

Antibiotics Efficacy Analysis on Diabetic Foot Ulcer Inpatients

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Abstract—Introduction: Diabetic foot ulcer known as infection, ulceration or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular diseases in lower limb. Treatment of diabetic foot ulcer required intensive empiric and definitive antibiotic therapies. Beside antibiotic, there are other factors that influence the diabetic foot ulcers healing. This study aims to determine the relationship between suitability and efficacy of antibiotics to wound improvement and other factors influence for wound improvement. **Methods:** This prospective cohort study was perform in Haji General Hospital Surabaya since June until August 2015 on 17 diabetic foot ulcer inpatients age ≥ 20 years old. Suitability of empiric antibiotic was compared to hospital standard procedure and suitability of definitive antibiotic was compared to the result of microbial culture and sensitivity test of each patient. **Result:** The relationship between suitability of empiric antibiotics and other factors influence for wound improvement could not be analyzed by inferential statistic because of limited data variation. The relationship between suitability and efficacy of definitive antibiotics to wound improvement was not significant (13,1%, $p=0,585$). Other factors beside antibiotics which significantly associated with wound improvement was debridement in surgery room 66,2% ($p=0,000$). **Conclusions:** Suitability of antibiotics was not the most influence on the process of improvement in diabetic foot ulcer. The most important factor for wound improvement was debridement in operation room.

Index Terms—suitability, efficacy, antibiotic, diabetic foot ulcer, inpatient

I. INTRODUCTION

Diabetic foot ulcer is a complication of diabetes. Diabetic foot ulcer is caused by poor circulation associated with peripheral neuropathy and peripheral vascular disease and without early treatment may become infected and can lead to amputation and death. Several factors that influence the healing of diabetic foot ulcers such as blood sugar levels, debridement, offloading, dressing and antibiotic therapy [1]-[6].

A study former prospective study at Haji General Hospital Surabaya in June until August 2011 concluded that the empirical antibiotics in patient with diabetic foot ulcers 100% were not matched with bacterial culture

result but 57,7% were effective and 42,3% were not effective. Definitive antibiotic were 30% matched, 15% were not matched with bacterial culture and there were 55% samples lack of bacterial culture (75% were effective and 25% were not effective) [7]. Another retrospective study at Haji General Hospital Surabaya in October 2014 until February 2015 concluded that the empirical antibiotics in patient with diabetic foot ulcers were 100% not matched with bacterial culture but 38,9% effective and 61,1% not effective. Definitive antibiotic 57,2% matched with bacterial culture (42,9% were effective and 14,3% were not effective) [8]. This indicates that there were other factors that could affect wound healing in addition to antibiotics. Thus study aims were to determine the relationship between suitability and efficacy of antibiotics to wound improvement and to study other factors influence the wound improvement.

II. METHODS

A. Study Design

This prospective cohort study was perform in the Haji General Hospital Surabaya since June until August 2015. The study was approved by the Haji General Hospital Surabaya Ethics Committee on May 2015.

B. Inclusion Criteria

All inpatient diabetic foot ulcer were age ≥ 20 years old with or without confounding disease. Patients who receive empirical antibiotics therapy and definitive antibiotics and testing bacterial culture.

C. Exclusion Criteria

Patients with other infections other than diabetic foot ulcers infection.

D. Loss to Follow-up

Patient could not finished all of the study procedure or died in the follow-up period.

E. Operational Definition

Empiric antibiotic is antibiotics given before susceptibility test result were known. Definitive antibiotic is antibiotics given after susceptibility test result were known [9]-[11].

Suitability assessment of empirical antibiotic stated as appropriate when the antibiotics has the types, dosage, frequency and route of administration of antibiotics the

same as the standart procedure with Haji General Hospital. It was stated an inappropriate when there are minimal differences in the type, dose frequency or route of administration of antibiotics. Empirical antibiotic used for diabetic foot ulcers according to standart operating procedure of Haji General Hospital is a combination of ceftriaxon and metronidazole.

Suitability assessment of definitive antibiotic stated as appropriate if susceptibility test result indicate that the bacteria are sensitive to the antibiotics and it is stated as inappropriate when the susceptibility test showed that bacteria are intermediate or resistant to the antibiotics. If there was a combination of antibiotics are not tested than it is adjusted to the tested antibiotic sensitivity.

Diabetic foot ulcer grade were evaluated based on Infectious Disease Society of America Classification (IDSA) [5], [6], [10]. IDSA clasification are shown in Table I. Patients performance status was evaluated based on Karnofsky performance status [12]. Karnofsky performance status is shown in Table II.

Debridement is the cleaning of dead tissue, damaged or infected tissue [13].

Body massa index were categorized according to Asia Pasific body massa index category [14].

Wound condition is said to be improved if there was a reduction compared to initial grade ulcers. Wound condition was not improved if there was no improvement or there was an increased in grade ulcers.

TABLE I. INFECTIOUS DISEASE SOCIETY OF AMERICA CLASSIFICATION

Clinical Manifestation of Infection	Grade/ Infection Severity
No symptoms or sign of infection	1/Uninfected
Infection present, as defined by the presence at least 2 of the following items: - Local swelling or induration - Erythema - Local tenderness or pain - Local warmth - Purulent discharge (thick, opaque to white or sanguineous secretion)	2/Mild
Local infection involving only the skin and the subcutaneous tissue (superficial tissue lesion or without involvement of deeper tissues and without systemic signs as described below). If erythema, must be $>0,5\text{cm}$ to $\leq 2\text{cm}$ around the ulcer. Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).	
Local infection (as described above) with erythema $>2\text{cm}$, or involving stustures deeper than skin and subcutaneous tissues (eg, abcess, osteomyelitis, septic arthritis, fascitis), and no SIRS sign (as described below)	
Local infection (as described above) with the signs of SIRS, as manifested by ≥ 2 of the following: - Body temperatur $>38^\circ\text{C}$ or $<36^\circ\text{C}$ - Pulse >90 beats/min - Respiratory rate >20 breaths/min or $\text{PaCO}_2 <32$ mmHg - White blood cell count >12.000 or <4000 cell/ μL or $\geq 10\%$ immature (band) forms	4/Severe

TABLE II. KARNOFSKY PERFORMANCE STATUS

Condition	Percentage	Explanation
- Able to carry on normal activity and to work - No special care is needed	100	Normal, no complaints, no evidence of disease
	90	- Able to carry on normal activity - Minor signs or symptoms of disease
	80	- Normal activity with effort - some signs or symptoms of disease
- Unable to work - Able to live at home, care for most personal needs. A varying degree of assistance is needed	70	- Cares for self - Unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his needs
	50	Requires occasional assistance and frequent medical care
- Unable to care for self - Requires equivalent of institutional or hospital care - Disease may be progressing rapidly	40	- Disable, requires special care and assistance - In bed more than 50% of the time
	30	- Severely disabled, hospitalization is indicated although death not imminent - Almost completely bedfast
	20	- Hospitalization necessary, very sick, active supportive treatment necessary - Totally bedfast and requiring extensive nursing care by professionals and/or family
	10	- Moribund, fatal processes progressing rapidly, comatose or barely arousable
	0	dead

F. Follow-up

Patient were followed-up before receiving empiric antibiotic, 3 days after receiving empiric antibiotic, before receiving definitive antibiotic and 3 days after receiving definitive antibiotics. Follow-up procedure include blood glucose level, albumin, white blood cell, body temperature, respiratory rate, wound condition such as odour, granulation, necrotic tissue and pus production.

III. RESULTS

A total of 35 inpatients were recruited in study period. Thirteen patients were excluded from this study because of 11 patients lack of bacterial cultures, 1 patient with tuberculosis and 1 patient with pneumonia. There were 3 patients drop out and 2 patients died. Sample of this study were 17 patients aged $53 \pm 12,51$ years (53% male and 47% female). 76,5% patients with co-morbidities and 23,5% patients without co-morbidities. Patient recruitment profile is as shown in Fig. 1 and participant characteristics as shown in Table III.

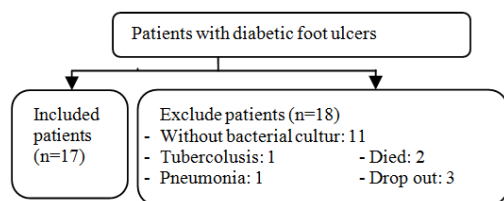


Figure 1. Patient recruitment profile

TABLE III. BASELINE CHARACTERISTICS OF PATIENTS

Characteristics	n(%)
Gender	
Male	9 (53 %)
Female	8 (47 %)
Age (years)	
41-45	1 (5,88 %)
46-50	2 (11,76 %)
51-55	7 (41,18 %)
56-60	2 (11,76 %)
61-65	4 (23,53 %)
66-70	1 (5,88 %)
BMI (Kg/m²)*	
< 18,5	0
18,5 - 22,9	9 (52,94 %)
23,0 - 24,9	2 (11,76 %)
25,0 - 29,9	5 (29,41 %)
NA	1 (5,88 %)
HbA_{1c} (%)	
< 7,0	2 (11,76 %)
7,1 - 9,0	1 (5,88 %)
9,1 - 11,0	4 (23,53 %)
11,1 - 13,0	3 (17,65 %)
13,1 - 15,0	3 (17,65 %)
> 15,1	2 (11,76 %)
NA	2 (11,76 %)
Co-morbidities	
With co-morbidities	76,5 % (13)
Without co-morbidities	23,5 % (4)
IDSA Grade	
1	0
2	1 (5,88 %)
3	7 (41,18 %)
4	9 (52,94 %)

*Asia Pacific Category¹⁴

The results of isolated organism on wound swabs of diabetic foot ulcer were taken at inpatient room. The result were Gram-positive bacteria of 35,29% and Gram-negative bacteria of 64,71%. *Pseudomonas aeruginosa* was the most predominant Gram-negative organism (17,65%) and *Enterococcus faecalis* and MRSA was the most predominant Gram-positive bacteria (11,76% and 11,76%). A wide range of organisms were identified from the ulcer as shown in Table IV.

Empiric antibiotics used in this study were ceftriaxone (11,76%), combination of ceftriaxon and metronidazole (82,35%), combination of ceftriaxon and clindamicyn (5,88%) but none were effective. Definitive antibiotics used were ceftriaxone (5,88%), combination of ceftriaxon and metronidazole (76,47%), were 5,88% respectively combination of ciprofloxacin and clindamicyn, combination of meropenem and metronidazole and combination of cefixim and gentamycin. Definitive antibiotics combination tested were ceftriaxon, ciprofloxacin, meropenem, sand gentamycin but metronidazole, clindamicyn, and cefixim were not tested.

Definitive antibiotics 35,29% mathced with bacterial culture (17,65% were effective, 17,65% were not effective), not mathced with bacterial culture 64,71% (41,18% were effective, 23,53% were not effective).

TABLE IV. ORGANISMS IMPLICATED IN DIABETIC FOOT ULCER

Bacteria	n (%)
Gram +	
<i>Enterococcus faecalis</i>	2 (11,76)
MRSA*	2 (11,76)
<i>Staphylococcus aureus</i>	1 (5,88)
<i>Staphylococcus epidermidis</i>	1 (5,88)
Gram -	
<i>Acinetobacter baumannii</i>	1 (5,88)
<i>Enterobacter aerugenes</i>	1 (5,88)
<i>Klebsiella pneumoniae</i>	1 (5,88)
<i>Pantoea agglomerans</i>	1 (5,88)
<i>Proteus vulgaris</i>	2 (11,76)
<i>Pseudomonas aeruginosa</i>	3 (17,65)
<i>Serratia morcescens</i>	1 (5,88)
<i>Shigella sp.</i>	1 (5,88)

*MRSA: Methicillin resistant *Staphylococcus aureus*

All patients had normal random blood glucose level because all patients receive insulin therapy except for 1 patient because of nomal random blood glucose level already. All patient had hypoalbuminemia (<3,5g/dL) despite being given albumin therapy. There was reduction in hemoglobin profile of all the patients. Hemoglobin profil was changed in some patients because of tranfusion PRC but only 58,82% patient had increased hemoglobin level and 41,18% had reduction hemoglobin level but not lower than >9,1g/dL.

The result were at performance scale of 10 (5,88%), were 11,77% respectively of performance scale of 30, 40 and 70, were performance scale 50 (17,65%), were performance scale 60 (23,53%). Grade ulcer of patients on early administration of definitiv antibiotics based on Infectious Disease Society of America Classification (IDSA) were at grade 3 (17,65%) and grade 4 (82,35%).

There 58,82% patients were with offloading and 41,18% without offloading. All patients used were the same dressing (steril gauze, soft bandage and elastic bandage). Before debridement in operation room they use only steril gauze and after debridement in operation room use steril gauze, soft bandage and elastic bandage.

Debridement at inpatient room was performed everyday but debridement in operation room only done once during hospitalization, eccept for 2 patients (1 patient died before debridement in operation room and 1 patient have had debridement in operation room twice). But the time elapsed before debridement in operation room had done were varies between patients.

IV. STATISTIC AND DISCUSSION

The relationship between suitability of empiric antibiotic and the influence for wound improvement could not be analyzed by inferential statistic because of limited data variation. The relationship between suitability and efficacy of definitive antibiotics to wound improvement was not significant (13,1%, p=0,585). Other factors beside antibiotics which significantly

associated with wound improvement was debridement in surgery room 66,2% ($p=0,000$). There not significantly associated with wound improvement were gender (29,6%, $p=0,201$), age (5,1%, $p=0,845$), co-morbidities (9,9%, $p=0,682$), ulcer grade (36,1, $p=0,110$), offloading (2,9%, $p=0,906$), performance ($p=0,281$) and BMI ($p=0,318$).

Debridement aims to removal necrotic tissue, damaged tissue, slough, callus or grime in the wound. Additionally debridement can eliminate bacterial colonization of the ulcer, helps the formation or granulation tissue, reshaping the damaged epithelium and reduce the pressure on the area contained callus. Infection causes a microvascular circulation disorder which limits the access of phagocytic cells to the infected area and results in a poor concentration of antibiotics in the infected tissues [1], [10], [13], [15], [16]. This is why debridement is the most important thing to diabetic foot wound improvement.

Diabetic foot ulcer were causes polymicrobial [1], [17], [18]. This is accordance with the bacterial culture result in this study show the variation of bacteria that cause ulcers. This study was detected only one type of bacteria on each specimen tested are Gram positive or Gram negative bacteria because the microbiology laboratory to analyze only the largest bacterial colonies and did not test the anaerob bacteria. The type and incidence of bacteria in this study as a previous study conducted in 2011 at the same hospital was same the longest species of bacteria were Gram negative (*Pseudomonas aeruginosa*) dan Gram positif (*Staphylococcus sp*). In this study bacterial culture specimens collected from tissue deep ulcer. Tissue spesimens from deep ulcer was assessed more representative types of bacteria that caused infection than tissue spesimens collected from the surface ulcer [1], [19], [20].

In this study all patient had hypoalbuminemia ($<3,5\text{g/dL}$) despite being given albumin therapy. Low albumin causing poor wound healing by prolonging the inflammatory process, interfere the synthesis of collagen, which plays an important role in tissue regeneration and increased risk of edema because albumin has a function regulate oncotic pressure. In addition, low albumin significantly linked to poor wound healing [21], [22]. In this study also found low hemoglobin in some patients. Hemoglobin has a fuction as a carrier of oxygen in the body requirement. Hemoglobin is an important factor in wound healing because oxygen is required in the wound healing process [23].

The relationship between grade ulcers and wound improvement was not significant. The severity of the wound is required to determine the need for hospitalization, the selection of empiric antibiotics, route of drug administration and evaluation of the need for surgery so that in this study using Infectious Disease Clasification of America Scale (IDSA) for this classification could indicate the severity. IDSA classifies the severity of injuries such as; mild category when the wound is only on the surface of tissues size and depth are limited, moderate when the wound deeper and more

widespread and severe when associated with abnormalities of systemic or metabolik signs [4], [19].

V. CONCLUSION

The relationship between suitability and efficacy of definitive antibiotics to wound improvement was not significant, this because were factors other than antibiotics related to wound improvement. Most related factor to the wound improvement was debridement in operation room.

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