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SENSITIVITY OF ANTIBIOTIC IN DIABETIC ULCER BACTERIA AND ITS MANAGEMENT IN INDONESIA. A LITERATURE REVIEW

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ABSTRACT

Introduction: Diabetic ulcer is one of the complications of Diabetes Mellitus (DM) which is characterized by an open wound on the skin layer up into the dermis. One of the inhibitors of wound healing process is infection. The bacteria that present in the ulcer are a combination of aerobic and anaerobic bacteria. Treatment of infection is closely related to the use of antibiotics.

Methods: The method used in this paper is literature review and was conducted from 2010 – 2016. The research articles were reviewed from electronic databases including Science Direct, CINAHL, Pub Med, Pro Quest, and from relevant textbooks. The keywords used include diabetic ulcer, antibiotic, management ulcer, and wound care.

Results: The entry of bacteria into the early occurrence of diabetic ulcers and high glucose levels become strategic places of bacterial development. The most common types of bacteria found in diabetic ulcers, Staphylococcus sp, Streptococcus sp, Pseudomonas sp, and E.Coli, are still sensitive to antibiotic class of balaktam (Imepenam and Meropenam) whereas antibiotics that are resistant to these bacteria are amoxicillin and penicillin. Provision of antibiotic therapy should still be combined with wound care with a dressing that has antimicrobial properties, given the many types of bacteria found in diabetic ulcers with different types and sensitivity patterns to antibiotics.

Conclusions: Many cases in diabetic ulcer are infection and many types of bacteria are resistant to antibiotic. Prevention of resistance can be done with the selection of specific antibiotics, the combination of aerobic and anaerobic antibiotics, and the regularity of antibiotics including the timeliness and dose. Management of diabetic ulcers should be carried out comprehensively, not just focusing on antibiotics, but also with wound care, given the many types of bacteria found in diabetic ulcers with different types and sensitivity patterns to antibiotics.

Keywords: Diabetic ulcer, Bacteria, Ozone

INTRODUCTION

Diabetes Mellitus (DM) is a disease characterized by elevated blood glucose levels caused either by pancreatic damage or insulin resistance or both [1], which can lead to increased glucose levels in the body [2]. By 2014, the estimated prevalence of DM in the world reached 9% at the age of 18 years. DM is responsible for 1.5 million deaths worldwide and over 80% of deaths occur in developing and low and middle income countries [3]. The study results from the International Diabetic Federation (IDF) showed that DM patients were in a young age between 20-60 years [4]. The data also showed that Indonesia (4.43%) was included in the 5 countries with the highest number of DM patients [4]. The national prevalence of DM disease was 1.1%, the highest prevalence of DM was found in West Kalimantan and North Maluku (11.1%), followed by Riau (10.4%) and NAD (8.5%) [4, 5].

One complication of DM is diabetic ulcers [6]. Diabetic ulcer is open sore of the skin layer up into the dermis due to blockage of blood vessels in the limbs and peripheral neuropathy due to high blood glucose levels so the patient is unaware of any injuries [6]. The prevalence of diabetic ulcer patients in the United States is 15-20%, the risk of amputation is 15-46 times higher than non-DM patients, while the prevalence of diabetic ulcer patients in Indonesia is about 15%, and diabetic ulcers are the biggest cause of hospital care, 80% for DM [7].

One of the factors that have a major role for the duration of diabetic ulcer healing process is infection [8]. The entry of bacteria into the early occurrence of diabetic ulcers and high glucose levels become strategic places of bacterial development [9]. The bacteria present in the ulcer are a combination of aerobic and anaerobic bacteria. Infection is not only a health problem in Indonesia even in the world. Treatment of infection is closely related to the use of antibiotics. The use of irrational antibiotics can lead to the problem of germ resistance against some antibiotics. Therefore, rational use of antibiotics is absolutely imperative because antibiotics that are not used properly can cause widespread losses in terms of cost, economy and in future terms. Management of infection in diabetic ulcers is not sufficient only with antibiotic therapy, but should also be combined with wound care management, because if drainage is inadequate, it will cause sepsis to infect the tendons, bones, and joints beneath it[10].

METHODS

Method used in this paper is Literature Review. The research articles were reviewed from electronic database including Science Direct, CINAHL, Pub Med, Pro Quest and from relevant textbooks was conducted from 2010 – 2016. The numbers of keywords were used including about ulkus diabetic, antibiotik, ulkus management, and wound care.

RESULTS

Table 1. List of species identified bacteria in diabetic ulcer and sensitivity with antibiotic

No	Author	Year	Title	Samples	Kind of bacteria in ulkus diabetic	Result Sensitivity with Antibiotic resistance
1.	Abidah Nur and Nelly Marissa	2016	Description Of Diabetic Ulcers Bacteria At Zainal Abidin and Meuraxa Hospital in 2015	57	Consecutively, most of bacteria found were Staphylococcus sp, Klebsiella sp, Proteus sp, Shigella sp, E. Coli sp, Pseudomonas sp	Amoxicillin had the highest level resistance to bacterial, except for Staphylococcus sp., Klebsiella sp., And Escherichia coli still Sensitive to antibiotic sulbactam meropenem, imipenem, norfloxacin, Amikacin, nelticmicin sulfate, cefotaxime, Seftriaxone, and ciprofloxacin.
2.	Kannan Iyanar, Premavathy R,K, Sambandam Cecilia,	2014	Isolation and antibiotic susceptibility of bacteria from foot infections in the patient	60	Pseudomonas aeruginosa, Streptococcus aureus, and Peptostreptococ us sp,	Penicillin and Amoxicillin Amikacin, cefepine, ciprofloxacin, cotrimoxazole, and roxythromycin are sensitive to many



No	Author	Year	Title	Samples	Kind of bacteria in ulkus diabetic	Result Sensitivity with Antibiotic resistance
	Jayalakshmi M, Sruthi Priyadarsini S, Shantha S		with diabetes mellitus type 1 and type II in the district of Kancheepuram, Tamil Nadu, India			gram positive bacterial isolates.
3.	Sulistianingsih, Dirk Y.P, Runtuboi and Lucky V, Waworuntu	2014	Antibiotic Sensitivity to Bacteria Isolated from Diabetic Ulcer in Abepura Hospital, Jayapura City		E.Coli, K. Pneumoniae, E. Faecalis, S. Aereus	ciprofloxacin in RSUD Abepura to 6 types of bacteria in diabetic ulcers patient has resistance of 83.3% Imipenem has a sensitivity of 100% against 6 types of infectious bacteria ulcer patients, for other types of antibiotics with a sensitivity above 50% are Nitrofurantoin (83.3%), Gentamicin, Kanamycin and Polymyxin B respectively 66.7%
4.	Fawad Rahim, Fahim Ullah, Muhammad Ishfaq, Ayesha Khan Afridi, Sadiqur Rahman, Hassan Rahman	2016	Frequency of Common Bacteria and Their Antibiotic Sensitivity Pattern In Diabetics Presenting With Foot Ulcer	131	Staphylococcus aureus, Psudomonas aeruginosa	Staphylococcus aureus were resistance to Penicillin. Pseudomonas were resistance to Amoxicilin Staphylococcus aereus sensitive tp Moxifloxacin, Imipenam/Meropenam. Pseudomonas sensitive to Ceftriaxone, Ceftazidime, and Moxifloxacin
5.	Pratiwi Apridamayanti, Khairunnisa Azani Meilinasary, Rafika Sari	2016	Antibiotic Sensitivity in Pseudomonas aeruginosa of Diabetic Patient's Foot Ulcer	15	Streptococcus, Pseudomonas aeruginosa	Staphylococcus aureus were resistance to Cefadroxil and Amoxicillin. Pseudomonas were resistance to Amoxicillin Staphylococcus aereus sensitive to Imipenam/Meropenam. Pseudomonas sensitive to Ceftriaxone, Cefotaxime, and Imipenam/Meropenam
6.	Wulan Priatiwi, M. Kuswandi, EM Sutrisna	2014	Microbial Maps and Antibiotic Resistance Of Gangrene Diabetic Patiens In Dr. Moewardi Hospital Periode 2014	50	Almost bacteria were gram-negative (82%), Escherichia coli was dominant with amount 17.74%	Penicillin, Amoxicillin, Gentamicin Meropenam
7.	Ardiansyah Kahuripan, Retno Andrajati,	2009	Antibiotic Anticipating Analysis	98	From 11 kind of bacteria, Staphylococcus bacteria Aureus is a germ	Penicillin and Amoxicillin Meropenam

No	Author	Year	Title	Samples	Kind of bacteria in ulkus diabetic	Result Sensitivity with Antibiotic resistance
	Tetty Syafridani		Based On Test Result Of Sensitivity On Achievements Clinical Outcome Patients Infection Of Diabetic Ulkus In Rsud Dr. H. Abdul Moeloek Lampung		Many infect ulcer patients Diabetic at 27.45%	
8.	Liong Boy Kurniawan, Tenri Esa, Nurhayana Sennang	2011	Aerob Microbes Pattern and Antimicrobial Sensitivity of Diabetic Foot Ulcer	31	The common microbes were gram negative bacteria (73.52%) including Enterobacter agglomerans, Proteus mirabilis and Klebsiella pneumonia, while the most common gram positive microbe was Streptococcus sp and Staphylococcus	Gram positive and gram negative microbes was resistance with amoxicillin Gram positive microbes were sensitive to meropenem, ceforoxim, Gram negative microbes were sensitive to meropenem

Table 1 shows that the bacteria present in diabetic ulcers are a combination of aerobic and anaerobic bacteria. Aerobic bacteria are bacteria that in the process metabolism require oxygen, anaerob bacteria is a bacterium that in the process of metabolism does not require oxygen. Bacteria present in diabetic ulcers have different sensitivity to antibiotics [11]. Variations of bacterial inhibition zone in bacterial sensitivity test using diffusion method and obtained by doing pus culture on diabetic ulcers depict bacterial sensitivity level [12, 13]. There are several types of antibiotic-resistant bacteria , most of the bacteria found in diabetic ulcers namely Staphylococcus sp , Streptococcus sp, Pseudomonas sp, and E.Coli are still sensitive to class of balaktam (Imepenam and Meropenam), While antibiotics that are resistant to these bacteria are antibiotic amoxicillin and penicillin [10].

DISCUSSION

Diabetic ulcers are one of the complications of Diabetes Mellitus which is characterized by the presence of open sores on the skin layer up into the dermis [6, 14]. This diabetic ulcer is a major cause of hospitalization of patients with DM and is the most expensive complication and requires a relatively long time in the healing process [15]. One of the factors that contributed greatly to the duration of the diabetic ulcer healing process is infection [16]. The entry of bacteria into the early occurrence of diabetic ulcers and high glucose levels become strategic places of bacterial development [17, 18]. The bacteria present in the ulcer are a combination of aerobic and anaerobic bacteria [19]. Infection often becomes a complicating or inhibiting factor in the healing process of diabetic ulcers, even leading to death from systemic infection[20]. Infectious

diseases in diabetics can increase morbidity and mortality. Treatment for the infection uses antibiotics. A problem will arise if most bacteria have been resistant to the antibiotics given. Kuswandi (2011) states that to treat an infection antibiotics are needed that can kill germs selectively, and resistance occurs when the antibiotic is not able to kill pathogenic bacteria that can lead to therapeutic effects of an antibiotic is not achieved. Foot infections in diabetics should be treated immediately and initiated with broad-spectrum antibiotics, but after the action of bacterial culture it is necessary to be given more specific antibiotics. Morbidity and mortality caused by diabetic ulcers will be higher so optimal treatment management is necessary. As many as 40% -60% of diabetic ulcers require treatment with antibiotics. Bacterial resistance to antibiotics will increase as diabetic ulcer disease is caused by polymicrobials consisting of pathogens that have been resistant to many antibiotics plus other accompanying diseases that not only affect the treatment regimen but also inhibit the healing process [7, 9, 21].

In Table 1, Streptococcus sp and Staphylococcus sp is the most common bacteria found in diabetic ulcers, amoxicillin and penicillin holds the highest rates of resistant antibiotics. In line with a study conducted by Hena at the government Hospital of Coimbatore India which showed that mostly Staphylococcus aureus bacteria were found (42.3%) in diabetic ulcers [17]. A study conducted by Mathangi also mentioned that the mostly common bacterium found in diabetic ulcer was Staphylococcus aureus (97%) [17, 22, 23]. The most common cause of infection in DM lesions is a combination of aerobic and anaerobic bacteria [24]. Visvanathan (2008) revealed that from DM patients pus culture, there were aerobic and anaerobic bacteria in Enterobacteriaceae family (48%), Staphylococcus sp (19.2%), Streptococcus sp (15.4%) and Pseudomonas sp (17%)[17]. Staphylococcus sp was reported to be the type of bacteria that was still sensitive to ten antibiotics tested for sensitivity [11].

Staphylococcus sp and Streptococcus sp is a gram-positive bacteria and pathogenic bacteria species commonly found in pus specimens, spreading on the skin surface as normal flora[16]. These bacteria produce coagulase which catalyzes the change of fibrinogen into fibrin and can help these organisms to form a protective sequence. Skin infections can occur in warm humid conditions or when the skin is exposed due to disease. The spread can be through the air and hands of medical personnel[17, 21]. Pseudomonas and E. coli are gram negative bacteria that are often found in diabetic ulcers. E. coli is one of the group of Enterobacteriaceae that producing ESBL (Extended Spectrum Beta Lactamase) which is a nosocomial bacteria and is widely available in the hospital. Diabetic ulcers are a disease that requires prolonged and recurrent treatment in the hospital so the risk of becoming infected with Escherichia coli is also greater. The number of negative Gram germs found in diabetic ulcers may be caused by chronic or recurrent injuries to the patient. An extra virulence factor in Escherichia coli can make this germ is pathogenic [21, 25, 26]. Staphylococcus sp, Streptococcus sp, Pseudomonas, and E.coli have sensitivity to antibiotics class balaktam (Imepenam and Meropenam) and resistant to Penicillin and Amoxicillin. The high number of resistances that occur due to antibiotics of this class is most widely available in health care units and is often used for middle to lower society. So the possibility of resistance that occurs in antibiotics is also greater[26, 27]. Staphylococcus sp and Streptococcus is a germ can produce β -lactamase enzyme that attacks the β -lactam ring in the penicillin and amoxicillin molecules. This enzyme is responsible for the increased resistance to the antibiotic. In grams positive, enzymes are released into the medium and destroy antibiotics before reaching the cell[28-30]. Imepenam and Meropenam are antibiotics that have high sensitivity to Staphylococcus sp, Streptococcus, Pseudomonas, and E.Coli bacteria. Meropenam and Imepenam are balactam-type antibiotics that act through betalactam-resistant in betalactam rings that have activity for gram-negative and positive organisms. Antibiotics of the class of balaktam are effectively administered to patients who are already resistant to penicillin and amoxicillin antibiotics[31]. Bacterial resistance to antibiotics can result from the use of antibiotics in a relatively long period of time and continuously allowing the bacteria to form a self-defense mechanism when later will be attacked by the same antibiotic. In addition, the use of antibiotics in diabetics ulcer therapy in every hospital treatment is different[28]. It also makes the amount of antibiotic sensitivity and resistance different. Infection from the hospital is part of the

prevalence of the patient's disease, but is often associated with the presence of pathogenic microorganisms present in the treatment environment [26]. Prevention of resistance can be done with several things, namely the selection of specific antibiotics, because the wrong antibiotics can cause allergies, resistant, even organ damage, the combination of aerobic and anaerobic antibiotics, and the regularity of antibiotics and the timeliness and dose [28, 32-34].

Management of infection in diabetic ulcers is not only sufficient with antibiotic therapy, but should also be assisted by wound management through wound care, because if ineffective drainage can cause rapid bacterial growth. Wound care techniques used with the principle of moist balance, because the moist condition can reduce the risk of infection and accelerate the formation of active cells with growth factor so the process of wound healing can be fast [6].

CONCLUSION

One of the factors that inhibit the healing process of diabetic ulcer is infection. There are several types of antibiotic-resistant bacteria, most of the bacteria found in diabetic ulcers namely *Staphylococcus* sp, *Streptococcus* sp, *Pseudomonas* sp, and *E.Coli* are still sensitive to class of beta-lactam (Imipenem and Meropenam), While antibiotics that are resistant to these bacteria are antibiotic amoxicillin and penicillin. Management of diabetic ulcers should be carried out collaboratively with other health personnel. Pharmacological therapy in the form of antibiotics is a therapy that becomes the responsibility of a doctor and has positive and negative values. Provision of antibiotic therapy should still be combined with wound care with a dressing that has antimicrobial properties. Given the many types of bacteria found in diabetic ulcers with different types and sensitivity patterns to antibiotics.

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