JURNAL ILMU KEFARMASIAN INDONESIA, October 2023, page. 300 - 307 Vol. 21, No. 2
ISSN 1693-1831

Evaluation of Antibiotic Use with Quantitative Methods in Hospitalization Pneumonia Patients at West Nusa Tenggara Hospital

(Evaluasi Penggunaan Antibiotik dengan Metode Kuantitatif pada Pasien Pneumonia Rawat Inap di Rumah Sakit Nusa Tenggara Barat)

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Submitted 16 July 2023, Accepted 3 October 2023

Abstract: Overuse of antibiotics is a public health challenge that can lead to antimicrobial resistance. To reduce the occurrence of antibiotic resistance, it is necessary to evaluate the use of antibiotics to determine the rational use of drugs using quantitative methods, namely the ATC/DD method. The purpose of the study was to determine the use of antibiotics and describe the pattern of antibiotic use in inpatients at West Nusa Tenggara Hospital using the ATC/DD method and DU90%. The research method is a cross-sectional study design with retrospective data collection on adult pneumonia patients hospitalized in the period January-December 2019 and 2022, data obtained from medical records. The results of the study met the inclusion criteria of 218 patients with the majority being male 117 (53.67%) and the most age >65, namely 66 (30.28%). Antibiotic use has a total DDD value of 185.56 DDD/100 days of care with the highest antibiotic DDD value being ceftriaxone which is 104.00 DDD/100 days of hospitalization while antibiotics that are included in the DU 90% are ceftriaxone, levofloxacin, cefoperazon and meropenem. Conclusion most antibiotics used were ceftriaxone 104.00 DDD/100 days of length of stay.

Keywords : Antibiotics, define daily dose, drug utilization 90%, resistance.

Abstrak: Penggunaan antibiotik secara berlebihan adalah tantangan kesehatan masyarakat yang dapat menyebabkan resistensi terhadap antimikroba. Untuk mengurangi terjadinya resistensi antibiotik diperlukan evaluasi penggunaan antibiotik untuk menentukan penggunaan obat secara rasional dengan menggunakan metode kuantitatif yaitu metode *anatomical therapeutic chemical and defined daily dose* (ATC/DDD.) Tujuan penelitian yaitu mengetahui penggunaan antibiotik dan gambaran pola penggunaan antibiotik pada pasien rawat inap di Rumah Sakit Nusa Tenggara Barat menggunakan metode ATC/DDD dan *drug utilization* (DU) 90%. Metode penelitian yaitu desain s*tudy cross sectional* dengan pengambilan data secara retrospektif pada pasien pneumonia dewasa rawat inap periode 2019 dan 2022, data diperoleh dari rekam medis, Hasil penelitian yang memenuhi kriteria inklusi 218 pasien dengan mayoritas laki-laki 117 (53,67%) dan umur paling banyak >65 yaitu 66 (30,28%). Penggunaan antibiotik memiliki nilai total DDD sebesar 185,56 DDD/100 hari rawat dengan nilai DDD antibiotik tertinggi adalah seftriakson yaitu 104,00 DDD/100 hari rawat inap sedangkan antibiotik yang masuk dalam DU 90 % yaitu seftriakson, levofloxacin, sefoperazon dan meropenem. Kesimpulan antibiotik yang digunakan paling banyak adalah seftriakson dengan nilai 104,00 DDD/100 hari rawat inap.

Kata kunci: Antibiotik, *defined daily dose*, *drug utilization* 90%, resistensi.

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INTRODUCTION

PNEUMONIA is an acute infectious disease of the respiratory tract, which is an inflammation or irritation of one or both of the lungs caused by an infection caused by bacteria, viruses or fungi[1]. In Indonesia, there are 988 cases per 100,000 hospitalized cases caused by pneumonia. Indonesia has one of the highest mortality in Southeast Asia for adult cases of pneumonia is up to 11.3%[2]. According to Riskesdas 2018 data, the prevalence of infectious pneumonia, as determined by health workers' diagnoses has increased by 2% from 2013's 1.8%[3]. The purpose of pneumonia therapy is to kill the infecting organism, cure the patient, reduce morbidity and mortality[4].

Antibiotics are one of the pneumonia therapies. Antibiotics are a class of compounds, both naturally produced by microbes, and synthetically. Antibiotics have the effect of decrease bacterial growth by impeding, halting, or eliminating microorganisms' metabolic activities[5]. WHO has recommended the rational use of antibiotics, namely ATC (anatomical therapeutic chemical) and DDD (defined daily dose) as global standards to increase the quantity of drug use[6]. Research that has been conducted found a total DDD value of 144.58 DDD / 100 days of hospitalization with the highest antibiotic DDD value is levofloxacin which is 48.83 DDD / 100 days of hospitalization while antibiotics included in 90% DU are levofloxacin, azithromycin, cefixime, ceftriaxone, meropenem and moxifloxacin[8]. If the total value of DDD / 100 days of hospitalization is getting greater can indicate high use of antibiotics so it can be an indication that the use of drugs is irrational[9].

One of the most significant challenges in the global health sector is the development of bacterial resistance to antibiotics[10]. The World Health Organization (WHO) released recommendations on global action plans to be implemented in worldwide at all levels of healthcare facilities according to the immediate requirement for urgent action to solve the increasing incidence of antibiotic resistance[11]. One among these suggestions, as well as one of the pillars in the implementation of antibiotic stewardship, is to use antibiotics as effectively as possible in infection management[12]. Continuous evaluation of the profile and quality of antibiotic use, both quantitatively and qualitatively, is one of the most important actions for optimizing antibiotic consumption[11].

Results obtained through these evaluations can be put into consideration for future policy changes regarding the use of antibiotics in healthcare facilities with the purpose to increase the rationality of antibiotic use. As one of the pillars in the implementation of antimicrobial stewardship policies to increase the efficacy and decrease the side effects of antibiotics, pharmacists and hospital pharmacy departments have a significant role[13,14]. Based on global data by 2050, mortality causes by inappropriate antibiotic use is expected to increase from 700.000 per year to 10 million and higher than cancer at 8.2 million [2,15]. The high empirical use of broad-spectrum antibiotics in Indonesian hospitals, along with the lack of documentation and adherence to antibiotic use recommendations, are thought to be contributing factors to the emergence of resistance[16]. Based on above of scenario, the purpose of this study is to evaluate the use of antibiotics in hospitalized pneumonia patients at West Nusa Tenggara (NTB) hospital using the anatomical therapeutic chemical and defined daily dose ATC DDD method.

MATERIALS AND METHODS

MATERIALS. Data Collection. Data obtained from medical records of patient characteristics (gender, age, social status, insurance costs, class of treatment, length of stay and comorbid diseases) and use of antibiotics (type, dose, route).

METHODS. Research Design. Hospitalized pneumonia patient at NTB hospital during the study period and met the inclusion and exclusion criteria were included in the study. The inclusion criteria were hospitalized pneumonia patient adult period Januari-December 2019 and 2022, with or without comorbid diagnose non communicable disease (treatment not with antibiotic) and personal payment or social health insurance administration (BPJS). Exclusion criteria were patients personally go home or pass away, incomplete and difficult to read medical records. This research has received ethical clearance from West Nusa Tenggara Hospital with approval no. 070.1/05/KEP/2022.

Research Instruments. The collected data was processed using the ATC DDD method quantitatively. ATC and DDD antibiotic codes are obtained from the WHO website which can be accessed https://www.whocc.no/atc_ddd_index/. DDD calculations are performed for each ATC code. DDD can be calculated using the formula[17]. Drug use in DDD = (Quantity of Use X strength)/(DDD WHO (g) DDD/100 days of treatment is calculated using the following formula: DDD/100 days of treatment = (Total DDD)/(Total LoS) x 100. DU 90% is obtained by arranging the use of antibiotics from highest to lowest then determining the cumulative percentage up to 90%.

Data Analysis. Univariate data were analysed descriptively by displaying mean±SD for continuous

data and percentages for categorical data. Bivariate data using Statistical Package for the Social Sciences (SPSS) 25 the Mann-Whitney U test was conducted to see the relationship between characteristic factors.

RESULTS AND DISCUSSION

Characteristic of Hospitalized Pneumonia Patient. The number of hospitalized pneumonia patients at NTB hospital during the study period 2019 and 2022, met the inclusion were 218 patients. Based on characteristic patient 117 (53.67%) >65 is 66 (30.28%), of patients are male with an age range of >65 is 66 (30.28%). Complete data characteristic patient can be seen in Table 1.

RISKESDAS in 2018 states the prevalence of smoking when viewed from gender, where men are 44.32% and women are 1.48%[3]. Research that has been conducted at RSUD M. Djamil Padang states that as many as 34 (69.39%) men and 15 (30.61%) women, have similarities in sex in pneumonia patients[17]. According to Torres, judging from the physiology of the bodies of men and women are different, men are more at risk of pneumonia than women[18]. Based on data from *the world health organization*, pneumonia cases increased in prevalence from 2.1% in 2007 to 2.7% in 2013. Based on age groups, the increase in prevalence occurs at the age of 45-54 years and still increases at a later age[20]. Decreased lung function in elderly patients affects the risk of pneumonia and morbidity and pneumonia mortality also increases[21].

NTB province where the majority of patients use BPJS, which is 70.42%, office insurance or private insurance as much as 1.27% and personal payments as much as 28.31%[22]. In line with research conducted by Vita *et al* (2021), based on the status of financing, the most patients use BPJS, which is 97 patients (85.84%)[23]. The high use of BPJS is due to the large number of people who are aware of health insurance, education level and knowledge[22].

The distribution of comorbid diseases was 80 (12.74%) patients, with 61 (23.28%) patients with cardiovascular diseases such as hypertension and congestive heart failure (CHF) ranked first. Complete data comorbid disease can be seen in Figure 1.

Research that has been conducted by Torres *et al* 2013 mentions types of comorbid diseases in pneumonia patients such as congestive heart failure (CHF), chronic kidney disease (CKD), liver disease, malignancy, diabetes mellitus, cerebrovascular disease, and immunodeficiency[24].

In this study, the length of stay patients was at most 6-10 days were 124 (54.2%), there are 2

Table 1. Characteristic hospitalization pneumonia patients.

Characteristic patients	n	%	p value
Male	117	53.67	0.000
Female	101	46.33	
Age (years)			0.000
17-25	13	5.96	
26-35	17	7.8	
36-45	23	10.55	
46-55	36	16.51	
56-65	63	28.9	
> 65	66	30.28	
Social status			0.000
Marry	199	91.28	
Single	7	3.21	
No data	12	5.50	
Pekerjaan			0.000
Housewife	8	3.67	
Private sector employee	25	11.47	
Goverments employee	9	4.13	
Enterpreneur	21	9.63	
Farmer	4	1.83	
Pensionary	7	3.21	
No data	144	66.06	
Fee guarantee			0.000
Insurance	2	0.76	
BPJS	206	94.27	
Private	10	4.96	
Treatment class			0.000
Class 1	77	36.26	
Class 2	37	17.56	
Class 3	104	46.18	
Length of stay (days)			0.000
≤ 5	55	26.72	
6-10	124	54.2	
11-15	31	13.74	
16-20	6	3.05	
21-25	2	2.29	
Comorbid disease			0.000
Yes	80	36.70	
No	138	63.30	

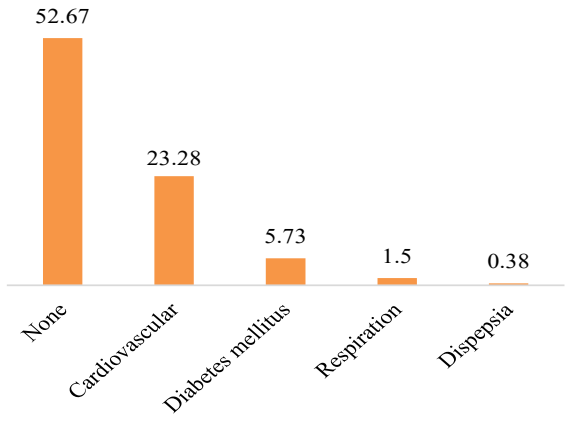

Figure 1. Precentage comorbid diagnose hospitalization pneumonia patients.

Table 2. Antibiotic use in hospitalized pneumonia patients.

Antibiotic use	Antibiotics	n	%
Single use antibiotic	Azithromycin tab 1x500 mg tab	2	0.92
	Levofloxacin 1x750 mg infus	56	25.69
	Meropenem 3x500 mg iv	1	0.46
	Meropenem 2x1 g iv	1	0.46
	Moxifloxacin 1x400 mg iv	14	6.42
	Cefixime 2x200 mg tab	3	1.38
	Cefoperazone 2x1 g	5	2.29
	Ceftazidime 3x1 g	2	0.92
	Ceftriaxone 2x1 g	39	17.89
	Ceftriaxone 1x2 g	2	0.92
Two combination use antibiotics	Levofloxacin 1x750 mg + cefixime 2x200 mg	2	0.92
	Ceftriaxone 2x1 g + cefixime 2x200 mg	3	1.38
	Ceftriaxone 2x1 g + ceftazidime 3x1 g	1	0.46
	Ceftriaxone 3x1 g + ceftazidime 3x1 g	1	0.46
	Ceftriaxone 1x2 g + moxifloxacin 1x400 mg tab	2	0.92
	Ceftriaxone 2x1 g + moxifloxacin 1x400 mg tab	2	0.92
	Ceftriaxone 1x2 g + azithromycin 1x500 mg tab	4	1.83
	Ceftriaxone 2x1 g + azithromycin 1x500 mg tab	3	1.38
	Ceftriaxone 1x2 g + levofloxacin 1x750 mg tab	11	5.05
	Ceftriaxone 2x2 g + levofloxacin 1x750 mg tab	1	0.46
	Ceftriaxone 2x1 g + levofloxacin 1x750 mg tab	8	3.67
	Levofloxacin 1x750 mg iv + moxifloxacin 1x400 mg tab	5	2.29
	Levofloxacin 1x750 mg iv + levofloxacin 1x750 mg tab	12	5.5
	Meropenem 3x1 g + levofloxacin 1x750 mg tab	2	0.92
	Meropenem 1x1 g + levofloxacin 1x750 mg tab	1	0.46
	Meropenem 2x1 g + levofloxacin 1x750 mg tab	1	0.46
	Moxifloxacin 1x400 mg iv + levofloxacin 1x750 mg tab	2	0.92
	Gentamicin 1x1g + ceftriaxone 2x1 g	1	0.46
	Ceftazidime 3x1g + levofloxacin 1x750 mg tab	2	0.92
	Levofloxacin 1x750 mg iv + ceftriaxone 2x1 g	2	0.92
	Levofloxacin 1x750 mg iv + cefixime 2x200 tab	2	0.92
	Meropenem 2x500 mg + moxifloksasin 1x400mg tab	1	0.46
	Cefotaxime 1x2g + cefixime 2x200 tab	1	0.46
	levofloxacin 1x750 mg iv + ampicillin sulbactam 3x1,5 g	1	0.46
	Ciprofloxacin 2x1g iv + ciprofloxacin 2x500 mg tab	1	0.46
	Ceftazidime 3x1 g + cefixime 2x200 mg tab	2	0.92
	Levofloxacine 1x750 mg iv + meropenem 2x1 g	1	0.46
	Cefoperazon 2x1 g + moxifloxacin 1x400 mg tab	2	0.92
	Ceftriaxone 1x2g + amoksiclav 3x1 tab	1	0.46
	Levofloxacin 1x750 iv + sefotaxime 3x1 g	1	0.46
	Moksifloxacin 1x400 mg iv + moksifloxacin 1x400 mg tab	1	0.46
Three combination use antibiotics	Azithromycin 1x500 iv + ceftriaxone 2x1 g + levofloxacin 1x750 iv	1	0.46
	Ceftriaxone 1x2 g + moksifloxacine 1x400 mg tab + azithromycin 1x500 mg tab	2	0.92
	Cefotaxime 1x1 g + cefixime 2x200 mg oral + azithromycin 1x500mg oral	1	0.46
	Levofloxacin 1x750 mg iv + ceftazidime 2x1 g + azithromycin 1x500 mg tab	1	0.46
	Meropenem 3x1 g + levofloxacin 1x750 mg tab + cefixime 2x200 mg tab	1	0.46
	Ceftriaxone 2x1 g + azithromycin 1x500 mg tab + levofloxacin 1x500 mg tab	1	0.46
	Cefotaxime 3x1 g + levofloxacin 1x750 iv + levofloxacin 1x500 mg tab	1	0.46
	Levofloxacin 1x750 mg iv + amicacyn 1x1 g + ceftriaxone 2x1g	1	0.46
	Ceftriaxone 2x1 g + ciprofloxacin 2x500 mg iv + ciprofloxacin 2x500 mg tab	1	0.46
	Ceftriaxone 1x2 g + meropenem 3x1 g + levofloxacin 1x750 mg oral	1	0.46
	Meropenem 3x1 g + levofloxacin 1x750 mg tab + cefixime 2x200 mg tab	1	0.46
Four combination use antibiotics	Ceftriaxone 1x1 g + vancomycin 2x1 g + levofloxacin 1x750 mg + cefixime 2x200 mg tab	1	0.46

patients with a length of stay is 24 days with a secondary diagnosis of CHF at the age of 59 and 70 years. Generally, patients with bacterial infections including pneumonia are hospitalized for 7-10 days, and coupled with the severity of the disease, the presence of comorbidities, complications and non-clinical factors. congestive heart failure, COPD, diabetes and cerebrovascular disease are known to be the most common comorbidities[24].

Evaluate Quantitative of Antibiotic Use. Pattern of Antibiotic Prescribing in Hospitalized Pneumonia Patients. The antibiotics used varied from a single antibiotic type of 125 (57.34%) patients, two combinations of antibiotics 80 (36.70%) patients, three combinations of antibiotics 12 (5.50%) patients and four combinations of antibiotics 1 (0.46%) patients. When based on the class of antibiotics obtained the most are fluoroquinolone group 152 (50%), cephalosporins 121 (39.80%), macrolides 15 (4.93%), beta lactam 13 (4.28%) and aminoglycoside 3 (4.28%) the amount obtained is based on prescriptions written by the doctor during the day of treatment of the patient. Complete data pattern of antibiotic by use and prescribing can be seen in Table 2 and 3.

The Indonesian Lung Doctor Association (PDPI) for pneumonia has recommended, antibiotics used for hospitalization are single-administration fluoroquinolones and beta lactam plus macrolides[21]. The pattern of antibiotic use in this study is in line with other studies where the most widely used antibiotics are cephalosporins with the type of ceftriaxone[18]. Ceftriaxone is a broader spectrum of third-generation cephalosporin antibiotics that have a longer half-life than other cephalosporins[26]. Levofloxacin is a third-generation fluoroquinolone class whose bacterial power increases, widens the antibacterial spectrum, improves absorption in the gastrointestinal tract, and prolongs the action of effective drugs for pneumonia[18]. Meropenem is a carbapenem class antibiotic that has a broad spectrum of activity, including Gram positive, anaerobic and aerobic and gram-negative bacteria with a mechanism of action inhibiting wall formation bacterial cells[27].

Evaluate ATC DDD. Antibiotic overuse lead to in antibiotic resistance, hence a drug use evaluation is required to determine whether the medicine is being used sensibly. Both qualitative and quantitative approaches were used to evaluate the use of drugs. The qualitative assessment approach is used to evaluate drug use accuracy based on the conformance of preset drug use criteria related to prescribing and prescribing indications. Meanwhile, quantitative evaluation was carried out using Drug usage 90%, which was related with anatomical therapeutic chemical (ATC)

Table 3. Pattern of antibiotic prescribing in hospitalized pneumonia patients.

Classification of antibiotics	n	%
Fluoroquinolon	152	50
Cephalosporin	121	39.8
Macrolide	15	4.93
Beta lactam	13	4.28
Aminoglycoside	3	4.28

categorization and drug usage by defined daily dose (DDD) for drug units[28]. ATC is a method for categorizing medications based on their medicinal and pharmacological qualities. DDD is a drug-related unit of measurement.

In this study, it was found that the total use of antibiotics in pneumonia patients, namely hospital A, the total use of antibiotics was 185.36 DDD / 100 *patient-days*, with an average length of stay of 8.02 days. The results of previous studies that have been carried out obtained the total use of antibiotics in July-December 2020 was 5887.56 DDD, with the highest use of levofloxacin 1987 DDD while for antibiotics with the lowest use was cefoperazon sulbactam 1.5 DDD[8]. For more details, see Table 4.

This result is similar to the study conducted by Vita *et al* (2021), the results showed that the most widely used antibiotics were ceftriaxone by 53.10% with a value of 38.79 DDD/100 days of hospitalization and total use of antibiotics of 77.25 DDD/100 days of hospitalization[23]. The results of a previous study prospectively observational on pneumonia patients at Dr. Soetomo Hospital also showed that ceftriaxone was the most widely used antibiotic with a value of 9.23 DDD / 100 days of hospitalization[29].

If the results of quantity measurements have relation to rationality, and the DDD value is less than the standard set at the WHO DDD standard value (www.whocc.no/atcddd), this shows the prospect of being more selective in prescribing antibiotics to patients. Giving antibiotics is actually only based on certain indicators that need antibiotic therapy, which is closer to the principle of carefully antibiotic usage. When the quantity of antibiotics used exceeds the WHO DDD standard value, it indicates which antibiotics are not being prescribed and used selectively in patients. There is a concern that unselective prescribing and use of antibiotics may lead to a high number of prescriptions and use of antibiotics that are not properly indicated, thereby compromising the rational use of antibiotics in patients[30]. Fluoroquinolones or beta-lactams plus macrolides are the antibiotics recommended by the PDPI for hospitalized patients with pneumonia[21].

Drug Utilization (DU) 90%. Based on Figure 2, the proportion of the DU segment was 90%, it was

Table 4. ATC/DDD antibiotic use in hospitalization pneumonia patients.

No	Antibiotics name	ATC	DDD use	DDD/100 patient-days	%
1	Amicacyn	J01GB06	2.00	0.11	0.06
2	Ampicillin Sulbactam	J01CR01	81.00	4.63	2.50
3	Amoxicillin Clavulanat	J01CR02	27.00	1.54	0.83
4	Azithromycin	J01FA10	8.15	0.47	0.25
5	Gentamicin	J01GB03	0.24	0.01	0.01
6	Levofloxacin	J01MA12	394.38	22.56	12.17
7	Meropenem	J01DH02	277.55	15.88	8.56
8	Moxifloxacin	J01MA14	26.40	1.51	0.81
9	Cefixime	J01DD08	8.96	0.51	0.28
10	Cefoperazone	J01DD12	200.00	11.44	6.17
11	Cefotaxime	J01DD01	96.00	5.49	2.96
12	Ceftazidime	J01DD02	276.00	15.79	8.52
13	Ceftriaxone	J01DD04	1818.00	104.00	56.11
14	Ciprofloxacine	J01MA02	8.45	0.48	0.26
15	Vankomisin	J01XA01	16.00	0.92	0.49
	Total		3240.08	185.36	100.00

found that the segments that entered 90% were used, namely ceftriaxone 56.11%, levofloxacin 12.17%, meropenem 8.56% and cefoperazone 6.17%. Drug Use (90% DU) is a list of drugs that are included in the accumulation of 90% of drug use.

According to WHO, the use of antibiotics must be minimized in treating infections[31]. The smaller the DDD value, the lower the possibility of resistance. The small quantity of antibiotics used leads doctors to be increasingly confused in choosing therapy for patients, so that it is closer to the principle of rational use of antibiotics[32]. The use of antibiotics needs to be monitored because it is known that excessive use of antibiotics can increase the occurrence of resistance and this has become a focus both nationally and globally[33].

The DU 90% method is a method that aims to make a grouping of data from drug use, so as to assess the quality of drug use that is often used. Assessment of drugs that fall into the 90% DU segment is needed to emphasize the drug segment in terms of evaluation, control of use and drug procurement planning[32].

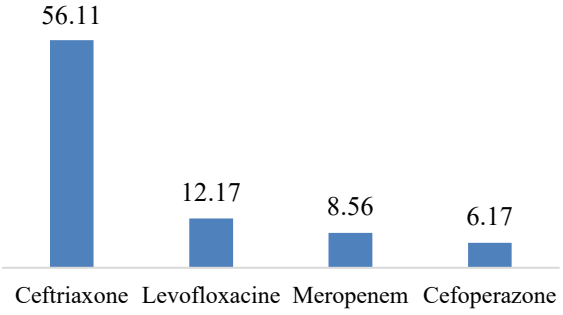

Figure 2. Percentage DU 90% in hospitalization pneumonia patients.

Studies have shown a link between antibiotic use rates and the incidence of resistance[34]. According to WHO, resistant bacteria are conditions in which bacteria become resistant to antibiotics. So that antibiotics that were initially effective for the treatment of infection become no longer effective. WHO data shows the death rate due to resistance until 2014 is around 700 thousand per year. With the rapid development and spread of infections due to resistant bacteria, by 2050 it is estimated that these deaths will be greater than deaths from cancer[31]. Antibiotics that fall into the 90% DU segment are very important to monitor their use to prevent resistance. Medical personnel who are authorized to administer drugs, need to properly control the delivery of antibiotics in health facilities. People should also not use antibiotics without a doctor's diagnosis first. It is expected that medical personnel authorized in administering drugs can monitor and evaluate the use of antibiotics in health facilities[35]. One of the policies in reducing the incidence of resistance is limiting the use of antibiotics so that changes can be made to the trend of antibiotic use in a certain period[34].

CONCLUSION

Conclusions were obtained based on the characteristics of the patient, most male with the age of > 65 years. For the type of antibiotic that is commonly prescribed is levofloxacin. Based on the class of antibiotics, the most abundant is fluoroquinolone. ATC/DDD values in hospitalized pneumonia patients with the most antibiotics are ceftriaxone and antibiotics that fall into the 90% DU segment, namely ceftriaxone, levofloxacin, cefoperazon and meropenem.

ACKNOWLEDGMENTS

Thank you to the Research and Community Service Unit of the Faculty of Pharmacy, Universitas Pancasila, which has funded this research.

FUNDING

Research were funded by Universitas Pancasila with number 4010/R/UP/VI/2021.

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