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### Multidrug Resistant Organisms in Diabetic Foot Ulcers-Analysis of Risk Factors and Clinical Outcome

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#### ABSTRACT

**Background:** Diabetes Mellitus is one of the most important health problem in the world. Foot infection is a common sequelae of diabetes, which once established progressively worsens and become more difficult to treat and is associated with substantial morbidity and mortality. Multidrug resistance organism infection is extremely common in hospitalized patients with diabetic foot ulcers.

**Aim of Study:** To detect multidrug resistant organism among isolates from diabetic foot ulcers, identification of risk factors and clinical outcome.

**Materials and Methods:** A prospective study conducted in 150 patients admitted in Department of Surgery in a tertiary care center in south India.

**Results:** In this study 76.6% of patients were infected with multidrug resistant organisms.

Among the risk factors analyzed, ulcer duration more than 2 weeks showed significant association with this infections. 68% of patients showed good response to treatment and 24% underwent amputations.

Keywords: Diabetic Foot Ulcer, Multidrug Resistant Organisms, Foot Ulcers.

### INTRODUCTION

Diabetes mellitus is a chronic disorder affecting large segment of population. Diabetes and foot problems are almost synchronous<sup>1</sup>. Foot disorders such as ulcerations, infections and gangrene are leading causes of hospitalization in patients with diabetes mellitus<sup>2,3</sup>. Foot ulcers and its sequelae account for a lot of medical expenditure as well as lengthy hospital stay and periods of disability<sup>4</sup>. A diabetic foot ulcer is defined as "a non healing or poorly healing full or partial thickness wound below ankle in individuals with diabetes mellitus". The critical triad of these ulcers are peripheral sensory neuropathy, vascular changes and infections which constitute diabetic foot syndrome<sup>1</sup>. Infections in diabetic foot ulcers are generally polymicrobial with 2-3 species per culture and early diagnosis of microbial infections is aimed to institute appropriate antibiotic therapy and to avoid further complications<sup>1</sup>.

### AIM OF STUDY

- 1. To detect multidrug resistant organisms among isolates from diabetic foot ulcers.
- 2. To access potential risk factors for these infection and its clinical outcome.

### MATERIALS AND METHODS

This is a prospective study conducted in Dept of Surgery and Microbiology with a sample size of 150. Only admitted patients with Wagner's grade 2 and more are included in this study. All patients are assessed with the help of a proforma including personal details, diabetic history, control and complication of diabetes, neurovascular evaluation, details regarding the foot ulcers and blood investigations.

Specimen:

- 1. Tissue specimen and curetting from ulcer
- 2. Aspirates in case of abscess

Specimens are collected from the deeper part of the wound under strict aseptic precaution and homogenized using sterile mortar and pestle. Gram staining and culture done using these specimen and it is inoculated in Blood agar, McConkey agar, Salt agar and Glucose broth. After overnight incubation culture plates were read and organisms identified using biochemical reaction. Antibiotic sensitivity testing done by standard disc diffusion method. Screening for Methicillin Resistant Staphylococcus Aureus (MRSA) is done with Cefoxitin disc diffusion method as per CLSI guidelines. ESBL screening done for gram negative isolates by using combined disc diffusion method.

### STATISTICAL ANALYSIS

In this study quantitative variables were expressed as mean  $\pm$  standard deviation and qualitative variables expressed as percentage. Statistical analysis were done by SPSS software. The associations of study variables were analyzed using chi-square test and a P- value of <0.05 was taken as significant.

### RESULTS

As per the criteria 150 patients admitted in surgery wards were studied over a period of 1 year and all patients were followed up until discharge from hospital. Results were analyzed with appropriate statistical methods. Maximum number of patients were in the age group of 60-69 years (Table 1). Male patients were predominant with male: female ratio of 3.04:1. 5 % of the patients had duration of diabetes less than 10 years. Other factors analyzed include neuropathy (54%), PVD (35.3%), prior foot ulcer (27.3%), poor glycemic control (46.7%) and smoking (29.3%) (Table 2). Co morbid conditions were analyzed and maximum number of patients had hypertension followed by anemia, nephropathy, osteomyelitis, ischemic heart diseases and sepsis (Table 3). Majority of patients were in Wagner's Grade 3 (Table 4) . 61.33% of the patients had ulcers more than 2 weeks duration (Table 5). 56.7% of patients had poly microbial infection, 41.3% had monomicrobial infection and no organisms were isolated from remaining 2%. Out of 241 isolates, 62.6% organisms were multidrug resistant (Table 6). Distribution of mechanism of drug resistance among gram negative isolates were as follows (Table 7). Ulcers were healing in 68%, non healing 3.3%, underwent surgical procedure 24% and 4.6% were expired. Distribution of different surgical procedure among these patients is as follows (Table 8).

Age group	No of patients	Percentage
<29	6	4
30-39	6	4
40-49	24	16
50-59	45	30
60-69	48	32
>70	21	14
Total	150	100

**Table 1:** Distribution of cases according to age:

**Table 2:** Risk factor for DM foot ulcer:

Risk factors	Number	Percentage
Neuropathy	81	54
PVD	53	35.3
Prior ulcer	41	27.3
Poor glycemic control	70	46.7
Smoking	44	29.3

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<b>Je 5.</b> Distribution of comorbia conditions.						
Number	Percentage					
63	42					
42	28					
70	46.7					
13	8.7					
14	9.3					
5	3.3					
	Number         63           42         70           13         14           5         5					

### Table 3: Distribution of comorbid conditions:

**Table 4:** Distribution of cases according toWagner's grade:

Grade	Number	Percentage
Grade 2	59	39.3
Grade 3	62	41.3
Grade 4	28	18.7
Grade 5	1	0.7
Total	150	100

Table	5:	Distribution	of	cases	according	to
duratio	n of	ulcer:				

Duration	Number	Percentage
≤2wk	58	38.67
>2wk	92	61.33
Total	150	100

Table	6:	Distribution	of	multidrug	resistant
organis	ms:				

Organism	Total isolates	MDRO-No	Percentage
Staphylococcus aureus	45	27	60
S. epidermidis	5	3	60
E.coli	48	36	75
P. aeruginosa	61	27	44.3
Klebsiella pneumoniae	27	24	88.8
Proteus mirabilis	23	13	56.5
Proteus vulgaris	6	2	33.3
A.baumannii	18	17	94
Enterobacter cloacae	3	2	66.6

**Table 7:** Distribution of mechanism of drug resistance among Gram negative isolates:

Resistance Mechanism	E. (4	<i>coli</i> 48)	K.pnei (2	umoniae 27)	P.mir (2	abilis 3)	P.vul (6	lgaris 5)	E.cle (	pacae 3)
	No.	%	No.	%	No.	%	No.	%	No.	%
ESBL	30	62.5	20	74	9	39	2	33.3	2	66.6
Amp C	6	12.5	4	14.8	4	17.4	0	0	0	0

**Table 8:** Distribution of different surgical procedures:

Surgical Procedures	Number (%)
Mid tarsal amputations	15 (41.7)
Toe disarticulation	9 (25)
BK amputation	8 (22.2)
AK amputation	4 (11.1)

#### DISCUSSION

Diabetes mellitus is the one of the most important public health problem in the world. Foot infection is a common sequelae of diabetes which once established progressively worsens and is associated with substantial morbidity and mortality. The decision regarding proper management of diabetic foot infection is difficult. While optional therapies are yet to be established, most authors agree that the management requires isolation and identification of microbial flora and appropriate antibiotic therapy according to the sensitivity pattern.

Majority of patients were in an age group of 60-69yrs (32%) followed by 50-59yrs (30%). Similar results are shown in a study by Ekta Bansal et al<sup>6</sup>. Majority were male patients (75.3) with a male to female ratio of 3.04:1. Similar results in studies conducted by Said Mohammed Alavi et al and Sasikala et al<sup>7,8</sup>. The mean duration of DM was  $10.2 \pm 7.31$  years. It is well recognized that a number of contributory factors working together ultimately result in foot ulceration in diabetic patients. The commonest causes for diabetic foot ulceration include peripheral neuropathy, foot deformity, external trauma and peripheral vascular disease. With the exception of trauma, none of the above risk factors will cause ulceration in isolation<sup>9</sup>. Because of its low case fatality rate in diabetes, prevalence of associated chronic complication is expected to increase. In our study 54% had neuropathy and 35.3 % had peripheral vascular disease. Several other studies also shows a high prevalence of neuropathy and peripheral vascular disease, <sup>10,11</sup><sup>12,13</sup>. Other risk factors that were studied include past history of ulcer and

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smoking. Almost similar prevalence were reported by Ekta Bansal et al<sup>6</sup>. A diabetic patient with a history of previous ulceration and amputation is at increase of subsequent ulceration and amputation. This fact highlight the need of giving special care to those with past history of ulcer<sup>5</sup>. Close monitoring of blood sugar is very important in diabetes because a raise in blood sugar suggest worsening of infection even though other signs and symptoms are absent. Co morbid conditions like anemia, nephropathy, hypertension and IHD have been studied. 42% of this patients had anemia. Correction of anemia is important as it impair wound healing. Prevalence of HT, nephropathy and IHD were 46.7%, 28%, and 8.7% respectively and similar results were shown studies by Ekta Bansal and Ozer et al<sup>6,14</sup>. in Majority of patients in our study had Wagner's grade 3 ulcer whereas study by Bansal et al and Ozer et al showed maximum number of patients in grade 4<sup>6, 14</sup>. MRSA infection is common in diabetic foot ulcer and is associate with prior antibiotic treatment and non healing of wound. Over use of antibiotics and selection of broad . rather than narrow spectrum agents contributed to high prevalence of MRSA colonization in diabetic foot wound. Among the gram positive isolates, 60% of staphylococci were Methicillin resistant. Almost similar results were seen in study conducted by Zubair et al<sup>10</sup>. Multidrug resistant gram negative organisms isolated include ESBL and AmpC ß lactamase producing enterobacteriaceae and multidrug resistant isolates of P. aeruginosa and Acinetobacter boumannii. Several studies conducted showed a progressive increase in the incidence of ESBL producing strain over years<sup>15,16,17</sup>. This constitute a serious threat to current beta lactam therapy leading to treatment failure in diabetic foot infection. Common risk factors associated with multidrug resistant organism are prolonged antibiotic treatment, chronic ulcer, prolonged hospital stay and past history of ulcer. These factors were analyzed using univariate analysis in which the only factor significantly associate with MDRO infection was

the presence of the ulcer duration more than 2 weeks (P value 0.02). Prior history of antibiotic therapy fails to shows any association with multidrug resistant status. This may be due to inadequate information from patients regarding antibiotic therapy from peripheral center. In univariate analysis patient's poor prognosis showed significant association of PVD, age and Wagner's grade. 68% of the patients showed good response to treatment and ulcers were healing well. 24% of the patients undergone amputations of which majority had midtarsal amputation followed by toe disarticulation. Ulcers were not healing in 5 patients and 7 patients expired during treatment.

### CONCLUSION

- Most important risk factors for diabetic foot ulcers were neuropathy (54%), poor glycemic control (46.7%) and PVD (35.3%) and other comorbid conditions include anaemia (42%), nephropathy (28%) and hypertension (46.7%)
- Most of the patients had ulcer duration > 2 wks (61.33%)
- Majority of patients were included in Wagner's grade 3 (41.3%) followed by grade 2 (39.3%)
- 60% of *Staphylococcus aureus* isolates were methicillin resistant (MRSA)
- 68% of gram negative isolates were multidrug resistant
- Ulcer duration > 2wks were found to be an indicator of infection with multidrug resistant organisms
- Poor prognosis of patient showed significant association with PVD, higher age group and higher Wagner's grade
- 36 patients underwent surgical intervention in this study (mid tarsal amputation-15, toe disarticulation-9, BK amputation-8 and AK amputation-4)

We hope this study will help clinicians to determine the appropriate antibiotics for diabetic foot infections, thereby reducing morbidity

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associated with prolonged hospital stay and reduced risk of amputations.

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