

**Research Article**

**Antibiotic Use Evaluation in ICU/HCU of Muhammadiyah University General Hospital Malang using DDD and Gyssens Methods**

**Evaluasi Penggunaan Antibiotik di ICU/HCU Rumah Sakit Umum Universitas Muhammadiyah Malang menggunakan Metode DDD dan Gyssens**

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**ABSTRACT**

*Infection is a condition caused by the propagation of harmful microorganisms with or without clinical symptoms. Improper use of antibiotics can lead to antibiotic resistance. The Ministry of Health of the Republic of Indonesia recommended a quantitative evaluation of the use of antibiotics using the Defined Daily Dose (DDD) method and a qualitative evaluation using the Gyssens method. This study evaluated antibiotics usage using DDD and Gyssens methods in ICU/HCU of the Muhammadiyah University General Hospital Malang. Employing retrospective observational method, data were collected from patient medical records hospitalized during January-December 2020. Results of the DDD quantitative analysis showed that the most widely used antibiotic was Ceftriaxone with a 35.79 DDD/100 patient-days. The Gyssens qualitative analysis showed that the category VI (incomplete patient's medical record data) was 3%, category IVa (antibiotic use is more effective) (2%), category IIIb (duration of antibiotic use is too short) (3%), category IIb (antibiotic use is not at the right interval) (3%).*

**Keywords:** Antibiotic utilization, Defined Daily Dose, gyssens

**ABSTRAK**

Infeksi disebabkan oleh penyebaran mikroorganisme yang merugikan, baik yang dapat maupun tidak menimbulkan gejala klinik. Penggunaan antibiotik yang tidak tepat dapat menyebabkan resistensi antibiotik. Kementerian Kesehatan Republik Indonesia merekomendasikan evaluasi penggunaan antibiotik secara kuantitatif dengan metode Defined Daily Dose (DDD) dan secara kualitatif dengan metode Gyssens. Penelitian ini bertujuan untuk mengevaluasi penggunaan antibiotik dengan metode DDD dan Gyssens pada pasien di ICU/HCU Rumah Sakit Umum Universitas Muhammadiyah Malang. Penelitian ini bersifat retrospektif observasional dan data diambil dari rekam medik pasien yang dirawat pada periode Januari-Desember 2020. Dari analisis kuantitatif metode DDD (Defined Daily Dose) didapatkan antibiotik yang paling banyak digunakan adalah ceftriaxone dengan nilai 35,79 DDD/100 patient-days. Analisis kualitatif menggunakan metode Gyssens menunjukkan kategori VI (data pasien tidak lengkap) 3%, kategori IVa (penggunaan antibiotik lebih efektif) 2%, kategori IIIb (durasi pemberian antibiotik terlalu singkat) 3%, kategori IIb (interval tidak tepat) 3%.

**Kata Kunci:** Defined Daily Dose, gyssens, penggunaan antibiotik

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## INTRODUCTION

Infection is a condition caused by the propagation of adverse microorganisms that cause the emergence of clinical symptoms or without clinical symptoms (1,2). Infections are caused by pathogenic microorganisms, such as bacteria, viruses, parasites, or fungi (3). Infectious diseases have high morbidity and mortality and are among the top 10 diseases that cause death in Indonesia. Infection is caused by bacteria that are able to pass through the mucosal barrier or skin and penetrate the body tissues (2).

According to WHO data in 2019, there were nine types of infections with the highest incidence that threaten public health, i.e. cholera, plague, yellow fever, meningitis, hemorrhagic fever, influenza, HIV/AIDS, African trypanosomiasis, and leishmaniasis. Their high incidence associated with complicated epidemic patterns, ability to develop new strains, and the tendency to spread rapidly to new locations(3-7).

One of the drugs used to overcome these problems is antimicrobial agent, namely antibiotic or antibacterial, antiviral, antiprotozoal, and antifungal (2). Antibiotics are mostly effective for mild to severe infections (8). The high prevalence of infectious diseases is followed by the increased use of antibiotics in hospital wards, including the Intensive Care Unit (ICU) and the High Care Unit (HCU). Antibiotics use must follow some guidelines to ensure efficacy and to prevent antibiotic resistance. Failure to apply the antibiotic use guidelines may cause the occurrence of antibiotic resistance and may increase, cost of services, length of treatment, undesirable side effects, and the risks for pain and even death(3).

An effort is needed to control the problem of antibiotic resistance. These control efforts can be done by evaluating the use of antibiotics quantitatively using the *Defined Daily Dose* (DDD) method and qualitatively using the Gyssens method (9,10). The DDD method aims to determine and assess the quantity of antibiotic use. Meanwhile, the Gyssens method evaluates the use of antibiotics more specifically by grouping patients in 6 categories based on appropriateness of indication, efficacy, toxicity, spectrum, dose, interval dose, duration of antibiotics use, and time of drug administration to price (10-12).

This study evaluated the use of antibiotics in the ICU/HCU of Muhammadiyah University General Hospital Malang (UMM General Hospital) by quantitative analysis using the DDD method and qualitative analysis using the *Gyssens* method. The results of the evaluation will serve as basis to improve antibiotics use, in particular to reduce inappropriate use of antibiotics at the ICU/HCU of Muhammadiyah University General Hospital Malang.

## METHODS

The study was observational and conducted in April 2021. Data collection was retrospective, extracted from medical records of patients who hospitalized in the ICU/HCU of the UMM General Hospital in the period of January 1 – August 31, 2020. The inclusion criteria was adult patients ( $\geq 18$  years old) of the ICU/HCU who received antibiotics. Data collected were gender, age, diagnosis, indications for antibiotic use, and length of hospitalization. Evaluation of the use of antibiotics employed the DDD method, by

calculating the DDD value/100 *patient days* with the following calculation formula—(9,13) :

$$\frac{\text{DDD}}{100} \text{ patient days} = \frac{\text{amount of antibiotics used (gram)}}{\text{WHO standard of DDD provision}} \times \frac{100}{\text{Total LOS}}$$

DDD/100 *patient days* is calculated by dividing the total DDD usage by the total Length of Stay (LOS) previously divided per 100 patient-days. DDD values were calculated all antibiotic usage, whether as prophylactic and/or therapeutic purposes. Qualitative evaluation of antibiotic using the Gyssens method was carried out by collecting data (indication, length/duration of administration, dose, frequency, route of administration) then analyzing them following the Gyssens flow, as described previously (10,11,14).

## RESULTS

### *Patient Demographic Characteristics*

Total sample was 40 patients i.e. 22 females (55%) and 18 males (45%). The majority was in the age range of over 65 yo (40%) and 56–65 yo (33%).

**Table 1. Patient demographic characteristics**

Characteristics	Number of Patients	%
<b>Gender</b>		
Male	18	45
Female	22	55
Total	40	100
<b>Age</b>		
19/25	1	3
26-35	2	5
36-45	0	0
46 – 55	8	20
56 – 65	13	33
>65	16	40
Total	40	100

The LOS was calculated from hospital admission to discharge—(15). In this study, the range of LOS patients was mostly 1-5 days (29 patients, 73%) and the shortest LOS was 2 days. Antibiotics were classified into two categories whether as prophylactic or as therapeutic (definitive therapy). Prophylactic antibiotics were given to 5 (8%) patients, and most patients received empirical antibiotics (92%) which meant that the organism(s) causing the disease not yet known or microbiologically data not available yet. There were no patients with antibiotics as definitive therapy, which microbiological supporting data available and organism causing the disease was established (Table 2).

**Table 2. Length of Stay (LOS) and indications for antibiotic use**

Variable	Number of patients*	%
<b>LOS (Day)</b>		
1/5	29	73
6–10	9	23
11-15	2	5
Total	40	100

**Table 2. Length of Stay (LOS) and indications for antibiotic use (Cont.)**

Variable	Number of patients*	%
<b>Indications for antibiotic use/ therapy</b>		
Prophylactic	5	
Empirical	60	92
Definitive	0	
Total	65	100

**Note:** \*Number of Patients: there were patients who get more than one antibiotic

Clinical diagnosis of patients with antibiotics were mostly sepsis (9, 16%), end stage renal disease (8.14%), and Cerebro Vascular Accident (7, 13%). Only a small percentage of patients underwent surgical measure (Table 3).

**Table 3. Diagnosis of patients with antibiotic therapy**

Classification of cases	Diagnosis	Number of Patients*	%
<b>Surgery</b>			
Urinary Tract Infection	Op. Pro with Double Lumen	2	4
Infection of head	Op. VPSLA	1	2
Abdominal Infection	Op. Exploratory Laparotomy	2	4
<b>Non-Surgical</b>			
Neurology Problem	Cerebro Vascular Accident (CVA)	7	13
Urology Problem	Chronic Kidney Disease (CKD)	6	11
	End Stage Renal Disease (ESRD)	8	14
	Sepsis	9	16
	Sepsis + UTI	2	4
	Sepsis + ESRD	1	2
	Urosepsis + CKD	1	2
Skin and Tissue Infections	Tetanus	1	2
Abdominal Infection	Gastritis	1	2
	Peritonitis	1	2
Central Nervous System Infections	Hepatic Encephalopathy	1	2
Head and Neck Infections	Hydrocephalus	2	4
	ICH + IVH	2	4
Respiratory Tract Infections	Pneumonia	5	9
	Pneumonia + CVA	4	7
Total		56	100

**Note:** \*patients with single or multiple diagnosis

#### Quantitative Evaluation of Antibiotics Use Using DDD Method

The calculation of DDD values in the ICU/HCU Room was using total LOS patients for 190 days with total antibiotic use of 98.22 DDD/100 patient-days. Ceftriaxone is an antibiotic with the greatest DDD value of 35.79 DDD/100 patient-days which means that every 100 days of hospitalization there are 35 – 36 patients who get Ceftriaxone antibiotics in accordance with WHO standards of 2 grams. The next highest DDD value was Gentamycin as

22.68 DDD/100 patient-days and Levofloxacin as 16.05 DDD/100 patient-days (Table 4).

**Table 4. Quantitative data of antibiotic (DDD/Patient-days) in ICU/HCU**

Class of Antibiotics	Antibiotic Name	DDD WHO	Total DDD*	DDD/100 Patient days**
Cephalosporin III	Ceftriaxone	2	68,00	35.79
	Cefoperazone	4	5.75	3.03
	Ceftazidime	4	3.00	1.58
Cephalosporin I	Cefazolin	3	1.33	70
	Meropenem	3	10.33	5.44
Penicillin	Ampicillin	6	0.13	0.07
	Sulbactam			
Fluoroquinolones	Ciprofloxacin	0.8	7.5	3.95
	Levofloxacin	0.5	30.5	16.05
	Moxifloxacin	0.4	12.00	6.32
Aminoglycosides	Gentamicin	0.24	43.08	22.68
Nitroimidazole	Metronidazole	1.5	12.00	2.63
	Total LOS***		190	
	Total DDD/100 Patients-days			98.22

**Note:**

\*Total DDD =  $\frac{\sum \text{Antibiotic Use (gram)}}{\text{DDD WHO}} \times 100$

\*\*Total DDD/100 Patient-days =  $\frac{\text{Total DDD}}{\text{Total LOS}} \times 100$

\*\*\*Total LOS obtained from the total length of treatment of all samples in the ICU Room

#### Results of Qualitative Analysis of Antibiotic Use Using Gyssens Method

Data showed that of 40 patient of ICU/HCU, in total 65 antibiotics were prescribed (Table 5). There were some patients who received antibiotic therapy more than one. The results of qualitative evaluation using the Gyssens method in the ICU/HCU Room obtained 89% of antibiotic use in patients was appropriate and relevant or rational (Category 0). A total of 2 patients were found with incomplete medical records (Category VI) (3%). Incomplete medical record data such as there were patients without working diagnosis (clinical enforcement of anamnesis and physical examination) or there were missing medical record pages that could not be evaluated (9,14).

**Table 5. Results of qualitative evaluation using gyssens method in ICU/HCU room**

Category	Description	Number of patients*	%
	Incomplete Patient Data	2	3
VI	No indication of antibiotic administration	0	0
V	There were more effective antibiotics	1	2
IV A	There were safer/less toxic antibiotics	0	0
IV B	There were cheaper antibiotics	0	0
IV C	There were antibiotics in which the spectrum was narrower.	0	0
IV D	The use of antibiotics was too long	0	0
III A	The use of antibiotics was too short	2	3
III -			
II A	Inappropriate dosage of antibiotics use	0	0
II B	Inappropriate interval of antibiotic use	2	3

**Tabel 5. Results of qualitative evaluation using gyssens method in ICU/HCU room (Cont.)**

Category	Description	Number of Patients*	%
II – C –	Inappropriate route of antibiotic use	0	0
I	Inappropriate time of antibiotic use	0	0
0	Appropriate antibiotic use	58	89
	<b>Total</b>	<b>65</b>	<b>100</b>

Note: \* Patients with single or multiple antibiotics.

## DISCUSSION

The patients in this study were mostly females and age range over 65 yo. The patient profile is the same as the profile of sepsis sufferers in the ICU RSUP Prof. Dr. R. D. Kandou Manado with a greater proportion of females (54%) —(13). This was in contrast with the results of other studies that showed more male patients than female. The prevalence of severe sepsis is lower in females than in males, but the higher risk of death for patients with severe sepsis in the ICU was in female patients(12,16).

The high proportion of elderly patients in this study may be associated with that elderly was more prone to infection due to decreased endurance and physiological function of the body, sub-optimal nutrition, possessing more than one comorbidities and social environmental factors which less supportive (17). The diagnosis of sepsis in the elderly is rather difficult because the elderly provides or showed unclear responses and clinical symptoms of sepsis, and sometimes accompanied by delirium. The difficulty of establish the diagnosis of sepsis in the elderly can cause the management of sepsis to be delayed which in turn affects the final result of the treatment(18,19).

The LOS of patients in this study was mostly in the range of 1 – 5 days with the shortest LOS of 2 days. This is in accordance with the results of another study which showed that 57 patients (74%) were treated in the ICU for less than 7 days (20). LOS of patients depends on patient characteristics, clinical circumstances, medical actions, patient management, and administrative problems at the hospital —(15).

The study showed that the indication of antibiotic use in the ICU/HCU Room was mostly for empirical treatment (60, 92%). The purpose of administering antibiotics for empirical therapy is the eradication or inhibition of the growth of bacteria suspected to be the cause of the infection, before the results of microbiological examination are obtained, and the indication of its administration is the observation of clinical syndromes leading to the involvement of certain bacteria that are most often the cause of the infection(21).

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In this study, 51 patients (91.07%) received non-surgical measures and 9 patients (16%) were diagnosed with sepsis. Sepsis is a condition in which patients experience organ failure caused by a decrease in body regulation in response to infection, this condition will worsen into severe sepsis and sepsis shock which can cause death (4). The second most diagnosed were patients with ESRD (8 cases, 14%). Our study showed higher percentage patients compared with other study which reported patients with septic shock (7.7%) were also chronic dialysis patients (22).

Our study showed that the highest value DDD/100 patient-days was ceftriaxone at 35.79, and that the greater the value of DDD/100 patient-days, the greater the level of antibiotic use. Such results were similar with studies in Lampung and Bantul (23, 24), which showed in Internal Medicine Ward of Dr. H. Abdul Moeloek Hospital Lampung ceftriaxone value 62.31 DDD/100 patient-days (23) and in an hospital in Bantul ceftriaxone 45.83 DDD/100 patient-days in 2010 and 96.79 DDD/100 patient-days in 2011 (24), at PKU Muhammadiyah Gamping Hospital among community-acquired pneumonia with value of 22.49 DDD/100 patient-days in 2017 and 23.53 DDD/100 patient-days in 2018 (25), at an hospital in Bandung during 2016 with a value of 8.77 DDD/100 patient-days —(26). The top five diagnosis in this study were sepsis, urosepsis, CKD, ESRD, CVA and pneumonia. Based on the guidelines for antibiotic use, ceftriaxone is indicated in these cases so that the use of Ceftriaxone is also high (2). Ceftriaxone administration in combination with doxycycline macrolide is the first line in cases of sepsis. Therefore, the high use of ceftriaxone was apparently associated with the high incidence sepsis in the ICU(27,28).

Our study using Gyssens method showed that in the ICU/HCU, 89% of antibiotic use in patients was appropriate or rational. Patients which should have been prescribed with alternative antibiotics with better efficacy were of 2%, which probably require updating the existing local guidelines for antibiotic use according to the latest evidence based published data. In this study, inappropriate duration of antibiotics treatment was 3%. Too long or unnecessary administration of antibiotics may be due to delayed results of microbiological test/culture which usually took up to 5 days whereas the regulation of Ministry of Health RI (2,9) stated that empirical antibiotics are given for 48 – 72 hours. Inappropriate antibiotic administration at intervals was found in the ICU/HCU Room at 3%. In the administration of Ceftriaxone antibiotics 2 x 1g iv was administered every 12 – 24 hours (4,8,23,29), but in this study it was found that Ceftriaxone antibiotics were administered for less than 12 hours.

It can be concluded that quantitatively the most widely used antibiotic is ceftriaxone with a DDD value of 100 patient-days 35.79. Qualitatively, most antibiotics (89%) were appropriate for their use, although there was still a small percentage (2-3%) of incomplete patient data, more appropriate antibiotic options, duration of antibiotic therapy too short and intervals inappropriate.

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