JVHS-29122022-Bacterial Qonaah

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Bacterial Profile and Antibiotic Susceptibility Test among Diabetes Mellitus Patients with Gangrene in Surabaya (English)

Profil Bakteri dan Uji Kerentanan Antibiotik pada pasien Diabetes Melitus dengan Gangren di Surabaya (Indonesian)

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ABSTRACT
Background: *Gangrene is a severe complication of damaged tissue that can occur in people with diabetes mellitus and putting them at risk for bacterial infection. Pus culture can show diabetic gangrene patients' infecting bacteria.*
Purpose: *This study aims to determine the prevalence of infection-causing bacteria and antibiotic sensitivity tests in diabetic gangrene patients at Haji Regional General Hospital, East Java Province, for January-December 2021.*
Methods: *The method used in this study is Observational Analytical Cross-Sectional, which is based on secondary data and is analyzed using the percentage formula and chi-square test.*
Results: *The data obtained from 39 patients revealed 29 (74.4%) positive patients for bacterial infection. The Gram-negative bacteria were found to be the cause of infection more frequently (72.41%) than the Gram-positive bacteria (27.59%). The prevalence of Gram-negative bacteria species most frequently from Escherichia coli (ESBL) 13.79% (4/29), Klebsiella pneumoniae 10.35% (3/29), Proteus mirabilis 10.35% (3/29). While the dominant Gram-positive bacteria a Methicillin-Resistant Staphylococcus aureus (MRSA) 10.35% (3/29). The antibiotic sensitivity test showed that Gram-negative group were susceptible Ertapenem, Meropenem, Amikacin, Gentamicin, Piperacillin Tazobactam while resistant to Ampicillin and Cefazolin. The antibiotic sensitivity tests showed that the Gram-positive group were susceptible to Linezolid, Vancomycin and Tigecycline while resistant to Tetracycline and Ciprofloxacin.*
Conclusion: *it is importance to screen the bacterial profile causing gangrene and their antibiotic susceptibility pattern in DM patients in order to give a proper treatment for DM patients*

Keywords: *antibiotic resistance, diabetes melitus, E. coli, gangrene, pus*

ABSTRAK
Latar Belakang: Gangren merupakan komplikasi serius berupa jaringan rusak yang dapat terjadi pada penderita diabetes melitus dan sangat berisiko mengalami infeksi bakteri. Pemeriksaan menggunakan kultur pus dapat menunjukkan bakteri penyebab infeksi pada penderita gangren diabetik.
Tujuan: Penelitian ini bertujuan untuk mengetahui prevalensi bakteri penyebab infeksi dan uji kepekaan antibiotik pada penderita gangren diabetik di Rumah Sakit Umum Daerah Haji Provinsi Jawa Timur periode Januari - Desember 2021.

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Metode: Metode yang digunakan pada penelitian adalah *Observational Analytical Cross Sectional* dari data sekunder, yang dianalisis dengan rumus presentase dan *chi square*.
Hasil: Hasil data yang diperoleh dari total 39 pasien yaitu 29 (74,4%) pasien positif terinfeksi bakteri. Bakteri penyebab infeksi tertinggi oleh kelompok Gram negatif yaitu 72,41% (21/29), dan bakteri Gram positif yaitu 27,59 % (8/29). Prevalensi spesies bakteri Gram negatif yang dominan oleh *Escherichia coli* (ESBL) 13,79% (4/29), *Klebsiella pneumoniae* 10,35% (3/29), dan *Proteus mirabilis* 10,35% (3/29). Sedangkan pada Gram positif dominan oleh *Methicilin-Resistant Staphylococcus aureus* (MRSA) 10,35% (3/29). Uji kepekaan antibiotik yang diperoleh berdasarkan kelompok Gram negatif yang sensitif adalah *Ertapenem, Meropenem, Amikacin, Gentamicin, Piperacillin Tazobactam* serta resistan terhadap *Ampicillin* dan *Cefazoline*. Uji kepekaan antibiotik untuk kelompok Gram positif sensitif terhadap *Linezolid, Vancomycin* dan *Tigecycline*. Sedangkan antibiotik yang resistan yaitu *Tetracycline* dan *Ciprofloxacin*.
Kesimpulan: hasil dari penelitian ini menunjukkan perlunya skrining untuk melihat profil bakteri penyebab gangrene beserta pola kerentanannya terhadap antibiotic pada pasien DM sehingga dapat memberikan pengobatan yang tepat pada pasien DM.

Kata kunci: DM, *E. coli*, gangrene, pus, resistensi antibiotik

INTRODUCTION

Diabetes mellitus is a rapidly spreading health problem. In 2045, 700 million adults worldwide are predicted to have the disease (International Diabetes Federation (IDF), 2019). Diabetes patient commonly experience foot complications. Diabetes patients frequently experience foot problems, with foot ulcers being one of the more devastating effects. If diabetic foot infections (DFI) are not promptly and properly treated, these ulcers frequently get infected and can result in septic gangrene and amputation. Amputation is a possibility with diabetic foot ulcers (DFUs), a serious consequence of diabetes mellitus (Apelqvist *et al*., 2011; Spreen *et al*., 2016). Studies have indicated that diabetes persons are eight times more likely to experience a vascular lower limb amputation at or near the trans-metatarsal level than nondiabetic individuals under the age of 45 (Johannesson *et al*., 2009).

The most common way to define diabetic foot infections is as an inflammatory reaction and tissue harm brought on by an interaction between the host and microbial pathogens (Williams *et al*., 2004). Reduced peripheral circulation, inflammation, and infection have all been put out as potential causes of gangrene, though these theories have been contested (Gershater *et al*., 2009; Schaper *et al*., 2017). Although a few studies have described certain filamentous fungi and yeasts as the etiological agents of diabetic foot infections, the majority of infections in the diabetic foot are of aerobic and anaerobic bacterial origin, and in most cases polymicrobial (Bowler *et al*., 2001; Johnson *et al*., 1995).

Gram-positive bacteria like *Staphylococcus aureus* and *Enterococcus faecalis*, together with Gram-negative bacteria like *Escherichia coli* and *Pseudomonas aeruginosa*, were shown to be the most prevalent flora of diabetic foot infections, according to earlier investigations (Fejfarová *et al*., 2002; Mantey *et al*., 2000). With the advancement of diabetes epidemiology and modifications in the use of antimicrobial medications, the bacterial spectrum of diabetic foot infections has changed significantly in recent years (Chen *et al*., 2017; Saltoglu *et al*., 2018). It is crucial to concentrate on evaluating the risk factors of multi-drug resistant bacterial infections in order to find a more effective treatment because the increasingly severe

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form of prevention and treatment of diabetic foot ulcer infections is associated with a high rate of detection of multi-drug resistant bacteria (Agbi *et al*., 2017; Belefquih *et al*., 2016). Commonly in diabetic foot infection we can found Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), Enterobacteriaceae that produce ultra-broad spectrum -lactamases (ESBLs), such as *Escherichia coli* and *Klebsiella pneumoniae*, carbapenem-resistant Enterobacteriaceae, multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA)(Yan *et al*., 2022). Thus, this study aims to listed bacterial profile causing gangrene (wet gangrene) among diabetic patient in Surabaya.

MATERIAL AND METHOD

Study site and population

A retrospective cross-sectional study was carried out from January to December 2021at East Java Province Government Hospital, Surabaya Indonesia. The ethical clearance was obtained from ethical committee of this hospital. This hospital is a government building which also act as a teaching facility. With at least 200 beds, this hospital is classified as a type B hospital in Indonesia, and patients with National Health Insurance coverage are welcome to receive care there. Additionally, several district hospitals in Surabaya and the province of East Java used this hospital as their model facility. This hospital offers seventeen different specialties, including pediatrics, anesthesia, dental specialties, internal medicine, radiology, and others.

Data and specimen collection

Pus sample was collected from 39 DM patients with gangrene. Pus samples were collected using swab methods. Samples were then processed to the Microbiology Laboratory Department.

Culture and identification techniques

Swab samples were inoculated onto plates of 5% blood agar, MacConkey agar (Oxoid Ltd, Basingstoke, UK). Incubation was carried out overnight under aerobic conditions at 37°C. The VITEK® 2 device (bioMérieux, USA) was utilized to identify the isolates using conventional bacteriological techniques and biochemical testing. These tests included those for motility, catalase, oxidase, urease, indole, citrate utilization, gas production, H_2S production, and sugar fermentation. In order to preserve pure cultures, subcultures of many distinct colonies were carried out in cultures that were yielding more than one bacterium.

Antimicrobial Susceptibility Testing

Antibiotics sensitivity testing was performed on sensitivity test agar using VITEK® 2 apparatus (bioMérieux, USA) in accordance with National Committee for Clinical Laboratory Standards. Antibiotic class penicillin (ampicillin); penicillin and beta lactamase inhibitor (ampicillin sulbactam, piperacillin tazobactam), class cephalosporins (cefazolin, ceftazidime, ceftriaxone, cefepime), class carbapenems (ertapenem, meropenem), class beta lactamase inhibitor (aztreonam), class nitrofurantoin (nitrofurantoin), class aminoglycosides (amikacin, gentamicin), class fluoroquinoles (ciprofloxacin), and class glycycline (tigecycline) were used for gram-negative bacteria. Antibiotic class penicillin (ampicillin, oxacillin, benzylpenicillin); class aminoglycosides (gentamicin); class glycycline (tigecycline); class sulfonamides (trimethoprim/sulfamethoxazole); class tetracycline (tetracyclin); class fluoroquinoles (moxifloxacin, levofloxacin,ciprofloxacin); class lincomycin (clindamycin); class oxazolidinone (linezolid), class

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glycopeptide (vancomycin), class macrolides (erythromycin); class nitrofurantoin (nitrofurantoin) and class rifampisin (rifampisin) were used for gram-positive bacteria. Antibiotics were classified using the 2019 WHO AwaRe classification of antibiotics for evaluation and monitoring of use. Results were classified as either resistant (R) or sensitive (S) to the tested antibiotics using the interpretive guidelines given by the Clinical and Laboratory Standards Institute (CLSI). The tested antibiotics can still be utilized for therapy because of the sensitive results. Since there are bacterial resistances to the antibiotics being tested in this investigation, the readings utilizing this technique (S or R type) reveal this. Multi-Drug Resistance was defined as bacterial isolates that were resistant to three or more antimicrobials from various structural classes (MDR).

Statistical analysis

The results obtained in this study are number of bacteria based on species identification and results of antibiotic susceptibility tests. Categorical data is presented in the form of frequency and percentage.

RESULT

Our results show that among 39 DM patient with gangrene, 19 patients (48.3%) were male and 20 patients (51.7%) were female. Among those patients, 76.9% (30/339 patients) were included in productive age category (45-59 years), while 7.7% (3/39 patients) were categorized as young adult or 25-44 years old and 15.4% (6/39 patients) were included in elderly category or above 65 years olld (Table 1). Pus culture showed microbial growth in 29 patients (74.4%) while 10 patients (25.6%) showed no microbial growth.

Table 1. Demographic information of DM patient with gangrene

Sample	Number of patients (Percentage)
Gender	
Male	19 (48.7)
Female	20 (51.3)
Age (years)	
25-44	3 (7.7)
45-59	30 (76.9)
60-75	6 (15.4)

Pus culture showed the appearance of microbial drug resistance organisms (MDRO) which is *Escherichia coli*- extended spectrum beta lactamase (ESBL) in 4 patients (13.8%). Our result also found another MDRO which is methicillin resistant *Staphylococcus aureus* (MRSA) in 3 patients (10.4%) (Table 2). In comparison the appearance of gram-negative bacteria is dominant compare to gram-positive bacteria (72.4% compare to 27.6%). In case of gram negative, the study showed Enterobacteriaceae were seen enormously causing gangrene in DM patients such as *Klebsiella pneumoniae* (3 patients, 10.4%), *Proteus mirabilis* (3 patients, 10.4%).

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Table 2. Bacterial profile causing gangrene among DM patient from pus sample

No	Bacteria	Number (Percentage)
Gram negative bacteria		
1	*Escherichia coli (ESBL)*	4 (13.8)
2	*Klebsiella pneumoniae*	3 (10.4)
3	*Proteus mirabilis*	3 (10.4)
4	*Citrobacter freundii*	2 (6.9)
5	*Citrobacter koseri*	2 (6.9)
6	*Enterobacter cloacae*	2 (6.9)
7	*Enterobacter aerogenes*	1 (3.5)
8	*Morganella morganii*	1 (3.5)
9	*Proteus hauseri*	1 (3.5)
10	*Shigella sp*	1 (3.5)
11	*Pseudomonas putida*	1 (3.5)
Gram positive bacteria		
12	*Methicillin Resistant Staphylococcus aureus* (MRSA)	3 (10.4)
13	*Enterococcus faecalis*	2 (6.9)
14	*Enterococcus avium*	1 (3.5)
15	*Staphylococcus haemolyticus*	1 (3.5)
16	*Staphylococcus hominis*	1 (3.5)
Total		29 (100)

Antibiotic resistance test showed that gram negative bacteria showed resistant to ampicillin (penicillin type of antibiotic), cefazolin (cephalosporin type of antibiotic) (Table 3). Through antibiotic resistance test, we found *Pseudomonas putida* showed resistance to almost all antibiotic tested except ampicillin and ampicillin sulbactam, meropenem and furantoin (Table 3). In case of *E. coli* ESBL it is shown that beside cephalosporin resistance (cefazolin, ceftriaxone), it was also showed resistance to ampicillin and ciprofloxacin (Table 3). While *E. coli*- ESBL showed susceptibility to carbapenem antibiotics such as ertapenem and meropenem; aminoglikosida such as amikacin; furantoin, amikacin and tigecyline. Other gram-negative bacteria showed resistance to cephalosporins (cefazolin) and penicillin class (ampicillin) (Table 3). But it showed susceptibility to carbapenem class (ertapenem and meropenem); aminoglikosida class (amikacin and gentamicin); beta lactamase inhibitor class alone or in combination with penicillin class (azretonam, piperacillin tazobactam); class cephalosporins (ceftazidime, ceftriaxone, cefepime) (Table 4).

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Table 3. Antibiotic Resistance Results from Gram Negative Bacteria Causing Gangrene among DM patients

Antibiotics	AMP	SAM	TZP	KZ	CAZ	CRO	FEP	ATM	ERTA	MEM	AK	GN	CIP	F	SXT	TGC
Escherichia coli (ESBL) n=4 (%)	**4 (100)**	2 (50)	1 (25)	**4 (100)**	2 (50)	**4 (100)**	1 (25)	3 (75)	0 (0)	0 (0)	0 (0)	1 (25)	**4 (100)**	0 (0)	3 (75)	0 (0)
Klebsiella pneumoniae n=3 (%)	0 (0)	1 (33)	0 (0)	2(67)	2 (67)	2 (67)	2 (67)	2 (67)	0 (0)	0 (0)	0 (0)	2 (67)	**3 (100)**	0 (0)	1 (33)	0 (0)
Proteus mirabilis n=3 (%)	2 (67)	1 (33)	1 (33)	**3 (100)**	1 (33)	1 (33)	1 (33)	2 (67)	0 (0)	0 (0)	0 (0)	1 (33)	1 (33)	**3 (100)**	2 (67)	2 (67)
Citrobacter freundii n=2 (%)	**2 (100)**	**2 (100)**	0 (0)	**2 (100)**	0 (0)	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	0 (0)	1 (50)	0 (0)
Citrobacter koseri n=2 (%)	**2 (100)**	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0(0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Enterobacter cloaae n=2 (%)	**2 (100)**	**2 (100)**	1 (50)	**2 (100)**	1 (50)	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	**2 (100)**	0 (0)	1 (50)	0 (0)
Enterobacter aerogenes n=1(%)	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Proteus hauseri n=1(%)	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Morganella morganii n=1(%)	**1 (100)**	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Shigella sp n=1(%)	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)
Pseudomonas putida n=1(%)	0 (0)	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**

AMP, Ampicillin; SAM, Ampicillin Sulbactam; TZP, Piperacillin Tazobactam; KZ, Cefazolin; CAZ, Ceftazidime; CRO, Ceftriaxone; FEP, Cefepim; ATM, Azteronam; ERTA, Ertapenem; MEM, Meropenem; AK, Amikacin; GN, Gentamicin; CIP, Ciprofloxacin; F, Nitrofurantoin; SXT, Trimethopprim/sulfamethoxazole; TGC, Tigecyline.

Table 4. Antibiotic Susceptibility Results from Gram Negative Bacteria Causing Gangrene among DM patient

Antibiotics	AMP	SAM	TZP	KZ	CAZ	CRO	FEP	ATM	ERTA	MEM	AK	GN	CIP	F	SXT	TGC
Escherichia coli (ESBL) n=4 (%)	0 (0)	0 (0)	3 (75)	0 (0)	2 (50)	0 (0)	3 (75)	1 (25)	**4 (100)**	**4 (100)**	**4 (100)**	3 (75)	0 (0)	**4 (100)**	1 (25)	**4 (100)**
Klebsiella pneumoniae n=3 (%)	**3 (100)**	1 (33)	**3 (100)**	0 (0)	1 (33)	1 (33)	1 (33)	1 (33)	**3 (100)**	**3 (100)**	**3 (100)**	1 (33)	0 (0)	0 (0)	2 (67)	0 (0)
Proteus mirabilis n=3 (%)	1 (33)	2 (67)	2 (67)	0 (0)	2 (67)	2 (67)	2 (67)	1 (33)	1 (33)	**3 (100)**	**3 (100)**	2 (67)	2 (67)	0 (0)	1 (33)	0 (0)
Citrobacter freundii n=2 (%)	0 (0)	0 (0)	1 (50)	0 (0)	1 (50)	1 (50)	**2 (100)**	0 (0)	**2 (100)**	**2 (100)**	**2 (100)**	1 (50)	1 (50)	1 (50)	1 (50)	**2 (100)**
Citrobacter koseri n=2 (%)	0 (0)	1 (50)	**2 (100)**	0 (0)	**2 (100)**	**2 (100)**	**2 (100)**	**2 (100)**	**2 (100)**	**2 (100)**	**2 (100)**	**2 (100)**	**2 (100)**	0 (0)	**2 (100)**	1 (50)
Enterobacter cloaae n=2 (%)	0 (0)	0 (0)	1 (50)	0 (0)	1 (50)	1 (50)	**2 (100)**	1 (50)	1 (50)	**2 (100)**	**2 (100)**	**2 (100)**	0 (0)	0 (0)	1 (50)	1 (50)
Enterobacter aerogenes n=1(%)	0 (0)	0 (0)	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**
Proteus hauseri n=1(%)	0 (0)	0 (0)	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	0 (0)
Morganella morganii n=1(%)	0 (0)	0 (0)	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	0 (0)
Shigella sp n=1(%)	0 (0)	0 (0)	**1 (100)**	0 (0)	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pseudomonas putida n=1(%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AMP, Ampicillin; SAM, Ampicillin Sulbactam; TZP, Piperacillin Tazobactam; KZ, Cefazolin; CAZ, Ceftazidime; CRO, Ceftriaxone; FEP, Cefepim; ATM, Azteronam; ERTA, Ertapenem; MEM, Meropenem; AK, Amikacin; GN, Gentamicin; CIP, Ciprofloxacin; F, Nitrofurantoin; SXT, Trimethopprim/sulfamethoxazole; TGC, Tigecyline.

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The results of antibiotic resistance test of gram-positive bacteria showed resistant to tetracyclin and ciprofloxacin. Apart from beta lactam antibiotics, MRSA showed resistance to aminoglycosides class (gentamicin), tetracycline, fluoroquinolone class (moxifloxacin, levofloxacin,ciprofloxacin), lincomycin class (clindamycin) and macrolides class (clindamycin) (Table 5). MRSA showed susceptibility to tigecycline, linezolid, vancomycin and furantoin. Others gram positive bacteria showed susceptible to linezolid, vancomycin, tigecycline, ampicillin (Table 6). While other gram-positive bacteria showed resistance to tetracycline and showed susceptibility to linezolid and vancomycin (Table 5 and 6).

Table 5. Antibiotic Resistance Results from Gram Positive Bacteria Causing Gangrene among DM patients

Antibiotics	AMP	OXA	BEN	GN	TGC	SXT	TE	MXF	LEV	CIP	CC	LZD	VA	E	F	Rif
Methicillin Resistant Staphylococcus aureus (MRSA) n=3 (%)	0 (0)	**3 (100)**	0 (0)	**3 (100)**	0 (0)	1 (33)	**3 (100)**	**3 (100)**	**3 (100)**	**3 (100)**	**3 (100)**	0 (0)	0 (0)	**3 (100)**	0 (0)	2 (67)
Enterococcus faecalis n=2 (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**2 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)
Enterococcus avium n=1 (%)	0 (0)	0 (0)	0 (0)	**1 (100)**	0 (0)	0 (0)	**1 (100)**	0 (0)	0 (0)	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**	0 (0)
Staphylococcus haemolyticus n=1 (%)	0 (0)	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Staphylococcus hominis n=1 (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AMP, *Ampicillin*; OXA, *Oxacillin*; BEN, *Benzylpenicillin*; GN, *Gentamicin;* TGC, *Tigecyline*; SXT, *Trimethoprim Sulfamethoxazole*; TE, *Tetracycline*; MXF, *Moxifloxacin*; LEV, *Levofloxacin*; CIP, *Ciprofloxacin; CC*, *Clindamycin*; LZD, *Linezolid*; VA, *Vancomycin*; E, *Erythromycin*; F, *Nitrofurantoin*; Rif, *Rifampicin*.

Table 6. Antibiotic Susceptibility Results from Gram Positive Bacteria Causing Gangrene among DM patients

Antibiotics	AMP	OXA	BEN	GN	TGC	SXT	TE	MXF	LEV	CIP	CC	LZD	VA	E	F	Rif
Methicillin Resistant Staphylococcus aureus (MRSA) n=3 (%)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (100)**	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (100)**	**3 (100)**	0 (0)	**3 (100)**	1 (33)
Enterococcus faecalis n=2 (%)	**2 (100)**	0 (0)	0 (0)	0 (0)	**2 (100)**	0 (0)	0 (0)	0 (0)	**2 (100)**	**2 (100)**	0 (0)	**2 (100)**	**2 (100)**	0 (0)	1 (50)	0 (0)
Enterococcus avium n=1 (%)	**1 (100)**	0 (0)	0 (0)	0 (0)	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**	**1 (100)**	0 (0)	0 (0)	0 (0)
Staphylococcus haemolyticus n=1 (%)	0 (0)	0 (0)	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**
Staphylococcus hominis n=1 (%)	0 (0)	0 (0)	0 (0)	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	**1 (100)**	0 (0)	**1 (100)**	0 (0)	**1 (100)**	**1 (100)**	0 (0)

AMP, *Ampicillin*; OXA, *Oxacillin*; BEN, *Benzylpenicillin*; GN, *Gentamicin;* TGC, *Tigecyline*; SXT, *Trimethoprim Sulfamethoxazole*; TE, *Tetracycline*; MXF, *Moxifloxacin*; LEV, *Levofloxacin*; CIP, *Ciprofloxacin; CC*, *Clindamycin*; LZD, *Linezolid*; VA, *Vancomycin*; E, *Erythromycin*; F, *Nitrofurantoin*; Rif, *Rifampicin*.

DISCUSSION

Demographic information of DM patient reveals that in term of gender there is no different in probability of DM patient to develop gangrene. While in term of age, DM patients in group of 45-59 years old showing high probability of developing gangrene. This study also in accordance with other studies by Tong et al in 2020 that stated DFU (diabetic foot ulcers) is common in middle-aged patients. Also study conducted in Saudi Arabia that showed > 45 years of age can poses a threat for developing DFU (Al-

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Rubeaan *et al*., 2015; AlSadrah, 2019). Our study demonstrated that middle-aged patients with DFUs had worse glycemic control, made worse lifestyle decisions like smoking and drinking, had more severe ulcers, and were more likely to have microangiopathy problems. However, these individuals subsequently recovered more quickly and were at a lower risk of death and significant amputation (Tong *et al*., 2020).

Our result showed that bacterial found in pus culture dominated by gram negative bacteria. With *E. coli* ESBL, MRSA, *Klebsiella pneumoniae, Proteus mirabilis* being the most common bacteria causing gangrene. Gram-negative rods were mostly found in patients with chronic wounds that had already been treated. Beginning in the late 1970s, studies showed that aerobic Gram-positive cocci, particularly *Staphylococcus aureus*, were the most common pathogens in DFIs, frequently as monomicrobial infections. Aerobic DFIs brought on by multidrug-resistant organisms, including extended-spectrum beta-lactamase-producing Gram-negative rods (Varaiya *et al*., 2008) or methicillin-resistant *S. aureus* (MRSA), have become a significant issue in recent years. The choice of an agent active against that isolate is undoubtedly necessary in the event of an infection with an antibiotic-resistant bacterium, but therapeutic management should remain unchanged (Uçkay *et al*., 2012).

When we adding the number of *E. coli* ESBL and MRSA we found that 24 % cases were causing by Multidrug-resistant bacterial infection. Another factor contributing to the appearance of MDRO in other study by Dubsky et al ini 2013 were because of long term poor glucose control in DM patient (Dubský *et al*., 2013). By reducing the therapeutic efficacy of antibiotic therapy, MDRO infection in diabetic foot ulcers makes treatment more difficult and may even result in fatalities or amputations (Agbi et al., 2017; Yan et al., 2022). The risk factors of drug-resistant negative bacilli in patients should be assessed in the development of the initial anti-infective treatment regimen in clinical practice due to the increased resistance rate of E. coli ESBL among gram-negative bacteria. Another study also noted that the appearance of MDRO might be related to the patients with serious illness admitted to our hospital as a tertiary care hospital and the more complex history of antibacterial drug use (Yan *et al*., 2022).

Systemic antibiotic therapy is required for patients with poor systemic resistance, which typically coexists with bacteremia or sepsis. As a result, it's crucial to perform a thorough evaluation of each patient with diabetic foot ulcers, keep an eye on the severity of the infection and any changes in the pathogenic bacteria, and administer anti-infective therapy in a consistent manner (Tang, 2019).The majority of diabetic foot infections (DFIs) require systemic antibiotic therapy, with empirical selection being the norm at first. Even though there are numerous antibiotics available, it is unclear which one is best for treating DFIs. Antibiotic susceptibility that gram negative bacteria (wild type and MDRO) showed susceptibility to meropenem class, aminoglikosida class and beta lactamase inhibitor antibiotic. While for gram negative bacteria without MDRO, cephalosporin, beta lactamase antibiotics still susceptible in this study. In case of gram-positive bacteria, it showed susceptibility to tigecycline, linezolid, vancomycin. Other studies suggested that ertapenem with or without vancomycin also tigecycline can be used to treat DFI infection (Selva Olid *et al*., 2015). Study by Du et al in 2022 also showed that gram positive bacteria were susceptible to linezolid, vancomycin, teicoplanin (Du *et al*., 2022).

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CONSLUSION

The gangrene or diabetic foot infection occur in the middle age group (45-59 years) old accounted for 76.9%. Pus culture showed *E. coli* ESBL, MRSA, *Klebsiella pneumoniae, Proteus mirabilis* as the dominant bacteria found. Gram negative bacteria were highly sensitive to meropenem class (ertapenem and meropenem, aminoglikosida class (amikacin, gentamicin) and tigecycline class of antibiotics *Ertapenem,* meropenem, amikacin, gentamicin, piperacillin tazobactam. While gram positive bacteria were highly sensitive to tigecycline, linezolid and vancomycin.

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