetic foot infections are caused by low-virulence pathogens such as *Staphylococcus aureus*, *Streptococcus viridans*, *Staphylococcus epidermidis* and other gram-negative pathogens [18].

The other possible explanation is that the infection in the present study could be superficial, as 50% of the samples were infected wound cases. With regards to the types of pathogens cultured, our cohort reported predominance of gram-negative pathogens (59.5%), as compared to gram-positive pathogens (39.5%). Our findings mimic the results of other studies carried out in most Southeast Asia countries., which reported higher prevalence of gram-negative pathogens in DFIs with a range of 52% to 73.4% [6]. In our cohort, *Proteus sp.* (19.6%) was the most common gram-negative pathogen, followed by *Klebsiella sp.* (10.1%) and *Pseudomonas sp.* (9.8%). It differs from findings of other local studies, as they reported *Pseudomonas sp.* to be the most common gram-negative pathogen isolated [6,7,9,23]. Different geographical

area may have contributed to diverse types of microorganisms isolated.

In the present study, Gram-positive pathogens demonstrated relatively good susceptibility to erythromycin (80%) and vancomycin (76.2%). The preserved activity of vancomycin against Gram-positive organisms is consistent with previous reports, which have shown high susceptibility of *Staphylococcus aureus*, *Streptococcus*, and *Enterococcus sp* to vancomycin in diabetic foot infections, making it an important therapeutic option for severe infections, particularly when methicillin-resistant strains are suspected [24]. However, susceptibility to macrolides such as erythromycin varies widely between studies due to increasing resistance among staphylococcal isolates [25]. Most literature reports high levels of macrolide resistance in DFIs. For example, one study found erythromycin susceptibility as low as 4.65% [25], while others consistently report it as an "ineffective" or "resistant" agent for Gram-positive DFI pathogens [26-28]. Our high susceptibility rate (80%) indicates a unique local microbiological landscape where macrolide resistance has not yet become pervasive, potentially allowing for its use in specific outpatient or milder infection scenarios.

Among Gram-negative organisms in our cohort, ceftazidime showed the highest susceptibility (100%), followed by cefepime (65.9%) and gentamicin (65%). The observed 100% susceptibility to ceftazidime among Gram-negative pathogens should be interpreted with caution. This finding is attributable to the fact that ceftazidime susceptibility testing was limited to *Pseudomonas sp.* only, which are typically susceptible to this agent. As such, the result does not necessarily represent the susceptibility profile of other Gram-negative organisms in this cohort. Putting that aside, similar findings have been reported in previous studies of diabetic foot infections, where ceftazidime and other third- or fourth-generation cephalosporins demonstrated good activity against *Enterobacter* and *Proteus sp*, while aminoglycosides such as gentamicin also showed moderate effectiveness against Gram-negative isolates [25,27]. The fact that ceftazidime (a third-generation cephalosporin) outperformed cefepime (a fourth-generation cephalosporin) in our hospital is noteworthy. While cefepime typically offers broader coverage, local susceptibility patterns can often invert the expected hierarchy of antibiotic generations [26].

Regarding Methicillin-resistant *Staphylococcus aureus* (MRSA), its prevalence varies based on geographical factors. It is estimated to be commonly isolated from 10-40% of diabetic wounds [22,29]. In an underprivileged region in India, the prevalence of MRSA was reported to be as high as 66% [14], while a local study showed MRSA incidence rate of 2.8% [13], which is close to the incidence rate of MRSA in our study (3.5%). Theenesh et al. reported no MRSA infection in their study cohort of 67 patients. The success of it was attributed to various factors, namely the strict infection control practise and surveillance system that are held in place, as well as the practise of antibiotic stewardship programmes that optimizes the use of antibiotics to treat infections effectively and combat antibiotic resistance at the same time [14,30].

In our study, three cases of multidrug-resistant (MDR) *Acinetobacter sp.* were identified among patients with diabetic foot infections (DFIs), highlighting the growing role of this pathogen in DFI. *Acinetobacter sp.*, particularly *Acinetobacter baumannii*, is recognized for its ability to rapidly acquire antimicrobial resistance through mechanisms such as  $\beta$ -lactamase production, possesses efflux pumps, and reduced membrane permeability, resulting in resistance to multiple antibiotic classes including cephalosporins, fluoroquinolones, and carbapenems. MDR *Acinetobacter sp* has increasingly been reported in DFIs and is associated with limited therapeutic options and poorer clinical outcomes, including prolonged hospitalization and increased risk of lower limb amputation. Therefore, the presence of MDR *Acinetobacter* in our cohort underscores the importance of routine microbiological surveillance and targeted antimicrobial therapy in the management of diabetic foot infections [31-33]. In our center, all three cases were referred to the hospital antimicrobial stewardship team for their input, and Polymyxin E was prescribed.

The involvement of fungal pathogens in DFI is not often studied. A study by Bansal et al. has shown that fungal pathogens accounted for 9% of all pathogen isolated [15]. According to Chellan et al., fungal infection has high prevalence (28%) in deep tissues of lower extremity wounds of diabetic patients, of which *Candida parasilopsis* tops the list [34]. In contrast, we observed a low prevalence of fungal infection in our cohort (1%).

There are several limitations to our study. We were unable to determine the type of antibiotic the patients had taken before coming to the hospital because of missing data. Also, we did not assess the patients' response to the antimicrobial therapy recommended by the lab testing, as most of our patients were discharged before receiving the definitive culture report. In our practice, as soon as patients show clinical improvement evidenced by reducing septic parameters and presence of clean wound, they can be discharged home. We recommend that future research should include both the clinical and biochemical treatment response to the antimicrobial therapy as suggested by the laboratory culture and sensitivity.

**CONCLUSIONS**

This study provides a vital microbiological map for clinicians in Johor Bahru, demonstrating that local pathogen distributions and resistance patterns differ from international averages. These findings advocate for the development of localized empirical antibiotic protocols that prioritize Gram-negative coverage while maintaining strict antimicrobial stewardship to manage emerging resistant strains.

**Conflict of interest**

The authors have no conflict of interest to declare.

**Table 1: Description of the demographic data of patients included in this study**

Factors	Number (n)	Percentage (%)
Gender		
Male	197	57.9
Female	143	42.1
Race		
Malay	257	75.6
Chinese	34	10.0
Indian	41	12.0
Others	8	2.4
Age Group (years)		
<30	4	1.2
30-39	26	7.6
40-49	65	19.1
50-59	98	28.8
60-69	108	31.8
70-79	34	10.0
>80	5	1.5
Type of infection		
Infected wound	170	50.0
Abscess	5	1.5
Necrotizing fasciitis	138	40.6
Gangrene	27	7.9
Type of Surgery		
Wound debridement	114	33.5
Incision and drainage	5	1.5
Ray amputation or toe disarticulation	111	32.6
Mid- or hindfoot amputation	9	2.7
Below knee amputation	82	24.1
Above knee amputation	19	5.6
Tissue Cultures (336 samples)		

No growth	114	34.0
Monomicrobial	158	47.0
Polymicrobial	64	19.0
Types of microorganism isolated (286 pathogens)		
Gram positive	113	39.5
Gram negative	170	59.5
Fungal	3	1.0

**Table II: Cultured microorganisms in this study.**

Microorganisms	Number (n)	Percentage (%)
Gram-positive organisms		
Staphylococcus sp	53	18.5
Streptococcus sp	48	16.8
Enterococcus sp	11	3.9
Bacillus sp	1	0.5
Other gram-positive	0	0
Gram-negative organisms		
Pseudomonas sp	28	9.8
Klebsiella sp	29	10.1
Enterobacter sp	12	4.2
Escherichia Coli sp	13	4.5
Proteus sp	56	19.6
Serratia sp	1	0.3
Morganella sp	19	6.7
Citrobacter sp	5	1.7
Acinetobacter sp	3	1.0
Other gram-negative	4	1.4
Fungal		
Candida sp	3	1.0
Total	286	100

**Table III: Sensitivity patterns of all isolated Gram-positive organisms**

Antibiotics	Staphylococcus sp (n=43)	MRSA (n=10)	Streptococcus sp (n=48)	Enterococcus sp (n=11)	Bacillus sp (n=1)	Total (113)
Penicillin	20		43	3		66/102 (64.7%)
Erythromycin	43		30			73/91 (80%)
Clindamycin		1	5			6/58 (10.3%)
Ampicillin			5	7		12/59 (20.3%)
Oxacillin	36		3		1	36/92 (43.5%)
Cefepime				1		1/11 (9.1%)
Gentamycin	1			5		6/54 (11.1%)
Vancomycin		10		6		16/21 (76.2%)
Bactrim		1				1/10 (10.0%)

**Table IV: Sensitivity patterns of all isolated Gram-negative organisms**

Antibiotics	Pseudomonas sp (n=28)	Klebsiella sp (n=29)	Enterobacter sp (n=12)	Escherichia Coli sp (n=13)	Proteus sp (56)	Serratia sp (n=1)	Morganella sp (n=19)	Citrobacter sp (n=5)	Acinetobacter sp (n=3)	Total (170)
Augmentin		22	3	6	41		1			73/129 (56.6%)
Unasyn		18	2	5	36		1			62/129 (48%)
Gentamycin		22	4	8	38		12			84/129 (65%)
Ceftazidime	28									28/28 (100%)
cefepime	28	1	10			1	17	5		62/94 (65.9%)
Piperacillin/tazocin	28	1		1	5		1			35/145 (24.1%)
Ampicillin		1	1		8		2			12/116 (10.3%)
Cefuroxime		6	1	3	6		1			17/129 (13.2%)
Cefotaxime		1		1	2					4/98 (4.1%)
Imipenem		1	5	2	7	1	5	5		26/135 (19.3%)
Ertapenem		1	4	3	7	1	6	5		27/135 (20%)
Meropenem		1	4	2	7	1	6	5		26/135 (19.2%)
Amikacin					2					2/56 (3.6%)

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