Pharmaciana
Vol.12, No.1, March 2022, Page. 83-93
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v12i1.21376

Cost-effectiveness analysis of empiric antibiotics in hospitalized community-acquired Pneumonia

Yeni Farida[1]*, Qisty Aulia Khoiry[2], Muchtar Hanafi [3], Maryani [4]
[1,2]Department of Pharmacy, Faculty of Mathematics and Science, Universitas Sebelas Maret
Jl. Ir. Sutami No.36A Jebres Surakarta, Central Java, Indonesia
[3,4]UNS Hospital, Faculty of Medicine, Universitas Sebelas Maret

Submitted: 27-08-2021 ***Reviewed: 27-09-2021*** ***Accepted: 23-11-2021***

ABSTRACT

Community-Acquired Pneumonia (CAP) remains an important infectious disease due to its impact on patient outcomes. This study aimed to investigate the clinical outcome and especially costs of hospitalization for community-acquired pneumonia (CAP) concerning empirical antibiotics. This research was conducted to estimate the cost-effectiveness of levofloxacin, ceftriaxone, and a combination of ceftriaxone and azithromycin aiming to improve the clinical outcome of CAP. A retrospective observational study was conducted in secondary care, University Hospital in Surakarta, Central Java, Indonesia. The study enrolled all CAP patients hospitalized in the period January until December 2018, with ages ≥ 18 years old, and at least used antibiotic for three days. We compared cost-effectiveness, as measured by total cost and proportion of patients successfully treated, of 3 empirical antibiotics for inpatient CAP, involving ceftriaxone, levofloxacin, or combination ceftriaxone + azithromycin. Our analyses were conducted based on a healthcare perspective. In all groups were analyzed based on severity classification (Pneumonia Severity Index score). The use of levofloxacin instead of ceftriaxone improved clinical response, but it is more expensive. Levofloxacin was the most cost-effective based on ACER value. Treatment using a combination of ceftriaxone + azithromycin was more expensive without added benefit. Based on this study, the use of levofloxacin as the first-line therapy for CAP could be maintained because it was more cost-effective than other alternatives. Since the limitations, a study on a broader population is needed to confirm these findings.

Keywords: effectiveness, empirical antibiotics, community-acquired pneumonia, cost-effective

Corresponding author:
Yeni Farida
Department of Pharmacy, Faculty of Mathematics and Science, Universitas Sebelas Maret
Jl. Ir. Sutami No.36A Jebres Surakarta, Central Java, Indonesia
Email: yenifarida@staff.uns.ac.id

INTRODUCTION

Pneumonia as one of the top leading causes diseases in hospitalized patient become a serious problem as it's not handled properly the inflammation process will continue and cause various complications (Ramirez et al., 2017; Smith et al., 2021). Clinicians must balance the need to accurately diagnose and treat pneumonia while ensuring that these efforts do not lead to the overuse of antimicrobial therapy. Whether drug choices of antibiotics improve patient outcomes or merely add to the financial cost, length of stay, and patient discomfort remains to be determined. Rationale empiric antibiotic selection is become important, to ensure the success of treatment. Only by minimizing toxicity, pathogen selection, and resistance development can the best treatment outcomes be attained (Walger, 2016). Antibiotic choice can be influenced by the possibility of etiology, local resistance to pathogenic patterns, and patient factor (Ho & Chu, 2009). The selection of rational antibiotic therapy considers some aspects such as the right dosage, patient condition, location of the infection, antibiotic sensitivity, pharmacokinetics, pharmacodynamics, side effects, and price (Kourkouta et al., 2017). Empiric antibiotic therapy is recommended to be given within 4 hours after diagnosis was established (File et al., 2021). Antimicrobial treatment should be started as soon as possible to enhance the prognosis of individuals with serious infections (Ruiz-Ramos et al., 2017). The effectiveness of antibiotics is indicated by the improvement of clinical signs and symptoms in 48–72 hours (Wongsurakiat & Chitwarakorn, 2019).

Ceftriaxone is a first-line antibiotic that has been indicated for various infections, including CAP. Currently, CAP treatment recommendations propose empiric antibiotic therapy that covers both standard and atypical pathogens (Murter et al., 2019). Suggested antibiotics were a combination of beta-lactam and macrolide or monotherapy of respiratory fluoroquinolone as a standard regimen for inpatient pneumonia (Burhan et al., 2020; Metlay et al., 2019). One of the most popular CAP treatment regimens is ceftriaxone (CTX) in combination with azithromycin (AZH); nevertheless, studies demonstrate that monotherapy is as effective as the combination for the empiric treatment of CAP (Murter et al., 2019). Therefore, further investigation regarding the effectiveness of levofloxacin and ceftriaxone alone or in combination with azithromycin.

The main cause of inefficient antibiotic treatment on CAP is experiencing worsening or failure of therapy and burdening costs (Wunderink & Yin, 2016). Pneumonia is the most common reason for admission to the hospital, in the United States with 1.5 million hospital admissions per year, costing between $11,000 and $51,000 per admission (Sato et al., 2013). In Indonesia, the average cost of care in one period of hospitalization for each patient diagnosed with CAP is USD 1208, this cost is more expensive when compared to Malaysia (USD 927) and the Philippines (USD 254) (Azmi et al., 2016).

For the last decade, there have been limited reports for Community-Acquired Pneumonia evaluating the cost-effectivity of empirical antibiotics. Most presented about the cost-effectiveness antibiotic choice culture-based by a specific antimicrobial agent or drug effectivity in Hospital-Acquired Pneumonia (McKinnell et al., 2018; Niederman et al., 2014; Ruiz-Ramos et al., 2017). Somehow, several presented about burden cost in community-acquired pneumonia only or effectivity antibiotic only (Konomura et al., 2017; Kosar et al., 2017; Queen et al., 2014). However, study about the relation between cost and effectivity of empirical antibiotic for Community-Acquired Pneumonia are rare. To better understand the effectiveness by cost comparison and the most cost-effective antibiotics among empirical antibiotics used for the hospitalized patient, studies of cost-effectiveness analysis across clinical stability as a parameter of effectivity empirical antibiotics concerning direct cost are required. Such approaches are urgently needed for recommendations for suitable empirical drug choice. Here, to address this gap in the literature, the present study evaluated the effectiveness of empirical antibiotics by guideline using patient's clinical response with the direct medical cost of CAP stratified by severity level using PSI Scoring.

MATERIALS AND METHOD

Materials

Patient demographic, antibiotic use, and clinical response, laboratory examination data were extracted from the medical record, while cost data were obtained from insurance claim bills. The effectiveness of antibiotics was assessed using clinical responses taken from medical records.

Methods

A retrospective observational study was conducted in secondary care, University Hospital in Surakarta, Central Java, Indonesia. The study enrolled all CAP patients hospitalized in the period January until December 2018, with ages ≥ 18 years old, and at least used antibiotics for three days. Patients admitted to intensive care within hospitalized or immunocompromised patients were excluded. The study was approved by the Health Research Ethics Committee School of Medicine Universitas Muhammadiyah Surakarta No. 1853/C.2/KEPK-FK-UMS/I/2019.

The outcome was defined as clinical stability and clinical instability after 72 hours of antibiotics therapy. Clinical stability defined as heart rate ≤ 100x/minutes; respiration rate < 24x/minutes; systolic blood pressure > 90 mmHg or diastolic blood pressure > 60mmHg; temperature < 37,8℃; compos mentis; and pO2 > 60 mmHg or SaO2 > 90% (Ewig et al., 2016). The clinical response outcome results were calculated as a percentage of patients in each antibiotic group. Direct medical costs were calculated from the average of the individual cost of administration, pharmacy costs, laboratory and radiology expenses, cost of the bed, and medical staff costs.

Data Analysis

Effectiveness differences in each group were statistically analyzed using the Chi-square test compared to ceftriaxone, which is used as the reference antibiotic. Cost-effectiveness analysis was performed by calculating the average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER). The results from ACER are interpreted as the average cost per unit of clinical outcome. The average cost-effectiveness ratio value of a choice of several alternative therapies that have the same goal is the ratio with the lowest value (Kemenkes, 2013). A large ACER value indicates that the costs incurred are greater than the effectiveness, and the lower the ACER value, the higher the effectiveness value than the costs incurred.

The incremental cost-effectiveness ratio (ICER) in terms of total hospitalization costs and percentage effectiveness by clinical response was calculated with the following Formula. Notably, in case the numerator was negative is means cost-saving, and the denominator was positive is means improving effectivity, then ICER indicated dominant (Nalang et al., 2018).

We performed a sensitivity analysis to address the robustness of the model ACERs on the changes of the upper and lower limits of the parameter values. The parameters included in the test were costs and the improvement of clinical response outcomes. Sensitivity analysis is the main method for dealing with uncertainty in analysis (Kemenkes, 2013). Sensitivity analysis is conducted to determine the extent to which changes in the cost value used to calculate ACER can affect conclusions. The sensitivity analysis for the cost-effectiveness analysis of antibiotics was carried out by varying the decrease and increase of 10% and 25% of the total cost (Suratini et al., 2017).

RESULT AND DISCUSSION

Patients characterisctic

The population of CAP patients in 2018 was 138 patients, but not all of the patients were enrolled in this study. The subject selection process is presented in Figure 1. Patients using the empirical antibiotics levofloxacin, ceftriaxone, and ceftriaxone + azithromycin were then used as study subjects (66 patients). The reason for choosing the use of these antibiotics is because the three antibiotics are the choice of use for inpatients with non-ICU comorbid diseases based on the guideline of PDPI (2014).

Baseline characteristics of the studied subject can be seen in Table 1. We input data of patients whose average age was 59.6 years; they were predominantly males (57.6%). Assessment of patient

severity uses the Pneumonia Severity Index (PSI) scoring to provide an objective classification of patients into low (class I-III), medium (class IV), and high-risk categories (class V) that have been validated. PSI scoring has the highest specificity compared to CURB-65 and APACHE II. In addition, PSI scoring showed good results in predicting 3 outcomes (risk of mortality at 28 days, risk of ventilator insertion, and increased severity) in the same patient subjects. (Madhu et al., 2017; Noguchi et al., 2017; Xiao et al., 2013). We addressed PSI class in subgroup analyses since this cut-off increases the risk of 30-day mortality by ten times compared to severity class I-III (low) (Alavi-Moghaddam et al., 2013).

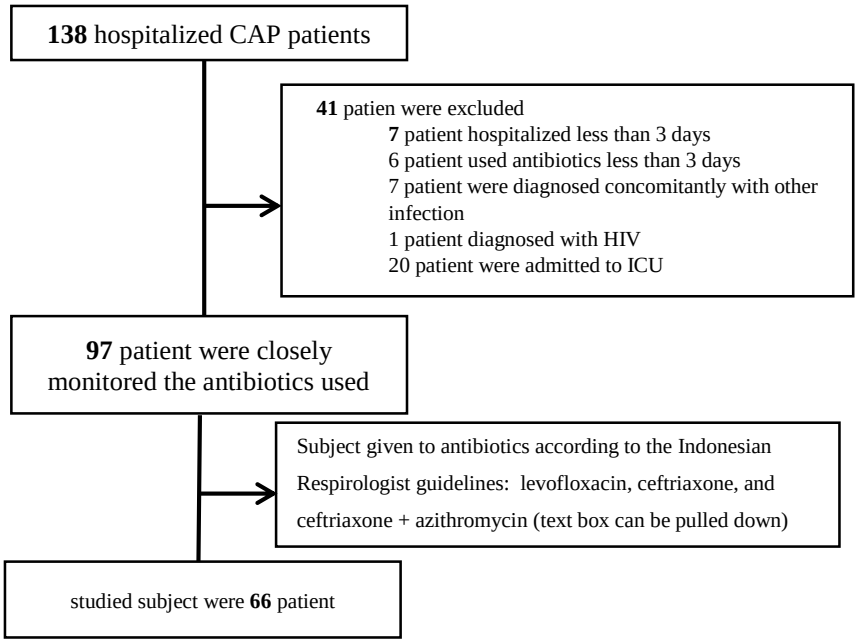

Figure 1. The flow of study subject selection and reasons for exclusion is described in this diagram. CAP (community-acquired pneumonia), HIV (human immunodeficiency virus), ICU (intensive care unit)

The baseline characteristic of the study subject is shown in Table 1. The same baseline criteria must be met to compare the clinical effectiveness of different antibiotic groups. Therefore, a nominal categorical comparative test or a numerical comparative test was performed on each of the characteristics between groups of antibiotics. In this study, the results of patient characteristics from the antibiotic group levofloxacin, ceftriaxone, and the combination of ceftriaxone + azithromycin did not have a significant difference so that the three groups could be compared (p value> 0.05).

In this study, subjects were dominated by males in all groups. The majority of the subjects were classified as elderly (> 65 years old) based on their age. A previous study found that being male and elderly was a risk factor for pneumonia, and mortality also increases by age (Cillóniz et al., 2011; Farida et al., 2019). One of the primary causes of CAP development in seniors is a decline in immunological function. On the other hand, several physiologic alterations in the elderly have been linked to the development of CAP (Stupka et al., 2009). Based on the PSI severity score, mainly the subject was in low severity. The severity assessment is becoming a more significant part of CAP management to help clinicians predict the disease's fate upon presentation and reduce CAP-related mortality (Xiao et al., 2013).

Most of the subjects were hospitalized in 3-5 days. In line with this study, based on statistical data in the US, the average length of stay (LOS) of pneumonia non ICU was 4.7 days (Elflein, 2018). A study

in Indonesia reported that the median LOS of pneumonia in Levofloxacin therapy was 5 days (Suratini et al., 2017).

Cardiovascular disease (CVD) was the most common comorbidity among the participants. Some studies reported that patients with CVD had a higher risk of CAP (Corrales-Medina et al., 2011; Restrepo & Reyes, 2018; Yeh et al., 2019). Moreover, pneumonia hospitalization in older adults was linked to an increase in the risk of CVD. Infections can promote proinflammatory alterations in atherosclerotic lesions' cellular makeup, making them more prone to coronary and cerebrovascular events. Chronic systemic inflammatory activity is an established risk factor for CVD (Kaptoge et al., 2014).

Table 1. Baseline characteristic of the studies subject

Characteristics	LVX (n=30)	CRO (n=23)	CRO + AZM (n=13)	Total (n=66)	p value
Sex, n (%)					
Female	13 (43.3%)	10 (43.5%)	5 (38.5%)	28 (42.4%)	0.949
Male	17 (56.7%)	13 (56.5%)	8 (61.5%)	48 (59.2%)	
Age, mean (SD) years	59.9 (17.8)	58.9 (18.1)	59.9 (19.8)	59.6 (18.0)	0.976
Age classification, n(%)					
18-25 years old	1 (3.3%)	1 (4.3%)	2 (15.4%)	4 (6.1%)	0.629
26-35 years old	3 (10%)	2 (8.7%)	0 (0%)	5 (7.6%)	
36-45 years old	3 (10%)	2 (8.7%)	0 (0%)	5 (7.6%)	
46-55 years old	2 (6.7%)	4 (17.4%)	2 (15.4%)	8 (12.1%)	
56-65 years old	8 (26.7%)	5 (21.7%)	3 (23.1%)	16 (24.2%)	
>65 years old	13 (43.3%)	9 (39.1%)	6 (46.2%)	28 (42.4%)	
LOS, n (%)					
3-5 days	21 (70%)	12 (52.2%)	8 (61.5%)	41 (62.1%)	0.492
6-7 days	7 (23.2%)	6 (26.1%)	4 (30.8%)	17 (25.8%)	
8-10 days	2 (6.7%)	5 (21.7%)	1 (7.7%)	8 (12.1%)	
Scoring PSI					
I-III (*Low)*	14 (46.7%)	10 (43.5%)	6 (46.2%)	30 (45.5%)	0.662
IV (*Moderate*)	11 (36.7%)	10 (43.5%)	3 (23.1%)	24 (26.4%)	
V (*High*)	5 (16.7%)	3 (13%)	4 (30.8%)	12 (18.2%)	
Comorbidities, n (%)					
Type 2 Diabetes Mellitus	12 (26.1%)	4 (14.8%)	6 (27.3%)	22 (23.2%)	0.658
Cardiovascular disease	19 (41.3%)	11 (40.7%)	8 (36.4%)	38 (40%)	
Cerebrovascular	2 (4.3%)	0 (0%)	1 (4.5%)	3 (3.2%)	
Renal disease	1 (2.2%)	5 (18.5%)	3 (13.6%)	9 (9.5%)	
Hepatic disorders	1 (2.2%)	2 (7.4%)	0 (0%)	3 (3.2%)	
Asthma	1 (2.2%)	1 (3.7%)	1 (4.5%)	3 (3.2%)	
COPD	2 (4.3%)	1 (3.7%)	1 (4.5%)	4 (4.2%)	
Tuberculosis	1 (2.2%)	1 (3.7%)	0 (0%)	2 (2.1%)	

CRO: Ceftriaxone; AZM: Azithromycin; LVX: Levofloxacin; LOS: Length of Stay; PSI: Pneumonia Severity Index; COPD: Chronic Obstructive Pulmonary Disease. p-value: Significance value, p value>0.05 there is no significant difference between the two groups

Effectiveness of empirical antibiotics

The effectiveness profile of all antibiotic groups is shown in Table 2. Ceftriaxone was set as a comparator because the newest guideline suggested a combination of ceftriaxone and azithromycin or levofloxacin as the standard regimen for inpatient CAP (Burhan et al., 2020). The study showed that levofloxacin demonstrated the best ability compared to ceftriaxone and the combination of ceftriaxone + azithromycin at low, moderate, and high severity levels. Treatment was defined as effective if no more than one of the clinical instability criteria related to CAP. The primary outcome was measured 72 hours after antibiotics were used (Mandell et al., 2007). In line with other research on a prospective randomized trial comparing the effectiveness of clinical responses between levofloxacin and ceftriaxone, it was stated that levofloxacin was better than ceftriaxone with a success rate of 96% in the levofloxacin group and by 89% in the ceftriaxone group. However, this finding was contradictive with a study in India that stated that ceftriaxone was more cost-effective than levofloxacin (Sriram et al., 2013). It proved that antibiotics' effectiveness profile can differ from one region to another.

Table 2. The Effectiveness comparison between antibiotic groups based on CAP severity level

Antibiotic group	Severity level	Effectiveness (%)		P value
		Clinical stability	Clinical instability	
LVX (n=14)	*Low*	14 (100%)	0 (0%)	0,163
CRO (n=10)		8 (80%)	2 (20%)	Reference
CRO + AZM (n=6)		4 (66,7%)	2 (33,3%)	0,604
LVX (n= 11)	*Moderate*	11 (100%)	0 (0%)	0,214
CRO (n=10)		8 (80%)	2 (20%)	Reference
CRO + AZM (n=3)		3 (100%)	0 (0%)	1,000
LVX (n=5)	*High*	4 (80%)	1 (20%)	1,000
CRO (n=3)		2 (66,7%)	1 (33,3%)	Reference
CRO + AZM (n=4)		2 (50%)	2 (50%)	1,000

CRO: Ceftriaxone; AZM: Azithromycin; LVX: Levofloxacin.; p-value: Significance value (Fisher's test), p*: effectiveness significantly different; p value>0.05 there is no significant difference between the two groups

This study has shown that in low severity cases, a combination of ceftriaxone and azithromycin was not effective in 33,33% of patients. A meta-analysis review also reported that overall levofloxacin was superior because the number of clinical failure rates that occurred was less than the combination of ceftriaxone + azithromycin in nine studies in non-ICU hospitalized patients [RR = 0.72 (0.57- 0.91)]. A study reported that ceftriaxone and azithromycin combination therapy showed an increase in CD86 ligand, a major class II histocompatibility complex in neutrophils and cytotoxic T lymphocytes compared to ceftriaxone alone, this can result in a decrease in the amount of normal flora in the respiratory system and thus result in worsening clinical response. Hence, azithromycin addition didn't give a better effect. However, combination ceftriaxone and azithromycin could be a choice of therapy for CAP to minimize the occurrence of bacterial multi-resistant and treatment options inpatient with atypical pneumonia or Streptococcus pneumonia resistant to antibiotics (Izadi et al., 2018). Unfortunately, this study could not evaluate the causative antibiotics susceptibility profile due to the lack of retrospective data.

Cost Analysis

In this study, costs were calculated using a healthcare perspective so that the total costs calculated were direct medical costs. Limited access to detailed cost data is a weakness in this study. Investigators were unable to calculate the percentage for each component of direct medical costs. Because the

antibiotics being compared at different levels of severity have no significant differences, the cost calculations can be combined. The cost-effectiveness analysis was carried out by comparing the direct total medical cost with the effectiveness, which was calculated by the success rate in each treatment group. The results of cost-effectiveness analyses are shown in Table 3.

Table 3. CEA outcomes and ICER calculation

Antibiotic Groups	Average Total Cost (Rp)(±SE)	Effectivity (%)	Incremental Cost (Rp)	Inceremental Effectivity (%)	CEA Outcomes	ICER (Rp/%effectivity)
CRO (n=23)	4,744,221 ± 2,181,360	78.3	Reference			
LVX (n=30)	5,171,054 ± 2,280,582	96.7	426,833	18.4	Need ICER Calculation	23,197
CRO+AZM (n=13)	4,886,010 ± 2,826,587	69.2	141,789	-9.1	Dominated [not worthy of being chosen]	-

AZM: Azythromicin; CRO: Ceftriaxone; LVX: Levofloxacin; CEA: Cost-Effectiveness Analysis; ICER: Incremental Cost-Effectiveness Ratio

The use of levofloxacin instead of ceftriaxone improved clinical response, but it is more expensive. Therefore, it was necessary to calculate ICER whether the required increase in costs was reasonable. The study showed that it needs to cost Rp 23,197 to get a 1% increase in effectiveness. In contrast to levofloxacin, the combination of ceftriaxone and azithromycin showed a higher cost with lower effectiveness. It means that a combination of ceftriaxone and azithromycin is not worthy of being chosen. Based on this study, the use of levofloxacin as the first-line therapy for CAP could be maintained because it was more cost-effective than other alternatives.

Sensitivity analysis is carried out to determine the extent to which changes in the cost or effectiveness value used to calculate ACER can affect the conclusions. Sensitivity analysis is the main method for dealing with uncertainty in analysis (Kemenkes, 2013). For the existing uncertainty to be properly calculated, the impact of the uncertainty element must be identified, assessed, and interpreted, especially for the most dominant parameter in the study results. To analyze the impact of uncertainty, it is commonly used a sensitivity analysis. The results of sensitivity analyses are shown in Table 4.

Sensitivity analysis is not to conclude choosing the most cost-effective intervention only for calculating ACER because changes in costs can affect the conclusion. At baseline cost, levofloxacin was the most cost-effective, seen from the lowest ACER value. The results of the levofloxacin sensitivity analysis show that levofloxacin is sensitive to changes in cost. At the highest cost, the cost-effectiveness of levofloxacin changes to be less cost-effective than ceftriaxone. This contrasts with the combination of ceftriaxone + azithromycin which is insensitive to cost changes. This shows that the results of the cost-effectiveness of ceftriaxone + azithromycin are not affected by changes in costs. Ceftriaxone will be the most cost effective in the lowest cost compared to baseline cost of levofloxacin and combination of ceftriaxone and azithromycin.

However, this study was conducted only in a hospital so generalizability for the Indonesian population is limited. The disproportionate number of samples based on the antibiotic group is also a limitation of this study. Studies in a large number of subjects in different regions in Indonesia and the proportionate number of each group were strongly recommended. Lastly, we did not include costs associated with the side effects of the treatments in the present research. Common undesirable side effects of antibiotic treatment, such as diarrhea, Clostridium difficile infections, and allergic reactions can extend the length of hospitalization and increase costs.

Table 4. Sensitivity analysis

Sensitivity	Cost(Rp)	Effectiveness (%)	ACER (Rp/%effectiveness)
CRO			
baseline	4,744,211	78.3	60590
lowest cost	2,103,743	78.3	26868
highest cost	10,153,232	78.3	129671
LVX			
baseline	5,171,054	96.7	53.475
lowest cost	1,408,936	96.7	14.570
highest cost	12,704,170	96.7	131.377
CRO+AZM			
baseline	4,886,010	69.2	70.607
lowest cost	1,878,729	69.2	27.149
highest cost	10,834,413	69.2	156.567

LVX = Levofloxacin; CRO = Cefriaxone; AZM = Azitromisin, ACER = Average Cost Effectiveness Ratio

CONCLUSION

The use of levofloxacin instead of ceftriaxone improved clinical response, but it is more expensive. Levofloxacin was the most cost-effective seen from the ACER was the lowest than the other two groups. Treatment using a combination of ceftriaxone + azithromycin was more expensive without added benefit. Based on this study, the use of levofloxacin as the first-line therapy for CAP could be maintained because it was more cost-effective than other alternatives. However, a study on a broader population is needed to confirm these findings.

ACKNOWLEDGEMENT

We would like to thank the Research and Service Institutions of Universitas Sebelas Maret for Research Grant to support this study.

REFERENCES

Alavi-Moghaddam, M., Bakhshi, H., Rezaei, B., & Khashayar, P. (2013). Pneumonia severity index compared to CURB-65 in predicting the outcome of community acquired pneumonia among patients referred to an Iranian emergency. *Brazilian Journal of Infectious Diseases*, *17*(2), 179–183. https://doi.org/10.1016/J.BJID.2012.10.012

Azmi, S., Aljunid, S. M., Maimaiti, N., Ali, A.-A., Muhammad Nur, A., De Rosas-Valera, M., Encluna, J., Mohamed, R., Wibowo, B., Komaryani, K., & Roberts, C. (2016). Assessing the burden of pneumonia using administrative data from Malaysia, Indonesia, and the Philippines. *International Journal of Infectious Diseases*, *49*, 87–93. https://doi.org/10.1016/J.IJID.2016.05.021

Burhan, E., Isbaniyah, F., Susanto, A. D., Aditama, T. Y., Soedarsono, Sartono, T. R., et al., (2020). *Pneumonia Covid-19 Diagnosis dan Penatalaksanaan di Indonesia*. Persatuan Dokter Paru Indonesia

Cillóniz, C., Ewig, S., Polverino, E., Marcos, M. A., Esquinas, C., Gabarrús, A., Mensa, J., & Torres, A. (2011). Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax*, *66*(4), 340–346. https://doi.org/10.1136/thx.2010.143982

Corrales-Medina, V. F., Suh, K. N., Rose, G., Chirinos, J. A., Doucette, S., Cameron, D. W., &

Fergusson, D. A. (2011). Cardiac Complications in Patients with Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis of Observational Studies. *PLoS Medicine*, *8*(6), e1001048. https://doi.org/10.1371/journal.pmed.1001048

Elflein, J. (2018, August). *Pneumonia patient hospital stay duration by age and setting U.S. 2014 | Statista*. https://www.statista.com/statistics/913891/pneumonia-patient-average-hospital-stay-length-icu/

Ewig, S., Höffken, G., Kern, W., Rohde, G., Flick, H., Krause, R., Ott, S., Bauer, T., Dalhoff, K., Gatermann, S., Kolditz, M., Krüger, S., Lorenz, J., Pletz, M., de Roux, A., Schaaf, B., Schaberg, T., Schütte, H., & Welte, T. (2016). Management of Adult Community-Acquired Pneumonia and Prevention– Update 2016. *Pneumologie*, *70*(03), 151–200. https://doi.org/10.1055/s-0042-101873

Farida, Y., Puspita, K., & Yusvida, Z. (2019). Empirical Antibiotics Study on Pneumonia in Intensive Care Unit. *Proceedings of the 1st Muhammadiyah International Conference on Health and Pharmaceutical Development (MICH-PhD 2018)*, *36*, 48–53. https://doi.org/10.5220/0008239200480053

File, T. M., Bartlett, J. G., & Thorner, A. R. (2021). *Treatment of community-acquired pneumonia in adults who require hosp ... Treatment of community-acquired pneumonia in adults who require hosp ...* UptoDate. https://www.uptodate.com/contents/treatment-of-community-acquired-pneumonia-in-adults-who-require-hospitalization

Ho, P.-L., Cheng, V. C.-C., & Chu, C.-M. (2009). Antibiotic Resistance in Community-Acquired Pneumonia Caused by Streptococcus pneumoniae , Methicillin-Resistant Staphylococcus aureus , and Acinetobacter baumannii. *Chest*, *136*(4), 1119–1127. https://doi.org/10.1378/chest.09-0285

Izadi, M., Dadsetan, B., Najafi, Z., Jafari, S., Mazaheri, E., Dadras, O., Heidari, H., SeyedAlinaghi, S., & Voltarelli, F. (2018). Levofloxacin Versus Ceftriaxone and Azithromycin Combination in the Treatment of Community Acquired Pneumonia in Hospitalized Patients. *Recent Patents on Anti-Infective Drug Discovery*, *13*(3), 228–239. https://doi.org/10.2174/1574891x13666181024154526

Kaptoge, S., Seshasai, S. R. K., Gao, P., Freitag, D. F., Butterworth, A. S., Borglykke, A., Angelantonio, E. Di, Gudnason, V., Rumley, A., Lowe, G. D. O., Jørgensen, T., & Danesh, J. (2014). Editor's choice: Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *European Heart Journal*, *35*(9), 578. https://doi.org/10.1093/eurheartj/eht367

Kemenkes, D. J. B. K. dan A. K. (2013). *Pedoman Penerapan Kajian Farmakoekonomi* (P. Sarnianto, Z. Fadia, & E. Gusnellyanti (eds.); 1st ed.). Kementrian Kesehatan Republik Indonesia

Konomura, K., Nagai, H., & Akazawa, M. (2017). Economic burden of community-acquired pneumonia among elderly patients: a Japanese perspective. *Pneumonia 2017 9:1*, *9*(1), 1–10. https://doi.org/10.1186/S41479-017-0042-1

Kosar, F., Alici, D. E., Hacibedel, B., Arpınar Yigitbas, B., Golabi, P., & Cuhadaroglu, C. (2017). Burden of community-acquired pneumonia in adults over 18 y of age. *Human Vaccines and Immunotherapeutics*, *13*(7). https://doi.org/10.1080/21645515.2017.1300730

Kourkouta, L., Kotsiftopoulos, C. H., Papageorgiou, M., Iliadis, C. H., & Monios, A. (2017). The Rational Use of Antibiotics Medicine. *Journal of Healthcare Communication*, *2*(3), 27–30

Madhu, S., Augustine, S., Ravi Kumar, Y. S., Kauser M. M., K., Kumar, S. R. V., & Jayaraju, B. S. (2017). Comparative study of CURB-65, Pneumonia Severity Index and IDSA/ATS scoring systems in community acquired pneumonia in an Indian tertiary care setting. *International Journal of Advances in Medicine*, *4*(3), 693. https://doi.org/10.18203/2349-3933.ijam20172088

Mandell, L. A., Wunderink, R. G., Anzueto, A., Bartlett, J. G., Campbell, G. D., Dean, N. C., Dowell, S. F., File, T. M., Musher, D. M., Niederman, M. S., Torres, A., & Whitney, C. G. (2007). *Infectious Diseases Society of America / American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults*. *44*(Suppl 2). https://doi.org/10.1086/511159

McKinnell, J. A., Corman, S., Patel, D., Leung, G. H., Gordon, L. M., & Lodise, T. P. (2018). Effective Antimicrobial Stewardship Strategies for Cost-effective Utilization of Telavancin for the

Treatment of Patients With Hospital-acquired Bacterial Pneumonia Caused by Staphylococcus aureus. *Clinical Therapeutics*, *40*(3), 406-414.e2. https://doi.org/10.1016/j.clinthera.2018.01.010

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

Murter, F., Dimond, K., Gilstrap, C., Grubbs, R., Vowell, C., Maldonado, C., & Jansen, J. W. (2019). Ceftriaxone Monotherapy vs. Ceftriaxone Plus Azithromycin for the Treatment of Community-Acquired Pneumonia in Hospitalized, Non-ICU Patients. *Open Forum Infectious Diseases*, *6*(Suppl 2), S748. https://doi.org/10.1093/OFID/OFZ360.1877

Nalang, A., Citraningtyas, G., & Lolo, W. A. (2018). Analisis Efektivitas Biaya (Cost Effectiveness Analysis) Pengobatan Pneumonia Menggunakan Antibiotik. *Pharmacon*, *7*(3), 321–329. https://doi.org/10.35799/pha.7.2018.20599

Niederman, M., Chastre, J., Solem, C., Wan, Y., Gao, X., Myers, D., Haider, S., Li, J., & Stephens, J. (2014). Health economic evaluation of patients treated for nosocomial pneumonia caused by methicillin-resistant Staphylococcus aureus: secondary analysis of a multicenter randomized clinical trial of vancomycin and linezolid. *Clinical Therapeutics*, *36*(9), 1233–1243. https://doi.org/10.1016/j.clinthera.2014.06.029

Noguchi, S., Yatera, K., Kawanami, T., Fujino, Y., Moro, H., Aoki, N., Komiya, K., Kadota, J., Shime, N., Tsukada, H., Kohno, S., & Mukae, H. (2017). Pneumonia Severity Assessment Tools for Predicting Mortality in Patients with Healthcare-Associated Pneumonia: A Systematic Review and Meta-Analysis. *Respiration*, *93*(6), 441–450. https://doi.org/10.1159/000470915

Queen, M. A., Myers, A. L., Hall, M., Shah, S. S., Williams, D. J., Auger, K. A., Jerardi, K. E., Statile, A. M., & Tieder, J. S. (2014). Comparative Effectiveness of Empiric Antibiotics for Community-Acquired Pneumonia. *Pediatrics*, *133*(1), e23–e29. https://doi.org/10.1542/peds.2013-1773

Ramirez, J., Wiemken, T., Peyrani, P., Arnold, F., Kelley, R., Mattingly, W., Nakamatsu, R., Pena, S., Guinn, B., Furmanek, Persaud, A., Raghuram, A., F, F., L, B., R, B., R, F.-B., R, C., J, B., C, V., … RM, C. (2017). Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *65*(11), 1806–1812. https://doi.org/10.1093/CID/CIX647

Restrepo, M. I., & Reyes, L. F. (2018). Pneumonia as a cardiovascular disease. *Respirology*, *23*(3), 250–259. https://doi.org/10.1111/RESP.13233

Ruiz-Ramos, J., Frasquet, J., Romá, E., Luis Poveda-Andres, J., Salavert-Leti, M., Castellanos, A., Ramirez, P., & Rom, E. (2017). *Cost-effectiveness analysis of implementing an antimicrobial stewardship program in critical care units*. https://doi.org/10.1080/13696998.2017.1311903

Sato, R., Gomez, G., Stephanie, R., & Pinsky, B. (2013). Community-Acquired Pneumonia Episode Costs by Age and Risk in Commercially Insured US Adults Aged ‡ 50 Years. *Appl Health Econ Health Policy (2013)*, *11*, 251–258. https://doi.org/10.1007/s40258-013-0026-0

Smith, M., Fee, C., Mace, S., Maughan, B., Perkins, J., Kaji, A., & Wolf, S. (2021). Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department With Community-Acquired Pneumonia. *Annals of Emergency Medicine*, *77*(1), e1–e57. https://doi.org/10.1016/j.annemergmed.2020.10.024

Sriram, S., Aiswaria, V., Cijo, A., & Mohankumar, T. (2013). Antibiotic sensitivity pattern and cost-effectiveness analysis of antibiotic therapy in an Indian tertiary care teaching hospital. *Journal of Research in Pharmacy Practice*, *2*(2), 70–74. https://doi.org/10.4103/2279-042x.117386

Stupka, J. E., Mortensen, E. M., Anzueto, A., & Restrepo, M. I. (2009). Community-acquired pneumonia in elderly patients. *Aging Health*, *5*(6), 763–774. https://doi.org/10.2217/ahe.09.74

Suratini, S., Sauriasari, R., Hamadah, F., & Kusumaeni, T. (2017). Cost-effectiveness analysis of ceftriaxone-azithromycin combination and single levofloxacin as empirical antibiotics in

community-acquired pneumonia inpatients at persahabatan hospital. *Asian Journal of Pharmaceutical and Clinical Research*, *10*(Special Issue October), 118–123. https://doi.org/10.22159/ajpcr.2017.v10s5.23112

Walger, P. (2016). [Rational use of antibiotics]. *Der Internist*, *57*(6), 551–568. https://doi.org/10.1007/S00108-016-0071-5

Wongsurakiat, P., & Chitwarakorn, N. (2019). Severe community-acquired pneumonia in general medical wards: outcomes and impact of initial antibiotic selection. *BMC Pulmonary Medicine*, *19*(1). https://doi.org/10.1186/S12890-019-0944-1

Wunderink, R. G., & Yin, Y. (2016). *Antibiotic Resistance in Community-Acquired Pneumonia Pathogens*.

Xiao, K., Su, L., Han, B., Yan, P., Yuan, N., Deng, J., Li, J., & Xie, L. (2013). Analysis of the severity and prognosis assessment of aged patients with community-acquired pneumonia: a retrospective study. *Journal of Thoracic Disease*, *5*(5), 626–633. https://doi.org/10.3978/J.ISSN.2072-1439.2013.09.10

Yeh, J.-J., Lin, C.-L., & Kao, C.-H. (2019). Relationship between pneumonia and cardiovascular diseases: A retrospective cohort study of the general population. *European Journal of Internal Medicine*, *59*, 39–45. https://doi.org/10.1016/j.ejim.2018.08.003