

# Qualitative Evaluation of Antibiotics Use with Gyssens Method in Sepsis Patients at Fatmawati Central General Hospital Jakarta

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## ABSTRACT

Sepsis still becomes a major health problem worldwide, with a fairly high mortality rate ranging from 20 to 50%. Antibiotic therapy with rational use can reduce the mortality rate. In contrast, the irrational use of antibiotic therapy will increase the occurrence of resistance, which impacts the increase of morbidity, mortality, and health costs. The objective of this study was to evaluate the quality in the use of antibiotics using the Gyssens method in patients with sepsis. This study was an observational study with a cross-sectional method conducted at Fatmawati Central General Hospital Jakarta from January to December 2020. The research subjects were 110 patients with sepsis who met the inclusion criteria. In this study, 49.09% of patients used rational antibiotics and 50.91% of patients used irrational antibiotics that were found in category VI (0.91%), V (17.28%), IVa (3.63%), IVb (0.91%), IVc (0.91%), IIIa (3.63%), IIIb (20%), IIa (0.91%), and IIb (2.73%). The duration of antibiotic therapy was the only factor that affected the quality of antibiotic use ( $p = 0.012$ ). There was no difference in mortality between patients with rational and irrational use of antibiotics ( $p = 0.333$ , OR = 1.654, 95% CI 0.714-3.829). However, after adjusting for the duration of therapy, irrational use of antibiotics significantly affected mortality ( $p = 0.017$ , OR = 3.5, 95% CI 1.255-9.761). In conclusion, the antibiotic use in half of the sepsis patients were irrational. Since irrational use was associated with mortality, efforts need to be taken to improve the quality of antibiotic use.

**Keywords:** antibiotics; gyssens method; sepsis

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## INTRODUCTION

Sepsis still becomes a major health problem worldwide, with a relatively high mortality rate ranging from 20 to 50% (Hotchkiss et al, 2016; WHO, 2020). Based on data from the Ministry of Health of the Republic of Indonesia, severe sepsis and septic shock were found in 23 of 84 cases, with a mortality rate in care reaching 47.8% and a mortality rate in the early phase reaching 34.7% (Ministry of Health of the Republic of Indonesia, 2017).

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al, 2016). Clinically, organ dysfunction can be represented by an increase in the SOFA (Sequential Organ Failure Assessment) score of 2 points or more. Septic shock is sepsis with circulatory and cellular/metabolic abnormalities that causes a greater risk of mortality (Rhodes et al, 2017; Singer et al, 2016).

Sepsis is a life-threatening infection, so the 2016 Surviving Sepsis Campaign (SSC) guideline recommends that antibiotics for sepsis patients should be broad spectrum and be given immediately within the first hour of a patient being diagnosed with sepsis. This

is necessary because delay in antibiotic administration is associated with adverse outcomes. Several studies have shown that delay in antibiotic administration is associated with increased mortality. In addition, there are other adverse outcomes such as increased length of stay, acute kidney injury, acute lung injury, and the presence of worsening organ dysfunction caused by an exacerbated inflammatory response. The selection of empiric antibiotic therapy for sepsis patients is broad-spectrum antibiotics, because they have activity that can inhibit the growth and kill all types of bacteria, both gram-positive and gram-negative. Broad-spectrum antibiotics not only provide benefits for patients with sepsis, but can also provide some disadvantages such as the emergence of side effects due to the use of antibiotics and life-threatening complications due to antimicrobial resistance (Martínez et al., 2020).

The selection of empiric antibiotics must be rational and appropriate and based on considerations of the infected organ underlying the sepsis. Furthermore, it is necessary to consider other factors such as age, organ function, degree of disease, and the causative organism such as the map of germs/resistance map and the nature of germs (community or nosocomial) (Gushka, 2015). In order for antibiotics to be used rationally, it is necessary

to evaluate the use of antibiotics (Ministry of Health of the Republic of Indonesia, 2011b). Rational use of antibiotics can improve patient outcomes and, at the same time, reduce the potential for antibiotic resistance. Otherwise, the irrational use of antibiotics can increase the occurrence of antibiotic resistance. The high rate of antibiotic resistance will increase morbidity, mortality, and health costs (Andrajati, Tilaqza, & Supardi, 2017).

Culture results has an important role in optimizing antibiotic therapy in septic patients. Based on the 2016 SSC recommendations, appropriate microbiological culture results should be obtained before initiating antimicrobial therapy (Martínez et al., 2020). Previously obtained culture results can be used to assist the doctor in identifying the organism causing the infection and de-escalation may be possible so that the goal of definitive antibiotic therapy according to the results of the culture can be achieved. However, if cultures are taken after administration of antibiotics, there may be a decrease in the blood culture yield, which can increase patient costs and length of stay (Giuliano et al., 2019).

A study on the qualitative evaluation of the use of antibiotics in patients with sepsis in the Intensive Care Unit (ICU) of the Serang Regional General Hospital using the Gyssens method conducted by Gushka (2015) showed that only 2 (6.9%) of antibiotic use is appropriate (Category 0 = rational), while 27 (93.1%) of antibiotic use is inappropriate (Category I–V = irrational). Another study conducted at the Department of Internal Medicine of Dr. Soetomo Regional General Hospital Surabaya showed that 80.2% of antibiotic use is appropriate while 19.8% of antibiotic use is inappropriate in patients with sepsis (Adiwinoto et al., 2018).

Based on previous literature searches, studies related to the qualitative evaluation of the use of antibiotics using the Gyssens method at Fatmawati Central General Hospital Jakarta have been conducted on patients with neonatal sepsis and have shown irrational use of antibiotics (Ismaya et al., 2017). Therefore, further research is needed in adult patients with sepsis due to the high mortality rate for sepsis and the irrational use of antibiotics.

## METHODS

This study was an observational study using a cross-sectional design with retrospective data collection methods. This study was conducted at the Medical Record Installation of Fatmawati Central General Hospital Jakarta. The study population was all patients diagnosed with sepsis at Fatmawati Central General Hospital Jakarta from January to December 2020. The sample in this study was patients diagnosed with

sepsis at Fatmawati Central General Hospital Jakarta from January to December 2020, who met the inclusion criteria. Inclusion criteria were adult patients aged over 18 years with sepsis receiving antibiotic therapy. Exclusion criteria were patients with incomplete medical record data (which does not meet the basic information needed in the study). Sampling was done using the total sampling method.

The independent variables in this study were the types, the number, and the duration of antibiotic therapy. While the dependent variable was the quality of the use of antibiotics and the patient's clinical outcome, namely discharged/recovered, or died. In addition, there were other variables/confounding variables in this study, including the number of comorbidities and length of stay.

The quality of antibiotic use in the subjects of this study was evaluated using a Gyssens flowchart by assessing the use of antibiotic therapy received by patients with treatments found in the literature related to sepsis. The primary literatures used were Guidelines for Antibiotics Use (PPAB) and Guidelines for Clinical Practice (PPK) of Fatmawati Central General Hospital Jakarta. If the antibiotic administered was not listed in the literature, then the search was continued in the Lexicomp Drug Information Handbook or related journals. The quality evaluation of the use of antibiotics was carried out by the researcher together with a team of doctors and at least 2 antimicrobial reviewers who were included in the antimicrobial resistance control program (PPRA) team at Fatmawati Hospital, Jakarta. This was intended to reduce subjectivity in the evaluation process.

Based on the 2016 SSC recommendation, the antibiotics used for septic patients are broad-spectrum antibiotics and should be given at least one hour when the patient is diagnosed with sepsis. However, this is quite different from administering antibiotics in a hospital ward to indicate a low level of compliance to the 2016 SSC recommendations. A South Korean study found that a lack of critical care personnel was significantly associated with low compliance rates (Kim & Park, 2019). There are several steps that might be taken to prevent delays in the administration of antibiotics, including forming a multi-professional team consisting of critical care doctors, nurses, pharmacists, microbiologists, administrators who work cooperatively and also developing programs such as education and training that can aims to improve the management of sepsis in hospitals (Martínez et al., 2020).

In this study, the use of antibiotics was considered rational if it met the criteria for each evaluation stage with a Gyssens flow chart so that it was included in

**Table 1. Characteristics of patients with sepsis receiving antibiotics (n = 110)**

Characteristics	Number	Percentage (%)
Age group		
1. 19–65 years	73	66.4
2. above 65 years	37	33.6
Mean (SD)	60.60 ( $\pm$ 13.88)	
Sex		
1. Male	52	47.3
2. Female	58	52.7
Sepsis category		
1. Sepsis	59	53.6
2. Septic shock	51	46.4
Number of comorbidities		
1. 1	15	13.6
2. >1	95	86.4
Types of comorbidities		
Malignancy/cancer	10	9.1
Metabolic disorders	41	37.3
Kidney diseases	54	49.1
Liver diseases	14	12.7
Cardiovascular disorders	25	22.7
Respiratory disorders	81	73.6
Indigestion	6	5.5
Nerve disorders	16	14.5
Infection/other disorders	8	7.3
Infection sources		
Lung infection	73	66.4
Intra-abdominal infection	11	10
Skin and soft tissue infections	9	8.2
Urinary tract infection	2	1.8
Unknown	15	13.6
Length of stay		
1. $\leq$ 14 days	94	85.5
2. >14 days	16	14.5
Outcome		
1. Discharged/ Recovered	31	28.2
2. Died	79	71.8

category 0. Meanwhile, the use of antibiotics was considered irrational if it met categories I to VI (shown in Table 5). The patient's clinical outcome was indicated by mortality and recovery based on the clinician's assessment (the doctor in charge of the patient) listed in the patient's medical record.

In this study, culture examination was also carried out on several patients with various sampling sites adjusted to the site of infection including blood cultures, respiratory cultures (sputum), urine cultures and skin and tissue cultures (wound swabs). The culture results were used as the basis for definitive antibiotic therapy according to the type of microorganism causing the infection.

Statistical data analysis was conducted using SPSS version 23.0, where the significance value (p-value) was set at <0.05, indicating a significant relationship between

variables. Univariate analysis (descriptive statistics) was used to obtain an overview of patient characteristics, distribution of antibiotic use, quality of antibiotic use using the Gyssens method, and patients' clinical outcomes by grouping and presenting the data in percentage form. Bivariate analysis was conducted using the chi-square test to see the effect of the independent variables on the dependent variable and to test whether there was a relationship between the confounding variables and the dependent variable. Multivariate analysis was performed using logistic regression. The analysis was considered significant if it had a p-value <0.05.

## RESULTS AND DISCUSSION

A total of 963 patients with sepsis and septic shock at Fatmawati Central General Hospital from January to December 2020 were divided into three categories:

**Table 2. Distribution of antibiotic use by types of antibiotic in patients with sepsis (n = 110)**

Types of Antibiotic	Number	Percentage (%)
Empirical	103	93.66
Meropenem	14	12.72
Ceftriaxone	15	13.64
Cefoperazone	8	7.28
Levofloxacin	6	5.45
Ampicillin + Sulbactam	5	4.54
Cefotaxime	1	0.91
Ceftriaxone + Levofloxacin	19	17.28
Meropenem + Levofloxacin	12	10.91
Cefoperazone + Levofloxacin	8	7.28
Ceftriaxone + Metronidazole	2	1.81
Meropenem + Amikacin	1	0.91
Ampicillin Sulbactam + Amikacin	1	0.91
Meropenem + Ciprofloxacin	1	0.91
Meropenem + Moxifloxacin	1	0.91
Ceftriaxone + Ciprofloxacin	1	0.91
Cefoperazone + Metronidazole	1	0.91
Levofloxacin + Metronidazole	1	0.91
Cefepime + Levofloxacin	1	0.91
Ceftazidim + Levofloxacin	1	0.91
Ceftriaxone + Levofloxacin + Metronidazole	1	0.91
Levofloxacin + Vancomycin + Metronidazole	1	0.91
Meropenem + Amikacin + Azithromycin	1	0.91
Levofloxacin + Ampicillin Sulbactam + Amikacin	1	0.91
Definitive	7	6.34
Meropenem	2	1.81
Ceftriaxone + Levofloxacin	2	1.81
Meropenem + Levofloxacin	2	1.81
Meropenem + Amikacin	1	0.91
Total	110	100

168 patients with the primary diagnosis, 792 patients with comorbid diagnosis, and 3 patients with the initial diagnosis. The sampling technique in this study used total sampling from the total number of patients with the primary diagnosis of sepsis and septic shock as many as 168 patients. Of the 168 patients, 13 pediatric patients, 7 patients who did not receive antibiotics, 13 patients with incomplete medical records, and 25 patients whose medical records could not be accessed were excluded. Therefore, the total number of patients as the research subjects was 110 patients. The basic characteristics of 110 patients with sepsis from January to December 2020 can be seen in Table 1.

The mean age of the patients was 60.60 ( $\pm 13.88$ ) years, with the proportion of patients in the age group 19–65 years (66.4%) having a higher percentage than the age group over 65 years (33.6%). The proportion of male and female is comparable, which were 52 patients (47.3%) and 58 patients (52.7%), respectively. A total of 95 patients (86.4%) had more than one comorbidity, while only 15 patients (13.6%) had one comorbidity. The most common types of comorbidities are respiratory disorders (73.6%), followed by kidney disorders (49.1%), metabolic disorders (diabetes mellitus) (37.3%) and other organ disorders. These results are slightly different from studies conducted in the United States, which showed

that diabetes mellitus was the most common comorbid disease in patients with sepsis (35%), followed by cardiovascular disorders (32%), kidney disorders (23%), and respiratory disorders (20%) (Novosad et al., 2016).

The most common sources of infection in this study were pneumonia (66.4%). This result is consistent with a study conducted in the United States, which showed that the most common disease that cause sepsis was pneumonia (35%) (Novosad et al., 2016). The length of the patient's hospitalization ranged from 2 to 24 days, with an average of 8 days. This is similar from the study conducted by Neira et al. (2018), which showed that the average length of stay for sepsis patients in the hospital was nine days and the average length of stay in the Intensive Care Unit (ICU) was eight days. Sepsis is the leading cause of death in hospitals, and early therapy is considered important to achieve a better clinical outcome. The average length of stay for sepsis patients is also longer, requires high treatment costs, and becomes a main economic burden for a country (Sudat, 2021).

The clinical outcome of patients diagnosed with sepsis was mostly dead, as many as 79 patients (71.8%). This number is higher than that of sepsis patients discharged or recovered, with 31 patients (28.2%). This result is similar from a study conducted at the Dharmas Cancer Hospital

Jakarta, which showed that 68.3% of sepsis patients died (Dewi et al., 2018). The high mortality rate in sepsis patients can be influenced by various factors, such as the presence of comorbidities, sources of infection, use of respiratory support devices (ventilators), and others (Do et al., 2021).

Most of the sources of infection in patients with sepsis are caused by bacteria, so antibiotics are the primary therapy in the treatment of patients with sepsis and septic shock. Antibiotic therapy given is broad-spectrum and appropriate to the source of infection (Rhodes et al., 2017). An overview of the distribution of antibiotic use by type of therapy is presented in Table 2.

The use of antibiotics was mostly for empirical therapeutic purposes (93.66%). The combination of ceftriaxone and levofloxacin (17.28%) was the most commonly used antibiotic as empiric therapy, while the most common antibiotics for definitive purposes were meropenem alone (1.81%), a combination of ceftriaxone and levofloxacin (1.81%), and a combination of meropenem and levofloxacin (1.81%). The high use of empirical antibiotics in patients with sepsis and septic shock is because, in these conditions, it is necessary to give antibiotics as soon as the patient is diagnosed with sepsis or septic shock.

Based on the number of antibiotics therapy, antibiotics are divided into single-antibiotic therapy and combinations antibiotic therapy. The most widely used antibiotics treatments for patients with sepsis and septic shock were a combination of ceftriaxone and levofloxacin (19.09%), meropenem alone (14.55%) and so on according to Table 3. The combination of ceftriaxone and fluoroquinolone groups, such as levofloxacin, can be administered to patients with sepsis or septic shock with community-acquired pneumonia (CAP) infection sources (Ministry of Health of the Republic of Indonesia, 2017).

The most common single antibiotic was meropenem, followed by ceftriaxone. Both are broad-spectrum antibiotics, but the accuracy of the selection of the two antibiotics can be adjusted according to the clinical condition of the patient and the presence or absence of comorbidities. A study that has been conducted at NTB Regional General Hospital showed that ceftriaxone and meropenem were significantly effective for the treatment of sepsis. In the comparison of the effectiveness of the two drugs, it was found that there was no significant difference between ceftriaxone and meropenem in the treatment of patients with sepsis (Eri, 2019).

Based on the duration of antibiotics therapy, most (92.73%) antibiotics were given for less than 14 days, and some (7.27%) were given for more than 14 days.

**Table 3. Distribution of antibiotic use by number of antibiotics therapy in patients with sepsis (n = 110)**

Number of Antibiotics Therapy	Number	Percentage (%)
Single therapy	51	46.37
Meropenem	16	14.55
Ceftriaxone	15	13.64
Cefoperazone	8	7.28
Levofloxacin	6	5.45
Ampicillin + Sulbactam	5	4.54
Cefotaxime	1	0.91
Combination therapy	59	53.63
Ceftriaxone + Levofloxacin	21	19.09
Meropenem + Levofloxacin	14	12.72
Cefoperazone + Levofloxacin	8	7.28
Ceftriaxone + Metronidazole	2	1.81
Meropenem + Amikacin	2	1.81
Ampicillin Sulbactam + Amikacin	1	0.91
Meropenem + Ciprofloxacin	1	0.91
Meropenem + Moxifloxacin	1	0.91
Ceftriaxone + Ciprofloxacin	1	0.91
Cefoperazone + Metronidazole	1	0.91
Levofloxacin + Metronidazole	1	0.91
Cefepime + Levofloxacin	1	0.91
Ceftazidime + Levofloxacin	1	0.91
Ceftriaxone + Levofloxacin + Metronidazole	1	0.91
Levofloxacin + Vancomycin + Metronidazole	1	0.91
Meropenem + Amikacin + Azithromycin	1	0.91
Levofloxacin + Ampicillin Sulbactam + Amikacin	1	0.91
Total	110	100

**Table 4. Distribution of antibiotic use based on the duration of therapy in patients with sepsis (n = 110)**

Regimen of Antibiotic Therapy	Number	Percentage (%)
Administration of antibiotic therapy ≤14 days	102	92.73
Meropenem	15	13.64
Ceftriaxone	14	12.73
Cefoperazone	8	7.28
Levofloxacin	6	5.45
Ampicillin + Sulbactam	5	4.54
Cefotaxime	1	0.91
Ceftriaxone + Levofloxacin	17	15.45
Meropenem + Levofloxacin	13	11.82
Cefoperazone + Levofloxacin	8	7.28
Ceftriaxone + Metronidazole	2	1.81
Meropenem + Amikacin	2	1.81
Ampicillin Sulbactam + Amikacin	1	0.91
Meropenem + Ciprofloxacin	1	0.91
Meropenem + Moxifloxacin	1	0.91
Ceftriaxone + Ciprofloxacin	1	0.91
Cefoperazone + Metronidazole	1	0.91
Levofloxacin + Metronidazole	1	0.91
Ceftazidime + Levofloxacin	1	0.91
Ceftriaxone+ Levofloxacin + Metronidazole	1	0.91
Levofloxacin + Vancomycin + Metronidazole	1	0.91
Meropenem + Amikacin + Azithromycin	1	0.91
Levofloxacin + Ampicillin Sulbactam + Amikacin	1	0.91
Administration of antibiotic therapy >14 days	8	7.27
Ceftriaxone	1	0.91
Meropenem	1	0.91
Ceftriaxone + Levofloxacin	4	3.63
Meropenem + Levofloxacin	1	0.91
Cefepime + Levofloxacin	1	0.91
Total	110	100

The combination of ceftriaxone and levofloxacin was the most common regimen given for less than 14 days (15.45%) or more than 14 days (3.63%), as shown in Table 4.

One of the factors that support the success of antibiotic therapy is the use of antibiotics that are adjusted to culture results, namely as definitive therapy. In general, if the administration of therapy has moved from empirical to definitive therapy it may be possible to reduce the scope of antibiotic treatment because there is no need for antibiotics that work to target organisms other than the cause of the patient's infection. In addition, broad-spectrum antibiotics can also cause the development of superinfections, namely the occurrence of infections caused by organisms that are resistant to antibiotics that have been used and this occurs while the patient is receiving therapy. Of the 110 patients, only 39 patients (35.46%) were cultured. Of the 39 patients who underwent culture testing, a total of 48 isolates were obtained. The most isolates were sputum (41.67%), followed by blood (37.50%), urine (14.58%), and wound swabs (6.25%). There were 27 isolates (56.25%) with negative cultures in the culture test results, or no microorganisms were found. Positive cultures were mostly found in gram-negative rods as many as 15 isolates (31.25%), with

*Acinetobacter baumannii* (10.42%) as the most common bacteria, followed by gram-positive coccus bacteria with five isolates (10.2%), with *Staphylococcus haemolyticus* as the most common bacteria (4.17%), and one isolate (2.08%) found *Candida tropicalis* spores (data are not shown).

The guidelines used to evaluate the quality of antibiotic use include the Guidelines for Antibiotics Use (PPAB) of Fatmawati Central General Hospital Jakarta in 2019, Guidelines for Clinical Practice (PPK) of Fatmawati Central General Hospital Jakarta, Germs Map of Fatmawati Central General Hospital Jakarta, and related research journals. Based on Table 6, the evaluation results of antibiotics used in 110 patients with sepsis and septic shock showed slight difference between rational and irrational antibiotics. A total of 54 patients (49.09%) used rational antibiotics and 56 patients (50.91%) used irrational antibiotics. This result is supported by a study conducted at the best Referral Hospital in West Java, which showed that there were fewer rational antibiotics (35%) than irrational antibiotics (65%) (Adani et al., 2017). However, the results of this study are different from the research conducted at the Department of Internal Medicine of Dr. Soetomo Regional General Hospital Surabaya, which showed 80.2% of antibiotic

**Table 5. The rational and irrational use of antibiotics based on the Gyssen Category**

Number	Gyssens Category		Rational (category 0)	Irrational (category I–VI)
1.	The completeness of data	Complete data	√	–
		Incomplete data	–	√ (category VI)
2.	Indication	Appropriate indication	√	–
		Inappropriate indication	–	√ (category V)
3.	Effectiveness	Effective antibiotics (According to the culture results and germ maps)	√	–
		Other antibiotics are more effective	–	√ (category IVA)
4.	Toxicity	Antibiotics are safe/non-toxic	√	–
		Other antibiotics are less toxic	–	√ (category IVB)
5.	Cost	Cheap antibiotics	√	–
		Other antibiotics are cheaper	–	√ (category IVC)
6.	Spectrum	Narrow spectrum antibiotics	√	–
		Other antibiotics have a narrower spectrum	–	√ (category IVD)
6.	Duration	Appropriate duration	√	–
		Duration is too long (> 14 days)	–	√ (category IIIA)
		Duration is too short (< 2 days)	–	√ (category IIIB)
7.	Dose	Proper dose	√	–
		Inproper dose	–	√ (category IIA)
8.	Interval	Proper interval	√	–
		Inproper interval	–	√ (category IIB)
9.	Route	Proper route	√	–
		Inproper route	–	√ (category IIC)
10.	Time	Proper time	√	–
		Inproper time	–	√ (category I)

use were appropriate (category 0 = rational), while 19.8% of antibiotic use were inappropriate (category I–VI = irrational) in patients with sepsis (Adiwinoto et al., 2018). The distribution of the use of antibiotics (241 regimens) and the Gyssens category is shown in Table 7. Patient included in category VI was patients whose time and duration of antibiotic administration were not stated in the medical record, so the data was declared incomplete and could not be continued with evaluation to the next category. In category V, 19 patients did not match the indication for the administration of the antibiotics. Ceftriaxone, cefoperazone, levofloxacin, and ampicillin-sulbactam were administered to patients with clinical conditions who were already experiencing septic shock and supported by high PCT values >32 ng/mL. It would be more appropriate if patients with such conditions were given antibiotics, such as meropenem, since the initial diagnosis was septic shock. Thus, it is expected to improve the patient's clinical outcome (PPAB of Fatmawati Central General Hospital). Moreover, some patients received a combination therapy

of meropenem and levofloxacin. However, the patient was still in a state of sepsis, and had kidney problems, namely a decrease in the glomerular filtration rate (GFR) value to 28.41 ml/minute. Thus, the therapy was not as indicated. Meropenem (third line) can be replaced with second-line antibiotics (ceftriaxone/cefoperazone). In addition, meropenem therapy in sepsis patients with kidney disease still needs to be adjusted to the dose of the drug, while in this study, it was not carried out (Chaijamorn et al., 2017).

There were four patients who received ineffective antibiotics (category IVa) because they were not in accordance with the culture results. The sensitivity value of the antibiotic is seen in the germs map in each treatment room of Fatmawati Central General Hospital. There was one patient with *Pseudomonas aeruginosa* isolates from sputum culture, which initially received empiric antibiotics with a combination of ceftriaxone and levofloxacin. However, based on the results of the culture examination, it would be more appropriate for

the patient to receive ceftazidime, which had a sensitivity of 91.7%, and ciprofloxacin which had a sensitivity of 83.3%, while the data sensitivity to ceftriaxone and levofloxacin was not found. The next patient was a patient with *Acinetobacter baumannii* isolate from sputum culture who received a combination of cefoperazone and levofloxacin as empiric therapy. Based on the results of the culture examination, the recommended antibiotics were ampicillin sulbactam with a sensitivity of 17.5% and ciprofloxacin with a sensitivity of 11.1%, while the data sensitivity related to cefoperazone and levofloxacin were also not found. Another case was a patient with isolates of *Enterococcus faecium* from sputum cultures who received meropenem as empirical therapy. However, based on the examination results of the antibiotic culture, vancomycin with a sensitivity of 100% was recommended, while data on meropenem sensitivity was not found. The last patient in category IVa was a patient with *Staphylococcus haemolyticus* isolate from blood culture who received a combination of cefepime and levofloxacin as empirical therapy. However, based on the results of the culture examination, both were resistant, and the recommended antibiotic was vancomycin (germs map and the PPAB of Fatmawati Central General Hospital). The possible reason why antibiotics are given not according to the culture is that patients with sepsis or septic shock are almost resistant to all antibiotics available in the therapy, so the doctor decides to give the antibiotic with the lowest resistance. The reason for the absence of antibiotics can be the cause of inappropriate use of antibiotics in patients with sepsis or septic shock. The results of category IVb showed that there was one

patient who received a combination of meropenem and amikacin. According to the Drug Information Handbook, amikacin has a nephrotoxic effect than levofloxacin. This patient also had a comorbidity, namely chronic kidney disease with a GFR value of 7.78 ml/minute, so giving a less toxic antibiotic, such as levofloxacin, would be more appropriate. In category IVc, one patient received an branded antibiotic, whose composition was ampicillin sulbactam. The price of branded antibiotic is more expensive compared to generic ampicillin sulbactam injection preparations.

In this study, there were four patients who received antibiotic therapy with too long duration of administration (>14 days) or included in category IIIa. The reason for the long duration may be that the patient's clinical condition had not improved. However, excess use of antibiotics, including long-term broad-spectrum antibiotic therapy, can promote antibiotic resistance and cause side effects in about 20% of patients, ranging from allergic reactions to *Clostridioides difficile* infection (Lee et al., 2021).

The highest number of patients using irrational antibiotics was in category IIIb (too short duration of administration), with 22 patients. These 22 patients received antibiotic therapy for only one day or less than the provision for empiric antibiotics (48–72 hours). The reason for giving antibiotics for only one day was because the patients' condition had worsened since the beginning of hospital admission, and they were diagnosed with sepsis or septic shock. Therefore, these patients had poor clinical outcomes, namely dead.

**Table 6. Evaluation of the quality of antibiotic use using the Gyssens method in patients with sepsis (n = 110)**

Category	Parameter	Conformity		Description
		Yes	No	
VI	Complete data	109	1	One patient discontinued in category VI
V	Antibiotics indicated	109	19	19 patients discontinued in category V
IVa	Effective choice of antibiotics	90	4	Four patients discontinued in category IVa
IVb	Less toxic alternative	86	1	One patient discontinued in category IVb
IVc	Cheaper alternative	85	1	One patient discontinued in category IVc
IVd	Narrower spectrum	84	0	
IIIa	Long duration of administration	84	4	Four patients discontinued in category IIIa
IIIb	Short duration of administration	80	22	22 patients discontinued in category IIIb
IIa	Proper dose	58	1	One patient discontinued in category IIa
IIb	Proper interval	57	3	Three patients discontinued in category IIb
IIc	Proper route	54	0	
I	Proper time	54	0	
0	Appropriate/ Rational	54	0	



**Table 7. Distribution of antibiotics use and Gyssens category (n = 241)**

Regimen of Antibiotics	Gyssens Category							Number (%)
	0	I	II	III	IV	V	VI	
Levofloxacin	36	0	12	14	5	9	0	76 (31.53)
Ceftriaxone	25	0	6	7	5	21	0	64 (26.55)
Meropenem	30	0	4	8	2	1	1	46 (19.08)
Cefoperazone	10	0	1	3	2	6	0	22 (9.12)
Ampicillin + Sulbactam	2	0	0	4	1	1	0	8 (3.31)
Metronidazole	6	0	0	2	0	0	0	8 (3.31)
Amikacin	4	0	1	1	1	0	0	7 (2.90)
Ciprofloxacin	1	0	0	1	0	1	0	3 (1.24)
Cefotaxime	0	0	0	1	0	0	0	1 (0.41)
Doxycycline	1	0	0	0	0	0	0	1 (0.41)
Ceftazidime	1	0	0	0	0	0	0	1 (0.41)
Vancomycin	1	0	0	0	0	0	0	1 (0.41)
Azithromycin	1	0	0	0	0	0	0	1 (0.41)
Cefepime	0	0	0	1	0	0	0	1 (0.41)
Moxifloxacin	1	0	0	0	0	0	0	1 (0.41)

Category 0: rational use of antibiotics

Category I – VI: irrational use of antibiotics

Category IIa is related to the appropriate antibiotic dose. In this study, there was one patient who received the combination antibiotic therapy of ceftriaxone and levofloxacin with a dose of levofloxacin that was less than the recommended dose of 500 mg, while the recommended dose of levofloxacin was 750 mg–1 g for patients with no kidney disease, such as in this particular patient. If the patient had kidney disease, it is necessary to adjust the dose of levofloxacin for patients with a creatinine clearance (CrCl) of 20-49 ml/minute starting with a dose of 500 mg, then 250 mg/24 hours, and for patients with CrCl 10-19 ml/minute starting with 500 mg, then 250 mg/48 hours (Indonesian Lung Doctors Association, 2014).

The last category is IIb, which relates to the appropriate interval of antibiotic use. Two patients received meropenem with intervals of administration every 6 hours and 12 hours. Based on PPAB of Fatmawati Central General Hospital Jakarta and Drug Information Handbook, meropenem is given at intervals of every 8 hours. Another patient received levofloxacin with an interval of every 48 hours even though the patient had no history of kidney disease, meanwhile the more appropriate interval of administration is every 24 hours. The chi-square test results showed that the duration of therapy ( $p = 0.012$ ) was related to the quality of antibiotic use. The test results data are presented in Table 8. The results showed that duration of >14 days of antibiotic therapy is more likely to cause irrational

use of antibiotics. The long duration of antibiotic therapy affects the quality of antibiotic use because it is included in the evaluation stage using the Gyssens method (Gyssens, 2005).

In some patients, prolonged empiric antibiotic therapy is sometimes necessary. This was done because of several factors that might be the basis, such as the patient's slow clinical response, the presence of *S. aureus* bacteria (especially methicillin-resistant *Staphylococcus aureus*), fungal infections, viral infections, and other immunological problems (Rhodes et al., 2017). Meanwhile, the administration of antibiotics that are too short (only one day) is common in patients who have experienced a worsening of clinical conditions when they are admitted to the hospital, so it will also affect the assessment of the quality of antibiotic use.

This is in line with the results of the study conducted by Kristiani et al. (2019), which showed that one of the factors that affect the quality of antibiotic use was the duration of antibiotic therapy. In the Antimicrobial Stewardship Program (ASP), it is found that the duration of antibiotic therapy has an important role in optimizing the use of antibiotics and preventing resistance. Optimal duration of antibiotic therapy should be recommended by considering factors such as clinical and microbiological efficacy and the possible risk of side effects (tolerance, recurrence, and increased resistance) (Pezzani et al., 2019).

**Table 8. The relationship between variables and the quality of antibiotic use (n = 110)**

Variable	Characteristics	Rational		Irrational		P	OR (95% CI)
		Total	%	Total	%		
Types of Therapy	Empiric	49	47.6	54	52.4	0.406	Ref
	Definitive	5	71.4	2	28.6		0.363 (0.067-1.957)
Number of Therapy	Single Therapy	22	43.1	29	56.9	0.332	Ref
	Combination Therapy	32	54.2	27	45.8		0.640 (0.301-1.361)
Duration of Therapy	≤14 days	54	52.9	48	47.1	<b>0.012</b>	Ref
	>14 days	0	0	8	100		N/A
Number of Comorbidities	1	8	53.3	7	46.7	0.940	Ref
	>1	46	48.4	49	51.6		1.217 (0.409-3.625)
Length of Stay	≤14 days	47	50	47	50	0.848	Ref
	>14 days	7	43.8	9	56.3		1.286 (0.442-3.738)

**Table 9. The relationship of independent variables, confounding variables, and quality of antibiotic use with outcome in sepsis patients (n = 110)**

Variabel	Characteristics	Discharged/ recovered		Died		P	OR (95% CI)
		Total	%	Total	%		
Types of Therapy	Empiric	29	28.2	74	71.8	1.000	Ref
	Definitive	2	28.6	5	71.4		0.980 (0.180-5.337)
Number of Therapy	Single Therapy	11	21.6	40	78.4	<b>0.222</b>	Ref
	Combination Therapy	20	33.9	39	66.1		0.536 (0.227-1.264)
Duration of Therapy	≤14 days	24	23.5	78	76.5	<b>0.001</b>	Ref
	>14 days	7	87.5	1	12.5		0.044 (0.005-0.375)
Number of Comorbidities	1	3	20	12	80	0.653	Ref
	>1	28	29.5	67	70.5		0.598 (0.157-2.284)
Length of Stay	≤14 days	21	22.3	73	77.7	<b>0.003</b>	Ref
	>14 days	10	62.5	6	37.5		0.173 (0.056-0.530)
Quality of Antibiotic Use	Rational	18	33.3	36	66.7	0.333	Ref
	Irrational	13	23.2	43	76.8		1.654 (0.714-3.829)

**Table 10. Number of patients recovered or died in each Gyssen category (n = 110)**

Number	Gyssens Category	Discharged / Recovered (n)	Died (n)
1.	0	18	36
2.	I	0	0
3.	II	1	3
4.	III	4	22
5.	IV	2	4
6.	V	6	13
7.	VI	0	1

**Table 11. Factors affecting mortality in sepsis patients (n = 110)**

Step	Variable	P	OR	CI (95%)	
				Lower	Upper
1	Quality of Antibiotic Use				
	Rational	0.028	Ref		
	Irrational		3.240	1.137	9.233
	Number of Therapy				
	Single therapy	0.511	Ref		
	Combination therapy		0.727	0.281	1.881
	Duration of Therapy				
	≤14 days	0.011	Ref		
	>14 days		0.030	0.002	0.453
Length of stay					
≤14 days	0.706	Ref			
>14 days		0.740	0.155	3.537	
2	Quality of Antibiotic Use				
	Rational	0.022	Ref		
	Irrational		3.342	1.188	9.397
	Number of Therapy				
	Single therapy	0.485	Ref		
	Combination therapy		0.714	0.278	1.838
Duration of Therapy					
≤14 days	0.001	Ref			
>14 days		0.022	0.002	0.216	
3	Quality of Antibiotic Use				
	Rational	0.017	Ref		
	Irrational		3.500	1.255	9.761
	Duration of Therapy				
≤14 days	0.001	Ref			
>14 days		0.020	0.002	0.196	

Several randomized controlled trials (RCTs) have shown that receiving longer antibiotic therapy does not improve patient survival. It also has more severe side effects and can increase significantly by 5% for each additional day of antibiotic therapy. In addition to side effects, other disadvantages are superinfection conditions and antibiotic resistance can also increase (Spellberg & Rice, 2019). On the other hand, research evidence showed that a shorter duration of therapy could reduce the incidence of side effects in patients. The clinical outcome between the two was similar between patients who received antibiotic therapy longer or shorter than recommended (Wilson et al., 2019).

Table 9 showed that the variable of number of therapy, duration of therapy and length of stay have a value of  $p < 0.25$  so that these variables were analyzed by the logistic regression method. While the type of therapy,

the number of comorbidities and the quality of the use of antibiotics have  $p > 0.25$  which indicates that these variables have no relationship with the outcome.

Basically, the quality of antibiotic use can affect the clinical outcome of patients with sepsis. Based on Table 9, it can be seen that both patients who used rational and irrational antibiotics had the same bad outcome (died), which is higher than the good outcome (discharged/recovered) with a p-value of 0.333, which means that there is no difference in the outcome between patients with the rational and irrational quality of use of antibiotics. Therefore, it can be concluded that there is no significant relationship between the quality of antibiotic use and outcomes of patients with sepsis and septic shock. The explanation of the use of irrational antibiotics and its outcome are contained in Table 10.

The results of this study are consistent with the results of a study that has been conducted at Dr. Sardjito Central General Hospital Yogyakarta, which showed that there was no significant relationship between the appropriate use of antibiotic therapy and mortality of sepsis patients in ICU (Sunartejo, Fitriani & Kurniawaty., 2019). The results indicate that there may still be other factors that cause the patient's outcome to deteriorate (dead), so it's not just because of the irrational use of antibiotics.

A study that has been conducted at Dharmais Cancer Hospital Jakarta showed that inappropriate antibiotic doses, diagnosis of septic shock, and the presence of two or more comorbidities could significantly increase the mortality of patients with sepsis (Dewi et al., 2018). Further, a study at the Vietnam Hospital also mentioned several other factors that could affect the high mortality rate in sepsis patients, such as the presence of comorbidities, sources of infection, use of respiratory support devices (ventilators), and others (Do et al., 2021).

Multivariate analysis with logistic regression in this study was shown in Table 11. Bivariate analysis showed no difference between rational and irrational antibiotic to clinical outcome. However, after controlling covariates, irrational use of antibiotic significantly affected mortality ( $p = 0.017$ , OR = 3.5, 95% CI 1.255-9.761), which indicates that irrational use of antibiotic can increase the mortality by 3.5 times. Duration of therapy may affect the outcome of patients, therapy >14 days was shown to be a protective factor on patient mortality ( $p = 0.001$ , OR = 0.020, 95% CI 0.002-1.96). This is different from the results of a systematic review and meta-analysis which showed there was no significant difference in mortality at a maximum follow-up of 30 days between the shorter vs prolonged course antibiotic for sepsis (Kubo et al., 2022).

In bivariate and multivariate analysis, the duration of therapy >14 days was protective to mortality even though all patients (8 patients) had irrational antibiotics and irrational proven to cause death. These results need further confirmation because the number of patients who used antibiotics for >14 days was relatively small or maybe it was other factors that caused the 8 patients to recovered instead of the quality of antibiotics.

The limitations of this study are that data collection was conducted retrospectively from secondary data, including patient medical records. Therefore, the completeness of the data was very dependent on the recording of medical records carried out by health workers. Data that were difficult to obtain include data on culture results, which were only obtained completely in a small proportion of patients with sepsis and septic

shock who performed culture examinations to determine the causative pathogenic bacteria. Researchers also had not explored further about the data of culture results in the laboratory due to limited time. Thus, the data of culture results could not be accessed. Data on the side effects of antibiotics were also difficult to obtain. These data can be obtained more fully when the study is conducted prospectively. Moreover, not all research samples in this study could be evaluated for the quality of the use of antibiotics with the team of doctors and the Antimicrobial Resistance Control Program (PPRA) team at Fatmawati Central General Hospital Jakarta. This was due to the limited time of some of these evaluators.

## CONCLUSION

As much as 50.91% of the subjects in this study received irrational antibiotics, with the biggest proportion was at category IIIb (duration too short). Owing to study result that found an association between irrational use and mortality, this suggest that we must take efforts to improve the quality of antibiotic use in sepsis patients.

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## CONFLICT OF INTEREST

All authors declared no conflict of interest related to this research and publication of this article.

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