Original Article

A study on diabetic foot ulcers in Central rural India to formulate empiric antimicrobial therapy

Amit Kumar Singh[1], Meenakshi Yeola[1], Namrata Singh[2], Smita Damke[3]

Departments of [1]Surgery, [2]Radiodiagnosis and [3]Microbiology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed University) Sawangi (Meghe), Wardha, Maharashtra, India

Abstract

Aim: This study was carried out on patients with diabetic foot ulcer (DFU) to assess the clinical characteristics, spectrum of microbial flora, antibiotic sensitivity, and devise an empiric antimicrobial therapy. **Material Methods:** Clinical data and tissue samples were collected from 105 diabetic foot ulcer patients between December 2018 and November 2019. The collected samples were processed as per Clinical and Laboratory Standards Institute guidelines and clinical and microbiological data was analyzed. **Results:** In this study of 105 patients, DFU was most common in males in 5th and 6th decade of life. Majority of patients had poor glycemic control and neuropathy. Of 110 bacterial isolates obtained from 97 samples, 73.7% were Gram-negative bacteria, and 27.3% were Gram-positive. Most of samples (48.6%) showed growth of single bacteria, growth of two bacteria and polymicrobial growth was seen in 28.6% and 15.2% of tissue samples respectively of which. *Pseudomonas* was predominant isolate (27.3%) sensitive to imipenem (90%), amikacin (86.6%), gentamicin (83.3%), and cefotaxime (80%) followed by *Staphylococcus aureus* (19.1%) sensitive to amikacin and gentamicin (100%), and ofloxacin (90%). *Pseudomonas, E. coli, Proteus* and *Klebsiella* were highly resistant to ampicillin and amoxicillin-clavulanic acid. **Conclusion:** This study showed DFU are common in 5th and 6th decades of life. Gram-negative bacteria are predominant infective organism. Most of both Gram-negative and Gram-positive bacteria are resistant to variable degrees to commonly used antibiotics and sensitive to aminoglycosides. Amikacin and gentamicin can be used as empiric antibiotics for treatment of DFU infections.

Keywords: Antibiotic sensitivity, Central India, diabetic foot ulcer, empiric treatment, infection

Introduction

Diabetes in India with more than 62 million diabetic population, is rapidly gaining status of a potential epidemic.[1] Prevalence of diabetes in India differs according to region varying from 5.3% in central India to 13.6% in Northern India.[2] Since diabetes is not a notifiable condition its actual burden is unknown and there may be underestimation of burden of diabetes in India.[3] Foot ulceration is one of the most common complication of diabetes, estimated affecting 15% of diabetic patients during their lifetime. Prevalence of DFU ranges from 4% to 10% and most common cause of morbidity and mortality in (DFU) is infections, which are seen in 40%–80% of the cases.[4] Initially antimicrobials are selected empirically for treatment of DFU infections. With declining number of novel antibiotics being developed and impetuous use of available antibiotics, antibiotic resistance has become a universal issue in healthcare institutions.[5] Diabetic nephropathy which occurs in approximately third of diabetic patients and increasing incidence of multi drug resistant infections in DFU compounds the challenge faced by clinicians in treating these patients.[6]

Address for correspondence: Dr. Amit Kumar Singh, Department of Surgery, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences (Deemed University) Sawangi (Meghe), Wardha - 442 107, Maharashtra, India.
E-mail: endosurgamit@gmail.com

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This study was aimed to determine the clinical and microbiological profile of DFU patients, establish antibiotic susceptibility pattern of microbes in DFU patients and formulate empiric antibiotic treatment. As there are no such studies from this region which have formulated an empiric therapy for diabetic foot infections, knowledge of antibiotic sensitivity pattern would help make empiric antibiotic treatment protocol for this region and help primary care physicians as well as specialists in initiating more effective empiric antibiotic therapy which in turn may reduce antibiotic resistance and cost of treatment to patients.

Material and Methods

This prospective and observational study was conducted at a tertiary care teaching hospital where 105 patients of DFU attending diabetic foot clinic were recruited from December 2018 to November 2019. The study adhered to the Declaration of Helsinki guidelines and was duly approved by the Institutional Ethics Committee. The research was approved by Institutional Ethical committee on 01Oct 2018. Written informed consent was obtained from all study participants. According to the International Working Group on the Diabetic Foot (IWGDF), a diabetic foot ulcer (DFU) is a full-thickness wound penetrating through the dermis located below the ankle in a diabetic patient.[7] Based on Meggitt Wagner Classification System, Foot ulcers were categorized into six grades (grade 0–grade 5).[8] as shown in Table 1.

Inclusion criteria

Diagnosed DFU patients attending diabetic foot clinic who were consenting to participate in study.

Exclusion criteria

Wagener grade 0 and grade 1 DFU patients were excluded.

After due consent the basic demographic data was collected from all patients and entered in excel sheet. Detailed history was obtained from each study patient regarding their present complaint, duration of diabetes, personal habits of smoking, alcohol intake, and diabetic foot self-care practices. Sensory neuropathy was assessed by Semmes Weinstein monofilament test. The sensation of 5.07 Semmes Weinstein monofilament was examined on the sole of foot. Monofilament was applied at a point on the sole of foot perpendicular to the skin and pressure was applied just enough to bend it when it applies a pressure equal to 10 grams. The inability of the patient to sense the monofilament at 1 or more sites was recorded as abnormal.[9] Results of blood investigations were recorded in excel sheet. Nephropathy was considered positive when serum creatinine level was 1.5 mg/dL or more. Fasting blood glucose more than or equal to 126 and glycosylated hemoglobin (HbA1c) equal or more than 7 was considered abnormal, respectively. Tissue culture specimen collection was done in minor operation room, after cleaning the wound and washing vigorously with saline followed by debridement of superficial exudate and slough if any to avoid picking up superficial colonization flora. Specimens were collected in sterile culture bottles containing normal saline after scraping the ulcer base or deep portion of the wound edge with a sterile curette and taking incised tissue specimen of around 0.5 centimeters from different sites of wound. Deep tissue samples collected after curetting provides more authentic microbiological cultures than culturing swab samples.[10] Standard methods of sample processing, isolation, and identification of aerobic bacteria were done. The tissue samples were homogenized and inoculated on Blood agar and MacConkey agar. These samples were incubated under aerobic condition for 24–48 hours at 37 degree centigrade. Colonies obtained were identified and antibiotic sensitivity was done using Kirby Bauer's disc diffusion technique method as described in the Clinical Laboratory Standard Institute guideline 2012.[11]

Table 1: Wagner's grading of foot ulcers

GRADE 0	High risk foot, no ulcer
GRADE 1	Superficial Ulcer, not clinically infected
GRADE 2	Deeper ulcer, often with cellulitis, no abscess or bone infection.
GRADE 3	Deep ulcer with abscess formation or bone involvement.
GRADE 4	Localized gangrene
GRADE 5	Gangrene of whole foot

The results of microbiological culture-sensitivity were entered in the master-chart using MS EXCEL. Statistical analysis was done by using descriptive and inferential statistics using Chi square test. Software used in the analysis were SPSS (Statistical Product and Service Solutions) 17.0 version and Graph Pad prism 6.0 and $P < 0.05$ is considered as level of significance.

Results

One hundred and five patients of DFU were included in study. Out of total 105 patients, 73 (69.5%) were male and 32 (30.47%) were females and male: female ratio was 2.3:1. Maximum number of cases were in 45–54 year and 55–64 years group (27.6% each), followed by 65–74 years group (20%), then 35–44 years group (16.2%), and lastly 75–84 years (8.6%). The mean age of the population was 57.56 ± 12.5 years. Mean age of males was 51.16 ± 10.2 years and of the females was 58.16 ± 12.6 years. In this study, 80% of cases were from the rural area and 20% from urban area.

Majority of our study cases (63.8%) had diabetes for more than 10 years and 50.5% patients had ulcer for more than a month and while remaining 49.5% had ulcer for less than a month. History of regular alcohol intake was seen in 23.8% of cases, 40% either smoked or chewed tobacco. Practice of diabetic foot self-care was seen in 16.2% of our cases. Numbness in the foot was the most common complaints (68.6%) followed by foot pain (51.4%) and pedal edema (51.4%). Claudication was present in 29.6% of cases. Majority of patients had abnormal fasting blood sugar levels (88.6%) and abnormal serum HbA1c

levels (76.2%). Nephropathy was seen in 41% cases and Wagner's grade 2 ulcer was most common (40.95%), followed by grade 3 (31.4%), grade 5 (16.2%) and then grade 4 (11.4%). Loss of perception of 5.07 Semmes Weinstein monofilaments was seen in 62.9% of the patients suggestive of sensory peripheral neuropathy.

In this study 7.62% culture samples were sterile, 48.6% samples showed growth of single organism, two organisms were grown in 28.6% of samples and polymicrobial growth was observed in 15.2% of tissue samples. *Pseudomonas* (27.3%) was the most common single bacterial isolate followed by *Staphylococcus aureus* (19.05%) and E coli (15.5%) as shown in Table 2.

In this study *Staphylococcus aureus* was sensitive to amikacin and gentamicin (100%), ofloxacin (90%), vancomycin (85%), ampicillin, ciprofloxacin, erythromycin (80% each), amoxicillin-clavulanic acid (75%), and Clindamycin (70%). Other Gram-positive bacteria were 100% sensitive to amikacin and gentamicin as shown in Table 3.

In present study *Pseudomonas* was sensitive to imipenem (90%), amikacin (86.6%), gentamicin (83.3%), and cefotaxime (80%). Other effective antibiotics were ceftazidime (70%) and ceftriaxone (66.67%). Antibiotics effective against *E. coli* were imipenem (94.1%), amikacin (88.2%), ceftazidime (82.3%), cefotaxime (76.4%), gentamycin (76.4%), ceftriaxone (70.5%) and ofloxacin (70.5%). *Proteus* and *Klebsiella* were highly sensitive to amikacin (100% each), imipenem (100% each), cefotaxime (84% and 100%, respectively), gentamicin (84.6 and 87.5%, respectively). *Pseudomonas, E. coli, Proteus* and *Klebsiella* were resistant to ampicillin and amoxicillin-clavulanic acid. *Acinetobacter* was highly sensitive to Ciprofloxacin (100%) and resistant to ceftriaxone, ceftazidime, gentamicin, amikacin, amoxicillin-clavulanic acid, and ofloxacin. *Citrobacter* was sensitive to amoxicillin-clavulanic acid (100%) and ceftazidime (60%) as shown in Table 4.

Table 2: Distribution of bacterial isolates according to Gram stain and growth on culture media

	Tissue Culture	No. of isolates	Percentage (%)
Gram-negative (73.7%)	*Acinatobacter*	8	7.3
	Psedomonas	30	27.3
	Citrobacter kosari	5	4.5
	E. coli	17	15.5
	Klebsiella pneumonia	8	7.3
	Proteus vulgaris	13	11.8
Gram-positive (27.3%)	*Staphylococcus aureus*	20	19.05
	Streptococcus spp	5	4.5
	Enterococcus	4	3.81

Discussion

Foot ulcer is one of the most debilitating complications in diabetics. Nearly half of all lower extremity amputations are diabetes related. Foot infection is the most frequent indication, next only to gangrene for diabetic lower limb amputation.[4] Antibiotic therapy for diabetic foot infections is started empirically in accordance with likely causative organism. The definitive treatment is later modified according to bacterial culture and sensitivity report. Duration of treatment varies from 1–2 week to more than 4 weeks according to severity of infection.[12] Diabetic nephropathy which occurs in approximately third of diabetic patients and increasing incidence of multi drug resistant infections in DFU compounds the challenge faced by clinicians in treating these patients.[6]

In this study mean age of patients was 57.56 years. Maximum numbers of patients were in age group 45–64 years and male to female ratio was 2.28 which is similar to the study conducted by Yerat *et al.*[4] As this center located in rural area, 80% patients were from rural area and 20% were from urban areas in this study, similar to study of Shahi *et al.*[13] Majority of the patients (63.81%) with DFU had diabetes for more than 10 years duration which was also noted in study by Maskari *et al.*[14] and Gadepalli *et al.*[15] Diabetic foot self-care practices were found in 16.2% of the subjects while a similar study from South Ethiopia by Deribe *et al.*[16] reported self-care practice in 55.1% of the subjects whereas Mamo *et al.*[17] reported it in 4.5% subjects. Variation in self-care practices between these two studies may be attributed to difference in geographical area of study population. In present

Table 3: Antibiotic sensitivity pattern of Gram-positive organisms

Antibiotics	*Staphylococcus aureus* (*n*=20)		*Streptococcus spp.*(*n*=5)		*Enterococco spp.*(*n*=4)	
	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)
Amikacin	20 (100%)	0 (0%)	5 (100%)	0 (0%)	4 (100%)	0 (0%)
Ampicillin	16 (80%)	4 (20%)	2 (40%)	3 (60%)	2 (50%)	2 (50%)
Amoxicillin-clavulanic acid	15 (75%)	5 (25%)	4 (80%)	1 (20%)	3 (75%)	1 (25%)
Gentamicin	20 (100%)	0 (0%)	5 (100%)	0 (0%)	4 (100%)	0 (0%)
Erythromycin	16 (80%)	4 (20%)	4 (80%)	1 (20%)	3 (75%)	1 (25%)
Clindamycin	14 (70%)	6 (30%)	3 (60%)	2 (40%)	2 (50%)	2 (50%)
Ciprofloxacin	16 (80%)	4 (20%)	3 (60%)	2 (40%)	3 (75%)	1 (25%)
Ofloxacin	18 (90%)	2 (10%)	4 (80%)	1 (20%)	4 (100%)	0 (0%)
Vancomycin	17 (85%)	3 (15%)	5 (100)	0 (0%)	3 (75%)	1 (25%)
Methicillin	14 (70%)	6 (30%)	2 (40%)	3 (60%)	3 (75%)	1 (25%)

Table 4: Antibiotic sensitivity pattern of Gram-negative organisms

Antibiotics	*Pseudomonas spp* (*n*=30)		*E-Coli* (*n*=17)		*Proteus Vulgaris* (*n*=13)		*Klebsiella spp* (*n*=8)		*Acinactobactor* (*n*=8)		*Citrobactor* (*n*=5)	
	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)
Amikacin	26 (86.67%)	4 (13.33%)	15 (88.24%)	2 (11.76%)	13 (100%)	0 (0%)	8 (100%)	0 (0%)	3 (37.50%)	5 (62.50%)	-	-
Ampicillin	1 (3.33%)	29 (96.67%)	4 (23.53%)	13 (76.47%)	5 (38.46%)	8 (61.54%)	1 (12.50%)	7 (87.50%)	-	-	-	-
Amox-clav*	2 (6.67%)	28 (93.33%)	5 (29.41%)	12 (70.59%)	7 (53.85%)	6 (46.15%)	2 (25%)	6 (75%)	3 (37.50%)	5 (62.50%)	0 (0%)	5 (100%)
Gentamicin	25 (83.33%)	5 (16.67%)	13 (76.47%)	4 (23.53%)	11 (84.62%)	2 (15.38%)	7 (87.50%)	1 (12.50%)	2 (25%)	6 (75%)	-	-
Ciproflox	13 (43.3%)	17 (56.67%)	9 (52.94%)	8 (47.06%)	7 (53.85%)	6 (46.15%)	4 (50%)	4 (50%)	0 (0%)	8 (100%)	-	-
Oflox	14 (46.67%)	16 (53.33%)	12 (70.59%)	5 (29.41%)	9 (69.23%)	4 (30.77%)	6 (75%)	2 (25%)	3 (37.50%)	5 (62.50%)	-	-
Ceftazidime	21 (70%)	9 (30%)	14 (82.35%)	3 (17.65%)	10 (76.92%)	3 (23.08%)	6 (75%)	2 (25%)	2 (25%)	6 (75%)	3 (60%)	2 (40%)
Ceftrioxone	20 (66.67%)	10 (33.33%)	12 (70.59%)	5 (29.41%)	11 (84.62%)	2 (15.38%)	5 (62.50%)	3 (37.50%)	1 (12.50%)	7 (87.50%)	-	-
Cefotaxim	24 (80%)	6 (20%)	13 (76.47%)	4 (23.53%)	11 (84.62%)	2 (15.38%)	8 (100%)	0 (0%)	-	-	-	-
Imipenem	27 (90%)	3 (10%)	16 (94.12%)	1 (5.88%)	13 (100%)	0 (0%)	8 (100%)	0 (0%)	-	-	-	-

*Amoxicillin clavulanic acid

study, out of 105 cases, 54 (51.4%) cases had DFU for more than a month while 48.6% were having it for less than one month which was similar in studies by Kaur *et al*.[18] and Alva *et al*.[19] Numbness was reported in 68.6% cases of present study and in 74.1% cases of Boyko *et al*.[20] In this study 51.4% of cases had pedal edema while Jiang *et al*.[21] reported it in 36.3% cases. Foot pain was symptom in 51.4% cases in this study, while Boyko *et al*.[20] reported it in 66.1% cases. Claudication was found in 31.4% of cases in this study, 20.5% in study of Jiang *et al*.[21] and 22.2% in study of Boyko *et al*.[20]

In present study neuropathy was observed in 62.8% of the cases which was similar to other studies.[18,22-24] Wagener grade 2 and grade 3 ulcers were predominant in this study which was similar to study of Jiang *et al*.[21] Poor glycemic control (serum HbA1c ≥ 7) found in this study (76.2%) was also documented by Mendes *et al*.[25] which showed it in 79.6% cases. In the present study, diabetic nephropathy was present in 40.9% of study subjects, similar results were reported by Jiang *et al*.[26]

In 105 patients studied in this study, a total of 110 isolates were obtained from 97 samples, which represented an average of 1.13 bacteria per lesion whereas Kaur *et al*.[18] and Bansal *et al*.[27] reported wound bioburden of 1.38 and 1.52 bacteria per culture positive patient respectively. The relatively low isolation rates in our study may be due to non-isolation of anaerobic organisms as culture and sensitivity for anaerobic organisms was not done due to logistic and cost issues. In this study 105 samples were evaluated, out of these microbes were isolated from 92.79% samples. Out of these, 48.57% showed growth of single organism, 28.57% showed growth of two organisms and 15.24% showed polymicrobial growth. Bansal *et al*.[27] evaluated 103 patients, monomicrobial growth was noted in 61.8% cases and polymicrobial growth was noted in 37.08% cases while sterile culture was found in 7.2% of cases. Out of the total bacterial isolates, Gram-negative bacteria accounted for 73.7% of isolates while Gram-positive accounted for 27.3%. Similar findings were reported in other studies by Manikandan *et al*.[28] and Kaur *et al*.[18] which is consistent with higher prevalence of Gram-negative pathogens in low income countries as reported by Perez-Fevila *et al*.[29]

Diabetic foot infections in India are commonly caused by gram-negative bacilli.[30] There are many studies from West like Mendes *et al*.[25] which have reported predominance of Gram positive organisms in diabetic foot ulcers.[31] Difference in predominant prevalence of Gram-negative organisms in East and Gram-positive organisms in West is largely unknown. However Turhan *et al*.[32] suggested environmental factors such as sanitary habits like use of water for perianal wash after defecation causing contamination of hands with fecal flora, could be attributed to increased Gram-negative infections in the developing world compared with the West.[32] In this study most frequently isolated organism was *Pseudomonas* (27.3%), followed by *Staphylococcus Aureus* (19%), *E. coli* (15.5%) and *Proteus vulgaris* (11.8%). Mehta *et al*.[33], Bansal *et al*.[27] Kamtikar

et al.[34] and Boulton *et al.*[30] also reported *Pseudomonas* as the most common isolate which was similar to the present study. In the present study, *Staphylococcus aureus* was sensitive to amikacin and gentamicin (100%), ofloxacin (90%), vancomycin (85%). Other Gram-positive organisms were 100% sensitive to amikacin and gentamicin. *Streptococcus spp.* was also 100% sensitive to vancomycin and *Enterococcus spp.* was 100% sensitive to ofloxacin, amoxicillin-clavulanic acid, erythromycin, clindamycin, and ciprofloxacin were relatively less effective against Gram positive organism. It may be due to common use of these antibiotics in community.[35] There was difference in antibiotic sensitivity pattern in different studies. Manikandan *et al.*[28] showed that most of the Gram positive organisms were sensitive to ofloxacin, vancomycin, ciprofloxacin, erythromycin, and Amoxicillin-clavulanic acid. Kaur *et al.*[18] reported amikacin, vancomycin, and linezolid were most sensitive antibiotics against Gram positive organisms while Jain *et al.*[36] reported *Staphylococcus aureus* was 100% sensitive to vancomycin, Linezolid and daptomycin and 83% were sensitive to gentamicin. This difference in sensitivity pattern may be due to differences in demography of patients and differences in testing. In present study, it was found that *Pseudomonas* and *E. coli* were sensitive to imipenem, amikacin, gentamicin, and cefotaxime. Most effective drugs against Gram-negative organisms were imipenem, amikacin, gentamicin, and cefotaxime. Other lesser effective antibiotics were ceftazidime and ceftriaxone. Most of the Gram-negative bacteria showed variable degree of resistance to commonly prescribed ampicillin and amoxicillin-clavulanic acid except Citrobacter which was 100% sensitive to amoxicillin-clavulanic acid in this study. Manikandan *et al.*[28] reported that most effective antibiotics against Gram-negative organisms were amikacin, cefotaxime, ceftazidime, ceftriaxone, gentamicin, and imipenem which compares well with present study.

Studies by Kotwani *et al.*[35] and Farooqui *et al.*[37] have reported wide use of beta lactam cephalosporins, beta-lactam penicillin and fluroquinolones in Indian community. As a result, there is increasing resistance to not only these antibiotics but last resort antibiotics like carbapenem.[37] Aminoglycosides were the least used antibiotics in community.[35] These studies corroborate microbial resistance and sensitivity pattern as found in our study. We attribute it to extensive and irrational use of antibiotics for common infections as it is well established that antibiotic use and antibiotic resistance are correlated.[37] Antibiotic therapy to treat diabetic foot infections should be selected based on likely or proven causative organism and its sensitivity.[38]

We consider rational empiric therapy is important part of management of DFU infections. Based on findings of this study and similar studies from different geographical location it was concluded that aminoglycosides were the most active antibiotics against both Gram-positive and Gram-negative bacteria in DFU infections. We attribute these findings to less use of these antibiotics in community.[35] Hence, we recommend amikacin or gentamicin as empiric antibiotics in patients with DFU with infection, and to switch to definitive antimicrobial therapy after culture and sensitivity report. However, dose adjustments may be required based on patient's creatinine clearance.

Limitations of study

This study has some limitations like small sample size and non-testing of anaerobic flora due to logistical and resource constraints.

Conclusion

Results of this study show DFU are common in males in 5th and 6th decades of life. Majority of DFU patients have poor glycemic control and neuropathy and a significant number have nephropathy and very less proportion of DFU patients practice diabetic foot self-care. Gram-negative bacteria are the predominant infections. *Pseudomonas* is the most common Gram-negative and *Staphylococcus aureus* is most common Gram-positive infective bacteria in DFU. Due to less use of injectable aminoglycosides in community, both Gram negative and Gram-positive bacteria are sensitive to aminoglycosides, while wide resistant has developed in community to commonly prescribed extended spectrum penicillin and cephalosporins. It is time to reconsider empiric antibiotic therapy for diabetic foot infections. As this study had most participants from rural population, we recommend Amikacin and gentamicin may be considered empiric treatment of choice for infected DFU especially in rural areas especially by primary care physicians as well as specialists till definitive treatment based on sensitivity pattern is started. This is first study of its kind which has advocated use of injectable aminoglycosides as first line empiric antimicrobial therapy for treatment of all diabetic foot infections in this region. This will help reduce cost to patients by un-necessary use of resistant antibiotics.

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Conflicts of interest

There are no conflicts of interest.

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