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CLINICAL CHARACTERISTICS OF PATIENTS WITH DIABETIC FOOT ULCERS AND PATHOGENS ISOLATED FROM WOUND CULTURES

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Objective: Diabetic foot ulcers (DFUs) are a major cause of morbidity and mortality and develop in the presence of peripheral vascular ischemia and neuropathy. Poorly controlled diabetes is an additional risk factor. DFUs are often polymicrobial. The types of isolated microorganisms (MOs) show regional variations: Gram-negative MOs are more common in temperate climate regions such as Africa and Asia and Gram-positive pathogens are more prevalent in western regions.
We conducted a retrospective review of microorganisms isolated from 24 patients with DFUs.
Methodology: Twenty-four patients (17 males, 7 females) with a mean (±SD) age of 64.5±8.7 years were included. There was no significant difference in age between males and females. All patients had type 2 Diabetes Mellitus (DM) with a mean disease duration of 15±7 years.
Results: Considering the type of ulceration, 5 patients had superficial infections such as cellulitis, 16 patients had ulcers with the involvement of subcutaneous tissues and 3 patients had gangrenous ulcers. The diameter of ulcer was less than 2 cm in 9 patients, 2 to 4 cm in 11 patients and greater than 4 cm in 4 patients. The growth of the following MOs as single agents were detected in the wound cultures: *Staphylococcus aureus in* 5 patients, *Escherichi acoli in* 4, *Morganella morganii* in 4, *Pseudomonas aeruginosa* in 3, *Klebsiella pneumoniae* in 1, *Serratia marcescens* in 1, *Proteus mirabilis* in 1, *Enterococcus faecalis* in 1, and *Stenotrophomonas maltophilia* in 1 patient. Three patients showed concomitant growth of 2 pathogens (*Enterobacter aerogenes+Escherichia coli*; *Enterobacter aerogenes+Staphylococcus aureus*; *Pseudomonas aeruginosa+Staphylococcus aureus*).
Peripheral artery disease (PAD) was present in 10 patients. Six

patients were being treated with antibiotics (ABs) and local wound care including regular dressing changes and 18 patients required surgical treatment (debridement and local flap in 14 and amputation in 4). Of 4 amputated patients, 2 had a history of toe amputation. The average length of hospitalization was 12.9 ±7.1 days, mean HbA1c level was 8.1±1.6%, and mean duration of AB treatment was 11.7±3.2 days.

Discussion and Conclusion: Despite earlier diagnosis of DM and current availability of more effective therapeutic options, DFUs are still the leading cause of amputation. Along with blood glucose regulation, careful follow-up of diabetic complications and timely implementation of preventive actions would substantially reduce hospitalization and loss of productivity.

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1. INTRODUCTION

Diabetic foot ulcers (DFUs) are a major cause of morbidity and mortality and develop in the presence of peripheral vascular ischemia and neuropathy. Poorly controlled diabetes is an additional risk factor. Diabetic individuals with impaired pain and heat sensation caused by diabetic sensory neuropathy are at an increased risk for development of DFU because of the inability to protect their lower extremities and particularly feet from trauma. Foot deformities due to motor neuropathy and altered sweating pattern and dry skin caused by autonomic neuropathy lead to cracks on the feet, facilitating the invasion of the affected site by microorganisms (MOs). Ischemia of the peripheral blood vessels poses an additional risk by delaying wound healing. Other factors contributing to DFU development include impaired neutrophil functions and reduced defense mechanisms in diabetic individuals.[1-4]

DFUs are often polymicrobial. The number of isolated MOs may be up to 7 depending on the depth and extent of the ulcers. The types of isolated MOs show regional variations: Gram-negative microorganisms are more common in temperate climate regions such as Africa and Asia and Gram-positive pathogens are more prevalent in western regions. MOs including *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, and coagulase-negative streptococci are more frequently isolated in DFUs presenting as cellulitis or superficial ulceration without previous antibiotic (AB) treatment, whereas prolonged, deep-seated diabetic foot ulcers previously exposed to ABs are more likely to be polymicrobial. *Enterococci*, Enterobacteriaceae, *Pseudomonas aeruginosa* and anaerobes are the MOs that are mostly isolated in polymicrobial cases. [5,6,7]

If the area affected by ulcers is wide and deeply inflamed and signs of systemic toxicity are present such as necrosis, foul-smelling purulent drainage, fistulization or gangrene, anaerobic MOs including *anaerobic streptococci*, *Bacteroides* spp. and *Clostridium* spp. might be considered as the causative agents in addition to the aforementioned MOs. [8,9]

We conducted a retrospective review of microorganisms isolated from 24 patients with DFUs.

2. METHODOLOGY

Patients: A total of 24 patients (17 males, 7 females) with a mean (± SD) age of 64.5±8.7 (min-max: 53-88) years were included in the study. The mean (± SD) age was 65.1±8.7 years (min-max: 55-85) in males and 63.1±9.3 years (min-max: 53-82) in females with no significant age difference observed between sexes. All patients had type 2 Diabetes

Mellitus (DM) with a mean DM duration of 15±7.6 years (min-max: 2-32). The mean (± SD) DM duration was 15.3±7.8 years (min-max: 2-32) in males and 14.3±7.7 years (min-max: 8-30) in females. DM duration did not differ significantly between male and female patients (**Table 1).**

Table 1: Demographic, clinical and diabetic characteristics of patients

Parameter	**Mean**	**Standard Deviation (SD)**	**Min**	**Max**
Age, years (n=24) **Male (n=17)** **Female (n=7)**	64.5 65.1 63.1	±8.7 ±8.7 ±9.3	53 55 53	88 85 82
DM duration, years (n=24) **Male (n= 17)** **Female (n= 7)**	15 15.3 14.3	±7.6 ±7.8 ±7.7	2 2 8	32 32 30
Length of hospital stay (days)	12.9	±7.1	2	23
HbA1c	8.1	±1.6	6.1	11.3
Duration of antibiotic therapy (days)	11.7	±3.2	7	18

Notes: SD= Standard deviation; min: minimum; max: maximum; the n= number of patients, DM: Diabetes Mellitus, HbA1c: Glycosylated Hemoglobin A1c

3. MATERIALS AND METHODS:

Samples obtained were inoculated into 5% sheep blood agar, EMB agar, SDA agar, and chocolate agar. Growing bacteria were identified using VITEK2 (BioMérieux, France) automated system and conventional systems. Antibiotic susceptibility was determined in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria using the same automated systems and Kirby-Bauer disk diffusion method. [10]

4. RESULTS:

Among patients, 12 were being followed at the endocrinology clinic, 10 at the plastic surgery clinic and 1 patient each at the orthopedics and cardiovascular surgery clinics. Peripheral artery disease was present in 10 patients. Renal function assessment showed that 3 patients had end-stage renal failure and were receiving hemodialysis treatment. Remaining 21 patients had GFR values greater than 60 ml/min/1.72 m^2. Considering comorbidities excluding DM, peripheral artery disease (PAD) and renal failure, 21 patients had other concomitant diseases. Based on chart review, 7 patients had hypertension (HT), 9 patients had coronary artery disease (CAD), 2 patients had prior to amputation and 1 patient each had hypertriglyceridemia, breast cancer and rheumatoid arthritis (RA) (**Table 2**).

Table 2: Clinical characteristics of patients

Departments following the patients n=24	**Endocrinology**	**PRS**	**Orthopedics**	**CVS**		
	n=12	n=10	1	1		
Type of follow-up n=24	**Hospitalization**		**Outpatient**			
	n=18		n=6			
Type of Surgery n=18	**Local procedure including debridement**		**Amputation**			
	n=14		n=4			
Peripheral Artery Disease n=24	**Present**		**Absent**			
	n=10		n=14			
Renal function n=24	**GFR> 60 ml/min/1.72 m^2**		**ESRF**			
	21		3			
Comorbidity n=24	**Present**		**Absent**			
	n=21		n=3			
Type of comorbidity n=21	**HT**	**CAD**	**Prior toe amputation**	**HyperTG**	**Breast CA**	**RA**
	n=7	n=9	n=2	n=1	n=1	n=1
Ulcer characteristics n=24	**Superficial ulcer, cellulitis**		**Extending into subcutaneous tissue**		**Gangrenous**	
	n=5		n=16		n=3	
Ulcer size n=24	**Diameter< 2 cm**		**Diameter 2 to 4 cm**		**Diameter > 4 cm**	
	n=9		n=11		n=4	
AB therapy n=24	**Yes**		**No**			
	n=10		n=14			
Type of AB n=10	**AMC**	**AMP-SB**	**TZP**	**SZL**	**CRO**	**SKS**	**SFSB**
	n=3	n=2	n=1	n=1	n=1	n=1	n=1
Outcome	**Healed with wound care and antibiotic therapy**		**Local procedure including debridement**	**Amputation**	**Deceased**	
	n=6		n=14	n=4	n=0	

Notes: n= number of patients, PRS:Plastic-reconstructive surgery, CVS: cardiovascular surgery, GFR: glomerular filtration rate, ESRF: end-stage renal failure, HT: hypertension, CAD: coronary artery disease, HyperTG: Hypertriglyceridemia, CA: Cancer, RA: Rheumatoid arthritis, AB: Antibiotic,AMC: Amoxicillin-Clavulanic acid, AMP-SB: Ampicillin-sulbactam, TZP: Piperacillin-Tazobactam, SZL: Cefazolin, CRO: Ceftriaxone, SKS: Cefuroximeaxetil, SFSB:Cefoperazone-sulbactam

Considering the type of ulceration, 5 patients had superficial infections such as cellulitis, 16 patients had ulcers with the involvement of subcutaneous tissues and 3 patients had gangrenous ulcers. The diameter of ulcer was less than 2 cm in 9 patients, 2 to 4 cm in 11 patients and greater than 4 cm in 4 patients. Six patients were being treated with ABs and local wound care including regular dressing changes and 18 patients required surgical treatment (debridement and local flap in 14 and amputation in 4). Of 4 amputated patients, 2 had a history of toe amputation. None of the patients died during follow-up (**Table 2**).

The growth of the following MOs as single agents was detected in the wound cultures: *Staphylococcus aureus in* 5 patients, *Escherichia coli in* 4, *Morganella morganii* in 4, *Pseudomonas aeruginosa* in 3, *Klebsiella pneumonia* in 1, *Serratia marcescens* in 1, *Proteus mirabilis* in 1, *Enterococcus faecalis*

in 1, and *Stenotrophomonas maltophilia* in 1patient. Three patients showed concomitant growth of 2 pathogens (*Enterobacter aerogenes+Escherichia coli*; *Enterobacter aerogenes+Staphylococcus aureus*; *Pseudomonas aeruginosa+Staphylococcus aureus*) (**Table 3**).

Antibiotic susceptibility of MOs that grew in wound cultures is shown in **Table 4**.

Table 3: Microorganisms growing in cultures of diabetic foot ulcer samples

Pathogens		**Number of patients**	**Number of times pathogen isolated**
MOs growing as a single agent	*Staphylococcus aureus**	5	7
	*Escherichia coli**	4	5
	Morganella morganii	4	4
	*Pseudomonas aeruginosa**	3	4
	*Enterobacter aerogenes**	-	2
	Klebsiella pneumoniae	1	1
	Serratia marcescens	1	1
	Proteus mirabilis	1	1
	Enterococcus faecalis	1	1
	Stenotrophomonas maltophilia	1	1
MOs growing concomitantly	*Enterobacter aerogenes+ Escherichia coli*	1	
	Enterobacter aerogenes+ Staphylococcus aureus	1	
	Pseudomonas aeruginosa+Staphylococcus aureus	1	
	Total	**24**	**27**

**Note: ***Multiple microorganisms growing concomitantly in a wound culture

Table 4: Antibiotic susceptibility of the pathogens that grew in cultures of diabetic foot ulcer samples

Pathogens	**Susceptibility (%)**										
	CAR	**AMC**	**CRO**	**TZP**	**AK**	**CIP**	**CAZ**	**SXT**	**MET**	**DA**	**VA**
Enterobacteriaceae: *Escherichia coli (n=5)* *Morganella morganii (n=4)* *Enterobacter aerogenes (n=2)* *Klebsiella pneumoniae (n=1)* *Serratia marcescens (n=1)* *Proteus mirabilis(n=1)*	100	7	50	50	86	57		29			
Pseudomonas aeruginosa	100			75	100	25	100				
Staphylococcus aureus						86		100	86	71	100

AK: Amikacin, AMC: Amoxicillin-Clavulanic acid, CAR: Carbapenem, CAZ: Ceftazidime, CRO: Ceftriaxone, CIP: Ciprofloxacin, DA: Clindamycin, MET: Methicillin, SXT: Trimethoprim-Sulfamethoxazole, TZP: Piperacillin-Tazobactam, VA: Vancomycin

The average length of hospital stay was 12.9 ±7.1 days and mean HbA1c value was 8.1±1.6% (**Table 1**). Antibiotic (AB) therapy was administered to 10 patients

(**Table 2**) and the mean duration of AB treatment was 11.7±3.2 days (**Table 1**). Out of 24 patients, 14 patients did not receive AB therapy. Of the 10 patients treated with antibiotics, 5 (50%) patients received penicillin class ABs including amoxicillin-clavulanic acid (AMC) in 3 patients and ampicillin-sulbactam (AMP-SB) in 2 patients. Remaining 4 patients (n=4/10) received cephalosporin classes. Only 1 patient was treated with piperacillin-tazobactam (TZP) based on culture antibiogram.

5. DISCUSSION:

With the dramatic increase in the global prevalence of diabetes, management of complications associated with diabetes has become an integral part of the treatment.DFUs are the leading cause of non-traumatic lower extremity amputations both in Turkey and worldwide.[11,12,13] Predisposing factors for the development of diabetic foot ulcers include poorly controlled diabetes, advanced patient age and longer duration of diabetes as well as the presence of diabetic neuropathy, diabetic nephropathy and PAD.[14] In our study sample, prior toe amputation (n=2/24), PAD (n=10/24), end-stage renal failure requiring dialysis (n=3/24) and comorbidities directly or indirectly associated with diabetes (n=21/24) were risk factors for the occurrence of diabetic foot ulcer. Three patients followed at PRS and orthopedics clinics with no reported comorbidities and no other diagnoses specified in their medical charts had PAD and ischemia and therefore, all patients, (n=24/24) had one or more predisposing factors for the development of DFU. Thus, comorbidities other than diabetes were the primary risk factors for DFU in our sample.

All DFU patients followed at endocrinology clinic (n=12/24) had some degree of diabetic neuropathy which could at least be described as peripheral distal sensory neuropathy; however, since diabetic neuropathy was not mentioned in the medical charts for patients followed at other departments, “diabetic neuropathy” was not included in **Table 2** as a parameter. It was found that irrespective of the department following the patients, all patients were evaluated at least once for PAD with Doppler ultrasound scan and also with advanced imaging modalities such as MRI when deemed necessary. Therefore, the number of PAD patients shown in **Table 2** (n=10/24) better reflects the actual number of these patients.

All of our patients were older than 60 years of age, had comorbidities and mean diabetes duration of 15 years with an average HbA1c of 8.1% (an indication of poorly controlled DM) which is higher than the targeted value. Thus, consistent with the literature, all of them had comorbidities which rendered them susceptible to the development of DFU. [13, 14]

Due to the retrospective design of our study, data on DFU were obtained from the medical charts of patients. There was no clear information on osteomyelitis in the medical records which precluded our ability to grade DFU cases according to Wagner’s classification.[15] Ulcers were divided into 3 groups as superficial ulcer and cellulitis, an ulcer that extends into subcutaneous tissues and gangrenous ulcer based on information about the depth and size of DFU. The Infectious Diseases Society of America (IDSA) and International Working Group on the Diabetic Foot (IWGDF) classify diabetic foot infections (DFIs) into 3 groups as mild, moderate, and severe DFI and we adopted the same approach for classification of our DFU cases.[6,16] In line with Seth et al.’s study, most of our patients had a DFU with a diameter ranging from 2 to 4 cm that involved subcutaneous tissues.[17]

Staphylococcus aureus was the most prevalent causative MO which was isolated from a total of 7 wound cultures, followed by *Enterobacteriaceae* spp. and *Pseudomonas aeruginosa*. This finding is consistent with those reported from global and national DFU studies. [6, 18, 19, 20] A multidisciplinary approach is needed for the management of DFIs. Empirical antibiotic therapy should include narrow-spectrum antibiotics that are active against the pathogens most commonly encountered in DFIs. Undesirable

consequences such as spreading of infection due to inadequate treatment and progression to limb amputation should be prevented taking into account the severity of infection, coexisting peripheral artery disease and the presence of drug-resistant MOs. In general, narrow-spectrum AB regimens should be chosen for superficial infections caused by aerobic and Gram-positive cocci and extended-spectrum antibiotic regimens for severe infections due to Gram-positive, Gram-negative, and anaerobic MOs. [6, 21] In cases involving the growth of Pseudomonas spp., it is crucial to identify whether these MOs are causative agents or colonization. These strains are usually a part of polymicrobial growth and account for long-standing infections.[8,22]

In Turkey, AB treatment for DFU is initiated against the most commonly isolated MOs in accordance with IDSA and IWGDF recommendations and subsequently changed based on MOs growing in cultures and their AB susceptibility.[6,16] A similar therapeutic approach is implemented in our hospital. As can be seen from our results, more than half of our patients (n=14/24) were not given AB and remaining patients received ABs with the narrowest spectrum possible. One might wonder why antibiotic treatment was not given to all patients despite the growth of MOs in all cultures. This is because wound cultures were obtained during surgical procedures including debridement and culture results were available after microbial growth in the cultures. AB treatment was not required since MOs have already been possibly removed from the affected site using procedures such as debridement, flap or amputation in most patients. AB therapy was changed in accordance with culture antibiograms when infection control could not be achieved during follow-up of patients.

A noteworthy finding was that oral AMC was given to 5 patients out of a total of 10 patients receiving AB treatment. This could raise the question of whether this oral drug has a spectrum of activity enough to achieve adequate infection control in DFIs. However, a recent study reported that oral AMC could be effective even in DFIs with osteomyelitis.[23]

As with all hospitals in Turkey, our hospital has an infection control committee and special care is exercised when selecting AB therapy for patients to prevent resistance development and unnecessary use of ABs. As a result, ABs were not started in most of the patients and MOs could be successfully removed from the ulcers with local treatment modalities. Indeed, the fact that none of our patients died from sepsis corroborates our approach. As can be seen from **Table 4,** MOs growing in the wound cultures showed a high AB susceptibility. This is a positive finding reflecting the diligent efforts of our hospital in rational use of antibiotics.

6. CONCLUSION

Missing data in our hospital's records indicate that we have problems with inter-departmental communication and collaboration despite the best possible efforts made by individual departments for the management of DFU. In our country facing a rapid increase in the diabetes prevalence, there is a need to ensure greater collaboration between departments, conduct multidisciplinary team meetings where decisions for DFU patients are taken jointly and build dedicated DFU teams in order to protect patients from chronic complications of diabetes such as DFU and the worst consequence, i.e. limb amputations.

Limitation of the study: Our study was a retrospective, single-center study and had a small sample size, so we recommend a larger sample size and multi-centric study.

Conflict of interest: The authors declare no financial support or potential conflict of interest.

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