Ivana Shafira Putri, Rebriarina Hapsari, V. Rizke Ciptaningtyas

APPROPRIATE USAGE OF ANTIBIOTICS AND ITS COST-EFFECTIVENESS

Ivana Shafira Putri[1*], Rebriarina Hapsari[2], V Rizke Ciptaningtyas[2]
[1]Under graduate student of Faculty of Medicine, Diponegoro University, Semarang
[2]Department of Microbiology, Faculty of Medicine, Diponegoro University, Semarang
*ivanashafira06@gmail.com

ABSTRACT

Background: Inappropriate use of antibiotics not only cause resistance, but also indirectly increase morbidity, mortality, and prolong the length of stay, which can lead to increased health care costs. Pneumonia is one of the infectious diseases with a high prevalence in Indonesia. It requires various antibiotic treatment that makes the antibiotic selection need to be considered in both clinical terms and cost-effectiveness. **Aim:** This study aimed to determine the association between the quality of antibiotic and cost-effectiveness in hospitalized pneumonia patients at Diponegoro National Hospital Semarang in the period 2015 - 2019. **Methods:** A cross-sectional study was performed in fifteen patients with community-acquired pneumonia (CAP). The medical records as samples were retrospectively obtained by total sampling method. The categories of antibiotic quality (appropriate and inappropriate) were determined according to the Gyssens criteria and analyzed using a cost-effectiveness table. The outcome measure was length of stay (LOS). **Results :** Mean LOS, mean antibiotic cost, and median total direct hospital cost of appropriate and inappropriate antibiotic quality respectively 3,27 days versus 6 days (p = 0.275), 123,302 IDR versus 286,000 IDR (p = 0.020), and 3,317,100 IDR versus 3,878,600 IDR (p = 0,602). Based on the cost-effectiveness table, the position of appropriate antibiotic quality was in column G (dominant), while the position of inappropriate antibiotic quality was in column C (dominated). **Conclusions:** The appropriate usage of antibiotics was more cost-effective than inappropriate. There was a significant differences of LOS between both categories.

INTRODUCTION

Pneumonia is one of the leading causes of death with a high incidence rate in the world, which is 15-20%. In Indonesia, it is included in one of the top 10 hospitalization diseases.[1,2] Based on the latest basic health research by the Indonesian government, there has been an increase in the prevalence of pneumonia from 1.6 to 2%.[3]

Empirical antibiotics have been the initial therapy for pneumonia due to obstacles in identifying etiology. However, the excessive and indiscriminate use of these so-called miracle drugs has led to the emergence and dissemination of resistant organisms which associated with greater morbidity and mortality. In addition, it has a substantial economic impact because of the need for more expensive second-line drugs and longer length of stay (LOS) associated with therapy failure.[4] Gyssens algorithm is used to evaluate and ensure the quality of antibiotic which can be cathegorized as appropriate and inappropriate.[5] Appropriate use of antibiotic means choosing not only the correct antibiotic but also the appropriate dose

and duration, factors that can influence the development and carriage of resistant organisms.[6]

In era of spiraling health care costs and limited resources, policy makers and health care payers are also concerned about the cost effectiveness of antibiotics which can be assessed by cost-effectiveness analysis (CEA).[7] Diponegoro National Hospital Semarang has been established for four years, but there was no research on cost-effectiveness analysis. This study aimed to determine the association between quality of antibiotic and cost-effectiveness in hospitalized pneumonia patients at Diponegoro National Hospital Semarang in 2015 - 2019.

METHOD

This research used an observational study with cross-sectional approach. This study was conducted in Diponegoro National Hospital, Semarang, with retrospective data collection using medical records of hospitalized patients with CAP in the period 2015 – 2019. Samples were obtained by the total sampling method. The inclusion criteria were age ≥18 years and <65

Ivana Shafira Putri, Rebriarina Hapsari, V. Rizke Ciptaningtyas

years; clinical picture compatible with CAP, with two or more of the following sign and symptoms: fever, new or increasing cough or sputum production, dyspnea, pleuritic chest pain, new focal sign on chest examination, and appearance of a new infiltrate in a simple chest radiography; treated with antibiotic; using public health insurance with one cycle of therapy. The exclusion criteria were incomplete and unclear data; quality category of medicines VI according to the Gyssen method; nosocomial pneumonia (HAP or VAP), with immunocompromised diseases, other infections, cancer, and aspiration; discharged without a recommendation from the doctor or died. The independent variable was the quality of antibiotics, while the dependent variable was cost-effectiveness. The study was approved by the Medical Research Ethical Committee of Faculty of Medicine, Diponegoro University, and director of Diponegoro National Hospital Semarang. Data collection included demographic and clinical data: medical record number, age, sex, diagnosis, date of entry and exit inpatient installation, data of public health insurance, name, type, indication, method of administration, dosage, frequency, and duration of antibiotics obtained, as well as cost of treatment. The quality of the initial antibiotic regimen for each patient was evaluated and categorized as appropriate and inappropriate according to the Gyssen criteria. Cost-effectiveness was analyzed by determining the position of each category of antibiotic quality in the cost-effectiveness table. The costs calculated were total direct hospital costs consisting of the expenses of hospitalization, antibiotics, medicines, medical devices, health care, emergency measures, supporting examinations, and administration. The standard of the overall effectiveness of treatment was LOS. Statistical analysis was used to determine the difference in LOS, antibiotic costs, and total direct hospital costs between the appropriate and inappropriate use of antibiotics. The t-independent test was used if the data had a normal distribution and Mann-Whitney test if the data has abnormal distribution. The result said to be significant if $p < 0.05$.

RESULT

The study was held from June to July 2019. There were fifteen samples obtained under the inclusion and exclusion criteria. Table 1 summaries the demographic characteristics.

Table 1. Demographic characteristic

Variables	Subjects (n)	%
Sex		
Male	3	20.0
Female	12	80.0
Age group		
< 40 years		
40 – 60 years	2	13.3
> 60 years	8	53.3
	5	33.3

Of the fifteen medical records, seventeen antibiotics were prescribed. Fifteen patients received a single antibiotic, and two patients received a combination of 2 types of antibiotics.

Table 2. Distribution of antibiotic use

Antibiotic	Subjects (n)	%
Single		
Ceftriaxone (iv)	7	46.7
Levofloxacin (iv)	4	26.7
Levofloxacin (po)	1	6.7
Cefixime (po)	1	6.7
Combination		
Ceftriaxone (iv) + Azithromycin (po)	2	13.3

iv = intravenous
po = peroral

Quality of Antibiotic

Based on the Gyssen method, the quality uses of antibiotics were divided to become a appropriate and inappropriate category. Category 0 indicated a appropriate use of antibiotics, while category I-V indicated inappropriate use of antibiotics.

Ivana Shafira Putri, Rebriarina Hapsari, V. Rizke Ciptaningtyas

Table 3. Results of antibiotic quality evaluation based on Gyssen method

Category	Frequency (number of prescriptions)	%
0 (appropriate)	13	73.3
IIA (inappropriate)	3	20.0
IIA + IIIA (inappropriate)	1	6.7

Statistical Analysis

The LOS dan antibiotic costs between two categories of antibiotic quality were normally distributed while the total direct hospital costs between two groups of the antibiotic class was not. Data on LOS and antibiotic costs fulfilled parametric tests; therefore, the difference in LOS and antibiotic costs between the two categories of antibiotic quality were analyzed using t-independent analysis. Data on total direct hospital costs between two groups of antibiotic quality fulfilled non-parametric tests; therefore, the difference in total direct hospital costs between the two categories of antibiotic quality was analyzed using Mann-Whitney test.

Table 4. Distribution and statistical analysis of LOS, antibiotic costs, and total direct hospital costs on each category of antibiotic quality

Variable	Appropriate quality of antibiotic (n=11)	Inappropriate quality of antibiotic (n=4)	P-value
LOS (days)			
- Mean	3.27	6	0.275
- Median	3	4.5	
- Range	2 – 5	3 – 12	
Total direct hospital cost (IDR)			
- Mean	3,980,677	6,696,050 3,878,600	0.020
- Median	3,317,100	3.028.300 –	
- Range	1,621,850 – 8,665,700	15.998.700	
Antibiotic cost (IDR)			
- Mean	123,302	981,012 286,000	0.020
- Median	121,914	178,750 –	
- Rentang	3,424 – 234,012	3,173,300	

Cost-effectiveness Analysis

Both mean and median LOS of the appropriate category had a shorter duration than the inappropriate group. It means the appropriate group had higher effectiveness. On the other hand, the mean and median total direct hospital costs of the appropriate category were lower than the inappropriate group. The position of the appropriate and inappropriate antibiotic quality based on total direct hospital costs and LOS are displayed in table 5.

Table 5. Position of each antibiotic quality in cost-effectiveness table

Cost-Effectiveness	Lower cost	Equal cost	Higher cost
Lower effectiveness	A (need ICER calculation)	B	**C Inappropriate** (dominated)
Equal effectiveness	D	E	F
Higher effectiveness	**G Appropriate** (dominant)	H	I

Ivana Shafira Putri, Rebriarina Hapsari, V. Rizke Ciptaningtyas

DISCUSSION

The most relevant results of the present study were : 1) the appropriate use of antibiotics was quite high; 2) the appropriate quality use of antibiotic was a dominant alternative since the outcome was more effective compared with inappropriate (mean 3.27 days versus 6 days; median LOS 3 days versus 4.5 days) and less expensive (mean 3,980,677 IDR versus 6,696,050 IDR; median 3,317,100 IDR versus 3,878,600 IDR), as demonstrated by cost-effectiveness analysis in cost-effectiveness table.

Our study reported a higher prevalence of pneumonia in females (80%) compared to males (20%). It is supported by previous research in Regional General Hospital, Cengkareng that the number of female pneumonia patients was higher (51.5%) than male patients (48.5%).[8] Another study in Pakistan showed different results. It was found that the percentage of male patients was higher compared to female patients.[9] However, a study in Spain reported that there was no significant relationship between sex and CAP.[10] There were different risk factors for each sex, obesity and lack of physical activity were risk factors for women but not for men, while age and smoking history were risk factors for men but for women only for those who were active smokers.[11] The most frequent age group in the present study were in the range of 40-60 years (53.3%). It is consistent with the data of Indonesia's basic health research in 2013, the highest prevalence of pneumonia cases occurred in 2 age groups which were 1-4 years and 45-54 years, and is increasing in the next age group.[12]

In the present study, antibiotic prescriptions included in the appropriate usage category were dominant (73,33%) and were similar to the previous research conducted in Padang, which showed that the number of rational antibiotic usage was higher compared to irrational antibiotic usage.[13] In contrast to study in Surakarta, it was found that 88.89% of antibiotic use was unreasonable.[14] The high accuracy of antibiotic use in the present study is estimated due to the use of antibiotics enough to be considered by various parties, ranging from doctors who prescribed antibiotics based on guidelines and literature to clinical pharmacists who monitored antibiotic prescribing.

The LOS in two antibiotic categories did not show a significant difference (p=0.275). A similar finding was found in the previous study in Turkey that there was no significant difference between LOS for CAP patients given empirical antibiotics according to and not according to guidelines. That study referred to the Turkish Thoracic Society (TTS) CAP guideline, while the present study referred to ATS/IDSA and Gyssens method.[15] This is different from research in a hospital in Jakarta that there was a significant difference between LOS of CAP patients adhered to ATS/IDSA 2007 compared to those not (p<0.001). That study explained that limitations of motion activity (immobilization) were a confounding variable that can affect the LOS of CAP patients receiving empirical antibiotics, while in this study, no analysis of confounding variables can affect the LOS of the patient.[16] The LOS of patients with CAP is influenced by several factors such as health care system and hospital management, clinical practice by physicians, and patient characteristic.[17]

Both median total direct hospital costs and mean antibiotic costs in pneumonia patients with the appropriate usage of antibiotics was less than the inappropriate. Statistical test results showed no statistically significant difference of total direct hospital costs in the two categories of antibiotic quality (p=0.602), but there was a significant difference in antibiotic expenses in both categories (p=0.020). Previous study in Turkey reported that there was no statistically significant difference between total direct medical cost in CAP patients given antibiotics in accordance with guidelines and not (p=0.311). But there was an approximate difference of 500 Euro between groups. In addition, the grouping of subjects and cost analysis were carried out based on the PSI score. It was also explained that the most influential factor in total direct hospital costs was a comorbid disease. Total direct hospital costs in the high-risk group according to the TTS CAP guideline, PSI score, and comorbid have a higher amount than the low-risk group.[15] The test result of differences antibiotic costs is in line with research in Florida that there was a significant difference between the cost of antibiotics in CAP inpatients given antibiotics according to IDSA and those not

Ivana Shafira Putri, Rebriarina Hapsari, V. Rizke Ciptaningtyas

(p=0.038).[18] Previous research in Yogyakarta also reported that rational use of antibiotic had lower antibiotic costs compared to irrational.[19] However, these studies did not perform any cost-effectiveness analyses. Another study showed that LOS affected antibiotic costs (p<0,001).[20] The statement is in accordance with the present study, where patients with appropriate antibiotic use had shorter median LOS. This may cause the antibiotic cost can be reduced to a minimum.

In the present study, it was found that the appropriate quality use of antibiotics was more cost-effective since its position in the cost-effectiveness table was in column G versus column D for inappropriate quality use of antibiotics. It was decided that column D, G, H (dominant columns) indicated a predominant alternative that should be chosen due to its cost-effectiveness. Meanwhile, all columns except D, G, H (dominated columns) showed that alternative therapy should not be considered as an option.[21]

As a limitation of the present study it should be highlighted that this study only used retrospective data which researchers only depended on medical records, the number of samples was small even though total sampling methods have been used, the samples have not been reviewed in terms of severity and have not paid attention to other factors such as comorbid diseases, nutritional status, immunity, severity of disease, and clinical condition of patient.

CONCLUSION

In summary, the appropriate usage of antibiotics was more cost-effective than inappropriate. There was a significant differences of LOS between appropriate and inappropriate group.

REFERENCES

[1]   Perhimpunan Dokter Paru Indonesia. Pneumonia Komunitas Pedoman Diagnosis Penatalaksanaan Di Indonesia. II. Badan Penerbit FKUI; 2014.

[2]   Dahlan Z. Pneumonia. Dalam (Siti S, Idrus A, Aru W S, Marcellus S K, Bambang S, Ari F S) Buku Ajar Penyakit Dalam Jilid II. VI. Jakarta: Interna Publishing; 2014. Pneumonia.

[3]   Balitbang Kemenkes RI. Potret Sehat Indonesia dari Riskesdas 2018 [Internet]. Biro Komunikasi dan Pelayanan Masyarakat, Kementerian Kesehatan RI. 2018 [dikutip 2 Maret 2019]. Tersedia pada: http://www.depkes.go.id/article/view/18110200003/potret-sehat-indonesia-dari-riskesdas-2018.html

[4]   Hulscher MEJL, Grol RPTM, Meer JWM Van Der. Antibiotic Prescribing in Hospitals : A Social and Behavioural Scientific Approach. Lancet Infect Dis. 2010;10:165–75.

[5]   Aryani DE, Hasmono D, Zairina N, Setiawan L. Analysis of Antibiotics Use in Pediatric Pneumonia Patients Aged 3 Months - 5 Years. Folia Medica Indones. 2014;52(2):108–15.

[6]   Lieberman JAYM. Appropriate Antibiotic Use and Why It Is Important : The Challenges of Bacterial. Pediatr Infect Dis J. 2003;22(12):1143–51.

[7]   Simoens S. Factors Affecting the Cost Effectiveness of Antibiotics. Hindawi Publ Corp. 2011;

[8]   Nabil A, Jalil A, Studi P, Dokter P, Kedokteran F, Ilmu DAN, et al. Profil Pasien Pneumonia Komunitas di Rumah Sakit Umum Daerah Cengkareng Tahun 2013 - 2014. 2015;

[9]   Malik AS KM. Profiles of Community Acquired Pneumonia Cases Admitted to a Tertiary Care Hospital. Park J Med Sci. 2012;(28(1)):75–8.

[10]   Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, Raga-Luria X, Gomez-Bertomeu F. Epidemiology of Community-Acquired Pneumonia in Older Adults: a Population-based Study. Respir Med. 2009;103:309-316.

[11]   Baik I, Curhan G, Rimm E, Bendich A, Willett W, Fawzi W. A Prospective Study of Age and Lifesyle Factors in Relation to Community-Acquired Pneumonia in US Men and Women. Arch Intern Med. 2000;160(20):3082–8.

[12]   Kemenkes : Kementrian Kesehatan Republik Indonesia. Riset Kesehatan Dasar. Jakarta. 2013;

[13]   Ade TW. Evaluasi Kualitas Penggunaan

Ivana Shafira Putri, Rebriarina Hapsari, V. Rizke Ciptaningtyas

Antibiotik pada Pasien Pneumonia Komunitas di Bangsal Penyakit dalam RSUP Dr. M. Djamil Padang dengan Metode Gyssens. 2018;

[14] Dewi NT. Kajian Penggunaan Antibiotik Pada Pasien Pneumonia Dengan Metode Gyssens Di Balai Kesehatan "X" Surakarta Tahun 2012-2013. 2014;3–16.

[15] Doruk S, Tertemİz KC, Kömüs N, Uçan ES, Kilinç O, Sevİnç C. Community-Acquired Pneumonia and Direct Hospital Cost. Tüberküloz ve Toraks Derg. 2009;57(1):48–55.

[16] Munarsih FC, Natadidjadja RI, Syamsudin. Pengaruh Pemberian Antibiotik Berdasar Panduan terhadap Lama Tinggal pada Pasien Pneumonia Komunitas di Rumah Sakit. J Penyakit Dalam Indones. 2018;5(3):141–5.

[17] Mataro H De, Mataro H De, Service ID, Bellvitge H. Factors Influencing Length of Hospital Stay in Community-Acquired Pneumonia : a Study in 27 Community Hospitals. 2004;821–9.

[18] Orrick JJ, Segal R, Johns TE, Russell W, Wang F, Yin DD. Resource Use and Cost of Care for Patients Hospitalised with Community Acquired Pneumonia: Impact of Adherence to Infectious Diseases Society of America Guidelines. 2004;22(11):751–7.

[19] Erwanti G. Evaluasi Penggunaan Antibiotik dan Analisis Biaya Pasien Rawat Inap dengan Community Acquired Pneumonia (CAP). Gadjah Mada University; 2018.

[20] Kristiani F, Radji M, Rianti A. Evaluasi Penggunaan Antibiotika Secara Kualitatif dan Analisis Efektivitas Biaya pada Pasien Pediatri di RSUP Fatmawati Jakarta. 2019;6(1):46–53.

[21] Kementerian Kesehatan Republik Indonesia. Pedoman Penerapan Kajian Farmakoekonomi. Vol. 6. 2013.