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Evaluation of antimicrobial therapy and patient adherence in diabetic foot infections

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ABSTRACT

Background/objectives: Diabetic foot infections (DFI) are common complications among diabetics. These wounds can cause discomfort and often become infected. In India, currently there is a paucity of data on patient adherence towards antibiotic use in DFIs. Therefore, this study was aimed to evaluate antimicrobial susceptibility pattern, antimicrobial therapy and its adherence in DFI patients.

Method: A prospective observation study (N = 150, newly diagnosed DFI patients) was conducted in Kasturba hospital, Manipal over a period of 6 months. Culture and Sensitivity pattern of the microbes of the patients were obtained from hospital data management system to develop cumulative antimicrobial susceptibility pattern. Medication adherence was measured by using Culig adherence scale at the first follow-up visit.

Results: The most common microbes were Methicillin-sensitive *Staphylococcus aureus* (23.9%), *Klebsiella pneumonia* (13.3%) and *Escherichia coli* (13.3%). Inj. Amoxicillin-Clavulanic acid 1.2 gm (28.6%) was highest prescribed empirical therapy in DFI's followed by Inj. Cefuroxime-Sulbactam 2.25 gm (14.6%), Ceftriaxone (0.7%) and Trimethoprim- Sulfamethoxazole (2%) was the most sensitive antibiotic. Cumulative antimicrobial susceptibility pattern shows Chloramphenicol, Colistin, Levofloxacin, Rifampicin has developed resistance towards most of the common organisms in DFI. Statistically significant association was observed between empirical therapy with T.Cefuroxime 625 mg and improved clinical outcomes ($p < 0.001$). Adherence shows that only 14% of patients have high adherence rates during first follow-up visit.

Conclusion: Ceftriaxone and Trimethoprim-Sulfamethoxazole are most sensitive antibiotics towards most common organisms in DFIs. T. cefuroxime 625 mg showed statistically significant improvement in clinical outcomes while adherence is very low in most of the DFI patients.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder with multifactorial etiology characterized by chronic hyperglycemia with disturbances of carbohydrates, fats and protein metabolism. This results from defects in insulin secretion, insulin action or both.[1] International Diabetes Federation (IDF) estimates that India ranks second after china for most diabetics. Low to middle income countries has 80% of world's diabetics. Estimated disease burden were 177 million in 2000, 285 million in 2010.[2] This value is predicted to rise to 642 million by 2040. The number of deaths due to diabetes was estimated as 5 million until 2015.[3] Globally, Diabetic foot infections (DFIs) are defined as skeletal and soft tissues infection in diabetics. In USA, incidence of amputation was 40,000 per year and incidence rate is 80,000 to one lakh amputations per year.[4] DM prevalence has hiked to 30% in developed countries. Furthermore, its prevalence surges with age, and more in working age population.[5] It has been estimated by IDF that 193 million people, or close to half (46.5%) of all people with diabetes, are unaware of their disease.[6] In India, 69.1 million diabetics contribute the overall prevalence of 9.3%. Provincial prevalence of diabetes ranges from region to region, for instance, in Jharkhand (5.3%), Tamil Nadu (10.4%), and Chandigarh (13.6%).[7] A community-based study from north India demonstrates that age standardized prevalence of diabetes and prediabetes were 11.2% and 13.2% respectively. It is also accounted that majority of the population remain undiagnosed (52.1%) and this may account for another 36.1 million.[8]

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Diabetics with infections are difficult to treat since they have impaired micro-vascular circulation, which limits the access of phagocytic cells of infected area. This results in poor penetration of antibiotics in the infected tissues.[9] Diabetics with foot infections become more severe and take longer time to cure compared to persons without diabetes. DFI occurs because of hyperglycemia and several other co-morbidities, especially neuropathy, vasculopathy, sight threatening retinopathy and defects in immunity and wound healing. DFI are the most frequent causes of hospitalization and amputation (20%).[10] Some studies also report that 15% of all diabetics develop foot ulcer in their lifetime. Of this around 28% of them require some kind of amputation.[11] Among diabetics and non-diabetics, the risk of lower limb amputation has been accounted as 8 to 12.3 times higher. Furthermore, diabetics are 2.5 times more likely to have onychomycosis and *Tinea Pedis* infection that can lead to skin disruption and ulcers. In population-based studies, the annual incidence of diabetic foot ulcer, DFU is 1.0–4.1% and has a prevalence of 4.5–10%, with an overall lifetime incidence of 25%.[12] All lower limbs amputations (50%–70%) are attributed to DFU.[13] In India, a multicentric study on diabetics report prevalence of neuropathy as 15% and peripheral vascular disorder (PVD) as 5%.[14] Foot infections may results from many different microbial species (single or combination). Most of the time, response to treatment may be poor, particularly when vascular disease is also present with diabetes. *Staphylococcus* and *Streptococci* are the most commonly isolated pathogens. They were susceptible to oral antibiotic treatment like Amoxicillin-Clavulanate, Cephalexin, Clindamycin, Doxycycline, Levofloxacin, Linezolid, Minocycline, Trimethoprim-Sulfamethoxazole. For moderate to severe infections, parenteral antibiotics like Ceftriaxone, Cefoxitin, Clindamycin, Ertapenem, Daptomycin, Moxifloxacin, Piperacillin-Tazobactam, Tigecycline and Vancomycin are useful.[15] Longer duration of treatment, lack of awareness and poor self-care are well known factors that culminates to medication non-adherence in DM. Patient non-adherence to therapeutic strategies is a serious concern that poses a great challenge to the successful delivery of healthcare. Prevalence of poor adherence treatment ranges from 67% to 74%.[16] Poor adherence in diabetics has been associated with increased health care resource utilization and increased rate of hospitalization. It is essential to evaluate adherence on a regular basis due to changes in culture and lifestyles, in addition to introduction of new medicines with varied dosing schedule, efficacy and adverse drug reactions, which in turn, alter adherence. In India, there are extremely limited data on systematic assessment of adherence to diabetic medication from different parts of the country.[17] Hence, purpose of the study was to evaluate antimicrobial susceptibility pattern, antimicrobial therapy and its adherence in DFI patients.

2. Methods

This prospective observational study was carried out in Kasturba Hospital, Manipal; during the period of 6 months. All newly diagnosed patients with DFIs who were prescribed with antibiotic therapy and had an antibiotic culture and sensitivity test were included in the study. Patients excluded were of ≤18 years. The detailed history of the patients, demographics, drug therapy given, and other laboratory investigations were recorded in a specially designed data collection form. To measure the adherence levels in these patients, we used the Culig adherence scale. This is a general adherence questionnaire consisting of 16 questions about the personal and emotional problems, social functioning and general health perceptions. The adherence scale provides causes of non-adherence identified by 'never', 'sometimes', 'often' and 'rarely'. Total scores represent the percentage of total possible score achieved. All items are scored with above 80% as favorable high adherence and medium score as 60–80% and low adherence as below 60%.

2.1. Study procedure

A total of 150 diabetic foot infection patients were included for the study. The gender wise distribution of data were categorized and presented with the number of patients. The majority of the patients were male [139(92.6%)] and whereas, female were 11(7.4%). In the adherence study among 100 patients, majority of the patients were male (91%) and female were only 7%. The susceptibility testing and sensitivity pattern were obtained from hospital lab data management system. By using this, cumulative susceptibility chart (Antibiogram) were prepared. The patients were followed from the first day of admission until discharge. Before initial antibiotic therapy, tissue or pus specimen were collected and sent for culture and susceptibility testing. Given empirical therapy, definitive therapy; the timing of empirical therapy and definitive therapy has been obtained. After discharge patients were followed at next outpatient visit at the Surgery Department. During the visit, patients were provided with self-administered Culig Adherence Scale to measure antibiotic related medication adherence levels in DFIs.

2.2. Statistical analysis

Nominal data were expressed as frequency and percentage. Chi-square test was performed to find association between prescribed empirical therapy and improved outcome. Data were collected and analyzed by SPSS 20.0 statistical software. A p value of < 0.05 was considered as statistically significant.

2.3. Ethical clearance

Ethical clearance was obtained from the Institutional Ethical Committee of Kasturba Hospital, Manipal (Ref. No: IEC 588/2016).

3. Results

Among 150 DFU patients included in our study, only 100 of them completed the adherence questionnaire. Majority of the study population were males with 92.6% and 7.4% were female. Out of 150 patients, Gram-positive organisms were found in 42.5% patients, Gram-negative organisms were found in 44.6% patients and no growth of organisms was seen in 12.6% patients. Majority of Gram-positive organisms (23.9%) were Methicillin-sensitive *Staphylococcus aureus* (MSSA) followed by Methicillin resistant *Staphylococcus aureus* (MRSA) (11.3%) and least organism was *Enterococcus faecalis* (7.3%). While in Gram-negative organisms, majority of them were *Klebsiella pneumonia* (13.3%) and *Escherichia coli* (13.3%) and least being *Proteus mirabilis* (0.7%) and *Proteus vulagris* (0.7%).

3.1. Cumulative antimicrobial susceptibility pattern (antibiogram)

The sensitivity patterns of causative organisms were represented in the form of antibiogram [Table 1]. Antibiotics like Chloramphenicol, Colistin, Levofloxacin, Rifampicin is found to have developed resistance for most of the organisms. Moreover, decreased sensitivity of *Enterococcus faecalis, Enterococcus cloacae, Klebsiella pneumonia, MRSA and Escherichia coli* towards Erythromycin, Tetracycline and Benzyl Penicillin and Ceftriaxone was also observed.

Data from 150 patients shows Inj. Amoxicillin-Clavulanic acid 1.2 gm (28.6%) is the highest prescribed empirical therapy in diabetic foot Infections patients. The second highest prescribed empirical therapy is Inj. Cefuroxime –Sulbactam 2.25 gm (14.6%). T. Cefuroxime 625 mg (0.7%), inj. Amikacin750 mg (0.3%), inj. Amoxicillin-Clavulanic acid with inj. Cefoperazone-Sulbactam (0.7%) was found to be least prescribed empirical therapy. The study revealed that prescribing patterns of empirical antibiotic therapy was inappropriate when compared with antibiotic policy of the hospital, 2016.

Table 1
Cumulative antimicrobial susceptibility pattern of microbes in DFIs (Antibiogram).

Isolated organism	*P. aeruginosa*	*K. pneumoniae*	*S. aureus*	*E. coli*	*M. morganii*	S. agalactiae	*E. faecalis*	E. aerogenes	MRSA	*E. cloacae*	S. pyogenes	*P. mirabilis*	S. dysgalactiae	P. vulgaris
No .of isolates	**13**	**20**	**18**	**20**	**3**	**6**	**11**	**3**	**17**	**6**	**7**	**1**	5	1
Antibiotics														
Amikacin	69.2	70	5.5	25	100			100		83.3		100		100
Amoxicillin-Clavulanic acid		35	5.5	65						16.6		100		100
Amoxicillin/Ampicillin			15			100			5.8		85.7	100	100	
Benzyl penicillin	30.7	20		5		83.3	54.5	50	5.8	33.3	100	100	100	
Cloxacillin			94.4						52	66.6				
Chloramphenicol	7.7	5												
Cefuroxime/Cefotaxime		5		5										
Ceftraixone	12.5	30	33.3	5	100	100		100	5.8	50	100	100	100	100
Ceftazidime	53.8													
Cefuroxime		15		5								100		
Ceftazidime/Cefuroxime	7.7	5												
Cefaperazone-Sulbactam	7.7	40		40			9							
Clindamycin	30.7		77.7	4.5		100		50					60	
Cefipime/Cefiprome	7.7	35		20			18.1			16.6				
Ciprofloxacin/Ofloxacin	30.7	40	50	5	66		45.4		66	66.6	14.2	100		100
Colistin	7.7								5.8					
Cefotaxime	30.7	50	11.1	15		100	45.4		33	50	100	100	100	
Erythromycin		5	61.1	5		100		9	11.7		42.8		60	100
Gentamycin	76.9	80	75	71.4			54.5	100	70.5	33.3	71.4	100	100	100
Imipenem	15.3	55	5.5	20			9			33.3	85.7			
Linezolid		10					27.2		47					
Levofloxacin	15.3					15				5.8		66.6	80	
Piperacillin-Tazobactam	7.7	20		40			9							
Rifampicin									41					
Trimethoprim-Sulfamethaoxazole	15.3	50	75	20	100	100	9	100	70.5	33.3	71.4	100	100	100
Tetracycline/Doxycycline		15	88.8	5		33.3	45.4		82.3	16.6	14.2		60	100
Teicoplannin		10					27.2		50					
Vancomycin		10		14.2			27.2		30					

Table 2
Timeline for culture and sensitivity test after admission.

Timing	No. of patients (%)
< 12hrs	60(40.0%)
12–24hrs	46(30.6%)
24–48hrs	21(14.0%)
> 48hrs	6(4.0%)
Not done	17(11.3%)

While looking at the culture and sensitivity test, in 60 (40.0%) patients it was performed in ≤12hrs of admission and 6(4.0%) patients was performed ≥48hrs after admission [Table 2]. In 72(48.0%) patients were given empirical therapy within ≤12hrs of admission and 4(2.7%) patients were given empirical therapy ≥48hrs after admission. Only 109 (72.6%) had definitive therapy given while 41(27.3%) were not given definitive therapy. We also analyzed the time taken from empirical therapy to definitive therapy after the culture and sensitivity test results were obtained. Majority of the patients, 59(54.1%) had an average timeline of 12–24 h while there was just 5(4.6%) of them had therapy changed in < 12 h.

In 65(43.3%) patients' clinical conditions had improved and 84 (56.0%) of patients had become stable and remaining 1(0.6%) of patient had expired. From the chi-square test, Statistically significant association was observed between T.Cefuroxime 625 mg and improved outcomes ($p < 0.001$). While similar kind of analysis using chi-square test showed that there was no statistically significant association observed between the time of empirical therapy and improved clinical outcome ($p = 0.487$), time of definitive therapy and improved clinical outcome ($p = 0.229$) and time difference between empirical and definitive therapy ($p = 0.639$).

3.2. Measurement of antibiotic adherence

Among 100 DFU patients, who completed the adherence questionnaire, majority of the patients were in the age group of 50–60 years (n = 33, 33%), and males 91 (91%).The medication adherence was assessed using Culig Adherence Scale when the patients came for first follow-up for their DFI treatment. Overall adherence patterns showed that among DFI patients there is predominantly low (44%) and medium (42%) adherence levels seen and only 14% of our study population showed high adherence levels of above 80%.

4. Discussion

A total of 150 patients were included in the study for cultural sensitivity assessment. The timing of empirical therapy and definitive therapy given, and culture test timing was evaluated. In our study the Gram-positive organisms included were MSSA (23.9%), *MRSA* (11.3%), *Enterococcus faecalis* (7.3%), *Streptococcus pyogenes* (4.6%), *Streptococcus agalactiae (*4%) and *Streptococcus dysgalactiae* (3.3%). Gram-negative organisms included were *Klebsiella pneumoniae* (13.3%), *Escherichia coli* (13.3%), *Pseudomonas aeruginosa* (8.6%), *Enterobacter cloacae* (4%), *Enterobacter aerogenes* (2%), *Morganella morganii* (2%), *Proteus mirabilis* (0.7%) and *Proteus vulgaris* (0.7%).

This study concluded that all the prescribed empirical therapy for DFI is not appropriate according to the hospital policy where the study was conducted. Empiric antibiotic prescribing guidelines lead to quality and standardized care for common infectious diseases by helping prescriber's select an appropriate empirical therapy for a variety of infections. Appropriate antibiotic therapy can improve clinical outcome when administered adequately in correct dose, via the right route, given in a timely manner and with intended penetration to site of infection.

A prospective observational study conducted in surgery department of a hospital in Bengaluru, India for a period of 1 year found different results than our study and showed that culture and sensitivity test that were carried out in 17 cases and the causative organisms identified were *Staphylococcus aureus, Pseudomonas species, Proteus species, Klebseilla oxytoca.* The Pharmacotherapy revealed that monotherapy with antibiotics was chosen in 43.2% patients closely followed by therapy with combination of two antibiotics in 42.4% patients. Only 4% patients received more than 3 antibiotic regimens.[18] In our study monotherapy with antibiotics was found to be 79.5% and dual therapy with antibiotics was found to be 3.9%. A prospective study of 80 patients with DFI admitted to Cairo University hospitals found that Gram-negative bacteria accounted 56.1% and Gram-positive bacteria accounted 27.7%. The common isolate was *Proteus mirabilis* (16.8%) followed by *Escherichia coli* (13.5%), MSSA (11.4%), *Pseudomonas* species (10.8%) and MRSA (10.1%). Vancomycin was found to be the most effective against Gram-positive bacteria, whereas Imipenem, Amikacin and Colistin were most effective against Gram-negative bacteria.[19]

The timing of empirical therapy should be based on patient conditions and urgency of the situation. Initial therapy for infections can be an empirical therapy. This is a method to use wide-ranging antibiotics as initial therapy for the purpose to cover numerous pathogens commonly identifying clinical syndrome. The representation of antibiotics is to clinch the infection and ensure it does not spread across.

In majority (40%) of the patient's culture and sensitivity test was done within 12hrs of their admission, 12–24hrs (30.6%), 24–48hrs (14%), > 48hrs (4%) and was not done in 11.3%. Time for empirical therapy within 12hrs was given to most of the patients (48%), 12–24hrs (28%), 24–48hrs (10%), > 48hrs (2.7%), not given in rest of the patients (11.3%).The culture test has not been performed in 11.33% because the patient has admitted only for three days and the patients wants discharge without treatment. Definitive therapy was given to 109 (72.6%) patients and not given in 41(27.3%) patients. Time difference between empirical therapy and definitive therapy was found to be < 12hrs in majority of the patients (54.1%), 12–24hrs (36.7%), 24–48hrs (4.6%) and 48–72hrs (4.6%). No growth was seen in 19 out of 150 patients. Association for empirical therapy found T. Cefuroxime 625 mg use was statistically significant with improved clinical outcomes in DFIs ($p < 0.001$). While, time for empirical, definitive therapy and time difference between empirical and definitive therapy was not statistically significant with improved clinical outcome.

Medication adherence is the extent to which a patient to follow the prescription prescribed by the physician to achieve better outcomes. Adhering to the medications prescribed by the physicians can lead to better health of the patient. Non-adherence is mainly due to lack of patients interest to take the medications. Method to measure adherence has been attempted in too many researches. A quality procedure must be developed to prevent complications of the problem. The absence of authentic technique for measuring non-adherence is the major obstacle in adherence research.[19] Our study assessed the adherence in DFI patients and compared the appropriateness of antibiotics prescribed in these patients against the hospital antibiotic policy. We used Culig Adherence Scale for which the permission was obtained from developer, Joseph Culig as a suitable tool to evaluate medication adherence in diabetic foot ulcer (DFU) patients.

The age of the study population who participated for the medication adherence assessment were included and the maximum number of participants came under the age groups 50–60 years (33%). Most of the studies showed that age was related to compliance. Although few researches found age being not a factor causing non-compliance. Elderly patients may have problems in vision, Hearing and memory. In addition, they may have more difficulties in following therapy instructions due to cognitive impairment or other physical difficulties, such as having problems in swallowing tablets, opening drug containers, handling small tablets, distinguishing colors or identifying marking on drugs. On the contrary, older people might also have more concern about their health than younger patients, so that older patient's non-adherence is non-intentional in most cases.[20]

Forgetfulness and multiple medications was the main reason for non-adherence in majority of our patient population while away from home and concern of side effect were less frequent reasons. Patients did not have issue with the drug whether it was expensive or not, but they just wanted to get cured as soon as possible with less financial burden and shorter duration of stay in hospital. More than three-quarter of our patients belonged to low adherence (44%) and medium adherence (42%). The question arises that how and why people forget to take medication. Working stress and psychosocial factors might be the reason for same. An innovative approach using modern technology for continuous reminder might help to overcome this obstacle. A Zagreb University who also did study with Culig adherence scale found that unawareness regarding the medication was the main reason for non-adherence while absence from home was the second leading reason in most age category. 66 + age category ranked sixth to seventh place for medication non-adherence. In 56–65 age categories, away from home (52.9%) and drug shortage were main reasons for the non-adherence (51.2%).[21] Male predominance was observed in our study population (91%). This might be due to the cultural factors arising due to the decreased motivation among the females in India to seek medical consultation.

5. Conclusion

DFU is the major source of morbidity and mortality among diabetes patients from the past two decades. The management of DFIs is the major challenge for surgeon. This study showed most common organisms present in the DFIs were Gram-negative aerobes. However, MSSA was the most predominant organism isolated from the lesions while Inj.Amoxicillin-Clavulanic acid 1.2 gm was most prescribed empirical therapy. The fact is that this empirical therapy was inappropriate according to hospital policy, shows importance of antibiotic treatment guidelines and strict adherence to the guidelines. Findings of this study propose that large prospective studies are essential to assess the suitable empirical antibiotic regimen in DFIs and interventions to improve glycemic control and medication adherence in DM.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

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