Original Article

Common pathogens associated with infected diabetic foot ulcers: A retrospective cohort study in a specialized medical center in Jeddah, Saudi Arabia

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Abstract

Background: Foot infections, a frequent complication of diabetes mellitus, are associated with heavy resource utilization, including antibiotic therapy and surgeries. However, the most common type of isolated pathogen in diabetic foot infections remains unknown. We aimed to identify the most common types of isolated pathogens in diabetic foot infections. **Methods:** This retrospective cohort study was conducted in a specialized medical center in Jeddah, Saudi Arabia. A total of 96 patients diagnosed with diabetes and presented with a foot ulcer showing clinical signs of infection were included. **Results:** The mean age was 63.03 ± 10.88 years, and 67.7% were males. The mean duration of diabetes diagnosis was 21.86 ± 9.66 years, and the majority had foot ulcers for over six weeks. Bacteria were present in 65 patients (67.7%), Gram-negative organisms were observed in 37 patients (38.5%), and Gram-positive organisms were present in 28 patients (29.2%). In the 65 patients with bacterial culture, *Staphylococcus aureus* was the most common isolated organism and was observed in 18 patients (27.7%), followed by *Escherichia coli* in 11 (16.9%) and *Pseudomonas aeruginosa* in 10 (15.4%). Binary regression analyses found that Gram-negative organisms were significantly more multidrug-resistant than Gram-positive organisms ($P = 0.012$, OR = 7.172, 95% CI = 1.542–33.352). Patient outcomes included healed ulcers ($n = 10$, 10.4%), minor amputation ($n = 16$, 16.7%), major amputation ($n = 1$, 1%), and debridement ($n = 48$, 50%). **Conclusion:** Gram-negative organisms were predominant in patients with diabetes and foot ulcers having clinical signs of infection. Treatment with an individualized antibiotic regimen is vital in ensuring optimal outcomes and preventing major amputations.

Keywords: Amputation, antibiotic therapy, diabetes, diabetic foot infection, diabetic foot ulcer, multidrug resistance

Introduction

Diabetes mellitus (DM) is a noncommunicable, metabolic disorder in which patients have high blood sugar levels owing to insufficient insulin production.[1,2] DM is endemic in Saudi Arabia, which ranks in the top 10 countries worldwide in the prevalence of DM.[3] The prevalence of DM in Saudi Arabia increased from 18.2% in 2004 to 31.6% in 2011.[4] Given the high prevalence of diabetes, new complications, primarily in the feet, have recently been noted.[5,6] Foot complications constitute a significant burden to patients with diabetes and increase healthcare costs.[7]

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Diabetic foot ulcers (DFUs) and diabetic foot infections (DFIs) are frequent complications of DM and are associated with heavy resource use, including antibiotic therapy and surgical procedures.[8-10] The lifetime incidence of DFUs in patients with DM is 15–20%, with a 30–40% possibility of recurrence within the first year.[11,12] While the global prevalence of diabetic foot (DF) is approximately 6%,[6] every 30 seconds, a leg is amputated owing to DM.[13] In Saudi Arabia, approximately 1.9% of patients with DM have undergone amputations.[14] Different classification systems are used to assess the severity of DF. The most historically used classification system is the Wagner–Meggitt system, which considers the depth of the ulcer and tissue viability, and the Infectious Diseases Society of America/International Working Group on the Diabetic Foot classification system, which defines the presence and severity of DFIs.[15]

Aerobic Gram-positive cocci typically cause acute DFIs, while deep or chronic wounds often harbor aerobic Gram-negative and obligate anaerobic organisms, frequently with polymicrobial flora.[16,17] A 2020 study in Romania reported that *Staphylococcus aureus* and *Escherichia coli* were the predominant strains isolated from DFUs.[18] A multicenter study in Egypt in 2020 also showed that polymicrobial infections were found in 48.5% of patients, with more Gram-positive pathogens isolated than Gram-negative organisms and anaerobes. The pathogens detected were *S. aureus*, methicillin-resistant *S. aureus*, *Enterococcus* spp., *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella* spp., *Proteus mirabilis*, Coagulase-negative staphylococci, anaerobic organisms, and fungi. Their results may indicate an alarming progression of antimicrobial resistance among patients with DFIs.[19] Furthermore, a retrospective study in Riyadh in 2018 revealed that the most common Gram-negative pathogen isolated from the forefoot was *P. aeruginosa*. In contrast, *S. aureus* was the most common Gram-positive organism.[20]

Our study may provide more consistency in the prevalence rates of isolated organisms in DFUs in Saudi Arabia, which have been mostly studied in small sample sizes and have shown varying results. Additionally, by knowing the most common organisms leading to DFIs in our country, a pathogen panel may assist in future research and physician choices on empirical antibiotics before tissue culture results, especially in emergency settings. This can help decrease the rate of antibiotic resistance in our country. Furthermore, proper choice of empirical antibiotics can prevent deep extension of the wound, and further reduce the risk of lower limb amputations in affected patients. Therefore, this study aimed to identify the most common type of isolated pathogens in infected DFUs in our region, and the management differences and difficulties among Gram-positive and Gram-negative organisms.

Materials and Methods

Study design, setting, and population

A retrospective cohort study was conducted from October 2021 to January 2022 in patients diagnosed with DFIs at a specialized medical center in Jeddah, Saudi Arabia. This study included all patients with diabetes who presented to the clinic between 2019 and 2021 with foot wounds or ulcers showing clinical signs of infection. Patients without diabetes who presented with a foot wound or ulcer were excluded. A list of all patients who underwent tissue culturing at the clinic was obtained, and 96 patients were enrolled in the study after applying the exclusion criteria.

Data extraction and study variables

Data were extracted from patient files using a preprepared Google form, validated by specialized physicians at the clinic, including specific variables that might affect the types of organisms. The variables included age, sex, type of DM, years of diagnosis with DM, duration of ulcer, and presence of osteomyelitis. Additionally, we obtained tissue culture results with names (as nominal variables) and classifications of the isolated organism (Gram-positive or Gram-negative). A microorganism was classified as multidrug resistant (MDR) if it was found resistant to two or more classes of antimicrobial agents.

Tissue cultures were performed on deep tissue samples after rinsing the wound with only normal saline; no alcohol or antiseptic solution was used. Cultures were sent to a private laboratory in an invasive sterile collection swab (Amies Transport Medium), and results were obtained after one week.

Data analysis

Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA) was used for data entry, and statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). Descriptive statistics, presented as frequencies and percentages, were used for categorical variables. Clinical characteristics for normally distributed data were summarized by their mean and standard deviation. Chi-square and independent sample t tests were used to compare data, as appropriate. An enter binary logistic regression analysis was conducted to identify the independent variables associated with the likelihood of MDR. The model included six variables using the enter method: sex, age, years of diagnosis with DM, duration of the ulcer, classification of the organisms, and presence of osteomyelitis. The confidence interval (CI) was set at 95%, and a *P* value was considered statistically significant at <0.05.

Ethical considerations

Informed consent was obtained from each participant before commencing the data collection process, clearly indicating that participation was voluntary. Privacy and confidentiality were maintained throughout the study. Ethical approval for this study was obtained from the institutional review board of the center (reference number DEC.002.22).

Results

Patients' characteristics

Overall, 96 patients were included in this study: 65 were males (67.7%) and 31 were females (32.3%). Most of them had

type 2 DM (n = 93, 96.9%), and the mean age of the patients was 63.03 ± 10.884 years, with the majority being in the age group of "Older than 65 years." Most patients had foot ulcers for over six weeks (n = 52, 54.2%).

Tissue culture and foot problems

Bacteria were isolated in 65 patients. Among which, *S. aureus* was the most commonly isolated organism and was observed in 18 patients (27.7%), followed by *E. coli* in 11 patients (16.9%) and *P. aeruginosa* in 10 patients (15.4%). Additionally, Candida infections were found in two patients. Figure 1 illustrates the most common organisms isolated from the tissue culture.

Gram-negative organisms were observed in 37 patients (38.5%), while Gram-positive organisms were identified in 28 (29.2%). The rest of the patients showed no growth in their cultures (n = 29, 30.2%), and two had isolated fungal infections (2.1%).

MDR organisms were isolated in 39 of 65 patients (58.2%). Additionally, osteomyelitis was identified in 57 patients (59.4%). Wet, dry, and gas gangrenes were found in 13 (13.5%), three (3.1%), and one (1%) patients, respectively. Furthermore, patient outcomes included 10 (10.4%) patients with healed ulcers, 16 (16.7%) with minor amputation, one (1%) with a major amputation, and 48 (50%) with debridement. Table 1 demonstrates the patients' sociodemographic and clinical characteristics.

Relationships with the organism classification

A statistically significant difference was noted between the organism classification and being MDR, as Gram-negative organisms were more likely to be MDR than Gram-positive organisms (75.7% vs 39.3%, P = 0.007). However, no significant difference was observed in the effect of the duration of the ulcer (which was categorized into six weeks or less and more than six weeks) on the percentage of occurrence of Gram-negative vs. Gram-positive organisms (P = 0.378). Similarly, no statistical differences were observed in the percentage of occurrence of Gram-negative vs. Gram-positive organisms in the cases of osteomyelitis (64.9% vs 57.1%, P = 0.707). Table 2 demonstrates the relationships between different variables and organism classification.

Multivariate binary logistic regression analysis was performed to assess the impact of several factors on the likelihood of MDR. The results demonstrated that the classification of the isolated organism was the only independent factor affecting the rate of MDR, as Gram-negative organisms were more likely to be MDR than Gram-positive organisms (P = 0.012, OR = 7.172, 95% CI = 1.542–33.352). Table 3 demonstrates the results of the multivariate analysis.

Table 1: Sociodemographic and clinical characteristics

	Mean	SD
Age (years)	63.03	10.884
Years of diagnosis with DM	21.86	9.665
	n	**%**
Sex		
Male	65	67.7%
Female	31	32.3%
Age group (years)		
34–55	23	24.0%
56–65	35	36.5%
Older than 65	38	39.6%
Type of DM		
Type 1	3	3.1%
Type 2	93	96.9%
Duration of the ulcer		
Six weeks or less	32	33.3%
More than six weeks	52	54.2%
N/D	12	12.5%
Osteomyelitis		
Yes	57	59.4%
No	39	40.6%

Notes: Age and years of diagnosis with DM data are expressed as mean±SD, and others are expressed as numbers (n) and percentages (%). n: Number, SD: Standard deviation, N/D: Not documented, DM: Diabetes mellitus

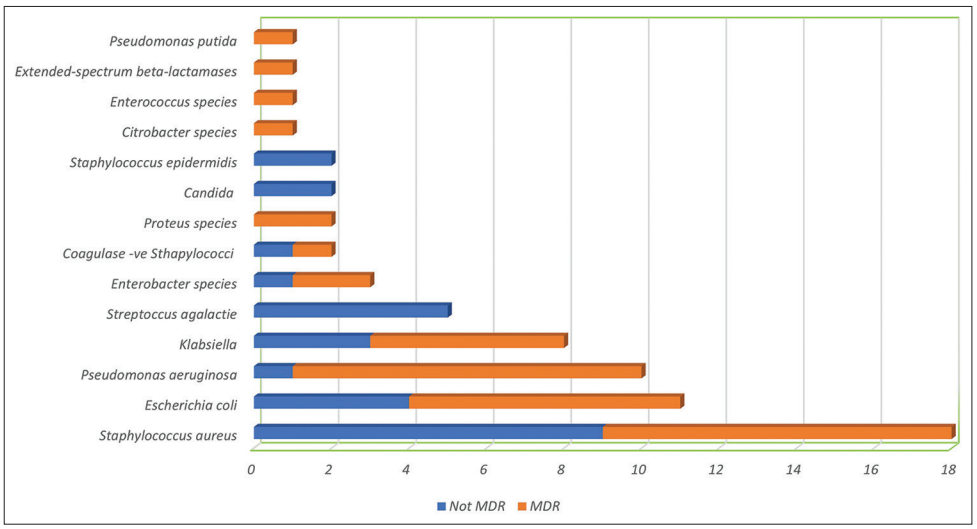

Figure 1: Most common organisms isolated from the tissue culture

Table 2: Relationships with organism classification

	Gram-positive organism Mean±SD	Gram-negative organism Mean±SD	*P*
Age (years)	60.18±9.100	65.43±12.258	0.061
Years of diagnosis with DM	19.86±10.435	23.11±9.077	0.219
	Gram-positive organism *n* (%)	**Gram-negative organism *n* (%)**	***P***
Sex			
Male	21 (75.0%)	23 (62.2%)	0.408
Female	7 (25.0%)	14 (37.8%)	
Age group (years)			
34–55	9 (32.1%)	9 (24.3%)	0.174
56–65	11 (39.3%)	9 (24.3%)	
Older than 65	8 (28.6%)	19 (51.4%)	
Type of DM			
Type 1	0 (0.0%)	1 (2.7%)	1.000
Type 2	28 (100%)	36 (97.3%)	
Duration of the foot ulcer			
Six weeks or less	11 (44.0%)	9 (29.0%)	0.378
More than six weeks	14 (56.0%)	22 (71.0%)	
MDR			
Yes	11 (39.3%)	28 (75.7%)	0.007*
No	17 (60.7%)	9 (24.3%)	
Osteomyelitis			
Yes	16 (57.1%)	24 (64.9%)	0.707
No	12 (42.9%)	13 (35.1%)	

n: Number, %: Percentage, SD: Standard deviation, DM: Diabetes mellitus, MDR: multidrug resistance. *Statistical significance was set at $P<0.05$

Table 3: Multivariate analysis of factors influencing MDR

	MDR		
	OR	**95% CI**	***P***
Sex			
Male	2.728	0.605–12.300	0.192
Female	Ref	Ref	Ref
Duration of the foot ulcer			
6 weeks or less	2.688	0.530–13.634	0.233
<6 weeks	Ref	Ref	Ref
Classification of the organisms			
Gram-negative	7.172	1.542–33.352	0.012*
Gram-positive	Ref	Ref	Ref
Osteomyelitis			
Yes	1.037	0.257–4.192	0.959
No	Ref	Ref	Ref
Age (years)	0.965	0.902–1.033	0.306
Years of diagnosis with DM	0.937	0.868–1.012	0.098

OR: Odds ratio, CI: Confidence interval, Ref: Reference, DM: Diabetes mellitus, MDR: Multidrug resistance, *P significant at <0.05

Discussion

This study aimed to identify the most prevalent types of isolated pathogens in DFIs and whether differences existed among patients visiting a specialized medical center in Jeddah, Saudi Arabia.

S. aureus was the most common pathogen responsible for DFIs in our study population, followed by Gram-negative organisms, which was consistent with the existing literature. For instance, Laakso *et al.*[21] investigated current data on bacterial cultures in 325 patients treated for DFI. They found that *S. aureus* was the most common pathogen in both superficial and deep samples, accounting for 36.9% of infections, followed by Gram-negative bacilli (24.6%), and β-hemolytic streptococci (19.5%). In addition, an observational study in Beirut substantiated our findings regarding the increased prevalence of Gram-negative organisms compared with Gram-positive organisms. That study aimed to determine the microbiologic profile and antimicrobial susceptibility of 179 DFI admissions at a large tertiary center. Overall, 314 bacterial isolates were identified across 179 deep tissue cultures, of which 54% had a polymicrobial infection. Additionally, a higher prevalence of aerobic Gram-negative rods was noted than that of Gram-positive cocci, with values of 55% and 39%, respectively. However, their results differed regarding the most common isolate; they reported *E. coli* (15%) as the most prevalent, followed by *Enterococcus* (14%) and *P. aeruginosa* (11%), and *S. aureus* being present in only 9% of their patients.[22]

Additionally, we observed a significantly higher number of MDR organisms in Gram-negative infections. This was consistent with the results of a study published by Yan *et al.*,[23] which investigated the bacteriological characteristics, risk factors, and treatment of MDR organisms in 180 patients with DFIs. Among the samples, 182 strains of bacteria were identified and cultured, with 104 of these strains being MDR. The prevalence of Gram-negative organisms among these resistant strains was almost two-fold higher than that of Gram-positive organisms (66 vs. 38 strains, respectively). Another study by Henig *et al.*[24] reported similar findings in a cohort of 648 patients with DFU, emphasizing the unexpectedly high prevalence of DFI pathogens resistant to recommended treatment. Furthermore, a history of the same

pathogen in previous DFIs and recent antimicrobial exposure were independent predictors of MDR infections. MDR infections have been associated with prolonged hospital stays and represent a major global public health issue.[25] However, the literature on the relationship between Gram-negative infections and MDR in DF remains limited. Future studies in this field are required to ensure that healthcare professionals fully understand the most prevalent pathogens in DFIs and determine the most effective initial empirical antibiotics.

Our findings were consistent with recent developments regarding antibiotic susceptibility.[26,27] For instance, Chai *et al.*[28] provided a comprehensive profile of microbiological pathogens in foot ulcers, specifically the antibiotic susceptibility of the pathogen spectrum. Secretions were collected and cultured from 102 patients, and antibiotic susceptibility was determined using the Kirby–Bauer test. The results indicated that the profile of microbiological pathogens, particularly the dominant pathogens in DFUs, differs substantially with age, duration of diabetes, blood sugar levels, and the initial cause of the ulcers. Additionally, the dominant pathogens were susceptible to at least one antibiotic despite the worldwide decrease in antibacterial efficacy observed in recent years. In our study, MDR organisms were found in most participants, which is consistent with the existing literature regarding antibiotic susceptibility.

A higher prevalence of osteomyelitis was observed in our study compared with similar studies. A comprehensive review by Giurato *et al.*[29] reported a collective incidence of osteomyelitis in DFIs of approximately 15% of moderate foot infections, compared with 59.4% in our cohort. However, the review reported that osteomyelitis was present in approximately 50% of severe infections, which was more consistent with our results. These results indicate the severity of DFIs in our cohort, even though the incidence of recorded amputations does not reflect this severity. However, the differences may be attributed to the conservative treatment provided in the clinics.

The outcomes of DFIs varied considerably; however, the existing literature contradicts several findings. Debridement was performed in 50% of our patients, minor amputations in 10%, and major amputations in 1%, yet the current literature reports substantially higher rates. For instance, Chaudhary *et al.*[30] exclusively investigated the prevalence of lower extremity amputations in 81 patients with DFIs and infected foot ulcers and found that 41% of patients had healed ulcers, 21% had undergone major amputations, and 30% had gone minor amputations. A study by Tan *et al.*[31] also showed similar results, as the outcomes of DFIs included minor amputations in 30% of cases and major amputations in 6%. A possible explanation for the low rate of amputations in our study compared to others could be because it was carried out in a private specialized medical center, limiting the population to mostly routine clinic visits and only a small number of advanced cases that needed admission and amputation. However, local evidence is still scarce, and further research is needed to investigate the outcomes of DFIs and whether differences in the virulence of organisms exist.

Study strengths and limitations

This study aimed to identify the most common types of isolated pathogens in infected DFUs in Saudi Arabia. This was one of the few studies regarding DFIs and the pathogens influencing them in our region, and it provided new data regarding MDR and the different factors affecting its occurrence. Additionally, it presented data regarding the outcomes for DFI patients. However, this study had some limitations. Given the study's retrospective nature, data such as the duration of the foot ulcer were missing in some patients. Additionally, the study setting, which was a private medical center, may have affected the generalizability of the results. Furthermore, some patients had been treated in other public hospitals or missed regular follow-ups for financial reasons, potentially making it challenging to obtain good outcomes. In some cases, antibiotics had already been empirically started before visiting the clinic, which may have affected the tissue culture results. Furthermore, we did not identify the antibiotics that the identified tissue-cultured organisms were sensitive or resistant to, as we focused on identifying the type of the organism.

Conclusion

Our findings indicated that *S. aureus* was the most commonly isolated organism, followed by *E. coli* and *P. aeruginosa*. We also observed that Gram-negative organisms accounted for over half of the pathogens in DFIs in our cohort. Furthermore, the prevalence of MDR in Gram-negative organisms was higher than that in Gram-positive organisms. In addition, the most prevalent outcome among patients was debridement, followed by minor amputations and healed ulcers. Therefore, ensuring that patients presenting with foot infections are treated with individualized antibiotic regimens is vital to achieve optimal outcomes and prevent major amputation. Moreover, as MDR rates were high, individualized antibiotic regimens can also aid in decreasing the rate of drug-resistant organisms. Future research should focus on substantiating our findings and updating current guidelines for this population.

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Conflicts of interest

There are no conflicts of interest.

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