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Assessment of Antibiotic Use in ICU Patients with Pneumonia Using ATC/DDD as a Quantitative Analysis Method

Mareta Rindang Andarsari[1*], Zedny Norachuriya[1], Sarah Mahmudatun Nabila[1], Toetik Aryani[1], Alfian Nur Rosyid[2]
[1]Department Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Pulmonary, Universitas Airlangga Hospital, Surabaya, Indonesia

*Corresponding author: mareta.ra@ff.unair.ac.id

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Abstract

Background: *Pneumonia is an infection of the lung tissue which is mainly caused by bacteria. High utilization and inappropriate use of antibiotics increase resistant bacteria, morbidity, mortality, and treatment cost. Quantitative evaluation becomes one of the indicators to assess the use of antibiotics which is one indicator of the quality of the antimicrobial resistance control program.* ***Objective:*** *This study aimed to evaluate the use of antibiotics an effort to increase the rationality of the use of antibiotics.* ***Methods:*** *This study was a retrospective observational study with a sampling method of time-limited sampling in Universitas Airlangga hospital from January until December 2019. Quantitatively using Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD).* ***Result:*** *The samples obtained were 68 severe pneumonia patients who met the inclusion criteria. From the result of the study, there were 13 types of antibiotics used for pneumonia therapy, and the three most used were Levofloxacin, Ceftriaxone, and Meropenem, with a total of all antibiotics 73.64 DDD/100 patients-days. Most useful is parenteral Levofloxacin at 21.92 DDD/100 patient-days, Ceftriaxone at 20.45 DDD/100 patient-days and Meropenem at 14.29 DDD/100 patient-days.* ***Conclusion:*** *The DDD value indicates high antibiotic usage, but high antibiotic use does not imply unreasonable drug use, so we must undertake a qualitative review of antibiotic use.*

Keywords*: pneumonia, severe pneumonia, ICU, antibiotics, ATC/DDD*

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INTRODUCTION

Pneumonia is a pulmonary inflammation caused by various microorganisms (PPDI, 2014), mainly caused by *Streptococcus pneumoniae (pneumococcus), Staphylococcus aureus, Streptococcus Group A, Klebsiella pneumoniae, Haemophilus influenzae* (Pahal et al., 2021), and atypical bacteria such as *Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila* (Stamm & Stankewicz, 2021). In a study of 7749 Community-Acquired Pneumonia (CAP) patients, 23% were admitted to the intensive care unit (ICU), and the mortality rate was 47% in 1 year (Cavallazzi et al., 2020). A patient has severe CAP if he has at least one of two major or at least three minor criteria, according to criteria developed and validated by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS). Septic shock and respiratory failure are major criteria. In contrast, minor criteria include a respiratory rate/frequency of breath of fewer than 30 breaths per minute, a PaO2/FIO2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) of less than 250 mmHg, multilocus infiltration on thoracic photos, decreased awareness or disorientation, uremia, and hypotension (Metlay *et al.*, 2019). Antibiotics are the most common treatment for bacterial pneumonia (Farida *et al*., 2017). Inappropriate antibiotic use leads to antibiotic resistance, the most serious concern in treating illnesses like pneumonia (Pratama *et al*., 2019). The World Health Organization (WHO) is working to reduce antibiotic resistance internationally, including developing a global action plan that increases antibiotic usage responsibility and assesses antibiotic use (Pratama *et al*., 2019). The Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) technique can be used to determine the kind quantitatively and amount of antibiotics taken, while the Gyssens method can be used to assess antibiotic use accuracy (Metley *et al.,* 2019; Farida *et a.l,* 2017) qualitatively. The WHO approved the ATC/DDD system as the international measurement standard for drug use research (Pratama *et al*., 2019). With the high frequency of severe pneumonia and the rising incidence of antibiotic resistance, the primary treatment for severe pneumonia, more study is needed to evaluate the use of antibiotics in severe pneumonia patients using ATC/DDD to enhance antibiotic utilization rationale.

MATERIALS AND METHODS

Materials

Research materials in the form of Medical Records (RM) of patients with pneumonia diagnoses who undergo hospitalization and get antibiotic therapy in the Intensive Care Unit (ICU) of Universitas Airlangga Surabaya Hospital in the period January-December 2019 that meet the criteria of inclusion

Methods

Study population and design

The observational study used data from pneumonia patients in the intensive care unit's medical records. The study included all patients with pneumonia admitted to the Universitas Airlangga Surabaya Hospital's ICU and received antibiotic therapy between January and December 2019. The inclusion criteria were Pneumonia patients over 18 who had been diagnosed with CAP or HAP and were being treated with antibiotics. Patients diagnosed with infections for which antibiotics were not administered, patients discharged from the hospital on their request, and patients who died were also excluded.

Data collection instrument

Research materials in the form of Medical Records of patients, with data collected in the form of Medical Record numbers, Patient Identity (name, gender, age, date of first treatment and completion of therapy), patient disease history, complaints and diagnosis, clinical data, laboratory data, microbiology data and antibiotic therapy, which includes the type of antibiotic, route, dosage, interval, and a length of stay (LOS). Then the data is recorded on the Data Collection Sheet (DCS) and the master table, which is the research instrument. The sampling technique uses time-limited sampling, so all inclusion samples are in this study.

Data analysis

Data analysis included sex, age, type of pneumonia, and comorbidity; analysis of bacterial patterns that cause severe pneumonia and bacterial sensitivity to various kinds of antibiotics based on the results of microbiological examinations of patients, and analysis of antibiotic use patterns in severe pneumonia patients, including type, route, dose, and interval of administration. ATC/DDD with DDD/100 patient days measurement unit was used to investigate antibiotic use quantitatively. Calculation of antibiotic consumption :

$$\text{DDD/100 days of hospitalization} = \frac{total\ antibotics\ sold\ in\ a\ year\ (grams)}{WHO\ DDD\ Standard\ (gram)}\ x\ \frac{100}{population\ x\ 365}$$

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The quantity of antibiotic use can also be expressed in DDD / 100 patient days using calculation using the formula (Kemenkes RI, 2011).

$$\text{DDD/100 patient days} = \frac{\text{total dose of antibiotics used by the patient (gram)}}{\text{WHO DDD Standard (gram)}} \; x \; \frac{100}{\text{Total Length Of Stay}}$$

RESULT

Demographic variables

Demographic variables include gender, age, type of pneumonia, symptoms, and accompanying disease. The results of the gender distribution showed that the number of male patients with severe pneumonia was more than female patients, which was 35 out of 68 patients (52%). In Europe, the incidence of CAP in men is higher than in women. Lifestyle is a high-risk factor for pneumonia, including smoking, alcohol, low BMI and malnutrition, household arrangements, and poor dental hygiene. In addition, the presence of immunocompetent and immunocompromised also increases the risk of pneumonia (Cillóniz *et al.,* 2017). Age distribution indicates dominated by the age group > 65 years. Age, especially 65 years and above, is one of the risk factors for pneumonia and clinical manifestations that generally appear severe (Barbara G. *et al.*, 2015; Torres *et al.*, 2013). The most common type of pneumonia was CAP, with 55 out of 68 patients (81%). Both CAP and HAP can develop into severe infections when an uncontrolled inflammatory reaction is caused by causative pathogenic factors and/or individual factors such as increasing age and comorbidities (Waterer, Grant W. and Wunderink, 2005). Clinical symptoms that are often found in cases of severe pneumonia are fever, cough accompanied by the production of sputum purulent, dyspnea (shortness of breath), and chest pain. In addition, there can also be changes in mental status/disorders of consciousness (Wendy I. & Thomas J., 2013). Based on data from 22 patients, shortness of breath is a symptom experienced by all patients. The characteristics of the patients studied are in Table 1.

Number of days hospitalized/length of stay

The number of days a patient spends in the hospital is measured from when they are diagnosed with pneumonia until they are diagnosed with pneumonia after leaving the hospital. The total length of stay for all patients was 616 days, with an average length of stay of 9.0 days, indicating that patients with severe pneumonia in RSUA Surabaya in 2019 spent 9 days in the hospital (table.2). Patients with bacterial infections are often admitted to the hospital for 7–10 days. However, this might be extended depending on comorbidities, consequences, and the severity of the infection (Menéndez *et al*., 2001).

Table 1. Characteristics of pneumonia patients at RSUA Surabaya period January-December 2019

Demographic characteristics		Number	Percentage (%)
Gender	Male	35	52
	Female	33	48
Age (years)	17-25	1	2
	26-30	0	0
	36-45	3	4
	46-55	10	15
	56-65	19	28
	>65	35	51
Type of pneumonia	CAP	55	81
	HAP	13	19
Clinical Symptoms*	Dyspnea	22	38.6
	Fever	7	12.3
	cough	9	15.8
	Productive cough	7	12.3
	chest pain	2	3.5
	Delirium	10	17.5

*Data from 22 patients; One patient may experience more than one clinical symptom.

Table 2. Number of hospitalization days of severe pneumonia patients at RSUA Surabaya period January-December 2019

Month	1	2	3	4	5	6	7	8	9	10	11	12	Amount
The number of patients	12	10	7	6	7	4	2	4	3	3	6	4	68
LOS	105	64	102	63	82	34	19	18	8	50	46	25	616
Average LOS	8.8	6.4	14.6	10.5	11.7	8.5	9.5	4.5	2.7	16.7	7.7	6.2	9.0

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Quantitative analysis of antibiotic use in severe pneumonia patients

The results showed that the total use of antibiotics in severe pneumonia patients who underwent hospitalization at ICU RSUA Surabaya in January 2019 was 73.64 DDD/100 patient-days (table 3.). Of the 13 antibiotics prescribed for severe pneumonia therapy, parenteral Levofloxacin is the most widely used antibiotic, with total use of 21.92 DDD/100 patient-days which can be interpreted that in 100 days of hospitalization at RSUA Surabaya, there are 21-22 severe pneumonia patients who get Levofloxacin parenteral therapy according to the WHO's defined daily dose of 0.5 grams per day. The second most antibiotic use is Ceftriaxone, with total use of 20.45 DDD/100 patient-days. The third most antibiotic is meropenem, with total use of 14.29 DDD/100 patient days.

Furthermore, the use of antibiotics in a row followed by parenteral Moxifloacacy (5.20 DDD/100 patient-days); oral Levofloxacin (2.76 DDD/100 patient-days); Amikacin (2.56 DDD/100 patient-days); Ceftazidime (2.31 DDD/100 patient-days); Trimethoprim-Sulfamethoxazole oral (1.87 DDD/100 patient-days); Cefazolin (0.54 DDD/100 patient-days); oral Erythromycin (0.49 DDD/100 patient-days); Gentamicin (0.43 DDD/100 patient-days). The least used of antibiotics is Cefoperazone -Sulbactam and Vancomycin with the same amount of use of 0.41 DDD/100 patient-days (Figure 1).

DISCUSSION

On average, severe pneumonia patients at RSUA Surabaya undergo nine-day hospitalisation. In general, patients who have a bacterial infection undergo hospitalization for 7-10 days but can be extended depending on the accompanying disease suffered, complications experienced, and the severity of the infection (Menéndez *et al.*, 2001). The use of antibiotics in severe pneumonia patients in RSUA Surabaya is still reasonably high (73.64 DDD/100 patient-days). This has the potential to trigger irrational use of antibiotics, so it is expected that in the future, this data can be a consideration in the prescribing of antibiotics in hospitals. The DDD/100 patient-days are linear with the rate of antibiotic use within 100 days of treatment, which means the greater the DDD/100 patient-days value, the higher the rate of antibiotic use (Sari & Safitri, 2016). Compared to 98 studies conducted in hospitals in Germany that showed total antibiotic use in sepsis and pneumonia patients of 51.0 DDD/100 patient-days (Scholze *et al.*, 2015)

Table 3. Results of quantitative evaluation of antibiotic use in severe pneumonia patients in RSUA Surabaya period January-December 2019 with ATC / DDD method

Class antibiotics	Code ATC	Name antibiotics	Route*	Total Use (gram)	DDD Standard WHO (gram)	Total DDD Use	LoS (day)	DDD/100 patientdays	DDD/100 patient-days Group
Cephalosporins	J01DB04	Cefazolin	P	10	3	3.33	616	0.54	23.71
	J01DD02	Ceftazidime	P	57	4	14.25		2.31	
	J01DD04	Ceftriaxone	P	252	2	126		20.45	
	J01DD62	Cefoperazone - Sulbactam	P	10	4	2.5		0.41	
Carbapenem	J01DH02	Meropenem	P	264	3	88		14.29	14.29
Sulfonamide	J01EE01	Trimethoprim-Sulfamethoxazole	O	22.08	1.92	11.5		1.87	1.87
Macrolides	J01FA01	Erythromycin	O	3	1	3		0.49	0.49
Aminoglycosides	J01GB03	Gentamicin	P	0.64	0.24	2.67		0.43	2.99
	J01GB06	Amikacin	P	15.75	1	15.75		2.56	
Fluoroquinolones	J01MA02	Moxifloxacin	P	12.8	0.4	32		5.20	29.88
	J01MA12	Levofloxacin	P	67.5	0.5	135		21.92	
			O	8.5	0.5	17		2.76	
Glycopeptide	J01XA01	Vancomycin	P	5	2	2.5		0.41	0.41
Total DDD/100 patient-days									73.64

*O= Oral, P= Parenteral

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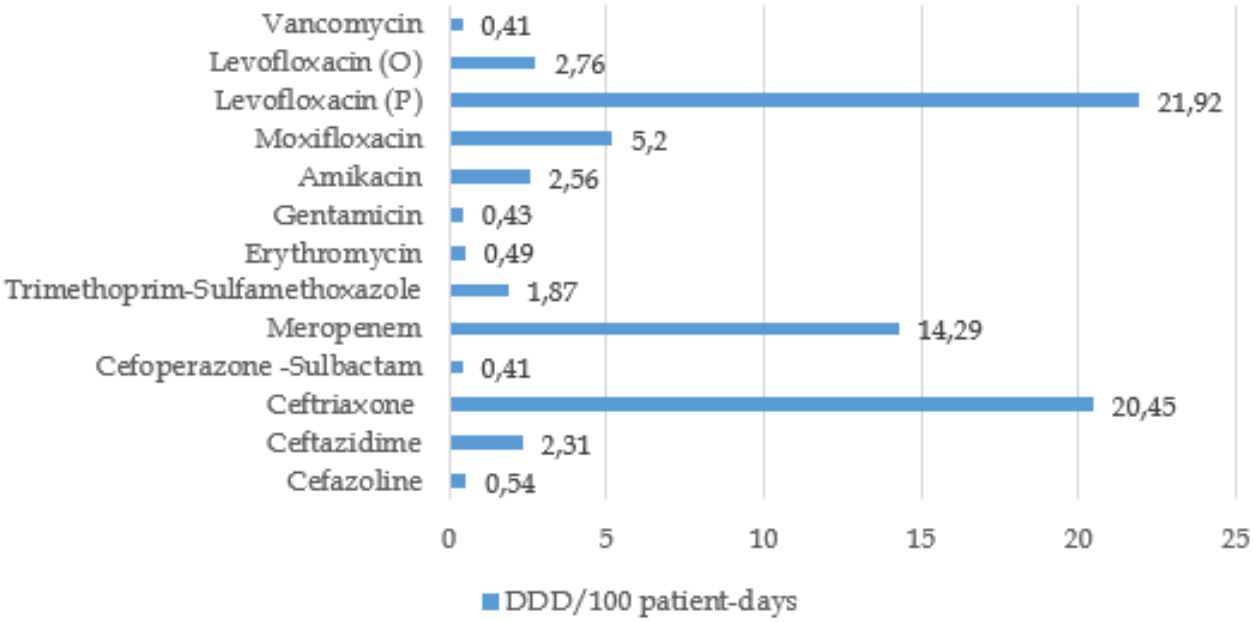

Figure 1. Quantity of antibiotic use by type in the patient severe pneumonia at RSUA Surabaya for the period January-December 2019

Parenteral Levofloxacin is the most widely used antibiotic in RSUA Surabaya. Similarly, it was found in studies conducted at Dr Iskak Tulungagung Hospital and Dr Moewardi Surakarta Hospital, with the number of Levofloxacin used for consecutive indications of pneumonia reaching 40.14 DDD/100 patient-days and 53.88 DDD/100 patient-days (Ilmi *et al.*, 2020; Muhammad & Mutmainah, 2018). Levofloxacin is among the most widely prescribed types of antibiotics for pneumonia therapy because it is a respiratory fluoroquinolone-class antibiotic that is effective in overcoming upper and lower airway infections with high activity against gram-positive bacteria and atypical bacteria cause pneumonia (Daniel H & Lisa G, 2015; Izadi *et al.*, 2019). Various studies have reported clinical cure rates of pneumonia patients who get l Levofloxacin ranging from 94-98% and, in severe cases, by 87% (Ball, 2003). However, it should be noted that Levofloxacin is a broad-spectrum antibiotic susceptible to the incidence of resistance when used excessively.

Ceftriaxone is one of the third-generation cephalosporins most active in penicillin-resistant *pneumococci* strains, so it is widely used as empirical therapy for severe infections caused by such pathogens (Daniel H & Lisa G, 2015). However, there is a study that proves an association between the increased use of third-generation cephalosporin groups and the increased incidence of ESBL-producing bacteria (Extended Spectrum Beta-Lactamase) (Urbánek *et al.*, 2007). Also the use of this group needs special attention. Meropenem of the carbapenem group is active against various aerobic and anaerobic bacteria, including penicillin-resistant *pneumococci* strains such as Ceftriaxone, and has shown promising effectiveness in severe pneumonia therapy (Baldwin et al., 2008).

Rational use of antibiotics in hospitals requires a restrictive policy in their application. Antibiotics are divided into two groups: those that are free to be prescribed by any clinician (non-restricted) and those that are restricted (restricted and reserved) (Ball, 2003).. For example, Vancomycin, which was classified as a reserved antibiotic in this study due to its low number of uses, must be prescribed with the approval of the Antibiotic Resistance Control Program (PPRA) at Universitas Airlangga Hospital. In addition to these restrictions, a policy of financing and procurement of antibiotics supports the rational implementation of antibiotic use in hospitals (Kemenkes RI, 2015).

There have been similar studies on antibiotics in pneumonia patients, but they showed different results. These differences can be caused by differences in local germ patterns and/or the severity of infection. In addition, the results of the culture and the clinical circumstances of the patients are taken into account while choosing a treatment. In a study conducted by Gayatri and Bestari (2017) at RSUPN Dr. Cipto Mangunkusumo Jakarta obtained data that azithromycin is the most widely used antibiotic by pneumonia patients, with total use of 62.5 DDD/100 patient days (Gayatri & Bestari, 2017).

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Evaluation of antibiotic use in hospitals both quantitatively and qualitatively needs to be done periodically to be able to know trends or changes in their use over time and become the material for assessing the success of PPRA in hospitals, namely by looking at the number or absence of improvement in the quantity and quality of antibiotic use. In terms of amount, the improvement in question is reducing the number and type of antibiotics used as empirical and definitive therapies (Kemenkes RI, 2015). Changes in the use of antibiotics kinds can also be used as a reference in the procurement of further drugs (Hasrianna *et al.*, 2015).

CONCLUSION

One method is to assess the use of antibiotics. ATC/DDD is the approach employed. According to the findings, the total use of antibiotics in 68 patients with severe pneumonia who were hospitalized in the ICU at RSUA Surabaya from January to December 2019 was 73.64 DDD/100 patient days. With 21.92 DDD/100 patient-days total use, parenteral Levofloxacin is the most commonly used antibiotic Ceftriaxone (20.45 DDD/100 patient-days) and meropenem (14.29 DDD/100 patient-days). Patient data from fully recorded medical records is limited to 22 of 68 patients. Hence some discussion points only include information from those 22 individuals. The DDD value suggests a high use of antibiotics, but increased usage of antibiotics does not necessarily indicate irrational use of antibiotics. Thus, a qualitative evaluation of antibiotic use is required.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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AUTHOR CONTRIBUTIONS

Conceptualization, M.R.A., A.N.R., T.A.; Software, M.R.A.; Methodology, M.R.A., A.N.R., T.A.; Validation, M.R.A., A.N.R.; Formal Analysis, M.R.A., S.M.N., Z.N.; Investigation, M.R.A., S.M.N.; Resources, M.R.A., S.M.N.; Data Curation, M.R.A., A.N.R., T.A.; Writing - Original Draft, M.R.A., S.M.N., Z.N.; Writing - Review & Editing, M.R.A., S.M.N., Z.N.; Visualization, M.R.A.; Supervision, M.R.A.; Project Administration, M.R.A.; Funding Acquisition, M.R.A.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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