ORIGINAL ARTICLE

ASSOCIATION BETWEEN TIME OF INITIATING EMPIRICAL ANTIBIOTIC AND OUTCOMES IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

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ABSTRACT

Background: Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality worldwide, with a significant burden in Indonesia. Early initiation of empirical antibiotics is considered crucial in improving outcomes, yet evidence has been inconsistent and local data are lacking. Objective of this study is to evaluate the association between the timing of empirical antibiotic initiation and clinical outcomes, specifically mortality and length of hospital stay, among CAP patients at RS Ngoerah, Denpasar.
Methods: A prospective observational study was conducted on adult inpatients with CAP between January and June 2024. Patients were stratified into two groups based on antibiotic initiation time: ≤4 hours and >4 hours after admission. Data were analyzed using Chi-square, Logistic regression, and Linier regression to adjust for confounders, including age, sex, comorbidities, and disease severity.
Results: A total of 235 patients were enrolled. Early antibiotic initiation (≤4 hours) significantly reduced 30-day mortality compared to delayed administration (>4 hours) (adjusted OR 4,97; 95% CI 1,50–16,47; p<0.05). No statistically significant difference was observed in the length of hospital stay (median 5 vs 5 days; p=0.95). Length of stay was more influenced by comorbidities, and antibiotic used.
Conclusion: Empirical antibiotic initiation later than 4 hours is associated with increase mortality in CAP patients, although it does not significantly affect length of hospital stay. These findings highlight the importance of timely antibiotic administration to improve clinical outcomes in CAP.
Keywords: community-acquired pneumonia, antibiotics, timing, mortality, hospital stay

ABSTRAK

Latar Belakang: Pneumonia yang didapat di komunitas (CAP) tetap menjadi penyebab utama morbiditas dan mortalitas di seluruh dunia, dengan beban yang signifikan di Indonesia. Inisiasi antibiotik empiris dini dianggap penting dalam meningkatkan hasil, namun bukti yang ada masih belum konsisten dan data lokal masih kurang. Tujuan penelitian ini adalah untuk mengevaluasi hubungan antara waktu inisiasi antibiotik empiris dan hasil klinis, khususnya mortalitas dan lama rawat inap, pada pasien CAP di RS Ngoerah, Denpasar.
Metode: Sebuah studi observasional prospektif dilakukan pada pasien rawat inap dewasa dengan CAP antara Januari dan Juni 2024. Pasien dikelompokkan menjadi dua kelompok berdasarkan waktu inisiasi antibiotik: ≤4 jam dan >4 jam setelah masuk rumah sakit. Data dianalisis menggunakan uji Chi-square, regresi logistik, dan regresi linier untuk menyesuaikan faktor perancu, termasuk usia, jenis kelamin, komorbiditas, dan tingkat keparahan penyakit.
Hasil: Sebanyak 235 pasien diikutsertakan. Pemberian antibiotik dini (≤4 jam) secara signifikan mengurangi angka kematian 30 hari dibandingkan dengan pemberian yang terlambat (>4 jam) (OR yang disesuaikan 4,97; 95% CI 1,50–16,47; p<0,05). Tidak ada perbedaan yang signifikan secara statistik yang diamati pada lama rawat inap (median 5 vs 5 hari; p=0,95). Lama rawat inap lebih dipengaruhi oleh komorbiditas dan antibiotik yang digunakan.
Kesimpulan: Pemberian antibiotik empiris lebih dari 4 jam dikaitkan dengan peningkatan angka kematian pada pasien CAP, meskipun tidak secara signifikan memengaruhi lama rawat inap. Temuan ini menyoroti pentingnya pemberian antibiotik tepat waktu untuk meningkatkan hasil klinis pada CAP.
Kata kunci: pneumonia komunitas, antibiotik, waktu pemberian, angka kematian, lama rawat inap

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INTRODUCTION

Pneumonia is a lung parenchyma infection caused by various pathogens and remains a leading cause of global morbidity and mortality.[1] Community-acquired pneumonia (CAP) is acquired outside hospital settings, ranging clinically from mild symptoms to severe respiratory distress and sepsis. In 2019, lower respiratory infections caused approximately 2.5 million deaths globally (CDR: 33.6/100,000), ranking as the fourth leading cause of mortality.[2] Indonesia's 2018 RISKESDAS reported over 1 million annual pneumonia cases, peaking in West Java and among those aged over 75. Nationally, pneumonia is a top ten cause of hospital admission with a 7.6% mortality rate,[3] though studies at RSCM Jakarta report higher mortality between 15.5% and 24.8%.[4] While CAP etiology varies globally, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* are the most frequent isolates in Indonesia.[5] At Ngoerah Hospital (2022), *K. pneumoniae* predominated (21.7%), followed by *A. baumannii* (19.3%) and *P. aeruginosa* (17.1%). Testing showed *K. pneumoniae* maintains high sensitivity (>80%) to amikacin, cefepime, carbapenems, piperacillin–tazobactam, and tigecycline. Timely antibiotic administration is the cornerstone of CAP management, with empirical therapy guided by disease severity, care setting, and resistance risks.[6] Regimens range from oral macrolides for outpatients to intravenous beta-lactam/macrolide combinations for ICU patients, potentially including antipseudomonal or anti-MRSA agents. Selection should ultimately be tailored to local antimicrobial resistance patterns. Timely initiation of empirical antibiotics is crucial because clinical and radiological findings are often nonspecific for determining etiology. However, premature administration of antibiotics before confirming a working diagnosis of bacterial pneumonia may contribute to antimicrobial resistance.[6] Several independent prognostic factors for CAP mortality have been identified, including disease severity, older age, comorbidities, microbial etiology, antibiotic selection, and timing of antibiotic initiation.[7–10]

Evidence regarding the impact of early antibiotic initiation remains mixed. A retrospective study of 13,771 Medicare patients found that antibiotic initiation within four hours of hospital arrival was associated with lower mortality (6.8% vs. 7.4%) and shorter hospital stays (by 0.4 days) compared with delayed therapy.[11] Similarly, a study of 13,725 patients reported lower adjusted 30-day mortality among those receiving antibiotics within four hours.[12] Conversely, a large U.S. cohort study involving 95,704 pneumonia patients found no significant association between timely antibiotic initiation and mortality.[13] These inconsistencies suggest that early antibiotic administration does not always guarantee better outcomes and may be influenced by variations in microbial etiology. Moreover, unintended consequences such as diagnostic errors, increased healthcare costs, and unnecessary antibiotic exposure with subsequent resistance must be considered.[13] To date, few published studies have evaluated the timing of antibiotic initiation and outcomes in CAP patients in Indonesia. Given the clinical relevance of this issue, the present study was designed to investigate the relationship between the timing of empirical antibiotic initiation and outcomes among patients with community-acquired pneumonia at RS Ngoerah General Hospital, Denpasar.

METHOD

This study is an observational analytic research with a prospective cohort design, aimed at determining the relationship between the timing of empirical antibiotic initiation (<4 hours vs. ≥4 hours) and outcomes in patients with community-acquired pneumonia (CAP). The study was conducted in the inpatient wards of Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, between August and October 2024. Patients were followed for 30 days after admission. The target population was all adult CAP inpatients. The study sample inclusion criteria: adults >18 years with a working diagnosis of bacterial CAP and who agreed to participate. Exclusion criteria:bpatients who had received antibiotics

before referral, those with systemic lupus erythematosus (SLE), and patients who discharged themselves against medical advice. Sampling was performed by consecutive sampling until the required sample size was achieved.

The independent variable was the timing of empirical antibiotic initiation (<4 hours or ≥4 hours after admission). Dependent variables were 30-day mortality, length of stay, duration of antibiotic therapy, and readmission within 30 days. Potential confounding variables included age, sex, comorbidities, pneumonia severity (based on IDSA/ATS 2007 criteria), PSI score, and sputum culture results. Data were collected from medical records, including demographics, clinical characteristics, laboratory results, antibiotic administration time, and patient outcomes. Statistical analysis was performed using SPSS version 25. Descriptive statistics were presented as mean ± SD or median (IQR) for numerical variables and as frequencies and percentages for categorical variables. The Chi-square test (or Fisher's exact test when appropriate) was used to analyze the association between antibiotic timing and mortality.

RESULT

During the study period, 328 patients with community-acquired pneumonia were hospitalized at Ngoerah Hospital. After applying the inclusion and exclusion criteria, 67 patients were excluded (46 had received prior antibiotics, 3 had SLE, 1 left against medical advice, and 17 had incomplete data). A total of 261 eligible patients were enrolled, comprising 46 patients in the ≤4-hour antibiotic initiation group and 215 in the >4-hour group. During the 30-day follow-up, 25 patients were lost to follow-up. After removing extreme values, 235 patients (41 in the ≤4-hour group and 194 in the >4-hour group) were included in the final analysis. The mean age of the cohort was 54.2 ± 14.9 years, with 78% aged ≤65 years, and 62.9% were male. Non-severe pneumonia accounted for 61.6% of cases. There were 54 deaths (23%). The median length of hospital stay was 5 days (range: 1–10), and the median time to antibiotic initiation was 9.79 hours (range: 0.28–23.82), with medians of 3.21 hours in the ≤4-hour group and 8.97 hours in the >4-hour group.

Table 1: Baseline characteristics of subjects according to timing of antibiotic administration

Variable	All Sample	Time of Antibiotic Initiation		p value
		≤4hours	>4hours	
Age; years, (Mean±SD)	54,2 ± 14,9	55,3 ± 17,4	54,1 ± 14,6	0,71
<65 tahun (N, %)	181 (78)	17 (9,4)	164 (90,6)	0,36
≥65 tahun (N, %)	51 (22)	7 (13,7)	44 (86,3)	
Sex				0,06
Female (N, %)	86 (37,1)	13 (15,1)	73 (84,9)	
Male (N, %)	146 (62,9)	11 (7,5)	135 (92,5)	
Pneumonia Severity				0,72
Non-severe (N, %)	143 (61,6)	14 (9,8)	129 (90,2)	
Severe (N, %)	89 (38,4)	10 (11,2)	79 (88,8)	
Mortality				0,03
Death (N, %)	181 (77)	37 (20,4)	144 (79,6)	
Alive (N, %)	54 (23)	4 (7,4)	50 (92,6)	
Length of Care; Days (Median (Minimum-Maximum)	5,0 (1 - 10)	5,0 (2 - 10)	5,0 (1 - 10)	0,94
Time to Antibiotic Initiation; Hours (Median (Minimum-Maximum)	9,79 (0,28 - 23,82)	3,21 (0,28 - 3,97)	8,97 (4,02 - 23,82)	0,001
Comorbidities				
Without comorbidities (N, %)	46 (19,6)	11 (23,9)	35 (76,1)	0,19
With comorbidities (N, %)	189 (80,4)	30 (15,9)	159 (84,1)	
Chronic Kidney Disease (N, %)	83 (35,3)	9 (10,8)	74 (89,2)	0,05
Type 2 Diabetes Mellitus (N, %)	60 (25,5)	10 (16,7)	50 (83,3)	0,85
Congestive Heart Failure (N, %)	48 (20,4)	7 (14,6)	41 (85,4)	0,55
Hypertension (N, %)	43 (18,2)	6 (14)	37 (86)	0,50
Malignancy (N, %)	41 (16,8)	7 (17,1)	34 (82,9)	0,94
Cerebrovascular Disease (N, %)	30 (12,9)	3 (10)	27 (90)	0,25
Chronic Liver Disease (N, %)	17 (6,9)	2 (11,8)	15 (88,2)	0,52
Chronic Obstructive Pulmonary Disease (N, %)	8 (3,4)	3 (37,5)	5 (62,5)	0,13
HIV (N, %)	6 (2,6)	1 (16,7)	5 (83,3)	1,00
Type of Antibiotics				
Single β-lactam (N, %)	12 (4,3)	2 (16,6)	10 (84)	0,21
	47 (20)	10 (21,3)	37 (78,7)	0,43
Single Fluoroquinolone (N, %)	88 (37,4)	13 (14,8)	75 (85,2)	0,40
β-lactam + macrolide (N, %)	88 (37,4)	18 (20,5)	70 (79,5)	0,34
β-lactam + Fluoroquinolone (N, %)				

Sputum Culture				0,06
Yes (N, %)	69	43 (62,4)	26 (37,6)	
No (N, %)	(29,7)	16 (9,8)	147 (90,2)	
Sputum Culture: *no growth* (N, %)	166	7 (13,3)	46 (86,7)	0,12
Pathogen Identified (N, %)	(70,3)	2 (12,5)	14 (87,5)	0,49
Klebsiella pneumoniae	53	1 (20)	4 (80)	
Pseudomonas aeruginosa	(22,8)	1 (25)	3 (75)	
Acinetobacter baumanii	16 (6,8)	0 (0)	2 (100)	
Staphylococcus aureus	5 (2,1)	0 (0)	1 (100)	
Escherichia coli	4 (1,7)	0 (0)	1 (100)	
Enterobacter spp.	2 (0,8)	0 (0)	1 (100)	
Candida spp.	1 (0,4)	0 (0)	2 (100)	
	1 (0,4)			
	1 (0,4)			
	2 (0,8)			

The most common comorbidity was chronic kidney disease (35.3%), followed by type 2 diabetes mellitus (25.5%), congestive heart failure (20.4%), hypertension (18.2%), malignancy (16.8%), cerebrovascular disease (12.9%), chronic liver disease (6.9%), chronic obstructive pulmonary disease (3.4%), and HIV (2.6%). The most frequently used antibiotic regimens were β-lactam plus fluoroquinolone and β-lactam plus macrolide (each 37.4%). Sputum culture was performed in 69 patients (29.7%), with 22.8% showing no growth and only 6.8% yielding identifiable pathogens, predominantly *Klebsiella pneumoniae*.

Table 2: Bivariate Analysis of Variables Associated with Mortality

Variable	Mortality, n (%)		OR (CI95%)	p value
	Alive	Death		
Antibiotic initiation	37 (90,2)	4	3,21 (1,09	0,03*
≤4 hours	144	(9,8)	- 9,46)	
>4 hours	(74,2)	50		
		(25,8)		
Age				
<65 hours	144	40	1,36 (0,67 -	0,39
≥65 hours	(78,3)	(21,7)	2,76)	
	37 (72,5)	14		
		(27,5)		
Sex				
Female	70 (78,7)	19	1,16 (0,61 -	0,64
Male	111 (76)	(21,3)	2,19)	
		35		
		(24)		
Comorbid	45 (97,8)	1	17,5 (2,35 -	<0,001*
None	136 (72)	(2,2)	130,47)	
Present		53		
		(28)		
Pneumonia severity	129	14	7,09 (3,56 -	<0,001*
Non-severe	(90,2)	(9,8)	14,11)	
Severe	52 (56,5)	40		
		(43,5)		
Antibiotic				
Single	49 (83,1)	10	1,63 (0,76 -	0,20
Combination	132 (75)	(16,9)	3,49)	
		44		
		(25)		
Type of bacteria	10 (76,9)	3	0,77 (0,57 -	1,00
Gram negative	1 (100)	(23,1)	1,04)	
Gram positive		0 (0)		

Bivariate analysis was performed to evaluate the association between clinical characteristics and 30-day mortality among patients with community-acquired pneumonia. Patients who received antibiotics more than 4 hours after diagnosis had a 3.21-fold higher risk of death compared with those receiving antibiotics within ≤4 hours, and this association was statistically significant (OR 3.21; 95% CI 1.09–9.46; p = 0.03). Age ≥65 years was associated with a 1.36-fold higher mortality risk compared to younger patients, although this was not statistically significant (OR 1.36; 95% CI 0.67–2.76; p = 0.39). Male sex also showed no significant association with 30-day mortality (OR 1.16; 95% CI 0.61–2.19; p = 0.64). Comorbidities demonstrated a strong and significant relationship with mortality. Patients with comorbid conditions had a 17.5-fold increased risk of death compared with those without comorbidities (OR 17.5; 95% CI 2.35–130.47; p < 0.001). Pneumonia severity was also significantly associated with mortality; patients with severe CAP had a 7.09-fold higher risk of death than non-severe cases (OR 7.09; 95% CI 3.56–14.11; p < 0.001). The type of antibiotic regimen showed no statistically significant association with mortality, although combination therapy tended to have higher mortality (OR 1.63; 95% CI 0.76–3.49; p = 0.20). The type of pathogen (gram-positive vs gram-negative) was not associated with 30-day mortality (p = 1.00). Full results are presented in Table 2.

Variable	N (%)	Median, days (Min-max)	p value
Antibiotic initiation			
≤4 hours	41 (17,4)	5,0 (2 - 10)	0,95
>4 hours	194 (82,6)	5,0 (1 - 10)	
Age			
<65 hours	184 (78,3)	5,0 (1 - 10)	0,52
≥65 hours	51 (21,7)	6,0 (1 - 9)	
Sex			
Female	89 (37,9)	5,0 (1 - 10)	0,98
Male	146 (62,1)	5,0 (1 - 10)	
Comorbid			
None	189 (80,4)	5,0 (1 - 10)	0,04*
Present	46 (19,6)	5,5 (2 - 10)	
Pneumonia severity			
Non-severe	143 (60,8)	5,0 (2 - 10)	0,27
Severe	92 (39,2)	6,0 (1 - 10)	
Antibiotic			
Single	59 (25,1)	5,0 (1 - 10)	0,03*
Combination	176 (74,9)	5,0 (1 - 10)	
Type of bacteria			
Gram negative	13 (92,8)	7,0 (2 - 9)	0,29
Gram positive	1 (7,2)	-	

Table 3: Bivariate Analysis of Study Variables Associated with Length of Hospital Stay

Bivariate analysis was also conducted to assess factors associated with length of hospital stay. Mann–Whitney testing revealed no significant association between time to antibiotic initiation and length of stay (p = 0.95). Median length of stay was 5 days (range 2–10) for patients receiving antibiotics within ≤4 hours and 5 days (range 1–10) for those receiving antibiotics >4 hours. Age and sex similarly showed no significant association with length of stay (p = 0.52 and p = 0.98, respectively). Comorbidity was significantly associated with prolonged hospitalization (p = 0.04), with patients having comorbidities exhibiting a median stay of 5.5 days compared to 5 days in those without. Type of antibiotic regimen was also associated with length of stay (p = 0.029); although the median stay was identical (5 days), the mean rank indicated a tendency toward longer hospitalization in patients receiving combination therapy. Pneumonia severity and pathogen type were not significantly associated with length of stay (p = 0.26 and p = 0.29, respectively). Complete results are shown in Table 3.

Variable	B	S.E.	aOR	CI95%	p value
Antibiotic initiation (>4hours)	1,54	0,60	4,67	1,44 - 15,16	0,01*
Comorbid (Present)	3,02	1,04	20,43	2,62 - 159,19	0,004 *
Pneumonia severity (*Severe*)	2,27	0,39	9,65	4,42 - 21,09	<0,00 1*
Antibiotic (Combinatio n)	0,28	0,47	1,33	0,52 - 3,39	0,54

Table 4: Associations Between Clinical Factors and Mortality

Multivariate logistic regression was performed including variables with p < 0.25 in the bivariate analysis to control for potential confounders influencing 30-day mortality. After adjustment, delayed antibiotic initiation (>4 hours), comorbidities, and pneumonia severity remained significantly associated with mortality (Table 4). Patients receiving antibiotics after >4 hours had a 4.67-fold higher adjusted risk of death (aOR 4.67; 95% CI 1.44–15.16; p = 0.01). Comorbidities increased the adjusted mortality risk by 20.43-fold (aOR 20.43; 95% CI 2.62–159.19; p = 0.004). Severe pneumonia was also a strong independent predictor of mortality (aOR 9.65; 95% CI 4.42–21.09; p < 0.001). In contrast, the use of combination antibiotics was not significantly associated with mortality after adjustment (aOR 1.33; 95% CI 0.52–3.39; p = 0.54). These findings indicate that delayed antibiotic initiation, comorbidities, and pneumonia severity are independent predictors of mortality, whereas antibiotic regimen type is not. Multivariate linear regression was subsequently performed to identify predictors of hospital length of stay. After adjustment, time to antibiotic initiation >4 hours was not significantly associated with length of stay (B = –0.001; p = 0.98). Conversely, comorbidities were associated with a significantly longer hospital stay (B = 0.737; p

= 0.03), and the use of combination antibiotic therapy was associated with an increase of 0.75 days in length of stay (B = 0.751; p = 0.02). Combination therapy was more frequently administered to patients with severe pneumonia or higher risk of resistant pathogens, explaining the longer hospitalization seen clinically. Variance Inflation Factor (VIF) values for all variables were approximately 1.00 (<10), indicating absence of multicollinearity and confirming model stability and interpretability. Overall, these findings suggest that comorbidities and antibiotic regimen are significant predictors of length of stay, whereas time to antibiotic initiation has no association (Table 5).

Table 5: Associations Between Clinical Factors and Length of Hospital Stay

Variable	B (Unstd.)	Beta	p value
(Constant)	3,25	-	<0,001
Antibiotic initiation (>4jam)	-0,008	-0,001	0,982
Comorbid (Ada)	0,737	0,139	0,03*
Antibiotic (Combination)	0,751	0,154	0,02*

DISCUSSION

The demographic profile of CAP patients in this study (mean age 54.2 ± 14.9 years; 62.9% male) is consistent with international reports showing higher CAP incidence in older adults and males, driven largely by age-related immune decline.[14,15] Comorbidities were common, particularly type 2 diabetes mellitus, hypertension, congestive heart failure, and cerebrovascular disease, which are known predictors of poorer outcomes due to impaired immune function, increased aspiration risk, and heightened inflammatory burden.[16] Most patients had non-severe pneumonia, similar to global data showing severe CAP comprises only 5–15% of non-ICU hospitalizations. Although fewer in number, severe cases carry significantly higher mortality risk and clinical complexity. Sputum culture collection was low (≈30%), consistent with prior studies reporting similarly low yield from non-invasive sampling methods[17], with pathogen identification in only 6.8% of samples. Delayed antibiotic initiation (>4 hours) was significantly associated with increased 30-day mortality (adjusted OR 4.67; 95% CI 1.44–15.16). This finding aligns with experimental and clinical evidence demonstrating that early antibiotic administration reduces systemic inflammation, prevents pulmonary injury, and improves survival.[12,18,19] Large observational studies similarly report reduced short-term mortality when antibiotics are initiated within the first 4–8 hours of hospital presentation. Collectively, these results reinforce the importance of prompt antibiotic therapy, particularly in patients at higher clinical risk. Antibiotic initiation time did not significantly influence hospital length of stay (median 5 days in both groups), even after adjusting for confounders. This is consistent with studies showing that LOS is more strongly influenced by disease severity, comorbidities, and treatment response rather than antibiotic timing alone.[14,15,20] While early antibiotics reduce mortality, LOS is often determined by broader clinical factors and hospital discharge practices. These findings highlight the need to optimize comorbidity management and early detection of complications to further reduce hospitalization duration.

CONCLUSION

Patients with community-acquired pneumonia who received empiric antibiotic initiation after more than 4 hours had a higher mortality rate compared with those who received empiric antibiotics within 4 hours. There was no significant difference in the length of hospital stay between patients receiving empiric antibiotic initiation >4 hours and those receiving empiric therapy within ≤4 hours.

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