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Original Article

Microbiology of diabetic foot infections in a teaching hospital in Malaysia: a retrospective study of 194 cases

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Background and Purpose: Diabetes mellitus is a progressive disease with chronic complications. Foot infections are a major complication of diabetes and eventually lead to development of gangrene and lower extremity amputation. The microbiological characteristics of diabetic foot infections have not been extensively studied in Malaysia. This study investigated the microbiology of diabetic foot infections and their resistance to antibiotics in patients with diabetic foot infections treated at University of Malaya Medical Centre in Kuala Lumpur, Malaysia.
Methods: A retrospective analysis was conducted of clinical specimens taken from patients with diabetic foot infections over a 12-month period from July 1, 2004 to June 30, 2005. A total of 194 patients with positive clinical specimens were identified. The clinical specimens were cultured using standard aerobic and anaerobic microbiological techniques. Antibiotic sensitivity testing to different antimicrobial agents was carried out using the disk diffusion method.
Results: 287 pathogens were isolated from 194 patients, an average of 1.47 organisms per lesion. The most frequently isolated pathogens were Gram-negative bacteria (52%), including *Proteus* spp. (28%), *Pseudomonas aeruginosa* (25%), *Klebsiella pneumoniae* (15%) and *Escherichia coli* (9%). Gram-positive bacteria accounted for 45% of all bacterial isolates. *Staphylococcus aureus* was predominant (44%) among Gram-positive bacteria, followed by Group B streptococci (25%) and *Enterococcus* spp. (9%). Antimicrobial susceptibility results showed that Gram-negative bacterial isolates were sensitive to imipenem and amikacin while vancomycin showed good activity against Gram-positive bacteria.
Conclusion: The antibiogram results of this study suggest that pathogens remain sensitive to a number of widely used agents. Imipenem was equally effective against Gram-negative bacilli and Gram-positive cocci.

Key words: Bacterial infections; Diabetic foot; Etiology; Microbial sensitivity tests; Retrospective studies

Introduction

Diabetes mellitus (DM) is a serious public health problem and remains an important cause of morbidity and mortality worldwide. In Malaysia, the prevalence of DM has significantly increased from 0.6% in 1960 to 2.1% in 1982, 6.3% in 1986, 8.3% in 1996 and 14% in 1998 [1]. DM is now estimated to affect 16-18% of Malaysians [1,2]. There are three major ethnic groups in Malaysia: Malay, Chinese and Indians. Indians with diabetes tend to have more coronary artery disease, ulcer and gangrene as compared to other ethnic groups. Patients with uncontrolled diabetes often develop diabetic complications, some of the most clinically important which are foot ulcers, retinopathy, neuropathy and macrovascular complications [1,2]. Foot complications such as foot ulcer constitute a major public health problem and impose a heavy burden on health services [3]. Foot infections are responsible for the majority of diabetes-associated hospital admissions. It was estimated that approximately 15% of all diabetics develop foot ulcers and eventually progress to osteomyelitis [4]. Approximately 20% of diabetic patients develop diabetic foot ulcer due to peripheral neuropathy, muscle atrophy, foot deformity and neuropathic fractures. These ulcers eventually lead to diabetic foot infections. Diabetic foot

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infections may present as ulceration, gangrene, Charcot joint, or fracture and are a major risk for amputation [5]. In a previous study, approximately half of 223 diabetic patients with severe diabetic foot infections required amputation at some stage of life before healing or death [6]. Diabetic foot infections are usually polymicrobial in nature due to aerobic bacteria (*Staphylococcus* spp., *Streptococcus* spp. and *Enterobacteriaceae*), anaerobic flora (*Bacteroides* spp., *Clostridium* spp. and *Peptostreptococcus* spp.) and fungi [7,8].

Most reported studies on diabetic foot infections, which investigated the prevalence of microbes and their antibiotic susceptibility patterns, have been published in developed countries. By contrast, the microbiology of diabetic foot infections in Malaysia has not been extensively studied. The aim of this study was to analyze the prevalence of bacterial pathogens in diabetic foot infections and the antibiotic susceptibility patterns of isolates at the University of Malaya Medical Centre (UMMC), in Kuala Lumpur, Malaysia.

Methods

This retrospective study was carried out in the Department of Medical Microbiology, UMMC. Being one of the major teaching hospitals in the city with 900 beds, UMMC receives patients from Kuala Lumpur city and the surrounding areas. All 194 patients with diabetic foot infections were identified from request forms which were sent to the clinical microbiology laboratory along with clinical specimens. These forms are designed to provide pertinent demographic and clinical information of patients including age, gender, race, nature of specimen, examination required, diagnosis and details of antimicrobial therapy. The request form is completed and signed by the treating physician.

Patient selection

Patients with diabetic foot infections were included in this study if they had an infected ulcer, wound, oesteomyelitis or previous amputation and received treatment either as an inpatient or outpatient from July 1, 2004 to June 30, 2005. Each patient was included only once in this study. Data including age, gender, ethnicity, nature of clinical specimen, species of the isolated pathogen and antibiogram of the clinical isolates were recorded.

Microbiology

Two clinical specimens including either curettage of the base of the ulcer, tissue from skin or deep wound, or needle aspiration of the abscess or bone in cases of osteomyelitis were taken from each patient with diabetic foot infection. One specimen was placed into a sterile universal bottle and the other specimen was introduced into anaerobic media (thioglycollate broth). These specimens were sent to the clinical microbiology laboratory for culture and antibiotic sensitivity testing. All specimens were Gram stained for direct examination. Pus, tissue or swab samples were processed for isolation of aerobes by incubating specimens onto blood agar, MacConkey agar and chocolate agar plates in an aerobic chamber and in 5-10% carbon dioxide at 37°C for two days. For the isolation of anaerobes, specimens were inoculated on blood agar plate and incubated in an anaerobic chamber at 37°C and examined at 48 h and 96 h. A thioglycollate broth was also inoculated. All isolated organisms were identified by conventional microbiological methods. Gram-negative aerobes and anaerobes were identified by API 20E and API 20A (bioMérieux, Marcy l'Etoile, France).

Antibiotic susceptibility tests

Antibiotic susceptibility testing by the disk susceptibility method was in accordance with the guidelines of the National Committee for Clinical Laboratory Standards [9]. Antibiotic susceptibility tests were done by use of disk diffusion methods on Mueller-Hinton agar plates. A microorganism was classified as multidrug resistant 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), oxacillin (1 μg/mL), fusidic acid (10 μg/mL), rifampin (5 μg/mL), vancomycin (30 μg/mL) metronidazole (50 μg/mL), ampicillin-sulbactam (20 μg/mL), amoxicillin-clavulanic acid (30 μg/mL), gentamicin (10 μg/mL), netilmicin (30 μg/mL), amikacin (30 μg/mL), cefuroxime (30 μg/mL), cefoperazone (75 μg/mL), ceftazidime (30 μg/mL), ceftriaxone (30 μg/mL), ciprofloxacin (5 μg/mL), imipenem (10 μg/mL), piperacillin (100 μg/mL) and piperacillin-tazobactam (110 μg/mL).

Results

Demographic characteristics

In total, 194 patients with diabetic foot infections were included in this study. Among them, 119 (61%) were males and 75 (39%) were females, a male-to-female ratio of 1.58:1. Their age ranged between 32 and 92 years

Table 1. Age and gender distribution of 194 patients with diabetic foot infections

Age (years)	Gender		No. of patients (%)
	Male	Female	
≤40	4	5	9 (4.6)
41-50	19	16	35 (18)
51-60	58	21	79 (40.7)
61-70	30	24	54 (27.8)
71-80	6	4	10 (5.2)
81-90	1	4	5 (2.6)
≥91	1	1	2 (1)
Total	119	75	194 (100)

and the mean age was 57.6 years. Indians and Malays accounted for 40% (n = 78) and 36% (70), Chinese 20% (39) and others 4% (7). The age and gender distribution of patients is summarized in Table 1.

Microbiology

287 pathogens were isolated from 194 patients, an average of 1.47 organisms per lesion. The specimens yielding pathogens included swabs (107), tissue (73), pus (19) and bone (1). The organisms isolated from different specimens are summarized in Table 2. The most commonly isolated organisms were *Staphylococcus aureus* (17%), *Proteus* spp. (15%), *Pseudomonas aeruginosa* (13%), Group B *Streptococcus* (11%) and *Bacteroides* spp. (1%). Five anaerobes (*Peptostreptococcus* spp., three *Bacteroides* spp. and *Clostridium* spp.) were isolated, and of the 5 anaerobes, 4 were recovered from polymicrobial flora. Two *Candida* spp. were also isolated. Aerobic Gram-negative bacteria (52%) were the most commonly isolated pathogens, comprising 150 species from 125 patients. The five most frequently isolated Gram-negative pathogens were *Proteus* spp. (n = 42, 28%), *P. aeruginosa* (n = 38, 25%), *Klebsiella pneumoniae* (n = 23, 15%), *E. coli* (n = 14, 9%) and *Enterobacter cloacae* (n = 13, 9%). A total 130 (45%) strains of aerobic Gram-positive bacteria were isolated from 104 patients. The most commonly isolated Gram-positive cocci were *S. aureus* (44%), Group B streptococci (25%) and *Enterococcus* spp. (9%). Polymicrobial growth was found in positive cultures from 83 patients, while 111 patients had pure growth. In the pure growth cultures, *S. aureus* was the most prevalent organism, isolated from 31 patients (28%), followed by *Proteus* spp. (n = 25, 23%), *P. aeruginosa* (n = 24, 22%), *K. pneumoniae* (n = 10, 9%), and Group B streptococci (n = 8, 7%). The most commonly isolated organism from polymicrobial growth was Group B streptococci, isolated in 24 patients (29%), followed by *Proteus* spp. (20%) and *S. aureus* (n = 17, 20%).

Table 2. Bacteria isolated from diabetic foot infections of 194 patients

Bacteria	No. of isolates/ % of patients
Gram-positive bacteria	
Staphylococcus aureus	48/25
Methicillin-resistant *Staphylococcus aureus*	9/5
Other *Staphylococcus* spp.	14/7
Group B streptococci	32/16
Enterococcus spp.	12/6
Other streptococci	15/8
Gram-negative bacteria	
Proteus spp.	42/22
Pseudomonas aeruginosa	38/20
Klebsiella pneumoniae	23/12
Escherichia coli	14/7
Enterobacter cloacae	13/7
Other Gram-negative bacteria	20/10
Anaerobes	5/3
Candida spp.	2/1
Total	287

Antibiotic susceptibility

Resistance to methicillin was found in 16% of *S. aureus* isolates. All *S. aureus* isolates were sensitive to vancomycin and rifampin while 7% were resistant to fusidic acid. Sixteen percent of *S. aureus* isolates were found to be resistant to erythromycin and 7% were resistant to clindamycin. All isolates (100%) of Group B streptococci were sensitive to penicillin, ampicillin, vancomycin, imipenem, cefuroxime and clindamicin. On the other hand, 8%, 17%, and 25% of enterococci were resistant to imipenem, ampicillin and co-trimoxazole, respectively. The antimicrobial sensitivity pattern of Gram-positive cocci is summarized in Table 3.

Gram-negative bacilli were least likely to show resistance to imipenem and amikacin. Ciprofloxacin, piperacillin-tazobactam, ceftazidime, cefoperazone, gentamicin, amoxicillin-clavulanic acid, and ampicillin-sulbactam showed satisfactory activity against the isolated Gram-negative pathogens. Metronidazole, imipenem and clindamicin had activity against all anaerobes. The antibiotic resistance pattern against Gram-negative bacilli is summarized in Table 4.

Discussion

Optimal management of diabetic foot infection can decrease infection-related morbidity, need for and

Table 3. Antibiotic resistance of Gram-positive bacteria

Antibiotic	*Staphylococcus aureus* (n = 57) No. (%)	Group B streptococci (n = 32) No. (%)	*Enterococcus* spp. (n = 12) No. (%)	Other *Streptococcus* spp. (n = 15) No. (%)
Oxacillin	9 (16)	-	-	-
Penicillin	-	0	0	0
Erythromycin	9 (16)	1 (3)	6 (50)	0
Ampicillin	-	0	2 (17)	0
Co-trimoxazole	8 (14)	3 (9)	3 (25)	1 (7)
Vancomycin	0	0	0	0
Rifampin	0	-	-	-
Fusidic acid	4 (7)	-	-	-
Gentamicin	10 (18)	-	-	-
Cefuroxime	-	0	7 (58)	0
Cephalexin	-	0	-	0
Clindamycin	4 (7)	1 (3)	0	12 (80)
Imipenem	-	0	1 (8)	0

duration of hospitalization stay and the incidence of major limb amputations. Unfortunately, diabetic foot infections are usually inadequately managed due to lack of understanding of microbial prevalence and therapeutic approaches [10].

Severe diabetic foot infections usually yield polymicrobial isolates, whereas mild infections are frequently monomicrobial. In cases of severe diabetic foot infection, three to five organisms may be cultured [11]. Several studies have previously described a high prevalence rate (80% to 87.2%) of polymicrobial infections in diabetic foot infections [12,13]. However, the polymicrobial infection rate was low (43%) in this study. There were more monomicrobial cultures than polymicrobial cultures (111 vs 83) in this study, with an average 1.47 pathogens isolated from diabetic foot infection. This rate of isolated pathogens per lesion was low compared to other studies [14,15]. The low prevalence of polymicrobial infection and low rate of isolated pathogens per lesion may be attributable to the lack of severity of most infections and the low virulence of isolated organisms in this study.

Wheat et al reported that low-virulence organisms such as *S. aureus*, *Streptococcus viridans*, *Staphylococcus epidermidis*, enterococci and certain Gram-negative bacteria caused two-thirds of mild diabetic foot infections [16]. The majority of diabetic foot ulcers are superficial and are frequently colonized by aerobic

Table 4. Antibiotic resistance of Gram-negative bacteria

Antibiotic	*Pseudomonas aeruginosa* (n = 38) No. (%)	*Proteus* spp. (n = 42) No. (%)	*Klebsiella pneumoniae* (n = 23) No. (%)	*Escherichia coli* (n = 14) No. (%)	*Enterobacter cloacae* (n = 13) No. (%)
Ampicillin	-	26 (62)	23 (100)	13 (93)	13 (100)
Co-trimoxazole	-	14 (33)	6 (26)	10 (71)	4 (31)
Ampicillin-sulbactam	-	5 (12)	4 (17)	7 (50)	10 (77)
Amoxicillin-clavulanic acid	-	8 (19)	2 (9)	3 (21)	12 (92)
Gentamicin	5 (14)	4 (10)	3 (13)	4 (29)	1 (8)
Netilmicin	4 (11)	-	-	-	-
Amikacin	1 (3)	0	0	0	0
Cefuroxime	-	2 (5)	3 (13)	2 (14)	2 (15)
Cefoperazone	7 (19)	0	3 (13)	4 (29)	3 (23)
Ceftazidime	4 (16)	0	2 (9)	1 (14)	3 (23)
Ceftriaxone	-	1 (2)	2 (9)	2 (14)	2 (15)
Ciprofloxacin	4 (11)	3 (27)	2 (9)	4 (29)	0
Imipenem	2 (5)	0	0	0	0
Piperacillin	7 (19)	-	-	-	-
Piperacillin-tazobactam	7 (19)	0	2 (2)	1 (2)	0

Gram-positive bacteria [17]. The most commonly isolated bacteria from diabetic foot infections are *S. aureus*, Group B *Streptococcus*, *S. epidermidis*, enterococci and other *Streptococcus* spp. [17]. One study has also reported the predominance of *S. aureus* in 50% of wound specimens [18]. On the contrary, other studies reported that Gram-negative bacteria (*K. pneumoniae, E. coli, Proteus* spp., *Enterobacter* spp., etc.) were dominant in infected diabetic foot ulcers [19-21]. Gram-negative bacteria were the predominant isolates in our patients (52%). Of the patients with Gram-negative isolates, *Proteus* spp. and *K. pneumoniae* were found in 28% and 15%, respectively, while *E. coli* and *E. cloacae* each made up 9% of isolates. The Gram-positive bacteria isolated (45%) included *S. aureus* and Group B streptococci, enterococci and other *Streptococcus* spp. *S. aureus* and Group B streptococci were the most commonly isolated Gram-positive bacteria, a finding consistent with previous reports [18,22,23].

Patients who had received prolonged or inappropriate or broad-spectrum antibiotics or had lengthy hospitalization, chronic wound or surgical procedure were most likely to have infection and/or colonization with methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *P. aeruginosa*. A study in 2001 from the UK revealed an MRSA isolation rate of 30% from infected diabetic foot ulcers, which was almost double the proportion of MRSA-affected patients in a study done three years previously in same centre [24]. Another study reported that the MRSA isolation rate was 18% and that most patients had previous hospital admissions for the same wound. These MRSA infections were considered to have developed due to exposure to the contaminated hands of caregivers rather than to the overuse of antibiotics [25].

In contrast, the MRSA isolation rate was very low (5%) in our patients with diabetic foot infections. The low MRSA isolation rate in UMMC is probably attributable to implementation of strict guidelines for antibiotic prescribing by the Medical Advisory Committee in 2004 and adherence to infection control measures issued by the Infection Control Committee of UMMC. *Enterococcus* is often isolated in diabetic foot infections; a previous study reported that *Enterococcus faecalis* was cultured from 29% of 825 infected diabetic foot ulcers [26]. However, *Enterococcus* poses minimal threat to patients with diabetic foot infections in our facility.

Although rarely pure isolates, isolates of anaerobic organisms can be cultured in up to 80% of patients with severe foot infection [11,18]. The isolation rate of anaerobes was very low in this study, in concurrence with previous studies [17,25]. Three factors are important to the microbiological diagnosis of anaerobes: 1) collection of an appropriate clinical specimen such as blood, pus, pleural fluid or tracheal aspirate; 2) transportation of the specimen in anaerobic conditions to the microbiology laboratory without further delay; and 3) handling and incubation under anaerobic conditions. Low isolation rates could be due to improper sampling and unnecessary delay in transportation of samples to the microbiology laboratory, as well as previous treatment of patients with multiple antibiotics [17,25].

Management of diabetic foot infections usually requires combination therapy with surgical drainage and debridement or osseous resection. The choice of antibiotic therapy is influenced by the sensitivity of the encountered bacterial pathogens. Empirical antimicrobial therapy should be comprised of antibiotics to cover Gram-negative and Gram-positive microorganisms and anaerobes, if anaerobes are suspected in infected foot ulcers. Accurate microbiological working is imperative to the choice of appropriate antibiotic therapy for diabetic foot infections. Several drugs have been used to treat non-limb-threatening infections including beta-lactamase inhibitors, third-generation cephalosporins, aminoglycosides, ampicillin, penicillin, quinolones, piperacillin-tazobactam and linezolids [27]. Third-generation cephalosporins are not active against enterococci and anaerobes, while fluoroquionolones have low activity against streptococci and anaerobes [17].

The antibiogram results in this study suggest that pathogens remain sensitive to a number of agents. Imipenem was equally effective against Gram-negative bacilli and Gram-positive cocci. Vancomycin was found to be the most effective drug overall against Gram-positive organisms. These findings are consistent with a previous study [22]. No single antimicrobial agent can cover all of the possible organisms isolated from diabetic foot infections. Our findings illustrate that antimicrobial therapy needs to be selected based on actual culture findings and antimicrobial sensitivity patterns of isolates.

The selection of empiric antibiotic therapy depends on various factors such as infection severity, overall patient condition, medication allergies, previous antibiotic treatment, antibiotic activity, toxicity and excretion, and glycemic control. Proper identification of causative agents, appropriate antibiotic therapy and management of complications of diabetes foot infections remain essential to the achievement of a successful outcome.

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