



Correlation of Rationality Empiric Antibiotic with Clinical Outcome in Hospital Acquired Pneumonia Patients

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Abstract

Background: Irrational use of antibiotics causes high mortality rates from Hospital Acquired Pneumonia (HAP), resulting in the worsening of patients' clinical outcomes. This study aims to determine the correlation between the rationality of empirical antibiotic use and the clinical outcomes of HAP patients.

Methods: The research was conducted using a retrospective cohort and consecutive sampling with a research sample of adult patients diagnosed with HAP at Gadjah Mada University Academic Hospital who were treated in the period January 2021-October 2023. HAP patients who received empiric antibiotics for less than 48 hours, had infections other than HAP, and cancer were excluded from this study. The rationality of antibiotics was assessed using a Gyssens' flow diagram, the patients' clinical outcomes were seen on days 2 to 3rd of empirical antibiotic use, and the chi-square test to see the correlation of antibiotic rationality with clinical outcomes.

Results: A total of 52.63% of patients received rational empirical antibiotics, and 47.37% received irrational empirical antibiotics. Clinical outcomes that did not improve often occurred in the rational group, specifically in 13 patients out of 40 patients. The results of the chi-square test showed that the rationality of empirical antibiotic use did not correlate with clinical outcomes in HAP patients at Gadjah Mada University Academic Hospital, with a p-value of 0.317.

Conclusion: The rationality of empirical antibiotic use does not have a significant relationship with clinical outcomes.

Keywords: *Clinical Outcome, Empiric Antibiotics, Gyssens, Hospital-Acquired Pneumonia (HAP), Rationality.*

Introduction

Hospital-acquired pneumonia (HAP) is a type of nosocomial infection that occurs in patients who are hospitalized. The incidence of HAP in the world is 0.55 cases per 100 patients who are hospitalized, with a mortality rate of 22.4%, and 8% are referred to another hospital due to worsening¹. The results of research in Indonesia showed that the prevalence of HAP causes deaths by 30-70% were 4-5 cases of HAP in every 1000 cases of patients hospitalized². The results of the 2018 Ministry of Health basic health report stated that there were 450 million cases of pneumonia, which has increased to 2 percent from 2013³. HAP can increase the risk of death by 20-50%⁴. The prognosis of HAP increases in elderly patients, comorbid diseases, severe infections outside the lungs, sepsis, severe bleeding, length of stay, smoking, use of immunosuppressant drugs, and bronchiectasis^{5,6}.

The treatment for HAP therapy is the same as for other bacterial infections, namely using empiric antibiotics with a broad spectrum and then de-escalating by narrowing the antibiotic spectrum after the bacterial culture results come out⁷. The choice of antibiotic must also be based on the turpis sensitivity

of the antibiotic in both the hospital environment and the patient^{8,9}. Irrational use of antibiotic regimens will have an impact on the occurrence of antibiotic resistance, which can cause worsening of clinical conditions or can cause new diseases and longer hospital stays. This will have an impact on increasing the costs that must be incurred while undergoing treatment in hospital^{10,11}. The classification of rational and irrational antibiotic therapy regimens is based on qualitative test evaluation using the Gyssens' method. The Gyssens' method is a qualitative analysis to assess the appropriateness of antibiotic use based on aspects of effectiveness, toxicity, cost, spectrum, duration of administration, route, interval of administration, and time of administration of therapy¹².

The patients' clinical outcomes are not only influenced by the effectiveness and efficiency of the therapy administered, but are also influenced by other factors that are interconnected with each other, including age, comorbidities, and the severity of HAP^{13,14}. A retrospective study conducted on 147 patients aged 19-98 years showed that the highest mortality rate due to HAP infection was 69.9 ± 15.9 years of age¹⁵. Comorbid or chronic diseases that can

affect the patients' clinical improvement. Research states that the mortality rate in patients who have comorbidities is higher than in patients who do not have comorbidities. The mortality rate increases in line with the increase in the number of comorbidities the patient has^{16,17}.

The study of antibiotic rationality is one of the steps to control antibiotic use. This background encourages researchers to research the correlation between the rationality of empirical antibiotic use and clinical outcomes in HAP patients.

Methods

The variables contained in this study include the rationality of antibiotic use as an independent variable. The clinical outcome as the dependent variable. Age and comorbidities as confounding variables. The distribution of rationality for antibiotic use, clinical outcomes, age, and comorbidities in each group was analyzed using univariate descriptive analysis and presented in tables. The relationship between the rationality of antibiotic use and clinical outcomes was analyzed using the chi-square statistical test. Meanwhile age and comorbidities were analyzed using a binary logistic regression test to see how much influence they had on clinical outcomes.

Data collection instruments used 2 forms, the first form was a patient data form including patient identity (initial name, age, comorbidities), antibiotic use data (name of antibiotic, dose of antibiotic, duration of administration of antibiotics, interval of antibiotics), vital signs examination (respiration rate dan SpO₂), clinical symptoms (cough, shortness of breath, sputum), laboratory examination of leukocytes and thorax rontgen. The second form is a form for analyzing the appropriateness of therapy. Decision making on improving and not improving is based on the main parameters including the patients' clinical symptoms, and vital signs, as well as supporting examinations including leukocyte examination, and thorax rontgen on days 2-3 of empirical antibiotic use. If using empirical antibiotics in combination with one of the antibiotics does not meet the Gyssens' flow chart then it is said to be irrational. Rationality assessment using a Gyssen' flow diagram based on the Indonesian Ministry of Health in 2021. Assessment of the rationality of antibiotic use refers to the Gyssens' flow chart including, completeness of data (patient identity, main parameters include respiratory rate, presence or absence of cough, tightness, and sputum condition, supporting parameters include leukocytes and thorax

rontgen), the accuracy of indications, the accuracy of antibiotic selection in aspects of effectiveness, toxicity, antibiotic coverage, duration, dose, interval, route, and time of administration. The guidelines used include the Gadjah Mada University Academic Hospital Antibiotic Use Guideline, the 2021 General Guidelines for Clinical Practice in Pulmonary and Respiratory Diseases, and the Indonesian Hospital Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP) Diagnosis and Management Guidelines in 2018. The first antibiotic review was based on Gadjah Mada University Academic Hospital Antibiotic Use Guideline. If the antibiotic is not listed in the Gadjah Mada University Academic Hospital Antibiotic Use Guideline, it is then reviewed based on the Guidelines for the Diagnosis and Management of Hospital Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP) in 2018.

Result

A total of 125 patients were excluded because 32 patients were diagnosed with Community Acquired Pneumonia (CAP), 58 patients had other bacterial and fungal infections other than pneumonia, 12 patients had a history of cancer, and received empirical antibiotic therapy for less than 48 hours. Patients' characteristics are identified based on age, gender and comorbidities. The largest number of age is elderly group (63,16%). Men have a greater percentage of HAP incidents (55,26%) and hypertension has the highest percentage (35,53%) compared to other comorbidities. Patients' characteristics are shown in Table 1.

Table 1. Patients' characteristics

No	Characteristics	n=76	%
1	Age		
	Adult (18-60 years)	28	36.84
	Elderly (>60 years)	48	43.16
2	Gender		
	Male	42	55.26
	Female	34	44.74
3	Comorbidities		
	Asthma	1	1.32
	Diabetes Mellitus type II	20	26.32
	Heart Failure	18	23.68
	Renal Failure	17	22.37
	Hypertension	27	35.53
	Stroke	5	6.58

Rationality of Empirical Antibiotic Use Based on Gyssens' Flow Chart

The rationality of empiric antibiotic use is shown in Table 2. Category VI analysis was not carried out because incomplete data were excluded. The IVC category was also not analyzed because Gadjah Mada

University Academic Hospital has lower purchasing costs than e-catalogue. The price of medicines in the e-catalogue is much cheaper than the price of medicines purchased from distributors. So, the price of antibiotics at Gadjah Mada University Academic Hospital is much more affordable than the prices in general. Antibiotics that are not rational in this research are in category IVa (there are more effective antibiotics) with 40.79%, and category IIb (the dose of antibiotics is less precise) with 6.58%. The list of Irrational Empirical Antibiotics is shown in Table 3.

Based on Gadjah Mada University Academic Hospital empirical antibiotics in HAP patients are divided into 2 based on the onset of occurrence, namely early and late. In early onset without impaired renal function, antibiotic choices that can be given are levofloxacin, ampicillin-sulbactam + levofloxacin,

ceftriaxone + levofloxacin, and moxifloxacin. In late onset, the antibiotic options that can be given are meropenem, levofloxacin, and moxifloxacin. Moxifloxacin is only given to early and late onset HAP patients with impaired renal function or patients with normal renal function but no improvement in therapy after using levofloxacin²¹. The use of azithromycin as a single or combination empirical antibiotic is not an option for therapy in HAP. Azithromycin can be given to CAP patients. The use of cefoperazone sulbactam is not an option for therapy in HAP patients with impaired renal function. Cefixime, co-amoxiclav, and gentamicin antibiotics are not an option in HAP. Ceftazidime and gentamicin are definitive treatment options for HAP. Meanwhile, ceftriaxone is not an empirical antibiotic choice in late-onset HAP patients.

Table 2. Rationality of empirical antibiotic based on Gyssens' analysis

No	Gyssens' Category	n=76	%
1	Rational		
	Category 0	40	52.63
2	Irrational	36	47.37
	Category VI (incomplete data)	0	0.00
	Category V (no indication for antibiotic use)	0	0.00
	Category IVa (there are other antibiotics that are more effective)	31	40.79
	Category IVb (there are other antibiotics that are less toxic)	0	0.00
	Category IVc (there is another antibiotic with a lower price)	0	0.00
	Category IVd (there are other antibiotics that have a narrower spectrum)	0	0.00
	Category IIIa (duration of antibiotic use is too long)	0	0.00
	Category IIIb (duration of antibiotic use is too short)	0	0.00
	Category IIa (inappropriate antibiotic dose)	5	6.58
	Category IIb (inappropriate antibiotic administration interval)	0	0.00
	Category IIc (inappropriate route of antibiotic administration)	0	0.00
	Category I (inappropriate timing of antibiotic administration)	0	0.00

Table 3. List of irrational empirical antibiotics

No	Gyssens' Category	Antibiotics	n=76	%
1	Category IVa	Azithromycin	3	3.95
		Cefixime		
		Cefoperazone sulbactam		
		Ceftazidime		
		Ceftazidime + Gentamicin		
		Ceftriaxone		
		Ceftriaxone +Azithromycin		
		Co-amoxiclav		
		Meropenem		
		Moxifloxacin		
2	Category IIa	Ceftriaxone 2g/24 hours	2	2.63
		Levofloxacin 500mg/24 hours	2	2.63

Rationality of Empirical Antibiotic Use Based on Gyssens' Flow Chart

The results of the analysis of patient clinical outcomes and empirical antibiotic rationality were obtained, and then a chi-square test was conducted using SPSS software to determine whether there is a

correlation between clinical outcomes and empirical antibiotic rationality. It is said that there is a significant relationship if the p-value <0.05 and an insignificant relationship if the p-value>0.05. The results of the correlation analysis are presented in Table 4.

Table 4. Rationality of empirical antibiotic based on Gyssens' analysis

No	Rasionality	Patient Count		Total	p-value
		Improve	Non-Improve		
1	Rational	27 (67.50%)	13 (32.50%)	40 (52.63%)	0.317
2	Irrational	28 (77.78%)	8 (22.22%)	36 (47.37%)	
	Total	55 (72.37%)	21 (27.63%)	76 (100%)	

Based on Table 4, clinical outcomes improved more in the irrational antibiotic group (77.78 %) than in the rational antibiotic group (67.50 %). The p-value obtained was 0.317 which showed that there was no significant correlation between the rationality of antibiotic use and the clinical outcomes of HAP patient.

Discussion

Patients' Characteristics

The largest age group in this study is an elderly group (> 65 years) with 63.16%. This is supported by previous research which states that in elderly patients there is a decrease in respiratory physiology starting with respiratory muscle atrophy and then continuing with a decrease in cough reflexes and the immune system. Decreased physiology in the elderly is related to the presence of comorbidities, and malnutrition which has the potential to reduce the immune system. So, the severity of HAP increases 1.15 times with each increase in age¹⁸. Male has a greater percentage (55,26%) in incident HAP. Researchers attributed the higher incidence of pneumonia in men to the higher risk factors of smoking, alcoholism, and toxic exposure in the workplace compared to women¹³.

Hypertension is the largest number of comorbidities (35.53%). Patients with uncontrolled hypertension are susceptible to pneumonia and respiratory infections. For every 5 mmHg increase in systolic pressure, the incidence of pneumonia and respiratory infections increases significantly. The mechanism by which increased blood pressure can trigger pneumonia and respiratory tract infections is that increased blood pressure correlates with decreased lung function, hypertension stimulates dysregulation of the adaptive immune response, hypertension causes endothelial dysfunction thereby triggering infection, dysregulation of nitric oxide release and signals inflammation in the lungs. Research suggests that comorbidities or chronic diseases have a strong relationship with clinical outcomes and suppress the patients' immune system¹⁹.

Rationality of Empirical Antibiotic Use based on Gyssens' Flow Chart

In this study, ceftriaxone was given 2g/24 IV, but based on Gadjah Mada University Academic Hospital Antibiotic Use Guideline the dose of ceftriaxone that can be given is 1g/12 hours IV. Lexicomp states that ceftriaxone can be given at a dose of 1-2g/12-24 hours IV. However, a review of pharmacokinetics and pharmacodynamics states that the clinical efficacy of ceftriaxone increases as the frequency of administration increases. This is based on the time spent by Ceftriaxone during the Minimum Inhibitory Concentration (MIC) phase²².

Levofloxacin regimen is said to be irrational because the dose received by the patient is 500mg/24 hours IV. Based on the Gadjah Mada University Academic Hospital Antibiotic Use Guideline, the dose of levofloxacin that can be given is 750mg/24 hours IV. The HAP therapy guidelines issued by the 2021 General Guidelines for Clinical Practice in Pulmonary and Respiratory Diseases also state that the dose of levofloxacin is 750mg/24 hours IV²⁰. The patient received levofloxacin 500mg/24 hours IV due to consideration of the patients' condition which has entered the elderly age.

Correlation Between Rationality of Empirical Antibiotics with Clinical Outcomes

The results of the correlation analysis of empirical antibiotics with clinical outcomes showed that there was no significant correlation between the rationality of antibiotic use and the clinical outcomes of HAP patients. The results of this study are different from research conducted at the Regional Hospital in West Nusa Tenggara province, which states that there is a correlation between the rationality of empirical antibiotic use and patient clinical outcomes²³. The difference in results may be due to each hospital's antibiogram, antibiotic prescribing patterns, and patients' characteristics.

The absence of a significant correlation was due to confounding factors such as age and comorbidities. Statistical results using the binary logistic regression test show that age and comorbidities have an influence on clinical outcomes of up to 95.5%. Previous research states that increasing age makes patients vulnerable to infection. This is related to the decline in immune system function and inflammatory dysregulation with age. As

a result, the ability of the body's defense cells to prevent infection and protect against inflammation is not optimal²⁴. In addition, the presence of comorbidities can also make patients vulnerable to HAP infection with different pathways based on the type of comorbidities the patient has.

The development of research on the clinical efficacy of empirical antibiotics that are not included in the management of HAP therapy at Gadjah Mada University Academic Hospital Antibiotic Use Guideline, the 2021 General Guidelines for Clinical Practice in Pulmonary and Respiratory Diseases, and the Indonesian Hospital Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP) Diagnosis and Management Guidelines in 2018, such as cefoperazone sulbactam and azithromycin antibiotics, is also another factor that causes no significant correlation between rationality and clinical outcomes. Research states that cefoperazone sulbactam has a clinical efficacy of up to 87% in adult patients, and 81-83% in elderly patients²⁵.

This study has research limitations, including the difficulty of determining clinical outcome decisions (improving or not improving). The method of deciding to improve is based on the fulfillment of all the main parameters (breath rate, temperature, no coughing/coughing reduced, no shortness of breath/shortness of breath reduced, no sputum/sputum reduced) or a statement of improving or not improving from the doctor. However, in the field, some cases of HAP are found without symptoms. Diagnosis without symptoms is based on the results of thorax roentgen, and not always 3 days after empirical antibiotics are given, patients undergo a thorax roentgen.

So, the decision-making in such cases is based on the main parameters present in the patient or refers to the decision of, whether to improve or not to improve, made by the doctor. Meanwhile, the strength of this research is that the assessment of the rationality of antibiotic use and clinical outcomes was not only carried out by researchers but also by pharmacists and pulmonary specialists at the Gadjah Mada University Academic Hospital. So, it can reduce bias in research results.

Conclusions

The rationality of empirical antibiotic use has no correlation with clinical outcomes in HAP patients with a p-value of 0.317. Based on the research results obtained, it is recommended that further research be conducted regarding the efficacy of antibiotics that are often used but are not listed in therapeutic

management. So, it can be one way to improve the clinical outcomes of HAP patients.

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Author Contribution

Study design : TMA, DE
Data acquisition : AEB
Data analysis : TMA, DE, AEB
Manuscript writing : TMA, DE, AEB

Competing Interests

There is no competing interest in this study.

Abbreviation

CAP : Community Acquired Pneumonia
HAP : Hospital Acquired Pneumonia
ICU : Intensive Care Unit
MHREC : Medical and Health Research Ethics Committee
MIC : Minimum Inhibitory Concentration
VAP : Ventilator Associated Pneumonia

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