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COMPARISION OF MICROBIOLOGICAL PROFILE AND ANTIBIOTIC TREATMENT AMONG DIABETIC, NON DIABETIC PATIENTS HOSPITALIZED FOR LOWER LIMB CELLULITIS/ULCER

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ABSTRACT

Objectives: Acute bacterial skin infections in diabetics represent a spectrum of conditions ranging from cellulitis to more complicated infections such as infected ulcers or deep tissue infections. Studies evaluating microbiological etiology and treatment patterns are scarce. To Compare the Microbiological profile and antibiotic treatment among Diabetic, Non Diabetic patients hospitalized for lower limb cellulitis /foot ulcers. **Methods:** Prospective study was conducted on 80 patients. Relevant data pertaining to demographics characteristics, duration of diabetes was taken from the patients. Samples of pus were collected from deep wounds and bacterial isolates was detected using culture and sensitivity testing Antimicrobial susceptibility testing to different agents was carried out using the disc diffusion method. **Key findings:** There was no significant difference in the microbiological etiology and treatment patterns between diabetic and non diabetic subjects hospitalized with cellulitis/ulcer. Among the Ulcer cases, Gram positive organism was isolated in 11.4% of Diabetic and 11.7% of Non diabetic subjects; Gram negative organism was isolated in 60% of Diabetic and 64.7% Non diabetic subjects; Poly microbial species were isolated in 25.7% of Diabetic, 17.6% of Non diabetic subjects; *Candida albicans* were isolated in 2.87% of Diabetic, 5.88% of Non diabetic subjects respectively. Beta-lactamase inhibitor

(Amoxicillin+Clavulanic acid) combination is mostly prescribed as Initial treatment in both Ulcer **(16.77%)** and Cellulitis**(22.22%).** Whereas for Empirical treatment, Amoxicillin **(U; 33.78%, C; 33.33%)** along with Metronidazole**(U;24.32%, C;33.33%)** are commonly prescribed drugs irrespective of Diabetes Mellitus. **Conclusion:** Gram negative organisms were predominant in Diabetic and Non diabetic subjects hospitalized with cellulitis/ foot Ulcer. With this knowledge of causative organisms and their Antibiotic prescribing patterns the most suitable antibiotic can be started without waiting for the result. This would help in avoiding unnecessary medication with ineffective antibiotics and prevent development of drug resistance.

KEYWORDS: Diabetic foot ulcer, Cellulitis, Microbiological profile, Polymicrobial infection.

INTRODUCTION

Diabetes mellitus is one of the most common comorbid conditions among patients hospitalized for acute bacterial skin infections.[1] According to seventh edition of International Diabetes Federation (IDF) Diabetes Atlas, there are 415 million diabetics in the World. A study in India has shown that 30.4% of diabetics have infections, mainly wound infections.[2] India is ranked second (92.6 million) after China (109.6 million) for being home to largest number of adults with DM.[3] Approximately 25% of diabetics have a cumulative lifetime risk for foot ulcers with increased vulnerability for infections in 40-80% of cases.[4] These infections can be either soft tissue infections or complicated skin infections.[5]

Acute bacterial skin infections in diabetics represent a spectrum of conditions ranging from cellulitis to more complicated infections such as infected ulcers or deep tissue infections.[6-11] Aetiology of infection is variable, ranges from gram-positive organisms such as *Staphylococcus aureus, Streptocooci, Enterocoocus* to gram-negative bacteria such as *Pseudomonas aeruginosa, Escherichia coli, Klebsiella species, Proteus species,* sometimes these organisms shows polymicrobial infection according to it the treatment also varies.[12]

In a study including mostly patients with uncomplicated cellulitis or abscess, Gram-positive cocci, particularly *streptococci* and *Staphylococcus aureus*, are major causative organisms but Gram-negative rods and anaerobic bacteria are frequently detected in patients with acute bacterial infection.[13-15] Bacteriologic investigation of bacterial specimens is an essential tool for active surveillance of antimicrobial drug resistance. Knowledge of causative bacterial

species and their resistance profile enables targeted antimicrobial therapy, limits ineffective antimicrobial therapy. Therefore, broad-spectrum antimicrobial therapy that also covers Gram-negative infections is recommended by Infectious Diseases Society of America (IDSA) guidelines only in the treatment of moderate-to-severe DFI.[16] On the other hand, IDSA guidelines recommend antimicrobial therapy targeted only to Gram-positive cocci in treatment of cellulitis or abscess irrespective of the presence of diabetes.[17]

Selection of the antibiotic regimen involves decisions about the route of therapy, the spectrum of microorganisms to be covered, and the specific drugs to be administered and involves choosing the definitive regimen and the duration of treatment. Initial therapy is usually empirical and is based on the severity of the infection and on any available microbiological data, such as recent culture and antimicrobial sensitivity. The treatment should be modified subsequently, according to microbiological data, such as recent culture and antimicrobial sensitivity. On the basis of the available studies, no single drug or combination of agents appears to be superior to others, although the available data do not allow us to recommend any specific antibiotic regimen for acute bacterial infections such as cellulitis and ulcers.[18] The β-lactam antibiotics are most widely prescribed antibiotics and important components of empirical therapy. Because of its extensive use, resistance to drugs has become a major problem especially after the introduction of newer broad-spectrum cephalosporins, β-lactamase inhibitor, monobactams and carbapenems.[19] To the best of our knowledge, we observed that diabetic patients with acute bacterial infections had longer duration of antimicrobial treatment than non diabetics. Hence, it is important to monitor the changing trends in bacterial infection and their antimicrobial susceptibility pattern to provide appropriate antimicrobial therapy. We wanted to further analyze the factors beyond this phenomenon, i.e., possible differences in microbiological etiology and treatment practices between diabetics and non diabetics with low bacterial resistance.

MATERIALS AND METHODS

Patients and controls

Over a period of 6 months, we studied 80 consecutive patients. Inclusion criteria included age 30years or older, Patients who are Diabetic or Non diabetic and diagnosed with ulcer and cellulitis, Patients of either gender, Patient who are willing for study follow-up. Patients with uncontrolled diabetes in case of diabetic sub group, traumatic conditions, cellulitis and ulcers of upper limb, pregnant and lactating women, Gestational Diabetes, Patients have other

infections of limb apart from the ulcer or cellulitis, Patients with other co morbid conditions like HIV infection, chronic venous insufficiency and osteomyelitis, Patient who are not willing for follow-up, were excluded.

Clinical and biochemical studies

All participants underwent a standardized clinical evaluation. Height was measured using a stadiometer, while weight was recorded with a weighing machine with a beam balance.

(a) Detection of Bacterial isolates

Two specimens (pus, wound exudates) were obtained from the infected sites to detect the type of micro organism involved in infection. In fact, clinical signs of infection and also condition of patients make use swab culture. For ulcer, the wound before sampling was debrided with a sterile scalpel, rinsed with sterile normal saline to avoid contamination and then, samples were collected using sterile swabs, from the depth of wounds to check the presence of infective agents. The swabs were transferred into sterile tubes with brain-heart infusion broth. The tubes were immediately transported to the microbiology laboratory and isolates were identified by standard methods. The mold species were identified on the basis of microscopic and macroscopic appearance.

(b) Identification of antibiotics sensitivity and resistant patterns for bacterial samples

Susceptibility and resistance patterns of all the isolates to different antibiotics were determined by the disc diffusion methods, as recommended by the Clinical and Laboratory Standard Institute, using commercial antimicrobial discs (Mast. Co., UK).

RESULTS

Age and gender-wise distribution of the study subjects

A total number of 86 patients with diabetic foot ulcer/Cellulitis cases were reviewed during the study period and 80 patients who met the study criteria completed the study. During the study period, males [58(72.5%)] predominance was noted over females [22 (27.5)]%. According to the age wise distribution of the study subjects, the majority of the patients (26 patients) belonged to the age group of 42-51 years followed by 20 patients in the age group of 52–61 years.

Distribution of subjects according to Social habits

Among the study population, both Smoking and Alcohol were more predominant risk Factors for the development of Diabetic, Non Diabetic ulcer and Cellulitis. Usually being Diabetic itself is a risk factor which can leads to macro vascular or micro vascular complications including diabetic infections. But patients who are on Alcohol and Smoking developed Ulceration even if they were Non Diabetic. The social habits among the study populations were shown in the following Table 1.

Table 1: Distribution of subjects according to social habits.

SOCIAL HABITS	ULCER(n=52)		CELLULITIS(n=28)	
	DIABETIC (n=35)	NON DIABETIC (n=17)	DIABETIC (n=12)	NON DIABETIC (n=16)
SMOKING	6(17.14%)	--	2(16.66%)	5(31.25%)
ALCOHOL	5(14.28%)	1(5.88%)	----	---
CHEWING TOBACCO	1(2.85%)	--	----	----
SMOKING,ALCOHOL	9(25.71%)	7(41.17%)	5(41.66%)	7(43.75%)
SMOKING,CHEWING	2(5.71%)	1(5.88%)	----	----
ALCOHOL,CHEWING	1(2.85%)	--	----	---
NONE	11(31.42%)	8(47.05%)	5(41.66%)	4(25%)

Symptoms among the study populations

Considering the symptoms in the study populations, Multiple wounds (24(68.5%), 13(76.4%)] were the most common symptom identified among Diabetic and Non Diabetic ulcer and Swelling [10(83.3%), 11(68.7%)] was most predominant symptom identified among Diabetic and Non Diabetic Cellulitis, during the study period. The symptoms of the study populations were shown in the following Table 2.

Table 2: Distribution of patients according to symptoms.

SYMPTOMS	ULCER(n=52)		CELLULITIS(n=28)	
	DIABETIC (n=35)	NON DIABETIC (n=16)	DIABETIC (n=12)	NON DIABETIC(n
SWELLING	15(42.8%)	6(35.2%)	10(83.3%)	11(68.7%)
PAIN	15(42.8%)	8(47%)	5(41.6%)	10(62.5%)
PUS DISCHARGE	12(34.2%)	5(29.4%)	4(33.3%)	3(18.75%)
MULTIPLE WOUNDS	24(68.5%)	13(76.4%)	3(25%)	4(25%)
FEVER	7(20%)	2(11.7%)	7(58.3%)	6(37.5%)
SMELL	3(8.57%)	1(5.88%)	1(8.33%)	1(6.25%)

Distribution of bacteria isolated from study population

Microbiological evaluation of the ulcers revealed that the prevalence of gram-negative organisms 47 (57.75%) were found to be more than gram-positive organisms 14(17.5%),

Candida albicans3(3.75%) and poly microbial species17(21.25%).Among the organisms isolated, *Pseudomonas aeruginosa* was the most frequent pathogen isolated from 19 (23.75%) subjects followed by *Escherichia coli* isolated from 12(15 %) subjects. Distribution of bacterial isolates among study population were shown in F**igure 1** and different types of gram negative and gram positive bacteria isolated from ulcers are summarized in Table 3.

Table 3(a): Number of patients based on gram negative culture isolates.

GRAM-NEGATIVE ISOLATES	ULCER(n=52)		CELLULITIS(n=28)	
	Diabetic(n=35)	Non diabetic(n=12)	Diabetic(n=12)	Non diabetic(n=17)
Pseudomonas aueroginosa	5(10.63%)	5(10.63%)	1(2.12%)	8(17.02%)
Escherichia coli	8(17.02%)	2(4.25%)	1(2.12%)	1(2.12%)
Klebsiella pneumoniae	3(6.38%)	2(4.25%)	2(4.25%)	….
Proteus mirabilis	3(6.38%)	2(4.25%)	….	….
Proteus vulgaris	….	….	1(2.12%)	….
Citrobacter species	1(2.12%)	….	1(2.12%)	…..
Acenobacter species	1(2.12%)	….	….	….

Table 3 (b): Number of patients based on gram positive isolates.

GRAM POSITIVE ISOLATES	ULCER(n=52)		CELLULITIS(n=28)	
	Diabetic(n=35)	Non Diabetic(n=17)	Diabetic(n=12)	Non Diabetic(n=16)
Staphylococcus aureus	2(15.38%)	2(15.38%)	3(23.07%)	1(7.69%)
Enterococcus species	1(7.69%)	….	1(7.69%)	1(7.69%)
Methicillin Sensitive Staphylococcus aureus	1(7.69%)	….	1(7.69%)	…..
Beta haemolytic streptococci	….	….	….	1(7.69%)

Comparison of Empirical therapy and Therapy given after swab report in Foot ulcer and Cellulitis subjects

Considering Antibiotic prescribing patterns in the foot ulcer and Cellulitis subjects, Penicillin combinations 23(28.75%) in normal patients followed by Clindamycin 7(8.13%) and Amikacin 8(9.30%) in Intensive care patients were preferred as an empirical therapy in foot ulcer subjects. In cellulitis subjects Penicillin12 (22.22%) [Amoxicillin+Clavulonic acid], Cephalosporin's 10 (12.5%) are mostly prescribed drugs as Empirical treatment. Amoxicillin+Clavulonic acid **(U; 25(33.78%) C;13(33.33%)** is mostly prescribed drug after swab report because of its sensitivity against gram positive and gram negative activity in both foot ulcer and cellulitis subjects. Antibiotic utilization among study population is summarized in the Figures 1, 2.

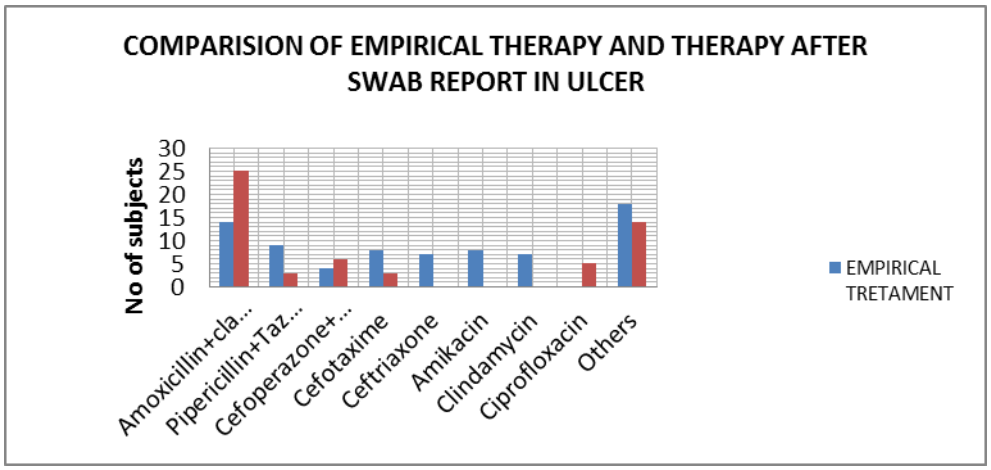

Figure 1: Illustrates Empirical treatment and therapy after swab report in Ulcer.

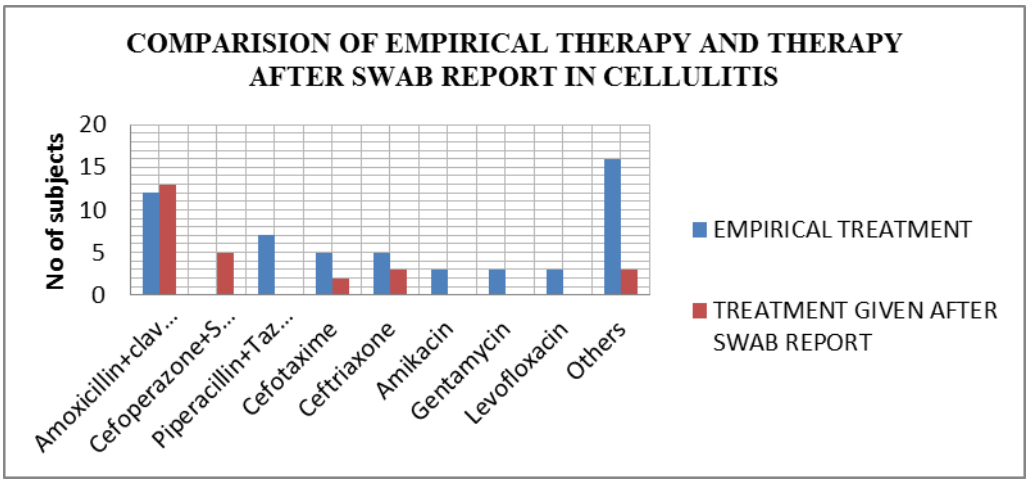

Figure 2: Illustrates Empirical treatment and therapy after swab report in Cellulitis.

Distribution of subjects among study population according to treatment plan

Among 80 subjects, Debridement 27(33.75%) followed by Split skin grafting (SSG) 9(11.25%) was most common surgical procedure among Diabetic and Non diabetic foot ulcer subjects. Conservative treatment shows better results in both Diabetic and Non diabetic Cellulitus. Considering the length of hospital stay, subjects who cured with Antibiotics shows improvement on an average of 8-15 days(18%), whereas subjects who didn't respond to antibiotics may be due to Severity of the condition and other factors were further preceded to surgery on an average of 31days (23.75%). The distribution f subjects according to treatment plan and length of hospital stay were summarized in Table 4, 5.

Table 4: Distribution of patients based on treatment plan.

Treatment Plan	Ulcer(N=52)			Cellulitis(N=28)		
	Diabetic (N=35)	Non Diabetic (N=17)	P	Diabetic (N=12)	Non Diabetic (N=16)	P
Debridement	23(65.7%)	4(23.5%)	0.25	1(8.3%)	7(43.7%)	0.31
Split skin Graft(SSG)	2(5.7%)	7(41.1%)	0.01	4(33.3%)	3(18.7%)	0.10
Amputation	5(14.75%)	2(11.2%)	0.08	1(8.3%)	….	0.02
Conservative	5(14.75%)	4(23.5%)	0.62	6(50%)	6(37.5%)	0.75

Table 5: Correlation between No. of days of hospital stay and clinical outcomes.

NO OF DAYS OF HOSPITAL STAY	CURED	SURGERY PLAN
1-7days	4(5%)	1(1.25%)
8-15 days	10(12.5%)	17(21.25%)
16-23days	4(5%)	7(8.75%)
24-31days	1(1.25%)	19(23.75%)
32-35days	2(2.5%)	5(6.25%)
40-47days	2(2.5%)	6(7.5%)
48-55days	….	1(1.25%)
56-63days	….	1(1.25%)

DISSCUSSION

The present study observed types of Microbial Infections and Patterns of antibiotics prescribed to subjects diagnosed with foot ulcer and cellulitis. In the present study, male predominance was noted over females. Previous studies have shown that the susceptibility to foot infections is greater in male patients than in female patients.[20,21] This may be due to the fact that males tend to be more active in the outdoor activities leading to injuries and prone to development of ulcers. In the current study, we found that patients with age range 42-51years constituted the majority with foot infections. The mean age of patients in the present study is 58.78 ± 20.09 years which is on the line of study by Sundresh NJ *et al.*[22] and Halpati A *et al.*[23] In our study, among social habits both smoking and Alcohol were important risk factors for development of Diabetic and Non diabetic Ulcer, Cellulitis and multiple wounds were the most common symptom identified among Diabetic and Non Diabetic ulcer and Swelling was most predominant symptom identified among Diabetic and Non Diabetic Cellulitis, during the study period. These findings are consistent with the earlier published literatures.[24,25]

Microbiological evaluation of diabetic foot ulcer infections showed that the prevalence of gram-negative organisms was found to be more than gram-positive organisms. *Pseudomonas aeruginosa* was the most frequent followed by *E.coli.* These findings correlated well with those of studies carried out in India which showed that gram-negative bacilli as the most

common organism and pseudomonas being the predominant pathogen.[26,27,28] Amoxicillin+ Clavulanic acid along with Metronidazole are commonly prescribed drugs irrespective of Diabetes Mellitus in this study. These findings support current ISDA guidelines that recommend Antibiotic therapy targeted towards Gram Negative isolates irrespective of Diabetes Mellitus.

The present study also adds to the literature by providing a detailed comparison of antibiotic utilization patterns among diabetics and non-diabetics. We demonstrated that diabetics were more likely to have significant exposure to antibiotics with broad gram-negative activity, particularly anti-pseudomonal agents (the broadest-spectrum antibiotics). Since initiation of broad gram-negative therapy in the emergency department or urgent care was *not* more common among diabetics, the increased use of these agents among diabetics appeared to be driven by inpatient providers. It is also notable that of patients who received any antibiotic with broad gram-negative activity, these agents accounted for similar proportions of the total days of therapy in both diabetics and non-diabetics. In aggregate, our findings demonstrate that diabetics are more likely to be started on antibiotics with broad gram-negative activity by inpatient providers, diabetics are not necessarily continued on longer durations of broad gram-negative therapy once started, and the total amount of exposure to broad gram-negative agents is substantial.

Overall, our findings suggest that inpatient providers perceive diabetics with cellulitis or abscess to be at increased risk for gram-negative pathogens. This perhaps reflects an extrapolation of recommendations to use broad-spectrum empiric therapy in diabetics with certain complicated skin infections.[28] However, for patients with cellulitis or cutaneous abscess, IDSA guidelines recommend antibiotic therapy targeted toward *S. aureus* and streptococcal species; there is no suggestion to use a broader spectrum of therapy in diabetics.[16] Our findings therefore highlight an important opportunity to improve antibiotic selection for all patients hospitalized with cellulitis and abscess, but particularly diabetics. It is also noteworthy that by linear regression, diabetes mellitus was independently associated with longer treatment durations. Although the average increase in treatment duration was small (1 day), this finding adds to the evidence that the presence of diabetes mellitus alters providers' treatment approach to cellulitis or abscess.

We found that despite more frequent treatment with broad gram-negative therapy, diabetics were more likely than non-diabetics to be classified as clinical failure. It is important to point

out that diabetics were also more likely than non-diabetics to have post-discharge outpatient follow-up visits raising the possibility of biased ascertainment of clinical failure events in this group. However, we also demonstrated that diabetics with cellulitis were more likely to be re-hospitalized than non-diabetics. This is similar to a finding by Suaya and colleagues who showed that diabetics with skin infections were about twice as likely to be re-hospitalized as non-diabetics.[28] One could hypothesize that the increased frequency of clinical failure events among diabetics was due to their older age, hyperglycemia, or vascular insufficiency; however, other factors may have contributed.

Our results shown that Debridment followed by Split skin grafting was most common surgical procedure among Diabetic and Non diabetic ulcer which was significant to Tian et al[29] study. In his study he reported that maggot débridement therapy was superior to the control group in diabetic foot ulcers to achieve full healing (RR, 1.8; 95% CI, 1.07-3.02), amputation rate (RR, 0.41; 95% CI, 0.20-0.85), time to healing (RR, −3.70, 95% CI, −5.76 to −0.64).

It was observed that the mean duration of hospital stay in our study was 8-15 days, comparable with Ozkara et al.'s[30] report of an average of 17.2 days. In studies from England[31], Tanzania[32], and Nigeria[33], the mean duration of hospital stay was 22.2, 36.2 days, and 60.3 days, the variation from study to study might be related to differences in clinical practice, severity of illness, and availability of supportive care in their hospital. However, the relatively lower duration of hospitalization in the present study may be an early healing or discharge from the hospital.

The present study demonstrates that a variety of organisms can be isolated from these ulcers. Knowledge about the microbes that cause infection and their susceptibility towards the antibiotics will allow physicians to make best out their choice. Considering the nature of the organism and the type of isolate appropriate empirical antibiotic therapy should be initiated especially for the patients who are at risk categories. Once the nature of the organism and the probable pathogens are isolated, de-escalation of empiric therapy with a single drug or combination therapy can be guided by relevant culture results.

CONCLUSION

In the present study, we detected that Gram negative organisms were predominant in Diabetic and Non diabetic subjects hospitalized with cellulitis/ foot Ulcer. With this knowledge of

causative organisms and their Antibiotic prescribing patterns the most suitable antibiotic can be started without waiting for the result. This would help in avoiding unnecessary medication with ineffective antibiotics; prevent development of drug resistance and minimizes the healthcare costs.

Since nearly one quarter of patients hospitalized with cellulitis or abscess are diabetic, these findings have relevance for national antimicrobial stewardship efforts aimed at curbing antimicrobial resistance through reducing use of antibiotics with broad gram-negative activity in hospitals.

Clinical pharmacists can play a vital role in suggesting suitable antibiotic treatment regimen for the proper management of Diabetic and Non diabetic foot ulcers and Cellulitis. They can also be involved in educating the patients about the importance of maintaining optimal glycemic control and avoiding the risk factors for developing ulcers which will help in improving the quality of life.

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Conflicts of Interest

No conflicts of interest have been declared.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical Standards of the Institutional Ethics Committee and with the 1964 Helsinki declaration and its later amendments or Comparable ethical standards.

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