

Appropriate Antibiotic Use for Community-Acquired Pneumonia in Inpatient Settings and Its Impact on 30-days Readmission and Mortality Rate

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Abstract

Background: Community-Acquired Pneumonia (CAP) is a lower respiratory tract infection with bacteria as the most frequent causative agent. Therapy for pneumonia includes appropriate antibiotic usage. Inappropriate antibiotic use supposedly increase 30-days readmission and mortality rate.

Objective: To evaluate the antibiotic use and the impact of appropriate antibiotic use on the 30-days readmission and mortality of CAP patients in inpatient non-ICU settings.

Method: A cross-sectional, analytic study was conducted. We collected data from Universitas Airlangga hospital's medical record to obtain the details of antibiotic usage. Result were evaluated using the Gyssens algorithm. A *chi-square* test was used to identify the impact of appropriate antibiotic use on the 30-days readmission and mortality.

Result: A total of 90 patients with CAP fulfilled the inclusion criteria. One gram of ceftriaxone IV was the most prescribed antibiotic for therapy of CAP. The amount of appropriate antibiotic use is 85.6%. Five patients (5.6%) went through the 30-days readmission. There was no death reported. The statistical test between antibiotic use and 30-days readmission obtained *p* value=0.894 (*p*>0.05).

Conclusion: There was no significant impact of appropriate antibiotic use on the 30-days readmission rate and the mortality rate could not be assessed.

Keywords: 30-days readmission, antibiotic use, community-acquired pneumonia, Gyssens algorithm, mortality

Introduction

Antibiotic resistance can occur due to inappropriate antibiotic use. This unabating phenomenon increasingly becomes a problem in public health issues. Antibiotic resistance will rapidly increase along with inappropriate antibiotic use¹⁻³. As methicillin was widely used in the 1960s, *Staphylococcus aureus* soon becomes resistant to the drug, treatment decision for MRSA infection can be challenging due to a change in its Penicillin Binding Protein (PBP) so that it is resistant to beta-lactam class antibiotics⁴⁻⁶. WHO stated that in 2013, at least 700.000 people died due to antimicrobial resistance to bacterial

infection, malaria, HIV/AIDS, and tuberculosis. WHO also predicted that there will be approximately 10 million death due to antimicrobial resistance in 2050⁷. Appropriate antibiotic usage is substantial to the success of therapy. Inappropriate Empirical Therapy (IET) is said to be associated with a potentially worse outcome such as higher 30-day readmission rates and mortality rate⁸.

Lower respiratory tract infections, such as CAP, are the most common infection cause of death in the world and are the third cause of global death in 2008⁹. The mortality rate among CAP patients in non-ICU general

ward setting is reported to be around 2%. This rate increases in the ICU setting, >65 years, male, and patient with co-morbid diseases¹⁰. This study was conducted to identify the appropriate antibiotic use in CAP patients and also to evaluate the impact of appropriate antibiotic use on the 30-days readmission and mortality of CAP patients.

Methods

This was a cross-sectional study that included all CAP patients (ICD code J18.9) admitted in inpatient non-ICU settings and were diagnosed with pneumonia in their first assessment examination. Patients were over 18 years old and hospitalized in the general ward of Universitas Airlangga hospital, Surabaya, East Java, from 1 January 2018 to 31 December 2018. We observed the antibiotic use in CAP patients through their medical records and collected data on patients' characteristics, i.e., sex, age, admission date, and length of stay. We also collected data on patients' antibiotic prescriptions, i.e., type of antibiotic, duration of therapy, dosage, route, timing, and interval time of prescription. Later we also observed the patients' outcomes; 30-days readmission and mortality. The independent variable in this study was the antibiotic usage in CAP patients and the dependent variables will be 30-days readmission and mortality. We excluded those with incomplete medical records, patients with other infections, and patients who had been discharged against medical advice (DAMA). Total sampling was used in this study. Antibiotic usage was evaluated using the Gyssens algorithm and on the clinical practice guideline of the ATS/IDSA 2019 as well as the local guideline from *Perhimpunan Dokter Paru Indonesia* (PDPI) 2014^{11,12}. The Gyssens algorithm is a qualitative measurement to assess antibiotic usage and

has been widely used in worldwide studies. The Gyssens algorithm will show the rationality of antibiotic usage based on grouping of 0—VI categories^{2,13}. A *chi-square* test was used to identify the impact of appropriate antibiotic use on the 30-days readmission and mortality.

Result

We collected 90 patients' medical records who fulfil the inclusion and exclusion criteria of the study. Patients characteristic is shown in **Table 1**. The majority of the patient was female (57.8%), aged 45—64 years old (50%), and with the length of stay for 4 days (37.8%). Ceftriaxone (56.7%) was the most prescribed antibiotic for CAP, followed by levofloxacin (28.9%), ceftazidime (7.8%), meropenem (3.3%), cefixime (1.1%), cefotaxime (1.1%), and azithromycin (1.1%). Evaluation of antibiotic usage using the Gyssens algorithm will be expressed as 'appropriate' and 'inappropriate' and is shown in **Table 2**. Antibiotic use in 77 prescriptions were considered as appropriate (85.6%) while in 13 prescriptions were inappropriate (14.4%), according to Gyssens algorithm. The most common type of error was category IIIB (shortened duration) (11.1%). One prescription (1.1%) was classified as category IVA (alternating agent is more effective) and two prescriptions (2.2%) were classified as category VI (incomplete medical record), one of them showed no data of the interval time and the other contained no data regarding the timing of the prescription. It is reported that 5 of 90 patients (5.6%) underwent the 30-days readmission (**Table 3**), in which 3 of them were more than 65 years old and 4 of 5 them had co-morbid diseases (**Table 4**). All five patients who underwent the 30-days readmission had already been given the appropriate antibiotic prescriptions in their initial treatment ($p=0.894$) (**Table 5**). No mortality is reported in this study (**Table 6**.)

Table 1. Characteristics of patient with CAP in 2018

Characteristics	Total (n)
Gender	
Male	38
Female	52
Age (years)	
18-24	2
25-44	7
45-64	45
>65	36
Length of Stay (day)	
2	4
3	28
4	34
5	12
6	5
7	2
8	3
9	2
Antibiotics	
Ceftriaxone	51
Ceftazidime	7
Meropenem	3
Cefixime	1
Cefotaxime	1
Levofloxacin	26
Azithromycin	1
Duration of Therapy (day)	
2	1
3	8
4	2
5	3
6	4
7	10
8	39
9	14
10	5
11	3
12	1
30-Days Readmission	
Yes	5
No	85
Mortality	
Yes	0
No	90

Table 2. Quality of antibiotic use expressed in Gyssens Category

Gyssens Category	Total (n)
0	77
Appropriate	77
I	0
II A	0
II B	0
II C	0
III A	0
III B	10
IV A	1
IV B	0
IV C	0
IV D	0
V	0
VI	2
Inappropriate	13
Total	90

Note: 0: Appropriate; I: Inappropriate timing; IIA: Inappropriate dose; IIB: Inappropriate interval, IIC: Inappropriate route; IIIA: Prolonged duration; IIIB: Shortened duration; IVA: More effective alternating agent; IVB: Less toxic alternative agent; IVC: Less cost alternative agent; IVD: Narrower spectrum alternative agent; V: Inappropriate indication; VI: Incomplete medical record

Table 3. 30-days readmission in CAP patients

30-days readmission	Total (n)
No	85
Yes	5
Total	90

Table 4. Risk Factors in Patients undergo 30-days readmission

	Risk Factors	
	Age	Co-morbid disease
Patient 1	>65	Malignant Neoplasm, Bronchus or Lung
Patient 2	>65	Mediastinum tumor
Patient 3	>65	-
Patient 4	45-64	COPD
Patient 5	45-64	Heart Failure

Table 5. Crosstabulation between 30-days readmission and Gyssens category

30-days readmission	Gyssens Category		Total	p value
	(Gyssens 0)	(Gyssens I—VI)		
No	72	13	85	0.894
Yes	5	0	5	
Total	77	13	90	

Table 6. Mortality in CAP patients

Mortality	Total (n)
No	90
Yes	0
Total	90

Discussion

Types of Antibiotic

According to the 2019 ATS/IDSA Guideline for adults with CAP, two regimens are strongly recommended for CAP therapy in an inpatient setting; monotherapy of levofloxacin and combination therapy of beta-lactam and macrolide. Alternative for adults with both macrolide and fluoroquinolone contraindications is the combination therapy of beta-lactam and doxycycline¹¹.

Monotherapy of levofloxacin was prescribed in 26 patients (29.3%). A systemic review from 16 randomized control study reported that monotherapy of levofloxacin significantly caused less clinical failure, withdrawal, and diarrhea compared to the combination therapy of beta-lactam and macrolide¹⁴.

Monotherapy of beta-lactam was prescribed in 63 patients (70%) and is the most prescribed antibiotic regimen for adults with CAP. Aside from combination therapy, monotherapy of beta-lactam can also be considered as an alternative for inpatients with non-severe CAP¹¹. A randomized controlled trial in 580 patients reported that monotherapy of beta-lactam failed to show noninferiority to combination therapy of beta-lactam and macrolide in moderately severe community-acquired pneumonia¹⁵. Another randomized controlled

trial study also reported that there is no difference in mortality, complication, and length of stay between monotherapy and combination therapy in CAP patients¹⁶.

One patient (1.1%) was prescribed with macrolide azithromycin as their empirical CAP therapy. Macrolide monotherapy is an antibiotic option for adults with CAP in outpatient settings, and is not recommended in inpatient settings¹¹. Macrolide works effective intracellularly and covers pathogens such as Gram-positive bacteria, *Legionella*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*¹⁷. However, macrolide monotherapy should be given based on the resistance level and that is based on studies of macrolide failures in patients with macrolide-resistant *S. pneumoniae*^{18,19}. The rate of macrolide resistance among *Streptococcus pneumoniae* isolates in the United States is reported for >30%, a high level of resistance²⁰.

Duration of Therapy

It is reported that 79 out of 90 prescriptions (87.8%) were given for no less than 5 days, while 11 prescriptions (12.2%) were given for <5 days. According to the guideline by ATS/IDSA 2019, the duration of therapy should be guided by clinical stability (resolution of vital sign abnormalities), ability to eat, and normal mentation. Antibiotics should be given until clinical improvement

is achieved and is strongly recommended to be given for no less than a total of 5 days. Recent data supported that administering antibiotics for less than 5 days is barely sufficient. As most patients will achieve clinical stability in the first 48–72 hours of therapy, the total duration of therapy for 5 days will be sufficient for most patients and 7 days for CAP due to suspected or proven MRSA or *Pseudomonas aeruginosa*^{11,21}.

Appropriate Antibiotic Use

There were 77 prescriptions (85.6%) classified as Gyssens 0, which means that the antibiotic use is appropriate. The result also shows that 10 prescriptions (11.1%) were classified as Gyssens IIIB, which means that the total duration of antibiotic therapy is too short (less than 5 days). Gyssens IIIB is the most common error found in this study. Another type of error is Gyssens IVA, which is found in 1 prescription (1.1%). Gyssens IVA implies that the antibiotic prescription is not appropriate because other antibiotics are more effective. One prescription in this category received azithromycin monotherapy. Azithromycin, which is a macrolide class of antibiotics, should be used together with beta-lactam antibiotics in empirical therapy for CAP in non-ICU inpatients^{11,12}. The combination of beta-lactam and macrolide antibiotic therapy is said to provide better results than monotherapy which associated with a reduction in mortality and / or a shorter length of stay compared to the monotherapy with beta-lactam²².

The use of antibiotics as empirical therapy for CAP in this study can be concluded to have a rate of 85.6% of appropriate antibiotic use and 14.4% in other categories (Gyssens I-VI).

30-days Readmission

Five patients (5.6%) underwent readmission with the same diagnosis within 30 days after the patient was discharged. Early hospital readmission is a common and costly occurrence in elderly and high-risk patients. To improve the quality of care and to reduce unnecessary health expense, policymakers have made reducing 30-days readmission as a priority²³. The incidence of 30-days readmission is often found in patients with CAP²⁴. Zillberg *et al* stated that the 30-days readmission rate would increase if patients received inappropriate empirical therapy⁸. However, all five patients who

underwent the 30-days readmission in this study had received appropriate therapy (Gyssens 0) on their initial CAP treatment. The statistical test between the 30-days readmission and the appropriate antibiotic use with chi-square test method obtained p -value = 0.894 ($p > 0.05$), suggesting that the incidence of 30-days readmission is not influenced by the appropriate antibiotic use and it can be concluded that the appropriate antibiotic use in this study has no significant impact on the 30-days readmission.

Undergoing the 30-days readmission while receiving appropriate therapy in the patients' initial infection can occur due to some considerations. Factors such as age, immunodeficiency, malignancy, heart failure, and chronic conditions can increase the proportion of pneumonia cases that fail to have complete resolution. In other words, readmission for pneumonia may occur due to unavoidable causes. Patients with COPD, heart failure, diabetes, and malignancy will increase the proportion of readmission for pneumonia cases²⁵

In this study, 3 patients who underwent readmission were > 65 years old. Old age is related to a decrease in the general condition of the functional organ so individuals are more at risk of developing pneumonia²⁶. Meanwhile, 4 patients had medical conditions other than CAP itself, such as malignancy, COPD, and heart failure. Those are known factors that cannot be avoided in readmission of CAP cases²⁵.

Mortality

No mortality was found in this study. According to the guideline by PDPI in 2014, the mortality rate of CAP in inpatient settings is 5–20% and it will greatly increase in intensive care unit by more than 50%. However, it is also stated that the prognosis for CAP is generally good depending on several factors such as patient factors, causative bacteria, and the use of appropriate antibiotics¹². We could not assess the impact of the appropriate use of antibiotics on mortality rate as there is zero mortality in both appropriate and inappropriate antibiotic use in this study.

Conclusion

Appropriate antibiotic use in adults with CAP in inpatient non-ICU settings of Universitas Airlangga

Hospital is 85.6%. The most common error in antibiotic usage is shortened duration (Gyssens IVA). The 30-days readmission rate is 5.6% and the mortality rate is zero. There was no significant impact of appropriate antibiotic use on the 30-days readmission and the impact of appropriate antibiotic use on mortality rate could not be assessed as there was no death in this study.

Ethical Clearance: This original research study had been approved by the Universitas Airlangga hospital Surabaya ethical committee in health research (3594/UN3.9.1/PPd/2019).

Conflict of Interest: The authors declare that they have no conflict of interest.

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