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Analysis of antibiotic use in diabetic ulcer patients at a private hospital in Surabaya

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ABSTRACT

Diabetic ulcer is one of the complications of diabetes mellitus in the form of chronic wounds due to neuropathy and peripheral arterial disease. Bacteria enter in a wound and cause a skin infection. Appropriate antibiotic therapy is needed to prevent antibiotic resistance. The purpose of this study was to evaluate the quantity profile of antibiotic use using the prescribed daily dose (PDD) and days of therapy (DOT) methods compared with the therapeutic guidelines (PPAB) in diabetic ulcer patients for the period January 2020 - June 2022 at a private hospital in Surabaya, Indonesia. This observational study with the retrospective data collection using medical records was analysed descriptively. The results showed that the total PDD value was 20.44 g/day. The highest antibiotic prescriptions were ceftriaxone (2.39 g/day) and metronidazole (1.46 g/day), respectively. The total days of therapy was 12.13 DOT; the DOT more than 4.00 were metronidazole (4.15 DOT) and ceftriaxone (4.09 DOT). This study reported a high PDD and DOT that will cause antibiotic resistance in the future.

ABSTRAK

Ulkus diabetikum merupakan salah satu komplikasi diabetes melitus berupa luka kronis akibatadanya neuropati dan penyakit arteri perifer. Adanya luka memudahkan bakteri berkembang hingga risiko terinfeksi. Terapi antibiotik yang sesuai diperlukan untuk mencegah resistensi antibiotik. Tujuan penelitian ini mengevaluasi profil kuantitas penggunaan antibiotik dengan metode *prescribed daily dose* (PDD) dan *days of therapy* (DOT) dibandingkan dengan pedoman terapi (PPAB) pada pasien ulkus diabetikum periode Januari 2020 – Juni 2022 di sebuah rumah sakit swasta di Surabaya. Penelitian ini merupakan penelitian observasional dengan arah pengambilan data retrospektif menggunakan rekam medis yang dianalisis secara deskriptif. Hasil penelitian menunjukkan bahwa total nilai PDD sebesar 20,44 g/hari dengan peresepan antibiotik paling tinggi, yaitu seftriakson (2,39 g/hari) dan metronidazol (1,46 g/hari). Total nilai DOT sebesar 12,13 DOT denga nilai DOT yang paling tinggi pada antibiotik metronidazol (4,15 DOT) diikuti seftriakson (4,09 DOT). Hal ini menunjukan bahwa tingginya nilai PDD dan DOT berpotensi menyebabkan resistensi antibiotik.

Keywords:
diabetic ulcers;
prescribed daily dose;
days of therapy;
antibiotic resistance;
therapeutic guide line

INTRODUCTION

The International Diabetes Federation (IDF) predicted that the number of people with diabetes mellitus (DM) will continue to increase to reach 642 million in 2040 globally.[1] The Indonesia Basic Health Research 2018 (*Riset Kesehatan Dasar* 2018/Riskesdas 2018), the prevalence of diabetes mellitus in Indonesia based on diagnosis at the age of 15 yr increased by 1.5 to 2%.[2] Uncontrolled DM can cause various kinds of complications, both acute and chronic. One of the chronic complications of DM is ulcers or gangrene.[3] More than 50% of ulcer patients can experience diabetic foot infections.[4] In Indonesia, the incidence of amputation is 31% and the mortality rate caused by diabetic foot infections is 17-32%.[5]

Diabetic foot infections are caused

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by several microorganisms.[6] The most common bacteria found in the diabetic foot infections in the world are *Staphylococcus aureus*, *Pseudomonas* spp, and *Enterobacter* spp.[7] In Indonesia, the most common pathogenic bacteria in diabetic foot infection are the Gram-negative bacteria *Enterobacter* spp and *Staphylococcus* spp.[3] Antibiotics are used for the diabetic foot with osteomyelitis (need long-term antibiotics up to 3 months), critical limb ischemia (given before revascularization), and cellulitis (caused by Gram positive and anaerobic cocci germs empirically).[8]

AMRIN-Study reported that 781 patients treated at the hospital found that 81% of *Escherichia coli* resistant to several antibiotics such as ampicillin, cotrimoxazole, chloramphenicol, and gentamicin.[9] Agistia *et al.*[10] reported that antibiotics is effective on 78.94% of diabetic patients with ulcer infections, only 21.05% is not effective and resistant to some types of antibiotics. The existence of antibiotic resistance in hospitals requires efforts to prevent antibiotic resistance. The CDC and the Global Antibiotic Resistance Partnership (GARP) recommend a strategy, one of which is the Antibiotic Stewardship Programs (ASP).[11]

Since 2015, the Ministry of Health of the Republic of Indonesia has launched the Antibiotic Resistance Control Program (PPRA) to control antibiotic resistance in hospitals.[9] One of the activities of the PPRA is conducting surveillance of antibiotic use patterns in hospitals in Indonesia. This study aimed to evaluate antibiotic use patterns on diabetic ulcer patients at a private hospital in Surabaya.

MATERIAL AND METHODS

Subject and design

It was a descriptive observational study with a cross-sectional design with a retrospective approach. The data of antibiotic use patterns from medical records of diabetic ulcer patients who were hospitalized at the Husada Utama Private Hospital, Surabaya for the period of January 2020 to June 2022. Total sampling was used to collected the data.

Data collection

The inclusion criteria of subject were patients with a diagnosis of diabetic ulcer with or without comorbidities, diabetic ulcer patients receiving antibiotic therapy, and type 2 DM patients with complications of peripheral vascular circulation with ICD-10 code E11.5. Patients transferred to other hospitals and unwilling to continue treatment (discharged without physician consent) were excluded from this study. Samples that met the inclusion and exclusion criteria, the quantity profile of antibiotic use was recorded. The antibiotic use in this study was analysed quantitatively utilizing the PDD and DOT methods. The PDD and DOT values were then calculated with the following equation:

$$\text{Prescribed daily dose (PDD)} = \frac{Number\ of\ drugs\ prescribed \times Medicinal\ power}{Total\ duration\ of\ antibiotic} \quad (1)$$

$$\text{Days of therapy (DOT)} = \text{Duration of antibiotics (d)} \times 1\ \text{DOT} \quad (2)$$

Data analysis

The data were presented as frequency and analysed descriptively. The assessment of the suitability of antibiotic therapy will be described descriptively and presented in the form of a table that explains the percentage of conformity in the form of appropriate and inappropriate. The suitability of the use of antibiotics can be calculated based on 4 aspects, namely the exact type of antibiotic, dose, an interval of administration, and duration of administration. Then the calculated data is presented in tabular form. The calculation of the suitability of the use of antibiotics as follows:

$$\text{The right antibiotic} = \frac{\textit{the number of cases with the right drug}}{\textit{total cases}} \times 100\% \quad (3)$$

$$\text{The right dose} = \frac{\textit{the number of cases with the right dose}}{\textit{total cases}} \times 100\% \quad (4)$$

$$\text{Exact dosing interval} = \frac{\textit{the number of cases with the right interval}}{\textit{total cases}} \times 100\% \quad (5)$$

$$\text{The duration of administration} = \frac{\textit{the number of cases with the right duration of administration}}{\textit{total cases}} \times 100\% \quad (6)$$

$$\%\ 4 = \frac{\textit{the number of cases with the right drug,dose,interval,duration of administration}}{\textit{total cases}} \times 100\% \quad (7)$$

RESULTS

A total of 47 patients with diabetic ulcer at Husada Utama Private Hospital who met the inclusion and exclusion criteria from January 2020 to June 2022 were involved in this study (TABLE 1). Among 47 patients, the age group 46-55 yr was the highest (15 patients or 31.91%), followed by the age group >65 yr (15 patients or 31.91%), and 56-65 yr (13 patients or 27.66%). The male patients (25 patients or 53.19%) were higher than the female patients (22 patients or 46.81%). The hospitalization for diabetic ulcer patients for 3-7 d was 72.34%, for 8-12 d was 14.89%, and for 11-21 d was 6.38%. The highest comorbidities in diabetic ulcer patients were anemia (9 patients or 19.15%) followed by hypertension (9 patients or 19.15%), and sepsis (8 patients or 17.02%).

The highest PDD value is the antibiotic ceftriaxone at 2.39 g/day, then the second order is the antibiotic meropenem at 2.28 g/day, and the third is the antibiotic cefepime at 1.86 and metronidazole at 1. 46 g/day (TABLE 2). In addition, the highest DOT value was with metronidazole antibiotics at 4.15 DOT, then the second was ceftriaxone at 4.09 DOT, and the third was meropenem at 1.62 DOT (TABLE 2).

TABLE 3 shows that ceftriaxone and metronidazole have a PDD value that exceeds the dose limit set by the therapy guidelines, while ciprofloxacin has a PDD value that is less than the dose set by the therapy guidelines. The DOT values of ceftriaxone, metronidazole, and ciprofloxacin for the duration of antibiotic administration were less than those established by therapy guidelines.

TABEL 1. Diabetic ulcer patients demographic data

Category	Frequency [n (%)]
Age (y.o.)	
• 36-45	5 (10.64)
• 46-55	15 (31.91)
• 56-65	13 (27.66)
• >65	14 (29.79)
Gender	
• Male	25 (53.19)
• Female	22 (46.81)
Length of stay (d)	
• 3-7	34 (72.34)
• 8-12	7 (14.89)
11-21	3 (6.38)
Comorbid	
• Anemia unspecified	9 (19.15)
• Hypertension	9 (19.15)
• Sepsis unspecified	8 (17.02)
• Observastion febris	6 (12.77)
• Chronic kidney disease	4 (8.51)
• Hyponatremia	3 (6.38)
• Cyst of kidney	2 (4.26)
• Hypoglikemia	2 (4.26)
• Diabetic nephropaty	2 (4.26)
• Acute renal failure	1 (2.13)
• Metabolic acidosis	1 (2.13)
• Hypernatremia	1 (2.13)
• Hypoalbumin	1 (2.13)
• Hypokalemia post hyperkalemia	1 (2.13)
• Hypotermia	1 (2.13)
• Observation dypsnoea	1 (2.13)
• Osteomyelitis	1 (2.13)
• Other and unspecified atrioventricular	
• Block	1 (2.13)
• Parkinson	1 (2.13)
• Pneumonia unspecified	1 (2.13)

TABEL 2. Profile prescribed daily dose (PDD) and profile days of therapy (DOT) of antibiotics at the Hutama Usada Private Hospital, Surabaya

ATC Code	Type of antibiotics	Total PDD (g/d) [n (%)]	Total DOT [n (%)]
J01DD04	Ceftriaxone	2.39 (19.78)	4.09 (33.68)
J01DD08	Cefixime	0.63 (5.22)	0.45 (3.68)
J01DE01	Cefepime	1.86 (15.40)	0.30 (2.46)
J01DH02	Meropenem	2.28 (18.87)	1.62 (13.3)
J01GB04	Kanamycin	0.92 (7.62)	0.28 (2.28)
J01MA02	Ciprofloxacin	1.00 (8.28)	0.15 (1.23)
J01MA12	Levofloxacin	0.68 (5.63)	0.96 (7.89)
J01XD01	Metronidazole	1.46 (12.09)	4.15 (34.21)
J02AC01	Fluconazole	0.86 (7.12)	0.15 (1.23)
		Mean	1.35
		SD	1.55

TABEL 3. Suitability with therapeutic guidelines (n=47)

Type of antibiotics	n	Dosage/d	Interval	Duration	Therapeutic Guidelines[12,13]	Description
Monotherapy						
• Ceftriaxone	8				Ceftriaxone 2 g/d	No suitable
• Cefepime	1				+ metronidazole 1.5 g/d	No suitable
Combination therapy					Duration 7-14 d	
• Ceftriaxone+metronidazole	4	2g; 1.5g	Every 12 hr; every 8 hr	7-9 d		Suitable (8.5%)
	15			<7 d		No suitable
	4	2g; 1.5g	Every 8 hr; every 12 hr			No suitable
	1	1g; 1.5g				No suitable
• Meropenem+ceftriaxone +metronidazole	3					No suitable
• Meropenem+metronidazole	3					No suitable
• Meropenem+ceftriaxone	2					
• Other*	7					No suitable

*There was one patient for every combination antibiotic therapy. Those combination antibiotics were ceftriaxone+cefixime; levofloxacin+metronidazole; meropenem+cefepime; cefixime+metronidazole; ceftriaxone+cefixime+metronidazole; ceftriaxone+metronidazole+kanamicin; meropenem +metronidazole+ fluconazole.

The antibiotics recommended by the therapeutic guidelines for ischaemic limb/necrosis/gas performing, moderate to severe diabetic foot wounds (osteomyelitis) infections are combination ceftriaxone 2 g/d and metronidazole 500mg every 8 hr for 1-2 wk (10 d).

DISCUSSION

Among 47 patients involved in this study, the age group of 46-55 yr was 31.91%, >65 yr was 29.79%, and 56-65 yr was 27.66% (TABLE 1). A study conducted by Sari *et al.*[3] at the inpatient installation of Dr. M Dajmil General Hospital, Padang showed that most patients were 45-60 yr (46.44%). Another study by Al-Rubeaan *et al.*[14] reported that diabetic ulcer patients were more common in men aged >75 yr and women aged between 65-74 yr. The incidence of diabetic ulcers will increase with age. The age of 40 is the age when glucose intolerance begins, caused by the decreased ability of pancreatic beta cells to produce insulin.[15] In addition, skin cells can experience a decrease in skin vascularization fluid and fat glands so that the skin become inelastic and reduce the ability of cell regeneration when exposed to wounds and slow wound healing.[3]

There were 25 patients of men (53.19%) and 22 samples of women (46.81) involved in this study (TABLE 1). This is in line with study conducted by Agistia *et al.*[10] at the Internal Medicine Unit which showed that there were 63.16% more diabetic ulcer sufferers in men compared to 36.84% in women. The increasing prevalence of diabetic ulcers in men is associated with decreased joint mobility and high pressure on the feet because they tend to wear inappropriate footwear.[14] Other studies have also shown that men with diabetes have twice the risk of developing neuropathy, which is the main factor causing diabetic ulcers, compared to women. Therefore, the incidence of diabetic ulcers is higher in men than women.[16]

The results of the length of hospitalization for diabetic ulcer patients for 3-7 d was 72.34%, for 8-12 d was 14.89%, and for 11-21 d was 6.38% (TABLE 1). Most of the hospitalization period was in the range of 3-7 d because, on average, the patients treated receive referrals, surgery, and debridement. The length of hospitalization is influenced by several factors such as the severity of acute and chronic infections, sources of funding, and comorbid factors.

The most common comorbid diseases experienced by diabetic ulcer patients were hypertension (9 patients or 19.15%), anemia (9 patients or 19.15%), and sepsis (8 patients or 17.02%) (TABLE 1). The emergence of anemia in diabetic ulcers is caused by several factors such as chronic inflammation, malnutrition, and diabetic nephropathy.[17] A study at the Surabaya Tertiary Hospital showed that 78.66% of diabetic ulcer patients were anemic.[18] The chronic inflammation suppresses hematopoietic function and reduces serum iron levels, leading to a shortage of hematopoietic raw materials.[18] Decreased hemoglobin can lead to reduced oxygen throughout the tissue resulting in worsening healing and control of ulcer infection.[19] Hypertension at high blood pressure can cause endothelial lesions, damage to the endothelium through the process of platelet adhesion and aggregation can result in vascular deficiency resulting in tissue hypoxia and ulcers.[20,21] The next comorbidity after anemia and hypertension is sepsis; sepsis in diabetic ulcer patients is 17.02%. A study at the Surabaya Tertiary Hospital showed that 86.30% of diabetic ulcer patients had comorbid sepsis.[19] Sepsis is caused by an impaired blood supply, thereby significantly reducing the wound healing process.[22]

The PDD value showed that the largest value for the antibiotic ceftriaxone was

2.39 g/d, the second was meropenem at 2.28 g/d, and the third was metronidazole at 1.46 g/d (TABLE 2). The antibiotic ceftriaxone in the therapeutic guidelines was 2 g/d. This value was smaller than the ceftriaxone value (2.39 g/d), while the metronidazole antibiotic was greater than the therapeutic guideline (1.5 g/d). Both PDD values of antibiotics were greater than the therapeutic guidelines; this was caused by several factors such as the duration of antibiotic administration and the number of grams of antibiotics given. In addition, a high PDD value indicates that more doses of antibiotics prescribed in a day may increase toxicity if the dose prescribed exceeds the usual prescribed dose and will pose a risk of antibiotic resistance or bacterial resistance to antibiotics.[23]

The DOT value was obtained from the duration of antibiotic administration (d) multiplied by 1 DOT. Each antibiotic received over 24 hr is called 1 DOT. The highest DOT value was obtained for the antibiotic metronidazole at 4.15 DOT, followed by the antibiotic ceftriaxone at 4.09 DOT (TABLE 2).

The percentage of suitability low because of the antibiotic recommended for mild infection differ than for moderate or severe infections; metronidazole was antibiotic recommended for ischaemic limb/necrosis/gas forming moderate to severe infections. The antibiotics recommended by the therapeutic guidelines for no complicating features, moderate to severe diabetic foot wounds (osteomyelitis) infections are ampicillin sulbaktam I.V 3 g every 6 hr or ceftriaxone 2 g/d and oral clindamycin 300-450mg every 8 hr for patient that allergic to antibiotic penicillin for 1-2 wk (10 d). Combination antibiotic therapy, ceftriaxone and metronidazole indicated for moderate infections with ischaemic limb/necrosis/gas performing. A specific diagnosis including, level of severity and supporting by microbiological culture need for better antibiotic prescribing in the future.

CONCLUSION

The high PDD and DOT values do not align with treatment guidelines and could lead to antibiotic resistance. Antibiotic use in foot diabetics should consider the bacterial origin and antibiotic distribution to infected tissue or site of infection.

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