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Antimicrobial resistance pattern of cephalosporins in treatment of diabetic foot infection

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ABSTRACT

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Diabetes mellitus is a chronic disorder and affects large segment of population and is a major public health problem. Diabetic foot problems, such as ulcerations, infections and gangrene are the most common cause of hospitalization among diabetic patients. Although widely accepted as broad-spectrum antibiotics, cephalosporins are not active against all the bacteria commonly isolated in a hospital microbiological laboratory. Increasing prevalence of anti-microbial resistance is a major factor determining morbidity and mortality. The objective of the study is to study prescribing practice of cephalosporins, evaluate the sensitivity pattern of different generations of cephalosporins and to assess the treatment failure of cephalosporins in diabetic foot infections. A prospective study was done on 77 patients who fulfilled the inclusion criteria and had diabetic foot were included; prescribing pattern of cephalosporins and culture and sensitivity testing was studied for a period of 9 months. Retrospectively culture and sensitivity reports of 230 patients from last one year were screened. Cefotaxime was the most commonly prescribed antibiotic. Sensitivity pattern showed that 41.5% of gram-positive cocci were sensitive to cefotaxime, whereas 25% of gram-negative bacilli were sensitive. Gram-positive cocci were 29.3% resistant to Cefotaxime, whereas 57.1% of gram-negative bacilli were also resistant.Finally, organisms which were originally sensitive developed resistance approximately in a span of two weeks, probably due to antibiotic pressure. Treatment for longer duration may result in drug resistance. Finally, cefotaxime remains an active player in the treatment of diabetic foot infections, only when cautiously used resistance can be contained.

Keywords: Diabetic foot infections, Prescribing practices, Cephalosporins, Cefotaxime, Culture/sensitivity testing.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by high Blood sugar levels that result from defects in Insulin secretion, or action, or both. Diabetes mellitus, commonly referred to as diabetes was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycaemia) lead to spillage of glucose into the urine, hence the term sweet urine. Diabetes mellitus is a chronic disorder and affects large segment of population and is a major public health problem. In general 252 million people are diabetics worldwide. India alone currently counts over 40 million people with Diabetes, which is estimated to touch 73.5 million by 2025 as a consequence of longer life expectancy, sedentary lifestyle and changing dietary patterns. The population of India is more than 1 billion, and with a prevalence of type 2 diabetes of between 2.4% and 6.5%, it is estimated that there are 35 million Indians with type 2 diabetes.

Foot infections are the most common problems in people with diabetes. Diabetic foot infections are infections that can develop in the skin, muscles, or bones of the foot as a result of the nerve damage and poor circulation that is associated with diabetes. People who have diabetes have a greater than average chance of developing foot infections because a person who has diabetes may not feel foot pain or discomfort, problems can remain undetected until fever, weakness, or other signs of systemic infection appear. As a result, even minor irritations occur more often, heal more slowly and / or more likely to result in serious health problems.[1]

Foot infections increases drastically in hospital stays. In this 4% of diabetics develop foot ulcer annually, 25% in lifetime, 45-75% of all lower extremity amputations are in diabetics, 85% of these preceded by foot ulcer, two-thirds of elderly patients undergoing amputation do not return to independent life, studies have shown less cost for saving a limb than amputation.

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Diabetic foot infections result from the simultaneous action of multiple contributing causes. The major underlying causes are noted to be peripheral neuropathy and ischemia from peripheral vascular disease. More than 60% of diabetic foot ulcers are the result of underlying neuropathy. The development of neuropathy in affected patients has been shown in animal and in vitro models to be a result of hyperglycemia-induced metabolic abnormalities. Peripheral arterial disease (PAD) is a contributing factor to the development of foot ulcers in up to 50% of cases. It commonly affects the tibial and peroneal arteries of the calf. Endothelial cell dysfunction and smooth cell abnormalities develop in peripheral arteries as a consequence of the persistent hyperglycemic state. There is a resultant decrease in endothelium-derived vasodilators leading to constriction.[2]

Antibiotics are chemotherapeutic agents that inhibit or abolish the growth of microorganisms, such as bacteria, fungi or protozoans, and are developed to kill microorganisms. Microorganisms develop and disseminate resistance as a reaction to antimicrobials in accordance with the rules of physics, evolution and natural selection. In spite of considerable developments in antibiotics, antibiotherapy, science, medicine and medical care, infectious diseases and infectious complications related to resistant bacteria, such as staphylococci, respiratory pathogens (e.g., *Streptococcus pneumoniae*), Gram-negative bacilli, as well as fungi and viruses, remain important causes of human morbidity and mortality.[3]

Antibiotics fight bacteria through a variety of mechanisms. Penicillins, cephalosporins, carbapenems, and vancomycin kill bacteria by damaging or inhibiting the synthesis of bacterial cell walls. Other antibiotics act through effects on bacterial DNA or RNA (quinolones and rifampin), proteins (aminoglycocides, chloramphenicol, tetracyclines, and macrolide antibiotics), or metabolism (trimethoprim and sulfonamides).

Bacteria are said to have "intrinsic resistance" to an antibiotic when their normal characteristics render them immune to the antibiotic's mechanism of effect. Intrinsic resistance is not affected by misuse of antibiotics. In fact, it is valuable in determining which antibiotic will be most effective against a certain microbe. For example, the outer membrane of gram-negative bacteria makes them relatively impermeable to hydrophobic compounds such as macrolide antibiotics, thus conferring intrinsic resistance to these drugs. Some bacteria can also use temporary strategies in which different genes are expressed or suppressed in order to enable survival in the presence of antibiotics, with expression patterns returning to normal once the threat posed by those particular drugs has passed.[4]

In 1945, after penicillin had been introduced into medicine, an antibiotic-producing species of Cephalosporium was isolated from a sewage outfall in Sardinia. Four years later in Oxford, this organism was found to produce several antibiotics, one of which was a penicillin with a new side-chain, penicillin N. During a chemical study in 1953, this penicillin was shown to be contaminated with a second substance, cephalosporin C, which contained a beta-lactam ring but was resistant to hydrolysis by a penicillinase (beta-lactamase). At that time, penicillinase-producing Staphylococci were causing a serious problem in hospitals. The isolation of the nucleus of cephalosporin C (7-ACA) enabled pharmaceutical manufacturers to produce many thousands of cephalosporins, some of which have been effective in the treatment of serious infections by a number of Gram-positive and Gram-negative bacteria. The cephalosporins, like the newer penicillins, have a very low toxicity and have greatly extended the range of chemotherapy. New, sensitive screening methods have revealed further families of clinically useful substances that contain a reactive beta-lactam ring. [5]

Antimicrobial Resistance:

Drug resistance is a global problem affecting both developed and undeveloped countries. Antimicrobial resistance is a natural consequence of antimicrobial use, which kills the sensitive organisms leaving the resistant ones to survive and multiply (selection of resistance).Overuse and misuse of antimicrobials do not help patients, they merely add to the problem of resistance and waste resources.

Antimicrobial resistance is on increase – threatening our ability to treat some of the infectious disease that causes most deaths. Infectious diseases still account for 45% of deaths in low income countries and for almost one in two premature deaths worldwide.

Today antibiotics remain the first line therapy for conquering bacterial infections. However, their indiscriminate use is no longer viewed as benign. Treatment with these drugs is acknowledged to be a two-edged sword. As antimicrobial agents have been misused or overused, bacteria have fought back with a selection process by which certain strains are no longer susceptible to one or more agents. Each new use of these drugs, in fact, contributes to the evolution of resistant microorganisms. [6] As a result bacteria that once seemed to be losing the battle for survival have re-emerged to create therapeutic dilemmas with resulting increased risk of treatment failure and disease complications.

Patients want antibiotics, and physicians continue to prescribe them in situations where antibiotics may be withheld for many reasons. From the patient's point of view, the prescribing of an antibiotic validates that the patient does

have an illness that a diagnosis has been made and the illness is amenable to treatment. The fact that there is a cure for their problem reassures them that the illness is not serious. [7]

The cephalosporin antibiotics have become a major part of the antibiotic formulary for hospitals in affluent countries. They are prescribed for a wide variety of infections every day. Their undoubted popularity relies upon lesser allergenic and toxicity risks as well as broad spectrum of activity. It is the latter feature; however, that encourages the selection of microorganisms that are resistant to these agents. There are long-term implications for the treatment and control of this heterogeneous group of super infections. When clinicians evaluate a septic patient, it is understandable that they choose empirical therapy with a cephalosporin whilst awaiting microbiological and other tests, since bacterial identification and antimicrobial testing usually require 24-48 h. The broad-spectrum capability of these drugs, however, encourages rapid overgrowth of some microorganisms that are neither eliminated nor inhibited by therapy. These organisms not only have pathogenic potential, they may also be multiply resistant to antibiotics. This review discusses the evidence that cephalosporin usage is the most important factor in the selection and propagation of microorganisms such as *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, Penicillin-resistant Pneumococci, multiply resistant coliforms and vancomycin-resistant Enterococci, the continuing increase of which threatens the future of antimicrobial therapy.

Although widely accepted as broad-spectrum antibiotics, cephalosporins are not active against all the bacteria commonly isolated in a hospital microbiology laboratory. Organisms that are not inhibited by cephalosporin therapy consequently overgrow, with varying potential to cause infection. Some of these are instantly recognizable as pathogens; others, although originally regarded as commensal or of low risk status, have subsequently been shown to cause disease. [8] Furthermore, there is an association between cephalosporin usage and the emergence of multiply resistant organisms.

Prescribing practices of physicians has become a major factor in today's scenario for treating foot infections. Inappropriate use of cephalosporins has become a major problem in the treatment, as there has been a marked increase in resistivity seen among bacterial pathogens due to over prescribing or under prescribing of antibiotics. The Objective of the study is to evaluate the prescribing pattern of different generations of cephalosporins, evaluate the sensitivity pattern and assess the treatment failure of cephalosporins in diabetic foot infections.

METHODOLOGY

The study was carried out and patients were selected from surgery ward after obtaining clearance from Ethical Committee.

Inclusion criteria:

- All male and female patients aged between 40-80 years, who were admitted to the surgical inpatient department with diabetic foot infections.
- Patients with type 1 diabetes, and above 40 years of age.
- Patients with type 2 diabetes.
- Patients prescribed with empirical treatment of cephalosporins.

Exclusion criteria:

- Patients who were admitted to the surgical inpatients units, both male and female below the age of 40 years who had foot infections but were not diabetic.
- Patients with type 1 diabetes, who were below the age group of 40 years.
- Diabetic foot infected patients prescribed with empirical treatment of cephalosporins, but who were not referred for anti-microbial sensitivity testing.
- Diabetic foot infected patients prescribed with treatment other than cephalosporins.

Prospectively 77 patients who met the initial inclusion criteria were selected for the study during the study period of 9 months from August 2009 to April 2010. Prescription data was collected from the medical records that contain all the prescriptions for each patient, providing information about the demographic details, drugs prescribed empirically, culture and sensitivity reports of the patients were collected for analysis.

The data of the first culture (to determine the effect of empirical treatment) and sensitivity reports of 77 patients, repeat one culture one sensitivity and repeat two culture two sensitivity were collected (to determine the effect of cephalosporins).

Similarly, retrospectively culture and sensitivity reports of 230 patients were screened to determine the prevalence of sensitivity and resistance pattern of particular organism to different cephalosporins were determined. The data obtained was tabulated and results are interpreted using cross tabulation for SPSS software has been used. Significance was reported by 95% Confidence Interval which was calculated by binomial probability method.

RESULTS AND DISCUSSION

A total of 77 patients who fulfilled the inclusion criteria and who were admitted to any one of 6 surgical units of Rajah Muthiah Medical College and Hospital were included in this study, which was carried out for 9 months between August 2009 to April 2010.

Among the 77 patients with diabetic foot infections from surgical units, 70% were male and 30% were female. According to Llanes, male population accounts for more hospital admission than females in diabetic foot infections. In our study 90.4% patients had type 2 diabetes and only 9.6% had type 1 diabetes (table-1). We observed that 48.2% patients had ulcer followed by 27.27% with cellulitis and 20.78% with gangrene. According to a study by Anandi C, out of 107 patients with diabetic foot lesion, 56% had ulcer followed by 26.1% cellulitis and 15.9% gangrene. [9]

The present study illustrates the infection is due to gram-positive cocci, gram-negative bacilli and polymicrobials. Among these 65.6% were gram-negative bacilli followed by 20.02% gram-positive cocci and 14.92% polymicrobials were isolated. Out of which four types of gram-positive cocci and seven types of gram-negative bacilli were recorded. Our study revealed that E. coli(19.5%), Klebsiella (14.35%), Pseudomonas (10.8%) and Citrobacter (10.3%) were the most common gram-negative organisms isolated. Staphylococcus aureus (14.4%) and Enterococcus (11.8%) were the most common gram-positive pathogen isolated in our study.

These results were comparable with a similar study which was conducted in Bangalore by Vidya D et al, in diabetic foot infections where the most commonly isolated organisms were Staphylococcus aureus, Citrobacter species, Pseudomonas species, Enterococcus and Pneumococci. [10]

According to Motta RN et al, entero bacteriaceae group (97.8%) were the most frequently isolated bacteria. [11]According to David BS, extended-spectrum â-lactamase (ESBL)-producing organisms are an increasing problem for practitioners dealing with infectious disease. Escherichia coli, Klebsiella pneumoniae and Klebsiella oxytoca are the most common ESBL-producing pathogens. [12]

Sensitivity testing was done for patients with gram-negative bacilli in diabetic foot infection and it was found that organisms showed increased resistance patterns to cephalosporins, while in case of infections due to gram-positive cocci, cephalosporins were effective. Prevalence of polymicrobials and efficacy of cephalosporins on them was not studied separately.

According to the reporting at ICAAC conference, ESBLs are beta-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. These cephalosporins include cefotaxime, ceftriaxone, and ceftazidime, as well as the oxyimino-monobactam aztreonam. The clinical relevance of ESBLs has been well documented by numerous published case reports describing clinical failures with the use of third generation cephalosporins such as these oxyimino-cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) as well as with the use of cefoxetin and the fourth generation cephalosporin, cefepime. Thus, the problem of ESBLs is clinically important, yet remains relatively unappreciated by most clinicians. This is because many clinical microbiology laboratories continue to mistakenly report these gram-negative bacillary isolates as

Table No.1 Age Distribution with Sex

Age in years years	Male (%)	Female (%)	Overall (%)
41-50	14(25.92)	7(30.43)	21(27.27)
51-60	15(27.77)	9(39.13)	24(31.16)
61-70	17(31.48)	4(17.39)	21(27.27)
71-80	8(14.81)	3(13.04)	11(14.28)
Total	54(100.0)	23(100.0)	77(100.0)

Table 2: Prescribing Pattern of Drugs

Drug combination of Drug	Dosage	Empirical N=77(%)	After first culture N=77(%)	After repeat culture one N=48(%)	After repeat Culture two N=9(%)
Cefotaxime	1gm IV BD	41(53.24)	26(33.76)	5(10.41)	1(11.1)
Ceftriaxone	1gm IV BD	4(5.19)	13(16.38)	6(12.50)	1(11.11)
Cefoperazone +Sulbactum	1.5gm IV BD	28(36.36)	19(24.67)	10(20.83)	4(44.44)
Cefepime(Cpm)	1gm IV BD	3(3.89)	3(3.89)	1(2.08)	-
Cefexime(Cfx)	1gm IV BD	1(1.29)	2(2.59)	1(2.08)	-
Drugs other than cephalosporins	-	-	14(18.18)	25(52.08)	3(33.33)

susceptible due to difficulties in identifying which isolates possess this important beta-lactamases.[13]

In the present study, injection cefotaxime (53.24%) was the most commonly prescribed drug followed by injection cefoperazone + salbactum (36.36%) and injection ceftriaxone (5.19%). (Table-2).

Out of the 77 patients in first culture, 47 patients yielded growth,17 had no growth and 13 had normal skin flora (Table-3).So the sample for repeat one culture is 47 (n=47) and similarly repeat two culture is 8 (n=8).(Table-3)

Out of 77 patients, 41 (53.24%) patients prescribed with cefotaxime as empirical treatment and pus sample were sent for culture and sensitivity test. In 19 (46.3%) patients, there was either no growth or normal flora and 22 (53.7%) patients yielded growth. Antibiograms were available only for 17 isolates. Out of these 17, 8 gram-negative bacilli (47.1%) and 1 polymicrobial (5.9%) were resistant to empirical drug after first culture [With 95% CI of 26.17-69.04 and 95% CI of 1.05-26.98 respectively].

Without following the antibiograms, cefotaxime was discontinued in 2 (11.8%) (95% CI: 3.29-34.34) patients of the 17 isolates, even though it was sensitive and in 5 (29.4%) (95% CI: 13.28-53.13) patients where antibiograms were not available. It is prudent to inform the microbiologist to include the empirical drug for testing sensitivity pattern of organism in antibiogram, before continuing or discontinuing the drug.

In 4 (23.5%) (95% CI: 9.56-47.26) patients (3 gram-negative and 1 gram-positive organisms isolated), the patients were sensitive to organisms after first culture and developed

Table 3: Growth of Organisms at different points of culture

Contents	First Culture (N=77)	Repeat Culture (N=47)	Repeat Two (N=8)
Normal flora skin	13(16.88%)	4(10.41%)	-
Growth	47(61.03%`)	39(81.25%)	8(100.0%)
No Growth	17(22.07%)	4(8.33%)	-
Total	77(100.0%)	47(100.0%)	8(100.0%)

Table 4: Frequency distribution of organisms isolated

Sl.No	Gram-positive cocci	First culture (n=47)	Repeat one (n=39)	Repeat two (n=8)
1	Enterococcus (E.f)	3(6.38%)	2(5.12%)	-
2	Coagulase positive Staphylococcus aureus (Cps)	4(8.51%)	2(5.12%)	-
3	Coagulase negative Staphylococcus aureus (Cns)	-	-	1(12.5%)
4	Streptococcus (St)	2(4.25%)	2(5.12%)	-
	Total Gram- positive Cocci	9(11.68%)	6(15.38%)	1(12.5%)
	Gram-negative bacilli	**First culture (N=47)**	**Repeat one (N=39)**	**Repeat two (N=8)**
Enterobacteriaceae group				
1	Citrobacter (S)	7 (14.89%)	9 (23.07%)	1 (12.5%)
2	Klebsiella (K)	3 (6.38%)	4 (10.25%)	-
3	E. coli (E.c)	8 (16%)	5 (12.82%)	1 (12.5%)
4	Proteus spp (Pr)	5 (10.63%)	2 (5.12%)	2 (25%)
5	Enterobacter (E)	-	-	-
Other than gram-negative bacilli				
6	Pseudomonas (P)	8 (17.02%)	3 (7.69%)	-
7	Nlfgnb	3 (6.38%)	5 (12.82%)	1 (12.5%)
	Total Gram-negative bacilli	34 (72.34%)	28 (71.79%)	5 (62.5%)
		First culture (n=47)	**Repeat one (n=39)**	**Repeat two (n=8)**
1	Polymicrobials	4 (8.51%)	5 (12.82%)	2 (25%)

Nlfgnb = Non-lactose fermentative gram-negative bacilli other than pseudomonas

Table 5: the percentage sensitivity pattern of organisms in relation to cephalosporins

Organism	Cefotaxime		Cefoperazone		Ceftriaxone		Cefepime		Cefdinir		Ceftazidime		Cefuroxime	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R
C	54.5	36.4	54.5	36.4	45.5	36.4	-	18.2	-	18.2	9.1	18.2	-	18.2
P	14.3	80.9	28.6	57.1	28.6	66.7	4.8	42.9	4.8	38.1	-	38.1	-	23.8
K	16.7	66.7	20.8	17.8	16.7	66.7	-	29.2	-	25.0	4.2	33.3	0	29.2
E.c	31.6	47.4	28.9	60.5	26.3	60.5	2.6	28.9	-	28.9	5.3	36.8	-	26.3
E.f	43.5	26.1	-	26.1	21.7	30.4	-	13.0	-	13.0	-	30.4	-	13.0
Cps	41.7	41.7	-	50.0	-	25.0	-	8.3	-	8.3	-	8.3	16.7	8.3
C	22.2	33.3	44.4	44.4	44.4	55.5	-	11.1	-	-	-	22.2	11.1	-
Pr	50.0	16.7	50.0	33.3	66.7	33.3	-	16.7	-	16.7	16.7	33.3	-	16.7
Nfgnb	-	75.0	8.3	91.7	8.3	75.0	8.3	33.3	-	50.0	-	41.7	-	33.3
St	66.7	-	-	-	33.3	-	-	-	-	-	-	-	-	33.3
K	25.0	75.0	75.0	50.0	25.0	50.0	-	25.0	-	50.0	-	75.0	-	50.0
E	50.0	-	-	50.0	-	-	-	-	-	-	-	-	-	-
Pr	-	100.0	-	-	-	-	-	100.0	-	-	-	-	-	-
Cns	-	33.3	33.3	33.3	-	-	-	-	-	33.3	-	33.3	-	33.3

S- Sensitive, R- Resistance.

Table 6: Frequency distribution of sensitivity pattern of gram-positive cocci and gram negative bacilli

Cephalosporins	Gram positive cocci		Gram negative bacilli	
	Sensitive	Resistant	Sensitive	Resistant
Cefotaxime	41.5%	29.3%	25.0%	57.1%
Cefoperazone	24.4%	31.7%	28.9%	59.4%
Ceftriaxone	14.6%	24.4%	27.3%	58.6%
Cefepime	-	9.8%	2.3%	28.9%
Cefdinir	-	12.2%	0.8%	26.6%
Ceftazidime	-	21.9%	3.9%	34.4%
Cefuroxime	4.9%	14.6%	0.8%	24.2%

resistance after repeat one culture. The CI value was significant at negative side. Irrational withdrawing or long-term prescription of cephalosporins can lead to such resistance.

In 22 patients, repeat culture one was done. Of which 18.2% yielded either commensols or remained sterile. Of the remaining where there was growth 13 (59.1%) (95% CI: 49.13-87.50) patients showed different organisms. Predominant organisms isolated in repeat one culture were: Pseudomonas, Klebsiella, Citrobacter, E. coli, Streptococcus and Enterococcus. The patients could have acquired these organisms as nosocomial spread. Out of 13 different organisms isolated in repeat one culture, 10 (76.92%), 95% CI (49.7%-91.8%) organisms were resistant to the drug. Resistance of nosocomial organisms to drug was biostatistically near to significant value.

Cefotaxime is an effective drug, provided appropriate barrier techniques are required in preventing nosocomial spread. Organisms' originally sensitive developed resistance approximately in span of two weeks, which may probably be due to antibiotic pressure.

Out of 77 patients, 28 (36.36%) patients were prescribed with cefoperazone + salbactum empirically. After treatment, pus samples were sent for culture and sensitivity. In 6 (21.4%) patients there was no growth or normal flora. Out of the remaining, 22 (78.6%) patients yielded growth, antibiograms were available for 20 (71.4%) patients.

Out of 20 patients, 8 (40%) (95% CI: 21.88-61.34) gram-negative isolates, 3 (15%) gram-positive and 1 (5%) polymicrobial were resistant to first culture [12 (60%), 95% CI: 38.06-78.12].

In 5 (25%) (95% CI: 11.19-46.87) patients, gram-negative organisms isolated were sensitive after first culture and developed resistance after repeat one culture. Resistance of gram-negative organisms to cefoperazone+salbactum was bio statistically significant at negative side. This shows that

cefoperazone+salbactum may not be an ideal alternative for cefotaxime; however confidence interval (CI value) is significant on the negative side.

In 22 (78.6%) patients, repeat one culture was done, out of which 4 (18.1%) yielded either commensols or remained sterile. Of the remaining 18 where there was growth, in 11 (61.11%) (95% CI: 38.62-79.69) patients different organisms were isolated. Out of 11 different organisms isolated, 5 (45.45%) (95% CI: 21.3-71.9) were resistant to empirical drug.

CONCLUSION

Although, Cefotaxime is still an active candidate in the treatment of Diabetic foot, the lengthening shadow of resistance implies that it may not be for long. Gram-negative bacilli dominated the resistant pattern compared to the gram positive cocci for Cephalosporin sensitivity.

Organisms which were originally sensitive, developed resistance approximately in a span of two weeks, which can probably be due to antibiotic pressure.

The control and containment of resistance towards antimicrobials by microbes represents universal challenge requiring national and international efforts, as ease of long distance to travel no longer limits spread.

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