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Qualitative Evaluation of Antibiotic Use in Bacterial Meningitis Patients using the Gyssens Method

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ABSTRACT

Bacterial meningitis is considered as neurologic emergency with high morbidity and mortality rates. Mortality can reach 34%, especially in infections caused by S. pneumoniae and L. meningitides, while morbidity in bacterial meningitis patients, namely long-term neurologic sequelae, can reach 50% amongst survivors. If antibiotics are used properly, they can lower mortality rates.On the other hand, the irrational use of antibiotic therapy will raise the likelihood of resistance, which raises morbidity, mortality, and costs for health care. This study aims to determine the quality of antibiotic use in bacterial meningitis patients using the Gyssens method. It is an observational study employing the retrospective cross-sectional method conducted at Fatmawati General Hospital, Jakarta. The research subjects were 24 patients with bacterial meningitis who met the inclusion criteria. In this study, 45.8% of the subjects had been administered appropriate antibiotics and 54.2% inappropriate ones, which were spread across several categories, namely category IVc for one subjects (4.2%); category IIIA for two subjects (8.3%); category IIIB for one subject (4.2%); category IIA for ten subjects (41.7%); and category IIB for two subjects (8.3%). The use of appropriate antibiotics based on evaluation using the Gyssens algorithm did not significantly affect patient outcomes (p=0.542). The independent variables (type of antibiotic therapy, number of antibiotics, duration of antibiotic use) and confounding ones (age, gender, number of comorbidities, type of comorbidities, length of treatment) also had no significant effect on the quality of antibiotic use, with a p value > 0.05.

Kata kunci:

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ABSTRAK

Meningitis bakterial dianggap sebagai kasus kegawatdaruratan neurologik dengan angka morbiditas dan mortalitas yang tinggi. Mortalitas akibat meningitis bakterial dapat mencapai 34% terutama pada infeksi yang disebabkan oleh S. pneumoniae dan L. meningitidis. Sementara morbiditas pada pasien meningitis bakterial yaitu sekuele neurologis jangka panjang dapat mencapai 50% pada survivor meningitis. Terapi antibiotik dengan penggunaan yang rasional dapat menurunkan angka kematian. Sebaliknya, penggunaan terapi antibiotik yang tidak rasional akan meningkatkan terjadinya resistensi yang berdampak pada peningkatan morbiditas, mortalitas, dan biaya kesehatan. Penelitian ini bertujuan untuk mengetahui kualitas penggunaan antibiotik pada pasien meningitis bakteri dengan metode Gyssens. Penelitian ini merupakan penelitian observasional dengan metode retrospektif cross-sectional yang dilakukan di Rumah Sakit Umum Fatmawati, Jakarta. Subyek penelitian adalah 24 pasien meningitis bakterial yang memenuhi kriteria inklusi. Pada penelitian ini, 45,8% subjek telah diberikan antibiotik yang tepat dan 54,2% yang tidak tepat, yang tersebar di beberapa kategori, yaitu kategori IVc (4,2%); kategori IIIA (8,3%); kategori IIIB (4,2%); kategori IIA (41,7%); dan kategori IIB (8,3%). Penggunaan antibiotik yang tepat berdasarkan evaluasi menggunakan algoritma Gyssens tidak berpengaruh signifikan terhadap luaran pasien (p=0,542). Variabel independen (jenis terapi antibiotik, jumlah antibiotik, lama penggunaan antibiotik) dan variabel perancu (usia, jenis kelamin, jumlah penyakit penyerta, jenis penyakit penyerta, lama pengobatan) juga tidak berpengaruh signifikan terhadap kualitas penggunaan antibiotik. dengan nilai-p> 0,05

INTRODUCTION

Bacterial meningitis is considered a neurologic emergency with high morbidity and mortality rates. Mortality due to bacterial meningitis can reach 34%, especially in infections caused by *S. pneumoniae* and *L. meningitidis*. Meanwhile, morbidity in bacterial meningitis patients, namely long-term neurologic sequelae, can reach 50% in survivors (Hoffman & Weber, 2009). Due to the high mortality and morbidity rates in patients with bacterial meningitis, diagnosis and management must be made as soon as possible to prevent poor outcomes.

One important component of management of patients with bacterial meningitis is the empirical administration of antibiotics before and after culture results are obtained, which is termed definitive therapy. Giving antibiotics as early as possible to patients with bacterial meningitis improves clinical outcomes and reduces neurological sequelae. One study found that if antibiotic administration were delayed more than 3 hours from when the patient was admitted to hospital, mortality would increase significantly. However, the widespread and uncontrolled use of antibiotics can increase the incidence of multi-drug-resistant bacteria, which is a global problem. Inappropriate use of antibiotics can not only impact clinical outcomes but also trigger the emergence of bacterial resistance and increase healthcare costs (Bantar et al., 2003). The Centers for Disease Control and Prevention in the United States estimates that antibiotic-resistant bacteria infect two million people, of whom at least 23,000 died yearly. Rational prescribing of antibiotics addresses global public health challenges by preventing their overuse and misuse (Kristiani et al., 2019). Antibiotic overuse and misuse can lead to an increase in resistant bacterial strains, adverse reactions, and financial strain on national health systems, making it a global public health concern (Alsayed et al., 2022).

Previous studies have shown that 9-64% of hospital antimicrobial therapy and prophylaxis had been reported inappropriately or not indicated. Reasons for inappropriate prescribing include uncertain differential diagnosis; complex comorbidities; lack of training or experience, or of trust in the responsible physician; lack of local epidemiological knowledge of antibiotic resistance; or incorrect interpretation of microbiology results, such as treatment of bacterial colonization (Cusini et al., 2010). The results of a literature study conducted by Baktygul et al., (2011) show that 41% to 91% of all antibiotic prescriptions in hospitals were inappropriate. In a comprehensive study conducted by Alsayed et al (2022) in Arabic countries the highest percentage range that was reported was 21%-50% of antibiotic prescriptions that were deemed to be inappropriate or unnecessary. Essentially, past information have shown that somewhere in the range of 20% and half of anti-microbial use is either pointless or improper. Hadi et al. (2008) also reported that 44-97% of patient antibiotic prescriptions were inappropriate or unnecessary in developing countries, while in Indonesia only 21% of prescriptions were considered appropriate. Limato et al. (2022) conducted a systematic review demonstrates that among the populations that were studied in Indonesia, the appropriateness of antibiotic prescribing was found to be poor overall (35.3 percent), 49.4 percent in primary care versus 33.5 percent in hospitals.

Evaluating antibiotic use is one of the quality indicators in hospitals' antimicrobial resistance control programs (Kemenkes RI, 2015). One method that can be used to evaluate antibiotic use is the Gyssens method. Gyssens et al. developed a new protocol to evaluate the appropriate use of antimicrobials while working at Nijmegen University Hospital in the Netherlands in 1996 (Luciana et al., 2015). Based on the accuracy and selection of the indication in terms of its effectiveness, toxicity, price and spectrum, duration of administration, dose, interval, route, and time of administration, they categorized the rationality of antibiotic prescription into categories 0-6. Numerous nations have utilized the Gyssens tool for assessing the quality of antibiotic use (Sitompul et al., 2016).

Fatmawati General Hospital is one of Indonesia's national referral hospitals with an Antibiotic Resistance Prevention and Control Team (PPRA), which is also part of the Infection Prevention and Control Committee (KPPI). Previous research at the hospital focused on antibiotic use intensity, quantity, and sensitivity. However, little research has been conducted on evaluating antibiotic use at the hospital using the Gyssens method. In 2015, Luciana et al. conducted a study on the use of antibiotics in the ICU room of Fatmawati General Hospital, while Kristiani et al. (2019) evaluated antibiotic use and cost analysis in pediatric patients at the same hospital. Both studies used the Gyssens method. No research on antibiotic use in bacterial meningitis patients at Fatmawati General Hospital has been conducted, even though such patients have the potential to experience high levels of morbidity and mortality, meaning that appropriate and adequate antibiotics are needed to provide hope for a good quality of life. The use of antibiotics for such patients needs to be evaluated to analyze the rationality of such use, the factors that influence it, and patient outcomes from January 2014 to December 2020 at Fatmawati Central General Hospital, Jakarta, Indonesia. The Gyssens method was used, as at the hospital the ATC/DDD method is employed automatically by the

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system so that data can be obtained directly. In addition, the Gyssens method has the advantage of being more thorough and detailed/clear. It can evaluate the use of antibiotics qualitatively and more precisely to prevent the development of resistant antibiotics.

METHODS

Participant characteristics and research design

This was an observational study, using a cross-sectional design. The study samples were all inpatients who met the inclusion and exclusion criteria. The inclusion criteria were that the patients had been diagnosed with bacterial meningitis and had received antibiotic therapy. The exclusion criteria were patients with incomplete medical record data and forced discharge status.

Sampling procedures

This study was conducted at Fatmawati General Hospital, Jakarta. The study population comprised patients with bacterial meningitis who had received antibiotic therapy at the hospital from January 2014 to December 2020. Sampling was performed by total sampling.

Sample size, power, and precision

Sample in this study was performed by total sampling because the population in this study is no more than 30 subject. Total sampling is an inspecting strategy when all individuals from the populace are utilized as tests. Total sampling is also known as a census, in which all members of the population are used as samples. This sample is used if the population is relatively small, i.e., no more than 30 people. SPSS version 20.0 was used for statistical data analysis, and the significance value (p-value) was set to 0.05 to show a significant relationship between variables.

Measures and covariates

The accuracy of antibiotic administration in the subjects who met the inclusion and exclusion criteria was evaluated using Gyssens's flowchart by comparing the therapy given to patients with the bacterial meningitis guidelines. The main guideline used was the Clinical Service Guidelines (PPK) for Bacterial Meningitis from PERDOSSI and the Antibiotic Use Guidelines (PPAB) used at Fatmawati General Hospital. If the antibiotics given were not listed in the guidelines, the search was continued at the Infectious Diseases Society of America (IDSA) and journals related to antibiotic therapy in bacterial meningitis. In this study, antibiotic administration was deemed to be appropriate if it met the Gyssens flow chart criteria in category 0. In contrast, it was considered to be inappropriate if it fell into categories I to VI. Based on the evaluation of the physician listed in the patient's medical record, the patient's outcome was determined by death or recovery. The number, types, and duration of antibiotic treatment were the study's independent variables. The quality of antibiotic use and the patient's clinical outcome—discharge, recovery, or death—were the dependent variables .In addition, this study contained additional variables/confounding variables.

Data analysis

By grouping and displaying the data in percentage form, univariate analysis (descriptive statistics) was used to obtain an overview of patient characteristics, the distribution of antibiotic use, the quality of antibiotic use using the Gyssens method, and patients' clinical outcomes.The chi-square test was used in bivariate analysis to see how the independent variables affected the dependent variable and to see if the confounding variables and the dependent variable were related. Logistic regression was used for multivariate analysis. If the p-value of the analysis was less than 0.05, it was considered significant.

RESULTS AND DISCUSSION

This research was conducted at Fatmawati General Hospital with inpatient research subjects suffering from bacterial meningitis for the period January 2014 to December 2020. The sampling technique was retrospective total sampling. Based on inpatient data from the medical record installation at Fatmawati General Hospital, a total of 50 patients with bacterial meningitis were obtained. A total of 25 patients were excluded because the patient's medical record data could not be accessed and 1 patient was excluded because the data was incomplete so that the number of patients who were the subject of the study was 24 subjects. Data collection of patients who met the inclusion and exclusion criteria was carried out based on the patient's medical records. Their basic and clinical characteristics can be seen in Tables 1 and 2.

Table 1
Basic Characteristics of Research Subjects

Patient Characteristics	Frequency (n)	Percentage (%)
Age Group		
1. 0 – 17 years	20	83,3
2. 18 – 65 years	4	16,7
3. > 65 years	0	0
Mean ± SD	12,36 ± 15,92	
Sex		
1. Male	15	62,5
2. Female	9	37,5
Number of comorbidities		
1. None	3	12,5
2. 1 comorbidity	5	20,8
3. > 1 comorbidities	16	66,7
Mean ± SD	2,54 ± 1,72	

Type of Comorbidities		
1. Non-infectious diseases	13	54,2
2. Infectious disease	11	45,8
Length of Stay		
1. ≤ 14 days	13	54,2
2. > 14 days	11	45,8
Mean ± SD	15,71 ± 9,05	
Type of antibiotic therapy		
1. Empiric	22	91,7
2. Definitive	2	8,3
Number of antibiotics		
1. Single	18	75
2. Combined	6	25
Duration of antibiotic use		
1. ≤ 14 days	19	79,2
2. > 14 days	5	20,8
Mean ± SD	10,21 ± 4,71	
Patient Outcome		
1. Improved	23	95,8
2. Died	1	4,2

Of the total 24 study subjects, 20 (83.3%) were in the age group 0-17 years and four (16.7%) were in the 18-65 year group. The highest levels of bacterial meningitis are found in pediatrics, especially in children aged under two months (Zainel et al., 2021), which is related to the undeveloped pediatric immune system.

In terms of gender, 15 subjects (62.5%) were male and nine (37.5%) were female. These characteristics are in line with research conducted by Polkowska et al. (2017) in Finland, who found that 58% of bacterial meningitis affected men, and 42% women. This increased incidence of bacterial meningitis in men may be related to differences in consumption habits between men and women, with men being more likely to have high-risk intake such as alcohol and to smoke (Dias et al., 2017). In addition to dietary factors, the increased incidence of bacterial meningitis in men may be due to genetic reasons. Men have only one X chromosome, not two as in women. The absence of the second X chromosome makes males more susceptible to infection because the X chromosome contains genes directly or indirectly involved in the synthesis of immunoglobulin (Libert et al., 2010)

In this study, 16 subjects (66.7%) had comorbidities with more than 1 comorbid disease, while 5 subjects (20.8%) and 3(12,5%) subjects had 1 comorbid disease and no comorbidities respectively. Type of comorbidities suffered by patients with bacterial meningitis were non-infectious diseases in 13 subjects (54.2%) and infectious diseases in 11 subjects (45.8%). Concomitant diseases in patients with bacterial meningitis based on a study conducted by Wee et al. (2016) retrospectively for 15 years in pediatric patients with bacterial meningitis include epilepsy (25%), sepsis (21%), vp shunt installation (10%), nutritional mall (8%), and anemia. It has been reported that bacterial meningitis has a poor prognosis when comorbidities like diabetes, cancer, and chronic, debilitating diseases are present. Comorbidities play a significant role in the death of infectious disease patients, as demonstrated by mortality rate studies (Faustini et al., 2007)

The average duration of hospitalization for bacterial meningitis patients in the study was 15.71 days. This finding was similar to the median length of stay for bacterial meningitis patients based on data analysis conducted by Holmquist et al. (2008) in USA, which was 16.6 days. The length of hospitalization is related to the duration of antibiotic administration. This ought to be founded on the causative microbes got from cerebrospinal liquid culture, yet not all patients consent to a lumbar puncture (Goodwin and Hartis, 2008). Therefore, empirical antibiotics are given to patients based on clinician experience supported by guidelines and clinical pathways in the Neurology Department of Fatmawati Hospital. In bacterial meningitis patients with severe clinical conditions, neurological and systemic complications further complicate the clinical manifestations that occur, which can affect the length of treatment (van de Beek et al., 2004)

Of the 24 research subjects, 22 (91.7%) had received empirical antibiotic therapy, while two (8.3%) had received definitive antibiotic therapy. Patients received empirical therapy as a result of negative bacterial culture results, so empirical antibiotics were given. Antibiotic therapy must be started immediately in the case of bacterial meningitis. The selection of empirical antibiotics should consider patients' age and underlying conditions until microbiological tests are conducted. Broad-spectrum antibiotics, for example, cephalosporins are suggested for empirical treatment since they have steady cerebrospinal liquid infiltration and can possibly battle bacterial meningitis microorganisms (Tunkel et al., 2004). Empirical antibiotic therapy ought to be bactericidal and accomplish sufficient cerebrospinal liquid (CSF) levels.

In this study, 18 (75%) subjects received single antibiotic therapy, while six (25%) received combined antibiotic therapy. This was because the results showed that the lumbar puncture patients were mostly suspected of infection. Empirical antibiotic therapy is given to patients with purulent meningitis and Gram-negative CSF staining results (Tunkel et al., 2004). Third-generation cephalosporin antibiotics (cefotaxime or ceftriaxone) are a form of empirical antibiotic therapy in bacterial meningitis patients, so in this study more patients were given single antibiotics than combinations. In terms of the duration of antibiotic use, 19 patients (79.2%) received antibiotic therapy for ≤ 14 days, while five (20.8%) received it for> 14 days. Unless there is a persistent parameningeal focus of infection (otitis or sinus), in which case longer treatment may be required, most cases of bacterial meningitis should be treated for 10 to 14 days (Ropper, Samuels, & Klein, 2014). Based on international guidelines, *H. influenzae* or *N. meningitidis* meningitis require a treatment period of seven to ten days, while *S. pneumoniae* meningitis require a treatment period of ten to fourteen days (Hathout et al., 2020).

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Table 2
Clinical Characteristics of Research Subjects

Patient Characteristic	Frequency (n)	Percentage (%)
Symtomps (admission)		
Fever	12	50
Headache	9	37,5
Neck stiffness	9	37,5
Reduced consciousness	12	50
Dexamethasone		
Yes	16	66,7
No	8	33,3
Lumbal puncture		
Yes	9	37,5
No	15	62,5
Causative bacteria (n=2)		
Raoultella (Klebsiella) terigena	1	4,2
Staphylococcus epidermidis	1	4,2

In this study, the condition of 23 patients (95.8%) improved, and one patient died (4.2%). The use of appropriate and adequate antibiotics is one of the factors determining prognosis, in addition to pathogenic and patient factors. Antibiotic administration within 1.5 hours of hospital admission had a favorable outcome in a retrospective data analysis of 187 adults and children with bacterial meningitis, whereas treatment with an average delay of 4.2 hours was unfavorable. According to Shin & Kim (2012), the primary independent risk factor for poor patient outcomes in adults with pneumococcal meningitis was antibiotic administration more than three hours after hospital admission.

The most common presenting symptoms of bacterial meningitis at initial hospital admission in this study (Table 2) were fever (50%), reduced consciousness (50%), neck stiffness (37.5%), and headache (37.5%). The majority of doctors would consider the possibility of meningitis in patients who presented with headache, fever, stiff neck, or altered mental status. 95% of patients with bacterial meningitis will exhibit at least two of these four symptoms, necessitating immediate diagnostic testing. Clinical manifestations and patient characteristics may vary based on the infecting pathogen (Young & Thomas, 2018). In one study, 95% of bacterial meningitis patients had somewhere around two side effects out of cerebral pain, neck stiffness, fever, or reduced conscioueness. Only 44% of patients presented with three symptoms. About one-third of patients had neurological deficits. Similar findings were reported in another study by Griffiths et al. (2018).

In which a total of 16 (66.7%) patients received dexamethasone therapy, while eight (33.3%) did not. In cases of suspected bacterial meningitis, dexamethasone should be started immediately before or simultaneously with antibiotics. It can be given up to 12 hours after antibiotic initiation (Griffiths et al., 2018). In experimental models of bacterial meningitis, dexamethasone can reduce inflammation, edema, and intracranial pressure in the brain. Early treatment with dexamethasone significantly reduced hearing loss and other neurological sequelae and reduced mortality in patients with pneumococcal meningitis from 36% to 30% in a meta-analysis of clinical trials (Young and Thomas, 2008). Dexamethasone administered by intravenous route at a dose of 0.15 mg/KgBB in children and 10 mg in adults every 6 hours for 2-4 days (PERDOSSI, 2016)

In this study, 9 (37.5%) of the patients were given lumbar punctures, while 15 (62.5%) were not. For diagnosing bacterial meningitis, a culture of the cerebrospinal fluid is considered to be the gold standard. To maximize pathogen detection, lumbar punctures should be performed as soon as possible (Griffiths et al.,2018). In this study, the reason why more patients were not given a lumbar puncture was that because some patient families did not agree to allow the procedure. Moreover, the patients in this study were mostly pediatric ones, which was another reason for their family not to allow the puncture. Most of the lumbar puncture results in this study showed suspected infections. Based on research conducted by Michael et al. (2010), unnecessary CT scan examinations in patients cause delays in lumbar punctures and reduce the possibility of cerebrospinal fluid cultures showing positive results after starting antibiotic therapy. The longer the delay between starting antibiotics and performing a lumbar puncture, the less likely that the cerebrospinal fluid culture results will be positive.

Culture examination using LCS, blood, sputum, and urine samples was performed on 15 patients, 13 of whom had negative culture results, while in two patients, isolates were found, these being *Raoultella* (*Klebsiella*) terigena (4.2%) and *Staphylococcus epidermidis* (4.2%). Colonization of *Staphylococcus epidermidis* on the skin of patients and the hands of medical services laborers is viewed as the most well-known wellspring of these infections. The most significant mechanism associated with *Staphylococcus epidermidis* is thought to be its capacity to adhere to foreign bodies and form biofilms on their surface. *Staphylococcus epidermidis* meningitis typically occurs in associated with neurosurgical devices like ventriculoperitoneal shunts (Noguchi et al., 2018). The patients with *Staphylococcus epidermidis* isolates in this study had a history of VP shunt action. This is in line with the theory mentioned by Noguchi et al. (2018).

Table 3
Overview of Antibiotic Use in Bacterial Meningitis Patients

Antibiotic Regimen	Use of antibiotics	
	Frequency (n)	Percentage (%)
Single	**18**	**75**
Seftriakson	10	41,6

Sefotaksim	8	33,3
Combined	**6**	**25**
Seftriakson + Metronidazol	1	4,2
Sefotaksim + amikasin	1	4,2
Sefotaksim + ampisilin	1	4,2
Seftriakson + amikasin	1	4,2
Metronidazol + Meropenem+ Levofloksasin + Co-Amoksiklav	1	4,2
Kloramfenikol + Seftriakson	1	4,2
Total	24	100

Table 3 illustrates the use of antibiotics in bacterial meningitis patients. 18 subjects (75%) received single antibiotic therapy, while six (25%) received a combination of antibiotics. In the case of a single antibiotic, the majority (75%) were given ceftriaxone (41.6%), followed by cefotaxime (33.3%). The using of these two antibiotics is in accordance with the recommendations of the bacterial meningitis management guidelines issued by PPAB Fatmawati Hospital, PERDOSSI and IDSA. The three guidelines recommend using third-generation cephalosporin antibiotics (cefotaxime or ceftriaxone) as empirical antibiotic therapy in patients with bacterial meningitis. A broad-spectrum cephalosporin, particularly cefotaxime or ceftriaxone, is typically the best empirical option. In the treatment of bacterial meningitis, cefriaxone and cefotaxime are both effective; however, cefriaxone has the advantage of being administered in a single daily dose (Hathout et al., 2020). Third-generation cephalosporins are recommended for treating pediatric bacterial meningitis due to their superiority in clinical trials over chloramphenicol and cefuroxime (both second-generation cephalosporins). Third-generation cephalosporins are recommended for meningitis caused by strains that are not susceptible to penicillin in patients with pneumococcal and meningococcal meningitis. These cephalosporins also have a moderate effect on meningitis caused by aerobic gram-negative bacilli (like *Klebsiella* species or *Escherichia coli*). Cure rates of 78% - 94% have been reported, compared to mortality rates of 40% - 90% for previous regimens, including aminoglycosides, with or without chloramphenicol (Tunkel et al., 2004)

Table 4
Evaluation of Antibiotic Use in Bacterial Meningitis Patients

Category	Parameter	Suitability	
		Yes	No
VI	Complete data	24	0
V	Antibiotics are indicated	24	0
IV a	The choice of antibiotics has been effective	24	0
IV b	Less toxic alternatives	24	0
IV c	Cheaper alternative	23	1
IV d	Narrower spectrum	24	0
IIIa	Delivery time is too long	22	2
IIIb	The duration of administration is too short	23	1
II a	Correct dosage	14	10
II b	Exact intervals	22	2
II c	Right route	24	0
I	Right time	24	0
0	Appropiate/correct	11	13

After evaluating the suitability of antibiotics using the Gyssens flow chart, the results show that 11 (45.8%) subjects were given appropriate antibiotics and 13 (54.2%) inappropriate ones. The use of antibiotics that were not appropriate was spread across several categories: category IVC for one subject (4.2%), category IIIA for two subjects (8.3%), category IIIB for one subject (4.2%), category IIA for ten subjects (41.7%), and category IIB for two subjects (8.3%). The guidelines used to assess the suitability of these antibiotics were PPK PERDOSSI 2016, PPAB RSUP Fatmawati, IDSA, and related research journals.

One patient in category IVc received an amikacin-containing brand-name antibiotic. Generic amikacin injection preparations are less expensive than brand-name antibiotics. In this study, there were 2 research subjects who used antibiotics for too long (category IIIA) because it was possible that evaluation and consideration of replacement of antibiotics had not been carried out based on the patient's clinical response to the use of antibiotics. Several things that can cause delays in changing antibiotics include ineffective communication with nurses, patient follow-up is generally carried out by residents so it takes time to ask for approval from the doctor in charge of the patient (DPJP) for plans to change the choice of antibiotics or permission to change antibiotics that have not been approved by d the Antimicrobial Resistance Control Program (PPRA) team.

Any use of antibiotics with too short a duration will stop at this stage and is included in category IIIb. In this study, there was 1 subject who received antibiotics with too short a duration. Based on the data the researchers obtained, the subjects only received antibiotic therapy for two days with a change of dose on the first day. This was due to the clinical condition of the subject who was already bad (looked seriously ill) when he entered the hospital, post seizures and experienced a decrease in consciousness. The subject was a referral patient and when he was referred his condition worsened until he finally died due to intracranial pressure (ICP). Regardless of the underlying pathogen, elevated ICP is a significant and frequent complication of meningitis. According to Tariq et al. (2017), 93% of patients admitted to the neurointensive care unit developed intracranial hypertension, making them more likely to have elevated ICP.

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Patients with severe bacterial meningitis (GCS score ≤ 8) had a higher reported incidence of elevated ICP.

The highest number of patients using irrational antibiotics was in IIa category. Category IIa is related to the appropriate antibiotic dose. In this study, 10 subjects received antibiotics at the inappropriate dose. A total of 7 patients received a dose that was less than the recommendation (underdose) and 3 patients received a dose that exceeded the recommendation (overdose). This dose calculation was carried out based on the IDSA Guidelines written by Tunkel et al (2004). In these guidelines, the dosage for each antibiotic used in the treatment of bacterial meningitis is stated.

In this study, there were 2 subjects who received antibiotics at inappropriate intervals (category IIb). Patient 1 received cefotaxime while patient 2 received ceftriaxone + amikacin. Patient 1 received cefotaxime with an interval of usage every 12 hours while based on the guidelines the interval of using cefotaxime for the treatment of bacterial meningitis is every 6-8 hours. While patient 2 received amikacin therapy with an interval of administration every 12 hours, while based on the guidelines, the interval for using amikacin for the treatment of bacterial meningitis is every 8 hours. Administration of antibiotics that are not in accordance with the interval will cause the level of antibiotics in the blood to be inadequate to eradicate the pathogen that causes the infection so that it will cause therapy failure.

Table 5
The relationship between independent variables and the quality of antibiotic use (n = 24)

Independent Variables	Category	Quality of antibiotic use		P value
		Rational	Irrational	
		n (%)	n(%)	
Type of antibiotic therapy	Emipiric	11(50)	11(50)	0,482
	Definitive	0(0)	2(100)	
Number of antibiotics	Single	10(55,6)	8(44,4)	0,166
	Combined	1(16,7)	5(83,3)	
Duration of antibiotic use	≤ 14 days	10(52,6)	9(47,4)	0,327
	> 14 days	1(20)	4(80)	

Table 6
The relationship between confounding variables and the quality of antibiotic use (n=24)

Confounding Variables	Category	Quality of antibiotic use		P value
		Rational	Irrational	
		n (%)	n (%)	
Age	0-17 years	8(40)	12(60)	0,300
	18-65 years	3(75)	1(25)	
	> 65 years	0(0)	0(0)	
Gender	Male	8(53,3)	7(46,7)	0,423
	Female	3(33,3)	6(66,7)	
Number of comorbidities	None	2(66,7)	1(33,3)	0,679
	1 comorbidity	1(20)	4(80)	
	>1 comorbidities	8(50)	8(50)	
Type of comorbidities	Non-infectious	6(46,2)	7(53,8)	1,000
	Infectious	5(45,5)	6(54,5)	
Length of stay	≤ 14 days	7(53,8)	8(46,2)	0,444
	>14 days	4(36,4)	7(63,6)	

Table 5 and table 6 shows the result of bivariate analysis using the Chi Square method. The independent variables (type of antibiotic therapy, number of antibiotics, and duration of antibiotic use) and confounding ones (age, gender, number of comorbidities, type of comorbidities and length of treatment) had no significant effect on the quality of antibiotic use, with a p value > 0.05. This could be because the number of patients who met the criteria was too small, so significant results were not obtained in the analysis.

Table 7
Covariate selection before logistic regression test

Variables	Category	P value	OR (CI 95%)
Type of antibiotic therapy	Empiric	0,106	NA
	Definitive		
Number of antibiotics	Single	0,085	6,25(0,602-64,862)
	Combined		
Duration of antibiotic use	≤ 14 days	0,178	4,444(0,416-47,503)

	> 14 days		
Age	0-17 years	0,194	0,222(0,019-2,533)
	18-65 years		
	> 65 years		
Gender	Male	0,338	2,286(0,410-12,732)
	Female		
Number of comorbidities	None	0,561	0,600(0,106-3,400)
	1 comorbidity		
	>1 comorbidities		
Type of comorbidities	Non-infectious	0,973	1,029(0,205-5,154)
	Infectious		
Length of stay	≤ 14 days	0,390	2,042(0,395-10,553)
	>14 days		

The variables included in the logistic regression test are variables that have a p value <0.25 as shown in table 7. The p value used to select covariates is the p value on the Omnibus test of model coefficients. The variable length of stay was still included in the logistic regression test even though the p value was > 0.25. This is because the length of stay is related to the duration of use of antibiotics which will affect the rational use of antibiotics.

Table 8
Multivariate analysis of factors affecting quality of antibiotic use in bacterial meningitis patients (n = 24)

Step	Variable	P	OR	CI (95%) Lower	CI (95%) Upper
1	Type of antibiotic therapy	0,999	NA	0,000	NA
	Emipiric				
	Definitive				
	Number of antibiotics	0,495	2,416	0,191	30,514
	Single				
	Combined				
	Duration of antibiotic use	0,777	0,616	0,022	17,616
	≤ 14 days				
	> 14 days				
	Age	0,999	0,000	0,000	NA
	0-17 years				
	18-65 years				
	> 65 years				
	Length of stay	0,418	2,878	0,223	37,167
	≤ 14 days				
	>14 days				
2	Number of antibiotics	0,220	4,630	0,399	53,700
	Single				
	Combined				
	Duration of antibiotic use	0,558	2,378	0,131	43,248
	≤ 14 days				
	> 14 days				
	Length of stay	0,887	1,157	0,156	8,577
	≤ 14 days				
	>14 days				
3	Number of antibiotics	0,220	4,635	0,400	53,711
	Single				
	Combined				
	Duration of antibiotic use	0,459	2,626	0,204	33,887
	≤ 14 days				
	> 14 days				
4	Number of antibiotics	0,125	6,250	0,602	64,862
	Single				
	Combined				

Multivariate analysis with logistic regression in this study was shown in Table 8. After controlling for all covariates in the logistic regression analysis, there were no factors that had a statistically significant effect on the quality of antibiotic use (p value > 0.05). However, the number of antibiotics used has the smallest p-value among all the covariates. The amount of antibiotic use did not have a statistically significant effect but had a clinically significant effect. Based on Table 8, the OR value of number of antibiotics variable is 6.250, which means that bacterial meningitis patients given a single antibiotic had a six times greater chance of receiving rational antibiotics than those given combined antibiotics. The more antibiotics used, the greater the possibility of their inappropriate use. Risks associated with combination therapy are fungal overgrowth, drug drug interactions, drug toxicity, irrational drug use and increase in cost of therapy (Mehta et al., 2014)

Table 9.
Differences in Outcomes of Bacterial Meningitis Patients Treated with Antibiotics Classified as Rational and Irrational

		Patient outcome		P value
		Improved	Died	
		n (%)	n (%)	
Quality of antibiotic	Rational	11 (100)	0 (0)	0,542
	Irrational	12 (92,3)	1(7,7)	
	Total	23(95,8)	1(4,2)	

Table 9 shows that the proportion of subjects who died in the groups that received rational and irrational antibiotics was 0% and 7.7% respectively. The proportion who recovered in the irrational and rational antibiotic groups was 100% and 95.8%. It is shown that the rational use of antibiotics based on evaluation using the Gyssens flow chart was not significant in improving the outcome of bacterial meningitis patients ($p > 0.05$). This could be due to the small number of patients who met the inclusion criteria, so meaningful results were not obtained in the analysis. The occurrence of improvements in patient outcomes is one of the parameters of the success of bacterial meningitis therapy. Clinical improvement indicates that the antibiotics given are appropriate at an adequate dose to eradicate the pathogen causing the infection.

LIMITATION OF THE STUDY

It is realized that there are many limitations in the study. Data collection was conducted retrospectively, sourced from secondary data through patient medical record searches. This meant that the completeness of the research data relied heavily on the medical record keeping of the health workers involved in treating bacterial meningitis patients in the hospital. Culture data was only obtained from two patients who found isolates, so it was not possible to map the bacteria that caused the meningitis. Due to a lack of time, the researchers also did not investigate the data of the culture results further in the laboratory. As a result, access to the culture results data was not possible. In addition, the number of patients who were not willing to undergo lumbar punctures also caused incomplete cerebrospinal fluid culture data, as the lumbar puncture is the gold standard in establishing a bacterial meningitis diagnosis.

CONCLUSIONS AND SUGGESTIONS

In this study, 54.2% of the subjects received irrational antibiotics, with category IIa (inappropriate antibiotic dose) being the most common. Study result that found no significant association statistically between irrational use and mortality. In the future, it is necessary to conduct research with prospective methods to obtain more complete data to better describe bacterial meningitis patients' characteristics and side effect of antibiotics. In addition, it is necessary to do this to obtain an overview of the causative germ pattern, antibiotic sensitivity and resistance data. Similar research could also be conducted with more data or in several locations so that better results can be obtained. Similar studies should be conducted using the cohort method so that the relationship between the rational use of antibiotics with patient outcomes can be ascertained.

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ETHICAL CONSIDERATION

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Conflict of Interest statement

All authors declare that there are no potential conflicts of interest related to this study's publication.

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