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COST-EFFECTIVENESS ANALYSIS OF CEFTRIAXONE-AZITHROMYCIN COMBINATION AND SINGLE LEVOFLOXACIN AS EMPIRICAL ANTIBIOTICS IN COMMUNITY-ACQUIRED PNEUMONIA INPATIENTS AT PERSAHABATAN HOSPITAL

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ABSTRACT

Objective: Community-acquired pneumonia (CAP) is one of the most common infectious diseases. Its prevalence is especially concerning, as the disease severely impacts health and has a high mortality rate. Although antibiotics have been used to treat CAP, their use is often costly and inefficient. Thus, this study aimed to determine the cost-effectiveness of using ceftriaxone-azithromycin combination and single levofloxacin as empirical antibiotics to treat patients with CAP. Cost-effectiveness was analyzed by comparing the direct total medical cost to clinical effectiveness, which was indicated by the respective success rates in each treatment group.

Methods: This study was conducted at Persahabatan Hospital in Jakarta and employed an observational study design, where data were obtained retrospectively from the secondary data contained in medical records for 2014-2016. A total of 100 patients were included in the analysis, with 64 patients using intravenous (iv) antibiotic ceftriaxone and oral azithromycin and 36 patients using iv single levofloxacin.

Results: The median costs of antibiotics were significantly different between the ceftriaxone-azithromycin group and the levofloxacin group: Rp.130.756 and Rp.286.952, respectively. The direct total medical cost in the ceftriaxone-azithromycin group (Rp.6.494.998) was higher than that of the single levofloxacin group (Rp.5.444.242). The success rate was 95.3% in the ceftriaxone-azithromycin group and 97.2% in the levofloxacin group, but there were no significant differences between the two groups. The medians for the length of stay (LOS) and length of stay antibiotic-related (LOSAR) measures in the levofloxacin group were 6 and 5 days, which were shorter than the LOS and LOSAR medians in the ceftriaxone-azithromycin group: 7 days and 6 days, respectively. The average cost-effectiveness ratio value in the levofloxacin group was 56.011% effectiveness lower than that of the ceftriaxone-azithromycin group, which was Rp.68.153% effectiveness.

Conclusions: Based on these results, it can be concluded that levofloxacin is more cost-effective than a combination of ceftriaxone-azithromycin for treating CAP.

Keywords: Cost-effectiveness, Antibiotic, Community-acquired pneumonia, Ceftriaxone, Azithromycin, Levofloxacin.

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INTRODUCTION

In the transition of global epidemics from communicable diseases to non-communicable diseases, developing countries carry a double burden in health. Despite the conclusion of the millennium development goals era, developing countries continue to experience problems with communicable diseases such as diarrhea, tuberculosis, HIV/AIDS, and pneumonia. Community-acquired pneumonia (CAP) is one of the most common infectious diseases. Its prevalence is especially concerning because the disease causes severe health problems and has a high mortality rate. Moreover, treating the disease constitutes a significant financial burden because of the high costs of a health service, especially staying in the hospital, which represents 70-90% of the total medical cost [1].

The total medical cost for patients with pneumonia in 2005 in the United States of America was about $40 million, with $34 million reflecting direct cost [2]. Pneumonia is one of the seven most common causes of death in the US, where it is estimated that there are 4 million cases of CAP every year, resulting in 10 million doctor visits, 1 million cases of inpatient care, and 45000 deaths [3]. In Indonesia, pneumonia represents one of big ten conditions requiring inpatient care, with case proportions of 53.95% male and 46.05% female and a 7.6% crude fatality rate, which is higher than other diseases. According to Riskedas, in 2013, there was an increasing inclination of pneumonia period prevalence in all ages: From 2.1% in 2007 to 2.7% in 2013. The five provinces that had the highest pneumonia incidence and prevalence for all ages were East Nusa Tenggara (4.6% and 10.3%), Papua (2.6% and 8.2%), Central Sulawesi (2.3% and 5.7%), West Sulawesi (3.1% and 6.1%), and South Sulawesi (2.4% and 4.8%) [4].

In Indonesia, the National Health Insurance (JKN) uses the Indonesia Case-based Groups (INA-CBG) payment system for higher level health-care facilities. Hospitals are paid based on the INA-CBG tariffs, which reflect the mean cost spent for a diagnosis group. Community-acquired pneumonia is included in the INA-CBG group in the disease class of simple pneumonia and whooping cough. According to the data from Indonesia National Health Insurance, pneumonia is one of the ten highest costing inpatient care conditions for JKN. Antibiotics are integral for treating infectious diseases. Because of increasing health-care costs and limited resources, policymakers, and health-care personnel could benefit from a study examining the cost effectiveness of antibiotics. Pharmacoeconomic evaluation is done to analyze the cost effectiveness of antibiotics and to understand whether antibiotics provide a good treatment outcome at a minimal cost.

According to the Infectious Disease Society of America (IDSA), the American Thoracic Society (ITS), and the Indonesia Society of Respirology (PDPI), the antibiotics used for treating CAP during inpatient care are from the beta-lactam group and are combined with macrolide or single respiratory quinolone antibiotics [5]. In

Indonesia, for JKN service, there is a significant different in price between the two antibiotic choices. Thus, the pharmacoeconomic analysis is needed to determine the cost-effectiveness of each option. Bhavnani and Ambrose compared gemifloxacin quinolone antibiotics to ceftriaxone-clarithromycin combination antibiotics and found that gemifloxacin is more cost-effective than ceftriaxone-clarithromycin combination [6]. Dresser *et al*. compared gatifloxacin-quinolone antibiotics to ceftriaxone-macrolide combination antibiotics and also stated that the quinolone antibiotics were more cost-effective than the beta-lactam-macrolide combination antibiotics [7]. This study was performed at Persahabatan Hospital, which is a Class A Government General Hospital and National Referral Hospital for respiratory health located in East Jakarta. This study sought to determine the cost-effectiveness of ceftriaxone-azithromycin combination and single levofloxacin as empirical antibiotics for the treatment of inpatients with pneumonia.

METHODS

This study is an observational study, where data were obtained retrospectively from secondary data (patients' medical records). The results of this study are provided in descriptive and analytical forms. This study was conducted at Persahabatan Hospital. The participants in this study were patients who had been diagnosed with CAP, had received inpatient care, and had been given empirical antibiotic therapy, as written in their medical records from 2014 to 2016 in Persahabatan Hospital.

Samples were only chosen if the patients met the following inclusion criteria: (1) Patients who received inpatient care and main diagnosis of CAP. The diagnosis of pneumonia was made based on signs and symptoms as well as adjunctive examination such as laboratory results or Roentgen photos, (2) adult patients above 18 years old, (3) patients who received ceftriaxone-azithromycin combination or single levofloxacin as empirical antibiotics to treat their CAP, and (4) patients with National Health Insurance (JKN) who had done one therapy cycle (i.e., patient who were not forcibly discharged). Exclusion criteria included the following: (1) Pregnant patients, (2) patients with other infections, and (3) patients with incomplete medical records.

Univariate analysis was used to describe patients' demographic data, which was then presented in tables. Bivariate analysis was used to understand patients' characteristic differences in each empirical antibiotic group and determine the relationship between the independent variable and the dependent variable. To understand characteristic differences of age, gender, treatment class, and PSI class, chi-square test was used. To determine the effect of the independent variable on the dependent variable, a mean difference test was done in two groups using a t-test if the data distribution was normal and a Mann–Whitney test if the data distribution was not normal. To determine whether a relationship existed between the cofounding variable and the dependent variable, a Chi-square test was used. A logistic regression test was used to determine and predict the cofounding variables, including age, gender, accompanying diseases, degree of severity, and length of stay (LOS).

Cost-effectiveness was analyzed by determining the positions of the treatments under study on a cost-effectiveness diagram and comparing those positions with those of alternative treatments. The treatment cost of each group of antibiotics was compared by calculating the average cost-effectiveness ratio (ACER), which reflected the total direct medical cost spent by patients with CAP receiving inpatient care divided by antibiotic usage effectiveness or "success rate:"

$$\text{ACER}=\frac{\text{Total direct medical cost}}{\text{Success rate}}$$

Sensitivity analysis was done to determine how far cost changes or effectiveness used to calculate ACER can affect the conclusion. Sensitivity analysis for antibiotic cost-effectiveness was done by increasing and decreasing the variation by 10% and 25% of the total cost.

RESULTS

There were 432 medical records in 2014-2016 in which CAP had been diagnosed; however, only 100 patients met the inclusion criteria and were thus included in this study. Of these 100 patients, 64 patients received empirical antibiotic therapy of intravenous (iv) ceftriaxone combination and azithromycin while 36 patients were treated with the empirical antibiotic of iv levofloxacin.

Descriptive data of the participants are presented in Table 1. The median age of patients with CAP who received empirical antibiotic therapy using ceftriaxone-azithromycin combination or levofloxacin from 2014 to 2016 was 59 years old; 50% of the patients were >60 years old. In the United States, it is estimated that there are around 5.2 million adult patients with CAP, and the majority of these individuals are above 65 years old (4.200 out of every 100.000 people) [8]. In the Netherlands, 45% of patients with CAP are above 65 years old [9]. Risk factors for CAP include old age and comorbidity. In geriatric populations, getting older is related to increased rates of contracting CAP, inpatient care, and death. Among around 1.1 million inpatients in hospitals due to pneumonia (including CAP) in 2007, 21% were 45-64 years old and 58% were 65 years old or older. To reduce CAP risks, the IDSA and the ITS consensus guidelines recommend that individuals above 50 years old receive annual vaccination with inactive influenza virus and individuals who are 65 years and older receive a pneumococcus vaccination [10].

In this study, there were 51 male patients (51%) and 49 female patients (49%), with 43.8% male and 56.3% female patients in the ceftriaxone-azithromycin treatment group and 63.9% male and 36.1% female patients in the levofloxacin treatment group. This study consisted of patients with JKN at Persahabatan Hospital with a main diagnosis of CAP. According to the treatment class, there was no significant difference between the ceftriaxone-azithromycin group and the levofloxacin group, where Class III represented the most frequent treatment class: 67% of the total patients. In the ceftriaxone-azithromycin group, there was 3.1% Class I patients, 23.4% Class II patients, and 73.4% Class III patients. In the levofloxacin group, there was 8.3% Class I patients, 36.1% Class II patients, and 55.6% Class III patients.

The conditions that were most comorbid with CAP among the patients in this study were hypertension (29%) and diabetes mellitus (25%) followed by acute chronic failure (16%), heart failure (13%), chronic obstructive pulmonary disease (COPD) (9%), asthma (6%), stroke (6%), malignancy (3%), and liver disease (2%). Comorbidity is a risk factor in CAP. According to study by Torres *et al*., comorbid conditions including respiratory disease and chronic cardiovascular disease, cerebrovascular disease, Parkinson's disease, epilepsy, dementia, dysphagia, chronic kidney or liver disease, and even HIV can increase the risk of CAP by 2-4 times [11]. In the geriatric population, chronic diseases (diabetes mellitus, COPD, cancer, heart failure disease, and chronic kidney disease), age, and immune system can give not only lead to the contraction of a pneumonia infection but also to the development of a pneumonia infection, resulting in poor health outcomes [12]. In this study, the effectiveness parameter is based on the success rate, the LOS, and the LOS antibiotic-related LOSAR (Table 2). The success rate reflects whether the antibiotic resulted in successful treatment. The treatment is a success if the patient was cured or experienced clinical improvement, and the treatment was a failure if the patients died. LOS was calculated as the total days from the patient's first day at the hospital until discharge by doctor's agreement due to being cured or experiencing clinical improvement. LOSAR was calculated as the total number of days patients received iv empirical antibiotics. Patients who were discharged at their own demand were excluded from this study.

The dosages given to the combination therapy group were 1×2 gr iv and 1×3 gr iv of ceftriaxone and 1×500 mg per oral of azithromycin. The

Table 1: Patients' characteristics organized by empirical antibiotics treatment at Persahabatan Hospital from 2014 to 2016

Patient's characteristics	Total (n=100)	Ceftriaxone iv and azithromycin (n=64)	Levofloxacin iv (n=36)	p-value
Age (%)				
18-39 years old	9 (9.0)	5 (7.8)	4 (11.1)	0.844
40-59 years old	41 (41.0)	27 (42.2)	14 (38.9)	
>60 years old	50 (50.0)	32 (50.0)	18 (50.0)	
Median	59	59	59	
Range	19-85	19-85	19-84	
Gender (%)				
Male	51 (51.0)	28 (43.8)	23 (63.9)	0.063
Female	49 (49.0)	36 (56.3)	13 (36.1)	
Degree of severity (%)				
PSI score	83.2+26.7	83.5+28.9	82.6+22.5	0.870
PSI class score (%)				
Class I	ND	ND	ND	0.879
Class II	35 (35.0)	23 (35.9)	12 (33.3)	
Class III	21 (21.0)	13 (20.3)	8 (22.2)	
Class IV	43 (43.0)	27 (42.2)	16 (44.4)	
Class V	1 (1.0)	1 (1.6)	0 (0)	
Inpatient care class (%)				
Class I	5 (5.0)	2 (3.1)	3 (8.3)	0.160
Class II	28 (28.0)	15 (23.4)	13 (36.1)	
Class III	67 (67.0)	47 (73.4)	20 (55.6)	
Comorbidity (%)				
Diabetes mellitus	25 (25.0)	19 (29.7)	6 (16.7)	0.229
Hypertension	29 (29.0)	19 (29.7)	10 (27.8)	1.000
Heart failure	13 (13.0)	8 (12.5)	5 (13.9)	1.000
COPD	9 (9.0)	4 (6.3)	5 (13.9)	0.277
Asthma	6 (6.0)	1 (1.6)	5 (13.9)	0.022*
Stroke	6 (6.0)	4 (6.3)	2 (5.6)	1.000
Chronic kidney failure	16 (16.0)	13 (20.3)	3 (8.3)	0.158
Liver disease	2 (2.0)	2 (3.1)	0 (0.0)	0.535
Malignancy	3 (3.0)	2 (3.1)	1 (2.8)	1.000
Amount of comorbidity (%)				1.000
0-1 comorbidity	68 (68.0)	43 (67.2)	25 (69.4)	
>2 comorbidity	32 (32.0)	21 (32.8)	11 (30.6)	

PSI: Pneumonia severity index, ND: Not defined, p value: Significance value, p value>0.05 there is no significant difference between the two groups, COPD: Chronic obstructive pulmonary disease, *p<0.05, significant

Table 2: Effectiveness difference between the two treatment groups

Parameter	Total (n=100)	Ceftriaxone iv and azithromycin (n=64)	Levofloxacin iv (n=36)	p value
Success rate (total)				
Heal	96 (96.0)	61 (95.3)	35 (97.2)	1.000
Dead	4 (4.0)	3 (4.7)	1 (2.8)	
LOS (days)				
Median		7	6	0.004*
Range	2-14	3-14	2-11	
LOSAR (days)				
Median		6	5	0.011*
Range	2-15	3-15	2-11	

LOS: Length of stay, LOSAR: Length of stay antibiotic-related, *p<0.05, significant

dosage used for the levofloxacin group was 1×750 mg iv. According to the literature, a high dose of levofloxacin (750 mg), produces similar results but in a shorter time than a dosage of 500 mg, especially for fever alleviation. In the ceftriaxone-azithromycin group, there were 3 patients (4.7%) who died; in the levofloxacin group, 1 patient (2.8%) died. The survival or success rates in both groups were not statistically significant (95.3% and 97.2%, respectively). A journal review by Raz-Pasteur *et al*. (2015) stated that there is no significant difference between fluoroquinolone antibiotics and beta-lactam/macrolide in the total number of deaths: RR (95%, CI) 0.99 (0.70-1.40) [13]. A meta-analysis done by Skalsky *et al*. stated that there is no significant difference in the mortality rate between quinolone groups and monotherapy macrolide or combination with beta-lactam RR (1.03. 95%, CI: 0.63-1.68) [14].

To investigate the effect of LOS using PSI score, age, gender, total and type of comorbidity, chi-square test was used. As shown in the results in Table 3, there was a significant relationship between LOS and degree of severity (PSI class) (p=0.022). Meanwhile, the results did not show a significant relationship between LOS and age (p=0.840), total of comorbidity (p=0.665), gender (p=0.686), presence (present or not present) of diabetes mellitus comorbidity (p=0.665), presence (present or not present of hypertension comorbidity (p=0.824), presence (present or not present) of heart failure comorbidity (p=0.228), presence (present or not present) of stroke comorbidity (p=0.235), presence (present or not present) of asthma comorbidity (p=0.080), presence (present or not present) of COPD comorbidity (p=0.486), presence (present or not present) of acute kidney failure comorbidity (p=0.787), presence (present or not present) of heart disease comorbidity (p=0.508), and presence (present or not present) of malignancy comorbidity (p=1.000). Based on bivariate analysis, a multivariate analysis with logistic regression of the confounding factors was conducted with a p<0.25. The results showed that degree of severity, especially Classes IV and V PSI was significantly related to LOS (p=0.020, OR: 2.963 with 95%, CI: 1.185-7.409).

Table 3: Bivariate analysis to determine the effects of confounding factors on LOS

Confounding	LOS (<7 days)		p-value
	n (%)	n (%)	
Degree of severity			
Class II and III PSI	30 (53.6)	26 (46.4)	0.014*
Class IV and V PSI	12 (27.3)	32 (72.7)	
Age			
<60 years old	22 (44.0)	28 (56.0)	0.840
>60 years old	20 (40.0)	30 (60.0)	
Gender			
Male	20 (39.2)	31 (60.8)	0.686
Female	22 (44.9)	27 (55.1)	
Total of comorbidity			
<2 comorbidity	30 (44.1)	38 (55.9)	0.665
>2 comorbidity	12 (37.5)	20 (62.5)	
Presence of diabetes mellitus			
Not present	33 (44.0)	42 (56.0)	0.640
Present	9 (36.0)	16 (64.0)	
Presence of hypertension			
Not present	29 (40.8)	42 (59.2)	0.824
Present	13 (44.8)	16 (55.2)	
Presence of CHF			
Not present	39 (44.8)	48 (55.2)	0.228*
Present	3 (23.1)	10 (76.9)	
Presence of stroke			
Not present	38 (40.4)	56 (59.6)	0.235*
Present	4 (66.7)	2 (33.3)	
Presence of asthma			
Not present	37 (39.4)	57 (60.6)	0.080*
Present	5 (83.3)	1 (16.7)	
Presence of COPD			
Not present	37 (40.7)	54 (59.3)	0.486
Present	5 (55.6)	4 (44.4)	
Presence of AKI			
Not present	36 (42.9)	48 (57.1)	0.787
Present	6 (37.5)	10 (62.5)	
Presence of malignancy			
Not present	41 (42.3)	56 (57.7)	1.000
Present	1 (33.3)	2 (66.7)	
Presence of heart disease			
Not present	42 (42.9)	56 (57.1)	0.508
Present	0 (0.0)	2 (100.0)	

AKI: Acute kidney failure, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, p<0.05 and p<0.25 are included in the multivariate analysis, LOS: Length of stay

Table 4 shows the cost component analysis from each treatment group. The two empirical antibiotics groups were significantly different in price. The price of ceftriaxone-azithromycin was less than that of levofloxacin. As known, the drugs supply in the National Health Insurance Scheme is organized based on a national e-catalog for drugs majority the e-catalog is an electronic information system that lists the drugs' type, technical specification, and stock price from several suppliers. Based on the e-catalog, the price of infusion levofloxacin per unit is Rp.22.318 in DKI Jakarta while the price of injection ceftriaxone is Rp.3.300 and 1.888 for azithromycin; Table 4 demonstrates that there is significant difference between the two antibiotics in terms of price.

Other costs that were analyzed were room cost, doctor's visit cost, drugs cost, adjunctive examination cost, and treatment cost. There was no significant difference between doctor's visit costs, room cost, and treatment cost. The patients included in the group were from treatment Classes I-III, and the composition was not statistically significant between each class. In room cost analysis, there was no significant difference between the ceftriaxone-azithromycin group and the levofloxacin group. In adjunctive examination, there was a significant difference between each group. In the different treatment classes, there was a statistical difference in the tariffs of the room cost and doctor's visit cost, but not in adjunctive examination. In this study, differences in adjunctive examination cost could have been affected by each group's LOS, as patients required varying levels of adjunctive examination.

Table 4: Direct medical cost distribution between the two treatment groups

Parameter	Cost median (rupiah)		p-value
	Ceftriaxone iv and azithromycin	Levofloxacin iv	
Empirical antibiotic cost	Rp. 130.756	Rp. 286.952	0.000*
Room cost	Rp. 675.000	Rp. 570.428	0.334
Doctor's visit cost	Rp. 568.456	Rp. 502.779	0.703
Drugs cost	Rp. 1.093.844	Rp. 1.012.074	0.239
Adjunctive examination cost	Rp. 2.232.492	Rp. 1.304.804	0.000*
Treatment cost	Rp. 741.716	Rp. 791.961	0.977
Other cost	Rp. 172.744	Rp. 383.851	0.071
Total direct medical cost	Rp. 6.494.988	Rp. 5.444.242	0.082

Table 5: ACER calculation of each antibiotic group

Empirical antibiotic type	Cost (C)	Effectiveness (E)	ACER (C/E)
Ceftriaxone iv and azithromycin	Rp. 6.494.988	95.3	Rp. 68.153% effectiveness
Levofloxacin iv	Rp. 5.444.242	97.2	Rp. 56.011% effectiveness

CER was done by comparing total cost (C) to effectiveness (E) in each treatment group. The result was interpreted as mean effectiveness per unit. The lower the cost was, the higher the effectiveness from the C/E ratio and the investment value obtained from that intervention was; therefore, this strategy is chosen [15]. The total cost reflected the total cost of each treatment median while effectiveness referred to the treatment success rate (cured or clinical improvement). The results of the CER calculation can be seen in Table 4. The calculation in Table 5 shows that the ACER value of the ceftriaxone-azithromycin group is Rp.68.153% effectiveness, which is higher than the ACER value of the levofloxacin group, which was Rp.56.011% effectiveness. Therefore, levofloxacin is considered more cost-effective than ceftriaxone-azithromycin combination.

A cost-effectiveness grid can be used to define cost-effectiveness. To understand a treatment or cost-effective service, cost and effectiveness should be calculated. If an alternative treatment is more effective and has a lower cost (cell G), is more effective but has the same cost (cell H), or has the same effectiveness and a lower cost (cell D), that treatment can be defined as cost-effective. However, if an alternative treatment is less effective and has a higher cost (cell C), has the same effectiveness but also has a higher cost (cell F), or has less effectiveness and the same cost (cell B), that drug is not considered cost effective (Table 6) [15].

The results of the sensitivity analysis show that choosing levofloxacin is sensitive to a 25% increase in cost, and this increase in cost yields a higher ACER result than the baseline ceftriaxone-azithromycin ACER value (Table 7). Choosing levofloxacin is sensitive to a 25% decrease in the cost of the ceftriaxone-azithromycin group, and this decrease in cost yields a lower ACER result in the levofloxacin group than the baseline ACER value.

DISCUSSION

This study examined the cost-effectiveness of ceftriaxone-azithromycin combination and single levofloxacin as empirical

Table 6: Position of levofloxacin and ceftriaxone-azithromycin on a cost-effectiveness grid

Cost-effectiveness	Lower cost	Same cost	Higher cost
Lower effectiveness	A ICER calculation	B	C dominated (ceftriaxone-azithromycin)
Same effectiveness	D	E arbitrary	F
Higher effectiveness	G dominant (levofloxacin)	H	I ICER calculation

Table 7: Sensitivity analysis calculation between the two treatment groups

Sensitivity	Cost (C)	Effectiveness	ACER (C/E)
Ceftriaxone and azithromycin (%)			
Decrease of 0	Rp. 6.494.988	95.3	Rp. 68.153
Decrease of 10	Rp. 5.845.489	95.3	Rp. 61.338
Increase of 10	Rp. 6.430.038	95.3	Rp. 67.472
Decrease of 25	Rp. 4.871.241	95.3	Rp. 51.115
Increase of 25	Rp. 8.118.735	95.3	Rp. 85.191
Levofloxacin (%)			
Decrease of 0	Rp. 5444242	97.2	Rp. 56.011
Decrease of 10	Rp. 4899818	97.2	Rp. 50.410
Increase of 10	Rp. 5389800	97.2	Rp. 55.451
Decrease of 25	Rp. 4083182	97.2	Rp. 42.008
Increase of 25	Rp. 6805303	97.2	Rp. 70.013

antibiotics for treating inpatients with CAP. The cost-effectiveness analysis was done by comparing the direct total medical cost to effectiveness, which was determined by the success rate in each treatment group. In this study, there was a significant difference in LOS between the two groups. The median LOS in the levofloxacin group was 6 days, while the median LOS in the ceftriaxone-azithromycin was 7 days. There was also a significant difference between the two groups in the LOSAR. The LOSAR median in the patients who received levofloxacin was 5 days, whereas the LOSAR median in the patients who received ceftriaxone-azithromycin was 6 days. This is in agreement with a previous study by Lodise *et al*., who stated that there was a significant difference in the LOS between the beta-lactam-macrolide group and the fluoroquinolone group (LOS median was 6 days and 5 days, respectively) [16]. A study done by Querol-Ribelles *et al*. stated that the median LOS for levofloxacin was 5 days, while the median LOS for ceftriaxone-clarithromycin was 6 days, but no significant difference was found [17]. According to a meta-analysis conducted by Vardakas *et al*., the LOS for patients who received fluoroquinolone was 1-2 days shorter than patients who received antibiotics of macrolide or beta-lactam or a combination of both [18].

Some studies have investigated the relation between length of treatment and degree of severity in patients with CAP. Menendez *et al*. found a positive relationship between LOS and PSI score, pleura effusion, and blood urea nitrogen concentration and found no correlation between LOS and age, gender, alcohol intake, smoking cigarettes, and comorbidity [19]. A study by Garau *et al*. also found a significant relationship between LOS and death as well as LOS and PSI score (especially in Classes IV and V PSI, positive blood culture, ICU admission, and alcohol consumption) in patients with CAP [20]. The results of the current study are in agreement with the two previous studies, as the current study found a significant relationship between LOS and PSI score (degree of severity) [14].

Cost analysis was done to understand the total cost components in both treatment groups [15]. The costs included in this study were antibiotic cost, total drugs cost, doctor's visit cost, treatment cost, and adjunctive examination cost. These costs are categorized as direct medical costs, which refer to the costs counted most often and are used directly to provide treatment [15]. According to the results, the effectiveness of levofloxacin therapy is higher than that of ceftriaxone-azithromycin, and the direct medical cost of levofloxacin is lower than that of ceftriaxone-azithromycin; therefore, in the cost-effectiveness grid, levofloxacin is in the dominant group. In this case, there is no need to calculate the ICER because it can be concluded that levofloxacin is more cost-effective.

This study has several limitations. First, this study was conducted retrospectively from medical records, thus limiting the total number of participants. Second, this study did not compare across treatment classes due to the minimal total sample. According to cost-effectiveness analysis, levofloxacin care (with an ACER value of Rp.56.011%) is more cost-effective than ceftriaxone and azithromycin combination antibiotics (with an ACER value of Rp.68.153% effectiveness) for treating inpatients with CAP.

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