

**Antibiotic Susceptibility of Bacteria Growing on Diabetic Foot Ulcer: A Prospective Observational Study from South India**Kanagasanthosh K<sup>1\*</sup>, Karthick P<sup>2</sup>, Prabhusaran N<sup>3</sup>, Maalavika H<sup>4</sup><sup>1</sup>Associate Professor, Department of Pharmacology, Trichy SRM Medical College Hospital and Research Centre, Trichy, Tamil Nadu<sup>2</sup>Professor, Department of General Surgery, Trichy SRM Medical College Hospital and Research Centre, Trichy, Tamil Nadu<sup>3</sup>Associate Professor, Department of Microbiology, Trichy SRM Medical College Hospital and Research Centre, Trichy, Tamil Nadu<sup>4</sup>CRMI, Trichy SRM Medical College Hospital and Research Centre, Trichy, Tamil Nadu

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Conflict of interest: Nil

**Abstract:**

**Introduction:** Antibiotic resistance is a significant problem in our country. The situation is such that India has even been called the antibiotic resistance capital of the world. Prescribing the antibiotics and antimicrobials play a major role in the prevalence of antibiotic resistance. Our objective was to find antibiotics that are effective against infections on diabetic foot ulcers and to find the prevalence of the Multidrug resistance organism (MDRO) infections in infectious diabetic ulcers.

**Materials and Methods:** It is a Prospective, observational and Cross-sectional study for all patients that have diabetic foot ulcers among the patients attending the in-patient departments of General Surgical wards from our tertiary hospital in the three months period between May to July 2019. After identifying diabetic foot ulcer, two swabs were collected from the ulcer after taking sterile precautions. The first swab is used for gram staining and second for culture sensitivity for antibiotic.

**Results:** A total of 72 samples were analyzed. There were 48 males (66%) and 24 females (33%). Predominantly gram-negative bacteria were more isolated than gram positive bacteria. The most common bacterial isolate was *Escherichia coli* (26%) followed by *Staphylococcus aureus* (19%), *Pseudomonas aeruginosa* (18%) and *Klebsiella pneumoniae* (15%). Among the antibiotics Piperacillin-Tazobactam, Gentamicin, Amikacin and Imipenem seemed to be comparatively effective. There was a high degree of resistance with amoxicillin; ampicillin, ciprofloxacin and 3rd generation cephalosporin were identified.

**Conclusion:** There has been a recent increase of resistant strains of bacteria which highlights the need to prescribe antibiotics for infections with care. The choice of appropriate antibiotics is very important in order to reduce treatment failure, antimicrobial resistance, adverse events and cost. The knowledge about the antibiotic susceptibility of the bacteria must be known to prescribe the correct antibiotics and reduce the chance for resistance of bacteria towards these antibiotics.

**Keywords:** Antibiotics, Diabetic foot, Sensitivity, Resistant.

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**Introduction**

Diabetes is a metabolic disorder in which insulin is deficient or in which cells are unable to take up glucose due to insulin resistance which leads to hyperglycemia. India with approximately 42 million cases is ranked first in the list of the ten nations most affected with diabetes [1,2].

Among diabetes mellitus related complications, foot ulceration is one of the most common, affecting approximately 15% of diabetic patients during their lifetime. This can be attributed to several social and cultural practices such as barefoot walking, inadequate facilities for diabetes

care and education, and poor socioeconomic conditions [3].

Diabetic foot ulcers (DFU) are the most disabling and costly complications of diabetes and are a leading cause of hospitalization and amputation among such patient [4]. The life expectancy of patients who have diabetic foot ulcers and undergo lower limb amputations has been found to be similar to those with aggressive cancer and end stage congestive heart failure [5]. Individuals with diabetes mellitus generally have a higher risk of lower limb amputations than normal individuals. A

recent study has found an increased morbidity and mortality in diabetic patients with diabetic foot ulcers compared to patients without diabetic foot ulcers. A considerable proportion of patients presenting with an uninfected DFU will develop an infection prior to healing. The most common cause of morbidity and mortality in DFU is infections, which are seen in 40%–80% of the cases [6,7]. Topical and systemic antimicrobials have been found to be effective in the treatment of these infections [8].

A diabetic foot ulcer is caused by neuropathic (nerve) and vascular (blood vessel) complications of diabetes. Nerve damage due to diabetes causes altered or complete loss of feeling in the foot and/or leg. This is known as peripheral neuropathy. Pressure from shoes, cuts, bruises, or any injury to the foot may go unnoticed. The loss of protective sensation stops the patient from being warned that the skin is being injured and may result in skin loss, blisters and ulcers. Vascular disease is also a major problem in diabetes and especially affects very small blood vessels feeding the skin (microangiopathy). In this situation a doctor may find normal pulses in the feet because the arteries are unaffected. However other diabetic patients may also have narrowed arteries so that no pulse can be found in the feet (ischemia) [9].

Diabetic patients are more prone to life-threatening infections than non-diabetic patients therefore, they have more exposure to antibiotics, and hence the risk of formation of resistant strains in diabetic patients increases due to peripheral vasculopathies in patients it is hard for the antimicrobial to reach its site of action which is the diabetic foot ulcer this also contributes to the formation of resistant strains. The formation of resistant strains of bacteria is also hastened by the fact that clinicians often prescribe antimicrobials in the treatment of uninfected diabetic ulcers to reduce the 'bio burden' on the wound [6,9,10].

The microbial colonization of diabetic ulcers has been found to be different of the ulcers present on non-diabetic persons, reasons for this difference are thought to be the altered environment of the diabetic foot ulcer (hyperglycemia, hypoxia) [11,12]. It has also been found that a linear relationship exists between the prevalence of organisms and increase in the Wagner's grade. Studies have shown that gram negative bacterial infections are more common than gram positive infections. Multiple MDRO (Multiple Drug Resistant Organisms) have also been found on the diabetic ulcer [13,14].

The common bacterial isolates are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, coagulase negative *Staphylococci* (CONS) and *Enterobacteriaceae* [15,16]. There has been a recent

increase of resistant strains of bacteria which highlights the need to prescribe antibiotics for infections with care. The choice of appropriate antibiotics is very important in order to reduce treatment failure, antimicrobial resistance, adverse events, and costs [17].

The aim of this the project is to find out the antibiotics that are effective against the bacteria present on infected diabetic ulcers, and to find the prevalence of infections with MDRO (Multiple Drug Resistant Organisms). The knowledge about the antibiotic susceptibility of the bacteria must be known to prescribe the correct antibiotics and reduce the chance for resistance of bacteria towards these antibiotics [18]. Antibiotic resistance is a significant problem in our country. The situation is such that India has even been called the antibiotic resistance capital of the world [19,20]. Antibiotic resistance in every region has unique contributors. In India prescribing the antibiotics and antimicrobials when it is not required, the environmental conditions play a major role in the prevalence of antibiotic resistance.

#### **Materials and Methods:**

##### **Study Design:**

This is a prospective, observational, cross-sectional study done for the Diabetic foot ulcer patients who are admitted to General Surgical wards at Trichy SRM Medical College Hospital and Research Centre, Trichy, Tamil Nadu. For the study settings we involved three major departments from our institute for the entire duration of study period. Department of pharmacology, Central lab attached to the department of microbiology and general surgery is the major departments involved. The study period designed for 3 months from May 2019 to July 2019. A total sample of 72 diabetic foot patients was identified for our entire duration of study.

**Inclusion Criteria:** All case of diabetic foot ulcer reported in our institute were included.

**Exclusion Criteria:** Foot ulcers in patients without diabetes were not included in the study and Ulcers in areas other than the foot were not included in the study

##### **Study Method:**

1. The patients attending in the Department of Surgery with DFU will be enquired and personal profile data, behavior data, pre-existing diseases and pro-morbid conditions will be collected in a standard, pre-tested Performa.
2. Diabetic foot ulcer patients were identified and two swabs were collected from the ulcer after taking sterile precautions. The first swab is used for gram staining to guess the microbe.

Depending on whether its gram positive or gram negative a few biochemical tests (Indole reaction, Triple sugar iron test, Citrate test, Urease test, Mannitol test) are carried out, after this the swabs are cultured on nutrient agar, blood agar and MacConkey agar is carried out a with the sample based on these tests a conclusion is made as to the infecting microbe.

3. Antibiotic susceptibility testing is then carried out by disc diffusion method on Muller Hinton agar plates. Different antibiotics are used for gram positive and gram-negative bacteria. The antibiotic discs that are used are Ampicillin (10U), Co-trimoxazole (10U), Ceftriaxone (30U), Gentamicin (5U), Ciprofloxacin (5U), Imipenem, Aztreonam, Erythromycin, Vancomycin, Linezolid, Norfloxacin, Cephalexin, Cefepime and Amikacin.
4. The antibiotic susceptibility is judged based on the zone of inhibition. The resistance pattern is then noted so that appropriate treatment can be given. Staphylococcus species isolated in this study was tested for methicillin resistance by using Cefoxitin (30 mg) disc.

**Statistical Analysis:** Simple descriptive statistical analysis was done.

**Ethical Considerations:**

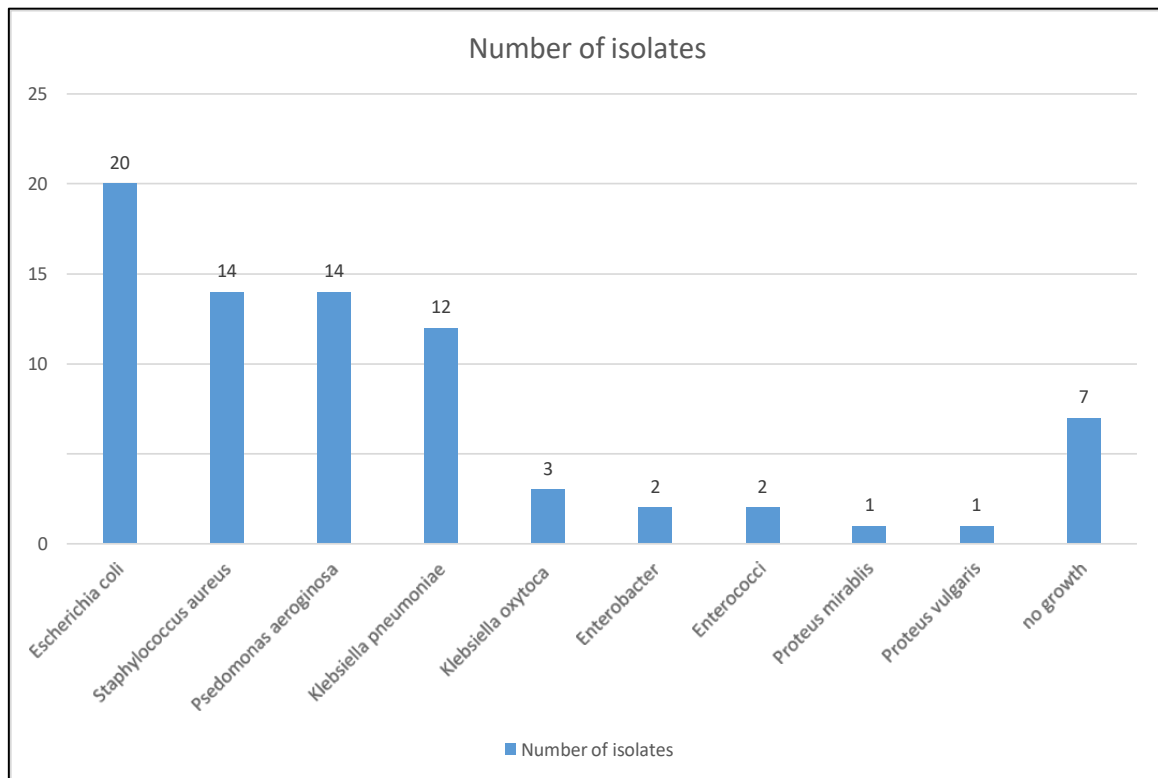
The project was carried out only after approval from the institutional ethical committee of Trichy SRM Medical College Hospital and Research Centre. Proforma details were collected from the patient only after assuring confidentiality and obtaining informed consent.

**Results**

A total of 72 samples were analyzed. There were 48 males (66%) and 24 females (33%). The range of ages from the study population was 35-90.

There were 5 patients who were hypertensive and one patient who was a hyperthyroid patient. Of these samples in 60 cases a single organism was isolated while in 5 cases two organisms were isolated, in 7 cases no growth was observed in the culture even after 48 hours.

The most common bacterial isolate was Escherichia coli (20, 26%) followed by Staphylococcus aureus (14, 19%), Pseudomonas aeruginosa (14, 18%), Klebsiella pneumonia (12, 15%), Klebsiella oxytoca (3, 4%), Enterobacter (2, 2%), Enterococci (2.2.7%), Proteus mirabilis (1, 1.3%) and Proteus vulgaris (1, 1.3%).



**Figure 1: Number of isolates**

The isolates were mostly gram-negative facultative anaerobes. The only gram-positive bacteria isolated were Staphylococcus aureus and Enterococci spp. The only obligate aerobe that was isolated was Acinetobacter spp. Totally 53 gram-negative bacteria were isolated and 16 gram-positive bacteria were isolated.

**Table 1: Resistance pattern of gram-negative bacteria**

Gram negative bacteria (%R)	E-coli	Pseudomonas aeruginosa	Acinetobacter	Klebsiella pneumoniae	Klebsiella oxytoca	Proteus mirabilis	Enterobacter	Proteus vulgaris
Amoxicillin/Ampicillin	100%	NT	100%	100%	100%	100%	50%	100%
Amoxicillin + Clavulanic acid	95%	NT	100%	81%	66%	100%	NT	100%
Piperacillin + Tazobactam	45%	7%	NT	45%	33%	100%	50%	100%
Cotrimoxazole	66%	NT	100%	72%	66%	100%	0%	0%
Ciprofloxacin	84%	38%	100%	72%	66%	0%	50%	0%
Gentamycin	35%	46%	0%	36%	66%	0%	50%	0%
Cefotaxime/Ceftriaxone/Ceftazidime	90%	7%	100%	72%	66%	0%	50%	0%
Imipenem	40%	15%	100%	45%	33%	100%	50%	100%
Aztreonam	55%	12%	100%	54%	100%	0%	50%	0%
Cefepime	78%	7%	100%	63%	66%	0%	50%	100%

**NT: Not Tested, R: Resistance**

Escherichia coli have a high level of resistance with all 20 of the isolates being resistant to Ampicillin and 19 of the isolates being resistant to amoxicillin clavulanic acid. Cephalosporins also cannot be used as 84% are resistant Cefazidime is more effective than ceftriaxone and cefotaxime as only 60% of Escherichia coli appear to be resistant to Ceftazidime. Escherichia coli seems to be less resistant to gentamycin and imipenem. These seem to be the better alternatives among the drugs that were used Amikacin seemed to be the best option as only 5 of the 20 isolates were resistant to it.

Therefore, on the whole Escherichia coli appear to be more susceptible to Aminoglycoside class of antibiotics. Out of the 20 isolates 4 of them were found to be MDR strains. MDR strains are those in which the bacteria are resistant to more than 3 classes of antibiotics. Pseudomonas aeruginosa had a low resistance rate to 3<sup>rd</sup> generation cephalosporins (Cefotaxime, Ceftriaxone, Ceftazidime) and to 4<sup>th</sup> generation cephalosporin (Cefepime). Only 1 of the 14 isolates was found to be resistant to the 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporins.

The highest rate of resistance was found with gentamycin. Only 2 isolates of Acinetobacter were isolated and both of them were found to be resistant to most of the beta-lactam antibiotics like ampicillin, amoxicillin clavulanic acid, Cotrimoxazole, ciprofloxacin, cefotaxime, ceftriaxone, ceftazidime, cefepime, aztreonam and imipenem. The only effective drug seemed to be gentamycin. All 12 isolates of Klebsiella

pneumonia were found to be resistant to Ampicillin and amoxicillin. There was a high rate of resistance with ciprofloxacin, co-trimoxazole and 3<sup>rd</sup> generation cephalosporins. There was a relatively lower resistance with gentamycin, piperacillin + tazobactam and imipenem. Only 3 isolates of Klebsiella oxytoca were analyzed. All 3 of them seem to be resistant to ampicillin and amoxicillin. 2 of the isolates were resistant to co-trimoxazole, ciprofloxacin, gentamicin and 3<sup>rd</sup> generation cephalosporins like cefotaxime, ceftriaxone and ceftazidime. Only one of the samples were resistant in the case of imipenem and piperacillin-tazobactam.

All 3 of the samples were susceptible to aztreonam. Only one sample of Proteus mirabilis was present in the sample size which was resistant to ampicillin and co-trimoxazole but sensitive to amoxiclav, piperacillin-tazobactam, ciprofloxacin, gentamycin, cefotaxime, imipenem and aztreonam. Only 2 samples of Enterobacteriaceae were isolated. Both were sensitive to co-trimoxazole, and piperacillin cotrimoxazole.

Only 1 sample was resistant in the case of ciprofloxacin, gentamycin, cefotaxime, cefepime, imipenem and aztreonam. Overall, for gram negative bacteria piperacillin-tazobactam, gentamicin and Imipenem seem to be comparatively effective.

Penicillin's such as Ampicillin, amoxicillin and amoxiclav seem to be less effective when compared to the other antibiotics. 3<sup>rd</sup> generation cephalosporins seem to be very effective in the treatment of Pseudomonas aeruginosa infection.

**Table 2: Resistance pattern for gram positive bacteria**

Gram positive bacteria (% R)	Staphylococcus aureus	Enterococci
Penicillin	100%	50%
Erythromycin	71%	100%
Cotrimoxazole	14%	100%
Ciprofloxacin	41%	100%
Gentamycin	21%	100%
Linezolid	13%	100%
Doxycycline	27%	NT
Vancomycin	NT	100%

NT: Not Tested, R: resistance

Total of 14 samples were collected in which *Staphylococcus aureus* was the isolate. All 14 samples were resistant to penicillin. Only 4 of the samples were susceptible to erythromycin. Ciprofloxacin showed average resistance towards ciprofloxacin. The drugs that were relatively more effective were Linezolid (only 1 sample was resistant), Co-Trimoxazole (only 2 samples were resistant towards it). Of the 14 isolates collected 7 (50%) were found to be MRSA (Methicillin Resistant *Staphylococcus aureus*). Only 2 samples of Enterococci were isolated. Both samples were resistant to erythromycin, co-trimoxazole, ciprofloxacin, gentamycin, linezolid and vancomycin. One of the samples was sensitive to penicillin. For gram positive bacteria penicillin is less effective. Linezolid Co-trimoxazole and gentamicin seem to be more effective than the rest of the antibiotics.

#### Discussion:

In our study the predominant organism that was isolated was *Escherichia coli* where as in a similar study conducted by Sugandhi, Prasanth et al [21,22] from Salem and Lalithambigai et al [28] from Trichy, Tamil Nadu found that *Staphylococcus aureus* was the organism that was isolated the most. The study in Salem found that Meropenem, Piperacillin, Piperacillin/ Tazobactam and Amikacin were the most effective for gram negative organism. In our study also Piperacillin-Tazobactam was found to be effective against most of the bacteria, Imipenem which is of the same class as meropenem was also found to be moderately effective especially against *Pseudomonas aeruginosa*. Amikacin was found to be very effective against MDR strains of *Escherichia coli*. Cefoxitin, oxacillin and vancomycin were found to be the most effective antimicrobial agents for therapy of gram-positive organism. In our study the most effective drugs for gram positive organisms were found to be linezolid, co-trimoxazole and gentamycin.

A study similar to ours was performed by Jain and Barman et al [23], similar to ours the majority of the organisms isolated were gram negative, in this

study the organism that was isolated the most were *S. aureus* (27%), followed by *E. coli* (20%) and *Enterococcus* (15.7%). In contrast to the previous study, in our study the most commonly isolated organism was *Escherichia coli* (20,26%) followed by *Staphylococcus aureus* (14,19%) and *Pseudomonas aeruginosa* (14,18%). Enterococci (2.2.7%) were one of the least isolated organisms in this study.

Another study conducted in North-East India shows that *E-coli* culture isolates were sensitive to amikacin (90%), imipenem (89%), meropenem (84%) and piperacillin-tazobactam combination (73%). On further continuation of the study shows that, amikacin and imipenem were found to be effective, but in addition to them gentamycin was also found to be effective more than the piperacillin-tazobactam combination. In this study *Pseudomonas* culture isolates were sensitive to amikacin (90%), imipenem (72%), meropenem (70%) and piperacillin-tazobactam combination (74%), whereas in our study *Pseudomonas* was more responsive to 3rd and 4th generation cephalosporins. Most of the *Staphylococcus* culture isolates were sensitive to linezolid (100%), daptomycin (100%), tigecycline (89%), teicoplanin (84%), and gentamicin (83%), In our study linezolid (87%) and co-trimoxazole was found to be effective (86%) against *Staphylococcus*.

Another study conducted in Tabriz, Iran [26] came up with the same results in terms of the bacterial isolates as the other two studies conducted in Salem and north east India. Similar study conducted in our institute during 2017 by Lalithambigai et al [28] reveals that *Staphylococcus aureus* was the most isolated bacteria followed by coagulase negative staphylococci and enterococcus. Methicillin resistant *S. aureus* (MRSA) was observed 39% of all *S. aureus* isolates whereas in our study a much higher proportion (50%) of the *Staphylococcus aureus* isolates were found to be MRSA, In both studies the MRSA was found to be sensitive to linezolid. In our study as well as the Iranian study *Enterococcus* was 100% sensitive to linezolid. Imipenem, gentamicin, and cefepime was found to be the most effective antimicrobial agents against isolated Gram-negative bacteria except

Acinetobacter species which coincides with the findings of our study.

In a study conducted in Kenya [24] shows Staphylococcus aureus was the most common isolate followed by Proteus mirabilis and then Klebsiella pneumoniae which is significantly different from the other samples this may be due to the fact that all the studies that were reviewed up until now were Asian studies whereas this one is an African study. This study also detected no MRSA in its sample size but in our study 50% of the Staphylococcus aureus isolates are MRSA. In the Kenyan study it was found that E.coli was highly resistant to aztreonam and ampicillin but sensitive to amikacin, while in our study it was only moderately resistant to aztreonam.

Another study that was conducted in Kerala [25] similar to this study isolated mostly E.coli after which Staphylococcus aureus was most commonly isolated. In this study aminoglycosides like gentamycin were found to be the ideal choice in case of gram-negative organisms followed by fluoroquinolones like ciprofloxacin. However, in our study co-trimoxazole and carbapenems like imipenem seem to be more effective than gentamycin and ciprofloxacin.

A Guyanese study was conducted in 2019 [27] the most common isolate was Pseudomonas aeruginosa followed by Escherichia coli. In this study, Ciprofloxacin, Chloramphenicol and Erythromycin showed higher percentage of resistance among Gram positive bacteria which was similar to our study in which there was a high resistance rate against erythromycin. In our study in addition to erythromycin, gram positive bacteria were found to be highly resistant to Penicillin but the in the Guyanese study there seems to be a higher rate of resistance against Ciprofloxacin when compared to our study. Piperacillin, Co-trimoxazole and Ciprofloxacin were the most effective antimicrobial agents for the Gram-negative organisms whereas in our study there was a high rate of resistance among gram negative bacteria towards Co-trimoxazole and Ciprofloxacin. Piperacillin – Tazobactam is relatively more effective and it was also found in our study that Amikacin was one of the more effective drugs.

All of the studies up until now have seen a predominance of aerobic gram-negative bacteria with overall a smaller number of gram-positive bacteria this has been the case in our study as well. This study when compared to similar studies has isolated E. coli the most followed by Staphylococcus aureus except in the Guyanese study where Pseudomonas aeruginosa was the most commonly isolated bacteria. Whereas in the studies done in Salem, North east India, Pakistan, Iran and Kenya all found Staphylococcus aureus to be the

most common organism. The only study mentioned here that had E.coli as the most isolated organism was the study done in Kerala

The antibiotic susceptibility of the isolates in comparison to the other studies appears to be similar. Overall, for gram negative bacteria piperacillin-tazobactam, gentamicin, amikacin and imipenem seem to be comparatively effective. This was the case in the other studies as well some studies found that gram negative bacteria were also highly susceptible to Ciprofloxacin and co-trimoxazole however that was not the case in our study. Acinetobacter was even resistant to amikacin and the only drug that seemed to be effective against it seemed to be gentamycin. Gram positive bacteria in our study were found to be more susceptible to linezolid and co-trimoxazole. In other studies, as well gram-positive bacteria seemed to be more susceptible to Linezolid.

#### Conclusion:

Swabs were taken from 72 patients with Diabetic foot ulcer and antibiotic susceptibility testing was done. The most common isolate obtained was E.coli which was followed by Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia, Klebsiella oxytoca, Enterobacter, Enterococci, Proteus mirabilis and Proteus vulgaris. Over all for gram negative bacteria piperacillin-tazobactam, gentamicin, amikacin and imipenem seemed to be comparatively effective. Among Gram negative bacteria there was a high degree of resistance with amoxicillin, ampicillin, ciprofloxacin and 3<sup>rd</sup> generation cephalosporin. Gram positive bacteria in our study were found to be more susceptible to linezolid and co-trimoxazole. Gram positive bacteria showed a high degree of resistance against Penicillin and erythromycin.

Pseudomonas aeruginosa appeared to be highly susceptible to 3<sup>rd</sup> generation cephalosporins unlike the other gram-negative bacteria. Acinetobacter was resistant to all other classes of drugs except gentamycin which was the only drug that was useful. Out of the 14 isolates of Staphylococcus aureus that were isolated, 7 of them were classified as MRSA. In the case of E.coli, 6 of the 20 isolates were found to be MDR strains. Our study is the first detailed study from south India, revealed much information about antibiotic sensitivity, which will be an eye-opener for near future research studies.

#### Limitation of the study:

Single centered study and limited to general surgery alone, as it was performed with a limited sample size. Antibiotic susceptibility was performed using superficial swab which has been found to be less effective in the past when compared to tissue sampling which provides a

more quantitative result. Previous antibiotic history was not taken into account.

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