Eduvest – Journal of Universal Studies
Volume 4 Number 11, November, 2024
p- ISSN 2775-3735- e-ISSN 2775-3727

THE IMPACT OF APPROPRIATENESS OF EMPIRICAL ANTIBIOTIC IN HOSPITALIZED PNEUMONIA PATIENTS ON CLINICAL OUTCOMES AND LENGTH OF STAY

Syahrul Fath Thoriq[1], Nadia Farhanah Syafhan[1], Muhammad Luthfi Aziz[2]
[1,2] Faculty of Pharmacy, University of Indonesia, Depok, West Java, Indonesia
[2] Secretary of the Antimicrobial Resistance Control Program Committee at X Hospital, Jakarta, Indonesia
Email: nadia.farhanah@farmasi.ui.ac.id

ABSTRACT

Pneumonia is the leading cause of morbidity and mortality in adults worldwide. The incidence of pneumonia is still very high in Indonesia. The main standard therapy for pneumonia is empirical antibiotic administration. The purpose of this study was to determine whether there was an impact of the appropriateness of empirical antibiotics therapy on clinical outcomes and length of stay of non-ICU pneumonia patients at X Hospital in Jakarta. This study used a retrospective cohort design to determine the appropriateness of empirical antibiotics use in non-ICU pneumonia patients. The samples taken are all non-ICU pneumonia patients during the period January 2022 – December 2023 who met the inclusion criteria. Data analysis was carried out descriptively for patient characteristics, drug use profile, and the appropriateness of empirical antibiotic. A chi-square test was used to determine the impact of appropriateness of empirical antibiotics on clinical outcomes and length of stay. The appropriateness of empirical antibiotics obtained 59,5% (173 regimens) met category 0 (appropriate), and 40,5% (118 regimens) met category I-VI (inappropriate). Based on the results, there is an impact of the appropriateness of empirical antibiotics on clinical outcomes (P = 0,000; RR =1,916; 95% CI = 1,558 – 2,357), and impact of of the appropriateness of empirical antibiotics on length of stay (P = 0,002; RR =1,410; 95% CI = 1,126 – 1,765). The analysis's results showed that the impact of appropriateness of empirical antibiotic on clinical outcomes and length of stay of non-ICU inpatients with pneumonia at X Hospital in Jakarta.

KEYWORDS *Empirical Antibiotic, Pneumonia, Clinical Outcome, Length of Stay*

How to cite:	Syahrul Fath Thoriq, et al. (2024). The Impact of Appropriateness of Empirical Antibiotic in Hospitalized Pneumonia Patients on Clinical Outcomes and Length of Stay. *Journal Eduvest. 4*(11): 10042-10056
E-ISSN:	2775-3727

INTRODUCTION

Pneumonia is the leading cause of morbidity and mortality in adults worldwide (Fagerli et al., 2023). The incidence of pneumonia in adults can reach 14 cases per 1.000. Up to 50% of cases require hospital admission, and the mortality rate reaches 0,7 per 1.000 people per year. The World Health Organization has reported that pneumonia causes 4 million deaths each year and 7% of the total annual mortality rate (Tsoumani et al., 2023). Riskesdas data shows pneumonia sufferers in Indonesia reached 2,21% at all ages. The prevalence of pneumonia in Jakarta has increased from 0,2% (2013) to 2,2% (2018) (Kemenkes, 2018).

The incidence of pneumonia is still very high in Indonesia. According to JKN data from 2014 to 2018, pneumonia is among the top ten most hospitalized cases. (Kemenkes, 2021a). The primary standard therapy for pneumonia is the administration of empirical antibiotics, with recommendations based on guidelines to start several antibiotics depending on the severity of the patient and risk factors such as pathogens (Metlay et al., 2019).

Evaluation of the appropriateness of antibiotics using gyssens flowcharts has previously been carried out in Indonesia. Research conducted by Achmad Quraisy et al. Shows that is no relationship between the rationality of empirical antibiotics in pneumonia patients and clinical outcomes at RSUP Dr. Kariadi Hospital in Semarang. The results showed that 11,22% of antibiotic use was irrational, and 88,78% was rational antibiotic use (Aljufri et al., 2021). Results that differ from research conducted at the Gatot Subroto Army Hospital explain that there is a relationship between the rational use of antibiotics and the clinical outcomes of pneumonia patients (Hardiana et al., 2021). Recent research conducted at hospitals in Bali shows that there is no significant relationship between the appropriateness use of antibiotics and length of stay (Meriyani et al., 2024). The same result as the research conducted at the PKU Muhammadiyah Gamping Hospital showed that there was no relationship between the suitability of empirical antibiotic use and the patient's clinical outcomes, in this case, length of stay (Mujiyanti et al., 2021).

Inappropriate antibiotic use is thought to be a significant factor in the increasing incidence and spread of antibiotic resistance in hospitals. The policy on the Antibiotic Resistance Control Program contained in Permenkes No. 8 of 2015 states that hospitals are expected to implement antibiotic resistance control by auditing antibiotics (Kemenkes, 2015). In patients with infections, appropriate antibiotic use can lower mortality, shorten the length of hospital stay, and reduce healthcare costs (Rello, 2007).

Research evaluating the appropriateness of empirical antibiotics in pneumonia patients at X Hospital in Jakarta still needs to be improved. Based on this background, this study was conducted to determine whether the appropriateness of empirical antibiotic therapy impacts clinical outcomes and length of stay of pneumonia patients hospitalized in one of the Jakarta hospitals.

RESEARCH METHOD

The study design was a retrospective cohort. Samples were taken from non-ICU inpatients at X Hospital in Jakarta who were diagnosed with pneumonia from January 2022 to December 2023. The test sample in this study was limited to inclusion and exclusion criteria estimated using the two-proportion difference formula.

This research has been approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, University of Indonesia, with number KET-327/UN2.F1/ETIK/PPM.00.00/2024. This research also received permission from X Hospital in Jakarta. The data collected include the patient's initials, medical record number, clinical condition status, history of antibiotic allergies, comorbidities, antibiotic therapy, duration of antibiotic therapy, radiological data (CT-Thorax), laboratory data (leukocytes) and vital signs patient (temperature, respiratory rate).

The appropriateness of empirical antibiotic was the independent variable in this study; the dependent variables were clinical outcomes and length of stay. Confounders in this study are age, sex, comorbidities, and clinically meaningful drug interactions. Comorbidities were measured using the *Charlson Comorbidity Index* (CCI) score system method. Drug interactions of levels C, D, and X are considered clinically significant. Interaction potential was assessed using Lexicomp® Drug Interaction.

The appropriateness of empirical antibiotic therapy was assessed using the gyssens method. Empirical antibiotics are considered appropriate when classified in category 0 and inappropriate when classified in category I-VI. Category I is inappropriate because the antibiotic administration time is not right. Category II is inappropriate because of the dose, interval of administration, and route of administration. Category III is inappropriate because the duration of antibiotic administration is too short and long. Category IV is inappropriate because other antibiotic alternatives are more effective, safer/less toxic, cheaper, and narrower spectrum. Category V is inappropriate because there is no indication of antibiotic use. Category VI is inappropriate because medical record data is incomplete and cannot be evaluated. The primary guideline is the *Pedoman Penggunaan Antibiotik* (PPAB) of X Hospital in Jakarta. If the antibiotic used is not listed in the guideline, the search continues at the *American Thoracic Society and Infectious Diseases Society of America* (ATS-IDSA).

Clinical outcome assessment is declared a "good outcome" if marked by clinical improvement in therapeutic response after 72 hours of empirical antibiotic administration. Good outcomes can be observed through the doctor's decision listed in the medical record by meeting one / more criteria for improvement parameters: radiological results (Thorax X-Ray), vital signs relative to normal (respiratory rate ≤ 24x/min, and temperature 36,0-37,8◦C), leukocyte numbers relative to normal (4,500 -10,000/mm²). Clinical outcomes were declared "unfavorable outcome" (including worsening) if there was no clinical improvement in therapeutic response after 72 hours of empirical antibiotic administration. The criteria for not improving can be observed through the decision of the doctor listed in the medical record by meeting one / more criteria of the parameters not improving: Radiology results (X-ray Thorax), vital signs (respiratory rate > 24x/min, and temperature <36,0◦C or > 37,8◦C), leukocyte number (< 4,500 or >10,000/mm²). The length of stay is calculated as the number of days from hospital admission to discharge. The length of hospitalization observed in the medical record is grouped into two: short ≤ 5 days and long > 5 days.

Statistical data analysis was performed using SPSS version 23.0, where the significance value (p-value) was set <0,05, indicating a significant relationship between variables. Univariate analysis (descriptively) is used to see the characteristic picture of the patient, the profile of antibiotic use, and the appropriateness of antibiotic use based on the gyssens method. To determine the impact of the appropriateness of empirical antibiotic use on clinical outcomes and length of stay, bivariate analysis was conducted using the chi-square test with a confidence interval of 95%.

RESULT AND DISCUSSION

This study was conducted at X Hospital in Jakarta on non-ICU adult pneumonia patients undergoing hospitalization in the period January 2022 - December 2023. The number of subjects in this study was 235 patients who had met the inclusion criteria. The research data was obtained by looking at the patient's medical record. Patient characteristics are presented in Table 1 in a descriptive form consisting of age, sex, CCI score, secondary infection, and clinically meaningful drug interactions.

Table 1. Characteristics of patients

Characteristics of patients	Number of patients	
	n = 235	%
Age group		
18-59 years	115	48,9
≥60 years	120	51,1
Mean (SD)	60,28 (±21,17)	
Sex		
Male	108	46,0
Female	127	54,0
Comorbidity - CCI		
No comorbidities (0)	77	32,8
Mild (1-2)	42	17,9
Moderate (3-4)	53	22,6
Severe (≥5)	63	26,8
Secondary Infection		
Yes	44	18,7
No	191	81,3
Clinically Meaningful Drug Interactions		
Yes	105	44,7
No	130	55,3

Characteristics of Patients

Based on patient characteristics data in Table 1, the number of pneumonia patients is more prevalent in the age category ≥ 60 years (51,1%) than in the age group 18-59 years (48,9%). The average age of patients was 60,28 (±21.17) years. Elderly age has been shown to be a risk factor for pneumonia (Albrich et al., 2019). Increasing age in adults increasingly plays a role as a factor in pneumonia, including changes in the immune system, decreased functional status, and multipathology (Pelton et al., 2015). The proportion of males and females was 108 patients (46,0%) and 127 patients (54,0%), respectively. Similar data on the epidemiology of pneumonia in adults hospitalized ≥18 years old in four districts of Ulan Bator, Mongolia, 2015−2019 were more female (58,4%) than male (41,6%) (Fagerli et al., 2023).

The comorbidities in this study were infectious and non-infectious. Pneumonia patients with secondary infection (18,7%) had a smaller proportion than patients without secondary infection (81,3%). Secondary infection occur in a succession of primary infections, co-infections caused by several pathogens of viral, bacterial, or fungal origin and co-occurring at the same time (Manohar et al., 2020). The concomitant infections in this study were urinary tract infections, COVID-19 infections, and fungal infections.

Comorbidity assessment is calculated by CCI score. CCI is a method for predicting mortality by classifying or assessing the severity of comorbidities. Therefore, CCI is a valid prognostic indicator for assessing mortality in elderly patients (Charlson, 1987). Most hospitalized pneumonia patients have one or more comorbidities. Table 1 presented 32,8% of patients with no comorbidities, 17.9% patients with CCI scores of 1-2 (mild), 22,6% patients with CCI scores of 3-4 (moderate), and 26,8% patients with CCI scores of ≥ 5 (severe).

Drug interaction studies suggest that polypharmacy is a risk factor for potential drug-drug interactions. The level of risk increases with the amount of drugs used simultaneously. The study found that the amount of antibiotics and several other drugs used was associated with a higher risk of potential drug-drug interactions. Improper use of antimicrobials can cause this to lead to unwanted drug side effects and high costs (Kuscu et al., 2018). Table 1 shows clinically meaningful drug interactions, 44,7%, and the remaining 55,3% have no drug interactions. Drug interactions measured are potential drug-drug interactions (PDDI) with antibiotics. Therefore, healthcare professionals should know all predictors increasing the risk of PPDI to individualize patients more at risk, optimize medication therapy, and minimize or prevent PPDI (Kuscu et al., 2018).

Empirical Antibiotic Use Profile

Antibiotics are the leading standard of therapy in pneumonia cases. The selection of antibiotic therapy for patients is individual, either monotherapy or combination (PDPI, 2014). In this study, the use of antibiotics is empirical. In administering empirical antibiotic therapy to patients, X Hospital in Jakarta uses the main guideline, namely PPAB. Table 2 shows the distribution of empirical antibiotics used in patients during the study period.

Of the 235 patients who met the inclusion criteria, 291 antibiotic regimens were obtained. Table 2 shows 179 patients (76%) receiving monotherapy antibiotics while 56 patients (24,0%) receiving combination antibiotics. The most widely used antibiotic, monotherapy or combination, is the fluoroquinolone group (47,4%). Moxifloxacin (23,4%), a fluoroquinolone group, is the first choice and most widely used as monotherapy in the treatment of pneumonia. Using moxifloxacin as empirical therapy is one of the pneumonia therapy options based on Hospital X PPAB and ATS-IDSA. Moxifloxacin has excellent broad-spectrum antibacterial activity against Gram-negative bacilli (Enterobacteriaceae, H. influenzae, M. catarrhalis) and increases activity against Gram-positive S. pneumoniae and S. aureus versus ciprofloxacin (Ferrara, 2007).

The most common combination antibiotic was moxifloxacin with meropenem (9.8%). The administration of combination antibiotics aims to broaden the spectrum of antibiotics, achieve a synergistic effect, and suppress the emergence of resistance. Indications of a combination of antibiotics are used as an empirical treatment for severe infections or when many bacteria may cause the infection. A consideration when choosing a combination is that antibiotics work on different targets, which can increase or decrease overall antibiotic activity (Kemenkes, 2021b). The results of this study are supported by a study reporting that fluoroquinolone antibiotic combination therapy improved survival in critically ill patients with pneumonia compared to those given beta-lactam monotherapy (Baddour et al., 2004).

Evaluation of Appropriateness of Empirical Antibiotic by Gyssens Category

Evaluate the quality of antibiotics by assessing the appropriateness of empirical antibiotic use. The assessment uses the gyssens flow method, which consists of categories I-VI. Completeness of patient data is needed as a reference for evaluation in each gyssens category (Gyssens, 2001) . Based on Table 3, the evaluation results of the appropriate use of antibiotics with the gyssens method obtained the proper antibiotic regimen (category 0) of 59,5%. In comparison, the inappropriate antibiotic regimen (category I-VI). was 40,5%. A study conducted by Kamila et al. shows the use of antibiotics as empirical therapy for CAP. In this study, it can be concluded that a rate of 85,6% of appropriate antibiotic use and 14,4% in other categories (category I-VI) (Kamila et al., 2021).

Table 2. Empirical Antibiotic Use Profile

Antibiotics	Number	%
Types of Antibiotics		
Monotherapy	179	76,0
Combination	56	24,0
Class of Antibiotics		
Carbapenem	85	29,2
Floroquinolones	138	47,4
Macrolides	2	0,7
Penicillin	3	1,0
Cephalosporin	62	21,3
Another (Fosfomycin)	1	0,3
Monotherapy		
Ampicillin - sulbactam	1	0,4
Cefepime	7	3,0
Cefoperazone - sulbactam	7	3,0
Cefotaxime	1	0,4
Ceftazidime	7	3,0
Ceftizoxime	5	2,1
Ceftriaxone	19	8,1
Cilastatin, imipenem	2	0,9
Ciprofloxacin	3	1,3
Levofloxacin	26	11,1
Meropenem	44	18,7
Moxifloxacin	55	23,4
Piperacillin, tazobactam	2	0,9
Combination		
Levofloxacin + cefoperazone sulbactam	2	0,9
Levofloxacin + ceftazidime	1	0,4
Levofloxacin + ceftriaxone	6	2,6

Levofloxacin + meropenem	15	6,4
Meropenem + azithromycin	1	0,4
Meropenem + fosfomycin	1	0,4
Moxifloxacin + azitromisin	1	0,4
Moxifloxacin + cefepime	3	1,3
Moxifloxacin + cefoperazone	1	0,4
Moxifloxacin + cefoperazone sulbactam	1	0,4
Moxifloxacin + ceftazidime	1	0,4
Moxifloxacin + meropenem	23	9,8
TOTAL	**235**	**100**

The most inappropriate antibiotics are in category IIIB (use of antibiotics too short), at as much as 1,.8%. The use of antibiotics needs to be longer, which means that the use of antibiotics is shorter than the standard guidelines used as a reference. In this study, it was said that the administration of antibiotics needed to be longer, less than three days. This is supported by research conducted by Elshenawy et al., which states that short-term antibiotics of 3-5 days for CAP and ≤8 days are enough for nosocomial pneumonia as effective as conventional treatment. The research contributes to antimicrobial management efforts promoting global commitments to suppress antibiotic resistance (Elshenawy et al., 2024). Meanwhile, most studies state that antibiotic therapy lasts 5 days for CAP (Metlay et al., 2019).

Category I is the inappropriate timing of antibiotic administration in 13,7% of regimens. The correct timing of antibiotic administration is critical, based on the ability to kill time-dependent antibiotics (penicillin, cephalosporins, monobactams, carbapenems, macrolides, and clindamycin) determined by the length of time the drug remains in its binding site and is optimal if the drug level in the blood is always at above the MIC in the interval between doses. Therefore, with time-dependent antibiotics, small doses are usually given at short intervals, for example, every 6 to 8 hours (Jacobs, 2001).

As many as 6,9% of regimens fall into category IIA (inappropriate drug dosage). The dose was not correct in this study because the antibiotic therapy regimen required dose adjustments for the patient's condition with kidney disorders. Studies of renal failure patients suggest dose adjustment to be a significant factor in achieving favorable clinical outcomes (Sridhara et al., 2020).

In category IV, 8 antibiotic regimens are included in category IVa (other antibiotics are more effective). Categories IVb, IVc, and IVd for all samples are considered appropriate. Inappropriate antibiotic selection not only increases mortality and morbidity but has other negative impacts. Impact These negatives include requiring additional days of hospitalization, additional testing costs, expensive isolation, and other infection control measures, and can influence the choice of subsequent empiric antibiotics, resulting in higher drug costs (Davey, 2008).

This study did not include patients in category VI because samples with missing data were excluded. None of the samples fell into category V because all of the patient's medical records were diagnosed with pneumonia with indications for administration of antibiotics. No samples were included in category IIIa because the duration of antibiotic administration in all patients was considered appropriate to the patient's clinical outcome. There are no samples included in category IIb because the antibiotic administration interval is deemed appropriate, and there are also no samples included in category IIc because the route of drug administration is considered appropriate.

Table 3. Evaluation of Appropriateness of Empirical Antibiotic by Gyssens Category
*IVc: No assessment was carried out

Gyssens Category	Number of Sample n = 291 (%)
Appropriate	
Category 0	173 (59,5)
Inappropriate	
Category VI (insufficient data)	0
Category V (inappropriate indication)	0
Category IVa (other antibiotics are more effective)	9 (3,0)
Category IVb (other antibiotics are less toxic)	0
Category IVc (other antibiotics less costly)	0*
Category IVd (other antibiotics have a narrower spectrum)	0
Category IIIa (duration too short)	0
Category IIIb (duration too long)	49(16,8)
Category IIa (incorrect dose)	20 (6,9)
Category IIb (incorrect interval)	0
Category IIc (incorrect rute)	0
Category I (incorrect timing)	40 (13,7)

Table 4. The Impact of Appropriateness of Empirical Antibiotic on Clinical Outcomes

Antibiotic Appropriateness	Clinical Outcomes: Good outcome n	%	Unfovarable outcome n	%	Total	P	RR	95% CI
Appropriate	137	58,30	6	2,55	143 (60,85)	,000	1,916	(1,558-2,357)
Inappropriate	46	19,57	46	19,57	92 (39,15)			
Total	**183**		**52**		**235**			

The Impact of Appropriateness of Empirical Antibiotic on Clinical Outcomes

The results of the assessment of the appropriateness of empiric antibiotic therapy that had been carried out were then sought for its influence on the clinical outcomes of pneumonia patients hospitalized at Hospital X Jakarta. The analysis of the relationship between these two variables can be seen in Table 4. Table 4 shows that 58,30% of the correct regimens provide improved clinical outcomes, and 19,57% of inappropriate regimens provide enhanced clinical outcomes.

Table 4 also shows a significant influence between the appropriateness of empirical antibiotics and clinical outcomes with a p-value of 0,000 ($p < 0.05$), RR value of 1,916, and 95% CI (1,558-2,357). This is also supported by the assertion that antibiotic management is appropriate for patients with CAP, which can help ensure responsible antibiotic use and optimal antimicrobial-related clinical outcomes (Viasus et al., 2017).

Many studies have been conducted regarding the relationship between the appropriateness of antibiotic use and therapeutic outcomes, but the results still vary.

The research conducted at RSUD. Dr. H. Abdul Moeloek Hospital stated that there is a significant relationship (p = 0,003) between the rational use of antibiotics and patient clinical outcomes (Widiyastuti et al., 2023). In line with research conducted by Gunduz et al., it shows that one of the factors in the failure of pneumonia treatment is the inappropriate use of antibiotics (Gunduz et al., 2016). The study's by Aryanti results suggest that using appropriate antibiotics according to clinical practice guidelines in CAP patients with Type 2 DM significantly impacts clinical outcomes (Ariyanti et al., 2022).

Meanwhile, other research conducted at RSUP Dr. Kariadi Hospital in Semarang showed no relationship between rational antibiotics and patient clinical outcome (Aljufri et al., 2021). The results of this research are also in line with research conducted at PKU Muhmamdiyah Hospital, Yogyakarta (Fatia et al., 2021).

The Impact of Appropriateness of Empirical Antibiotic on Length of Stay

The length of stay in this study is the time required to inpatient a patient at X Hospital in Jakarta. Based on Tab. 5, 43.83% of the appropriate regimens gave a short stay, namely ≤ 5 days, while 20% of inappropriate regimens gave a short stay. Research conducted at PKU Muhammadiyah Gamping Hospital showed that the average length of patient stay was ≤5 days by 52 patients (65,8%) and >5 days by 27 patients (34,2%) (Mujiyanti et al., 2021). As recent data support a 5-day course of antibiotics, treating patients for at least 5 days on a risk-benefit basis is recommended, even if their medical history is stable for 5 days. Most patients' total treatment duration is 5 days, as most patients achieve clinical stability within the first 48 to 72 hours (Metlay et al., 2019).

These results reinforce the research conducted by Munarsih et al., which statistically shows that empirical antibiotic administration affects the length of stay in community pneumonia patients treated based on antibiotic use guideline (Munarsih et al., 2018). Similar studies have also demonstrated that the use of appropriate antibiotics is associated with shorter length of hospitalization (Bosch et al., 2017).

This is different from other research, which states there is no such thing as a significant association between the appropriateness of antibiotic use and prolonged hospitalization (prolonged length of stay) (Meriyani et al., 2024).

Table 5. The Impact of Appropriateness of Empirical Antibiotic on Length of Stay

Antibiotic Appropriateness	Length of Stay				Total	P	RR	95% CI
	≤ 5 days		>5 days					
	n	%	n	%				
Appropriate	103	43.83	40	17.02	143	.002	1.410	(1.126-1.765)
Inappropriate	47	20.00	45	19.15	92			
Total	**150**		**95**		**235**			

The Impact of Cofounders to Clinical Outcomes

Table 6. shows the results of statistical tests for the three variables with a p-value < 0,05. These results indicate that age, CCI (non-infectious comorbidities) and secondary infection can impact the patient's clinical outcomes. Meanwhile, gender and clinically significant drug interactions do not relationship clinical outcomes. This is supported by the statement that higher CCI scores (more comorbidities) were associated with an increased risk of all-cause in-hospital mortality, and this association remained after controlling for confounders (Nguyen et al., 2019). In contrast, Cilli et al. conducted a study in a Turkish hospital on adult patients with a diagnosis of CAP, showing that there was no relationship between age with comorbidities and clinical outcomes, with a p value of >0.05 (Çilli et al., 2018). Tambun et al. conducted research stating that secondary infections did not impact clinical outcomes (Tambun et al., 2019).

Table 6. The impact of cofounders to clinical outcomes

Characteristics of patients	Clinical Outcome n = 235				P
	Good Outcome		Unforavable Outcome		
	n	%	n	%	
Age group					
18-59 years	101	87,8	14	12,2	0,001
≥60 years	82	68,3	38	31,7	
Sex					
Male	88	81,5	20	18,5	0,284
Female	95	74,8	32	25,2	
Comorbidity – CCI (Non-Infection)					
No comorbidities (0)	73	94,8	4	5,2	0,000
Mild (1-2)	32	76,2	10	23,8	
Moderate (3-4)	42	79,2	11	20,8	
Severe (≥5)	36	57,1	27	42,9	
Secondary Infection					
No	157	82,2	34	17,8	0,002
Yes	26	59,1	18	40,9	
Clinically Meaningful Drug Interactions					
No	104	80,0	26	20,0	0,474
Yes	79	75,2	26	24,8	

The Impact of Cofounders to Length of Stay

Table 7 shows the statistical test results of both variables (age and CCI/comorbidities) have a p-value of <0.05. These results show that age and CCI (comorbidities) can impact the length of stay. Sex, secondary infections, and clinically meaningful drug interactions did not impact the length of stay. This is supported by research conducted by Bosch et al., that age and comorbidities are cofounders that impact the length of stay, while gender does not affect the length of stay (Bosch et al., 2017). Research conducted by Corridori et al., shows that the predictors that influence the length of stay in pneumonia patients are age and gender (Lüthi-Corridori et al., 2023).

Table 7. The Impact of cofounders to length of stay

Characteristics of patients	Length of stay n = 235				P
	≤ 5 days		> 5 days		
	n	%	n	%	
Age					
18-59 years	82	71,3	33	28,7	0,028
≥60 years	68	56,7	52	43,3	
Sex					
Male	74	68,5	34	31,5	0,214
Female	76	59,8	51	40,2	
Comorbidity - CCI					
No comorbidities (0)	64	83,1	13	16,9	0,000
Mild (1-2)	23	54,8	19	45,2	
Moderate (3-4)	35	66,0	18	34,0	
Severe (≥5)	28	44,4	35	55,6	
Secondary Infection					
No	128	67,0	63	33,0	0,052
Yes	22	50,0	22	50,0	
Clinically Meaningful Drug Interactions					
No	87	66,9	42	33,1	0,336
Yes	63	60,0	43	40,0	

The limitation of this research is that the data was collected retrospectively, so the researchers needed to see the clinical condition of the patient and the reasons for choosing antibiotics. The lack of medical record information that mentions CAP or hospital-acquired pneumonia (HAP) is also a limitation for researchers. This research also uses a limited local sample size, soit cannot be generalized. Further research that is more specific to pneumonia cases and on a large scale involving samples from multicentre is necessary.

CONCLUSION

The appropriateness of empiric antibiotics in non-ICU inpatient pneumonia patients at X Hospital evaluated using the gyssens method showed that 59,5% of the empirical antibiotics given were appropriate. The remaining 40, 5% of inappropriate antibiotics are caused by the presence of other more effective antibiotics or too short a duration, dose, and time of drug administration. The statistical analysis results show an impact of the appropriateness of empirical antibiotics in non-ICU hospitalized pneumonia patients on clinical outcomes and length of stay.

REFERENCES

Albrich, W. C., Rassouli, F., Waldeck, F., Berger, C., & Baty, F. (2019). Influence of Older Age and Other Risk Factors on Pneumonia Hospitalization in Switzerland in the Pneumococcal Vaccine Era. *Frontiers in Medicine*, *6*(December), 1–10. https://doi.org/10.3389/fmed.2019.00286

Aljufri, A. Q., Yasin, N. M., & Wahyono, D. (2021). Rasionalitas Terapi Antibiotik Empiris Pada Pasien Pneumonia di Instalasi Rawat Inap RSUP Dr. Kariadi Semarang. *Majalah Farmaseutik*, *17*(1), 89. https://doi.org/10.22146/farmaseutik.v17i1.53702

Ariyanti, D., Sauriasari, R., & Yunir, E. (2022). Evaluation of Current Practice of Antibiotic Use and Clinical Outcomes of Community-Acquired Pneumonia Patients with Type 2 Diabetes Mellitus at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. *Indonesian Journal of Pharmacy*, *33*(4), 583–591. https://doi.org/10.22146/ijp.3572

Baddour, L. M., Yu, V. L., Klugman, K. P., Feldman, C., Ortqvist, A., Rello, J., Morris, A. J., Luna, C. M., Snydman, D. R., Wen, C. K., Chedid, M. B. F., Hui, D. S., Andremont, A., Chiou, C. C. C., Mosquera, R., De Mier, C., Famiglietti, A., Vay, C., Gentile, J., … Rihs, J. D. (2004). Combination Antibiotic Therapy Lowers Mortality among Severely Ill Patients with Pneumococcal Bacteremia. *American Journal of Respiratory and Critical Care Medicine*, *170*(4), 440–444. https://doi.org/10.1164/rccm.200311-1578OC

Bosch, C. M. A. Van Den, Hulscher, M. E. J. L., Akkermans, R. P., Wille, J., Geerlings, S. E., & Prins, J. M. (2017). *Appropriate antibiotic use reduces length of hospital stay*. *December 2016*, 923–932. https://doi.org/10.1093/jac/dkw469

Charlson, et al. (1987). *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation*. Journal of Chronic Diseases.

Çilli, A., Sayiner, A., Çelenk, B., Şakar Coşkun, A., Kilinç, O., Hazar, A., Aktaş Samur, A., Taşbakan, S., Waterer, G. W., Havlucu, Y., Kiliç, Ö., Tokgöz, F., & Bilge, U. (2018). Antibiotic treatment outcomes in community-acquired pneumonia. *Turkish Journal of Medical Sciences*, *48*(4), 730–736. https://doi.org/10.3906/sag-1709-144

Davey, P. G. (2008). Appropriate vs. inappropriate antimicrobial therapy. *Clinical Microbiology and Infection*, *14*(SUPPL. 3), 15–21. https://doi.org/10.1111/j.1469-0691.2008.01959.x

Elshenawy, R., Umaru, N., & Aslanpour, Z. (2024). Shorter and Longer Antibiotic Durations for Respiratory Infections: To Fight Antimicrobial Resistance—A Retrospective Cross-Sectional Study in a Secondary Care Setting in the UK. *Pharmaceuticals*, *17*(3). https://doi.org/10.3390/ph17030339

Fagerli, K., Ulziibayar, M., Suuri, B., Luvsantseren, D., Narangerel, D., Batsaikhan, P., Tsolmon, B., Gessner, B. D., Dunne, E. M., Grobler, A. C., Nguyen, C. D., Mungun, T., Mulholland, E. K., & Mollendorf, C. Von. (2023). Articles Epidemiology of pneumonia in hospitalized adults ≥ 18 years old in four districts of Ulaanbaatar ,. *The Lancet Regional Health - Western Pacific*, *30*, 100591. https://doi.org/10.1016/j.lanwpc.2022.100591

Fatia, ;, Supadmi Woro, Perwitasari Dyah Aryani, & Yuniarti Endang. (2021). Hubungan Ketepatan Peresepan Antibiotik dengan Metode Gyssens dengan Perbaikan Klinis Pasien Rawat Inap Pneumonia Komunitas. *Jurnal Ilmu Kefarmasian Indonesia*, *19*(1), 30–38.

Ferrara, A. M. (2007). A brief review of moxifloxacin in the treatment of elderly patients with community-acquired pneumonia (CAP). *Clinical Interventions in Aging*, *2*(2), 179–187.

Gunduz, C., Taşbakan, M. S., Sayiner, A., Çilli, A., Kilinç, O., & Şakar Coşkun, A. (2016). Factors affecting treatment success in community-acquired pneumonia. *Turkish Journal of Medical Sciences*, *46*(5), 1469–1474. https://doi.org/10.3906/sag-1502-87

Gyssens, I. C. (2001). Quality of antimicrobial drug prescription in hospital. *Clinical Microbiology and Infection*, *7*(SUPPL. 6), 12–15. https://doi.org/10.1046/j.1469-0691.2001.00079.x

Hardiana, I., Ratih Laksmitawati Dian, Ramadaniati Hesty utami, & sutarno. (2021). Evaluasi Penggunaan Antibiotika Pada Pasien Pneumonia Komunitas Di Instalasi Rawat Inap Rspad Gatot Subroto. *Majalah Farmasi Dan Farmakologi*, *25*(1), 1–6. https://doi.org/10.20956/mff.v25i1.11555

Jacobs, M. R. (2001). Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. *Clinical Microbiology and Infection*, *7*(11), 589–596. https://doi.org/10.1046/j.1198-743X.2001.00295.x

Kamila, R. S., Rochmanti, M., & Bakhtiar, A. (2021). Appropriate antibiotic use for community-acquired pneumonia in inpatient settings and its impact on 30-days readmission and mortality rate. *Indian Journal of Forensic Medicine and Toxicology*, *15*(1), 2765–2772. https://doi.org/10.37506/ijfmt.v15i1.13817

Kemenkes. (2015). Progran Pengendalian Resistensi Antimikroba. *Peraturan Menteri Kesehatan Republik Indonesia Nomor 8*, *151*, 10–17.

Kemenkes. (2018). Riskendas 2018. *Laporan Nasional Riskesndas 2018*, *44*(8), 181–222.

Kemenkes. (2021a). Pedoman Nasional Pelayanan Kedokteran Tata Laksana Pneumonia. *Kementerian Kesehatan RI*, 1–85.

Kemenkes. (2021b). Pedoman Penggunaan Antibiotik. *Permenkes RI*, 1–97.

Kuscu, F., Ulu, A., Inal, A. S., Suntur, B. M., Aydemir, H., Gul, S., Ecemis, K., Komur, S., Kurtaran, B., Kuscu, O. O., & Tasova, Y. (2018). Potential drug–drug interactions with antimicrobials in hospitalized patients: A multicenter point-prevalence study. *Medical Science Monitor*, *24*, 4240–4247. https://doi.org/10.12659/MSM.908589

Lüthi-Corridori, G., Boesing, M., Roth, A., Giezendanner, S., Leuppi-Taegtmeyer, A. B., Schuetz, P., & Leuppi, J. D. (2023). Predictors of Length of Stay, Rehospitalization and Mortality in Community-Acquired Pneumonia Patients: A Retrospective Cohort Study. *Journal of Clinical Medicine*, *12*(17). https://doi.org/10.3390/jcm12175601

Manohar, P., Loh, B., Athira, S., Nachimuthu, R., Hua, X., Welburn, S. C., & Leptihn, S. (2020). Secondary Bacterial Infections During Pulmonary Viral Disease: Phage Therapeutics as Alternatives to Antibiotics? *Frontiers in*

Microbiology, *11*(June), 1–11. https://doi.org/10.3389/fmicb.2020.01434

Meriyani, H., Sanjaya, D. A., Juanita, R. A., & Siada, N. B. (2024). Kualitas Penggunaan Antibiotik pada Pasien Community-Acquired Pneumonia di Salah Satu Rumah Sakit di Bali. *Jurnal Ilmiah Medicamento*, *10*(1), 35–42. https://doi.org/10.36733/medicamento.v10i1.7592

Metlay, J. P., Waterer, G. W., Long, A. C., Anzueto, A., Brozek, J., Crothers, K., Cooley, L. A., Dean, N. C., Fine, M. J., Flanders, S. A., Griffin, M. R., Metersky, M. L., Musher, D. M., Restrepo, M. I., & Whitney, C. G. (2019). Diagnosis and treatment of adults with community-acquired pneumonia. *American Journal of Respiratory and Critical Care Medicine*, *200*(7), E45–E67. https://doi.org/10.1164/rccm.201908-1581ST

Mujiyanti, M., Perwitasari, D. A., Darmawan, E., & Risdiana, I. (2021). Evaluasi Kesesuaian Pemberian Antibiotik Empiris Terhadap Antibiogram dan Luaran Klinis pada Pasien Pneumonia Dewasa. *Jurnal Ilmu Kefarmasian Indonesia*, *19*(1), 102. https://doi.org/10.35814/jifi.v19i1.920

Munarsih, F. C., Natadidjaja, R. I., & Syamsudin, S. (2018). Pengaruh Pemberian Antibiotik berdasar Panduan terhadap Lama Tinggal pada Pasien Pneumonia Komunitas di Rumah Sakit. *Jurnal Penyakit Dalam Indonesia*, *5*(3), 141. https://doi.org/10.7454/jpdi.v5i3.195

Nguyen, M. T. N., Saito, N., & Wagatsuma, Y. (2019). The effect of comorbidities for the prognosis of community-acquired pneumonia: An epidemiologic study using a hospital surveillance in Japan. *BMC Research Notes*, *12*(1), 1–5. https://doi.org/10.1186/s13104-019-4848-1

Pelton, S. I., Shea, K. M. S., & Weycker, D. (2015). *Rethinking Risk for Pneumococcal Disease in Adults: The Role of Risk Stacking*. *2*(September), 2633851. https://doi.org/10.1093/o

Rello, J. (2007). Importance of appropriate initial antibiotic therapy and de-escalation in the treatment of nosocomial pneumonia. *European Respiratory Review*, *16*(103), 33–39. https://doi.org/10.1183/09059180.00010302

Sridhara, S., Raj, E., Chandra, P., A Ravindra - Authorea, & 2020, U. (2020). Dose Optimization of Antibiotics in Renally Impaired Patients in Indian Settings: A Prospective Observational Study. *Authorea.Com*, 1–5.

Tambun, S. H., Puspitasari, I., & Laksanawati, I. S. (2019). Evaluasi Luaran Klinis Terapi Antibiotik pada Pasien Community Acquired Pneumonia Anak Rawat Inap. *JURNAL MANAJEMEN DAN PELAYANAN FARMASI (Journal of Management and Pharmacy Practice)*, *9*(3), 213. https://doi.org/10.22146/jmpf.47915

Tsoumani, E., Carter, J. A., Salomonsson, S., Stephens, J. M., Tsoumani, E., Carter, J. A., Salomonsson, S., & Stephens, J. M. (2023). Expert Review of Vaccines Clinical , economic , and humanistic burden of community acquired pneumonia in Europe : a systematic literature review Clinical , economic , and humanistic burden of community acquired pneumonia in Europe : a systematic literatur. *Expert Review of Vaccines*, *22*(1), 876–884. https://doi.org/10.1080/14760584.2023.2261785

Viasus, D., Vecino-Moreno, M., De La Hoz, J. M., & Carratalà, J. (2017). Antibiotic stewardship in community-acquired pneumonia. *Expert Review of*

Anti-Infective Therapy, *15*(4), 351–359. https://doi.org/10.1080/14787210.2017.1274232

Widiyastuti, A., Kumala, S., R, H. U., & Pratama, A. (2023). *Hubungan Rasionalitas Penggunaan Antibiotik terhadap Luaran Klinis Pasien Pneumonia Komunitas Rawat Inap The Relationship between the Rational Use of Antibiotics and the Clinical Outcomes of Community Pneumonia Acquired Patients*. *14*(1), 109–116.