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Original Article

Bacteriology of moderate-to-severe diabetic foot infections in two tertiary hospitals of Iran

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ABSTRACT

Background: Approximately 25% of people with diabetes will experience diabetic foot ulcers (DFUs) during their lifetime. The present study was designed to determine the type of microorganisms isolated from the DFUs and their antibiotic resistance pattern, and to determine predisposing factors contributing to antibiotic resistance at the authors' wound care clinic in Qazvin, Iran.

Methods: A cross-sectional study was conducted from May to December 2017. One specimen for microbiological studies was obtained from the deep tissue. All demographic, clinical, and laboratory data and results of ulcer culture were collected for each case. Antimicrobial susceptibility testing to different agents was carried out using the disc diffusion method. A p value < 0.05 was considered significant.

Results: 95 aerobic microorganisms were isolated from 105 specimens. Among Gram-positive and negative bacteria, *Staphylococcus spp.* and *Escherichia (E). coli* were the most frequent organisms isolated, respectively. Multidrug resistant (MDR) organisms constituted up to 48.4%, with 37.5% of isolated *Enterococcus spp.* being VRE, 48.8% of *Staphylococcus spp.* being methicillin-resistant, 77.8% of isolated *E. coli* being ESBL and 66.7% of isolated *Pseudomonas* being MDR. The minimum and maximum prevalence of resistance in Gram-negative bacteria were 17.6% and 87.5% for imipenem and ceftazidime, respectively. The prevalence of Gram-negative bacilli was higher in older patients (p value = 0.039) and rose markedly in patients with a higher number of hospitalizations (p value = 0.015).

Conclusion: Due to emergence of antibiotic resistance pathogens, culture specimens and antibiotic sensitivity testing are essential for correct management of the DFU infections and the selection of appropriate antibiotics.

1. Introduction

Diabetes mellitus (DM) is a chronic disease that its incidence and prevalence are increasing in developing countries such as Iran. In 2005–2011, trend analysis revealed a 35.1% increase in DM prevalence, so that more than four million Iranian adults have DM [1] Approximately a quarter of diabetic patients will experience a diabetic foot ulcer (DFU) during their lifetime (probably the major component of the diabetic foot) [2,3]. Diabetic foot (DF) and especially DFUs is a severe complication of diabetes in patients and can have a marked long-term influence on quality of life in all ages especially elderly [4]. Foot ulcers and infections are an important source of morbidity in patients with DM. Patients with a DF have a 150-fold increased risk of lower extremity amputation compared with patients with diabetes and no foot infection [5] and an infected foot ulcer accounts for about 60% of lower extremity amputations [3].

Early diagnosis of ulcers and prompt initiation of appropriate antimicrobial therapy are essential for preventing complication and improving the quality of life [6]. DFU treatment is difficult because weakened microvascular circulation, impaired granulocyte adherence, chemotaxis, and phagocytosis in the infected area in these patients [7]. When DFUs are infected, it is necessary control the infection with debridement and use antibiotics to prevent severe complications [5]. Widely used antibiotics are associated with the development of bacterial resistance during therapy of DFUs [8]. If there is a microbial resistance, empiric therapy of infected DFUs may not be effective. Therefore, antibiotic susceptibility test is a requirement for the management of DFUs infections which can help to make better therapeutic choices.

In our region in academic centers, antibiotics usually were selected

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according to published recommendations [9,10]. Systemic antibiotics (and additional topical antibiotics) were given in cases of clinically infected DFUs. Initial antibiotic therapy is usually empirical and chosen without knowledge of initial microbiological culture results. In shorter duration DFUs, the antibiotic regimen always includes an agent active against Gram-positive cocci, particularly S. aureus. In longer duration of the wounds, Gram-negative organisms has also covered. Usually the amoxicillin-clavulanic acid or a fluroquinolone (such as ciprofloxacin, ofloxacin, or levofloxacin) was started in patients with locally severe lesions (extensive cellulites or deep ulcer), in combination with an aminoglycoside if fever was present also and with clindamycin in patients with extensive tissue devitalization. However, in our region inappropriate antibiotic treatment, frequent hospital visits or admissions, and lapses in hygiene favoring cross-transmission are common.

This study was designed to identify the microorganisms isolated from the DFUs, determination of their antibiotic resistance pattern and risk factor for MDR infections at the authors' wound care clinic in Qazvin, Northern Iran.

2. Materials and methods

2.1. Patients and study protocol

This cross-sectional descriptive study was carried out on 105 patients admitted with infected diabetic foot at BouAli and Velayat University Hospitals, Qazvin, Iran. Wound infections were diagnosed clinically on the basis of local signs and symptoms of inflammation (erythema, edema) or purulent discharge and malodour [11,12]. The study design and methodology were approved by the Ethics Committee of Qazvin University of Medical Sciences and patients' consents were also obtained. We evaluated the data over an eight month period from May to December 2017. The study population was defined as the adult patients with DM with foot ulcers at initial visit. Patients' demographic and clinical features such as age, sex, patients' weights, duration of diabetes, nature of ulcer based on Wagner classification, neuropathy, ischemic heart disease (IHD), hypertension (HTN) and debridement of infected necrosis were first collected. Data related to clinical findings such as blood urea nitrogen (BUN), creatinine (Cr), erythrocyte sedimentation rate (ESR), C- Reactive protein (CRP) and hemoglobin A1c (HbA1C) were also collected. The vascular disease and neuropathy patients were firstly assessed based on characterization and position of ulcers and their history and then determined with additional tests. For neuropathy, nerve dysfunction, significant painful symptoms, classical signs of neuropathy (numbness, paresthesia and burning sensations), reflex test, and light touch sensory were evaluated [3].

2.2. Bacterial isolation

One specimen for microbiological studies was obtained from the deep tissue. All samples were collected on the patients' admission to the hospital, before antibiotic treatment. To avoid isolation of colonizing flora, the wound was first thoroughly cleaned with normal saline and then, samples were collected using punch biopsy from the depth of the wounds. If the surgical debridement was done, the specimens were taken in the operating room. Tissue biopsy/debrided fragments or a wedge of tissue was obtained during debridement using a sterile blade/knife from the base and/or margin of the ulcer, and transported in a sterile solution of normal saline. For aerobic culture, specimens were inoculated onto blood agar and MacConkey agar and incubated at 37 °C for 48 h. The isolates were identified by standard methods.

2.3. Antibiotic susceptibility patterns

All the isolates were tested for their antibiotic resistance. Susceptibility of all the isolates to different antibiotics was determined by the disc diffusion methods, as recommended by the Clinical and Laboratory Standard Institute, using commercial antimicrobial discs (Mast. Co., UK). Antibiotic susceptibility tests were done by use of disk diffusion methods on Mueller-Hinton agar plates. A microorganism was classified as MDR if it was found to be resistant to two or more classes of antimicrobials. The following antibiotic disks were employed: ampicillin (10 μg/mL), co-trimoxazole (25 μg/mL), penicillin (10 μg/mL), clindamycin (2 μg/mL), rifampin (5 μg/mL), vancomycin (30 μg/mL), gentamicin (10 μg/mL), amikacin (30 μg/mL), ceftazidime (30 μg/mL), ceftriaxone (30 μg/mL), ciprofloxacin (5 μg/mL), imipenem (10 μg/mL), and piperacillin-tazobactam (110 μg/mL).

Gram-negative bacilli were tested for extended spectrum β-lactamase (ESBL) production and *Staphylococcus species* were tested for methicillin resistance by using cefoxitin disc (30 mcg/disk). All *Enterococcus isolates* were examined for vancomycin susceptibility. MDR organisms were defined as methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant *Enterococci* (VRE), Gram-negative bacteria producing ESBL and methicillin-resistant coagulase-negative *Staphylococci*. Appropriate quality controls were used where indicated. *Escherichia (E). coli* ATCC 25,922 was used for quality control purposes.

2.4. Statistical analysis

Data were analyzed using SPSS 25.0 statistical analysis software (IBM Inc., USA). Distributions of continuous data were assessed for normality using the Kolmogorove Smirnov test. Continuous variables are described as mean ± SD or median, and were compared using the t-test for independent samples or the Manne–Whitney U as appropriate. Categorical variables are described as (%) of indicator value and compared by vital status using the chi square test or fisher exact test as appropriate. All tests were two-sided and considered significant at p value < 0.05.

3. Results

3.1. Patients' data

105 patients with a mean age of 60.1 years hospitalized were studied during the above mentioned period. They included 62 males (59%) and 43 females (41%). The mean duration of diabetes was 13.1 years. DFP weights ranged from 50 to 115 kg. Mean HbA1C was 7.9% and more than half DFU patients were poor glycaemic control. In this patient group, 19% Grade 2, 45.7% of the ulcer grade was 3 and 35% Grade 4. Most patients had history of previous wounds (95.2%) and previous antibiotic use (83.8%). Most DFU patients had diabetic neuropathy (93.3%), HTN (69.5%) and IHD (52.4%). The average of ESR was 63.5 mm/1 h with the minimum and maximum 3 and 150 respectively. The mean CRP value was 63.9, with a maximum of 135 and a minimum of 0. Only four and ten patients have normal CRP and ESR respectively. The mean BUN and Cr value was 26.9 and 1.7 mg/dl respectively. Fourteen patients (13.3%) were admitted for the first time and other admitted two or three times (68% and 18.1% respectively). All patients had ulcers graded as 2–4 in the Wagner classification with grade 3 as the most prevalent (45.7%) Table 1

3.2. Bacterial isolates and antibiotic susceptibility patterns

In total, 95 aerobic microorganisms were isolated from the patients. Data from our study show that Gram- positive organisms were the major infective pathogens as compared with Gram- negative isolates (62.1% vs 37.9%; p value = 0.023). The most common isolated bacteria were *Staphylococcus spp.* (39.5%), *E. coli* (17.1%) and *Enterococcus spp.* (15.2%). Other Gram-negative aerobes recovered were *Citrobacter spp.*, *Enterobacter spp.* and *Proteus spp*.

The prevalence of Gram-negative bacilli was higher in older patients than in younger ones (p value = 0.039) and rose markedly in patients with a higher number of hospitalizations (p value = 0.015). The count

Table 1
Demographic and clinical data of diabetic foot patients.

Parameter	Value	N (%)
Age	≤50	23 (21.9)
	50–70	58 (55.2)
	≥70	24 (22.9)
Weight range	≤70	26 (26.0)
	70–90	59 (59.0)
	≥90	15 (15.0)
Duration of diabetes (years)	≤10	51 (48.6)
	10–20	27 (25.7)
	≥20	27 (25.7)
Wagner grading of ulcer	2.00	20 (19.0)
	3.00	48 (45.7)
	4.00	37 (35.2)
Number of admissions	One	14 (13.3)
	Two	72 (68.6)
	Three	19 (18.1)
Wound debridement		57 (54.3)
Comorbid conditions	Neuropathy	98 (93.3)
	Hypertension	73 (70.2)
	Ischemic heart disease	55 (52.4)
	Previous ulcer	100 (95.2)
Recent antibiotic use (≤1 month)		88 (83.8)
Poor glycemic control (HbA1c ≥ 8.0%)		55 (52.9)

Table 2
Frequency of organisms isolated from diabetic foot patients.

Organism	Frequency N (%)
Gram-positive	
S.aureus	28 (26.7)
S.epidermidis	13 (12.4)
Enterococcus	16 (15.2)
Streptococcus	2 (1.9)
Gram-negative	
E coli	18 (17.1)
Pseudomonas	9 (8.6)
Citrobacter	5 (4.8)
Enterobacter	2 (1.9)
Proteus	2 (1.9)
Negative culture	10 (9.5)
Total	105

and percent of the organisms are presented in Table 2.

According to the in vitro antibiotic susceptibility testing, resistance to ciprofloxacin (66.0%) and ceftriaxone (63.4%) was noticeable. The minimum and maximum prevalence of resistance in Gram-negative bacteria were 17.6% and 87.5% for imipenem and ceftazidime, respectively. Ampicillin was the most effective antibiotic against *Enterococcus* isolates (all isolates were sensitive) and penicillin was the least effective antimicrobial. Resistant to vancomycin was found in 37.5% of the *Enterococcus* isolates, but for *Staphylococcus spp.*, vancomycin was the most effective antibiotic (only one resistant isolate). 44.0% of *S. aureus* isolates were MRSA. MDR organisms in this study constituted up to 48.4%, with 37.5% of isolated *Enterococcus spp.* being VRE, 48.8% of *Staphylococcus spp.* being methicillin-resistant, 77.8% of isolated *E coli* being ESBL and 66.7% of isolated *Pseudomonas* being MDR. The emergence of resistance among Gram-negative and Gram-positive bacteria against commonly used antimicrobials was presented in Table 3.

In addition, antibiotic resistance to clindamycin and cotrimoxazole was significantly highest in isolated organism from patients who recently received antibiotic (previous month) than other (p value = 0.005 and < 0.001 respectively).

4. Discussion

This study investigates etiology and their antibiotic susceptibility in DFU patients. The majority of our patients were male and older than 50 years (46.7% of patients), consistent with other reported studies [13,14]. This may be due to factors such as the differences in life styles and jobs, causing the feet to tolerate more pressure.

Table 3
Antimicrobial sensitivity profile of Gram-positive and negative bacteria.

		Resistance N (%)[a]	
Antibiotics	Total	Gram positive	Gram negative
Cotrimaxazole	44 (54.3)	33 (60.0)	11 (42.3)
Ciprofloxacin	62 (66.0)	39 (67.2)	23 (63.9)
Ceftriaxon	26 (63.4)	10 (71.4)	16 (59.3)
Ceftazidim	–	–	7 (87.5)
Cefepim	–	–	5 (83.3)
Imipenem	7 (20.0)	1 (100.0)	6 (17.6)
Tazocin	–	–	4 (66.7)
Gentamycin	49 (53.8)	32 (57.1)	17 (48.6)
Amikacin	26 (48.1)	12 (63.2)	14 (40.0)
Penicillin	–	51 (96.2)	–
Ampicillin (only enterococcus)	–	0 (0.0)	–
Cefoxitin	–	20 (55.6)	–
Erythromycin	–	32 (82.1)	–
Rifampin	–	1 (100.0)	–
Clindamycin	–	33 (80.5)	–
Vancomycin	–	7 (11.9)	–

[a] Gram-positive and negative cultures resistance to antimicrobials (%).

In the present study, neuropathy was the main risk factor among the patients (93.3%). A moderate to severe peripheral neuropathy (neuropathy disability score ≥6) encounter in the lower extremity affects up to 22% with diabetes [15]. Sensory loss due to peripheral neuropathy in the diabetic foot is always considered to be the earliest developed and prominent threat, features in the development of ulcers [3].

The present study reiterates the presence of gram-positive bacteria (especially *Staphylococcus spp.*), as the most common isolated organisms in clinically infected DFU. Similar findings have been noted previously by various authors from Iran [6,16]. The propensity of gram-positive microbes mainly *S. aureus* infection was because hematogenous infections are rare in diabetic foot and most of them are contiguous spread from the overlying soft tissue [12]. Similar to the previous study, *E coli* were the second most frequent microorganisms [16].

In our study, Isolation of single organisms could be due to the patients being empirically treated with multiple courses of antibiotics such as amoxicillin-clavulonate, quinolones (ciprofloxacin), oral cephalosporin or clindamycin before presenting to our tertiary diabetic foot care facilities. We presume that these DFU were polymicrobial to begin with, but because of improper antibiotic exposure without prior antimicrobial sensitivity patterns, the sensitive organisms like sensitive gram negative bacilli such as *E. coli* were killed, leaving behind the MDR organisms [14].

There was a significant correlation between the age and type of microorganisms so that with increasing age, the frequency of gram-negative bacilli increased. Also, there was a significant correlation between the etiology and the frequency of admission to the hospital, with an increase in the frequency of hospitalization, the prevalence of gram-negative bacilli was increased.

Culture and sensitivity profile of isolates from cultures showed increasing MDR among most isolates. In our study, MDR organisms constituted up to 48.4%, with 77.8% of isolated *E coli* being ESBL. Recent studies from Iran have reported the prevalence of ESBL producers to be between 31% and 53% [6,16]. Also, *Enterococci* were the third most commonly isolated organisms and 37.5% of isolated *Enterococcus spp.* was VRE. The presence of MDR diabetic foot ulcer *Enterococci* is of major importance also due to the possibility of transmitting those multi-drug resistances to other microorganisms sharing the same ecological niche, highly impairing the implementation of successful antibiotic treatment [17].

In our setting, resistance to commonly prescribed antibiotics for infected DFU particularly ciprofloxacin clindamycin and ceftriaxone was noticeable. Gram negative bacilli were resistant to the majority of cephalosporin and other antibiotics tested, except imipenem, partially consistent with the results of other studies. In most recent studies, similar ciprofloxacin resistance was reported [6,14]. Hence ciprofloxacin as an empirical antibiotic choice may not be appropriate in this setting. However, it should be noted that clindamycin is also used for anaerobic organisms but we did not examine such organisms in this study.

Concerning the association between recent use of antibiotics and antibiotic resistance, in the group received the recent antibiotics; more resistance to cotrimoxazole and clindamycin was founded (16.6% vs. 60.9% and 33.4% vs. 93.9% respectively). In the other words, antibiotic resistance to two antibiotics was significantly highest in isolated organism from patients who recently received antibiotic. Regarding the relationship between previous use of antibiotics and significant resistance to clindamycin and cotrimoxazole, it is recommended that these two drugs be avoided in people with a history of antibiotic use.

As for the alarming types of resistance (i.e., VRE, MRSA, and ESBL), our data showed that the percentages of VRE, MRSA, and ESBL were high. These rates are comparable with those in other studies from Iran [6,16]. Infections with these isolates are more difficult to treat than ordinary ones, because the strains do not respond well to many common antibiotics used to kill bacteria. The high rates of antibiotic resistance observed in the present study may be due to such factors including high hospitalization rate and recent use of broad-spectrum antibiotics. In other words, our DFU clinics are located in two tertiary care hospitals as we see patients after the referring hospital has already tried and failed to control infection using a combination of different antimicrobials. Since facilities for microbiological studies at the first contact physician are usually not available in district hospitals/smaller cities in Iran, indiscriminate antimicrobial therapy (i.e. without establishing the etiology of the infection) eradicates susceptible organisms and, as a result, selects resistant organisms, as well [18]. MDR microorganisms, including ESBL are becoming a serious concern in tertiary referral hospitals in developing countries [6,8,14,19,20].

Because of high burden of MRSA and other MDR pathogens in our hospitals, antibiotic coverage targeted against these pathogens remains unnecessarily high; therefore, antimicrobial stewardship programs for empiric MRSA coverage in DFIs are needed [21]. Prevalence of MRSA among patients with DFIs has recently been declining globally, especially in high-income countries, concomitant with improved hospital infection control measures [22]. To alleviate this situation, clinicians should prescribe antibiotics rationally, timely, and sufficiently and there should be periodic supervisions on the drug consumption by the respective organizations.

It is important to recognize that most isolated *E. Coli* and *Enterococcus* are probably non-pathogenic and therefore do not need treating, and clinicians should focus on the most likely infecting organism especially *S. aureus* and use the narrow spectrum high dose antibiotics recommended in international guidelines [9]. Antibiotics for MRSA and MDR infections should be kept in reserved for proven cases on culture, as this has been shown to reduce rates of antibiotic resistance [23,24]. This study had some limitations. First, most our admitted patients were quite sick (as noted by ESR/CRP) and had several admissions reflecting the severe end of the spectrum. On the other hand, we studied a limited population of DFUs patients in two university medical centers in the Iran; therefore, further large-scale validation studies have to be conducted before generalizability of findings. Second, there is no record of previous antibiotic use of patients.

5. Conclusion

Our data showed that the percentages of VRE, MRSA, and ESBL in moderate-to-severe DFIs are high. Due to emergence of antibiotic resistance pathogens, culture specimens and antibiotic sensitivity testing are essential for correct management of moderate-to-severe DFU infections and the selection of appropriate antibiotics.

Author contributions

Wrote the first draft of the manuscript: Abbas Allami. Contributed to the writing of the manuscript: Tahmine Karimian. ICMJE criteria for authorship read and met: Hamid Reza Najari, Tahmine Karimian, Abbas Allami, Hossein Parsa, Reza Qasemibarqi.

Conflict of interests

The authors declare no conflict of interests.

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