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Diabetic Foot Infection Characteristics and Antibiotics Susceptibility Patterns in a Regional Hospital in Libya

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Abstract

Introduction Diabetes is a major global health problem, among the top causes of death worldwide. Diabetic foot infection (DFI) is associated with an increased risk of amputation by 155 times and a mortality rate of 57% at 5 years. This study aims to characterize DFI epidemiology in a local hospital and analyze local microbiological patterns and antibiotic susceptibility testing.

Patients and Methods This is a retrospective review of Al Jala hospital Benghazi/Libya medical records. Eligible patients were included, if they had DFI with confirmed tissue /pus samples collections was submitted to the hospital laboratory for microbiology and Antibiotics susceptibility analysis.

Results Out of 126 patients, 77 (61.1%) were men, and 49 (38.9%) were women. The mean age was 55.4 years. Incision drainage with debridement was the most common surgical procedure (77.1%). 38.88% of growth was polymicrobial. Gram-negative rods were isolated in 70.9%, and gram-positive cocci in 27.4%. The most commonly isolated bacteria were *Pseudomonas aeruginosa* (15.9%) and *Proteus sps.* (14.2%), *Staphylococcus aureus* (11.3%), and Escherichia *coli* (10.2%). Methicillin-resistant Staphylococcus aureus (MRSA) constitutes 30% of isolated *S. aureus*. The most common effective antibiotic for *P. aeruginosa* was imipenem (90%), for *S. aureus* was linezolid (100%), and for MRSA was linezolid, vancomycin (100%), and ciprofloxacin 88.8%. Sixty-four percent of total bacterial isolates were MDROs (gram-positive isolates 65.3%, gram-negative isolates 63.6%).

Conclusions The emergence of antibiotic-resistant bacteria is a global health concern. This study attempts to evaluate the local microbiology and antimicrobial susceptibility to tailor the treatment choice for better patient outcomes.

Keywords
- antibiotic susceptibility
- DFI
- antimicrobial agents
- MRSA
- *Pseudomonas aeruginosa*

Introduction

Diabetes is a significant health problem, among the top causes of death worldwide, with an estimated global prevalence in 2019 of 9.3% (463 million people).[1] According to WHO, it is estimated that there were 88,000 diabetic patients in Libya in the year 2000. This prevalence is estimated to reach 245,000 patients with diabetes by 2030.[2] Diabetic foot

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complications such as ulcers, infections, and gangrene are the leading causes of admission in the hospital.[3] Diabetes is the leading cause of all non-traumatic lower extremity amputations globally.[4] Diabetic foot infection (DFI) is associated with an increased risk of amputation by 155 times[5,6] and a mortality rate of 57% in 5 years.[7]

DFI is defined clinically by the findings of local inflammation or purulent collection occurring in the site below malleoli in a diabetic patient that sometimes spreads proximally and is associated with systemic inflammation and sepsis.[1] Neuropathic or neuro-ischemic diabetic foot ulcers (DFUs) serve as the entry point of pathogens in most DFI.[8] DFIs are byproducts that result from progressive polyneuropathy with loss of protective sensations and resultant foot ulcers, foot deformity, vascular insufficiency, and ischemia in diabetic patients[4,9]. Up to 50% of diabetic patients with foot ulceration have peripheral artery disease (PAD).[10,11]

Risk factors for DFI were ulcer duration, bone contact on probing, neuropathy, peripheral vascular disease, trauma, and history of the previous amputation.[12] Many classification systems were used to classify DFUs. The most widely used was the Wagner classification system and DFI classification scheme of the International Working Group on the Diabetic Foot (IWGDF) and Infectious Diseases Society of America (IDSA).[13,14]

In western countries, the microbiology of DFI in mild superficial wounds is usually caused by gram-positive organisms, mainly *Staph. aureus*, and to a lesser extent by β-streptococci and coagulase-negative staphylococci.[15] DFI in chronic wounds with prior history of antibiotic treatment is more poly-microbial. It contains aerobic gram-negative and anaerobic bacteria.[4] In contrast, epidemiological surveys about DFI microbiology in under-developed countries showed a higher prevalence of gram-negative rods, especially *Pseudomonas aeruginosa*.[16]

DFI treatment requires a multidisciplinary approach involving different specialties such as general practitioner, surgeon, diabetologist, podiatrist, clinical microbiology, specialized nurse, and high-risk foot clinic helps reduce complications.[8,17,18] Different surgical interventions such as debridement or incision and drainage, limb-saving partial amputations, foot-sparing reconstructive procedures, and vascular interventions are recommended in clinical practice guidelines.[12,19] Antimicrobial therapy is the cornerstone in treating DFI in addition to surgery, pressure offloading, and proper wound care.[15] The choice of the initial antimicrobial regimen is usually empirical and shifts to a narrower spectrum bending on the results of adequately taken tissue specimens. Local policies and guidelines to tackle this complex clinical problem are needed due to differences in the risk factors and local microbiology prevalence, however, there are international guidelines to help in this regard, such as IWGDF and IDSA Clinical Practice Guidelines.[13,14] The increasing emergence of multidrug-resistant bacteria is a worrying public health problem associated with delays in antibiotic therapy and poorer clinical outcomes.[20,21]

This study aims to characterize DFI epidemiology in a local hospital and analyze local microbiological patterns and antibiotic susceptibility testing, to provide local policy in tailoring antibiotic therapy according to the study results for better patient care outcomes and toward antibiotic prescribing stewardship policy to minimize the resurgence of bacterial resistance in the local community.

Patients and Methods

A retrospective observational study was conducted in the department of general surgery, Al Jala Hospital, Benghazi/Libya, between January 01, 2017, to December 31, 2019. Aljala Hospital is the largest surgical hospital in the Eastern part of Libya.

During the study period, we searched the microbiology laboratory data of Al Jala Hospital and tracked the medical records of eligible subjects from the hospital medical archive. Adults aged 18 years or older admitted due to diabetic foot complications were included. Swabs taken either from a pus collection or a surgical wound related to diabetic foot treatment were included in the study. Furthermore, cultures unrelated to DFI, such as traumatic infections and tumor excision, were excluded.

The antimicrobial susceptibility tests were reportedly done by disk diffusion technique according to the Clinical and Laboratory Standards Institute Guidelines.[22] The cefoxitin disk diffusion method was used to detect methicillin-resistant *Staphylococcus aureus* (MRSA). The Wagner classification was used to classify DFUs. We have used the first recorded isolate from each patient to avoid repeat isolates.

Multidrug-resistant (MDR) organism was defined as resistance to at least one agent in three or more antimicrobial categories, while extensive drug resistance (XDR) was defined as susceptibility to only two or fewer antimicrobial categories. Pan-drug resistance (PDR) was defined as resistance to all antimicrobial agents in all antimicrobial categories, and an international expert group proposed these definitions from the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention.[21]

The results of antimicrobial susceptibility tests, patients' admission details, and epidemiological data were critically reviewed and analyzed using the Statistical Package for Social Sciences (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

Results

Clinical Characteristics

The total study population was 126 patients. 61.1% (77/126) were males, and 38.9% (49/126) were females. The mean age was 55.4 (18–88, SD 13.6). With a mean hospital stay of 16.6 days (SD 17.6), 11.7% had hypertension, 4.5% had ischemic heart disease, and 7.3% had multiple medical comorbidities in addition to having diabetes. 19.6% (35/179) had moderate to severe PAD confirmed by Doppler ultrasound. 25.7% (46/179) of pus swabs were pre-surgical, and 74.3% (133/179) were post-surgical. Debridement was the most common surgical procedure (77.1%), minor and major amputation rates were performed in 23 (13.0%) and 18 (10.1%)

patients, respectively, and the overall amputation rate in this study was 23%. The rest of the epidemiological and patient characteristics are shown in ►**Table 1**.[71]

Table 1 Epidemiological and clinical characteristics

Demographic parameters	Value
Age (Mean [SD])	55.24 (13.6)
Sex (Males/Females)	77 (61.1%)/49 (38.9%)
Type of growth	
No growth	6 (4.8%)
Mono-microbial	71 (56.3%)
Poly-microbial	49 (38.9%)
Type of surgery	
Incision and drainage with debridement	138 (77.1%)
Toe amputation	15 (8.4%)
Forefoot amputation (trans metatarsals)	8 (4.5%)
Below knee amputation	10 (5.6%)
Above knee amputation	8 (4.5%)
Comorbid conditions	
Hypertension	21 (11.7)
Ischemic heart disease	8 (4.5%)
Renal failure	2 (1.1%)
Multiple comorbidities	13 (7.3%)
None	135 (75.4%)
Wagner classification	
Grade 0 and 1	0 (0%)
Grade 2	2 (1.1%)
Grade 3	133 (74.3%)
Grade 4	36 (20.1)
Grade 5	8 (4.5)

Microbial Growth Patterns

Out of 126 subjects, 56.3% showed a mono-microbial growth pattern, 38.9% (49/126) showed polymicrobial growth, and in 4.8% (6/126), there was no growth. Out of 126 subjects, there were 176 positive-growth isolates. 70.9% (128/179) of bacterial growth was gram-negative rods, 27.4% (49/179) was gram-positive cocci (GPC), and 1.1% (2/179) was gram-positive rods. The most common bacteria among the gram negative isolates ($n = 128$) were *Pseudomonas*, i.e., 21.9% (28/128), Proteus species 19.5% (25/128), and Escherichia *coli* 14.1% (18/128). The most common gram-positive ($n = 51$) isolates were *Staph. aureus* 39.2% (20/51) and non-hemolytic streptococcus 29.4% (15/51). ►**Table 2** shows the type and frequencies of the bacterial isolates in the study sample.

Antibiotic Susceptibility and Resistance

Various combinations out of 36 antibiotic types were used for organism susceptibility testing. The most effective antibiotics for *Staph. aureus* were linezolid (100%), erythromycin (94%), ciprofloxacin (87.5%), levofloxacin (84.6%), and vancomycin (83.3%). The rest of the gram-positive isolates' susceptibilities are shown in ►**Table 3**. MRSA constitute 35% of all *Staph. aureus* strain. With its inherent resistance to penicillin and most β *β*-lactam antibiotics, MRSA showed susceptibility to quinolones such as ciprofloxacin 88.8%, levofloxacin 75%, and was almost 100% susceptible to vancomycin and linezolid. For *P. aeruginosa*, the susceptible antibiotics were imipenem (90%), aztreonam (86.3%), and the least sensitive antibiotic was co-amoxiclav (0%). The rest are shown in ►**Table 4**. Amoxicillin/clavulanic acid was the initially prescribed IV antibiotic at 96.1% (121/126), followed by ceftriaxone at 3.4% (4/126).

Among 181 bacterial isolates for which antimicrobial susceptibility test was done, 116/181 bacterial isolates

Table 2 The relative frequencies of various microbial isolates

Gram-negative bacteria ($n = 128$)		Gram-positive bacteria ($n = 51$)	
Organism	**Number (%)**	**Organism**	**Number (%)**
Pseudomonas aeruginosa	28 (22%)	*Staphylococcus aureus*	20 (39.2%
Proteus species	25 (19.7%)	Non-hemolytic streptococcus	15 (29.4%
Klebsiella	21 (16.5%)	*Staphylococcus albus*	7 (13.7%)
E. coli	18 (14.2%)	Group A hemolytic streptococcus	5 (9.8%)
Enterobacter	14 (10.9%	*Enterococcus faecalis*	2 (3.9%)
Acinetobacter	10 (7.9%)	*Bacillus species*	2 (3.9%)
Morganella morganii	6 (4.7%)		
Citrobacter	3 (2.4%)		
Serratia	1 (0.8%)		
Non-lactose fermenters	1 (0.8%)		
Kluyvera ascorbata	1 (0.8%)		

Table 3 Antimicrobial susceptibility results

	Gram negative					Gram positive			
	Pseudomonas	*Proteus*	*Klebsiella*	*Escherichia coli*	*Enterobacter*	*Staphylococcus aureus*	Non-hemolytic Streptococcus	*Staphylococcus albus*	Group A hemolytic Streptococcus
Levofloxacin	84.6	95.6	77.7	85.7	76.9	84.6	80	71.4	100
Amikacin	83.3	73.9	71.4	86.6	84.6				
Ciprofloxacin	84.6	82.6	70	70.5	71.4	87.5	61.5	75	100
Imipenem	90	95	92.8	100	92.3	81.8	75	100	100
Colistin	85	5.26	100	90	87.5	–	–	–	–
Aztreonam	86.3	83.3	46.6	44.4	66.6	–	–	–	–
Ceftazidime	71.4	77.7	26.6	50	50	–	–	–	–
Meropenem	81.25	100	75	100	85.7	66.6	71.4	75	50
Gentamicin	50	82.3	58.3	53.3	45.4	–	–	–	–
Ceftriaxone	30.7	72.7	26.3	53.3	55.5	50	20	50	–
Cotrimoxazole	12.5	52.1	21	29.4	53.8	–	–	–	–
Doxycycline	35.3	6.6	66.6	87.5	83.3	–	–	–	–
Amoxicillin/ clavulanic acid	0	26.6	7.6	30	12.5	46.1	71.4	0	50
Vancomycin	–	–	–	–	–	83.33-	100	100	50
Linezolid	–	–	–	–	–	100	100	100	66.6
Erythromycin	–	–	–	–	–	94.1	53.3	100	60
Clindamycin	–	–	–	–	–	92.3	54.5	50	75

Table 4 MDR rate for *Enterobacteriaceae* isolates

Enterobacteriaceae spp.	MDR rate
Proteus spp.	85%
E. coli	75%
Klebsiella	86%
Enterobacter	58%
Morganella	57%
Citrobacter	33%
Other (Kluyvera, Serratia and Non-fermenters)	67%

Note: MDR is defined as non-susceptible to ≥1 agent in ≥3 antimicrobial categories.

(64%) were multidrug resistant. For gram-positive bacterial isolates it was 32/49 (65.3%), and for gram-negative bacterial isolates it was 84/132 (63.6%). MDR rate for both *S. aureus* and *Enterococcus spp.* was 66.6%, while for, gram-negative isolates it was 14% for *P. aeruginosa*, 90.9% for *Acinetobacter spp.*, and 75.5% for *Enterobacteriaceae*. ►**Table 4** shows the MDR rate for individual isolated *Enterobacteriaceae spp.*

Discussion

In the present study, more than two-thirds of the study population were males, like the findings shown in other parts of Libya and other developing countries in the Middle East and North Africa (MENA) region.[23–25] This could be attributed to more outdoor physical activities among males putting them at higher risk of foot injury.[26] Wagner grade III ulcers were the most common grade of diabetic ulcers (74.3%), followed by Wagner grade IV ulcers (20.1%) in this study, which was higher in comparison with the results from a previous study conducted in the same hospital in which Wagner grade III and IV were the most common, 31 and 25%, respectively.[27] Furthermore, the results from the South of Libya showed that Wagner grade III and IV were 24.6 and 16.4%, respectively.[25] This difference could be explained by the difference in the study sample inclusion criteria (selection bias), where we only included patients with swabs taken from their wounds in our study. In contrast, the other studies included all patients admitted with DFIs. A systemic review and meta-analysis of characteristics, prevalence, and outcomes of DFUs in Africa showed that the prevalence of significant amputation was 15.5% and the prevalence of minor amputation was 16.0%,[28] which is higher than the results of this study. No details of vascular assessment and any intervention for their PAD could be retrieved from charts. Ideally, all diabetic patients should have a vascular assessment, and those with significant arterial insufficiency should have intervention with either open or endovascular approach accordingly, as arterial insufficiency is an important prognostic outcome for ulcer healing.[4,11]

In this study, polymicrobial infections were found in 38.9% of isolates. However, in the MENA region, polymicrobial growth varied widely between 15 and 90%.[24] In this study, the gram-negative rods (GNR) were the most common

isolated bacteria, 70.9%, followed by GPC, 27.4%, which is higher than the results reported in other parts of Libya, where the GNRs were 59.1 and 50.8% in the Southern and Western parts, respectively.[23,25] It reflects the gram-negative predominance in the less developed and hot tropical areas such as what is reported in a similar Malaysian study, which showed a higher gram-negative pathogen rate (54%),[29] while in the Western and well-developed world, GPC are the most typical isolated pathogen,[4] such as the finding of a prominent Korean study that reported gram-positive bacteria were isolated in 57.5%, followed by gram-negative bacteria (40.0%).[30] These geographical differences could be attributed to the laboratory techniques, specimen types, prior antibiotics, or reporting bias.[4]

Staphylococcus aureus was the most common among gram-positive organism and the fourth most isolated from this study (11.17%), with MRSA rate being 35%. The most common isolated gram-negative bacteria were *P. aeruginosa* (15.6%), *Proteus* (13.9%), and *Klebsiella* (11.7%). Compared with previous reports from Libya, the most common organisms isolated were *Staph. aureus* (31.7%) with MRSA (55%), *Pseudomonas aeruginosa* (17.5%), and coagulase-negative *Staphylococcus* (15.9%).[23] In the MENA region, *Enterobacteriaceae* (with *Proteus and E. coli* being the most common) were 34%, *Staphylococcus aureus* 20%, MRSA rate was 31%, and *P. aeruginosa* was 10%[24]. In a large academic hospital in the United States, *S. aureus* was present in 46% of culture-positive DFIs (MRSA, 15%).[31] This study's lack of data about anaerobic bacteria was attributed to lack of resources and facilities for obtaining and handling samples. Similarly, this was noted in a study by Sekhar et al in India[26]. Furthermore, the reported prevalence of anaerobic bacteria was variable in the MENA region from 0 to 20%.[24]

In this study, the most prescribed initial antibiotic was amoxicillin/clavulanic acid. However, its susceptibility ranges from 0 to 30% for the gram negative, and the overall sensitivity for the gram positive is 37.5%. Quinolones could be considered a potential initial choice of antibiotics with the advantage of oral form availability if indicated bending on the results of microbiology susceptibility tests, where ciprofloxacin and levofloxacin showed susceptibility rates to gram-positive isolates, 76.9 and 83.3% respectively. Gram-negative isolates susceptibilities were for ciprofloxacin (70–100%) and levofloxacin (77.7–100%), another option is carbapenems with imipenem susceptibility rate for gram-positive and gram-negative isolates were 85.2 and 75.6%, respectively. MRSA susceptibility in this study was 100% to vancomycin and linezolid and between 84 and 87% to quinolones. For severe cellulitis/soft tissue infection caused by MRSA, it is recommended to use intravenous glycopeptides (vancomycin or teicoplanin) and linezolid (oral or intravenous) or daptomycin (intravenous) as an alternative.[32] MDROs were reported in up to 53% of DFUs patients.[33] In comparison, in the present study MDR rate was slightly higher at 64%. By default, MRSA is an MDRO, and in this study, the rate of MRSA was 35%. A recent Chinese study[34] of 182 isolated bacterial strains, the MDR for gram-positive isolates was 50.6%% lower than in this study (65.3%), while MDR for gram-negative isolates was lower (61.68 vs. 63.6%).

Clinical practice guidelines by IDSA and IWGDF recommend starting antibiotics according to most likely and proven causative organisms and their susceptibility testing. Also, it is recommended to use parenteral route for moderate to severe infection and switch to oral therapy if there is clinical improvement.[13,14] Continuous antibiotics for 1 to 2 weeks or longer were suggested in cases of slower response and severe arterial disease. Consider *P. aeruginosa* coverage in severe infections, prior antibiotic history, previous recent gram-negative culture, and frequent exposure to water. Consider obligate anaerobes coverage in situations of ischemia and foul-smelling discharge. MRSA antibiotics coverage in patients with a previous history of MRSA infection and high local prevalence of MRSA (50% for mild infections and 30% for severe infections).[13,14]

This study population may not be representative of the general population. The majority of specimen collection was in the form of swab specimens which are less accurate than specimens from deep tissue collected by curettage or biopsy after wound cleaning and debridement, which could lead to a selection bias. Unfortunately, due to a lack of facility and unified national policy program, there were no data about anaerobic bacteria, MDR bacteria such as extended-spectrum β-lactamase producing gram-negative bacteria. There was no data about other modalities for diagnosing PAD apart from arterial Doppler nor any vascular interventions in patients with severe PAD in their medical records. However, the complex surgical interventions and their outcome are beyond the scope of this study.

Conclusions

The local prevalence of organisms is variable and unpredictable, necessitating continuous vigilance and surveillance. The present study is the first of its kind locally. Antimicrobial susceptibility data show that our microbial pattern is different from the Western regions suggesting a need for local guidelines for better treatment outcomes. Communication between the clinicians and laboratory staff is crucial for rapid access to information and emphasizing the importance of screening and confirmation of MDR, XDR, and PDR. Clinical microbiologist's input regarding antimicrobial therapy decisions within the multidisciplinary team is needed. Dedicated diabetic clinics for high-risk and post-amputation patients' care are valuable for better care delivery.

Gram-negative rods constitute the most infective organisms in DFIs, in contrast to what is reported in the literature in the Western world. Therefore, empirical antibiotics targeting gram-negative rods should be started empirically prior to culture results and susceptibility tests. A high prevalence of MRSA occurs, especially in situations of severe infections, history of recurrent infections or hospitalization, and a history of previous infections with antibiotic-resistant bacteria. Therefore, broad-spectrum

antibiotics with MRSA coverage in these situations may be valuable. Launching and implementing national and local policies for antibiotic stewardship programs to guide antibiotic dispensing to tackle the worrying emergence of drug-resistant bacteria is imperative.

Authors' Contributions
Both authors contributed to the conception of the study, data collection and analysis, and drafting and revising of the manuscript. They both take responsibility for its contents.

Conflict of Interest
None declared.

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None.

Compliance with Ethical Principles
The Research Ethics Board (REB) and Al Jala Hospital Surgical Department approved the study. The consent was waived, and all data were collected anonymously.

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