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Evaluation of Antibiotic Utilization in Respiratory Tract Infections Using ATC/DDD and Gyssens Methods

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Abstract
Respiratory tract infections affect both the upper and lower respiratory tract and remain a major global health problem, with pneumonia prevalence reaching around 23% across all age groups. The high incidence often leads to increased antibiotic use, which may contribute to antimicrobial resistance if used inappropriately. Therefore, antimicrobial stewardship (AMS) programs are essential to monitor and optimize antibiotic use in hospitals. This study aimed to analyze antibiotic utilization in patients with respiratory tract infections using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method and the Gyssens method at Dr. Soedarso Regional General Hospital, Pontianak. A prospective observational study was conducted using medical record data of 248 inpatients aged ≥18 years who received antibiotic therapy during January–December 2023. The results showed that most patients were male (62.9%). Quantitative analysis indicated that Ceftriaxone and Levofloxacin were the most frequently used antibiotics based on DDD/100 patient-days. Qualitative evaluation using the Gyssens method revealed that most antibiotic use was appropriate, although some cases still showed inappropriate indications, duration, alternative therapy selection, and timing of administration.

INTRODUCTION

Respiratory tract infections are infectious diseases that affect the upper and lower respiratory tract. These diseases can range from mild to severe, depending on the cause, environmental conditions, and a person's immune system. Respiratory tract infections are also a global health problem due to their high morbidity and mortality rates, especially in children and the elderly (Calderato et al., 2022). The prevalence of infection in developing countries reaches 22%, with significant variation across regions and income levels. Low-income countries show the highest prevalence at 37%, followed by lower-middle-income countries at 22%, and upper-middle-income countries at 13%. According to WHO regions, Southeast Asia has the highest prevalence (37%), followed by Africa (25%). These figures are significantly higher than those in developed countries such as Europe and the United States, indicating that infection control systems in developing countries contribute significantly to the high incidence of hospital infections (Odoom et al., 2024).

The increase in bacterial resistance to antibiotics globally is caused by various factors such as inappropriate antibiotic consumption and complex genome evolution (Canton R, et al., 2013). Antimicrobial Resistance (AMR) is a global health problem, despite various efforts being made at the global level, the use of broad-spectrum antibiotics continues to increase, leading to a significant increase in antibiotic resistance (Bertagnolio et al., 2024; Barlam et al.,

2016). In addressing AMR, antimicrobial stewardship (AMS) program activities are needed and changes in antibiotic use are needed. The application of accurate metrics can provide direct cost savings by reducing inappropriate prescriptions, reducing recurrent hospitalizations, and reducing therapy failures (Kandimahforoujaki et al., 2025).

The results of the study conducted by Andarsari et al., (2022) show that 68 patients with severe pneumonia treated in the ICU during 2019 met the inclusion criteria. A total of 13 types of antibiotics were used in the treatment of pneumonia. Quantitative analysis using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method indicated that the total antibiotic consumption reached 73.64 DDD per 100 patient-days. The three most frequently used antibiotics were Levofloxacin with 21.92 DDD/100 patient-days, Ceftriaxone with 20.45 DDD/100 patient-days, and Meropenem with 14.29 DDD/100 patient-days, most of which were administered parenterally. These findings indicate a relatively high level of antibiotic use among ICU patients with pneumonia. However, a high DDD value does not necessarily indicate irrational antibiotic use, therefore further qualitative evaluation is required to assess the appropriateness of antibiotic therapy.

Fajriansyah et al., (2023) evaluated antibiotic use in pediatric patients with acute respiratory infections at Hasanuddin University Hospital using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method. Using a cross-sectional design with retrospective data from medical records collected between January and December 2021, the analysis showed variations in antibiotic consumption among patients. The most frequently used antibiotic was Ampicillin with a value of 32.96 DDD/1000 patients/day, while the lowest utilization was Cefadroxil with 1.45 DDD/1000 patients/day. Furthermore, ampicillin from the penicillin group also showed the highest DDD/100 patient-days value, reaching 32.96 DDD/100 patient-days and exceeding the standard value recommended by the World Health Organization. These findings indicate that antibiotic use, particularly ampicillin, dominated the treatment of acute respiratory infections in children and highlights the importance of monitoring antibiotic utilization to prevent potential antimicrobial resistance.

The review study conducted by Syam & Karuniawati (2024) evaluated antibiotic use in hospitalized pneumonia patients using qualitative and quantitative approaches, namely the Gyssens method and the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method. The review analyzed articles published between 2013 and 2023 and examined parameters such as Gyssens categories, DDD/100 bed days, and DDD/1000 patient-days. The synthesis results indicated that Ceftriaxone and Meropenem were the most commonly used antibiotics, with values of 1547.735 DDD/100 bed days and 3011.2 DDD/1000 patient-days, respectively. Ceftriaxone was reported in 21 journals, while meropenem appeared in 8 out of 37 reviewed journals. In terms of the quality of antibiotic use, the highest proportion was found in Gyssens category 0 (appropriate use) at 93.7%, followed by category IVa at 67.6%. Additionally, the analysis of bacterial resistance revealed that Klebsiella pneumoniae showed the highest resistance, particularly to carbapenems such as Ertapenem and Doripenem, as well as third-generation and extended-spectrum cephalosporins and Piperacillin/Tazobactam. These findings highlight important patterns in antibiotic utilization and emphasize the need to improve antibiotic stewardship to optimize pneumonia treatment and reduce the risk of antimicrobial resistance.

Despite numerous studies evaluating antibiotic utilization in respiratory infections, several limitations remain in the existing literature. Previous research by Mareta Rindang Andarsari primarily focused on quantitative analysis using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method among ICU pneumonia patients, while studies by Fajriansyah mainly examined antibiotic consumption patterns in pediatric acute respiratory infections without assessing the appropriateness of antibiotic therapy. Furthermore, a review by Ricky Aditya Syam and Hidayah Karuniawati combined quantitative and qualitative approaches using the Gyssens method and ATC/DDD; however, it was limited to literature synthesis rather than primary clinical data analysis. These conditions indicate a research gap in comprehensive evaluations that simultaneously measure both the quantity and appropriateness of antibiotic use in patients with respiratory tract infections.

Therefore, the novelty of this study lies in integrating quantitative analysis using the ATC/DDD method with qualitative assessment using the Gyssens method to provide a more comprehensive evaluation of antibiotic utilization. Accordingly, this study aims to analyze the pattern and appropriateness of antibiotic use in patients with respiratory tract infections in order to support antimicrobial stewardship efforts and reduce the risk of antimicrobial resistance. This research is expected to enrich the scientific knowledge on antibiotic utilization evaluation through the integration of ATC/DDD and Gyssens methods. Practically, this study benefits clinical pharmacists and physicians in optimizing antibiotic therapy, serves as a foundation for hospitals to strengthen antimicrobial stewardship programs, and contributes to the literature as a reference for future research on antimicrobial resistance.

METHOD

This study was conducted as an observational cross-sectional study. Data were collected using medical records of inpatients with respiratory tract infections at Dr. Soedarso Pontianak Regional General Hospital. The sample size was determined using time-limited sampling during January-December 2023, resulting in a total of 248 patients. The inclusion criteria for this study were adult patients with respiratory tract infections aged ≥18 years and receiving antibiotic therapy during hospitalization. The exclusion criteria were patients who were hospitalized for <72 hours.

The research process began with data collection, compiling medical records of inpatients diagnosed with respiratory tract infections at Dr. Soedarso Regional General Hospital between January and December, meeting the established inclusion criteria. The data obtained were then recorded in a Data Collection Sheet (LPD). Next, antibiotic use was analyzed using the ATC/DDD method and therapeutic efficacy was assessed based on the Gyssens criteria.

Antibiotic use analysis was conducted using ATC/DDD and rational use was conducted using the Gyssens method. The World Health Organization (WHO) classifies antibiotic use using ATC. The Defined Daily Dose (DDD) is a standard unit of measurement established by WHO to describe the average daily dose of a drug used for its primary indication in adults, and is used as the basis for calculating antibiotic consumption quantification in the antimicrobial stewardship system (Natsch et al., 1998). The DDD calculation can be done using DDD/100 patient-days using the formula:

DDD/100 patient-days: (Jumlah dosis antibiotika yang digunakan pasien (gram)/(Standar DDD WHO (gram)x LOS) x 100

The DDD value is related to the amount of antibiotic use. A higher DDD value indicates high antibiotic use, which could indicate irrational drug use. Conversely, a lower DDD value indicates better, more selective antibiotic administration, and adherence to the principles of rational antibiotic use (Puspitasari, 2024).

The Gyssens method is a hierarchical algorithm that classifies antibiotic use into several categories based on appropriateness of indication, drug selection, effectiveness of alternatives, safety, cost, antibiotic spectrum, dose, interval, duration, route of administration, and time of administration. Each antibiotic therapy is assessed and assigned to category 0 (appropriate/Rational) or categories I–VI indicating certain forms of inappropriateness (Gyssens., 2001). Rational antibiotic use is defined as administering antibiotics appropriate to the infection indication, selecting appropriate drugs based on clinical guidelines, and considering effectiveness, safety, spectrum, dose, interval, duration, and route of administration (Aviatin et al., 2023). Appropriate and rational prescribing of antimicrobials and optimized antibiotics in accordance with the principles of antimicrobial stewardship, accompanied by quality diagnosis and aggressive infection control measures, can help prevent the occurrence of antimicrobial resistance (Lai et al., 2021).

This research method has been reviewed by the Health Research Ethics Committee (KEPK) of Dr. Soedarso Regional General Hospital with ethical approval number 43/RSUD/KEPK/V/2024.

RESULTS AND DISCUSSION

From 248 research samples, data was obtained on 156 male patients (62.9%), which was greater than the 92 female patients (37.1%).

Table 1. Socio-demographic characteristics of patients (n= 248) in hospital

Patient Characteristics	Number of Patients (n = 248)	Percentage (%)
Gender		
Man	156	62.9
Woman	92	37.1
Age		
19-44 years old	75	30.24
45-59 years	77	31.05
≥ 60 years	96	38.71
Length of Hospitalization		
5 days	27	10.9
6 – 10 days	170	68.5
11-15 days	32	12.9
≥ 15 days	19	7.6

Source: Medical records of Dr. Soedarso Regional General Hospital (2023)

Table 1 shows that more male patients experience respiratory tract infections than female patients. This condition can be influenced by lifestyle habits, particularly exposure to cigarette smoke, both as active and passive smokers. Furthermore, patients over 60 years of age also show a higher incidence rate. This is related to the increase in comorbidities that commonly appear with aging. The accumulation of these comorbidities leads to a decline in immunity and physiological function, thus decreasing the ability to fight respiratory tract infections (Calle et

al., 2016). The study found that 170 patients (68%) were hospitalized for 6–10 days. The duration of this treatment can vary depending on several factors, such as the patient's other health conditions, the presence of complications, the severity of the disease, and financial ability to support the treatment process (Hardiana, 2021).

Table 2. types of diagnosis in patients with respiratory tract infections

Types of Disease	Frequency (N)	Percentage (%)
Tuberculosis	122	38.5
Pneumonia	72	23.0
Chronic Obstructive Pulmonary Disease (COPD)	20	6.3
Covid-19	19	6.0
Sequelae of respiratory and unspecified tuberculosis	19	6.0
Pleural Effusion	15	4.7
Malignant Neoplasm of Unspecified part of bronchus or lung	12	3.8
Pneumothorax	10	3.1
Asthma	9	2.8
Hemoptysis	9	2.8
Bronchiectasis	5	1.6
Bronchitis	3	0.9
Interstitial Pulmonary disease with fibrosis	1	0.3

Source: Medical records of Dr. Soedarso Regional General Hospital (2023)

Table 2 shows that the most common respiratory tract infection was tuberculosis, with 122 cases (38.5%), followed by pneumonia with 72 cases (23%). Tuberculosis is a clinical condition where infection causes symptoms and can be confirmed through radiological and microbiological examinations. It is contagious and can be spread to others through respiratory droplets and is caused by the Mycobacterium tuberculosis bacterium (Lee et al., 2016). Indonesia is the country with the second highest number of tuberculosis sufferers in the world after India, with a proportion of new cases of 13% compared to all cases worldwide (Ministry of Health, 2023a).

The second most common disease profile is pneumonia, accounting for 23%. Pneumonia is a lung infection that can cause mild to severe illness in people of all ages (CDC, 2022). Globally, Streptococcus pneumoniae is known as the cause of community-acquired pneumonia. The bacteria frequently found in pneumonia patients are Streptococcus pneumoniae, Staphylococcus sp., atypical pathogens, anaerobic Gram-negative bacteria, and Pseudomonas aeruginosa. A study at the Indonesian National Referral Hospital for Infectious Diseases found that the most common bacteria found in sputum examinations was Klebsiella pneumoniae (Sitompul et al., 2022).

Table 3. Patterns of Single Antibiotic Use

Types of Antibiotics	Route	Number of Patients	Percentage (%)
Ceftriaxone	IV	90	36.92
Levofloxacin	IV	36	14.51
Azithromycin	PO	3	1.21
Cefotaxime	IV	1	0.40
Cefixime	PO	1	0.40

Source: Medical records of Dr. Soedarso Regional General Hospital (2023)

The pattern of single antibiotic use can be seen in Table 3. The antibiotics frequently used in patients with respiratory tract infections are Ceftriaxone (36.92%) and Levofloxacin (14.51%). Ceftriaxone is a third-generation cephalosporin antibiotic administered intravenously (IV) and intramuscularly (IM). Ceftriaxone is broad-spectrum, meaning it is active against gram-positive, gram-negative aerobic, and some anaerobic bacteria. Its activity against gram-negative bacteria is generally stronger than that of previous generation cephalosporins. However, its activity against some gram-positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) is very low (Richards et al., 1985). Ceftriaxone is given as an empirical antibiotic used to treat pneumonia (Bradley et al., 2011). This study found a high prevalence of tuberculosis diagnoses, as patients were admitted to the hospital with co-infections with other bacteria, such as Streptococcus pneumoniae, Staphylococcus aureus, and Klebsiella pneumoniae. Co-infections mimic acute pneumonia and often require empirical antibiotics or specific antibiotics other than tuberculosis drugs (Cioboata et al., 2025).

The second most frequently used is Levofloxacin at 14.51%. Levofloxacin is a broad-spectrum antibiotic from the fluoroquinolone group that works as an antibacterial agent with concentration-dependent characteristics, where its therapeutic effectiveness is greatly influenced by the AUC/MIC and Cmax/MIC ratios. This drug is used in the management of moderate to severe risk pneumonia (Shorr et al., 2006). In addition, levofloxacin has been shown to achieve bacterial eradication of up to 100% in pneumonia patients, regardless of the variation in dosage regimens used (Zhao et al., 2016).

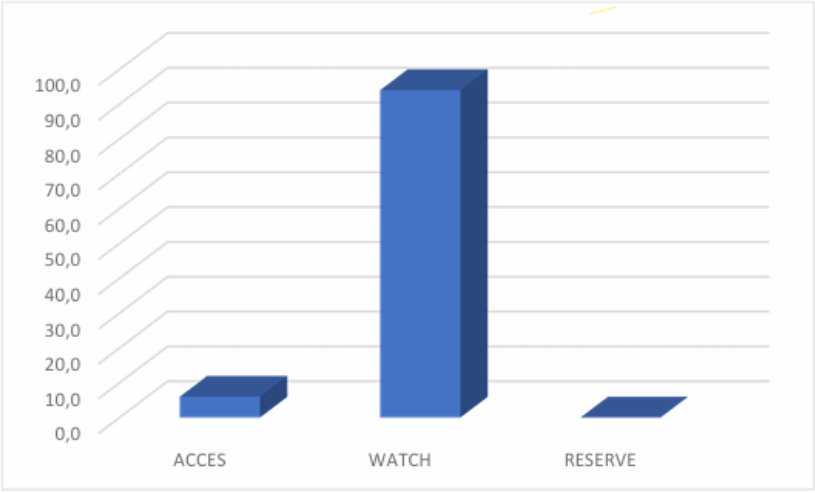

Figure 1. Percentage of Antibiotic Use AWaRe Classification

Source: Data analysis results (2023)

Antibiotic use is controlled by classifying antibiotics into AWaRe categories: Access, Watch, and Reserve. This classification aims to facilitate the implementation of antibiotic stewardship at the local, national, and global levels; improve treatment outcomes; suppress the emergence of resistant bacteria; and maintain the long-term effectiveness of antibiotics. This categorization also supports the WHO's global action plan for controlling antimicrobial resistance (Ministry of Health, 2021). The AWaRe classification was developed by WHO to help countries ensure that antibiotics are used in the most effective and safe manner, while minimizing the risk of antimicrobial resistance. WHO has set a target for at least 60% of total antibiotic consumption in countries to be from the Access category (WHO, 2021). The research results in Figure 1 show a prescribing pattern based on the AWaRe categories: Access 6.0%, Watch 94%, and Reserve 0%. Prescribing of antibiotics in the Watch category is the highest due to the high use of ceftriaxone in various cases of respiratory tract infections. The results of this study are similar to those conducted in tertiary and secondary hospitals in Bangladesh, which found that the highest use of antibiotics based on the WHO classification was the Watch group at 64%, Access 35.6%, and Reserve 0.1% (Rashid et al., 2022). The use of Watch antibiotics has a high prevalence in developing countries such as Indonesia, this is supported by research in 69 countries, which found that the use of Watch category antibiotics was very high in West Asia and Central Asia, with a proportion of Watch 66.1% and Access 28.4% (Pauwels et al., 2021).

Table 4. Results of Quantitative Analysis of Antibiotics using the ATC/DDD method

Types of Antibiotics	Route	ATC	WHO standard DDD (grams)	Amount (grams)	Amount (DDD)	DDD/100 patient days
Ceftriaxone	IV	J01DD04	2	1994.00	997.00	45.99
Levofloxacin	IV	J01MA12	0.5	388.78	777.56	35.87
Isoniazid	PO	J04AC01	0.3	134.90	449.67	20.74
Rifampicin	PO	J04AB02	0.6	182.70	304.50	14.05
Ethambutol	PO	J04AK02	1.2	306.75	255.63	11.79
Pyrazinamide	PO	J04AK01	1.5	316.00	210.67	9.72
4 FDC	PO	J04AM06	4 UD = 4 tablets	552.00	138.00	6.37
Azithromycin	PO	J01FA10	0.3	36.50	121.67	5.61
Metronidazole	IV	J01XD01	1.5	171.00	114.00	5.26
Streptomycin	IV	J01GA01	1	27.75	27.75	1.28
Cefotaxime	IV	J01DD01	4	66.00	16.50	0.76
Ciprofloxacin	IV	J01MA02	0.8	5.80	7.25	0.33
Co-trimoxazole	PO	J01ED01	2	10.08	5.04	0.23
Ampicillin Sulbactam	IV	J01CR01	6	145.50	24.25	1.12
Ciprofloxacin	PO	J01MA02	1	9.00	9.00	0.42
Levofloxacin	PO	J01MA12	0.5	1.50	3.00	0.14
Cefixime	PO	J01DD08	0.4	2.6	6.50	0.30

Source: Data analysis results (2023); WHO ATC/DDD Index (2023)

Evaluation of antibiotic use in patients with Respiratory Tract Infections was conducted using the DDD/100 patient-days method. The analysis results showed that there were 17 types of antibiotics used in this study, each accompanied by an ATC code and a DDD value according to the WHO standard for 2023 and a DDD/100 patient-days calculation. The antibiotic with the highest usage value was ceftriaxone, namely 45.99 DDD/100 patient-days. This figure indicates that ceftriaxone (2 grams according to the WHO standard) was prescribed to 45.99 adult patients out of every 100 hospitalized patients. The second highest use was levofloxacin with a value of 35.87 DDD/100 patient-days. In another study conducted at the Hospital in Probowangi during 2020 to 2022, the highest antibiotic use based on the DDD/100 patient-days value was found to be ceftriaxone, followed by Levofloxacin in second place (Zahra et al., 2023).

Table 5. Results of analysis using the Gyssens method

Category		Amount of Antibiotics	%
VI	Incomplete patient data	5	0.85
V	Use of antibiotics without any indication	5	0.85
IVA	There are other antibiotics that are more effective	1	0.17
IVB	There are other antibiotics that are safer/less toxic.	0	0
IVC	There are other antibiotics that are cheaper	0	0
IVD	There are other antibiotics that are more specific with a narrower spectrum.	5	0.85
IIIA	The duration of antibiotics is too long	16	2.72
IIIB	The duration of antibiotics is too short	3	0.51
IIA	Incorrect antibiotic dosage	0	0
IIB	Inappropriate antibiotic interval	0	0
IIC	Incorrect route of antibiotic administration	0	0
I	Incorrect timing of antibiotic administration	2	0.34
0	Appropriate and rational antibiotics		93.70

Source: Data analysis results (2023); Gyssens method classification (Gyssens, 2001)

Analysis using the Gyssens method showed that the rational use of antibiotics (Category 0) was 93.70%. There was 1 case (0.17%) given a more effective antibiotic (category IVA), 5 cases (0.85%) of patient data were incomplete so that the identification process could not be continued (Category VI), 5 cases (0.85%) of antibiotic use without indication (category V), another 5 cases (0.85%) should have been given a more specific antibiotic with a narrower spectrum (category IV D). In addition, there were 16 cases (2.72%) with too long a duration of administration (category IIIB), 3 cases (0.51%) of antibiotic duration were too short and 2 cases (0.34%) with inappropriate timing of antibiotic administration. The proportion of category 0 in this study was higher than the study conducted at Dr. Wahidin Surohusodo General Hospital, which was 58% (Hasan et al., 2025). This is similar to research conducted at Padang Hospital, which found that the use of antibiotics was appropriate and rational, namely 56.5% (Fadrian et al., 2024).

The analysis of antibiotic use based on the Gyssens method in this study showed that most antibiotic therapy was used appropriately and rationally, as reflected in the 93.70% category 0 proportion. This finding indicates excellent compliance with antibiotic use guidelines and antimicrobial stewardship principles. This high category 0 proportion compares

favorably with similar studies in tertiary hospitals, which generally report rational antibiotic use ranging from 40–70%. An antibiotic audit study in two teaching hospitals in Indonesia reported that only around 52–60% of antibiotic use was categorized as rational based on the Gyssens method, thus indicating a significant improvement in the quality of clinical practice (Syam et al., 2024). However, suboptimal antibiotic use was still found, particularly in category IIIA (too long antibiotic duration), which was the most dominant deviation (2.72%). This finding is consistent with various international studies that state that the most common error in antibiotic use is not in drug selection or initial dose, but rather in therapy duration exceeding clinical recommendations. A Swiss study showed that prolonging the duration of empirical antibiotic therapy without further clinical evaluation was a major cause of inappropriate antibiotic use, particularly in Gyssens category III, and contributed to the increased risk of antimicrobial resistance (Cusini et al., 2010). This finding is in line with the conceptual framework proposed by Gyssens et al. (2008), which emphasized that the duration of therapy without regular evaluation is one of the most common forms of antibiotic misuse in hospitals.

The categories of antibiotic use without indication (V) and the selection of antibiotics with a broader spectrum than necessary (IVD) were each found at 0.85%. Although relatively small proportions, these findings are still clinically significant because exposure to unnecessary and broad-spectrum antibiotics has been shown to increase selection pressure for resistant bacteria. A large cohort study in a European tertiary hospital showed that inappropriate or unnecessary use of antibiotics, including broad-spectrum antibiotics, is associated with an increased incidence of infections by multidrug-resistant organisms (MDROs) and prolonged length of hospital stay (Kollef et al., 2012).

Other categories such as dosage errors (IIA), administration interval (IIB), administration route (IIC), and toxicity (IVB) were not found in this study. This indicates that the aspect of antibiotic prescribing accuracy has been well considered, and reflects the important role of the involvement of the clinical pharmacy team and the antimicrobial resistance control program (ADR). This finding is in line with a systematic review report stating that hospitals with active implementation of antimicrobial stewardship have significantly lower rates of dosage and interval errors than hospitals without such programs (Davey et al., 2017).

CONCLUSION

Based on this study conducted at Dr. Soedarso Hospital, Pontianak, with 248 patients, it can be concluded that the evaluation of antibiotic use shows a comprehensive picture. Analysis using the ATC/DDD method showed that the most commonly used antibiotic was ceftriaxone with a value of 45.99 DDD/100 patient-days, followed by levofloxacin at 35.87 DDD/100 patient-days. These findings reflect the high use of broad-spectrum antibiotics in the management of respiratory tract infections, especially in hospitalized patients with certain levels of severity and comorbidities. Meanwhile, the analysis results using the Gyssens method showed that the majority of antibiotic use met rational criteria, with a proportion of 93.70%. However, 6.30% of irrational antibiotic use was still found, consisting of 0.85% of cases with incomplete patient data, 0.85% of antibiotic use without clear indications, 0.17% of cases where more effective antibiotic options were available, 2.72% of antibiotic use with excessively long duration, 0.51% with excessively short duration, and 0.34% with inappropriate antibiotic administration time. Although the proportion of inappropriateness is

relatively small, this finding emphasizes the importance of continuous evaluation of antibiotic use, particularly aspects of duration and timeliness of administration, to maintain rational therapy and support efforts to prevent antimicrobial resistance. Based on these findings, it is recommended that clinicians regularly evaluate the duration and timing of antibiotic therapy to prevent irrational use, that hospitals strengthen antimicrobial stewardship programs through continuous monitoring and periodic audits using the ATC/DDD and Gyssens methods, and that future researchers expand similar studies to other clinical settings or include resistance pattern analysis to obtain more comprehensive insights into antibiotic utilization and antimicrobial resistance.

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