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Original Article

Epidemiology and susceptibility profiles of diabetic foot infections in five hospitals in Lebanon

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Abstract

Introduction: Approximately 80% of diabetes-related lower extremity amputations are preceded by a foot ulcer. Global studies on the epidemiology of diabetic foot ulcer (DFU) infections and guidelines detailing the most common pathogens and their respective antimicrobial susceptibilities are available. While Gram-positive cocci, mainly *Staphylococcus* species (spp.), were the most common organisms cultured from DFU in the United States, the Gram-negative *Pseudomonas* spp. were found to be the most common in some Middle Eastern countries. In Lebanon, however, such studies remain scarce. This study, conducted in Lebanon, investigated the most common organisms in DFU infections and their antimicrobial profiles.

Methodology: We collected data from all documented diabetic foot infections between January 2015 and March 2016, 128 participants total, from 5 different hospitals in various regions of Lebanon.

Results: Among all isolates, *Enterobacteriaceae* (42%), *Pseudomonas* spp. (18.6%) and methicillin-sensitive *Staphylococcus aureus* (MSSA) (15.3%) were the most frequent bacteria. In addition, 72% of *Pseudomonas* spp. were susceptible to ciprofloxacin and 63.6% of *Enterobacteriaceae* were susceptible to either amoxicillin/clavulanate or ciprofloxacin, 91% were susceptible to piperacillin/tazobactam. Methicillin-resistant *Staphylococcus aureus* (MRSA) was only found in hospitalized patients or those who received prior antibiotics. Polymicrobial infections were documented in only 38% of patients.

Conclusion: In Lebanon, the most appropriate empirical oral outpatient treatment would be a combination of amoxicillin/clavulanate and ciprofloxacin. As for admitted patients who have failed the oral regimen, piperacillin/tazobactam would then be the treatment of choice.

Key words: diabetes; foot; infection; Lebanon; antibiotics.

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Introduction

Diabetes mellitus (DM) is a chronic disease and one of the leading causes of limb loss, currently affecting 382 million people worldwide [1]. It is predicted that by 2035, reported diabetes cases will reach 592 million [1]. The World Health Organization predicts that DM will be the seventh leading cause of death by 2030 [1]. In DM patients, when a foot ulcer develops; infection and peripheral artery disease are the major complications leading to subsequent amputation. Approximately 80% of diabetes-related lower extremity amputations are preceded by a foot ulcer [1].

Foot infections are a common and serious problem in diabetic patients. A classification system, specifying the depth and the severity of the foot infection, along with a vascular assessment helps determine which patients should be hospitalized and if they require special radiologic imaging or surgical intervention. According to the American Family Physician Association, the most common pathogens in diabetic

foot infections are aerobic Gram-positive cocci, mainly *Staphylococcus* spp. [2]. More specifically, methicillin-resistant *Staphylococcus aureus* (MRSA) is present in 10% to 32% of American diabetic's foot ulcer infections [2]. However, data has shown that moderate to severe infections and wounds that were previously treated with antibiotics are often polymicrobial, often including Gram-negative bacilli [2]. Moreover, obligate anaerobes may become co-pathogens in ischemic or necrotic wounds [3]. In a study conducted in Turkey [4], *Pseudomonas* spp. were the most frequently isolated organisms followed by *S. aureus*. Gram-positive and Gram-negative isolates represented 38.7% and 61.3% of the isolates, respectively. In addition, among the *S. aureus* isolates, MRSA scored as high as 44.2% [4].

Wound cultures usually take two to three days to produce results. In some instances, incubation is extended to give more opportunity for anaerobic bacteria to grow or to better assess the multiple organisms that are growing. This is why an empirical antimicrobial therapy that treats the most probable pathogens, and can be administered immediately, is key for the best management of diabetic foot ulcer infections [4].

As suggested by the Infectious Diseases Society of America (IDSA), the empirical antibiotic treatment for mild diabetic foot infections is dicloxacillin, clindamycin, cephalexin, levofloxacin, or amoxicillin-calvulanate, assuming that the most probable pathogens are methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Streptococcus* spp.. When MRSA is suspected, doxycycline and trimethoprim/sulfamethoxazole should be considered [3]. While according to the Scottish diabetic group, in antibiotic naïve patients, the most likely pathogens are beta-hemolytic streptococci [5]. The primary antibiotic is oral flucloxacillin with an increased prevalence of resistance after the first exposure to flucloxacillin. In a patient who is not antibiotic naïve (i.e. people with chronic infections, and have received antibiotics previously), infections are more likely to be polymicrobial and include aerobic Gram-negative bacilli. In that case, the first line of treatment is amoxicillin clavulanate [5].

DM affects developing countries disproportionately as more than 80% of diabetes deaths occur in low- and middle-income countries [1]. Some studies have shown that diabetes related complications are common in the Arab world with a higher prevalence in eastern Arab countries [6]. In Lebanon, epidemiological data about etiology and susceptibility profiles of bacteria that cause diabetic foot ulcers in in- and out-patients remains scarce. Some health care practitioners follow the American guidelines for treatment of diabetic foot ulcers while others follow the European guidelines. Local data and studies are crucial to empirical treatment and development of guidelines, which are essential in our fight against antimicrobial resistance in this region. DFU infections are one of the most serious infections in our country, so we decided to conduct a prospective multicenter study to document the local prevalence of the most common organisms incriminated in DFU infections along with their antimicrobial profiles.

Methodology

In our study, we collected demographic and microbiological data of all documented diabetic foot infections during the period between January 2015 and March 2016 from 5 different hospitals across various regions in Lebanon:

1-Mount Lebanon Hospital (City: Hazmieh, Governate: Mount Lebanon)

2- University Medical Center- Rizk Hospital (UMC-RH) (City: Beirut, Governate: Beirut)

3-Middle East Institute of Health (MEIH) (City: Bsalim, Governate: Mount Lebanon)

4-Sacré Coeur Hospital (City: Baabda; Governate: Mount Lebanon)

5-Nini Hospital (City: Tripoli; Governate: North)

The research included 128 participants in total, outpatient and inpatient. Data collected included:

- Peripheral vascular disease
- Previous hospitalization in the past 3 months
- Previous antibiotics in the past 3 months
- Previous surgeries in the same area as the infection in the past 3 months

Superficial culture samples were collected from all participants. Species identification and antibiograms were performed in the laboratories where the specimens were collected. However, susceptibility testing used either the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical & Laboratory Standards Institute (CLSI) breakpoints. All data were entered, quantified and analyzed using Microsoft Excel.

Results

A total of 128 wound cultures from diabetic foot ulcers were collected from 128 patients between January 2015 and March 2016. In this study, the 128 patients were divided into two groups: those who had been hospitalized or have received antibiotics in the past 3 months (Group A; 66 patients (51.6%)); and those who had not (Group B; 62 patients (48.4%)).

Among the 128 culture samples, a total of 182 bacteria were identified. Of the 128 samples, 49 (38%) were found to have polymicrobial infections. Among Group A, 20 patients (30.3%) and among Group B, 28 patients (45%) carried polymicrobial DFU infections.

From the collected organisms, there were 60 (33%) Gram-positive isolates, 120 (66%) Gram-negative isolates and 2 (1%) yeasts. Among all isolates, *Pseudomonas* spp. (n = 34, 18.6%) and MSSA (n = 28, 15.3%) were the most common bacteria, followed by *Proteus* spp. (n = 23; 12.6%) and *E. coli* (n = 22; 12.1%) (Figure 1). It is important to note that from the polymicrobial isolates 74% were *Enterobacteriaceae*, 39% were *Pseudomonas* spp. and 11% were MRSA.

Amongst all the isolates, 34 (18.7%) were *S. aureus*; of those, 28 were MSSA and 6 were MRSA. *S. aureus* was the most commonly isolated Gram-positive organism (57%), of which 17.6% were MRSA. *Enterococcus* spp. (n = 11; 18%) was the second most isolated (Figure 2).

Of the *S. aureus* isolated from patients in Group A, 6 (42.9%) were MRSA. Of the MRSA, 5 were tested for clindamycin susceptibility, of which 4 (80%) were susceptible and 1 (20%) was resistant. MSSA showed 100% susceptibility to clindamycin. It is important to note that MRSA were only found in Group A patients.

The most common Gram-negative isolate was *Pseudomonas* spp. (including *P. aeruginosa*) (28%) followed by *E. coli* (19%) and *Proteus* spp. (17%). Of *Pseudomonas* spp. Tested, 69% were susceptible to ciprofloxacin and 28% were resistant, whereas 3% had intermediate susceptibility.

Escherichia coli, *Klebsiella, Proteus, Enterobacter, Serratia, Citrobacter* constituted 42% of the pathogens collected from the patients in this study. The data showed that 48.6% of the *Enterobacteriaceae* tested were susceptible to ciprofloxacin. Of the 38 *Enterobacteriaceae* isolated in Group A ulcers, 16 (42%) were susceptible to ciprofloxacin. Out of 32 *Enterobacteriaceae* isolated from Group B ulcers, 18 (56%) were susceptible to ciprofloxacin. In addition, 96%, 91%, 70% and 43.7% of all *Enterobacteriaceae* tested were susceptible to imipenem, piperacillin/tazobactam, ceftazidime and amoxicillin/clavulanate, respectively. Also, 63.6% were susceptible to ciprofloxacin and/or amoxicillin/clavulanate.

Discussion

Most studies on diabetic foot ulcer infections reports that Gram-positive cocci are the most common organisms, followed by Gram-negative organisms. Our data, collected form 5 different hospitals in Greater Beirut, Tripoli and Mount Lebanon, showed different results. Among 182 species isolated, 66% were Gram-negative bacteria, compared to 61.3% in a study done in Turkey [4]. Our results also showed that of the 128 patients, 38% had polymicrobial infections, a finding that was in accordance with a similar study by Tiwari *et al.* [7]. Interestingly, patients who had neither been admitted to the hospital nor had received antibiotics in the past 3 months, had more polymicrobial infections. This may be due to prior antibiotic treatment selecting for one single organism.

Pseudomonas spp. were the most common (28%) among the Gram-negative organisms, followed by *E. coli* (19%). The increased incidence of *Pseudomonas* spp. has been reported in another study conducted in Turkey which reported 48.7% of *Pseudomonas* spp. among Gram-negatives and 29.8% among all isolates, compared to 18.6% in our study [4]. Similar results have been reported in other parts of the world such as India, where a study showed that the most commonly

Figure 1. Number of pathogens isolated in the study.

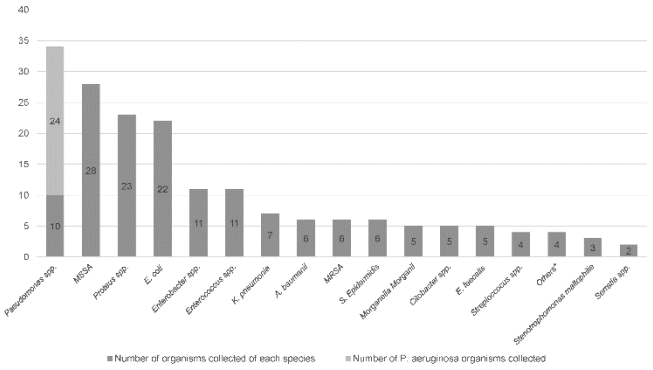
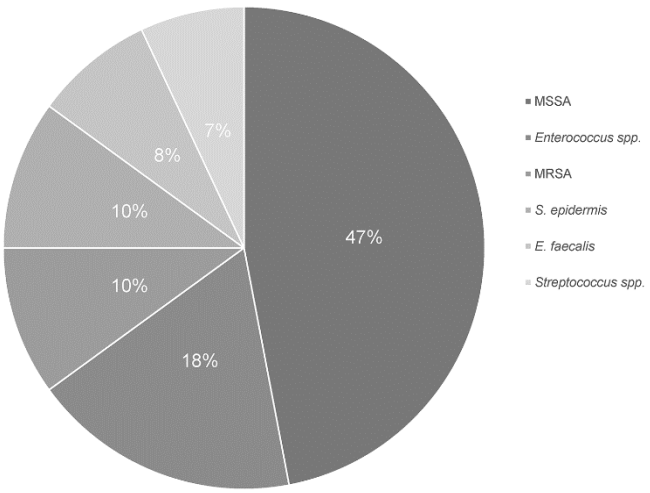


Figure 2. Overall Gram-positive percentages.



isolated pathogen was *Pseudomonas aeruginosa*, constituting 20.1% of all isolated pathogens [8]. In a similar study from Kuwait on the microbiology of diabetic foot infections, *Pseudomonas aeruginosa* constituted 17.4% of all isolates [9]. These results common among developing countries, possibly explained by the poor water sanitation systems and increased temperatures and humidity in these regions. Conditions where *Pseudomonas* spp. will be more likely to colonize and cause infections in diabetic patients than in developed countries with colder climates and where water sanitation systems is quality controlled.

Furthermore, the data collected in this study showed that a high percentage of *Pseudomonas* spp. (72%) were susceptible to ciprofloxacin, and these numbers are similar in Group A (61% susceptible to ciprofloxacin) and Group B (75% susceptible to ciprofloxacin). These findings indicate that ciprofloxacin should be included as part of the empirical treatment for diabetic foot infections in an outpatient setting in Lebanon to better cover the frequent *Pseudomonas* spp. infections.

Reviewing data related to *Enterobacteriaceae* collected from diabetic foot ulcer infections, there was a good susceptibility (96%, 91% and 70%) of these organisms to imipenem, piperacillin/tazobactam and ceftazidime, respectively. However, the susceptibility of *Enterobacteriaceae* to ciprofloxacin was only 48.6%. These numbers show that *Enterobacteriaceae* has significant resistance to ciprofloxacin in Lebanon, and the combination of ciprofloxacin and amoxicillin/clavulanate provide better coverage for our patient population (63.6%). Piperacillin/tazobactam is more likely to be used as an empirical therapy for inpatients who were admitted due to failure of the oral regimen.

Moreover, while *S. aureus* are the most prevalent pathogens in diabetic foot infections in the Western world, in Lebanon these constituted only 18.7% of overall isolates, a number similar to that found in a study in 35 centers in Turkey, which revealed that only 11.4% of the isolates were *S. aureus* [10]. Of the *S. aureus* isolated in our study, 17.6% were MRSA compared to 44.2% in another study done in Turkey [4]. Additionally, MRSA was only found in Group A patients. Rates of MRSA in Lebanon (3.3% of all isolates) are significantly lower than in Western countries where some studies found MRSA in 32% of all diabetic foot infections [2,11]. A study done in Israel found MRSA in only 3% of diabetic foot ulcer infections [12]. Therefore, since *S. aureus* does not constitute one of the most common pathogens isolated from diabetic foot ulcers in our study, MRSA coverage should only be considered for patients with high risk of acquiring the bacteria. Those are patients with prior use of antibiotics, previous hospitalization [13], long duration of foot infection, deeper ulcers reaching bone with signs of osteomyelitis and positive nasal MRSA carriage [11].

This study had some limitations, the most significant one being the small sample size. Despite the fact that the clinical data collected was from 5 major hospitals in Beirut, Tripoli and Mount Lebanon, representing 3 of the 5 regions in Lebanon, these hospitals are considered referral centers, so the population studied may cover more regions in Lebanon. Next, most Lebanese laboratories take diabetic foot ulcer culture samples from superficial tissue instead of collecting deeper specimens. However, with only 38% of cultures taken found to be polymicrobial, and single isolates were pathogenic organisms, we can assume that the organisms cultured were the true pathogens. In fact, *S. epidermidis* which is a widespread skin colonizer, was infrequently isolated (3%) in our study. Also, although some laboratories used EUCAST breakpoints while others used CLSI breakpoints, the latest guidelines of both were very similar to each other [14]. Finally, some laboratories reported only species of certain organisms but this did not affect our results and the data were sufficient to be analyzed as documented above.

Conclusion

Our study demonstrates that in Lebanon, Gram-negatives are the most common organisms isolated from DFU infections with *Pseudomonas* spp. being the most common followed by *E. coli*. In the era of antimicrobial resistance, combined treatment may provide a solution. *Pseudomonas* spp. were shown to have high susceptibility to ciprofloxacin, however in order to also cover the highly prevalent *Enterobacteriaceae*, the combination of amoxicillin/clavulanate and ciprofloxacin would be the recommended empirical regimen for outpatients. As for patients who are admitted due to failure of that oral regimen, piperacillin/tazobactam is then recommended. MRSA was found to be less frequent in Lebanon and should be empirically treated in high risk patients only. These results may be an incentive to check local DFU susceptibilities in the neighboring countries, instead of using European and American guidelines that do not necessarily apply. Obviously, the epidemiology of DFU differs from one country to another; therefore, local guidelines for treating diabetic foot infections are

needed in Lebanon and should be periodically revised because of the changing nature of bacterial resistance.

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