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Research Article

Microbiological Profile and Antibiotic Sensitivity Pattern of Bacteria in Diabetic Foot Ulcers in a Tertiary Care Hospital

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A B S T R A C T

Introduction: Diabetic foot is any foot pathology due to diabetes or sequelae of diabetes mellitus. This study was conducted to identify the common microorganisms isolated from diabetic foot and to analyse the antibiotic susceptibility pattern of bacteria isolated from diabetic foot.

Materials and Method: The study was a hospital based cross-sectional study where 146 foot ulcer samples (who had type 2 diabetes) were analysed. Swabs were collected from the edge and margins of ulcers, and organisms were identified by gram staining culture and biochemical reactions.

Result: Out of 146 patients, 69 specimens showed growth of organisms. Total 84 aerobic organisms were isolated and out of them, 64 cases showed bacterial growth, in which 84 bacteria were isolated, which represented an average of 1.28 organisms per case. Among these organisms, 62 gram-negative and 22 gram-positive organisms were isolated. *E. coli* was the most common gram-negative isolate (23.81%), followed by *Pseudomonas aeruginosa* (21.4%), and *Klebsiella pneumonia* (8.33%), while among gram-positive bacteria, *S. aureus* was the most common isolate (22.6%).

Conclusion: Incidence of growth was 47.2% in which *E. coli* (23.8%) was the most common isolate. Gram-negative bacteria were more common than gram-positive bacteria. Diabetic foot infections are polymicrobial in nature.

Keywords: Diabetic Foot, Gram-Negative, *E. coli, S. aureus*

Introduction

Diabetes mellitus is a rapidly expanding modern epidemic that currently affects 422 million people worldwide.[1] In 2000, Wild et al. predicted the global burden of diabetes to double globally from 171 million (in 2000) to 366 million (in 2030) with a maximum rise expected in India.[2] Besides mortality, diabetes mellitus also carries significant morbidity with it

in the form of cardiovascular complications, neuropathy, nephropathy, recurrent infections, obstetric complications, and foot ulcers.[2]

Diabetic foot is any foot pathology due to diabetes or sequelae of diabetes mellitus. Diabetic foot syndrome encompasses infections, ulcers and neuropathic osteoarthropathy. Global diabetic foot ulcer prevalence is 6.3%.It is higher in type 2 diabetes mellitus (6.4%) as compared to type 1 diabetes mellitus (5.5%).[3] The importance of diabetic foot ulcer can be understood from the fact that nearly a quarter (24.4%) of total health expenditure amongst the diabetic population was related to foot complication.[4] Diabetic foot accounts for significant morbidity in the form of skin changes, loss of sensation in feet, intermittent claudication, and development of calluses in feet followed by ulcer formation which may get infected and culminate in the need for amputation as the only viable measure of treatment. Diabetic patients with leg and foot ulcers also have a lower 5 year survival (43%) as compared to non-diabetic ulcerated subjects (56%) and general population controls (68%).[5]

Like any other infection, eventual treatment lies in administering the antibiotic based on an isolated organism and culture sensitivity. As sensitivity pattern is available only the 48-72 hours of inoculation and is highly variable amongst various institutes and even amongst patients admitted under ICU and general wards of the same hospital, the need for administering a common and effective antibiotic at the earliest is of paramount importance to accelerate healing and reducing morbidity. The present study was undertaken to identify the common microorganisms isolated from diabetic foot, analyse the antibiotic susceptibility pattern of bacteria, and suggest an effective empirical antibiotic therapy for diabetic foot infected with various bacteria in the medical wards of our hospital.

Materials and Methods

Study Design, Settings and Participants

It was a hospital based cross-sectional study conducted over a period of 18 months from November 2017 to April 2019 in the Department of Medicine and Microbiology of a tertiary care teaching hospital in New Delhi, India. 146 newly diagnosed or known diabetic patients aged 40 years and more and having diabetic foot ulcer (Wagner-Meggitt grade 2 or higher) were selected for the study. Patients with amputated feet or with other ulcers like traumatic ulcer, scar ulcer, venous ulcers, and malignant ulcers were excluded from the study.

Wagner- Meggitt Grading for Diabetic Foot Ulcers.

- Grade 0: Intact skin
- Grade 1: Superficial ulcer
- Grade 2: Deep ulcer extending to bone, tendon, or joint
- Grade 3: Deep ulcer with abscess or osteomyelitis
- Grade 4: Forefoot gangrene
- Grade 5: Whole foot gangrene

Data Collection

After taking written informed consent, patients were subjected to detailed history and physical examination with special emphasis on risk factors for diabetic foot. Haematological investigations like CBC, KFT, and lipid profile were done for all the subjects. Apart from haematological investigations, an x-ray of the affected limb including the site of ulcer, and a pus swab and/ or tissue biopsy were also done.

These patients' diabetic foot ulcers were washed with normal saline/ distilled water and necrotic materials (if any) were debrided. After that, a tissue biopsy/ pus swab was taken from the junction of healthy and unhealthy tissue. This sample was collected at the time of admission before starting antibiotic therapy. Pus swab was immediately sent to microbiology lab where gram staining was performed on the sample. After gram staining, the organisms were identified as per standard techniques mentioned in Mackie McCartney literature.[6]

Tissue specimens obtained by biopsy were transported to the microbiology lab in normal saline. The samples obtained from diabetic foot ulcer were inoculated on Blood agar and MacConkey agar. These samples were incubated at 37°C for 16-18 hours after which the growth obtained on culture plates were subjected to antibiotic sensitivity testing.

Antibiotic sensitivity testing was done by the Kirby Bauer disc diffusion method as per CLSI guidelines.[7] The following antibiotics were used for culture sensitivity testing:

- Amikacin
- Gentamicin
- Linezolid
- Piperacillin-tazobactam
- Meropenem
- Ciprofloxacin
- Teicoplanin
- Vancomycin
- Ceftazidime
- Amoxicillin-Clavulanate
- Clindamycin
- Polymyxin B/ Colistin
- Tigecycline

An attempt was made for isolation and identification of anaerobic microbes. Samples for anaerobic culture (pus/ swab/ tissue) were collected and immediately transported to the microbiology lab in thioglycolate broth. The samples were kept in an incubator for enrichment for 24 hours. After enrichment, they were inoculated on Brain Heart Infusion (BHI) agar and Blood agar, and were kept for anaerobic culture. *Pseudomonas* was used as control

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in anaerobic culture. Anaerobic media was created in a standard anaerobic jar using a gas-pack. The culture was read after 48 hours. The patients included in this study were treated empirically as per standard guidelines. Once culture sensitivity reports were available, the antibiotics were changed according to the antibiogram.

Statistical Analysis

Data were analysed and statistically evaluated using SPSS software, version 17 (Chicago II, USA). Quantitative data were expressed in mean and standard deviation, while qualitative data were expressed in percentage. Statistical differences between the proportions were tested by chi-square test or Fisher's exact test. 'p' value less than 0.05 was considered statistically significant.

Ethical Issues

The study was approved by the Institutional Ethical Committee. All the participants were explained the purpose of the study. Confidentiality was assured to them and informed written consent was obtained.

Result

The study population comprised 107 males and 39 females. The mean age of study subjects was 54.61±9.98 years while the mean BMI was 22.75±2.99 kg/m^2. 115 (78.8%) patients were taking OHA as treatment whereas 14 (9.6%) were on insulin. 17 (11.6%) patients were taking no treatment for diabetes. The mean duration of diabetes was 166.11 ± 94.05 months. 43% of the subjects were smokers and 27% were tobacco chewers. 58.9% of the patients had concomitant hypertension and 52.1% of the patients had involvement of right foot. 70 (47.9%) patients had active discharge at the time of presentation and 48.6% had neurological involvement.

Out of 146 patients, 69 (47.2%) patients showed microbiological growth, and out of them, 64 cases showed bacterial growth in which 84 bacteria were isolated, which represents an average of 1.28 organisms per case.

Majority of the infections were caused by gram-negative bacteria which constituted 73.81% of the infections, and gram-positive bacteria accounted for 26.19% (Table 1). Among gram-negative bacteria, *E. coli* was the most common isolate accounting for 23.81% of the infections, followed by *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Proteus mirabilis* constituting 21.4%, 8.33%, and 7.14% respectively, while among gram-positive bacteria, *S. aureus* was the most common isolate (22.6%).

Table 2, shows the result of the test for susceptibility to the commonly used antibiotics. Methicillin-Resistant *S. Aureus* (MRSA) showed 100% sensitivity to vancomycin, teicoplanin, and linezolid. The sensitivity towards tetracycline, clindamycin, clotrimazole, gentamicin, and erythromycin were 75%, 50%, 40%, 20%, and 11.1% respectively. *E. coli* showed 100% sensitivity to colistin, polymyxin B and netilmicin. The sensitivity of *E. coli* towards amikacin, gentamicin, and meropenem, were 66.67%, 64.7%, and 63.6% respectively. The sensitivity towards tobramycin, chloramphenicol, and tigecycline was 50%. The sensitivity of *E. coli* to piperacillin-tazobactam, imipenem, and ciprofloxacin were 35.7%, 33.3%, and 14.3% respectively.

Table 1.Microorganisms Isolated from Diabetic Foot Ulcers

Total Microbes Isolated (*n=91*)		
Bacteria (*n=84*)	**Number (n)**	**Percentage (%)**
Gram-positive Bacteria	22	26.19
Methicillin-resistant *S. aureus*	10	11.9
Methicillin-sensitive *S. aureus*	9	10.71
Beta-haemolytic *Streptococcus*	1	1.19
Enterococcus	2	2.38
Gram-negative Bacteria	62	73.81
E. Coli	20	23.8
P. Aeruginosa	18	21.4
K. (pneumoniae)	7	8.33
K. Oxytoca	2	2.38
P. Mirabilis	6	7.14
P. vulgaris	2	2.38
A. baumannii	5	5.95
Citrobacter	2	2.38
Fungi (*n= 7*)		
Candida albicans	3	3.2
Non-albicans *Candida*	4	4.3
Anaerobes (*n=0*)	0	0

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Table 2.Data regarding Sensitivity of Microorganisms to Various Antibiotics

	Methicillin-Resistant Staph aureus (n=10)	Staphylococcus aureus (n=9)	Pseudomonas aeruginosa (n=8)	Acinetobacter baumannii (n=5)	Enterococcus (n=2)	Escherichia coli (n=20)	Proteus mirabilis (n=6)	Proteus vulgaris (n=2)	Klebsiella pneumoniae (n=7)	Klebsiella oxytoca (n=2)	Citrobacter (n=2)	Beta-haemolytic Streptococci (n=1)
Clotrimazole	4 (40%)	5 (83.3%)	0	0	-	0	0	-	2 (40%)	1 (100%)	0	-
Vancomycin	7 (100%)	6 (100%)	-	-	2 (100%)	-	-	-	-	-	-	-
Teicoplanin	2 (100%)	1 (50%)	-	0	0	0	-	-	-	-	-	-
Gentamicin	1 (20%)	3 (100%)	7 (38.9%)	0	0	11 (64.7%)	0	1 (50%)	6 (75%)	2 (100%)	0	-
Amikacin	-	1 (100%)	6 (46.1%)	0	-	10 (66.7%)	1 (25%)	2 (100%)	7 (100%)	2 (100%)	1 (50%)	-
Netilmicin	-	-	2 (33.3%)	1 (100%)	-	3 (100%)	0	-	1 (50%)	-	1 (50%)	-
Tetracycline	3 (75%)	3 (100%)	-	-	0	-	-	-	-	-	-	-
Tigecycline	-	-	-	-	-	1 (50%)	-	-	1 (100%)	-	-	-
Erythromycin	1 (11.1%)	4 (66.7%)	-	-	-	-	-	-	-	-	-	0
Clindamycin	5 (50%)	4 (80%)	-	1 (100%)	-	-	-	-	-	-	-	0
Cefotaxime	0	-	0	0	-	0	0	1 (50%)	2 (33.3%)	1 (100%)	0	0
Ciprofloxacin	0	1 (50%)	3 (37.5%)	0	-	1 (14.3%)	0	-	2 (66.7%)	1 (100%)	-	-

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Cefoxitin	0	6 (100%)	-	-	-	-	-	-	-	-	-	-
Meropenem	-	-	9 (75%)	0	-	7 (63.6%)	2 (66.7%)	1 (100%)	6 (100%)	2 (100%)	1 (100%)	-
Imipenem	-	-	1 (50%)	0	-	1 (33.3%)	-	-	-	-	-	-
Ertapenem	-	-	-	-	-	-	-	-	-	-	0	-
Piperacillin-Tazobactam	0	-	7 (58.3%)	1 (33.3%)	-	5 (35.7%)	2 (50%)	1 (50%)	6 (85.7%)	2 (100%)	1 (100%)	-
Aztreonam	-	-	8 (57.1%)	0	-	1 (6.25%)	2 (66.7%)	1 (50%)	2 (33.3%)	1 (50%)	1 (33.3%)	-
Tobramycin	-	-	7 (50%)	0	-	2 (50%)	-	-	-	-	-	-
Ampicillin-Sulbactam	-	1 (100%)	-	0	-	-	-	-	-	-	-	-
Colistin	-	-	3 (100%)	1 (100%)	-	1 (100%)	-	-	-	-	-	-
Polymyxin-B	-	-	5 (100%)	2 (100%)	-	8 (100%)	-	-	2 (100%)	-	2 (100%)	-
Ampicillin	0	-	-	-	2 (100%)	0	-	-	-	-	-	-
Linezolid	6 (100%)	4(40%)	-	-	2 (100%)	-	-	-	-	-	-	-
Ceftazidime	-	-	8 (50%)	-	-	0	1 (33.3%)	-	2 (40%)	-	-	-
Chloramphenicol	-	-	-	0	1 (50%)	1 (50%)	0	-	-	-	0	-
Carbapenem	-	-	0	-	-	-	-	-	-	-	-	-
Levofloxacin	0	-	-	-	-	-	0	-	-	-	-	-

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Discussion

Diabetic foot ulcer is a common complication requiring hospitalization among diabetic patients. It is the most common cause of non-traumatic lower-extremity amputations.[8] In this study, we tried to evaluate the degree of this problem in our institution.

In our study, males outnumbered females by a ratio of 2.74:1. A similar ratio of males outnumbering females was also reported by Sekhar M et al.[9] with a male:female ratio of 2.5:1. Al Benwan et al. reported a ratio of 2.8:1 in a study from Kuwait.[10] Similarly, Jain et al. have reported a ratio of 2.1:1 in a study conducted in Gujarat.[8] The average age of patients enrolled in our study was 54.61± 9.98 years. As both macrovascular and microvascular complications such as neuropathy and vasculopathy in diabetes develop after several years of onset of type 2 DM, it was not surprising that our patients were in the middle age group.

Our study yielded bacterial growth in 47.25% of the samples, and 43.83% of the samples yielded a positive aerobic culture. This value was lower than that of various similar studies (90%).[11] A possible explanation for the same could be that they employed molecular PCR techniques for the isolation of bacteria which is more sensitive than the conventional culture techniques we used. Eurodiale study was a large multicentric study that used conventional culture based techniques to isolate bacteria from diabetic foot.[12] They reported a culture positivity of 58%. An explanation for the low yield on culture could be that our hospital is a tertiary care setup where most patients were referred cases and most of them received some amount of primary care before visiting our hospital. Since they were already exposed to antibiotics before visiting our hospital, a negative culture report was not very surprising.

In the present study, 84 bacteria were isolated from 64 cases which represented an average of 1.28 organisms per case, and majority of the organisms were gram-negative (73.8%). This was in accordance with most of the studies carried out worldwide that had also reported a greater prevalence of gram-negative organisms infecting diabetic foot ulcers.[13] Among gram-negative organisms, the most common organisms we isolated were *E. coli* (23.8%) and *P. aeruginosa* (21.4%) which was similar to the observations made by Murli TS et al.[14] Similar reports were also published by Bansal et al.[13] and Ramakant et al.[15]

A higher prevalence of gram-negative organisms in diabetic foot ulcer is a well-known fact. Ulcers which are deep, chronically infected, or previously treated with antibiotics are more likely to be co-infected with *Enterococci*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and anaerobes. Microbes infecting diabetic foot also vary with changing geographical location and climate that is exemplified by gram-negative organisms being the predominant culture isolate in tropical areas like Africa and Asia.[16]

Amongst the gram-positive organisms, *S. aureus* (22.61%) was the most common organism isolated, followed by *Enterococcus* (2.38%) and *Beta haemolytic streptococci* 1.19%. This finding was also in agreement with multiple studies conducted across India. Bansal E et al. also reported that *S. aureus* (19%) was the most common gram-positive organism isolated in their study.[13] Murali TS et al. also isolated microbes from diabetic foot and they too found that *S. aureus* was the most common gram-positive organism.[14] In a similar study conducted by Chavan SK et al., it was found that *S. aureus* was the commonest gram-positive organism isolated.[17]

In our study, MSSA strains were susceptible to piperacillin-tazobactam, meropenem, amoxicillin-clavulanate, clindamycin, and levofloxacin.[18] Endimiani et al.conducted a study to describe the emergence of linezolid-resistant *S. aureus* and to look into the reasons for increasing resistance.[19] MRSA has been considered as the pathogen of concern in diabetic foot ulcer for a very long time. Recently, the emergence of community-acquired MRSA has been recorded.[18] In our study, MRSA contributed to 11.9% of total isolates. Another study from France in 2004 has reported a much higher isolation rate (18%) of MRSA.[20]

Enterococcus showed 100% sensitivity to vancomycin, ampicillin and linezolid. Sensitivity to chloramphenicol was 50%. All the *Enterococci* isolated in our study were resistant to gentamicin. Similar results showing 100% sensitivity to vancomycin and linezolid along with lower sensitivity to gentamicin have also been reported by Shettigar K et al.[21]

E. coli has emerged as the major (23.8%) gram-negative pathogen in our study followed by *Pseudomonas aeruginosa* (21.4%). *Pseudomonas aeruginosa* is one of the prevalent organisms in diabetic foot infections. In various studies conducted across northern India, it has emerged as the most prevalent microorganism isolated from diabetic foot infections.[13,15] However, there have been studies like the one by Tiwari S et al.which reported *E. coli* as the most common gram-negative organism.[22] A study with a larger sample size is desirable to get a better estimate of the most common gram-negative organism infecting diabetic foot.

All the strains of *E. coli* isolated from our study were sensitive to colistin, polymyxin B and netilmicin. Sensitivity to piperacillin-tazobactam was 35.7%. This was in contrast with the findings of Shailesh K Shahi et al.[23] who analysed antibiotic sensitivity of *E. coli* isolated from diabetic foot and reported 100% sensitivity to piperacillin-tazobactam. This may be explained by the development of resistance. Possible reasons for the resistance of *E. coli* to piperacillin-

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tazobactam could be the presence of AmpC producers, possible TEM-1 hyperproducers, and multiple β-lactamases in individual organisms of a given isolate.[24]

We also attempted culturing anaerobic microorganisms.[26] samples from diabetic foot were also simultaneously tested for anaerobic growth. However, none of the samples yielded positive growth. Literature has revealed that anaerobes are implicated in a minority (<15%) of diabetic foot ulcer infections.[10]

Fungal infection was observed in 4.8% of the patients. In this study, we isolated three *C. albicans* and four non-albicans *Candida* from diabetic foot ulcers. A similar study conducted in southern Iran by M. Anvarinejad et al. reported a 6% fungal prevalence in diabetic foot ulcers.[25] Some studies noted a higher prevalence of *Candida spp*, whereas others reported opportunistic mould species as the causative agents of fungal infections in diabetic foot. [26,27]

An alarming observation was the resistance of multiple bacteria to piperacillin-tazobactam. The sensitivity of various bacteria was 58.3% for *Pseudomonas*, 33.3% for *Acinetobacter*, 35.7% for *E. coli,* and 50% for *Proteus*. The following mechanisms had been proposed for resistance to piperacillin-tazobactam: (i) presence of AmpC producers, (ii) TEM-1 hyperproducers, and (iii) multiple β-lactamases in individual organisms of a given isolate.[24]

In light of the globally increasing prevalence of drug-resistant organisms, the need for rational use of antibiotics is essential.[20] In order to minimize the emergence of antibiotic resistance during therapy, it is important to try and avoid antibiotics that encourage transfer of resistance genes, to avoid selection of resistant variants from susceptible pathogens and to avoid ablation of antibiotic susceptible normal flora. Careful antimicrobial sensitivity testing and formulation of guidelines that decide empirical antibiotic treatment in diabetic foot are highly desirable. In view of the findings in our study, we suggest using vancomycin for gram-positive isolates and meropenem + colistin/ polymyxin B for gram-negative isolates. The choice of antibiotics can later be modified as per culture and sensitivity reports.

Limitation

Anaerobic flora of diabetic foot could not be characterized as all the samples could not be put for anaerobic cultures due to limited availability of resources. We employed conventional culture methods to isolate microbes from samples. A study with newer techniques like 16s RNA sequencing is desirable for a better yield and characterization of microorganisms. Lastly, fungi isolated from cultures were not put for antimicrobial sensitivity testing owing to lack of resources.

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Conflict of Interest: None

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