Association between Antibiotic Resistance with Duration of Hospitalisation in Diabetic Foot Ulcer Inpatient at Internal Ward in Dr. Soetomo General Hospital

Priyadashini A.P. Surendra[1], Hermina Novida[2], Juniastuti[3], Bramantono[4]

[1]Medical Student, Faculty of Medicine, Airlangga University, Surabaya, Indonesia, [2]Specialist, Researcher, Department of Internal Medicine, Dr. Soetomo General Hospital, Airlangga University, Surabaya, Indonesia, [3]Professor, Researcher,Department of Microbiology, Dr. Soetomo General Hospital. Institute of Tropical Medicine, Airlangga University, Surabaya, Indonesia, [4]Specialist, Researcher, Department of Internal Medicine, Dr. Soetomo General Hospital, Airlangga University, Surabaya, Indonesia

Abstract

Introduction: Diabetic Foot Ulcer (DFU) are microvascular and macrovascular complications from diabetes and has potential pathological risks including infection, ulceration, and deep tissue damage and is associated with neurological abnormalities, peripheral arterial disease, and metabolic complications in the lower extremities. Diabetic foot injury is an infection of several pathogenic microorganisms that cause tissue damage, if the infection is not handled properly then the wound will worsen and have an impact on amputation. Those pathogenic microorganisms could be a mono-microbial infection or a poly-microbial infection and those infections could be multi-drug resistant organisms (MDRO).

Objective: To analyse the association between antibiotic resistance and the duration of the hospitalisation in diabetic foot ulcer patient at Dr. Soetomo General Hospital.

Method: This study is a cohort retrospective study that reviews medical records of all diabetic patients with diabetic ulcer that was admitted into Dr. Soetomo General Hospital.

Result: In Dr. Soetomo General Hospital the average duration of hospitalisation is 11.48 days. The species that caused the most infection under the category of gram-positive organisms are *Enterococcus faecalis* (7.8%), *Staphylococcus aureus* (5.2%) and *Staphylococcus haemolyticus* (3.9%). In the gram-negative category of bacterial species, *Proteus mirabilis* (10.5%), *Acinetobacter baumannii* (9.8%) and *Escherichia coli ESBL* (8.5%) Patients had a high resistance towards is Cephazolin with a rate of 85.5% followed by Ampicillin with 83.2% and Tetracyclin with 82.0%. Piperacillin-tazobactam (p-value 0.045) and Ceftazidime (p-value 0.046) showed an association between antibiotic resistance and duration of hospitalisation. All patients presented with MDRO and 35 (29.7%) were poly-microbial infection

Conclusion: There is an association between antibiotic resistance and duration of hospitalisation for Piperacillin-tazobactam and Ceftazidime as well as 100% of patient presented with Multi-drug resistant organism. Clinicians should refer to the periodic report from the internal ward on dominant species found and antibiotic resistance more.

Corresponding Author:
Hermina Novida
MD, Department of Internal Medicine, Dr. Soetomo General Hospital, Mayjen Prof. Dr. Moestopo Street No. 6-8, Airlangga University, Gubeng, Surabaya, Indonesia
e-mail: hermina-n@fk.unair.ac.id

Keywords: *Antibiotic resistance, Diabetic Foot Ulcer, Duration of hospitalization.*

Introduction

Diabetic foot ulcer (DFU) is a serious and common complication of patients with diabetes mellitus, it significantly increases the cost of treatment. Diabetes

is one of the most prevalent chronic diseases in 2010, one study reported that 285 million adults worldwide had diabetes and this figure is projected to rise to 439 million by the year 2030[1]This profound demographic shift is likely to result a corresponding increase in the prevalence of chronic diabetes complications, including those in the lower extremity, the diabetic foot[2]. Prevalence of risk and DFU is higher in Indonesia. The current study found that the prevalence of risk (neuropathy and angiopathy) in this study was 55.4% [3]. These findings are within global prevalence of risk 40% - 70%[3]. This percentage still remains higher compared to India[4]. Meanwhile, current prevalence of DFU is 12%. These findings are higher compared to China which is the most populated Diabetes Mellitus country[5]and in comparison with global prevalence 1.4% - 5.9%[6]. In Dr. Soetomo General Hospital, diabetic foot ulcer is the most common cause of inpatient registration in the Internal Medicine Department and with an average duration of 28 days of hospitalisation amongst those that has been admitted 30% had to undergo amputation, however this data was done from 2003-2007[7].

Many studies have reported on the bacteriology of Diabetic Foot Infections (DFIs) over the past 25 years, but the results had varied and often contradicted one another[8]. The varied results could be due to differences in causative agents, which had occurred over time, geographical variations, or the type and the severity of the infection, as were reported in the studies[8]. In Indonesia, based on a study conducted in Jakarta[9], has several limitations. This research was done before the implementation of BPJS which is was implemented in 2014 and more people had access to health care therefore and increase use of antibiotics which may result in resistance thus contributingto community based infections which are becoming increasingly common. Moreover, this research was done in a navy hospital which can't account for the entire Indonesian population as a navy officer lives a far more different lifestyle than the average Indonesian regardless. The sample size is also a matter of limitations with only 35 patients to study from.

Impairment of microvascular circulation limits the access of phagocytic cells to the infected area therefore causing a reduced concentration of antibiotics at the infected tissue area. Due to the reduced concentrations of phagocytic cells and antibiotic concentrations, diabetic foot wounds are easily infected leading to micro-thrombi causing ischemia, necrosis, and then gangrene which requires the need of limb amputation. Therefore, accurate diagnosis of causative organism is essential for the management of these cases especially with the implementation of the new government insurance scheme (BPJS) where only a government approved drug is given to patients with diabetic ulcer under this scheme. Patients with diabetes have a 10-fold higher chance of hospitalisation due to soft tissue and bone infection when compared with nondiabetic individuals[11]. Due to inadequate foot care and local, blood supply to the lower extremities is further compromised.

Diabetic neuropathy leads to repeated non-recognized trauma to the insensate feet and this causes callosities, cracks, fissures, and ulcer formation. Secondary infection of the ulcer with arterial abnormalities further complicates the condition leading to gangrene and limb loss. A compromised immune state in patient with diabetes favours rapid and relentless development of local sepsis and even life-threatening septicaemia. Massive infection is the most common factor leading to limb amputation[12].Patients with diabetes are often exposed to many antibiotics and therefore can develop multiple-drug resistant infections (MDRO) and most diabetic foot infections are caused by mixed bacterial infection (poly-microbial). Proper management of infections requires an appropriate antibiotic selection, based on the culture and the antimicrobial susceptibility testing results[13].

Although there is an abundance of research regarding the type of bacteria found and its antibiotic sensitivity, however there is none regarding its association to the duration of hospitalisation but there are research regarding its risk factors. Moreover, external data from Western countries cannot be generalized into Indonesian setting due todifference in demography, lifestyle and behaviour. This fact leads to limitation of preventive strategies for the presence of risk and DFU based on Indonesian[3]. Knowing the duration of therapy will greatly improve the efficiency of treatment, it will aid patients and insurance company to predict the average cost needed for treatment. Knowledge on bacterial antibiotic resistance will provide a more accurate empirical treatment and if there is a new emerging resistance amongst the diabetic ulcer community. The aim of this research is to determine the association between antibiotic resistance and duration of hospitalisation in patients with infected diabetic ulcer foot in Surabaya.

Methodology

Selection and description of Participants: This is an analytical study, a cohort retrospective studywith total sampling that reviews medical records of all diabetic patients with diabetic foot ulcer that was admitted into the Internal Ward at Dr. Soetomo General Hospital. It is the primary reference hospital in East Java and the main teaching hospital for the Medical Faculty, University of Airlangga. Patients with various diabetic complications are referred to this hospital. This study was conducted over a period of 3 years from January 2016 till December 2018.

Those without bacterial sensitivity tests/antibiotic resistance are excluded along with those without a proper record of the type of bacteria and the duration of hospitalisation based on the type of bacteria and its antibiotic resistance at the time of admittance. The types of bacteria and its sensitivity pattern were noted and the results were presented as descriptive statistic and analysed using IBM SPSS Statistics 26.0 on windows. Ethical clearance obtained by the medical research ethical committee at Dr. Soetomo General Hospital, Surabaya. Reference number: 1432/KEPK/VIII/2019

Statistical Analysis: Statistical analysis is done by categorising the type of antibiotics used with the type of bacterial infection and is measured using the chi-square test to discriminate between the groups that are significantly different from those that are not. Variable characteristics and frequency are expressed in terms of mean ± standard deviation and compared by one wat ANOVA. All statistical analysis is carried out using IBM SPSS Statistics 26.0 on windows.

In that period there were a total of 425 patients admitted with diabetic foot ulcer and 118 of them have culture done. Out of 118, 35 of them have poly-microbial infection therefore there is a total of 153 species and out of that 153, 86 of the infections are gram negative and 71 of the infections is gram positive. There are slightly more male patients than female patients with males making up 53.4% (63 cases) of the cases and females having 46.6% (55 cases).

Results

A total of 425 patients admitted with diabetic foot ulcer and 118 of them have culture done. Out of 118, 35 of them have poly-microbial infection therefore there is a total of 153 species and out of that 153, 86 of the infections are gram negative and 71 of the infections is gram positive.

The patients are characterized mainly by their gender and age, generally patients come in with a mean age of 58.2 and a range of 30-90 years old, and there are slightly more male patients53.4% (63 cases) than female patients46.6% (55 cases). The rate of mortality is 39.0% (46 patients).

Males have a mortality rate of 39.7% (25 cases) where else in females it is 38.2% (21 cases). The rate of mortality increases with age, as seen from the table below, Patients age 58 and above have a mortality rate of 50.8% (32 cases) and patients who are below 58 have a mortality rate of 25.5% (14 cases).

Distribution of Wagner's grading to assess the severity of DFU can be seen in the pie chart below. Wagner grade 1 makes up about 1% of the sample, grade 2 make up 13%, grade 3 occupies 20.2% of sample, which makes up the highest frequency, grade 4 has 17.1% and grade 5 makes up 9.8% of sample.

In Dr. Soetomo General Hospital, Surabaya there are 118 patients that present with both poly-microbial infection and mono-microbial infection.There are more gram negative60.8% (93 cultures) organisms that infect patients compared to gram positive organism 39.2% (60 cultures)

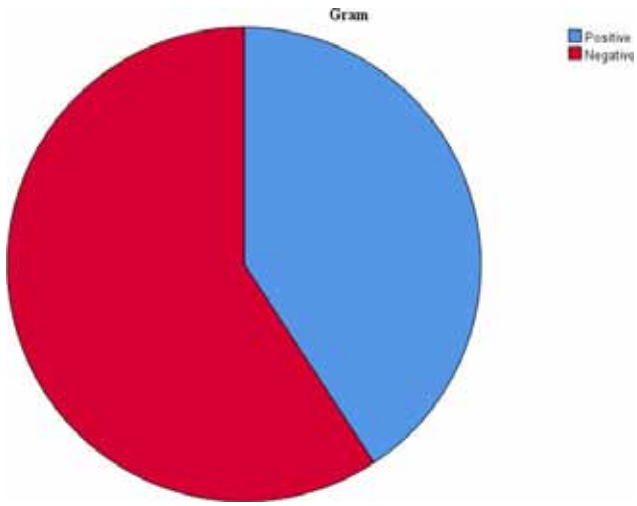

Fig. 1 Distribution of gram staining

There are a total of 40 different species and the most common gram-positiveorganisms are *Enterococcus faecalis* (7.8%), *Staphylococcus aureus* (5.2%) and *Staphylococcus haemolyticus* (3.9%). *Proteus mirabilis* (10.5%), *Acinetobacter baumannii* (9.8%), *Escherichia*

coli ESBL (8.5%), *Escherichia coli non ESBL* (7.2%) and *Pseudomonas aeruginosa* (7.2%) were common gram negative organisms. There were a total of 2 species of yeast infection, *candida albicans* (1.6%) and *candida tropicalis* (0.5%) but it was not included into the analysis.

Table 1. Distribution of 153 bacterial isolates

Bacterial species	Frequency	Percentage %
Gram-positive	60	39.20%
Corynbacterium non urealyticum	1	0.7
Corynbacterium striatum	1	0.7
Corynebacterium amycolatum	1	0.7
Corynebacterium ueralyticum.	1	0.7
Enterococcus faecalis	12	7.8
Enterococcus faecium	2	1.3
Gamella morbillorum	1	0.7
Methicillin-Resistant Staphylococcus aureus	6	3.9
Staphylococcus aureus	8	5.2
Streptococcus mutans	1	0.7
Staphylococcus haemolyticus	6	3.9
Staphylococcus hominis	3	2.0
Stapylococcus coagulase negative	1	0.7
Streptococcus agalactiae	4	2.6
Streptococcus anginosus	2	1.3
Streptococcus dysgalactiae	4	2.6
Streptococcus gordonii	1	0.7
Streptococcus parasanguinis	1	0.7
Streptococcus pyogenes	4	2.6

There are 35 poly-microbial infections and 79 mono-microbial infections bringing the total number of cultures to 153 for 114 patients with bacterial infection excluding yeast infections.

The antibiotic with the highest resistance rate is Cephazolin (85.5%)followed by Ampicillin (83.2%) and Tetracyclin (82.0%).

Based on the Centre of Disease Control (CDC) the definition of Multidrug resistant organisms (MDRO) are microorganisms' that are resistant to ≥ 1 antibiotic class/group (CDC, 2020).There are a total of 153 (100%) Multi-drug Resistant Organism in the patients of Dr.Soetomo General Hospital. A statistical analysis could not be done with MDRO due to consistency.

No statistics computed because MDRO is a constant Gram negative organisms are generally sensitive towards with an exception to *Acinetobacter baumannii* (53.3%). *Methicillin-Resistant Staphylococcus aureus* is 100% resistant towards Amikacin. *Enterococcus faecalis* (100%), *Methicillin-Resistant Staphylococcus aureus* (80%), 84.6% resistance *Acinetobacter baumannii, Escherichia coli* and *Pseudomonas aeruginosa* with a resistance of 66.7% towards Gentamycin

Gram negative organisms were resistant towards all β-Lactam-Penicillin except Piperacillin-tazobactam. β-Lactam-Penicillin has moderate to high resistance resistant to all species with an exception for *Enterococcus faecalis.* Cephazolam and 3rd generationcephalosporin's weere resistant to all bacterial isolates except for*Klebsiella pneumoniae* with a resistance of 42.9%. *Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris and Pseudomonas aeruginosa* were susceptible towards Cefepime.

Most isolates excluding *Escherichia coli* (30%),*Klebsiella pneumoniae*and *Morganella morgani* (33.3%), *Proteus vulgaris* and *Staphylococcus aureus* (0%) showed high resistance towards Trimethoprime-sulfamethoxazole. *Escherichia coli, Klebsiella pneumoniae ESBL, Kluyvera ascorbate* were susceptible towards Tigecycline.*Enterococcus faecium* (54.5%), *Streptococcus pyogenes* (66.7%),and all gram negative bacterial isolates except *Klebsiella pneumoniae ESBL* and *Proteus vulgaris* showed resistance towards Chloramphenicol.

Gram positive orgamisms showed resistance towards Daptomycin. *Streptococcus pyogenes* (25%), *Acinetobacter baumannii* (100%)and *Morganella morgana* (100%) were resistant to Clindamycin.*Kluyvera ascorbate* (0%), *Morganella morgani* (33.3%) and *Staphylococcus aureus* (0%) are all susceptible towards Ciprofloxacin and Quinolon. Imipenem, Ertapenem and Meropenem. Fosfomycin generally susceptible showed 100% resistance against *Acinetobacter baumannii* (100%) *and Morganella morgana* (100%). *Acinetobacter baumannii* (100%) resistant towards ertapenem. *Enterococcus faecalis, Methicillin-Resistant Staphylococcus aureus*, *Staphylococcus aureus* and *Streptococcus pyogenes* were all 100% susceptible toVancomycin and Linezolid.

Table 2. Antibiotic profile

Antibiotic	No. Sensitive (%)	No. Resistant (%)
Aminoglycoside		
Amikacin	79 (81.4%)	18 (18.6%)
Gentamycin	40 (36.7%)	69 (63.3%)
β-Lactam-Penicillin		
Aztreonam	36 (43.4%)	47 (56.6%)
Amoxcillin-clavulanic acid	27 (29.7%)	64 (70.3%)
Ampicillin	20 (16.8%)	99 (83.2%)
Ampicillin-sulbactam	23 (23.0%)	77 (77.0%)
Penicillin G	16 (30.2%)	37 (69.8%)
Piperacillin-tazobactam	64 (68.1%)	30 (31.9%)
Oxacillin	13 (39.4%)	20 (60.6%)
β-Lactam-Cephalosporin		
1st Generation		
Cephazolin	11 (14.5%)	65 (85.85%)
3rd Generation		
Ceftazidime	41 (45.6%)	49 (54.4%)
Cefotaxime	40 (42.1%)	55 (57.9%)
Ceftriaxone	15 (20.8%)	57 (79.2%)
Cefoperazone-sulbactam	54 (62.8%)	32 (37.2%)
4th Generation		
Cefepime	10 (50.0%)	10 (50.0%)
Trimethoprime-sulfamethoxazole	53 (39.0%)	83 (61.0%)
Tetracycline	20 (18.0%)	91 (82.0%)
Tigecycline	4 (22.2%)	14 (77.8%)
Chloramphenicol	50 (35.2%)	92 (64.8%)
Macrolides		
Erythromycin	23 (43.4%)	30 (56.6%)
Clindamycin	22 (39.3%)	34 (60.7%)
Daptomycin	10 (100.0%)	0 (0.0%)
Quinolon		
Ciprofloxacin	33 (36.3%)	58 (63.7%)
Carbapenem		
Imipinem	36 (69.2%)	16 (30.8%)
Ertapenem	18 (51.4%)	17 (48.6%)
Meropenem	58 (70.7%)	24 (29.3%)
Others		
Fosfomycin	54 (52.9%)	47 (46.1%)
Vancomycin	15 (100.0%)	0 (0.0%)
Linezolid	14 (100.0%)	0 (0.0%)

Duration of hospitalisation is categorised in to those who have stayed for more than or equals to 7 days (≥7) and for those who have stayed for lessthan 7days. Majorityofthepatientshave stayed for ≥ 7 days with a percentage of 73.7% (87 patients) and the remaining stayed for less than 7 days. The mean duration of hospitalization is 11.48±7.52 with a range of 2–37.

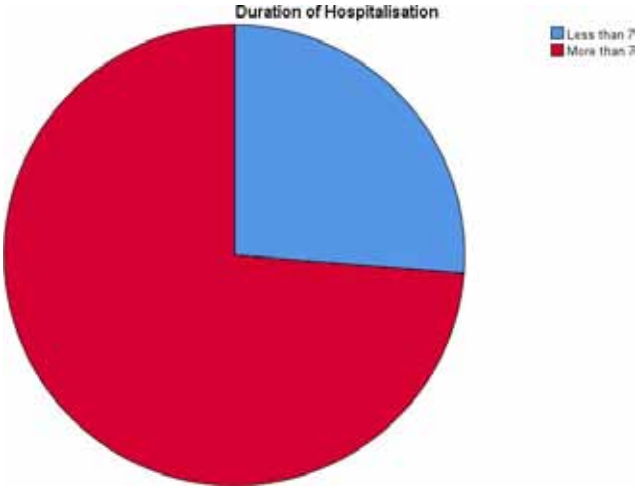

Fig. 2 Distribution of duration of hospitalisation

Antibiotic resistance is grouped based on their drug classes and its resistance or sensitivity towards the bacteria, Duration of hospitalisation consistes of those who stayed for less than 7 days and for those who stayed for 7 days or more and the severity of the foot ulcer by using Wagner's grading is subdivided into 2 groups of Wagner's grade less than 3 and those with Wagner's grade 3 or more. There is an association between Duration of hospitalisation and the severity of foot ulcer with a p-value of 0.039 and a moderate correlation between the 2 variables. There is significant correlation between antibiotic resistance and duration of hospitalisation although weak.

Amikacin and Gentamycin both showed no association. Piperacillin Tazobactam (p-value 0.045) showed an association with the duration of hospitalisation. Only the 1st generation cephalosporin showed an association. Ceftazidime (p-value 0.046) has an association with the duration of hospitalization. Trimethoprim-sulfamethoxazole has no association with the duration of hospitalisation. Chloramphenicol showed no association with duration of hospitalisation. Tetracyclin and tigecycline showed no association with duration of hospitalisation. Macrolides showed no association with duration of hospitalisation. Ciprofloxacin has no association with the duration of hospitalization. Imipenem, Meropenem, Ertapenem and Fosfomycin have no association with the duration of hospitalisation. Vancomycin and Linezolid are 100% sensitive to bacterial isolates therefore due to the consistency in data, a p-value could not be computed.

There is an association between the duration of hospitalization and the severity of foot ulcer based on Wagner grading ≥ 3 with p-value 0.034 and there is a strong correlation. There is also an association between duration of hospitalization and severity of infection based on poly-microbial infection or mono-microbial infection with a p-value of 0.032 and a weak correlation.

Discussion

In Dr. Soetomo General Hospital, Surabaya, there are more male patients 53.4% (63 cases) compared to female patients 46.6% (55 cases). The mean age of patients are 58.22 ± 10.05years with a range of 30 – 90 years. A similar trend found in studies conducted in India[16] and China[15].

Duration of hospitalisation was an average of 11.48 ± 7.52 days. A study done in Jakarta, Indonesia states that patients have a duration of hospitalisation of 2 weeks to more than 4 weeks[9]. A study carried by Wu et al, states that the duration of hospitalisation was significantly longer in patients with chronic ulcer wounds than in patients with acute ulcer wounds[17].

Distribution of Wagner's grading to assess the severity of DFU and majority of the sample has Wagner grade 3 and 4 which coincides with previous studies carried out[15,18]. There seems to be a trend in patients coming in with a much advanced DFU. Indonesia still has over 105 million people living just above the poverty line (Project, 2020). That being said, patients prefer to self-medicate or choose a more traditional or cheaper alternative before seeing a doctor which would further exacerbate the infection. It is also known that initial therapy is mainly an average of what has worked for most patients and is not tailored specifically until the cultures and antibiotic sensitivity test return[17]. Patients age 58 and abovehaveamortalityrateof50.8%(32cases) which is higher compared to non-asian countries but within range amongst certain Asian countries as seen in[19,20].

Patients presented with more gram negative 60.8% (93cultures) organisms compared to gram positive 39.2% (60cultures) organism.Similarly some studies showed

that gram-negative organisms were more common than gram-positive especially in South-east Asia and African countries[12,21,15].

This could be explained by using climate difference as a theory, a study conducted in Germany showed that warmer weathers are promote the growth of Gram-negative bacteria. In that study, Clinical pathogens vary by incidence density with temperature. Significant higher incidence densities of Gram-negative pathogens were observed during summer whereas S. pneumoniae peaked in winter. There is increasing evidence that different seasonality due to physiologic changes underlies host susceptibility to different bacterial pathogens[22,17].

Likewise, the distribution of pathogens will vary. Themost common gram positive organism were *Enterococcus faecalis* (7.8%), *Staphylococcus aureus* (5.2%) and *Staphylococcus haemolyticus* (3.9%) and *Proteus mirabilis* (10.5%), *Acinetobacter baumannii* (9.8%), *Escherichia coli ESBL* (8.5%), *Escherichia coli non ESBL* (7.2%) and *Pseudomonas aeruginosa*(7.2%). *Enterococcus faecalis* being the most common gram negative organismwhich could be due to contamination as all culture taken are from pus on gangrene or ulcer and not blood cultures. This is a similar finding to studies conducted in other parts of Indonesia, China and India and certain western countries however it varies in which is the dominant organism[9,12,15,18,21].

There are 35 poly-microbial infections and 83 mono-microbial infections in Dr. Soetomo General Hospital. Polymicrobial infection occurs due to composition of early colonizers that determines which microbes colonize at later time points[23]. This process of sequential attachment is commonly referred to as coaggregation[23]. Poly-microbial infections were found in subjects was associated with severity of DFU[24]. Gram negative bacteria are dominant in DFU patients. *Pseudomonas* sp. and *Staphylococcus aureus* were the most commonly identified Gram negative and Gram positive microorganism. The sensitivity patterns of common organisms suggested that they are susceptible to commonly use drugs[24].

According to this hypothesis, singular organism alone may not cause a disease but when they coaggregate or consort together into afunctional equivalent pathogroups the synergistic effect provides the functional equivalence of well-known pathogens, such as *Staphylococcus aureus*, giving the biofilm community the factors necessary to maintain chronic biofilm infections[25].

All patients presented with MDRO. In a study by Richard et al, MDRO were isolated in 45 (23.9%) of the 188 patients studied[26]. Deep and recurrent ulcer, previous hospitalization, HbA_{1c} level, nephropathy and retinopathy were significantly associated with MDRO-infected ulceration. By multivariate analysis, previous hospitalization and proliferative retinopathy significantly increased the risk of MDRO infection[26]. MDRO are pathogens frequently isolated from diabetic foot infection in our foot clinic[26].

Patients of Dr. Soetomo General Hospital, generally had a high resistance towards is Cephazolin with a rate of 85.5% followed by Ampicillin with 83.2% and Tetracyclin with 82.0%. Followed by, Ceftriaxone 79.2%, Tigecycline 77.8% and Ampicillin-sulbactam 77%. Which can be observed from Table 5.5 and Table 5.6. Most studies showed a various susceptibility to many drugs and what may be sensitive in on study isn't in another[9,17,27]. Thus, no one fix empirical treatment can be determined from studies alone, but requires detailed analysis of the patients that come in and has to be updated frequently.

All patients presented with multi-drug resistant organisms (MDRO) and 29.7% were poly-microbial patients. This study was carried out to find an association between Antibiotic resistance and duration of hospitalisation however out of 29 different antibiotics tested only 2 had a p-value of less than 0.05. Piperacillin-tazobactam (p-value 0.045) and Ceftazidime (p-value 0.046) which showed that there is an association. Moreover, there is significant correlation between all antibiotic resistance and the duration of hospitalisation. The hypothesis of this study is accepted for two antibiotics, further research is needed to determine the correlation for other antibioitcs. Diabetic foot ulcer patients are responsible for more hospital days than any other aspect of diabetes[28].

The authors noted that complexity of infection increases with inpatient care and duration of ulcers and suggested that MRSA antibiotic coverage be considered in cases of prolonged duration, inpatient management, or chronic kidney disease. Prolonged duration of hospitalisation patients are susceptible to nosocomial infections and drug resistant strains of organisms.

There appears to be a network of factors in the aging body, including degenerative changes and the declining immune response, that interact with and compound each other to markedly increase susceptibility to infection. Thus, this factor could contribute to the rise in multi-drug resistant organisms emerging.

The data and analysis obtained in this research further confirms that there is a need for an accurate diagnosis of causative organism is essential especially with the implementation of the new government insurance scheme (BPJS) where only a government approved drug is given to patients with diabetic ulcer under this scheme. Patients with diabetes are often exposed to many antibiotics and therefore can develop multiple-drug resistant infections (MDRO). Knowing the duration of therapy will greatly improve the efficiency of the treatment and help patients and insurance company predict the average cost of treatment and what risk factors prolongs the duration of treatment and hospitalisation.

Limitations: There are several limitations found during the course of this study among them are.

- This study did not prioritize the general profile of the patient which would include other risk factors such as glycaemic index and detailed description of foot ulcer.
- This study is a bivariate study which finds the correlation between antibiotic resistance and duration of hospitalisation. It isn't a multivariate study that takes into account multiple variables with the duration of hospitalisation.

Conclusion

Patients generally come in with a mean age of 58.2 Males make up 53.4% (63 cases) of the cases and females having 46.6% (55 cases). Rate of mortality is around 39.0% (46 patients).Majority of the sample has Wagner grade 3 and 4. The most common gram-positive organisms were *Enterococcus faecalis (*6.2%), *Staphylococcus aureus* (4.1%) and *Methicillin-Resistant Staphylococcus aureus* (3.1%) and *Proteus mirabilis* (7.8%), *Acinetobacter baumannii* (7.8%), *Escherichia coli ESBL (*6.2%), and *Escherichia coli* (5.7%) were common gram negative isolates. There is an association between duration of hospitalization and severity of infection based on poly-microbial infection or mono-microbial infection with a p-value of 0.032.Patients generally had a high resistance towards is Cephazolin (85.5%) followed by Ampicillin (83.2%) and Tetracyclin (82.0%). The average duration of hospitalisation is 11.48 days. Piperacillin-tazobactam and Ceftazidime showed that there is an association between antibiotic resistance and duration of hospitalisation.

Ethical Clearance: Taken from

The authors declare that they have no competing interests. (nil)

Source of Funding: Self

Conflict of Interest: The authors declare that they have no competing interests. (nil)

References

1. Bansal D, Gudala K, Muthyala H, Esam H, Nayakallu R, Bhansali A. Prevalence and risk factors of development of peripheral diabetic neuropathy in type 2 diabetes mellitus in a tertiary care setting. Journal of Diabetes Investigation [Internet]. 2014 [cited 11 December 2020];5(6):714-721. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4234236/
2. Barman R, Jain S. Bacteriological profile of diabetic foot ulcer with special reference to drug-resistant strains in a tertiary care center in North-East India. Indian Journal of Endocrinology and Metabolism [Internet]. 2017 [cited 11 December 2020];21(5):688. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5628537/
3. Boulton A. The diabetic foot: grand overview, epidemiology and pathogenesis. Diabetes/Metabolism Research and Reviews [Internet]. 2008 [cited 11 December 2020];24(S1):S3-S6. Available from: https://pubmed.ncbi.nlm.nih.gov/18442166/
4. Citron D, Goldstein E, Merriam C, Lipsky B, Abramson M. Bacteriology of Moderate-to-Severe Diabetic Foot Infections and In Vitro Activity of Antimicrobial Agents. Journal of Clinical Microbiology [Internet]. 2007 [cited 11 December 2020];45(9):2819-2828. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2045270/
5. Dowd S, Wolcott R, Sun Y, McKeehan T, Smith E, Rhoads D. Polymicrobial Nature of Chronic Diabetic Foot Ulcer Biofilm Infections Determined Using Bacterial Tag Encoded FLX Amplicon Pyrosequencing (bTEFAP). PLoS ONE [Internet]. 2008 [cited 11 December 2020];3(10):e3326.

Available from: https://pubmed.ncbi.nlm.nih.gov/18833331/

6. Gadepalli R, Dhawan B, Sreenivas V, Kapil A, Ammini A, Chaudhry R. A Clinico-microbiological Study of Diabetic Foot Ulcers in an Indian Tertiary Care Hospital. Diabetes Care [Internet]. 2006 [cited 11 December 2020];29(8):1727-1732. Available from: https://pubmed.ncbi.nlm.nih.gov/16873771/
7. Gardner I. The Effect of Aging on Susceptibility to Infection. Clinical Infectious Diseases [Internet]. 1980 [cited 11 December 2020];2(5):801-810. Available from: https://pubmed.ncbi.nlm.nih.gov/17363754/#:~:text=There%20was%20no%20association%20between,is%20associated%20with%20increased%20mortality.
8. Ismail K, Winkley K, Stahl D, Chalder T, Edmonds M. A Cohort Study of People With Diabetes and Their First Foot Ulcer: The role of depression on mortality. Diabetes Care [Internet]. 2007 [cited 11 December 2020];30(6):1473-1479. Available from: https://pubmed.ncbi.nlm.nih.gov/17363754/#:~:text=There%20was%20no%20association%20between,is%20associated%20with%20increased%20mortality.
9. 9. Jeyaraman K, Berhane T, Hamilton M, Chandra A, Falhammar H. Mortality in patients with diabetic foot ulcer: a retrospective study of 513 cases from a single Centre in the Northern Territory of Australia. BMC Endocrine Disorders [Internet]. 2019 [cited 11 December 2020];19(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30606164/
10. Jiang Y, Wang X, Xia L, Fu X, Xu Z, Ran X et al. A cohort study of diabetic patients and diabetic foot ulceration patients in China. Wound Repair and Regeneration [Internet]. 2015 [cited 11 December 2020];23(2):222-230. Available from: https://pubmed.ncbi.nlm.nih.gov/25682850/
11. MacDonald Y, Hait H, Lipsky B, Zasloff M, Holroyd K. Microbiological profile of infected diabetic foot ulcers. Diabetic Medicine [Internet]. 2002 [cited 11 December 2020];19(12):1032-1034. Available from: https://pubmed.ncbi.nlm.nih.gov/12647846/
12. Nather A, Bee C, Huak C, Chew J, Lin C, Neo S et al. Epidemiology of diabetic foot problems and predictive factors for limb loss. Journal of Diabetes and its Complications [Internet]. 2008 [cited 11 December 2020];22(2):77-82. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1056872707000530?via%3Dihub
13. Pemayun T, Naibaho R. Clinical profile and outcome of diabetic foot ulcer, a view from tertiary care hospital in Semarang, Indonesia. Diabetic Foot & Ankle [Internet]. 2017 [cited 11 December 2020];8(1):1312974. Available from: https://pubmed.ncbi.nlm.nih.gov/28649296/
14. Peters B, Jabra-Rizk M, O'May G, Costerton J, Shirtliff M. Polymicrobial Interactions: Impact on Pathogenesis and Human Disease. Clinical Microbiology Reviews [Internet]. 2012 [cited 11 December 2020];25(1):193-213. Available from: https://pubmed.ncbi.nlm.nih.gov/22232376/
15. Radji M, Putri C, Fauziyah S. Antibiotic therapy for diabetic foot infections in a tertiary care hospital in Jakarta, Indonesia. Diabetes & Metabolic Syndrome: Clinical Research & Reviews [Internet]. 2014 [cited 11 December 2020];8(4):221-224. Available from: https://pubmed.ncbi.nlm.nih.gov/25311820/
16. Richard J, Sotto A, Jourdan N, Combescure C, Vannereau D, Rodier M et al. Risk factors and healing impact of multidrug-resistant bacteria in diabetic foot ulcers. Diabetes & Metabolism [Internet]. 2008 [cited 11 December 2020];34(4):363-369. Available from: https://pubmed.ncbi.nlm.nih.gov/18632297/
17. Saltzman CL, Pedowitz WJ. 'Diabetic foot infections'. Instr Course Lect. 1999.[cited 11 December 2020]; 48:317-20.Available from: https://www.aafp.org/afp/2008/0701/p71.html#:~:text=In%20patients%20with%20diabetes%2C%20any,arthritis%2C%20tendinitis%2C%20and%20osteomyelitis.
18. Schwab F, Gastmeier P, Meyer E. The Warmer the Weather, the More Gram-Negative Bacteria - Impact of Temperature on Clinical Isolates in Intensive Care Units. PLoS ONE [Internet]. 2014 [cited 11 December 2020];9(3):e91105. Available from: https://pubmed.ncbi.nlm.nih.gov/24599500/
19. Shakil S, Khan A. Infected foot ulcers in male and female diabetic patients: a clinico-bioinformative study. Annals of Clinical Microbiology and Antimicrobials [Internet]. 2010 [cited 11 December 2020];9(1):2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821376/
20. Shanmugam P. The Bacteriology of Diabetic Foot Ulcers, with a Special Reference to Multidrug

Resistant Strains. JOURNAL of CLINICAL AND DIAGNOSTIC RESEARCH [Internet]. 2013 [cited 11 December 2020];. Available from: https://pubmed.ncbi.nlm.nih.gov/23634392/

21. Shaw J, Sicree R, Zimmet P. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice [Internet]. 2010 [cited 11 December 2020];87(1):4-14. Available from: https://pubmed.ncbi.nlm.nih.gov/19896746/
22. Sugandhi P, Arvind Prasanth D. Microbiological profile of bacterial pathogens from diabetic foot infections in tertiary care hospitals, Salem. Diabetes & Metabolic Syndrome: Clinical Research & Reviews [Internet]. 2014 [cited 11 December 2020];8(3):129-132. Available from: https://pubmed.ncbi.nlm.nih.gov/25087885/
23. Susan van D, Beulens J, Yvonne T. van der S, Grobbee D, Nealb B. The global burden of diabetes and its complications: an emerging pandemic. European Journal of Cardiovascular Prevention & Rehabilitation [Internet]. 2010 [cited 11 December 2020];17(1_suppl):s3-s8. Available from: https://journals.sagepub.com/doi/10.1097/01.hjr.0000368191.86614.5a
24. Sutjahjo, A. 'Kuman dan Uji Kepekaan Antibiotik di Kaki Diabetik'. Indonesia Journal of Clinical Pathology and Medical Laboratory [Internet]. 2016 [cited 11 December 2020]; 20(1), p.20.Available from: https://www.indonesianjournalofclinicalpathology.org/index.php/patologi/article/view/443
25. Syed Hitam S, Hassan S, Maning N. The Significant Association between Polymicrobial Diabetic Foot Infection and Its Severity and Outcomes. Malaysian Journal of Medical Sciences [Internet]. 2019 [cited 11 December 2020];26(1):107-114. Available from: https://pubmed.ncbi.nlm.nih.gov/30914898/
26. Wu M, Pan H, Leng W, Lei X, Chen L, Liang Z. Distribution of Microbes and Drug Susceptibility in Patients with Diabetic Foot Infections in Southwest China. Journal of Diabetes Research [Internet]. 2018 [cited 11 December 2020];2018:1-9. Available from: https://www.hindawi.com/journals/jdr/2018/9817308/
27. Xie X, Bao Y, Ni L, Liu D, Niu S, Lin H et al. Bacterial Profile and Antibiotic Resistance in Patients with Diabetic Foot Ulcer in Guangzhou, Southern China: Focus on the Differences among Different Wagner's Grades, IDSA/IWGDF Grades, and Ulcer Types. International Journal of Endocrinology [Internet]. 2017 [cited 11 December 2020];2017:1-12. Available from: https://pubmed.ncbi.nlm.nih.gov/29075293/
28. Yates C, May K, Hale T, Allard B, Rowlings N, Freeman A et al. Wound Chronicity, Inpatient Care, and Chronic Kidney Disease Predispose to MRSA Infection in Diabetic Foot Ulcers. Diabetes Care [Internet]. 2009 [cited 11 December 2020];32(10):1907-1909. Available from: https://pubmed.ncbi.nlm.nih.gov/19587371/