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Evaluation of Microbiological Profiles of Diabetic Foot Infections at a Tertiary Hospital

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Abstract

Objective: Diabetic foot wounds impair the quality of life of patients and may progress to amputation with the developing infection. In our study, we aimed to evaluate the microbiological profiles and antibiotic susceptibility of diabetic foot infections in this context.

Methods: Patients who were hospitalized with the diagnosis of diabetic foot infection and underwent surgical procedures in the orthopedics and traumatology clinic between January 2019 and March 2021 were retrospectively searched from the hospital database.

Results: A total of 71 patients were included in the study. Gram-negative bacteria were the most common cause of the infections (66.7%). The highest rate of culture growth was found in *Klebsiella pneumoniae* as 23.5%, followed by *Escherichia coli* as 19.8%. The Wagner Grade 4 classification was the most common grade in our patients. The extended-spectrum beta-lactamase rate of the *K. pneumoniae* isolates was the highest as 57.9%. There was meropenem resistance in 31.6% (n = 6) of the *Klebsiella* strains, 75% (n = 3) of the *Acinetobacter* strains, and 33.3% (n = 2) of the *Pseudomonas* strains. The methicillin resistance rate was 50% in the *Staphylococcus aureus* strains. Major amputation was performed in 88.7% of the patients, with a post-surgical mortality rate of 9.9%.

Conclusion: Diabetic foot ulcers is an important risk factor for extremity loss and can lead to morbidity and mortality. The increasing prevalence of antibiotic resistance in our country is a concern. It is extremely important in the management of infections to detect regional pathogens and susceptibility patterns and initiate empirical treatment by considering potentially influential factors.

Keywords: Antibiotic resistance, amputation, carbapenem, diabetic foot infections

Foot infections threaten both life and extremity health in people living with diabetes, and this threat is increasing in parallel with the increase in the number of diabetic people. According to the report of the International Diabetes Federation, it is estimated that 578 million adults in the world by 2030 and 700 million adults in the world by 2045 will be living with diabetes. It is expected that Turkey will be among the top 10 countries with the highest number of adult diabetic patients between the ages of 20 and 79 by 2045. In the last 20 years, the number of adults living with diabetes has tripled, which indicates that diabetes is one of the major growing health problem.[1]

Diabetic foot infection (DFI) development is associated with morbid conditions such as deterioration of daily living activities with a decrease in physical and mental quality of life. Patients may require admission to health institutions, receive wound care services, often antimicrobial treatment, and possible surgical interventions.[2,3] The probability of developing a foot ulcer at any time in the life of a person living with diabetes was reported as high as 25%.[4] Infection of diabetic foot ulcers is the most common complication requiring hospitalization in diabetic patients, and unfortunately, it can even progress to amputation.[2,3,5-7] Limb amputation is 10-30 times more common in diabetic people than in the general population. It was reported that 8 out of 10 non-traumatic amputations are due to diabetes, and the 5-year death rate following amputation is higher than the death rate for most of the cancer types.[4]

The appropriate approach to a patient with suspected DFI is to evaluate the infected wound and the relevant extremity in detail without any delay.[5] In the management of infection, identifying pathogens that play a role in the etiology and applying the appropriate antibiotic therapy for the associated factors and prevention of amputation is crucial whenever possible.[2,3,5] In the Diabetic Foot Diagnosis and Treatment Guidelines of the Infectious Diseases Society of America, it is recommended to start empirical antibiotic therapy according to the severity of the infection and possible cause and changing treatment with appropriate antibiotics according to the culture results. Empirical treatment should be chosen based on the region-specific prevalence of pathogens and antibiotic resistance in order not to increase antimicrobial resistance, drug-related adverse effects, and financial burden.[8]

The clinical profile of a pathogen varies by geographic regions, and determining local population data guides the prevention and treatment of the disease. In our study, we aimed to examine the causative microorganisms and antibiotic susceptibility of these microorganisms in patients with DFIs who were being followed and treated in the orthopedics and traumatology service of our hospital, as well as contribute to the relevant literature based upon the region.

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Methods

In our study, patients who were hospitalized in the orthopedics and traumatology clinic with the diagnosis of DFI and underwent surgical procedures between January 2019 and March 2021 were retrospectively searched and collected from the hospital database.

The patients' age, sex, comorbidities, HbA1c levels, blood leukocyte counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values, tissue cultures and antibiogram results, classifications of ulcers, and surgical procedures were recorded by the researchers. Tissue culture samples were taken from the deep tissues of the wound and edges of the ulcers. The samples were conveyed to the microbiology laboratory in sterile tubes. They were inoculated on MacConkey agar, 5% sheep blood agar, and thioglycolate media. The identification and antibiotic susceptibility tests of the isolates were performed with a Vitek 2 compact (bioMérieux, Marcy l'Etoile, France) device following the manufacturer's instructions. The results were interpreted according to the standards specified by the Clinical Laboratory Standards Institute.

The infected ulcers were evaluated with the Wagner classification method[9]. According to this classification:

- Grade 0: no open lesion on the skin, evidence of healed lesion;
- Grade 1: skin ulceration;
- Grade 2: deep ulceration;
- Grade 3: osteomyelitis, tendinitis, and/or deep abscess;
- Grade 4: gangrene on the forefoot;
- Grade 5: It is characterized by the presence of gangrene in the entire foot.

Ethics committee approval of the study was received from the İstanbul Medeniyet University Göztepe Training and Research Hospital with the Ethics Committee decision dated June 16, 2021, and numbered 2021/0308.

Statistical analysis

The symptoms found in the study were evaluated, and the collected data were statistically analyzed by using the Number Cruncher Statistical System (NCSS) Statistical Software (NCSS, LLC, Kaysville, Utah, USA). The data analysis process involving the descriptive statistics of mean, standard deviation, median, frequency, and percentage was used.

Results

A total of 71 diabetic foot ulcer patients, 74.6% (n = 53) male and 25.4% (n = 18) female, were included in the study. The ages of the patients ranged from 47 to 90, with a mean age of 67.73 ± 10.36 years. Comorbidity was found in 81.7% of the patients (n = 58). The most common comorbidity was hypertension with a rate of 73.2% (n = 52). It was observed that 93% (n = 66) of the patients had type 2 diabetes. The mean HbA1c value of the patients was 8.31 ± 1.76% (5.9-13.2), and the HbA1c values of 97.2% (n = 69) of the patients were found to be higher than 6% (n = 69), whereas 46.5% (n = 33) of the patients had values higher than 8%. The blood leukocyte counts of 62% (n = 44) were over 10 000/mm^3, the CRP levels of 97.2% (n = 69) were higher than 0.5 mg/L, the ESR was higher than 30/h in 88.7% (n = 63) of the patients, and 38% (n = 27) had ESR levels higher than 70 mm/h; 2.8% (n = 2) of the ulcers were Wagner Grade 2, 11.3% (n = 8) were Wagner Grade 3, 64.8% (n = 46) were Wagner Grade 4, and 21.1% (n = 15) were Wagner Grade 5. Of the patients, 2.8% (n = 2) received a Chopart amputation, 8.5% (n = 6) had debridement, 77.5% (n = 55) had below-knee amputation, and 11.2% (n = 8) had above-knee amputation. In the early follow-up period after the surgical procedure, 9.9% (n = 7) of the patients died due to medical comorbidities (Table 1).

While the growth of 81 bacterial strains was detected in 71 tissue culture samples that were collected, there was no growth in the tissue cultures in 26.8% (n = 19) of patients. In total, 57.6% (n = 30) of the culture-positive cases were monobacterial, and 42.3% (n = 22) were polybacterial. Of the bacterial culture results, 66.7% (n = 54) were Gram negative, 28.4% (n = 23) were Gram positive, and 4.9% (n = 4) were anaerobic (Table 2).

Among all microorganisms, rates of the Gram-positive bacteria were *Staphylococcus aureus* 12.3% (n = 10), followed by *Enterococcus faecalis* 8.6% (n = 7), coagulase-negative Staphylococci 4.9% (n = 4), and *Streptococcus agalactiae* 2.5% (n = 2). *S. aureus* was the most frequently isolated Gram-positive bacteria at a rate of 43.5% (Table 3). The rate of methicillin-resistant *S. aureus* (MRSA) was 50% (n = 5). When the antibiotic susceptibility pattern was examined in the *S. aureus* strains, no resistance was found against vancomycin, teicoplanin, linezolid, or trimethoprim–sulfamethoxazole, while the rate of quinolone resistance was 70%, clindamycin resistance was 50%, and gentamicin resistance was 10%. Glycopeptide resistance was not detected in any of the enterococci, while the ampicillin resistance rate was 42.9% (Table 4).

The most commonly detected Gram-negative bacterium (GNB) was *Klebsiella pneumoniae* at the rate of 23.5% (n = 19). This was followed by *Escherichia coli* at 19.8% (n = 16), *Pseudomonas aeruginosa* at 7.4% (n = 6), *Proteus mirabilis* at 6.2% (n = 5), *Acinetobacter baumannii* at 4.9% (n = 4), and *Morganella morganii* at 4.9% (n = 4) (Table 3). There was susceptibility to meropenem in 79.6% (n = 43), to amikacin in 68.5% (n = 37), and to tazobactam–piperacillin in 59.2% (n = 32) of the isolates. The extended-spectrum beta-lactamase (ESBL) rate was found to be 56.2% (n = 9) in the *E. coli* strains and 57.9% (n = 11) in the *Klebsiella* strains. There was meropenem resistance in 31.6% (n = 6) of the *Klebsiella* strains, 75% (n = 3) of the *Acinetobacte*r strains, and 33.3% (n = 2) of the *Pseudomonas* strains. While the colistin resistance rate was 15.8% (n = 3) in the *Klebsiella* strains, no such resistance was detected in the *Acinetobacter* and *Pseudomonas* strains. Twenty-five percent (n = 1) of the *Acinetobacter* strains were resistant to tigecycline (Table 5).

Discussion

Our study aimed to examine the demographic characteristics, causative microorganisms, and antimicrobial susceptibility of patients with DFIs. Retrospectively, 71 hospitalized patients were evaluated with infected diabetic foot ulcers. Of our patients, 74.6% were male, and the median age of the patients was 69 years. Our findings regarding gender and age were consistent with the literature.[10,11] Dinh and Veves[12] attributed the lower risk of foot ulcers in women compared to men to the lack of severe neuropathy, increased joint mobility, and less pressure applied on the foot.

In chronic and severely infected foot ulcers, the etiology is mostly polymicrobial with coexistence of Gram-negative aerobic and anaerobic strains.[3,5,8] It is now known that GNB are more dominant in the etiology of these cases in subtropical, relatively underdeveloped countries. Although the reasons have not been fully explained, it is thought that it may be related to the increased humidity content causing excessive foot sweating, differences in sampling and laboratory techniques, and excessive use of antibiotics and climate.[13,14] In our study, 57.6% of the microorganisms were monobacterial, and GNB grew in 66.7% of the culture samples. The most common organisms were

Table 1. Distribution of Patient Information

Age (years)	
X ± SD	67.73 ± 10.36
Median (min-max)	69 (47-90)
Sex, n (%)	
Female	18 (25.4)
Male	53 (74.6)
Diabetes type, n (%)	
1	5 (7)
2	66 (93)
Wagner classification, n (%)	
Grade 2	2 (2.8)
Grade 3	8 (11.3)
Grade 4	46 (64.8)
Grade 5	15 (21.1)
Surgical intervention, n (%)	
Chopart amputation	2 (2.8)
Debridement	6 (8.5)
Below-knee amputation	55 (77.5)
Above-knee amputation	8 (11.2)
Number of comorbidities, n (%)	
None	13 (18.3)
1	25 (35.2)
2	25 (35.2)
3	8 (11.3)
Comorbidity status, n (%)	
Absent	13 (18.3)
Present	58 (81.7)
Type of comorbidity,* n (%)	
RA	1 (1.4)
HT	52 (73.2)
CAD	31 (43.7)
CRF	10 (14.1)
Malignancy	2 (2.8)
CRP	
X ± SD	12.27 ± 7.90
Median (min-max)	10.4 (0.2-35.7)
CRP groups, n (%)	
<0.5	2 (2.8)
≥0.5	69 (97.2)
WBC	
X ± SD	12.91 ± 6.78
Median (min-max)	11.5 (4.8-44.5)
WBC groups, n (%)	
<10	27 (38)
≥10	44 (62)
Sedimentation	
X ± SD	63.58 ± 26.69
Median (min-max)	66 (11-120)
Sedimentation groups, n (%)	
<30	8 (11.3)
≥30	63 (88.7)
HbA1c	
X ± SD	8.31 ± 1.76
Median (min-max)	7.8 (5.9-13.2)
HbA1c groups, n (%)	
<6	2 (2.8)
≥6	69 (97.2)
Mortality	
Ex	7 (9.9)
Alive	64 (90.1)

*Multiple variables are given together.
CRP, C-reactive protein; WBC, white blood cell; RA, rheumatoid arthritis; HT, hypertension; CAD, coronary artery disease; CRF, chronic renal failure; SD, standard deviation.

Table 2. Evaluation of Culture Results

	n (%)
Bacteria type, n (%) (n = 81)	
Gram negative	54 (66.7)
Gram positive	23 (28.4)
Anaerobic	4 (4.9)
Bacteria status, n (%)	
Culture positive	52 (73.2)
Monobacterial	30 (57.6)
Polybacterial	22 (42.3)
Sterile	19 (26.8)

Table 3. Microorganisms Grown in Culture

Culture	n %
Gram-negative bacteria	54 (66.7)
Klebsiella pneumoniae	19 (23.5)
Escherichia coli	16 (19.8)
Pseudomonas aeruginosa	6 (7.4)
Proteus vulgaris	5 (6.2)
Acinetobacter baumannii	4 (4.9)
Morganella morganii	4 (4.9)
Gram-positive bacteria	23 (28.4)
Staphylococcus aureus	10 (12.3)
Enterobacter faecalis	7 (8.6)
Coagulase-negative Staphylococci	4 (4.9)
Streptococcus agalactiae	2 (2.5)
Anaerobic bacteria	4 (4.9)

K. pneumoniae and *E. coli* at a rate of 23.4% and 19.8%, respectively. In various previous studies in Turkey, the rate of GNB in diabetic foot cultures was reported to vary between 54.8% and 68.9%.[15-20] Saltoğlu et al.[15] Kara et al.[16] Turhan et al.[17] and Öztürk et al[18] found *P. aeruginosa* strains as the most common causative agent, while in the studies by Örmen et al[19] and Hatipoglu et al.[20] *E. coli* strains were isolated as the most common causative agent. In our cohort, 28.4% of the growing bacteria were Gram-positive cocci, and most were *S. aureus* at a rate of 43.5%. This result was consistent with those reported in previous studies.[15,17,19,20] We detected only anaerobic growth in 4.9% among the causative microorganisms. This can be explained by difficulties in the isolation of anaerobic bacteria and the failure to comply with the necessary conditions in sample collection and delivery to the laboratory.

In our study, we found the ESBL rates to be 56.2% in the *E. coli* strains and 57.9% in the *Klebsiella* strains. In the study by Saltoğlu et al.[15] the rate of ESBL in *E. coli* was reported as 33%. In a study conducted with 16 494 isolates in Turkey in 2016, the prevalence of ESBL was reported to be 47.8% in *E. coli* isolates and 58% in *K. pneumoniae* isolates. In the same study, carbapenem resistance was found to be 18%, 92%, and 37% for *K. pneumoniae, Acinetobacter* spp., and *P. aeruginosa* strains, respectively.[21] In another study conducted in an intensive care unit, the rate of carbapenem resistance was reported as 52.6% in *K. pneumoniae* isolates.[22] In our study, we found the rate of carbapenem resistance to be 31.6% in *K. pneumoniae*, 75% in *A. baumannii*, and 33.3% in *P. aeruginosa*. The high rate of ESBL production detected in the *E. coli* and *K. pneumoniae* strains limits the use of cephalosporins and directs the clinician to use carbapenem as the first choice in the presence or suspicion of sepsis.[21] As a result of the widespread use of carbapenems, carbapenem-resistant GNB infections occur more often.[21,23] The rapid increase in the prevalence of carbapenem-resistant Gram-negative pathogens has led to the consideration of colistin as a viable treatment option. The increasing use of colistin in the treatment of infections caused by these bacteria has also led to the emergence of colistin resistance in many countries around the world.[24] We also found colistin resistance in 15.8% of our *Klebsiella* isolates. In a multicenter retrospective study, it was reported that β-lactam/β-lactamase inhibitor combinations are as effective as

Table 4. Distribution of Gram (+) Isolates and Susceptibility to Antibiotics

Gram (+) Susceptibility	CNS (n = 4)	*Enterococcus faecalis* (n = 7)	*Staphylococcus aureus* (n = 10)	*Streptococcus agalactiae* (n = 2)
Ampicillin	-	4 (57.1)	-	-
Ampicillin sulbactam	1 (25)	4 (57.1)	1 (10)	2 (100)
Fusidic acid	2 (50)	-	2 (20)	-
Benzylpenicillin	-	-	-	2 (100)
Ciprofloxacin	2 (50)	1 (14.3)	3 (30)	-
Clindamycin	3 (75)	-	5 (50)	-
Erythromycin	-	-	2 (20)	-
Gentamicin	4 (100)	1 (14.3)	9 (90)	-
Linezolid	4 (100)	7 (100)	10 (100)	2 (100)
Teicoplanin	4 (100)	7 (100)	10 (100)	2 (100)
Trimethoprim–sulfamethoxazole	3 (75)	4 (57.1)	10 (100)	2 (100)
Vancomycin	4 (100)	7 (100)	10 (100)	2 (100)
Levofloxacin	2 (50)	3 (42.9)	3 (30)	2 (100)
Cefoxitin	2 (50)	-	5 (50)	-

CNS, coagulase-negative Staphylococci.

Table 5. Distribution of Gram (–) Isolates and Susceptibility to Antibiotics

Gram (–) Susceptibility	*Escherichia coli* (n = 16)	*Klebsiella pneumoniae* (n = 19)	*Pseudomonas aeruginosa* (n = 6)	*Acinetobacter baumannii* (n = 4)	*Morganella morganii* (n = 4)	*Proteus vulgaris* (n = 5)
Amikacin	13 (81.3)	11 (57.9)	4 (66.7)	1 (25)	4 (100)	4 (80)
Cefepime	7 (43.8)	8 (42.1)	4 (66.7)	0 (0)	4 (100)	4 (80)
Ceftazidime	7 (43.8)	8 (42.1)	4 (66.7)	0 (0)	4 (100)	4 (80)
Ciprofloxacin	5 (31.3)	8 (42.1)	3 (50)	0 (0)	3 (75)	1 (20)
Colistin	16 100)	16 (84.2)	6 (100)	4 (100)	-	-
Gentamicin	14 87.5)	11 (57.9)	3 (50)	1 (25)	4 (100)	3 (60)
Levofloxacin	2 (12.5)	2 (10.5)	3 (50)	-	3 (75)	1 (20)
Meropenem	16 (100)	13 (68.4)	4 (66.7)	1 (25)	4 (100)	5 (100)
Piperacillin–tazobactam	13(81.3)	10 (52.6)	2 (33.3)	0 (0)	4 (100)	3 (60)
Tigecycline	15(93.8)	14 (73.7)	-	3 (75)	-	-
Trimethoprim–sulfamethoxazole	9 (56.3)	12 (63.2)	-	2 (50)	3 (75)	-

carbapenems in ESBL-positive *Enterobacteriaceae*, which may be an effective approach in reducing carbapenem use.[25]

Methicillin-resistant *S. aureus* rates were reported to be between 14% and 50% in previous studies conducted with DFI in Turkey.[15-17,19] While we found the MRSA rate to be 50%, we did not detect glycopeptide resistance in any of the *S. aureus* strains. We attribute our high resistance rates to the fact that our patients were in a patient group with chronic infection using multiple antibiotics for a long time.

The World Health Organization reports that antibiotic resistance is increasing all over the world and has reached dangerous levels, as well as urging the development of new strategies. The emergence and spread of new resistance mechanisms complicate the treatment of infections, causing higher medical costs and increased mortality rates.[26] Knowing the local possible causative microorganisms and their resistance profiles is an important direction in empirical treatment in preventing the formation and spread of increasing antimicrobial resistance.

Diabetes-related limb loss occurs every 20 seconds in the world, and DFI plays an important role in this high incidence of amputation.[5] Major amputation was performed in 88.7% of our patients, and our mortality rate was 9.9% in the short term after surgery. A high Wagner Grade, gangrene, and poor glycemic control (HbA1c ≥ 8) have been identified as important risk and predictive factors for major lower extremity amputations in patients with hypertension, cardiac diseases, chronic renal failure, and type 2 diabetes.[27] When the ulcer classifications of our cases were examined, 86% were found to be classified as Wagner Grade 4 or Wagner Grade 5. The HbA1c values were higher than 8% in nearly half of the patients. At least one comorbid condition was present in 58% of the cases, and hypertension was the most common, followed by coronary artery disease and chronic renal failure, at 73.2%, 43.7%, and 14.1%, respectively. We think that our high amputation rates can be explained by the inclusion of chronic patients requiring hospitalization, the presence of comorbidities, advanced-Grade Wagner scores, and uncontrolled diabetes in about half of our case population and due to being a tertiary referral center. In addition, the fact that the study was conducted with patients admitted to the orthopedic clinic for surgical intervention may explain this situation.

We found leukocyte counts higher than 10 000/mm^3 in 62% of our patients, CRP levels higher than 0.5 mg/L in 97.2%, and ESR values higher than 70 mm/h in 38%. In the diagnosis of DFI, markers such as blood leukocyte count, CRP, ESR, and procalcitonin, which are indicators of inflammation, may increase in the case of infection and guide the clinician in diagnosing and showing the severity of the infection.[28] An ESR value greater than 70 mm/h increases the likelihood of osteomyelitis.[5,6,15,28]

It has been shown that the establishment of a multidisciplinary team in the management of diabetic foot disease is associated with a decrease in the incidence of major amputations in patients with diabetes.[29] In our hospital, diabetic foot patients are managed in a multidisciplinary manner with the decisions of the diabetic foot council, which consists of physicians from various branches of medicine.

Our study had some limitations including the facts that it was a retrospective study, and some data of the patients were missing.

In our study, in which we examined DFIs, we found the most common causative agent as Gram-negative bacteria. *K. pneumoniae* was the first among these and had the highest ESBL rate. We detected carbapenem-resistant strains among the causative GNB. Half of the *S. aureus* strains showed methicillin resistance, all strains were susceptible to glycopeptides and linezolid. In the antimicrobial treatment of DFI, empirical antibiotic therapy should be initiated based on region-specific potential factors and resistance data. Empirical antibiotic therapy should include Gram-negative, Gram-positive, and anaerobic microorganisms, especially in chronic cases, and it should be adjusted based on culture results. The increase in antibiotic resistance rates is a worrying situation, and new strategies must be determined accordingly. Antibiotherapy should not be used for the treatment of non-infected ulcers. It is important to avoid unnecessary and long-term antibiotic therapy and especially the irresponsible use of carbapenems in infected cases to prevent cost, resistance development, and mortality. We believe that in educating patients about diabetes and its complications, foot and wound care will play a key role in preventing ulcers and subsequent infections and extremity losses.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medeniyet University Göztepe Training and Research Hospital (Date: June 16, 2021, No: 2021/0308).

Informed Consent: Verbal/Written informed consent was obtained from the patients who agreed to take part in the study.

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