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Full Length Research Paper

An assessment of bacteriological and empiric antibiotic regimens for diabetic foot ulcers

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Hundred diabetic patients were admitted with clinically infected foot ulcers and were studied during the period of 1st January 2010 to 30th June 2011. Pus samples of bacterial culture were collected from 30 patients admitted with diabetic foot infection. Antimicrobial susceptibility testing of aerobic isolates was performed by the standard disc diffusion method as recommended by National Committee for the Clinical Laboratory Standards. Micro broth dilution test was arranged for susceptibility of anaerobic organisms to metronidazole and amoxicillin/clavulanate. A vencomycine screen agar (6 µg/ ml) was used to detect vencomycine intermediate isolates of Staphylococci. Clinical grading and bacteriological study of 100 patients revealed, 69 (69.0%) patients had Gram-negative organisms and *Pseudomonas aeruginosa* was the most common, while 21 (21.0%) patients had Gram-positive organisms and Staphylococci was the most common. Infection with anaerobic was found in one patient (1.0%). Both Gram-positive and – negative organisms were seen in 9 patients (9.0%). *P. aeruginosa* and *Staphylococcus aureus* exhibited a high frequency of resistance to the antibiotics tested. All the isolates were uniformly susceptible to fosfomycine, levofloxacin, amikacin and vencomycine. In this study *P. aeruginosa, S. aureus, Escherichia coli, S. epidermidis* and *Proteus* were the most common causes of diabetic foot infections. The rate of antibiotic resistance was 61.86% among the isolates. All the isolates were uniformly susceptible to fosfomycine, levofloxacine, amikacin and vencomycine.

Key words: Diabetic foot Ulcer, *Staphylococcus aureus*, common pathogens, antibiotic resistance.

INTRODUCTION

Foot ulceration and infection are one of the leading causes of mortality and morbidity, especially in deve-loping countries. The number and cases of problems associated with diabetic foot infection (DFI) has drama-tically increased in the recent years. The main reason for this infection is the growing diabetic population in younger groups. Ulceration of the foot in diabetes is very common and frequently leads to the amputation of the leg (Sharma et al., 2006). The risk of the lower leg amputation is 17 to 41 times higher in the diabetics than in persons who do not have diabetes mellitus. Furthermore foot complications are the most frequent reason for hospitalization in patients with diabetes (Alavi et al., 2007).

In diabetic foot ulcer patients mortality is high and healed ulcers often recur. The pathogenesis of foot ulceration is complex, clinical presentation is variable, and its management requires early expert assessment. Interventions should be directed towards infections control, peripheral ischemia management and abnormal pressure loading management caused by peripheral neuropathy and limited joint mobility. Despite treatment, ulcers readily become chronic wounds. Diabetic foot ulcers have been neglected in health care research and planning, and clinical practice is often made on opinions than the scientific figures and facts. Furthermore, pathological processes are poorly understood and taught. Communication between many specialists involved is disjointed and is insensitive to the needs of the patients. Ischemia, neuropathy and infection in patients with

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diabetes mellitus combined to produce tissues, bones, and a modification of host factors, that is, hyperglycemia, and concomitant arterial insufficiency is all equally important for successful outcome. Initial therapy of diabetic foot infections is frequently empiric because reliable culture data is lacking. There is variability in prevalence of common bacterial pathogens isolated, as shown in different studies (Frykberg et al., 2000; Gadepali et al., 2006; Viswanathan et al., 2002). The choice of empirical antimicrobial therapy is influenced by various factors. These include the severity of the illness (Wagner grading), the most likely type of causative organism, and coexisting complications, such as under-lying osteomyelitis. Host factors, for example co-morbid conditions, good glycemic control, concomitant renal and cardiovascular diseases can affect the need for hospital admission and choice of specific agents of their dosing intervals (Sharma et al., 2006). In terms of affecting microorganisms and the likelihood of successful treatment with anti-microbial therapy, acute osteomyelitis in people with diabetes is essentially the same as in those without diabetes. Chronic osteomyelitis in patients with diabetes mellitus is most difficult infection to cure. Adequate surgical debridement, in addition to anti-microbial therapy, is necessary to cure chronic osteomyelitis (Viswanathan et al., 2002). The aim of this study was to evaluate relative frequency of bacterial isolates cultured from diabetic foot infections presenting at the Leicester General Hospital, Leicester and Department of Microbiology, University of Cambridge, to assess their *in vitro* susceptibility to the commonly used antibacterial agents.

RESEARCH DESIGN AND METHODS

Hundred diabetic patients were admitted with clinically infected foot ulcers and were studied during the period of 1st January 2010 to 30th June 2011. Ulcers were graded using the Wegner classification. Age, sex, type and duration of diabetes, glycemic control during the hospital stay, presence of retinopathy, nephropathy (creatinine > 150 µmol/l or presence of micro- or macro albuminuria), neuropathy (absence of perception of the Semmes-Weinstein monofilament at 2 of 10 standardized planter sites on either foot), peripheral vascular disease (ischemic symptoms and intermittent claudication or rest pain, with or without absence of pedal pulses), duration and size of ulcer, clinical outcome and duration of hospital stay were noted on each patient. Clinical assessment for signs of infection (swelling, exudates, surrounding cellulites, odor, tissue, necrosis, crepitation, and pyrexia) was made. Ulcer size was determined by multiplying the longest and widest diameter and expressed in centimeter squared. Osteomyelitis was diagnosed on suggestive changes in the radiographs. All cases were monitored until discharge from the hospital. Written consent was obtained from all subjects, and clearance was obtained from the institute's ethics committee.

Specimen collection

Culture specimens were obtained at the time of admission, after the surface of the wound had been washed vigorously by saline, and followed by debridement of superficial exudates. Specimens were obtained by scraping the ulcer base or deep portion of the wound with a sterile curette. The soft tissue specimens were promptly sent to the laboratory and processed for aerobic and anaerobic bacteria.

Antimicrobial susceptibility testing

Anti-microbial susceptibility testing of aerobic isolates was performed by the standard disc diffusion method as recommended by National Committee for clinical laboratory standards. All anaerobic isolates were tested for susceptibility to metronidazole and amoxicillin clavulanate combination (1.2 g i.v. every 8 h) was started at the time of admission. This was switched to oral administration (625 mg p.o. every 8 h). Metronidazole (500 mg i.v. every 8 h) was added to the drug regimen if cellulites or gangrene were also present. Antibiotics were adapted based on the results of anti-microbial studies to target the most likely pathogenic organisms.

Statistical methods

Quantitative variables were expressed as means ± SD while qualitative variables were expressed as percentages. A P-value of <0.05 was taken as significant. All statistical data was analyzed on Stat SPSS 10.

RESULTS

The general and clinical statistics of 100 patients with diabetic foot are shown in Table 1. The mean age of the subjects was 56±4 years. The mean duration of the diabetes was 21.8±5.7 years and nearly two third (66.33%) had a condition of > 19 years. Nearly 34 (56.66%) had diabetic foot lesions for >1 month before presentation at hospital. In general the patients were of old age and had been on oral hypoglycemic agents. The recommended glycemic control was not seen in any of the sixty patients. The majority of patients had type 2 diabetes (88.8%).

Males were predominant (76.66%) in the study subjects. All diabetic foots were classified and grouped according to Wagner grading group (Table 2). In the modern Wagner classification, foot lesions are divided into six groups based on the depth of the wound and extent of the tissue necrosis. It's a simplified system which only attaches modifiers for ischemia (A) and infection (B) shown in Table

2. It's recognized that grade 3 through 5 have some degree of infection within lesions. In my study all patients had ulcer graded 3-5 in Wagner classification. The details of patients according to Wagner classification are shown in Table 2.The diabetic foot lesions were gangrenous in 74 patients (74.00%) cases. Twenty six (26.00%) patients had neuropathy, 82 (82.00%) had peripheral vascular disease,

13 (13.00%) had nephropathy, 15 (15.00%) had retinopathy and 72 (72.00%) were hypertensive. Osteomyelitis was present in 17 (17.00%) subjects Table 1.

Table 1. Clinical data of 100 diabetic patients with infected foot ulcers (n=100).

Features	No. of patients
Age (Years)	Range (30-75years)
< 4o	32
>40	68
Sex	
Male	71
Female	29
Co-morbidities	
Hypertension	63
Diabetic neuropathy	32
IHD	15
Diabetic nephropathy	9
Diabetic retinopathy	11
PVD	37
Osteomyelitis	19
Time of duration of infection	
<10 days	11
<29 day	27
>30 days	62

Table 2. Wagnner s classification and number of patients according to Wegner's Grade (n=100).

Modified Wagner classification system		
Grade 0	No open Leision. May have deformity or cellulitis a)Ischemic b) Infected	1
Grade 1	Superficial Ulcers a)Ischemic b) Infected	7
Grade 2	Deep Ulcers to tendons/joint capsules a)Ischemic b) Infected	11
Grade 3	Deep Ulcers with abcess, Osteomyelitis, joint sepsis a)Ischemic b) Infected	21
Grade 4	Localized gangarene forefoot or heel a)Ischemic b) Infected	53
Grade 5	Gangarene of entire foot a)Ischemic b) Infected	7

Table 3. Bacteria isolated from diabetic foot infection of 100 patients (n=100).

Bacteria isolated	Number
S. Aureus	21
S. epidermidis	03
Streptococci	01
Pseudomonas aeruginosa	48
B. pyocyaneus	01
Proteus mirabilis	01
Proteus vulgaris	03
E. coli	07
Klebseilla	04
Citrobacter	06
Entrobacter Spp.	02
Morganella morgani	03

Table 4. Antimicrobial sensitivity/resistance of common Gram negative bacteria (n=100).

Antimicrobial agents	*Pseudomonas aeruginosa* 74 (n=58)		*E. coli* (n=12)		*Proteus* (n=4)	
	Sensitive (%)	Resistance (%)	Sensitive (%)	Resistance (%)	Sensitive (%)	Resistance (%)
Ampicilin	0 (0)	58(100)	0 (0)	12 (100)	0 (0)	4 (100)
Coamoxiclave	22 (37.93)	36 (62.06)	7(58.34)	5(41.66)	1 (25.0)	3 (75.0)
Ciprofloxacin	25 (43.11)	33(56.89)	8(66.66)	4 (33.34)	4 (100)	0 (0)
Ofloxacin	10(17.25)	48(82.75)	12 (100)	0 (0)	4 (100)	0 (0)
Cefotaxime	28(48.27)	30 (51.73)	8(66.66)	4 (33.34)	4 (100)	0 (0)
Gentamicin	26 (44.83)	32 (55.17)	6 (50)	6 (50)	3 (75.0)	1(25.0)
Amikacin	45(77.59)	13(22.41)	7(58.34)	5 (41.66)	2(50)	2 (50)
Ceftazidime	35(60.35)	23 (39.65)	7 (58.34)	5 (41.66)	0 (0)	4(100)
Cefoperazone	23 (39.65)	35(60.35)	5 (41.66)	7 (58.34)	3 (75.0)	1 (25.0)
Cefazolin	27 (46.55)	31(53.45)	6 (50)	6 (50)	2(50)	2(50)
Fosfomycin	37 (63.79)	21(36.21)	0 (0)	12(100)	3(75.0)	1 (25.0)
Cefuroxime	16 (27.59)	42 (72.41)	4(33.34)	8(66.66)	4(100)	0 (0)
Levofloxacin	49(84.48)	9 (15.52)	5(41.66)	7(58.34)	4(100)	0 (0)
Doxycycline	9(15.52)	-	-	-	-	-

Seventy four (74.00%) patients had Gram-negative organisms with *P. aeruginosa* being the most common. While Gram-positive were found in 26 (26.00%) with staphylococci being the most common organism. Infec-tion with anaerobes was found in only one patient (1.00%). Both Gram-positive and –negative were seen in 14 patients (14.00%). The profile of the isolated organisms is detailed in Table 3.

Pseudomonas aeruginosa exhibited a high frequency of resistance to the antibiotics tested. High levels of resistance to ampicillin, co-amoxiclav, ciprofloxacin, ofloxacin, cefotaxime, cefoparazone, cefazoline, cefuroxime were noted. All the isolates were uniformly susceptible to fosfomycine, levofloxine, gentamycin and amikacin. *B. pyocyneus* (*Pseudomonas pyocyneus*) was found in only one patient and it was sensitive only to fosfomycine and doxycycline. *B. pyocyneus* showed resistance to aminoglycosides. The results of susceptibility studies for Gram-negative organism are shown in Table 4. While the results of susceptibility studies for Gram-positive organism are shown in Table 5. *S. aureus* exhibited a high frequency of resistance to antibiotics tested. High levels of resistance to ampicillin, ciprofloxacin, ofloxacin and cafazoline was noted. However, no high level aminoglycosides resistance was observed. All the isolates were uniformly susceptible to fosfomycine, levofloxacin and vancomycin.

DISCUSSION

This study represents the clinical and microbiological

Table 5. Antimicrobial sensitivity/resistance of common Gram positive bacteria (n=100).

Antimicrobial Agents	*Staph epidermidis* (n=3)		*Streptococci* (n=2)		*S. aureus* (n=21)	
	Sensitive (%)	Resistance (%)	Sensitive (%)	Resistance (%)	Sensitive (%)	Resistance (%)
Ampicilin	0 (0)	3(100)	2(100)	0(0)	0 (0)	21 (100)
Coamoxiclave	3 (100)	0 (0)	2(100)	03(0)	12 (57.14)	9(42.86)
Ciprofloxacin	3 (100)	0(0)	2(100)	0 (0)	15 (71.43)	6 (28.57)
Ofloxacin	3(100)	0(0)	2(100)	0 (0)	18 (85.72)	3(14.28)
Cefotaxime	1(33.34)	2 (66.66)	2(100)	0 (0)	15 (71.43)	6(28.57)
Gentamicin	2(66.66)	1 (33.34)	2 (100)	0 (0)	14 (66.66)	7(33.34)
Amikacin	2(66.66)	1(33.34)	2(100)	0 (0)	15(71.43)	6 (28.57)
Ceftazidime	1(33.34)	2 (66.66)	2(100)	0 (0)	10 (47.62)	11(52.38)
Cefoperazone	2(66.66)	1(33.34)	2(100)	0 (0)	13 (61.91)	8 (38.09)
Cefazolin	2 (66.66)	1 (33.34)	2 (100)	0(0)	9(42.85)	12(57.14)
Fosfomycin	2 (66.66)	1(33.34)	2 (100)	0(0)	19(90.47)	2(9.53)
Cefuroxime	2 (66.66)	1 (33.34)	2(100)	0 (0)	17(80.95)	4(19.05)
Levofloxacin	3 (0)	0 (33.34)	2(100)	0(0)	19(90.47)	2 (9.53)
Vancomycin	3(100)	0 (0)	2(100)	0 (0)	21(100)	0 (0)

assessment of infected diabetic foot ulcers in hospitalized patients. Foot ulcers are a significant complication of diabetes and often precede lower extremity amputation. The most frequent underlying etiologies are neuropathy, trauma, deformity, high plantar pressures and peripheral arterial disease (Frykberg et al., 2004). Although infection is rarely implicated in the etiology of diabetic foot ulcer, the ulcers are susceptible to infection once the wound is present.

Most of the patients were having grade 3 through 5 foot ulcers according to Wagner grade, and grade 4 being the most common, which is similar to the study conducted (Sharma et al., 2006). While foot infections in the persons with diabetes are initially treated empirically, therapy directed at known causative organisms may improve the outcome. Many studies have reported on the bacteriology of diabetic foot infections (DFIs) over the past 25 years but the result has varied and often has contradictory. A number of studies have found that *S. aureus* is the main causative pathogen, but other investigations have reported a predominance of Gram-negative aerobes, which is also evident in our studies (Goldstein et al., 2007). The ratio of Gram- positive aerobes to Gram-negative aerobes was 1:2.75 which is in reversal to the reported (Tentolouris et al., 1999). The difference in the age, sex, ulcer grades, study- settings etc. in our study population and those earlier studies might be a reason of difference.

We observed a recovery of multidrug resistance *P. aeruginosa*, which is similar as reported earlier (Gadepali et al., 2006). This raises concern as *P. aeruginosa* is an aggressive Gram-negative *Bacillus*. *S. aureus* was the most frequent Gram-positive pathogen, found in nearly 20% of infections. The majority of studies also noted a high frequency of these microorganisms in foot infections of diabetic patients (Gadepali et al., 2006; Viswanathan et al., 2002). Compared with earlier reports, we recovered fewer a species. Our patients had chronic draining wounds, and 73 (73.00%) cases had gangrene associated with their infections. This may be an indication of anaerobic species among non-threatening lower extremity infections, which is also reported earlier (Lipsky et al., 2000). *Clostridium* species were not isolated. The present study confirms that multidrug resistant organisms (MDRO) infection is extremely common in hospitalized patients with diabetic foot ulcers. This is in accordance with the report of Hertamann et al. (2004). Almost 67 (67.00%) of the patients were infected with MDROs. The high rates of antibiotic resistance observed in the present study may be due to the fact that ours is a tertiary care hospital with widespread usage of broad-spectrum antibiotics leading to selective survival advantage of pathogens. These findings are important, especially for patient management and the development of antibiotic treatment policies. The increasing prevalence of MDROs is disconcerting because infection with these organisms limits the choice of antibiotic treatment and may lead to worse outcome.

We could not elicit the previous hospitalization details for the same wound in our study subjects. This infor-mation could have helped in explaining the reasons for the high prevalence of MDROs in patients. Results indicate that higher mortality rates were reported in patients with diabetic foot syndrome whose blood glucose level were poorly controlled (Ikem et al., 2002). Thus, MDROs might lead to higher mortality among diabetic foot infections, which needs to be investigated. Though MDRO infections have been reported to increase hospital stay and cost (Bentkover et al., 1999), we found similar duration of hospital stay in both MDROs and non-MDROs.

Table 6. Selected empiric antibiotic regimens for diabetic foot ulcers.

Scenario	Drug of choice	Alternatives*
Mild to moderate, localized cellulitis (outpatient)	Dicloxacillin (Pathocil)	Cephalexin (Keflex); amoxicillin/clavulanate potassium (Augmentin); oral clindamycin (Cleocin)
Moderate to severe cellulitis (inpatient)	Nafcillin (Unipen) or oxacillin	Cefazolin (Ancef); ampicillin/sulbactam (Unasyn); clindamycin IV; vancomycin (Vancocin)
Moderate to severe cellulitis with ischemia or significant local necrosis	Ampicillin/sulbactam	Ticarcillin/clavulanate (Timentin); piperacillin/tazobactam (Zosyn); clindamycin plus ciprofloxacin (Cipro); ceftazidime (Fortaz) or cefepime (Maxipime) or cefotaxime (Claforan) or ceftriaxone (Rocephin) plus metronidazole (Flagyl); cefazolin (for *Staphylococcus aureus*); nafcillin (Unipen); oxacillin
Life- or limb-threatening infection	Ticarcillin/clavulanate or piperacillin/tazobactam, with or without an aminoglycoside	Clindamycin plus ciprofloxacin or tobramycin (Nebcin); clindamycin plus ceftazidime or cefepime or cefotaxime or ceftriaxone; imipenem/cilastin (Primaxin) or meropenem (Merrem); vancomycin plus aztreonam (Azactam) plus metronidazole; vancomycin plus cefepime; ceftazidime plus metronidazole

IV = intravenous: *— Persons with serious beta-lac tam allergy may be given alternative agents. Antibiotic coverage should subsequently be tailored according to the clinical response of the patient, culture results, and sensitivity testing. Surgical drainage, deep debridement, or local partial foot amputations are necessary adjuncts to antibiotic therapy of infections that are deep or limb-threatening (Frykberg et al., 2000) (Reference—Evidence level B: uncontrolled study).

The duration of hospital stay may also depend on the management policy of the hospital. In our hospital, patients are discharged once the healing begins and are advised to come for follow up at the outpatient clinic every week. Empiric antibiotic regimen for diabetic foot ulcers is given as in Table 6.

Conclusion

In conclusion *P. aeruginosa, S.aureus, E. coli, S. epidermidis* and *Proteus* were the most common causes of diabetic foot infections in our study. The rate of antibiotic resistance was 67% among the isolates. All the isolates were uniformly susceptible to fosfomycine, levofloxacin, amikacin and vancomycin.

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