Rationality Evaluation of Empirical Antibiotic Use in Inpatient Pneumonia of Bhakti Wira Tamtama Hospital, Semarang

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Abstract

Pneumonia is a serious lower respiratory tract infection, especially in developing countries. In Indonesia, pneumonia is one of the causes of death in hospitals, with a prevalence rate of 4.5%. Bacterial pneumonia infection can be cured with antibiotics. But in some cases there are many problem that can caused irrational use of antibiotics and leads to antimicrobial resistance. This study aims to analyze the rationality of antibiotic use in pneumonia patients at Bhakti Wiratama Hospital and its correlation to clinical outcomes. This research uses a descriptive analytical method with a cross-sectional design and retrospective data collection. The research subjects are medical records of patients with a primary diagnosis of pneumonia who were hospitalized at Bhakti Wira Tamtama Hospital in Semarang from June 1 to December 31, 2019 and meeting the inclusion and exclusion criteria. The results showed that the rationality of empirical antibiotic use based on IDSA/ATS in pneumonia patients from June to December 2019 indicated that 95.65% of antibiotic therapy regimens were irrational and 4.35% were rational. The results of statistical analysis showed that the rationality of empirical antibiotic therapy use was not related to the clinical outcomes of pneumonia patients at Bhakti Wiratama Hospital, Semarang.

Keywords: antibiotics, pneumonia, empirical, drug related problem, clinical outcomes

1. INTRODUCTION

Pneumonia is one of serious lower respiratory infection and may be the main cause of death, especially in developing countries (Setyoningrum, 2006). In Indonesia, pneumonia is the main cause of death in hospital with prevalence of 4.5% in 2023. The prevalence of pneumonia in Central Java Province is 5%, higher than the average prevalence of national (Kemenkes RI, 2015).

Pneumonia infections affect the respiratory tract at the ends of the bronchioles and alveoli. According to the World Health Organization (WHO), pneumonia affects many people worldwide each year, with around 450 million cases. This disease causes millions of deaths across all age groups, accounting for about 7% of total global deaths annually. The highest number of cases occurs in children under five years old and adults over 75 years old (Ruuskanen et al., 2011).

The prevalence of pneumonia rose from 6 per 1000 in the 18-39 age group to 34 per 1000 in the 75 and older age group (Pilotto et al., 2009). The mortality rate due to pneumonia is higher in those over 65 years old compared to younger age

groups, with around 85% of deaths occurring in this age group and only about 3% occurring under the age of 45 (American Lung Association, 2015). Bacterial pneumonia can be treated with antibiotics. The success rate of pneumonia treatment is influenced by several factors, including the use of antibiotics, healthcare facilities, and prevention of infection system by ATS. The use of antibiotics requires special attention to improve outcome therapy and prevent antimicrobial resistance (Kemenkes RI, 2015).

The initial approach in the treatment of pneumonia is the empirical use of antibiotics, in accordance with the Indonesian Pulmonary Disease Management Guidelines (PDPI, 2003). Antibiotics are commonly used to treat bacterial infections. According to research conducted by Vonny (2019), the appropriateness of empirical antibiotic use in pneumonia patients according to pneumonia therapy guidelines is only 43.4%. Inappropriate use of antibiotics is a major cause of the development of antibiotic resistance. Antibiotic resistance can lead to various consequences, including prolonged illness duration, increased risk of death, and extended hospital stays (Utami, 2012).

The limitation of antibiotic options occurs because of increasing bacterial resistance to antibiotics. This situation makes treating patients more difficult. The preventive measures can be achieved by ensuring that the current use of antibiotics is done appropriately (DeAngelis, et al, 2016).

Bhakti Wira Tamtama Hospital is a military hospital in Semarang, established in 1925. Pneumonia is the most common infection case at Bhakti Wiratama Hospital. Until now, there is no research regarding the evaluation of rationality of antibiotic use in pneumonia patients at this hospital. Therefore, based on the analysis of the pneumonia prevalence in Central Java, which is higher than the national average. The high cases of pneumonia at Bhakti Wiratama Hospital, and the lack data of antibiotic-related rationality at this hospital, the researcher aims to analyze the rationality of empirical antibiotic use in pneumonia therapy for inpatients at Bhakti Wiratama Hospital and its correlation to clinical outcomes.

2. METHODS

Research Design

This study uses a non-experimental descriptive-analytic research design with a cross-sectional approach to determine the relationship between drug-related problems in the use of empirical and definitive antibiotics and clinical outcomes. Data collection was conducted retrospectively at Bhakti Wira Tamtama Hospital in Semarang.

Location and Time of Study

The research was conducted in the medical records room of Bhakti Wira Tamtama Hospital in Semarang. The data collection and processing of medical records were carried out from June to December 2021.

Research Subjects

The research subjects are medical records of patients with a primary diagnosis of pneumonia who were hospitalized at Bhakti Wira Tamtama Hospital in Semarang from June 1 to December 31, 2019 and meeting the inclusion and exclusion criteria. The inclusion criteria for this study are adult male and female inpatients aged ≥ 18

years, with a primary diagnosis of pneumonia, and supplementary examinations such as thorax x-ray showing infiltrates and/or sputum microbiology tests. Patients who received antibiotic therapy within 48-72 hours since arrival and readable medical records, including age, weight, height, and clinical outcome parameters are also included. The exclusion criteria include patients who were discharged against medical advice or deceased, and patients with other infectious diseases.

Data Analyses

Data collection was performed by retrieving information from patient medical records, with patient identities coded by the researcher to maintain confidentiality. The data collected included age, weight, height, gender, comorbidities, and clinical outcomes after antibiotic therapy. The Independent variable is the use of antiobicts and the dependent variables is the rationality of antibiotic used. The confounding variables such as age, gender, non-infectious comorbidities, and clinical outcomes achieved, were collected and tabulated. The rationale of antibiotic used in patient will be analyzed with *Gyssen method.* Data analysis was conducted to determine the impact of the rationality of antibiotic use on patient clinical outcomes using SPSS 23rd. After data processing was completed, conclusions and recommendations were made based on the evaluation of these data, aligned with the research objectives.

1. Descriptive Analysis: This analysis was performed to determine the incidence rate of pneumonia, patient demographics (age and gender), comorbidities, and the prevalence of drug-related problems presented as percentages.
2. Qualitative analysis : The rational used of antibiotics in patient were analyzed with Gyssen methode. Evaluation using the Gyssens table is classify each antibiotic administration into 6 categories, such as category VI (inappropriate use because the medical record is incomplete to be evaluated), category V (inappropriate use because it is not in accordance with the indication), category IVa (inappropriate use because there are other antibiotics that are more effective), category IVb (inappropriate use because there are other antibiotics that are safer), category IVc (inappropriate use because there are other antibiotics that are cheaper), category IVd (inappropriate use because there are other antibiotics that have a narrower or more specific spectrum), category IIIa (inappropriate use because the administration is too long), category IIIb (inappropriate use because the administration is too short), category IIa (inappropriate use of the dosage), category IIb (inappropriate use of the interval of administration), category IIc (inappropriate use of the method of administration), and category I (inappropriate time of administration) and 0 is stated as appropriate and rational use of antibiotics (not included in category I to VI).
3. Bivariate Analysis: This analysis examined the relationship between drug-related problems in the use of empirical antibiotics in hospitalized pneumonia patients (independent variable) and clinical outcomes (dependent variable). The significance

level used was 5% ($\alpha = 0.05$) with a confidence interval (CI) of 95%. If $p < \alpha$, it indicates a relationship between the variables, and if $p \geq \alpha$, it indicates no relationship between the variables. The bivariate analysis used the chi-square test.

4. RESULTS AND DISCUSSION

The study obtained 23 medical records of pneumonia patients from June to December 2019 at Bhakti Wiratama Hospital Semarang that met the inclusion criteria. The demographic characteristics of the research subjects are presented in Table 1.

Table 1. Demographic of Patients

Variables	Frequency n=23 patients	%
Genders		
Male	9	39.13
Female	14	60.87
Age		
26 – 35 years old	2	8.70
36 – 45 years old	4	17.39
46 – 55 years old	2	8.70
56 – 65 years old	5	21.74
>65 year olds	9	39.13
Length of Stay		
<5 days	4	17.39
5-10 days	19	82.61
Comorbid	21	
Comorbid present	22	91.30
No comorbid	1	8.70
Rationality		
Rational	1	4.35
Irrational	22	95.65
Clinical Outcome		
Improve	22	95.65
Worsen	1	4.35

The descriptive analysis results show that pneumonia is more commonly found in female patients, with age of >65 years old. The length of stay (LOS) for patients is 5-10 days, with or without comorbid conditions, and the majority of clinical outcomes improve.

The distribution of patients by age indicates that pneumonia is most prevalent in those over 65 years old (39.13%). This finding is consistent with other studies that report the highest incidence of pneumonia in individuals over 60 years old (Sari et al., 2017). The age group of 65 years or older is at a higher risk of developing pneumonia (American Lung Association, 2015b). This is due to the decline in cell function, reduced immunity, and the presence of comorbidities, which can increase the risk of Community-Acquired Pneumonia (CAP) (Eurich et al., 2017).

In terms of gender, pneumonia is more common in females (60.87%) compared to males. This finding contrasts with other research by (Faisal et al., 2014), which showed that male patients with community-acquired pneumonia in inpatient settings were more prevalent (74.5%) compared to females. Another study on patients with Community-Acquired Pneumonia (CAP) receiving empirical antibiotic therapy in a hospital in China reported a higher number of males (61.7%) compared to females (38.3%) (Nie et al., 2018). Factors contributing to the increased vulnerability of males to pneumonia include lifestyle factors such as smoking and more frequent outdoor activities, chronic diseases, immune deficiencies, and environmental factors (Dahlan, 2006).

Length of Stay (LOS) is the period of time a patient spends in the hospital, calculated from the time of admission to discharge (PDPI, 2014). It was found that the most common duration of hospitalization for pneumonia patients at the hospital is 5-10 days. The minimum duration for administering antibiotics is 5

days, with a general course of 7-10 days for patients who show a response within the first 72 hours. In terms of comorbid conditions, the majority of patients have comorbidities (91.30%). Comorbid factors such as chronic respiratory diseases (COPD), diabetes mellitus, congestive heart failure, and renal failure can increase the risk of pneumonia infection (Dipiro, 2015).

Table 2. The Profile of Antibiotics Use

Variables	Frequency n=23 patients	%
Type of therapy		
Empirical	23	100
Definitive	0	0
Antibiotics Use		
Monotherapy		
Ceftizoxime	8	27.59
Cefuroxime	5	17.24
Ampicillin-Sulbactam	3	10.34
Levofloxacin	2	6.90
Cefoperazone	2	6.90
Cefuroxime sodium	2	6.90
Cefixime	1	3,45
Ceftriaxone	1	3,45
Cefotaxime	1	3,45
Combinations		
Ceftizoxime + Levofloxacin	1	3,45
Cefuroxime sodium + Levofloxacin	1	3,45
Ceftizoxime + Ciprofloxacin	1	3,45
Cefotaxime + Ciprofloxacin	1	3,45

Based on Table 2, among the 23 medical records, 29 documented antibiotic regimens were identified. All inpatient patients received empirical antibiotic therapy without accompanying culture results. The most commonly used antibiotic therapy was the monotherapy using ceftizoxime (27.59%).

Pneumonia treatment in the initial therapy involves empirical antibiotic use (PDPI, 2003). The initial empirical therapy for pneumonia uses broad-spectrum antibiotics, which are later narrowed based on specific pathogen results from bacterial culture tests (Woolfrey, 2012). Antibiotic administration in the early stages of therapy is empirical and not based on culture and sensitivity test results. The study data show that 100% of the therapy regimens used empirical antibiotics. Empirical antibiotic recommendations for Community-Acquired Pneumonia (CAP) are based on selecting agents that are effective against the main bacteria. Generally, the pathogens causing CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella* species, *Chlamydia pneumoniae*, and *Moraxella catarrhalis*. Empirical antibiotic therapy in the initial treatment is recommended for the eradication or inhibition of suspected bacterial pathogens before microbiological results are obtained (Metlay et al., 2019).

The antibiotic treatment guidelines for CAP patients refer to the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines from 2019. The IDSA/ATS 2019 guidelines recommend that non-ICU inpatient patients with non-severe CAP receive either a single fluoroquinolone or a combination of a β-lactam with a macrolide (Metlay et al., 2019; PDPI, 2014).

The distribution of antibiotic use in this study shows that cephalosporin antibiotics were the most commonly used in the therapy regimens. The most frequently used single antibiotic was ceftizoxime, with 8 regimens (27.59%). Ceftizoxime is a third-generation cephalosporin and a derivative of β-lactam. Other similar antibiotics used in the

therapy regimens include cefixime, cefoperazone, cefotaxime, ceftizoxime, and ceftriaxone. In terms of effectiveness, ceftizoxime is as effective as other β-lactam antibiotics such as cefotaxime and latamoxef in treating bacterial pneumonia in high-risk patients (Yangco et al., 1987). However, the use of single cephalosporins does not align with the IDSA/ATS guidelines, which recommend that β-lactam antibiotics should be combined with a macrolide. Specifically, the IDSA/ATS guidelines recommend that for outpatients with comorbidities, β-lactam or cephalosporin should be combined with a macrolide or doxycycline (Metlay et al., 2019).

Combination therapy can be beneficial if the patient is experiencing severe infection or has other infections. Combination therapy is used as a method to prevent emergent resistance during treatment for patients with severe pneumonia or those with additional infections, and to enhance the efficacy of antibiotics through the use of drugs with synergistic effects (Lisni et al., 2021). The IDSA/ATS 2019 guidelines also recommend combination therapy as a standard for empirical treatment of community-acquired pneumonia, specifically β-lactam + macrolide or β-lactam + fluoroquinolone.

Evaluation of the Rationality of Antibiotic Use

This study employs a qualitative evaluation of antibiotic use using the Gyssens method. The Gyssens method is a quality assessment method that evaluates the rationality of antibiotic use based on Gyssens flowchart, which consists of categories I-VI. The evaluation of the rationality of antibiotic use is presented in Table 3.

Table 3. Rationality of Antibiotics Use using Gyssens Criteria

Gyssens Criteria			Count	%
I		Incorrect timing	0	
II	**A**	Incorrect dose	3	5.08
	B	Incorrect interval	3	5.08
	C	Incorrect route	7	11.86
III	**A**	Duration too long	0	
	B	Duration too short	21	35.59
IV	**A**	More effective alternative	25	42.37
	B	Alternative less toxic	0	
	D	Alternative narrower	0	
V		No indication for antibiotics use	0	
VI		Incomplete medical records	0	
		Total	59	100%

*One antibiotic regimen can fall into more than one Gyssens category

From the 29 antibiotic regimens, a total of 59 cases of irrational antibiotic use were identified. The most common irrational use, according to the Gyssens criteria, was found in category IVA, accounting for 42.37%, indicating that a more effective antibiotic was available.

Empirical antibiotic use in category IVA was not appropriate based on its effectiveness, as it referred to the IDSA/ATS guidelines, which state that for non-severe inpatients, a single fluoroquinolone or a β-lactam combined with a macrolide should be administered (Metlay et al., 2019; PDPI, 2014). In this study, the most frequently used antibiotics were cephalosporins, which do not align with the treatment guidelines recommended by IDSA/ATS 2019.

Based on the duration of treatment, the rationality of antibiotic use is divided into two categories: Category IIIA

(duration of administration is too long) and IIIB (duration of administration is too short). The recommended treatment duration is 7 days, but it can be extended if there is no clinical improvement. According to the IDSA/ATS guidelines, empirical therapy for pneumonia patients should last no more than 7-10 days. The minimum duration of antibiotic therapy is 5 days, even if clinical improvement is observed 48-72 hours after the initiation of the regimen. Analysis results showed that 35.59% of antibiotic prescriptions fell into Category IIIB. Several factors might underlie the occurrence of a too-short duration, including the clinical improvement and stabilization of some CAP patients at Bhakti Wiratama Hospital Semarang, which allowed patients to be discharged before 5 days and continue antibiotic treatment as outpatients.

The irrational use of antibiotics in category IIC was 11.86%, which was incorrect routes of administration. This included cases where medication intended for injection was instead given orally. Category IIB accounted for 5.08% and involved incorrect dosing intervals, while Category IIA, also at 5.08%, involved incorrect dosing. An example is the use of ampicillin-sulbactam at a dose of 750 mg every 12 hours, which should be administered at 1.5g-3g every 6 hours. The choice of administration route, interval, and dosage was based on the IDSA/ATS 2019 guidelines.

Correlation Between the Rationality of Antibiotic Use and Clinical Outcomes

The clinical outcome is the goal to be achieved from a drug therapy. The clinical outcome of a patient can either improve or worsen. Improvement in a patient's clinical outcome is determined by improvements in the physician's clinical diagnosis, vital signs, symptoms, and clinical laboratory results. A worsening clinical outcome means that the patient does not show any clinical improvement after receiving antibiotic treatment.

An evaluation of the relationship between the rationality of antibiotic use and clinical outcomes showed that, out of 23 pneumonia patients who used antibiotics, the clinical outcome improved in 22 patients and worsened in 1 patient. In terms of the rationality of antibiotic use, 1 patient received rational treatment, while 22 patients received irrational antibiotic treatment.

Table 4. Analysis of the Relationship Between the Rationality of Antibiotic Use and Clinical Outcomes

	Clinical Outcomes		Total
	Improve	Worsen	
Rational	1	0	1
Irrational	21	1	22
Total	22	1	23

Based on the results of the bivariate chi-square statistical test, the analysis of the relationship between the rationality of antibiotic use and clinical outcomes shows that there is no significant relationship between the rationality of antibiotic use and the clinical outcomes of patients (p-value=0.827).

These findings align with other research, such as a study on antibiotic use in pneumonia patients at the Inpatient Unit of RSUD H Abdul Moeloek in 2015. This study found that 44.7% of antibiotic use was rational, while 55.3% was irrational (Rusmini, 2016).

Another study by Widiyastuti et al. (2023) showed different results, indicating that the rationality of antibiotic use in

community-acquired pneumonia patients at RSUD Dr. H. Abdul Moeloek was 79.91% for empirical antibiotics and 80% for definitive antibiotics. This study found a significant relationship between rational antibiotic use and clinical outcomes, suggesting that more rational antibiotic use led to better clinical outcomes in community-acquired pneumonia patients.

Further research on the appropriateness of empirical antibiotic use in CAP patients at RSUP Sardjito revealed that 76.4% of empirical antibiotic use was in line with guidelines, while 23.6% was not. Statistical analysis indicated a significant relationship between the appropriateness of empirical antibiotics and clinical outcomes in CAP patients (Sumaryana, 2016).

There are many factors that can affected clinical outcome in patients. The severity of the disease, respond from the physician during the report of drug related problem, and an adequate hospital services might be affect patient condition. Therefore, we need more data from prospective view to know exactly some cases being handled.

This study has limitations due to its retrospective method, as the determination of clinical outcomes is based on clinical decisions recorded in medical records, making it impossible to confirm them. Another limitation is that the assessment of antibiotic rationality using the Gyssens method was only performed by the researcher, which may introduce subjective bias into the assessment, so in the future a pharmacist should be collaborated with physician to get a better analysis result.

5. CONCLUSION

The rationality of empirical antibiotic use based on IDSA/ATS guidelines in pneumonia patients from June to December 2019 showed that 95.65% of antibiotic therapy regimens were irrational, while 4.35% were rational. The rationality of empirical antibiotic therapy use was not related to the clinical outcomes of pneumonia patients at Bhakti Wiratama Hospital Semarang.

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