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Management of Patients Hospitalized for Diabetic Foot Infection: A Local Evaluation

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ABSTRACT

Background: Diabetic foot ulcer (DFU) is the most increasing-trend complication of DM over previous decades. The present study was implemented to determine precisely how DFU was managed in the most referral hospital in Isfahan.

Methods: This prospective observational cross-sectional study was conducted from 1 July 2016 to 15 December 2017 in the biggest referral hospital, Al-Zahra, in Isfahan, Iran. The information was collected by a trained pharmacy student filling the designed checklist included: baseline characteristics, methods used to investigate the infected lesion, management of the infected wound, assessment of risk factors related to patient's outcome.

Results: The mean (±S.D) age of patients was 59.13±10.80 years. The majority of our patients had affected with Type 2 DM (96.3 %). Most of the patient (61%) had wound with grade 3 in the Wagner classification. Lesions mainly involved toes (46.3%). The most lesions (42%) had a mean size of the 5-10 cm^2.The most frequently prescribed combination antibiotics were meropenem and Targocid® (teicoplanin) (34.1%), Tazocin® (piperacillin + tazobactam) and Targocid® (24.3%). Mean (±SD) duration of parenteral therapy (alone or in associated with oral treatment) was 14.95±7.62 days. Ulcer size (cm^2) (P=0.04), and Wagner classification (P=0.012) had significant association with unhealed ulcer.

Conclusion: Although, our diabetic center is university-affiliated, there are still several points, and pitfalls must be considered and revised in DFU patients. Obtaining microbiological sampling, antibiotic management and baseline assessment of wound in patients are the most troublesome complications discovered by our investigation.

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Introduction

Diabetes mellitus (DM) is one of the devastating health system problems that lead to high economic burden worldwide (1). According to epidemiological surveys, the prevalence of DM increased from about 177 million cases in 2000 to 285 million in 2010, estimating reaches, more than 360 million cases by 2030 (2). Diabetic foot ulcer (DFU) is a most increasing-trend complication of DM over past decades (3). It is expected that whole life prevalence of DM for diabetic patients is more than 15% and between 40-80% of these ulcerations ultimately will be infected (4).

Moreover, it was reported that DFU is one of the leading causes of morbidity and hospitalization in diabetic patients (5). Indeed, once, DFU has developed the risk of ulcer progression leading to amputation and even death if necessary care is not applied (6).

It is estimated that the risk of hospitalization and lower-extremity amputation was around 56 and 155 times greater, respectively, in diabetic patients with DFU in comparison with diabetic patients without foot infection (7). Also, it is reported that every 30 second one leg amputates due to DFU in worldwide (8).Thus, DFU is responsible for emotional, physical distress, financial losses as well as quality of life reduction (6).

Although, several studies (9-11) have confirmed that the appropriate management of DFU can profoundly reduce, delay or even prevent DM-associated complications such as infection, gangrene, amputation, and death. Unfortunately, many of patients fail to receive guideline-base and standard treatment modalities. The optimal management of DFU like other DM's complication is based on the multi-disciplinary team that consists of a nurse, a general practitioner, an orthopedic specialist, and a podiatrist. Consulting with other professionals such as vascular surgeons, infectious disease specialists, dermatologists, endocrinologists, and dieticians seems to be essential (6).

The American Diabetes Association (ADA) has declared that treating according to the multidisciplinary team can reduce the risks associated with DFU as well as amputation by 50%-85% (12), consequently; it leads to overall quality of life improvement, longevity enhancement.

Several guidelines and valuable updated reviews (6, 13-15) have been published for better management of DFU and also burden reduction. However, to the best of our knowledge, there is no specific comprehensive report on DFU assessment and its regular monitoring in the Iranian diabetic center especially in Isfahan, the third largest city of Iran.

For this reason, the present study was implemented to determine precisely how DFU had been managed in most referral hospitals in Isfahan and what were the characteristics of DFU patients and also risk factors associated with DFU development.

Patients and Methods

This prospective observational cross-sectional study was conducted from 1 July 2016 to 15 December 2017 in the university-affiliated hospital, Al-Zahra, in Isfahan, Iran. A designed protocol by our research team was initially approved by the ethical and investigational committee in hospital. According to our study protocol, we included all inpatients who met the following criteria: (i) Type 1 or 2 diabetes; (ii) Age, more than 18 years old; (iii) Hospitalized for an infected foot ulcer [according to the Infectious Diseases Society of America/ International Working Group on the Diabetic Foot (IDSA/IWGDF)] classification (13); requiring antibiotic therapy.

The exclusion criteria were non-compliant patients in answering questions, patients with neuropathy symptoms due to other clinical condition except than DM such as hypothyroidism, pernicious anemia, discopathy, and malignancy.

Written consent was obtained from all included patients. The information was collected by a trained pharmacy student by filling the designed checklist containing these keynotes:

(i) Baseline characteristics of the study population (demographic data, and clinical data on diabetes and the wound); (ii) Methods used to investigate the infected lesion (neurological and vascular examinations, imaging, wound sampling and microbiological assays); (iii) Management of the infected wound and discharge plans; (iv)Assessment of risk factors related to patient's outcome.

Our checklist consited of data around demographic characteristics such as age, gender, HbA1C, diabetic type, body mass index (BMI), diabetic duration, diabetic complications such as neuropathy symptoms, nephropathy, retinopathy, vascular symptoms, having regular exercise, smoking, addiction, deformity, foot amputation and antibiotic consumption during three past months.

In this study, we difiened nephropathy, as a macro-albuminuria (>300 mg/day) or glomerular filtration rate (GFR) ≤45ml/min and retinopathy, as a presence of visual impairment (defined as non-proliferative diabetic retinopathy and proliferative diabetic retinopathy).

Coronary heart disease (CHD) defined as patient with history of angina, myocardial infraction and atherosclerosis and peripheral arterial disease (PAD) as insufficiency in lower extremity vascular diagnosed by absent of pedal pulses of the involved foot and/or positive finding in Doppler ultrasound sonography of lower limb.

Questions regarding symptoms of neuropathy and vascular disorder in patients including presence or absence of paresthesia, numbness or cramp, any pain or hot or cold sensation in the legs, intermittent claudication, rest pain, thin skin, glossy and bluish skin discoloration,

hyperkeratosis on foot, other foot deformities were asked by the investigator.

The investigator assessed the wounds condition during patients' hospitalization according to Wagner classification, size and number of the wound, local and systemic signs of inflammation on the wound, the presence of calluses or necrotic tissue.

According to Wagner classification, diabetic foot ulcers are graded to 5 groups including (16)

Grade 0 — No ulcer in a high-risk foot

Grade 1 — Superficial ulcer involving the full skin thickness but not underlying tissues

Grade 2 — deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation

Grade 3 — deep ulcer with cellulitis or abscess formation, often with osteomyelitis

Grade 4 — Localized gangrene

Grade 5 — Extensive gangrene involving the whole foot

The neurological examination was performed by a 5.07(10-g) Semmes-Weinstein monofilament and the 128-Hz tuning fork. The aim was to check the pressure sensation by monofilament at 12 places on foot and to test the vibration perception by tuning fork applied to the bony prominence at the dorsum of the first toe, just proximal to the nail bed.

Loss of the ability to detect this pressure and perception of the vibration sense at one or more sites on the plantar surface of the foot was considered as neuropathy.

On the other hand, an investigator was following the patient during the hospitalization and precisely recorded the data around DFU management. We noted all data around microbiological sampling, the results of the culture, antibiogram, and detection of resistant species. Data around local treatment modalities, antibiotic therapy including the type of antibiotic, dose, duration and the route of administration were collected.

We defined outcome as healed, unhealed patients. Unhealed patients were defined as patients who want to discharge without complete recovery or due to dissatisfaction to performing amputation or patients who died or ultimately the drug therapy was not successful, and amputation had occurred. We also considered the patient that continuing treatment was beyond the ward facilities as an unhealed category. Those patients had to leave the center for professional care into the other diabetic foot centers mandatory. Furthermore, healed patients were defines as those who were not considered in unhealed definition.

Statistical analysis

We used the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 20 for the data analysis. Student's t-test for parametric tests and Mann-Whitney U test for non-parametric tests were used to compare two-sample means. The Chi-square test ($\chi 2$) of association and Fisher exact test was used for analyzing the frequency of qualitative variables. An un-variable logistic regression analysis were performed for all potential predictor variables with the outcome of interest (non-healing), values presented as un-variable odds ratio (ORs) along with the respective 95% confidence interval (CI). A 2-tailed p-value <0.05 was considered as statistically significant.

Results

During six-month follow-up (from July 2016 to December 2016), we have included 92 patients initially, although we had to exclude ten patients due to missing data. We have conducted the final analysis on 82 patients with a real study population. The demographic and clinical characteristics of affected patients were depicted in Table 1. According to Table, most of the included patients were male (57.3%). The median age of patients was 59.1±10.8 years. The majority of our patients has affected by Type 2 DM (96.3% vs. 3.7% DM type 1). As shown in Table 1, most diabetic patients had diabetes duration of more than 20 years. In their past medical history before hospitalization, 79.3% of patients had a history of infected foot ulcer and, at the time of presentation, about 21% had had a previous lower-limb amputation, mainly at toe level (82%). Interestingly, more than 86% of patients had a history of antibiotic consumption during last three months. 13.4% of patients was an opium addict. The primal evaluation of diabetic complication based on patient's documents was as follows, retinopathy in 75.6%, CHD in 31.7%, neuropathy in 95.1% and nephropathy in 30.5% were noted. In this study, we had defined the physical activity as doing exercise at least 30 minutes per day, three times a week in which 86.6% of patients did not fulfill our definition.

Baseline wound characteristics

According to Table 1, most of the patient (61%) had wound with grade 3 in Wagner classification. Lesions mainly involved the toes (46.3%). The most lesions (41.5 %) had mean size of the 5-10 $(cm)^2$. Around 10% of patients had the lesion with the size of more than 30 $(cm)^2$. In 97.6 % of ulcers, a local inflammatory manifestation with purulent discharge was reported. In 36.6% of patients, the ulcers had ischemic feature, and more than 97.6% of patients had infected ulcer as documented by patient's symptoms or lab data. The results of magnetic resonance imaging (MRI) and bone probing test were positive in 62.9% of ulcers suggesting of underlying osteomyelitis.

The most reported causes of ulcer induction in our patients were minor trauma (7.3%), major trauma (1.2%), and insertion of sharp objects (4.9%), wearing the unsuitable shoes (41.5%) and others (45.1%). Among patients, 57.5 % had at least, one type of deformities such

Table 1. Demographic and clinical characteristics of patients and diabetic foot ulcer (n = 82).

Baseline characteristics	Patients (n [%])
Gender, n (%)	
Male	47(57.3)
Female	35(42.7)
Age(years) mean ± S.D [range]	59.13±10.80 [39–82]
Body mass index (BMI, kg/m^2), n (%)[a]	
Underweight (≤18.5)	2(2.4)
Normal weight (18.6-24.9)	28(34.1)
Overweight (25-29.9)	33(40.7)
Obesity (≥30 kg/m^2)	18(22.2)
Diabetes type, n (%)	
Type1	3(3.7)
Type2	79(96.3)
Diabetes duration (years), n (%)[a]	
<5	16(19.5)
≥5-10	16(19.5)
≥10-15	16(19.5)
≥15-20	12(14.6)
≥20	21(25.6)
Diabetes complication, n (%)[a]	
Retinopathy (NPDR[b] -PDR[c])	62(75.6)
Coronary heart disease	26(31.7)
Neuropathy	78(95.1)
Nephropathy	25(30.5)
HbA1C, n (%)[a]	
≤7%	7(8.5)
7.1-7.9%	11(13.4)
≥8%	56(68.3)
Mean±S.D [range]	9.041±1.6095[5.4-12.4]
ESR(mm/h) mean ±S.D [range]	72.02±38.678 [2-140]
History of foot ulcer, n (%)[a]	
Positive	65(79.3)
Negative	16(19.5)
History of foot amputation, n (%)[a]	
Minor	14(17.1)
Major	3(3.7)
None	64 (78.0)
History of addiction	
No addiction	62(75.6)
Nicotine addiction	9(11)
Opium addiction	11(13.4)
History of antibiotic consumption in past 3 months (oral or parenteral)	
Yes	71(86.6)
No	11(13.4)

Table 1. Continued.

Baseline characteristics	Patients (n [%])
Physical activity [d]	
Yes	11(13.4)
No	71(86.6)
Wound characteristic	**Patients(n [%])**
Wagner classification (grade 0 -5)	
0	0(0)
1	0(0)
2	14(17.1)
3	50(61.0)
4	16(19.5)
5	2(2.4)
Ulcer size (cm^2) , n (%)[a]	
≥1-2	2(2.4)
≥2-5	9(11.0)
≥5-10	34(41.5)
≥10-30	28(34.1)
≥30	8(9.8)
Ulcer location	
Toes only	38(46.3)
Toes and forefoot	20(24.4)
Heel, or heel and mid foot	24(29.3)
Deformity, n (%)[a]	
Hallux valgus or prominent metatarsal or both	30(36.6)
Charcot	16(19.5)
None	34(41.5)
PAD [e], n (%)[a]	
Yes	30(36.6)
No	51(62.2)
Presence of infection	
Yes	80(97.6)
No	2(2.4)
Ulcer cause, n (%)	
Minor trauma	6(7.3)
Major trauma	1(1.2)
Sharp object	4(4.9)
Unsuitable wear	34(41.5)
other	37(45.1)
Claudication , n (%)[a]	
Yes	41(50.0)
No	39(47.5)

[a] Percentages may not sum to 100 due to missing information
[b] NPDR: None proliferative diabetic retinopathy
[c] PDR: Proliferative diabetic retinopathy
[d] Physical activity is defined as physical exercise at least 30 minutes per day, 3 times a week
[e] PAD: Peripheral arterial disease

Table 2. Frequency of isolated bacteria from infected foot ulcers (n = 29 patient).

Type of microorganism	N (%)	MDROs
Gram positive aerobic cocci:	17(48.6)	5
Staphylococcus aureus :	4(11.42)	3
streptococcus spp :	3(8.6)	-
enterococcus spp :	5(14.3)	2
staphylococci epidermis(as normal flora of skin) :	5(14.3)	-
Gram negative aerobic bacilli:	18(51.4)	6
Enterobacter aerogenes:	1(2.85)	-
E.coli:	7(20)	2
proteus spp:	5(14.3)	-
Klebsiella spp:	1(2.85)	-
Acinetobacter baummannii :	4(11.4)	4
Total	35	11

Multidrug-resistant organism, including methicillin-resistance staphylococcus aureus (MRSA), Vancomycin-resistant enterococci (VRE), Escherchia coli(extended spectrum B-lactamase or ESBL producing) resistant to third-generation cephalosporins and fluroquinolones, Acinetobacter baummannii resistance to at least two of the following antibiotics: Cefepime, ciprofloxacin, levofloxacin, meropenem, amikacin, ceftazidim.

as prominent metatarsal heads, hallux valgus, contracture toes and Charcot's joint. Charcot foot reported in 16 (19.5%) patient.

Imaging and microbiology

According to investigated data, all patients at least received one medical imaging intervention, which was mostly soft tissue sonography (98%). Assessing arterial disease by (mostly Doppler sonography) was carried out in 64.6 % of patients. MRI was performed in 65.9%, while it was considered for all patients before amputation surgery. Due to technical reasons, unstable condition of patients and fault of management team, only 36.6 % of patients (n=30) underwent microbiological sampling during our assessment. Unfortunately, most of the sampling was done after the beginning of empirical antibiotic therapy (n=18), and the rest of sampling was carried out on the day of admission before first dose antibiotic administration. The most frequently used technique for microbiological sampling was swabbing the wound (60%). Cultures were positive in 29 of the 30 collected samples of patients (96%) and accounted for 35 microorganisms. The ratio of samples per patients in our investigation was about 0.36, and the ratio of the number of bacteria per positive culture was about 1.2. From all cultures 79.1% were monomicrobial, and interestingly, Gram-negative aerobic bacilli were the most founded pathogen, and among them, Escherichia coli (E-coli) was the most prevalent (about 20%). After that, in next most frequently cultured groups were Proteus (14.3%) and Staphylococcus epidermis (14.3%) recovered from 29 positive cultures. However, the most reported pathogen from other similar studies was Staphylococcus aureus (17, 18). Due to lack of data for all patients in culture era, Staphylococcus aureus just listed in four cultures. The rest of the cultures (20.9%) were polymicrobial ones.

Among cultures, probable Vancomycin-resistant Enterococci (VRE) and Methicillin-resistant Staphylococcus (MRSA), was reported in 5.7% and 8.6% respectively. On the other hand, we have reached two cultures (both E-coli) with extended-spectrum beta-lactamases (ESBLs) species, in which the microorganism was resistance to all beta-lactam antibiotics including third and fourth generation of cephalosporins. (Table 2)

We also found four multidrug-resistant (MDR) Acinetobacter baumannii cultures in our investigation. These microorganisms were only susceptible to colistimethate sodium (Colistin®).

Wound management and treatment of infection

Unfortunately, in spite of the international guidelines recommendations (13), in our centers, off-loading the wound was applied in none of the affected patients. But bedside debridement was repeatedly done for almost all patients (96.3%).Vascular reconstruction was carried out in 8 patients (9.7%), and minor amputation and major amputation was done in (15.9%) and (9.8%) of patients respectively. It is worth to mention that we recorded negative-pressure wound therapy by aiming vacuum in near 11% of patients.

All patients were treated with parenteral antibiotics at the day of admission in the emergency room, and some patients were considered intensive antibiotic therapy (6%) and even urgent amputation surgery (1.2%) due to suspicion of sepsis. Since, at least 86% of patients had a history of antibiotic consumption during previous three

months, in more than 30% of patients continued antibiotic as a parenteral form or changed into different antibiotic type.

Antibiotic regimen was parentally administrated for (100%) patients, and both oral and parenteral therapy was considered in 3.4% of patients. Mean duration of parenteral therapy (alone or in associated with oral treatment) was 14.95 ± 7.62 days (minimum and maximum days of treatment were: 4–60 days). In 74.4% of patients receiving parenteral therapy, treatment was continued with oral agents after discharge for a median duration of 14 days.

Sixteen antibiotic combinations were prescribed, among them, the most frequently prescribed combination antibiotics were meropenem and Targocid® (teicoplanin) (34.1%), Tazocin® (piperacillin + tazobactam) and Targocid® (teicoplanin) (24%). However, ciprofloxacin and clindamycin (14.6%), as well as meropenem and vancomycin (10.9%), were repeatedly used as well.

Of note, the most frequently prescribed antibiotic agents were Targocid® (teicoplanin) (72%), meropenem (47.6%), Tazocin® (30.5%) and clindamycin (46.3%). Other agents rarely prescribed in antibiotic regimens were linezolid (1.2%), ceftriaxone (2.4%), and ceftazidime (2.4%).

In 30.4 % of patients, the initial antibiotic regimens were ordered to change mainly due to a mismatch in antibiogram results, lack of clinical response and adverse antibiotic reaction.

In osteomyelitis management era, 15.5% of patients who underwent bone resection, received less than one-week parenteral antibiotic therapy after surgery and 11.3% have received more than one-week parenteral antibiotic therapy. Other patients with the diagnosis of osteomyelitis have received at least two weeks parenteral antibiotic therapy. They continued antibiotic consumption even after discharge by the aim of fulfilling the 4-6 weeks antibiotic treatment for treatment of osteomyelitis.

Outcome and risk factor correlations

The outcome of patients as described previously was assessed with several risk factors such as age, gender, duration of diabetes, type of diabetes, HbA1C, PAD, nephropathy, ulcer size, Wagner classification and etc. Neither age nor gender, duration of diabetes, type of diabetes, HbA1C, history of ulcer, history of amputation, opium addiction, history of neuropathy, retinopathy, PAD and CHD had significant statistical differences in prediction of unhealed patients.

Unhealed ulcers had a remarkably close association with ulcer's size (P=0.04), nicotine consumption (P=0.05). Wagner classification had significant differences with unhealed group (P=0.012). The more the Wagner classification grade, the least the healing process. Also there was a significant (P=0.04) inverse relationship between unhealed group and BMI. (Table 3).

In our investigation, mean hospital length of stay was two weeks. Accordingly, 50 patients were categorized as healed group and 32 patients in unhealed group. Among unhealed group, 21 patients underwent amputation, and two patients passed away during the investigational period.

Discussion

The present study aimed to evaluate the actual management of diabetic foot patients in spite of several guideline recommendations (13) in the most referral and university-affiliated diabetic foot's center in Isfahan. For this reason, it is logical to compare the procedures usually performed in our centers with those recommendations of the most important guideline (such as IDSA 2012)(13). Due to a high prevalence of DFU as well as high rate of morbidity, the importance of prompt and appropriate treatment is crucial. The management of DFU needs a multidisciplinary approach; it is extended from the local management to the surgical modalities.

According to the IDSA guideline (13), every new DFU cases must be evaluated for classifying and grading the wound based upon the appearance and presence of foot infection or ischemia. One of the problematic parts that do not get enough attention in our center is lack of wound classification and comprehensive assessment of wound in neurological and vascular aspect. For example, for assessing the ischemia in patients with diabetic foot ulcer measuring the ankle-brachial index (ABI) and toe pressure, is highly recommended while this performance rarely carries out in our center.

Other recommended clinical evaluation such as 10-g monofilament test or tuning folk for neurological assessment has not performed during our study in the aforementioned center. Furthermore, the importance of performing such a valuable assessment must be re-emphasized in our center. We also found that ulcer's size and Wagner classification are related to unfavorable outcome and amputation in diabetic patients. Oyibo et al., 2000 reported that ulcer area, as a measure of ulcer size, can predict the outcome of foot ulcers (19).

We can consider lack of performing microbiological sampling and not having precise microbial culture information as the most devastating pitfall in the management of DFU in our center. As we noted just 29 patients had a positive culture, and we believe that in reality the statics is even worse. According to the guideline (13) the preferred clinical specimens for positive culture include aspirate from an abscess or curettage from the ulcer base following superficial debridement of necrotic tissue while most of our cultures have been taken from swabbing the wound.

Dezfulian et al., from 2007 till 2009, of cultures obtained from Iranian patients with DFU, reported Staphylococcus aureus, Coagulase-negative Staphylococci (CONS) and

Table 3. Logistic regression analysis. Association of each potential predictor with non-healing in the studied population.

Variables	Healed (50) N (%)	Unhealed (32) N (%)	OR[1] (95% CI[2])	*P*- value
Age (years), mean ± S.D[3]	58.8 ±9.7	59.9±21.1	1.07 (0.96-1.19)	0.24
Duration of Antibiotic therapy (days), mean ± S.D	14.8±8.6	15.2±6.07	0.94 (0.84-1.06)	0.31
ESR[4] (mm/h), mean ± S.D	62.7±38.5	86.3±34.8	1.02 (0.99-1.06)	0.21
Gender				
Male	28(59.6)	19(40.4)	0.09 (0.006-1. 59)	0.10
Female	22(62.9)	13(37.1)		
Diabetes type				
Type1	1(33.3)	2(66.7)	0.15 (0.001-22.74)	0.45
Type2	49(62.0)	30(38.0)		
Neuropathy				
Yes	47(60.3)	31(39.7)	977.35 (0.09-30.34)	0.14
No	3(75.0)	1(25.0)		
Retinopathy				
Yes	39(62.9)	23(37.1)	1.98 (0.11-35.30)	0.64
No	11(57.9)	8(42.1)		
CHD[5]				
Yes	14(53.8)	12(46.2)	0.45 (0.038-5.32)	0.53
No	36(64.3)	20(35.7)		
Nephropathy				
Yes	5(38.5)	8(61.5)	0.30 (0.01-7.15)	0.46
No	45(65.2)	24(34.8)		
Addiction type				
Nicotine	4(44.4)	5(55.6)	107.68 (1.04-76.25)	0.13
Opium	6(54.5)	5(45.5)	13.28 (0.31-68.22)	0.05 0.18
PAD[6]				
Yes	8(26.7)	22(73.3)	2.29 (0.13-39.13)	0.57
No	41(80.4)	10(19.6)		
Previous amputation				
Yes	12(70.6)	5(29.4)	0.21(0.01-3.29)	0.27
No	37(57.8)	27(42.2)		
Previous DFU[7]				
Yes	41(63.1)	24(36.9)	1.87 (0.01-3.29)	0.67
No	8(50)	8(50)		
Diabetes duration (years)				
<5	10(62.5)	6(37.5)		
≥5-10	8(50.0)	8(50.0)	0.85 (0.47-1.55)	0.60
≥10-15	14(87.5)	2(12.5)		
≥15-20	8(66.7)	4(33.3)		
≥20	9(42.9)	12(57.1)		
Wagner classification				
2	13(92.9)	1(7.1)		
3	35(70.0)	15(30.0)	61.16 (2.43-38.31)	0.012
4	2(12.5)	14(87.5)		
5	0(0.0)	2(100.0)		

Table 3. Continued.

Variables	Healed (50) N (%)	Unhealed (32) N (%)	OR[1] (95% CI[2])	*P*- value
Ulcer size (cm^2)				
≥1-2	2(100.0)	0(0.0)	7.00 (1.05-46.50)	0.04
≥2-5	7(77.8)	2(22.2)		
≥5-10	25(73.5)	9(26.5)		
≥10-30	13(46.4)	15(53.6)		
≥30	2(25.0)	6(75.0)		
HbA1C (%)				
≤7%	2(28.6)	5(71.4)	3.07 (0.43-21.89)	0.26
7.1-7.9%	10(90.9)	1(9.1)		
≥8%	33(58.9)	23(41.1)		
BMI[8] (kg/m^2)				
Underweight (≤18.5)	2(100.0)	0(0.0)	0.15 (0.02-0.93)	0.04
Normal weight (18.6-24.9)	10(35.7)	18(64.3)		
Overweight (25-29.9)	23(69.7)	10(30.3)		
Obese (≥30 kg/m^2)	14(77.8)	4(22.2)		

[1]OR: Odds ratio, [2]CI: Confidence interval, [3]S.D: Standard deviation, [4]ESR: Erythrocyte sedimentation rate, [5]CHD: Coronary heart disease, [6] PAD: Peripheral arterial disease, [7]DFU: Diabetes food ulcer, [8] BMI: Body mass index, Renal disease included: Nephropathy, CKD and ESRD.

E-coli as most commonly isolated species. They also found that Out of 69 patients with positive cultures, 34 (49%) were only infected with one organism; while others 43 (51%) had mixed infections (17). Our results were in accordance with previous mentioned study (17), however, we reported Gram-negative aerobic bacilli (E-coli and Proteus) as the most found pathogen. In the next step, most frequently cultured group was reported as CONS culture. We think that the differences may be related to the missing cultures that we had for all patients. Furthermore, having an accurate conclusion about the pattern of microbial is not possible due to incorrect sampling and lack of complete data from all investigated patients.

Unfortunately, more than 86% of our patients had a history of antibiotic consumption during the last three months, and this issue directly effects on the rate of microorganisms' resistance to antibiotics. For example, we found that at least 75% of isolated Staphylococcus aureus is methicillin-resistant Staphylococcus (MRSA) or we had reported several resistant microorganisms such as Acinetobacter baumannii or Vancomycin-resistant Enterococci. Data revealed a great concern about the antibiotic therapy in our country and especially in our center. Antibiotics overuse, either prescribed or non-prescribed will lead to forming resistant microorganism in the future and lose of available antibiotics.

One of the worth part in antibiotic therapy in our center was, the act of not changing or deescalating the antibiotic treatment regimen after revealing laboratory results. In most of the situation, empirical antibiotic therapy continued for the whole duration of treatment even after the responsible microorganism had been found. We noted that most frequently prescribed combination antibiotic were meropenem and Targocid® (teicoplanin) (34.1%), Tazocin® (piperacillin + tazobactam) and Targocid® (teicoplanin) (24%). These combinations do not routinely reported as a most frequent use combination in other international centers. For example, in the study conducted in 386 diabetic centers in France, the most frequently prescribed antibiotic agents were penicillin derivatives associated with β-lactamase inhibitors (amoxicillin or ticarcillin/clavulanic acid) and in the next step fluoroquinolones were used in 32% of patients. They reported carbapenem, third-generation cephalosporin (3%) as rarely prescribed antibiotics' regimens (18).

Empiric antibiotic therapy with broad-spectrum probably leads to better survival in short time, while not only put health care system in a dangerous situation by gradual losing the expensive antibiotics, but also has a heavy economic burden for insurance systems and centers.

Irrational use of broad-spectrum antibiotics such as vancomycin (20), imipenem (21) and meropenem (22) has been noted in other hospital in Iran as well. For instance, after great effort of clinicians in modifying the rational use of antibiotics in at least university- affiliated hospitals, still in Imam Khomeini hospital, one of the biggest teaching hospitals, Tehran, Iran, appropriate meropenem prescription as an empiric therapy according to international guidelines was only about 41% (22).

As it is evident, empirical antibiotics are broad spectrum

and preserving of them for critical illness is so evitable. Moreover, overuse of these kinds of antibiotics per se leads to induction of resistant microorganisms.

Constant monitoring of clinicians and getting feedback of practice in choosing antibiotic is highly recommended in our center and other diabetic foot centers. Compliance with the guidelines and being updated are important factors in controlling the overuse of antibiotics in the infectious era.

Fortunately, the duration of antibiotic therapy in our patients was guideline-based and means length of stay in hospital was as similar as the other report (18).

The small sample size is the main limitation of our study. Checking several items during the investigation and long duration of follow up have not allowed us to continue the study for an expanded time with more number of patients. This study was an observational one; we tried to find the DFU treatment challenges in our center. The aim of study was to find the pitfalls in order to reduce the medical errors and give feedback to responsible healthcare professions. Our research has proved the necessity of interventional studies to improved DFU management in educational center. We believe that the health care professions must be updated and educated in DFU management team even in teaching diabetic centers.

Although our diabetic center is university-affiliated, there are still several points, and pitfalls must be re-considered in management of DFU patients. Obtaining microbiological sampling, antibiotic management and baseline assessment of wound are the most problematic issues. Ulcer evaluation in regard with finding symptoms of neuropathy, PAD was not acceptable and needs to consider for amendment.

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