Media Farmasi: Jurnal Ilmu Farmasi (Journal of Pharmaceutical Science) e-ISSN 2503-5223
Vol. 20, No. 2, Sep 2023, pp. 64-71
http://journal.uad.ac.id/index.php/Media-Farmasi/index

Relationship between Appropriate Antibiotics Used Based on 2019 ATS/IDSA Guideline and Clinical Improvement in Inpatient Community-Acquired Pneumonia Patients

Mensiana Ayu Maju, Christianus Heru Setiawan*

Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia
*corresponding author: chs_heru@usd.ac.id

ARTICLE INFO

Article history
Received: 14-07-2022
Revised: 03-04-2023
Accepted: 31-07-2023

Keywords
Antibiotics
Clinical Improvement
Community-Acquired Pneumonia (CAP)
2019 ATS/IDSA Guideline

ABSTRACT

Community-acquired pneumonia (CAP) can result from a bacterial infection that is acquired in the community. Without proper treatment, this infection can result in lung inflammation and death. An appropriate choice of empirical antibiotics can increase the success of therapy and prevent the development of bacterial resistance to various types of antibiotics. This study aims to assess the appropriateness of empiric antibiotic selection in CAP using the 2019 ATS/IDSA antibiotic guidelines and to analyze its relationship with the patient's clinical response. In this retrospective cohort study, we included patients aged >18 years with CAP who were hospitalized, received antibiotic therapy for pneumonia and had complete medical records. The medical record data, including antibiotics and clinical responses, were analyzed using the Mann-Whitney test. There was a difference in the average duration of clinical improvement (days), including body temperature, heart rate, and respiratory rate, in the group of pneumonia patients who used empiric antibiotics according to the guideline and those who did not follow it guidelines (p<.05). Empiric antibiotics based on the 2019 ATS/IDSA guidelines can improve therapy outcomes among inpatients with CAP. The results are expected to encourage doctors to select antibiotics following 2019 ATS/IDSA guidelines.

1. Introduction

Pneumonia is an infection that attacks the lungs and is one of the leading causes of morbidity and mortality worldwide. An estimated 3.2 million of the 56.4 million deaths globally in 2015 were due to lower respiratory tract infections. The annual incidence of pneumonia is estimated to be 1.07-1.2 cases per 1,000 person-years in Europe and 16.9 cases per 1,000 person-years in Asia (Htun et al., 2019). Pneumonia is included in Indonesia's top 10 hospital inpatient diseases, and the estimated national pneumonia cases in 2017 were 3.55% (Kementrian Kesehatan RI, 2019; PDPI, 2014). Community-Acquired Pneumonia (CAP) is a common and serious disease with high morbidity and mortality (Gonçalves-Pereira et al., 2013; Mantero et al., 2017). The main cause of pneumonia is bacteria, although viruses, mycoplasma, fungi, various chemical compounds, and particles can be the cause (Sari et al., 2017).

Treatment failure of CAP caused by bacteria was defined as a clinical condition with an inadequate response to antimicrobial therapy. When the response to treatment is inadequate, the persistence or development of infection occurs, resulting in worsening symptoms that can lead to the spread of infection, complications, and even death. The cause of treatment failure in pneumonia can be due to the impact of comorbidities on treatment response, e.g., in liver disease or the presence of unusual

microorganisms (tuberculosis, *Coxiella burnetii*). The other cause is that the initial empiric therapy does not cover these microorganisms adequately (Menendez & Torres, 2007). The ineffective antibiotics against pathogenic bacteria or the continuation of antibiotic therapy even after negative culture results ruled out an infection can be a problem in treating infectious diseases (Mettler et al., 2007). The increase in antimicrobial resistance also contributes to hindering healing in CAP. We should consider specific bacterial pathogens and calls for pathogen-specific antibiotic recommendations to manage these infections at different sites to ensure optimal patient care (Ho & Ip, 2019).

Antibiotic recommendations for empiric treatment of CAP based on the 2019 ATS/IDSA (American Thoracic Society/Infectious Diseases Society of America) guideline select effective agents against CAP's major treatable bacterial causes. Traditionally, these bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella species*, *Chlamydia pneumoniae*, and *Moraxella catarrhalis* (Metlay et al., 2019). The inaccuracy of antibiotics causes various problems and is a global threat to health, especially bacterial antibiotic resistance. This problem impacts morbidity and mortality and has negative economic and social implications. Adequate administration of empirical antibiotics is highly recommended for clinical improvement in pneumonia patients. A study is required to evaluate the accuracy of antibiotics used based on the 2019 ATS/IDSA guideline for clinical improvement in inpatient CAP patients.

2. Materials and Methods

This study is an analytical observational design with a retrospective cohort method. Secondary data was collected from medical records of inpatient Community-Acquired Pneumonia (CAP) patients for July-December 2019 at Dr. RSUP Sardjito Hospital Yogyakarta. This research has received permission from the Ethics Commission of the Faculty of Medicine, Gadjah Mada University (KE/FK/0381/EC/2020). The independent variable was the empirical antibiotic administration. The dependent variable was the duration of clinical improvement, including body temperature, heart rate (pulse), respiratory rate, and systolic blood pressure. Inclusion criteria consisted of patients aged >18 years with CAP who were hospitalized (ICD 10 code: J15.9), received antibiotic therapy for pneumonia, and completed medical records (diagnosis, gender, age, blood urea nitrogen, respiratory rate, blood pressure, body temperature, heart rate, leukocytes count, length of stay in hospital). The exclusion criteria are pregnant or lactating women, patients with organ or stem cell transplants who were taking immunosuppressant drugs, patients with low immune systems such as patients with HIV (Human Immunodeficiency Virus), CAP patients who decide to go home at their request, and patients with comorbidities (heart failure, chronic/acute kidney failure, tuberculosis).

The severity of CAP is assessed to determine the appropriateness of antibiotic use based on the 2019 ATS/IDSA guideline. The determination of CAP severe is based on the guideline, selected from the existing one major criterion (septic shock with need for vasopressors and respiratory failure requiring mechanical ventilation) or a minimum of three minor criteria (respiratory rate >30 breaths/min, PaO_2/FiO_2 ratio <250, multilobar infiltrates, confusion/disorientation, uremia (blood urea nitrogen level >20 mg/dL), leukopenia (white blood cell count <4,000 cells/µl), thrombocytopenia (platelet count <100,000/µl), hypothermia (core temperature <36°C), hypotension requiring aggressive fluid resuscitation (Metlay et al., 2019). Because of the incomplete medical record, we determined the severity of CAP only based on five minor criteria: leukocytes, platelets, blood urea nitrogen (BUN), respiratory rate, and hypothermia.

Empiric antibiotics are categorized into two groups: empirical antibiotics based on the 2019 ATS/IDSA guideline and empirical antibiotics not following the guideline. In hospitalized adults with non-severe CAP, the guideline recommends empiric antibiotics as a combination of β-lactams and macrolides or monotherapy with a respiratory fluoroquinolone. In contrast, in adults hospitalized with severe CAP, guidelines recommend empiric antibiotics combined with β-lactams and macrolides or β-lactams and respiratory fluoroquinolones (Metlay et al., 2019). The length of clinical improvement and stay in the hospital are collected for each patient. The criteria for clinical improvement based on the 2019 ATS/IDSA guideline include temperature, heart rate, respiratory rate, and blood pressure. The 2007 ATS/IDSA guideline describes the limit of clinically stable patient criteria: body

temperature 37.8°C, heart rate 100 beats/minute, respiratory rate 24 breaths/minute, and systolic blood pressure 90 mmHg (Mandell et al., 2007). The duration of stay in the hospital was collected from the first day the patient got hospitalized until the day the patient was allowed to go home.

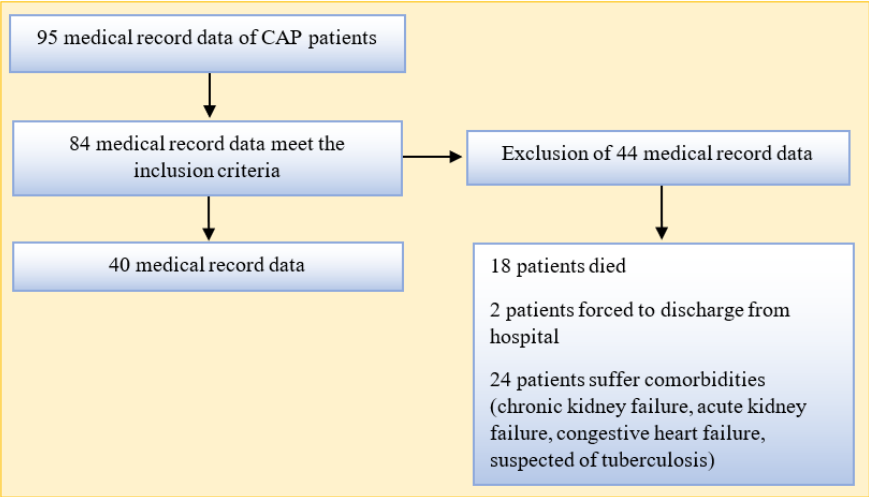

Fig 1. Research Scheme

Data analysis were carried out at the CE&BU (Clinical Epidemology & Biostatistics Unit) Study Center, Gadjah Mada University using the IBM SPSS Statistics 22 program. The statistical test used was the Mann-Whitney test using 95% confidence level ($\alpha = 0.05$).

3. Results and Discussion

A total of 40 patient records met the inclusion and exclusion criteria, including 20 records for patients who used empirical antibiotics according to the 2019 ATS/IDSA guidelines and 20 records for patients who did not. Approximately 38 patients have been diagnosed with non-severe Community-Acquired Pneumonia (CAP), and 23 patients are older than 60 (Table 1). Older adults have increased hospitalization rates and are more likely to die due to CAP. Several physiologic changes have been identified as risk factors for CAP in older adults, including a decreased mucociliary clearance, a diminished cough reflex, and an altered immune response (Stupka et al., 2009). Many Indonesians are affected by smoking, both actively and passively. In 2016, more than 75% of Indonesian adult males were active smokers (Satriawan, 2022). Smokers and passive smokers are more likely to suffer from lower respiratory tract infections (Crowin, 2009). CAP development has been associated with exposure to tobacco smoke in current and former smokers and in passive smokers aged 65 and older (Baskaran et al., 2019).

Most clinical improvements, including temperature, systolic blood pressure, heart rate, and respiratory rate, were achieved within 5 days as many as 92.5%, 97.5%, 85%, and 90%, respectively. The percentage of the length of stay patients who used empirical antibiotics according to the ATS/IDSA 2019 guideline for 5 days (55%) was higher than patients who used empirical antibiotics that did not comply with the ATS/IDSA 2019 guideline (20%). Research by (Rotter et al., 2012) found that applying medication according to the guidelines in 11 studies significantly reduced Length of Stay (LoS) in hospitals. The application of clinical practice guidelines can help patients speed up their treatment in hospitals treatment by reduce duplication and complications (Ellen et al., 2014). In addition, the research from Munarsih, Natadidjaja and Syamsudin 2018 (Munarsih et al., 2018) found that patients treated with antibiotics not in accordance with the 2007 ATS/IDSA guideline tended to stay in the hospital 10.25 times longer than those who were given therapy according to the guideline. Furthermore, this study explained that empirical antibiotics given according to the guidelines before the culture results came out would provide good clinical outcomes because antibiotic guidelines were made based on bacterial patterns and had considered the pharmacodynamics and pharmacokinetics of antibiotics.

Table 1. Characteristics of CAP Patients

Characteristics	n	%
Empirical antibiotic therapy		
According to ATS/IDSA guideline		
Non severe CAP	20	100
Severe CAP	0	0
Not according to ATS/IDSA guideline		
Non severe CAP	18	90
Severe CAP	2	10
Age (Years)		
19-40	4	10
41-50	5	12.5
51-60	8	20
>60	23	57.5
Duration of improvement in body temperature (days)		
1-5	37	92.5
≥ 6	3	7.5
Duration of improvement in systolic blood pressure (days)		
1-5	39	97.5
≥ 6	1	2.5
Duration of improvement in heart rate/pulse (days)		
1-5	34	85
≥ 6	6	15
Duration of improvement in respiratory rate (days)		
1-5	36	90
≥ 6	4	10
Length of stay (days)		
According ATS/IDSA 2019 guideline		
1-5	11	55
≥ 6	9	45
Not according to ATS/IDSA 2019 guideline		
1-5	4	20
≥ 6	16	80

Empiric antibiotics administration to nonsevere CAP at RSUP Dr. Sardjito are cephalosporin antibiotics, fluoroquinolone antibiotics, a combination of cephalosporin and fluoroquinolone antibiotics, a combination of cephalosporin and macrolides antibiotics, a combination of carbapenem and fluoroquinolone antibiotics, and a combination of penicilin and macrolides antibiotics (Table 2). The inappropriate administration of antibiotics occurs in nonsevere CAP and severe CAP as many as 18 cases and 2 cases, respectively. The inappropriate was consists cephalosporin antibiotics (10 cases), a combination of cephalosporin and fluoroquinolone antibiotics (9 cases), and a combination of carbapenem and fluoroquinolone antibiotics (1 case). A study conducted by Alfina (2019) analyzed the comparison between monotherapy and dual therapy with extended empirical antibiotics in CAP patients to the therapeutic outcomes at Fatmawati Hospital. The results show that there was no significant difference (p = 0.643) improvement in temperature, respiratory rate, and blood leukocytes to normal values between extended empirical antibiotic therapy with β-lactam monotherapy and a dual therapy of β-lactams and fluoroquinolones for 5 days. The cost-effectiveness of monotherapy is better than dual-therapy. The best choice of monotherapy is ceftriaxone and consideration ciprofloxacin-ceftriaxone for unconscious patients. There is a moderate relationship between the accuracy of use and extended empirical antibiotic cost.

Table 2. Empirical Antibiotic Therapy for CAP

Antibiotic therapy	Number of patients (n=40)	Non severe CAP (%)	Severe CAP (%)
Levofloxacin*	5	5 (12.5)	
Ciprofloxacin*	1	1 (2.5)	
Cefoperazone	4	4 (10)	
Moxifloxacin*	1	1 (2.5)	
Ceftazidime	6	4 (10)	2 (5)
Meropenem + Levofloxacin	1	1 (2.5)	
Ceftazidime + Ciprofloxacin	3	3 (7.5)	
Cefoperazone + Levofloxacin	2	2 (5)	
Cefotaxime + Azithromysin*	1	1 (2.5)	
Ampicillin – Sulbactam + Azithromycin*	1	1 (2.5)	
Ceftazidime + Levofloxacin	2	2 (5)	
Ceftriaxone + Ciprofloxacin	1	1 (2.5)	
Ceftriaxone + Azithromysin*	10	10 (25)	
Ceftazidime + Azithromysin*	1	1 (2.5)	
Cefotaxime + Ciprofloxacin	1	1 (2.5)	

** Conforms to ATS/IDSA 2019 guidelines*

Another consideration in selecting empiric antibiotics is CAP caused by methicillin-resistant Staphylococcus aureus (MRSA) as a causality of severe pneumonia that directs to critical illness and death. Despite a very low prevalence of S*taphylococcus aureus* and MRSA, nearly one-third of adults hospitalized with CAP received anti-MRSA antibiotics. The clinical manifestation of MRSA CAP overlapped substantially with pneumococcal CAP, emphasizing the challenge of accurately empirical anti-MRSA antibiotics (Self et al., 2016). *Pseudomonas aeruginosa*, a Gram-negative bacterium, can also be a problem because it is resistant to several groups of antibiotics, such as β-lactams. *Pseudomonas aeruginosa* is a challenging bacterium that infected most CAP patients. These findings support the recommendation of antibiotics that have an antipseudomonal activity to patients with severe pulmonary diseases (Restrepo et al., 2018).

Table 3. Duration of clinical improvement in CAP patients reviewed from the precision with guidelines 2019 ATS/IDSA guideline

Clinical Improvement	Empiric Antibiotic		*p-value*
	According to ATS/IDSA 2019 guideline (Days)	Not according to ATS/IDSA 2019 guideline (Days)	
Body Temperature	1.90	2.75	0.046
Heart Rate/Pulse	2.80	3.95	0.012
Respiratory Rate	2.20	3.75	0.019
Systolic Blood Pressure	1.40	1.55	0.672
Length of Stay	6.70	7.15	0.089

Table 3 shows a significant difference ($p<0.05$) in the duration of improvement body temperature, heart rate, and respiratory rate between CAP patients given empiric antibiotics according to ATS/IDSA 2019 guideline and CAP patients who do not. Meanwhile, the duration of improvement blood pressure and LoS show no significant difference ($p>0.05$) between CAP patients using empirical antibiotics according to the 2019 ATS/IDSA guideline and CAP patients who do not. Fever is one sign of an active infection, where a high temperature can indicate the severity of the illness, a decrease in fever in a patient is one indication of overcoming the infection (Pitaloka & Wibisono, 2015). CAP can make it difficult for the patient to breathe which cause oxygen deficiency. The presence of oxygen deficiency is characterized by a state of hypoxia, which can cause tissue death and even be life-threatening in the advanced process (Karmiza et al., 2017). Hypoxia is a dangerous condition because it can quickly disrupt the function of the brain, liver, and other organs. Hypoxia can be detected by

low oxygen saturation with other symptoms, including shortness of breath, which tends to be fast breathing/tachypnea, and rapid heart rate/tachycardia (Budi et al., 2019). An increased respiratory rate indicates a decrease in lung compliance or function, which will also affect the availability of oxygen in the blood. Fever and lack of oxygen supply may be exacerbated by a drop in blood pressure to mean arterial pressure (MAP) <60 mmHg or systolic blood pressure <90 mmHg, all of which are included in the criteria for sepsis and septic shock, which is quite common in CAP patients (Pitaloka & Wibisono, 2015).

The duration of administration of antibiotics (IV/oral) is at least 5 days and fever-free 48-72 hours, and no more than 1 sign of clinical instability of CAP before discontinuation of therapy, while the duration of treatment is generally 7-10 days in patients who show a response (improvement of treatment) within the first 72 hours. The duration of antibiotic administration may be extended if initial therapy is inactive against the identified pathogen or if it is complicated by an extrapulmonary infection, such as meningitis or endocarditis (Perhimpunan Dokter Paru Indonesia, 2003). As recommended by Japanese Respiratory Society (JRS) or IDSA guidelines, initial empiric treatment was associated with a better short-term prognosis in patients with severe pneumonia who required mechanical ventilation on hospital admission (Sakamoto et al., 2017).

The results of this study are in line with existing research by Sari et al. (2017), the study compared the pattern of antibiotic therapy for CAP in type A and type B hospitals. CAP patients in type A hospitals who used empiric antibiotics that matched ATS/IDSA would provide patient improvement therapy results on day 5 compared with inappropriate empiric antibiotics (p=0.007). Furthermore, there was no suitable antibiotic in type B Hospital, but 76.5% of patients who used empiric antibiotics did not comply with ATS/IDSA experienced improvement after 5 days. This study did not explain what clinical improvement outcomes were seen in assessing remedial therapy in patients with CAP. Applying practical clinical guidelines can improve clinical outcomes, reduce the length of hospitalization, referrals, emergency department visits, frequency of monitoring, and reduce costs. Several things are essential to consider in preparing antibiotic guidelines, one of which is antibiotics selected in line with the pattern of pathogens and local sensitivities (Fauzia, 2017). Liapikou and Tarres (2013) explain that one of the reasons that CAP guidelines should be local is that the etiology can differ between countries and different regions, related to resistance patterns.

It is important to note that we did not consider geriatric or other diseases that could affect the outcome of CAP. Additionally, we cannot determine empirical antibiotics based on risk factors for MRSA and *Pseudomonas aeruginosa* because the medical records did not provide them. The medical record is incomplete to determine the clinical outcome, only four criteria are seen, namely systolic blood pressure, body temperature, heart rate, and respiratory rate.

4. Conclusion

The relationship between the accuracy of giving antibiotics based on the 2019 ATS/IDSA guideline could help to improve clinical outcomes in inpatient Community-Acquired Pneumonia Patients (CAP) at RSUP Dr. Sardjito. The clinical outcomes, including body temperature, heart rate, and respiratory rate, are better in CAP patients who used empirical antibiotics according to the 2019 ATS/IDSA guideline than CAP patients who did not by assessing the duration to achieve the outcomes. We suggest doing further research to include risk factors for MRSA or *Pseudomonas. aeruginosa* to determine the accuracy of empirical antibiotics in medical record data based on the 2019 ATS/IDSA guideline. All clinical improvement criteria (temperature, heart rate, rate respiration, blood pressure, oxygen saturation, eating ability, and normal mental status) should be included in the next prospective study to see the impact of appropriate empiric antibiotics on the clinical outcome.

Author Contributions: Mensiana Ayu Maju conceived and design the study. She performed all data analyses. Christianus Heru Setiawan revised the paper. Mensiana Ayu Maju wrote the manuscript and Christianus Heru Setiawan revised it. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors.

Competing Interests

The authors declare no conflict of interests.

Acknowledgment

The authors would like to thank the Dr. RSUP Sardjito Hospital staff for providing medical records in this research.

References

Baskaran, V., Murray, R. L., Hunter, A., Lim, W. S., & McKeever, T. M. (2019). Effect of tobacco smoking on the risk of developing community acquired pneumonia: A systematic review and meta-analysis. *PLOS ONE*, *14*(7), e0220204. https://doi.org/10.1371/journal.pone.0220204.

Budi, D. B. S., Maulana, R., & Fitriyah, H. (2019). Sistem deteksi gejala hipoksia berdasarkan saturasi oksigen dengan detak jantung menggunakan metode fuzzy berbasis arduino. *Jurnal Pengembangan Teknologi Informasi Dan Ilmu Komputer*, *3*(2).

Crowin, E. J. (2009). *Buku saku patofisiologi (Handbook of Pathophysiology) edisi 3*. Jakarta EGC.

Ellen, M., Baker, G. R., & Brown, A. (2014). The impact of acute care clinical practice guidelines on length of stay: A closer look at some conflicting findings. *Journal of Hospital Administration*, *3*(4), 25. https://doi.org/10.5430/jha.v3n4p25.

Gonçalves-Pereira, J., Conceição, C., & Póvoa, P. (2013). Community-acquired pneumonia: identification and evaluation of nonresponders. *Therapeutic Advances in Infectious Disease*, *1*(1), 5–17. https://doi.org/10.1177/2049936112469017.

Ho, J., & Ip, M. (2019). Antibiotic-resistant community-acquired bacterial Pneumonia. *Infectious Disease Clinics of North America*, *33*(4), 1087–1103. https://doi.org/10.1016/j.idc.2019.07.002

Htun, T. P., Sun, Y., Chua, H. L., & Pang, J. (2019). Clinical features for diagnosis of pneumonia among adults in primary care setting: A systematic and meta-review. *Scientific Reports*, *9*(1), 7600. https://doi.org/10.1038/s41598-019-44145-y.

Karmiza, K., Muharriza, M., & Huriani, E. (2017). Left lateral positioning with head elevation increase the partial pressure of oxygen on patients with mechanical ventilation. *Jurnal Ners*, *9*(1), 59–65. https://doi.org/10.20473/jn.v9i1.2979.

Kementrian Kesehatan RI. (2019). *Profil Kesehatan Indonesia 2018*.

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. *Clinical Infectious Diseases*, *44*(Supplement_2), S27–S72. https://doi.org/10.1086/511159.

Mantero, M., Tarsia, P., Gramegna, A., Henchi, S., Vanoni, N., & Di Pasquale, M. (2017). Antibiotic therapy, supportive treatment and management of immunomodulation-inflammation response in community acquired pneumonia: review of recommendations. *Multidisciplinary Respiratory Medicine*, *12*(1), 26. https://doi.org/10.1186/s40248-017-0106-3.

Menendez, R., & Torres, A. (2007). Treatment failure in community-acquired pneumonia. *Chest*, *132*(4), 1348–1355. https://doi.org/10.1378/chest.06-1995.

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. An official clinical practice guideline of the American thoracic society and infectious diseases society of America. *American Journal of Respiratory and Critical Care Medicine*, *200*(7), e45–e67. https://doi.org/10.1164/rccm.201908-1581ST.

Mettler, J., Simcock, M., Sendi, P., Widmer, A. F., Bingisser, R., Battegay, M., Fluckiger, U., & Bassetti, S. (2007). Empirical use of antibiotics and adjustment of empirical antibiotic therapies

in a university hospital: a prospective observational study. *BMC Infectious Diseases*, *7*(1), 21. https://doi.org/10.1186/1471-2334-7-21.

Munarsih, F. C., Natadidjaja, R. I., & Syamsudin, S. (2018). Pengaruh pemberian antibiotik berdasar panduan terhadap Lama Tinggal pada Pasien Pneumonia Komunitas di Rumah Sakit. *Jurnal Penyakit Dalam Indonesia*, *5*(3), 141. https://doi.org/10.7454/jpdi.v5i3.195.

PDPI. (2014). *Pedoman diagnosis & penatalaksanaan Pneumonia edisi 2*. Perhimpunan Dokter Paru Indonesia.

Perhimpunan Dokter Paru Indonesia. (2003). *Pneumonia komuniti 1973 - 2003*. Pneumonia Komuniti (Pedoman Diagnosis Dan Penatalaksanaan).

Pitaloka, S. L. D., & Wibisono, B. H. (2015). Beberapa faktor risiko yang berhubungan dengan kematian pasien Pneumonia komunitas di Rsup Dr. Kariadi Semarang. *Jurnal Kedokteran Diponegoro*, *4*(4), 1495–1502.

Restrepo, M. I., Babu, B. L., Reyes, L. F., Chalmers, J. D., Soni, N. J., Sibila, O., Faverio, P., Cilloniz, C., Rodriguez-Cintron, W., & Aliberti, S. (2018). Burden and risk factors for Pseudomonas aeruginosa community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. *European Respiratory Journal*, *52*(2), 1701190. https://doi.org/10.1183/13993003.01190-2017.

Rotter, T., Kinsman, L., James, E., Machotta, A., Willis, J., Snow, P., & Kugler, J. (2012). The effects of clinical pathways on professional practice, patient outcomes, length of stay, and hospital costs. *Evaluation & the Health Professions*, *35*(1), 3–27. https://doi.org/10.1177/0163278711407313.

Sakamoto, Y., Yamauchi, Y., Yasunaga, H., Takeshima, H., Hasegawa, W., Jo, T., Matsui, H., Fushimi, K., & Nagase, T. (2017). Guidelines-concordant empiric antimicrobial therapy and mortality in patients with severe community-acquired pneumonia requiring mechanical ventilation. *Respiratory Investigation*, *55*(1), 39–44. https://doi.org/10.1016/j.resinv.2016.08.006.

Sari, I. P., Nuryastuti, T., Asdie, R. H., Pratama, A., & Estriningsih, E. (2017). Perbandingan pola terapi antibiotik pada community- acquired Pneumonia (CAP) di rumah sakit tipe A dan B. *Jurnal Manajemen Dan Pelayanan Farmasi*, *7*(4), 168–174.

Satriawan, D. (2022). Gambaran kebiasaan merokok penduduk di Indonesia. *Jurnal Litbang Sukowati : Media Penelitian Dan Pengembangan*, *5*(2), 51–58. https://doi.org/10.32630/sukowati.v5i2.243.

Self, W. H., Wunderink, R. G., Williams, D. J., Zhu, Y., Anderson, E. J., Balk, R. A., Fakhran, S. S., Chappell, J. D., Casimir, G., Courtney, D. M., Trabue, C., Waterer, G. W., Bramley, A., Magill, S., Jain, S., Edwards, K. M., & Grijalva, C. G. (2016). Staphylococcus aureus community-acquired pneumonia: prevalence, clinical characteristics, and outcomes. *Clinical Infectious Diseases*, *63*(3), 300–309. https://doi.org/10.1093/cid/ciw300.

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