A Clinico-microbiological Study of Diabetic Foot Ulcers in an Indian Tertiary Care Hospital

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OBJECTIVE — To determine the microbiological profile and antibiotic susceptibility patterns of organisms isolated from diabetic foot ulcers. Also, to assess potential risk factors for infection of ulcers with multidrug-resistant organisms (MDROs) and the outcome of these infections.

RESEARCH DESIGN AND METHODS — Pus samples for bacterial culture were collected from 80 patients admitted with diabetic foot infections. All patients had ulcers with Wagner's grade 3–5. Fifty patients (62.5%) had coexisting osteomyelitis. Gram-negative bacilli were tested for extended spectrum β-lactamase (ESBL) production by double disc diffusion method. Staphylococcal isolates were tested for susceptibility to oxacillin by screen agar method, disc diffusion, and *mec A*–based PCR. Potential risk factors for MDRO-positive samples were explored.

RESULTS — Gram-negative aerobes were most frequently isolated (51.4%), followed by gram-positive aerobes and anaerobes (33.3 and 15.3%, respectively). Seventy-two percent of patients were positive for MDROs. ESBL production and methicillin resistance was noted in 44.7 and 56.0% of bacterial isolates, respectively. MDRO-positive status was associated with presence of neuropathy ($P = 0.03$), osteomyelitis ($P = 0.01$), and ulcer size >4 cm^2 ($P < 0.001$) but not with patient characteristics, ulcer type and duration, or duration of hospital stay. MDRO-infected patients had poor glycemic control ($P = 0.01$) and had to be surgically treated more often ($P < 0.01$).

CONCLUSIONS — Infection with MDROs is common in diabetic foot ulcers and is associated with inadequate glycemic control and increased requirement for surgical treatment. There is a need for continuous surveillance of resistant bacteria to provide the basis for empirical therapy and reduce the risk of complications.

Diabetes Care 29:1727–1732, 2006

Worldwide, diabetic foot lesions are a major medical, social, and economic problem and are the leading cause of hospitalization for patients with diabetes. Infectious agents are associated with amputation of the infected foot if not treated promptly.

Proper management of these infections requires appropriate antibiotic selection based on culture and antimicrobial susceptibility results; however, initial management comprises empirical antimicrobial therapy, which is often based on susceptibility data extrapolated from studies performed on general clinical isolates (1). Several studies found methicillin-resistant *Staphylococcus aureus* (MRSA) in as many as 15–30% of diabetic wounds (1–3). Infection with multidrug-resistant organisms (MDROs) may increase the duration of hospital stay and cost of management and may cause additional morbidity and mortality (4).

Although increasing antimicrobial resistance is a pertinent problem in India, there is paucity of data on the frequency of MDRO infections and the outcome of such infections among diabetic foot ulcers in this region. The aim of this study was to determine the microbiological and antimicrobial susceptibility profile of organisms isolated from patients with diabetic foot ulcers. The risk factors for infection of ulcers with MDROs and the outcome of these infections were also studied.

RESEARCH DESIGN AND METHODS

Eighty diabetic patients with clinically infected foot ulcers admitted to the endocrinology ward at the All India Institute of Medical Sciences over a period of >2 years were studied. Ulcers were graded using the Wagner classification (5).

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 macroalbuminuria), neuropathy (absence of perception of the Semmes-Weinstein monofilament at 2 of 10 standardized plantar 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, exudate, surrounding cellulitis, odor, tissue necrosis, crepitation, and pyrexia) was made.

Ulcer size was determined by multiplying the longest and widest diameters and expressed in centimeters squared. Osteomyelitis was diagnosed on suggestive changes in the radiographs and bone scans. All cases were monitored until discharge from the hospital. Written consent was obtained from all subjects, and clear-

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Received for publication 17 January 2006 and accepted in revised form 19 April 2006.

Abbreviations: ESBL, extended spectrum β-lactamase; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0116

ance was obtained from the institute's ethics committee.

Microbiological methods

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 the deep portion of the wound edge with a sterile curette. The soft tissue specimens were promptly sent to the laboratory and processed for aerobic and anaerobic bacteria. Standard methods for isolation and identification of aerobic and anaerobic bacteria were used (6,7).

Susceptibility testing

Anti-microbial susceptibility testing of aerobic isolates was performed by the standard disc diffusion method as recommended by the National Committee for Clinical Laboratory Standards (8). All anaerobic isolates were tested for susceptibility to metronidazole and amoxicillin/clavulanate by microbroth dilution test (9). Gram-negative bacilli were tested for extended spectrum β-lactamase (ESBL) production by a double disc diffusion method, and *Staphylococcus* species were tested for methicillin resistance by using 1-μg oxacillin disc and oxacillin screen agar (6 μg/ml) recommended by the National Committee for Clinical Laboratory Standards (8). A vancomycin screen agar (6 μg/ml) was also used to detect vancomycin intermediate isolates of Staphylococci. Confirmation of methicillin resistance was done by *mec A*–based PCR (10).

MDROs, the primary study variable, were defined as MRSA, bacteria-producing (ESBL) (4), and methicillin-resistant coagulase-negative staphylococci (11).

Antibiotic treatment

Intravenous empirical antibiotic therapy of amoxicillin-clavulanate combination (1.2 g i.v. every 8 h) was started at admission for all the patients. 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 cellulitis or gangrene was 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. The association of study variables with MDRO and non-MDRO infections was tested by using Student's *t* test or Fisher's exact test as appropriate. The odds ratios (ORs) (with 95% CIs) for having MDRO-associated ulcers were calculated. Multiple logistic regressions were employed to identify independent predictors of MDRO infections and predictors of glycemic control. A two-tailed P value of <0.05 was taken as significant. All statistical analysis was implemented on Stata 8.0.

RESULTS — Males were predominant (85.0%) in the study subjects. All patients had ulcers graded 3–5 in the Wagner classification. The majority of subjects had type 2 diabetes (88.8%). The mean age of the subjects was 53.9 ± 12.1 years. The mean duration of diabetes was 11.8 ± 5.7 years, and nearly two-thirds (66.2%) had the condition for >10 years. Sixty-nine (86.2%) had neuropathy, 68 (85.0%) had peripheral vascular disease, 60 (75.0%) had nephropathy, 58 (72.5%) had retinopathy, and an equal number were hypertensive. Osteomyelitis was present in 50 (62.5%) subjects.

Nearly half (47.5%) had lesions for >3 months before presentation at the hospital. The ulcer was necrotic in 19 (23.8%) cases. More than two-thirds (71.2%) received surgical treatment, mainly in the form of debridement. Two patients died during the hospital stay.

A total of 183 isolates were detected from the 80 ulcer specimens, averaging 2.3 species per patient. Seventy percent of patients had infection due to two or three species, while more than three species could be seen in 12.5%. The majority (65.0%) were infected with aerobes only. Infection with anaerobes alone was observed in one patient (1.2%). Both aerobic and anaerobic organisms could be isolated in the remaining patients (33.8%). Gram-positive organisms only were found in 11 patients (13.8%), and 23 patients (28.7%) had only gram-negative organisms. The remaining 46 patients (57.5%) had both gram-positive and -negative organisms.

The profile of the organisms isolated is detailed in Table 1. Of the total 183 isolates, 155 (84.7%) were aerobic bacteria. The ratio of gram-negative to gram-positive in the aerobic category was 1.5: 1.0 (60.6 vs. 39.4%). Of the total, 51.4 and 33.3% were aerobic gram-negative and -positive bacteria, respectively. There were a total of 28 anaerobic isolates (15.3%) comprising a nearly equal number of gram-negative and -positive bacteria.

The results of susceptibility studies are summarized in Table 2. *S.aureus* exhibited a high frequency (56.0%) of resistance to the antibiotics tested. High levels of resistance to erythromycin, tetracycline, and ciprofloxacin (40% each) were found in *Enterococcus* species. However, no high-level aminoglycoside resistance was observed in the enterococcal isolates. All the isolates were uniformly susceptible to vancomycin and linezolid. ESBL production was noted in 42 (44.7%) gram-negative bacilli, with the highest production in *Proteus* species (65.3%) followed by *Escherichi coli* (54.5%).

Table 1—*Profile of bacteria isolated from infected foot ulcers in diabetic patients' specimens* (n = 80 *patients*)

Bacteria category	Frequency (%)
n isolates	183
Aerobic and facultative isolates	155 (84.7)
Gram negative	94 (51.4)
Proteus species	23 (12.6)
E.coli	22 (12.0)
Pseudomonas aeruginosa	18 (9.8)
Acinetobacter species	17 (9.3)
Klebsiella species	12 (6.6)
Citrobacter species	1 (0.5)
Enterobacter species	1 (0.5)
Gram positive	61 (33.3)
S.aureus	25 (13.7)
Enterococcus species	21 (11.5)
Coagulase negative *Staphlococci*	12 (6.6)
Micrococcus species	3 (1.6)
Anaerobic isolates	28 (15.3)
Gram negative	13 (7.1)
Veilonella species	3 (1.6)
Bacteroides species	3 (1.6)
Bacteroides fragilis	3 (1.6)
Bacteroides eggerthii	2 (1.1)
Bacteroides vulgaris	1 (0.5)
Bacteroides ovatus	1 (0.5)
Gram positive	15 (8.2)
Peptostreptococcus assachrolyticus	8 (4.4)
Peptostreptococcus species	3 (1.6)
Peptostreptococcus anaerobius	1 (0.5)
Clostridium perfringens	1 (0.5)
Clostridium septicum	1 (0.5)
Eubacterium lentum	1 (0.5)

Table 2—*Antimicrobial susceptibility pattern of aerobic bacterial isolates from infected foot ulcers in diabetic patients* (n = *80*)

Antimicrobial agent (μg)	Proportion susceptible (%) *S.aureus* (n = 25)	CoNS (n = 12)
Methicillin sensitive	11 (44.0)	6 (50.0)
Methicillin resistant	14 (56.0)	6 (50.0)
Amikacin (30)	8 (57.1)	4 (66.7)
Erythromycin (15)	2 (14.3)	2 (33.3)
Tetracycline (30)	5 (35.7)	4 (66.7)
Ciprofloxacin (5)	5 (35.7)	3 (50)
Clindamycin (2)	6 (42.8)	6 (100.0)
Chloramphenicol (30)	9 (64.3)	6 (100.0)
Rifampicin (5)	10 (71.4)	6 (100.0)
Cotrimixozole (1.25/23.75)	5 (35.7)	6 (100.0)

	Proteus spp	*Escherichia coli*	*Pseudomonas aeruginosa*	*Acinetobacter* spp	*Klebsiella pneumoniae*
n	23	22	18	17	12
Amikacin (30)	8 (34.7)	11 (50.0)	12 (70.5)	13 (76.4)	8 (66.6)
Amoxcillin-clavum (20/10)	8 (34.7)	10 (45.4)	11 (61.1)	13 (76.4)	8 (66.6)
Imipenem (10)	23 (100.0)	22 (100.0)	18 (100.0)	17 (100.0)	12 (100.0)
Cefotaxime (30)	8 (34.7)	10 (45.4)	11 (61.1)	13 (76.4)	8 (66.6)
Ceftazidime (30)	8 (34.7)	10 (45.4)	11 (61.1)	13 (76.4)	8 (66.6)
Ciprofloxacin (5)	20 (86.9)	11 (50.0)	10 (55.5)	17 (100.0)	6 (50.0)
Meropenem (10)	23 (100.0)	22 (100.0)	18 (100.0)	17 (100.0)	12 (100.0)
Piperacillin (100)	8 (34.7)	10 (45.4)	11 (61.1)	12 (70.5)	5 (41.6)
Pipercillin-tazobactam (100/10)	12 (52.2)	10 (45.4)	13 (72.2)	13 (76.5)	8 (66.6)
Cefperazone-sulbactam (75/10)	20 (86.9)	20 (86.3)	16 (88.8)	15 (88.2)	12 (100.0)
Ticarcillin-clavum (75/10)	20 (86.9)	16 (72.7)	16 (88.8)	14 (82.3)	10 (83.3)

Data are n (%). All strains of MSSA and methicillin-resistant coagulase-negative staphylococci were uniformly susceptible to the study drugs. All staphylococci resistant to oxacillin have been considered resistant to all β-lactams; all strains of staphylococci were susceptible to vancomycin, teicoplanin, and linezolid (all 30 μg). *Citrobacter* species (1) and *Enterobacter* species (1) were uniformly susceptible to the study drugs.

Thus, among the 80 patients, 58 had MDRO infected ulcers, 38 grew ESBL-producing bacteria only, 6 grew MRSA only, 8 grew both MRSA- and ESBL-producing bacteria, and 6 grew methicillin-resistant coagulase-negative staphylococci– and ESBL-producing bacteria in their ulcers. All the anaerobes were susceptible to metronidazole and amoxicillin/clavulanate.

Surgical debridement was done in 34 patients, of which 29 were MDRO-culture positive. Four of the six MDRO-positive patients underwent amputation below the knee. Hypertension was the only factor found to be significantly higher in patients with non-MDROs. Duration of hospital stay was similar in patients with and without MDROs ($P = 0.61$).

The association of study factors with MDROs is presented in Table 3. There were no significant differences in the demographic characteristics between the two groups. An ulcer of size >4 cm^2 was more likely to be associated with MDROs (OR 10.52, $P < 0.001$). Patients with MDRO ulcers had neuropathy (3.98, $P = 0.03$) and osteomyelitis (3.48, $P = 0.01$) more frequently. Peripheral vascular disease showed a borderline significant association with MDRO (3.25, $P = 0.06$). Significantly more patients with MDRO infections required surgical treatment (5.13, $P < 0.01$). Multiple logistic regressions showed a high degree of interaction between presence of neuropathy and ulcer size. Taking the absence of neuropathy as a baseline (OR 1.00), presence of neuropathy with an ulcer size <4 cm^2 showed an OR of 0.44 (95% CI 0.08–2.27) while the same with an ulcer size >4 cm^2 showed an OR of 17.2 (2.49–118.91). Thus, an ulcer size of >4 cm^2 with the presence of neuropathy appears to be a strong indicator of MDRO infections.

On the day of admission, patients with MDRO-infected ulcers had significantly higher blood glucose levels, both fasting and postprandial, than those with non-MDRO infected ulcers (difference: fasting 84.1 ± 14.66 mg/dl, $P < 0.001$ and postprandial 70.8 ± 14.2 mg/dl, $P < 0.001$). Similar trend was seen even 1 week after admission. Considering a fasting blood glucose level of <110 mg/dl and/or postprandial level of <160 mg/dl as glycemic control, the number of patients achieving glycemic control over the hospital stay was compared between those with and without MDRO infections. Patients with non-MDRO–infected foot ulcers showed a gradual rise in the number achieving glycemic control (13.6, 18.2, 27.3, 22.7, 45.0, 64.7, and 76.9% on days 2–8, respectively) while no such trend was visible among the MDRO-infected ulcers (14.0, 14.0, 18.5, 16.0, 22.7, 21.9, and 25.0% on days 2–8, respectively). The trend in the average blood glucose levels (both fasting and postprandial) for the two groups during the hospital stay is shown in Fig. 1. Taking the achievement of glycemic control at discharge (yes/no) as the outcome, the association of various study variables with this outcome was examined by multiple logistic regression. We found that MDRO status is the only significant, independent predictor of glycemic control (OR 0.25, $P = 0.01$). No other variable was found to

Table 3—*Association of study characteristics in two groups of diabetic patients according to infection of foot ulcers with MDROs and non-MDROs*

Characteristic	Non-MDRO	MDRO	*P* value	OR (95% CI)
n	22	58		
Age (years)	57.0 ± 11.29	52.7 ± 12.28	0.16	0.97 (0.93–1.01)
<50	4 (18.2)	18 (31.0)		1.00
50–59	10 (45.4)	22 (37.9)		0.49 (0.13–1.82)
≥60	8 (36.4)	18 (31.0)	0.52	0.50 (0.13–1.96)
Sex				
Male	18 (81.8)	50 (86.2)		1.00
Female	4 (18.2)	8 (13.8)	0.62	0.72 (0.19–2.68)
Type of diabetes				
Type 1	5 (22.7)	4 (6.9)		1.00
Type 2	17 (77.3)	54 (93.1)	0.10	3.97 (0.96–16.48)
Duration of diabetes (years)	12.9 ± 5.25	11.4 ± 5.81	0.31	0.95 (0.87–1.04)
<10	6 (27.3)	21 (36.2)		1.00
10–19	12 (54.5)	31 (53.4)		0.74 (0.24–2.28)
≥20	4 (18.2)	6 (10.3)	0.56	0.43 (0.09–2.03)
Duration of ulcer (months)	3.7 ± 2.60	2.9 ± 2.11	0.14	0.86 (0.70–1.05)
≤3	14 (63.6)	46 (79.3)		1.00
>3	8 (36.4	12 (20.7	0.15	0.46 (0.16–1.34)
Duration of hospital stay (days)	18.55 ± 5.58	19.31 ± 6.13	0.61	—
Size of ulcer (cm^2)				
≤4	13 (59.1)	7 (12.1)		1.00
>4	9 (40.9)	51 (87.9)	<0.001	10.52 (3.30–33.58)
Nature of ulcer				
Non-necrotic	19 (86.4)	42 (72.4)		1.00
Necrotic	3 (13.6)	16 (27.6)	0.19	2.41 (0.63–9.28)
Grade of ulcer (Wagner)				
3	17 (37.0)	29 (63.0)		1.00
4	5 (20.0)	20 (80.0)		2.34 (0.74–7.39)
5	0 (0.0)	9 (100.0)	0.04	—
Complications				
Hypertension	22 (100.0)	41 (70.7)	<0.01	—
Retinopathy	15 (68.2)	43 (74.1)	0.59	1.34 (0.46–3.91)
Nephropathy	16 (72.7)	44 (75.9)	0.77	1.18 (0.39–3.59)
Neuropathy	16 (72.7)	53 (91.4)	0.03	3.98 (1.07–14.76)
Peripheral vascular disease	16 (72.7)	52 (89.7)	0.06	3.25 (0.92–11.49)
Osteomyelitis	9 (40.9)	41 (70.7)	0.01	3.48 (1.26–9.67)
Treatment				
Medical	12 (54.5)	11 (19.0)		1.00
Surgical	10 (45.5)	47 (81.0)	<0.01	5.13 (1.77–14.88)
Discharge status				
Alive	22 (100.0)	56 (96.6)		—
Dead	0 (0.0)	2 (3.4)	0.38	
Glycemic control at discharge	15 (68.2)	20 (34.5)	0.01	0.25 (0.09–0.70)

Data are means ± SD or *n* (%) unless otherwise indicated.

have significant association with glycemic control. Thus, patients with non-MDRO ulcers have better glycemic control than those with MDRO ulcers during the hospital stay.

CONCLUSIONS— This study presents a comprehensive clinical and microbiological survey of infected diabetic foot ulcers in hospitalized patients.

We used soft tissue samples for bacteriological culture in all cases, including osteomyelitis. Though bone biopsy may be a better sample (12) in cases of osteomyelitis, it requires surgical expertise, can be potentially traumatic to the patient, and is not routinely performed in our institute. Further, samples taken from the base of the wound after debridement are adequate for identifying the infecting organism (13). Accordingly, we followed this procedure.

Though previous studies showed gram-positive aerobes as predominant in diabetic foot infections (14–16), we found gram-negative aerobic bacteria were most frequently isolated. Thus, the major infective organisms in diabetic foot ulcers in our patients appear to be different. The ratio of gram-positive aerobes to gram-negative aerobes was 2:3, which is in reversal to that reported earlier (2). The differences in the age-sex composition,

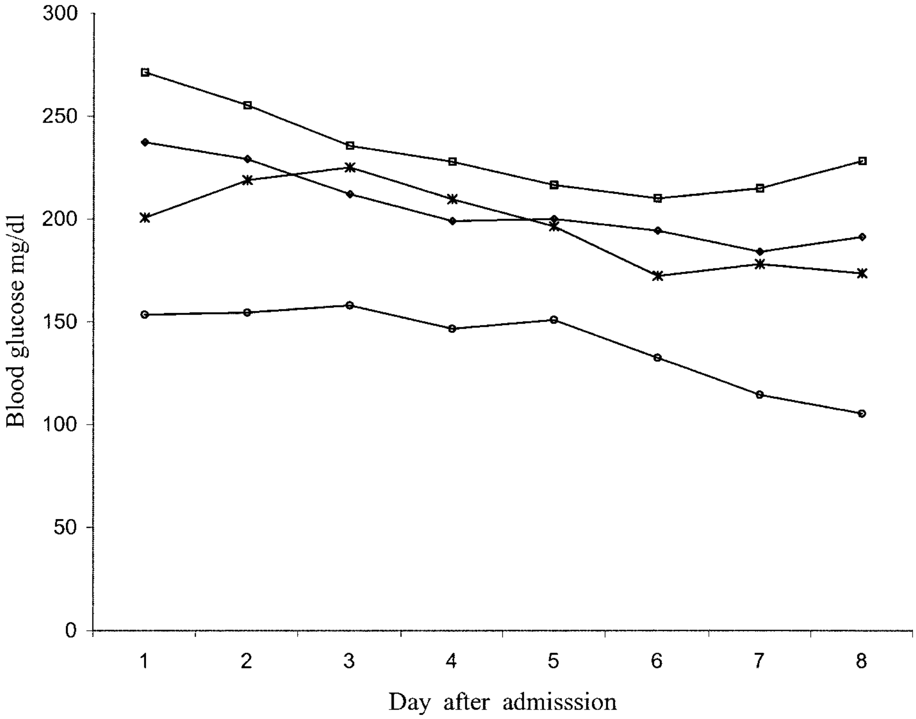

Figure 1—*Fasting and postprandial blood glucose levels among diabetic patients with foot ulcers infected with and without MDROs during the hospital stay.* ○, *non-MDRO fasting;* ●, *MDRO fasting;* *, *non-MDRO postprandial;* □, *MDRO postprandial.*

ulcer grades, study setting, etc. between our study population and those of earlier studies might be the reason for these differences. However, our results from the northern parts of the country are in tune with a similar study from the southern parts of India (3), which also showed that gram-negative were more common than gram-positive bacteria in diabetic foot infections. We too observed a high recovery of multidrug resistant *Pseudomonas aeruginosa*, as was reported from south India. This raises a serious concern as *P.aeruginosa* is an aggressive gram-negative *Bacillus* (17).

S.aureus was the most frequent pathogen, found in nearly 14% of infections. *Enterocccus* species were isolated nearly as frequently (21 isolates) as *S.aureus* (25 isolates). The majority of studies also noted a high frequency of these microorganisms in foot infections of diabetic patients (1,2,18).

Compared with earlier reports, we recovered fewer anaerobic species (1,18). Our patients did not have chronic draining wounds, and only 9% had gangrene associated with their infections. This may be an indication of fewer anaerobic species among nonthreatening lower-extremity infections, which is also reported earlier (19). *Clostridium* species were rarely isolated.

The present study confirms that MDRO infection is extremely common in hospitalized patients with diabetic foot ulcers. This is in accordance with the report of Heurtier et al. (4). Almost two-thirds of our patients were infected with MDROs. The prevalence of both MRSA isolates and ESBL-producing gram-negative bacteria was higher in our population as compared with previous studies (4).

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. This is reinforced by the fact that similarly high rates of MRSA and ESBL production were reported in soft tissue infections from our institute earlier (20,21). The majority of orthopedic wound infections were also caused by resistant bacteria; 48.8% of gram-negative bacteria were ESBL producers, and 30.0% of *S.aureus* were methicillin resistant (22). Thus, MDROs appear to be firmly entrenched in our patient population. 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 a worse outcome

We could not elicit the previous hospitalization details for the same wound in our study subjects. This information could have helped in explaining the reasons for the high prevalence of MDROs in our patients.

In the univariate analysis, the only factors significantly associated with MDRO infection were the presence of neuropathy, ulcer size >4 cm^2, and osteomyelitis. MDRO infection in foot ulcers was associated with the requirement for surgical treatment ($P < 0.01$). In the multivariate analysis, the presence of neuropathy and the ulcer size >4 cm^2 were still significantly associated with MDRO infections. Appropriate antibiotic therapy is required in such patients to reduce morbidity and amputations.

Our results indicate that adequate control of blood glucose levels is more common in patients with non-MDRO–infected ulcers as compared with MDRO–infected ulcers, and further, higher mortality rates were reported in patients with diabetic foot syndrome whose blood glucose levels were poorly controlled (23). 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 (24), we found similar duration of hospital stay in both MDROs and non-MDROs. 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.

In conclusion, this is perhaps the first Indian study to report on MDRO infection in diabetic foot ulcers. The prevalence of MDROs was alarmingly high and was associated with increased requirement for surgical treatment. These findings suggest that prospective multicenter studies are required to assess the appropriate empirical antibiotic regimen in diabetic foot ulcers taking into consideration the etiology of ulcers. In addition, the results alert us that proper management of antibiotics must be implemented to decrease the incidence of MDRO infection in this population, lest we soon run out of effective antimicrobials for our patients.

Acknowledgments— We thank the Indian Council of Medical Research, New Delhi, India, for supporting this study.

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