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Research article

Pattern of antimicrobials used to treat infected diabetic foot in a tertiary care hospital in Kolar

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ABSTRACT

Foot infections are common among diabetic patients and their sequelae are the most common cause of disability and hospital admissions. The objectives in the treatment of diabetic foot infections are to avoid major limb loss and to retain function. In this prospective study including 60 patients with diabetic foot infection, relevant data was taken as per the proforma designed for the study. Empirical antimicrobials administered were recorded. Following culture and sensitivity report, antimicrobials were changed if required. In our study, 42 were males with mean age of 56.69 ± 11.75 years and 18 females with mean age of 55.38 ± 11.77 years. Ulcers of the foot were the most common presentations. Foot infections were of Meggit Wagner grade II to grade IV. Ciprofloxacin, chloramphenicol, cephalexin or combination therapy of ciprofloxacin + metronidazole or ceftriaxone + metronidazole was empirically used. Wound cultures revealed predominance of E.coli, Staphylococcus aureus, Pseudomonas and Klebsiella. Surgical intervention was done in 41 patients. In 22 patients, antimicrobials were changed to amikacin, ceftriaxone with metronidazole and ciprofloxacin with clindamycin. Those who underwent amputation had a significantly higher ($P < 0.05$) incidence of ischemic diabetic foot, HbA_1C, blood sugar > 196 mg/dL and duration of administered antimicrobials for > 11 days. β lactam and aminoglycosides were the commonly used antimicrobials. Gram negative organisms were sensitive to amikacin, while MRSA to vancomycin, clindamycin and chloramphenicol. Additional local treatment of wound produced better outcome. Early surgical intervention with antimicrobials had a favorable outcome.

Key words: Antimicrobials, Early surgical intervention, Glycemic control, Infected diabetic foot

1. INTRODUCTION

Foot infections in diabetic patients are among the most common bacterial infections encountered in clinical practice [1]. These infections and their sequelae such as gangrene, osteomyelitis, septicemia and finally amputations are the most common cause of disability and the reason for most hospital admissions among diabetics [2]. Objective data about efficacy of various antimicrobial treatments is not clear. Hence this study was planned to evaluate the pattern of antimicrobials used in treatment of infected diabetic foot and to analyse the complications of diabetic foot.

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2. MATERIALS AND METHODS

A prospective study was conducted with 60 diabetic foot infection patients admitted to the wards of medicine and surgery at R.L. Jalappa Hospital and Research Centre, Kolar between 1/4/2008 to 1/3/2009. Age, sex, co-morbid disease, random blood sugar, HbA_1C, organism isolated, antimicrobials used, and duration of hospital stay were recorded. Empirical antimicrobials were administered after taking swab for pus culture and sensitivity. Antimicrobials were changed if warranted. The data obtained was analyzed using descriptive statistics. The results were expressed as mean ± standard deviation. Pearson's correlation was done to determine the association between blood glucose and wound healing. Known risk factors from the literature included in a multiple logistic regression model to analyse the independent association of these risk factors with a higher risk of

undergoing amputation. The median was used as cut-off point to dichotomise these variables. Variables independently associated with a higher velocity in this logistic regression analysis were defined as 'major risk factors'.

3. RESULTS

Among 60 patients included in the study, 42 (70%) were males and 18 (30 %) females, with male to female ratio of 2:1 approximately. The mean age of males and females was 56.69 ± 11.75 years and 55.38 ± 11.77 years respectively. 35 (58%) patients were from semi-urban and 25 (42%) were from rural areas. 59 (98%) patients had Type 2 diabetes and only 1 (2%) patient had Type 1 diabetes. Among Type 2 patients , 26 (60%) were on oral anti-diabetic agents, 10 (23%) patients were on intermediate acting insulin and oral anti-diabetic drugs and the rest 7 (16.27%) were on intermediate acting insulin. 16 patients were not on any treatment for diabetes and presented to the hospital for the first time. 9 patients presented with complication of diabetes like nephropathy, retinopathy, neuropathy and peripheral vascular disease, nephropathy being commonest. 10 (17%) patients had co-morbid illness of which hypertension was seen in 5 patients.

Foot infections varied from grade II to grade IV of Meggit Wagner (Table 1). 30 patients presented with ulcer (neuropathic, ischemic and neuro-ischemic type), 11 with cellulitis and 8 with gangrene. In patients presenting with ulcer, wound was cleaned with normal saline and hydrogen peroxide. Dressing was done with metronidazole gel and povidone iodine ointment. All 60 patients received empirical antimicrobials of which 41 underwent surgical intervention (mainly debridement). The empirically administered antimicrobial is shown in Table 2. 25 patients received single drug and the rest combination of drugs. 2 patients were started on empirical chloramphenicol based on previous clinical experience as osteomyelitis was suspected. Imipenem, ceftriaxone, and amikacin were started empirically when infection was of a severe nature like septicemia and gangrene.

Culture reports revealed two organisms in 30 (50 %), single organism in 23 (38%) and more than 2 organisms in 7 (12%) patients. Culture and sensitivity was not done for anaerobes, but based on the foul smell of pus discharge, anaerobic infection was suspected and metronidazole was administered systemically. Fig. 1 shows 99 bacterial isolates, of which 59 were gram negative bacilli and 40 gram positive cocci.

The patients who underwent amputation were compared with non-amputated patients. On the basis of logistic regression analysis in comparison with patients treated conservatively, those patients who underwent amputation presented a significantly higher incidence ($P < 0.05$) of ischemic diabetic foot, first blood sugar on admission > 196 mg/dL, $HbA_1C > 7$ and duration of antimicrobials administered for more than 11 days. The odds ratio and P values are shown in Table 3. Multivariate logistic regression was done for the above factors. The odds ratio was found to be 6.052 for ischemic diabetic foot, 6.959 for $HbA_1C > 7$.

Table 1

Duration of antimicrobial therapy, hospital stay, and appearance of granulation tissue

Diagnosis	No. of patients (n)	Duration of antimicrobials administered (days)	Duration of wound healing (days)	Duration of hospital stay (days)
Gangrene	8	10.6 ± 3.20	26.12 ± 26.46	36.37 ± 26.70
Neuroischemic ulcer	10	11.00± 1.00	19.88 ± 4.48	22.5 ± 8.11
Ischemic ulcer	10	12.67 ± 6.47	34.00± 22.90	34.50 ± 24.70
Neuropathic ulcer	10	12.62 ± 4.27	22.10 ± 5.70	31.30 ± 12.80
Cellulitis	11	12.00 ± 6.00	18.63 ± 7.81	31.63 ± 18.19
Infection in amputated stump	3	13.00 ± 9.50	22.66 ± 22.8	29.33 ± 24.00
Abscess	4	9.66 ± 0.577	21.50 ± 2.30	25.75 ± 3.86
Osteomyelitis	4	12.25 ± 5.25	23.75 ± 13.67	37.00 ± 16.20
TOTAL	60	11.71 ± 1.17	23.58 ± 4.79	31.04 ± 5.07

All values are given in mean ± SD.

Table 2

Empirically administered antimicrobials

Type	Monotherapy	Combination Therapy
β Lactam antimicrobials	cephalexin, amoxicillin, imipenem	ceftriaxone / cefotaxime / imipenem + metronidazole
Fluoroquinolones	ciprofloxacin, gatifloxacin	ciprofloxacin + metronidazole / tinidazole / amikacin
Aminoglycosides	amikacin	amikacin + metronidazole
Macrolides	azithromycin	-
Sulphonamides	cotrimoxazole	-
Broad spectrum	chloramphenicol	-

The mean duration of administration of changed antimicrobials was 11.17 ± 1.17 days. As shown in Table 4, debridement was the most frequent surgical intervention and 6 patients underwent split skin graft. Surgical intervention along with antimicrobials had a favorable outcome on the diabetic foot infections like better and faster wound healing and decrease in hospital stay. The mean glycated hemoglobin was 7.80 ± 0.80. Pearson's correlation analysis was done with wound healing (days) and mean blood glucose (mg/dL) as independent variable. The level of significance was $P < 0.05\%$. So there was a positive correlation between wound healing and glycemic control. In 22 patients, antimicrobials were changed to amikacin, ceftriaxone with metronidazole and ciprofloxacin with clindamycin (Table 5).

4. DISCUSSION

Diabetic foot ulcer is the most common complication requiring hospitalization and associated with non-traumatic lower extremity amputations. Role of physicians in the prevention, early diagnosis and management of diabetic foot complications is of utmost importance. In this study, most of

Table 3
Independent risk factors significantly associated with amputation

	Univariate analysis			Multi-variate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Ischemic diabetic foot	5.314	1.64 - 17.18	0.0050	6.052	1.35-26.96	0.0100
First blood sugar > 196 mg /dL	8.590	2.58 - 28.52	0.0001	0.111	0.02-0.68	0.0170
HbA_1C	4.660	1.13 - 19.24	0.0330	6.959	1.23-39.37	0.0200
Duration of antimicrobials administered	7.470	2.20 - 24.39	0.0010	0.069	0.01-0.40	0.0030

Table 4
Surgical intervention

Procedures done	No. of patients	Percentage
Debridement only	13	21.66
Disarticulation of toes	7	11.66
Below knee amputation	6	10
Ray amputation	3	5
Above knee amputation	1	1.6
Combined procedures		
Incision and drainage	4	6.6
Debridement and disarticulation	3	5
Debridement + Above knee amputation	1	1.6
Incision and drainage + debridement	1	1.6
Incision and drainage + disarticulation of toes	1	1.6
Secondary suturing	1	1.6
TOTAL	41	(68)

Table 5
Change of antimicrobials regimens after culture in 22 patients

Drugs	No. of patients	Percentage
ceftriaxone + amikacin	10	45.45
amikacin	6	27.27
chloramphenicol	3	13.63
ceftriaxone	1	4.54
ciprofloxacin + metronidazole	1	4.54
ciprofloxacin + clindamycin	1	4.54

the patients were from semi-urban areas (58.33%) who are predisposed to diabetes because of lifestyle changes due to urbanization such as decreased physical activity, consumption of excess calories. Similar finding were observed in another study [3]. The occurrence of diabetic foot infection in males is twofold higher than females with mean age of males and females 56.69 ± 11.75 years and 55.38 ± 11.17 years, respectively. Males appear to be at a greater risk for diabetic foot infection, because studies have shown higher prevalence of peripheral arterial occlusive disease, sensory neuropathy. Incidence of amputations and mortality are significantly lower in women. The others factors which influence the role of gender are activity level, smoking behavior, hormonal differences, degree of compliance, prevalence and severity of vascular disease, neuropathy, and uncontrolled diabetes [4,5]. So in general, women seem to have fewer complications and a better prognosis than men.

We observed that, 42% of the patients suffered from diabetes for a period of 5 years. Longer duration of diabetes with poor blood glucose control may contribute to increased incidence of foot infection. The occurrence of co-morbid illness was 17%, commonest being hypertension and 20% of patients had previous history of hospital admission for foot infections and surgical interventions indicating that the treatment for diabetes was inadequate.

Ulcers were commonly seen on the toes, dorsum of the foot and plantar surface. Majority of foot infections were of Wagner grade II to grade IV. Ischemic ulcers (31%) were present on dorsum of the foot and neuropathic ulcers (23%) were on the plantar aspect. Neuropathy predisposes a diabetic to unrecognized injury due to loss of sensation. Therefore these patients often present with advanced stages of ulcers. Table 1 shows the common complications like cellulitis, gangrene, osteomyelitis, abscess and infection in amputated stump.

Insulin is indicated for complications of Type 2 diabetes. In our study, patients with diabetic foot were administered human regular insulin. The dose of regular insulin was adjusted based on sliding scale using random blood sugar method. Thereafter, the mean random blood sugar was 196.6 ± 23.12 mg/dL. The mean glycated hemoglobin levels were 7.8 ± 0.8, normal being 6-7 which indicates glycemia was not under control during the past 3 months and so, the patients manifested with infection. Hyperglycemia should be monitored closely and controlled because it increases the virulence of microorganisms [6]. Good glycemic control has a positive impact on control of infection and wound healing as shown by Pearson's correlation analysis. Hence maintenance of tight glycemic control prevents development of diabetic foot and subsequent infection by retarding progression to peripheral neuropathy.

All the patients in our study received antibiotics empirically. 42 % were given single drug and 58 % were on combination therapy and their mean duration of administration being 9.79 ± 1.33 days. Wound cultures revealed 62% polymicrobial contamination and 38% monomicrobials. Gram negative bacilli were the commonly isolated organisms followed by gram positive. Predominant organisms were E.coli, Pseudomonas and Staphylococci aureus (Fig. 1). The studies of Chang *et al* [7] and Benedicto *et al* [8] also have gram negative isolates. We observed an increase in hospital acquired infections by Klebsiella, Pseudomonas. These findings correlated with a study done by Llanes *et al* [6]. Though S.epidermidis is a skin pathogen, it would have manifested with infection because of decreased immunity in these patients. WHO has included diabetes in classification of immuno-deficiency diseases. Infection occurs with a greater frequency and severity in diabetics than in non-diabetics [9].

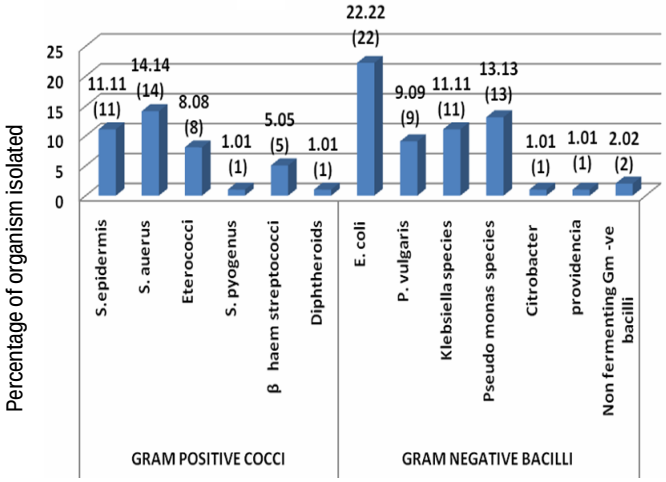

Fig.1. Percentage of organisms isolated in culture and sensitivity report (numbers in parenthesis indicate number of isolates).

Table 6
Anti-biogram

Sl. No.	Organism	Antimicrobials
1	E.coli	amikacin, chloramphenicol, gentamicin
2	MSSA	oxacillin, chloramphenicol, gentamicin, and imipenem.
3	MRSA	vancomycin, amikacin, chloramphenicol, clindamycin
4	Pseudomonas species	imipenem, amikacin , ciprofloxacin
5	Klebsiella species	ceftriaxone , gentamicin, amikacin
6	S. epidermidis	amikacin, chloramphenicol, clindamycin
7	Proteus vulgaris	amikacin, ceftriaxone, ciprofloxacin, chloramphenicol
8	Enterococci	chloramphenicol, vancomycin, amikacin, gentamicin
9	β hemolytic streptococci	chloramphenicol, gentamicin

MSSA- methicillin sensitive staphylococci; MRSA- methicillin resistant staphylococci

The 9 (15%) MRSA strains were isolated majority were resistant to ampicillin, cephalosporins and gentamicin but sensitive to amikacin and vancomycin (Table 6). Low virulence colonizers such as coagulase negative staphylococci and diptheroids were isolated because impaired host defenses around necrotic soft tissue of bone. Following culture and sensitivity report, 37 % of patients were changed over to ceftriaxone with amikacin (45%). Administration of amikacin was done by careful monitoring of kidney functions and dose reduction was done based on serum creatinine. Others received ceftriaxone with metronidazole. The mean duration of administration of changed antibiotics were for 11.17 ± 1.7 days. Other 60 % of patients were continued with empirical treatment of ciprofloxacin, cephalexin, chloramphenicol or combination therapy of ciprofloxacin + metronidazole or ceftriaxone + metronidazole. In patients with osteomyelitis, oral fluoroquinolones were administered because they have good tissue penetration including bone [10]. 15 % of MRSA were isolated of which 5% were from patients suffering from osteomyelitis and they were sensitive to amikacin, clindamycin, chloramphenicol and vancomycin. The patients were treated with amikacin, clindamycin or chloramphenicol. Oral clindamycin has excellent penetration into bone and maintains good activity against staphylococci, streptococci and anaerobes. 18% patients suffered from cellulitis. They were treated with cotrimoxazole, cephalexin, gatifloxacin and chloramphenicol.

It has been shown that aggressive surgical approach (within 72 h) combined with a broad-spectrum antibiotic has a favorable outcome with reduction in limb loss in diabetic foot infections [11]. This approach has decreased incidence of major amputations and readmissions [12]. This kills residual micro-organisms in the zone of inflammation at the margins of the surgical wound, the lymphatic system draining the site of infection or in the marrow cavities of involved bones and to treat bacteremia seeded from primary focus.

In 30% of patients debridement was done which involves removal of nonviable, infected tissue (including bone) from open wounds, as well as surrounding calluses, until a new border of healthy, bleeding soft tissue and uninfected bone is created [13]. Studies have shown that bacterial levels > 10^5 g/tissue appear to impede healing by producing proteases, causing migration of polymorphs to wound and predisposing to systemic spread. Therefore, debridement plus proper antimicrobials plays an important role in infection control and healing [14].

Disarticulation was done in 16% of patients, below knee and above knee amputations were 10% and 3%, respectively. Incision and drainage done in 7 % of patients which helped in opening of closed spaces that serve as a reservoir for anaerobic bacterium. Secondary suturing was done in 2% of patients. We observed patients undergoing amputation at an early age (mean 58 years) as compared to other studies which was around 61 and 75 years [15,16]. This could have been due to the patient being undetected for diabetes for prolonged period, which might have lead to the progression of the disease. The other factor could have been early onset of the disease and poor patient compliance giving ample time for development of chronic vascular complications and poor patient compliance.

Age, sex, duration of diabetes and previous history of diabetic foot infection were not associated with higher incidence of amputation [17]. Level of glycemic control assessed by HbA_1C was associated with significant risk of amputation [18,19]. Diabetics have a higher incidence of peripheral vascular disease and hence patients having ischemic diabetic foot have a increased incidence of amputation [17]. In this study, patients having blood sugar > 196 mg/dL have 8 times risk of amputation as compared with patients with blood sugar < 196 mg/dL. Amputation was most frequent in patients who were administered antimicrobials for a period of more than 11 days. Thus HbA_1C, blood sugar > 196 mg/dL, ischemic diabetic foot and duration of administered antimicrobials for > 11 days are independent risk factor for amputation.

Following surgical intervention, metronidazole and povidone iodine were used topically. Metronidazole was effective against anaerobes which were found in increased frequency in the wound because aerobes favour their growth by lowering of oxidation- reduction potential. Local treatments have the advantage of high local concentration of the drug and lack of systemic toxicity. Topical application of antimicrobials may help in good control of wound infection. In 32% of patients surgical intervention was not required.

In majority of patients, the granulation tissue appeared 19^{th} to 28^{th} day following surgical intervention. Mean duration of hospital stay was 31.04 ± 5 days. 2 % mortality was observed, the patient having wet gangrene leading to septicemia. Rest of the patients was discharged.

5. CONCLUSIONS

The β Lactam antimicrobials, fluoroquinolones, aminoglycosides, macrolides, chloramphenicol were the commonly used empirical antimicrobials. Gram negative organisms were sensitive to amikacin, while MRSA were sensitive to vancomycin, clindamycin and chloramphenicol. Additional local treatment of wound had produced better outcome. Early surgical intervention (within 72 h) with combination of antimicrobials and glycemic control had favorable outcome in our diabetic foot infection patients. Ischemic diabetic foot, HbA_1C, blood sugar > 196 mg/dL and duration of administered antimicrobials for > 11 days were independent risk factors for diabetic foot amputation.

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