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A Comprehensive Evaluation of Antibiotic Usage: Establishing a Foundation for Effective Antimicrobial Stewardship

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Abstract
Background: *The intensive care unit (ICU) is a significant area of antibiotic use, accounting for a substantial proportion of the overall antibiotic consumption. The inappropriate use of antibiotics in such settings has a notable impact on the emergence of antimicrobial resistance.* ***Objective***: *This study evaluated the rationality of antibiotic use in the ICU of RSUD Abdul Moeloek Hospital in Lampung Province.* ***Methods***: *This study was conducted between December 2022 and February 2023 using a prospective method and purposive sampling. An evaluation was conducted using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) system for quantitative analysis and Gyssens criteria for qualitative assessment. The research subjects comprised 55 individuals, the majority of whom were male (58.2%), aged > 65 years (29.1%), remained in the ICU for less than seven days (78.2%), and subsequently continued their treatment in a non-ICU (69.1%).* ***Results***: *Quantitative analysis demonstrated that the total number of antibiotics administered in this study was 394.83 DDD, with a DDD/100 patient-day value of 113.78. Ceftriaxone was the most frequently prescribed antibiotic (219 DDD), whereas gentamicin was the least frequently prescribed (1 DDD). Qualitative analysis revealed that 17.6% of the patients exhibited irrational antibiotic use.* ***Conclusion***: *Irrational use of antibiotics was observed in the following categories: IV A (1.1%); IV D (2.2%); III A (2.2%); III B (2.2%) IIA, (3.3%); IIB (5.5%); and I (1.1%). The study concluded that there was still a considerable degree of irrational antibiotic use.*

Keywords: *antibiotics rationality, antimicrobial stewardship program, ATC/DDD, gyssens, intensive care unit*

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INTRODUCTION

Antibiotics represent the primary therapeutic option for the prophylaxis and treatment of infectious diseases.(Gresie Astri et al., 2021) They are derived from living organisms and belong to a class of compounds and structural analogues synthesized in low amounts. These compounds can inhibit essential processes in the life cycles of one or more species of microorganisms. (Nasution et al., 2023) However, failure to appropriately select antibiotics when prescribing and using them leads to inappropriate prescription practices.

This inappropriate use has been linked to the irrational use of antibiotics, which can cause adverse drug reactions (ADRs) and contribute to the development of antimicrobial resistance (AMR).(Abdelkarim et al., 2023; Murray et al., 2022; Tan et al., 2022; World Health Organization, 2023) AMR occurs when pathogens become resistant to the drugs that were once effective against them, making infections harder and more expensive to treat. This resistance affects therapeutic success and increases the overall cost of treatment. (Dadgostar, 2019; Limato et al., 2022; Murray et al., 2022)

A review of the literature revealed that between 13-37% of patients in developed countries received antibiotics during their hospitalization. A higher proportion of cases was observed in developing countries, with figures ranging from 30% to 80%. In Indonesian hospitals, antibiotic use is relatively high. This resulted in a significant increase in the economic burden on hospitals, with rates reaching 44% to 97%.(Cereulos et al., 2019; Limato et al., 2022; Sofro et al., 2022) A number of studies have indicated that between 20%-62% of antibiotics are used inappropriately (Agustina & Prabowo, 2020; Bozkurt et al., 2014). Furthermore, antimicrobial resistance was estimated to be responsible for 1.27 million deaths globally in 2019. Furthermore, the economic impact is exacerbated by the emergence of antimicrobial resistance. (Murray et al., 2022)

To facilitate the rational use of antibiotics, the Ministry of Health of the Republic of Indonesia recommends the evaluation of antibiotics. It may be employed as an indicator of quality of control in hospitals. An evaluation may be conducted using qualitative and/or quantitative.(Kementrian Kesehatan Republik Indonesia, 2015) The Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method is the recommended approach for evaluating drug use quantitatively. Qualitative analysis can be conducted using the Gyssens method.(Andarsari et al., 2022; Hollingworth & Kairuz, 2021) The evaluation provides a foundation for understanding the patterns of antibiotic use within a hospital setting.

It is common for patients undergoing treatment in an intensive care unit (ICU) to contract infections as a result of the underlying disease, the necessity for invasive procedures, and surgical procedures. (Radji et al., 2011) The elevated risk of infection renders the ICU room one of the primary locations that contribute to the high utilization of antibiotics within hospitals.(Bozkurt et al., 2014; Patel et al., 2016; Ture et al., 2023) The objective of this study was to evaluate the utilization of antibiotics in the ICU at RSUD Abdul Moeloek Hospital, employing both the ATC/DDD and Gyssens methodologies. The findings of this study can inform the development of policies to optimize the use of antibiotics and facilitate interventions when necessary.

MATERIALS AND METHODS

Research design

This observational study utilized a prospective method at the RSUD Abdul Moeloek Lampung Province between December 2022 and February 2023. An evaluation utilizing both the ATC/DDD methodology and the Gyssens criteria was conducted. This study was approved by the Human Research Ethics Committee, Faculty of Medicine, University of Lampung (Number: 4279/UN26.18/PP.05.02.00/2022), and the Research Ethics Commission, RSUD Abdul Moeloek (Number: 420/36609/VII.01/10.26/XII/2022).

Research subjects

The subjects included in this study were patients who had received antibiotics in the ICU and who met the specified inclusion and exclusion criteria. Purposive sampling is also performed. The inclusion criteria for this study were patients aged > 18 years who were treated in the ICU between December 2022 and February 2023 and received antibiotics. Patients with unclear/missing data in medical records, incomplete records, those who were discharged against medical advice, those who were referred to another hospital, and those who died within 48 h of admission were excluded.

Data analysis

ATC/DDD antibiotic codes were obtained from the WHO website, which can be accessed at https://www.whocc.no/atc_ddd_index/. DDD was calculated using the following formula:

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$$\text{Drug use in DDD} = \frac{\text{Quantity Used x strength (g)}}{\text{DDD WHO (g)}}$$

$$\text{DDD/100 days of care} = \frac{\text{Total DDD}}{\text{Length of stay}} \times 100$$

Rational antibiotics were evaluated according to the categories indicated in the Gyssen flowchart. Antibiotic Guidelines created by the Antibacterial Resistance Control Program (ARCP) team at RSUD Abdul Moeloek Lampung Province were evaluated. Additional literature was consulted, including the Indonesia National Formulary, Management of Sepsis in Indonesia, and international guidelines such as the Drug Information Handbook 24th edition, NHS Antibiotic Guideline 2020, ASHP-IDSA-SIS Guideline 2018, and Johnss-Hopkhins Antibiotic Guideline 2016. The cost of the medication was ascertained through an e-catalog 5.0 system and by consulting nearby antibiograms.

RESULTS AND DISCUSSION

This study included 55 participants who met the inclusion criteria. The 'subjects' characteristics were dominated by men (58.2%), with an age range of 18-45 years (38.2%), and the longest length of stay of less than 7 days (78.2%). Of the patients discharged from the ICU, 69.1% continued treatment in non-ICUs (Table 1).

Table 1. Sample characteristics

Characteristics	Frequency (N=55)	Percentage (%)
Gender		
Female	32	58.2%
Male	23	41.8%
Age		
18-45	21	38.2%
46-65	18	32.7%
>65	16	29.1%
Length of Stay (LOS)		
≤7 days	43	78.2%
>7 days	12	21.8%
Discharge Condition		
Transferring others room	38	69.1%
Death	17	30.9%

The study revealed a predominance of female patients, consistent with findings from other studies.(Andarsari et al., 2022; Nasution et al., 2023; Putri et al., 2019; Qonita et al., 2023) The female sex is associated with an elevated risk of infection due to the inherent complexities of the immune system and the involvement of X chromosome-linked genes in IgG synthesis (Rusmini, 2016).

This study also found that adults aged 18-45 years had a higher percentage of ICU admissions than did older patients. However, when age categories were combined, the majority of the study population (61.8%) consisted of individuals over 45 years of age, classified as middle-aged to elderly based on the standard Indonesian demographic classifications from ' 'Indonesia's statistical reference. This finding aligns with data from Solok Hospital, West Sumatra, where ICU admissions were predominantly patients over 40 years of age compared to those under 40.(Mustiadji et al., 2024) Several studies have highlighted that older patients are more likely to experience a decline in immunity and physiology resilience as they age, increasing their risk of complications and the likelihood of ICU hospitalization.(Katarnida et al., 2014; Osman et al., 2021) This physiological decline often begins in middle age, around 40–45 years old, which coincides with the onset of several chronic diseases such as heart disease, diabetes, and cancer.(MacNee et al., 2014; Niccoli & Partridge, 2012)

Eleven antibiotics were administered to the 55 patients. Ceftriaxone (60.9 %) was the most widely used antibiotic followed by levofloxacin (10.3%). The third most common antibiotic, meropenem, is carbapenem and metronidazole. Ceftriaxone has emerged as the predominant group antibiotic utilized in intensive ICUs, as shown in various studies.(Andarsari et al., 2022; Nasution et al., 2023; Qonita et al., 2023) These studies have yielded results comparable to those observed in this current study. Antibiotic use is presented in Table 2.

A diagnosis is the primary reference point for determining the most appropriate antibiotic to prescribe.(Wang et al., 2021; Xingrong et al., 2022) In this study, diagnostic data is crucial for evaluating the rational use of antibiotics. Table 3 presents a list of the diagnoses of the 55 subjects and the types of antibiotics used. The highest diagnosis was post-craniotomy, accounting for 41.8% of cases, with the most common cause being SOL Sphenoorbital Meningioma. This was followed by sepsis (18.1 %) and post-laparotomy peritonitis (10.9 %). The choice of antibiotics administered to the patients depended on their diagnosis and severity. Among these patients, 20 received combination antibiotic therapy, whereas 35 were treated with a single antibiotic.

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Table 2. The utilization of antibiotics

Name of Antibiotics	Antibiotic Group	Quantity	Percentage
Ceftriaxone	Cephalosporin 3rd	53	60.9 %
Levofloxacin	Fluoroquinolon	9	10.3 %
Meropenem	Carbapenem	6	6.9 %
Metronidazole	Nitronidazol	6	6.9 %
Cefo-Sulbactam	Cephalosporin 4th	3	3.4 %
Cefotaxime	Cephalosporin 3rd	3	3.4 %
Moksifloksasin	Fluoroquinolon	2	2.3 %
Cefepime	Cephalosporin 3rd	2	2.3 %
Amikacin	Aminoglikosida	2	2.3 %
Ceftazidime	Cephalosporin 3rd	2	2.3 %
Gentamicin	Aminoglikosida	1	1.1 %
Total		87	100%

Table 3. Antibiotics used based on diagnosis

PATIENT CODE	DIAGNOSIS	TYPE OF ANTIBIOTIC	PATIENT CODE	DIAGNOSIS	TYPE OF ANTIBIOTIC
1	Sepsis + Pneumonia + Stroke + AKI	ceftriaxone, levofloxacin, Cefepime	28	Tumor tiroid, post subtotal thyroidectomy	ceftriaxone
2	Post craniotomy ec ICH	Ceftriaxone	29	Post-craniotomy tumor removal	ceftriaxone
3	Post Sc + tubectomy	Ceftriaxone	30	Post-craniotomy fracture cranial	Ceftriaxone, Meropenem, Gentamicin, cefepime
4	Sepsis + CKD On HD	Levofloxacin	31	Post SSTP ai eklampsi + hdd dini	Ceftriaxone
5	(benigna prostat hyperplasia) post turp	Ceftriaxone	32	Hydrocephalus Post-up shunt + CKD	Ceftriaxone
6	Sepsis + pneumonia + edema + gagal Jantung	Cefotaxime, Levofloxacin	33	Post cardioversion + dyspnea	Ceftriaxone
7	Pneumonia + CKD + stroke	Ceftriaxone, Levofloxacin	34	Post laparotomy/ tumor mesentery	Ceftriaxone, Cefo-sulbactam, Metronidazole
8	Post craniotomy ec stroke hemorrhagic + ICH+ HT	Ceftriaxone	35	DM + stem inferior + stroke infark	Ceftriaxone
9	Post craniotomy stroke pendarahan + AKI	Ceftriaxone, Amikacin, Meropenem	36	SLE+ALO + efusi perikard + CKD	Ceftriaxone
10	Post craniotomy intracranial space-occupying lesion + tracheostomy	Ceftriaxone	37	*Abscess* of the lung, post-thoracotomy	Ceftriaxone
11	Post craniotomy ec SOL sphenoorbital meningioma + Edema	Ceftriaxone	38	Pneumonia + post craniotomy ec SOL temporal base dextra meningioma	Ceftriaxone, Ceftazidime, Levofloxacin
12	Post craniotomy ec SOL sphenoorbital wing Meningioma	Ceftriaxone	39	Pneumonia + hydrocephalus vp shunt	Ceftriaxone,Ceftazidime, Levofloxacin, Amikacin
13	Post craniotomy intracranial	Ceftriaxone	40	Post craniotomy (tumor removal)+ DM	Ceftriaxone
14	Post craniotomy ec stroke hemorrhagic + ICH +CKD + hypertension	Ceftriaxone	41	Sepsis + post craniotomy ec SOL meningioma	Ceftriaxone, Cefo-sulbactam, Moxifloxacin
15	Post craniotomy ec ICH + CKD	Ceftriaxone	42	Sepsis + laparotomy peritonitis + pneumonia + DM	Meropenem

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16	Post craniotomy tumor removal + meningioma	Ceftriaxone	43	Sepsis + pneumonia + ALO	Ceftriaxone, Levofloxacin
17	Post-craniotomy tumor removal	Ceftriaxone	44	Sepsis + post hysterectomy	Ceftriaxone, Meropenem
18	Sepsis + CHF +CKD	Ceftriaxone Levofloxacin	45	Post craniotomy ec SOL sphenoorbital meningioma	Ceftriaxone
19	Sepsis + renal calculus + hypotension	Cefotaxime	46	Post craniotomy ec SOL sphenoorbital meningioma + edema cerebral	Ceftriaxone
20	Pneumonia + DM + ALO + hypertension	Ceftriaxone, Levofloxacin, Meropenem	47	Sepsis + CKD + post cardioversion	Ceftriaxone, Cefo-sulbactam, Moxifloxacin
21	Post laparotomy peritonitis	Ceftriaxone, Metronidazole	48	Post craniotomy ec edema cerebral	Ceftriaxone, Metronidazole Meropenem
22	Post laparatomy peritonitis+ anemia+ hiponatremia	Ceftriaxone, Metronidazole	49	Post craniotomy ec fraktur basis anterior	Ceftriaxone
23	Post laparotomy pertinotis	Ceftriaxone, Metronidazole	50	Post craniotomy ec ICH, stroke hemorrhagic, hypertension	Ceftriaxone
24	Post SSTP eklampsi antepartum	Ceftriaxone	51	Post craniotomy ec tumor cerebral	Ceftriaxone
25	Post craniotomy hemiperase	Ceftriaxone	52	Post craniotomy ec SOL tumor cerebelum	Ceftriaxone
26	Post laparotomy peritonitis	Ceftriaxone, Metronidazole	53	Post craniotomy ec Intracerebral hematoma	Ceftriaxone
27	Benign neoplasm of the thyroid gland, post subtotal thyroidectomy	Ceftriaxone	54	Post chelelistoyesiastomy, Malignant neoplasm: Pancreas	Ceftriaxone
			55	Post re-laparotomy packing abdomen.	Ceftriaxone, Metronidazole

Abbreviations: AKI = Acute kidney injury; ICH = Intracerebral hemorrhage; CKD = Chronic Kidney Disease; HD = hemodialysis; HT = Hypertension; SOL space-occupying lesion; CHF = Congestive heart failure; DM diabetes mellitus; ALO= acute lung oedema; SSTP= sectio caesarea transperitoneal profunda; SLE = Systemic Lupus Erythematosus.

When choosing an appropriate antibiotic, factors such as bacterial sensitivity to antibiotics must be considered. In this study, *Escherichia coli* was the most frequently isolated bacterium, followed by *Enterobacter aerogenes* and *Klebsiella pneumoniae*. The highest antibiotic sensitivity according to the antibiotic sensitivity patterns of microorganism pathogens was amikacin (82.1%), followed by meropenem (64%), and linezolid (62.5%). Ceftriaxone, the most commonly used antibiotic, showed resistance (66.7%) (Figure 1).

This aligns with the general trend in Asian countries, including Indonesia, where the most frequently isolated bacteria in ICU are *Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Enterococcus*, and *Staphylococcus aureus*.(Murray et al., 2022) A study conducted at another hospital in Indonesia, Fatmawati Hospital revealed that the predominant microorganisms isolated from the ICU were *Pseudomonas aeruginosa*, *Klebsiella* spp., and *Escherichia coli*. (Radji et al., 2011) The use of antibiotics has been identified as a contributing factor in the emergence of antimicrobial resistance. The greater the variety of antibiotic types employed, the greater the likelihood of antibiotic resistance.(Hanifah et al., 2022)

In this study, ceftriaxone was widely used in the ICU. However, as shown in Figure 1, the antibiogram indicates that the use of antibiotics (AB) as empirical therapy is not recommended because their effectiveness is below 75%, with a specific emphasis on ceftriaxone. Ceftriaxone is a third-generation cephalosporin with low toxicity, an affordable price, no coagulase problems, a good therapeutic index, and a broad spectrum.(Ayele et al., 2018; Katarnida et al., 2014) This antibiotic demonstrates greater activity than first- and second-generation cephalosporins against gram-negative microorganisms. Conversely, this antibiotic has been

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demonstrated to exhibit reduced efficacy against gram-positive microorganisms. The antibiotic was recommended for a dosage of 1-2 grams once daily.(Radji et al., 2011; Richards et al., 1984; Rosana et al., 2007) In numerous instances, this factor serves as a rationale for the prevalent utilization of ceftriaxone. Nevertheless, one study indicated that the resistance rates for this antibiotic increased from 2002 to 2005. This percentage has increased in recent years. (Rosana et al., 2007; Van Besien et al., 2022)

Drug consumption can be expressed in several ways, including cost, number of units, number of prescriptions, or physical quantity of the drug itself. However, it should be noted that these variables are subject to variation, which represents a limitation when comparing drug consumption. The Defined Daily Dose (DDD) is a unit of measurement that assumes the average maintenance dose per day for a given drug type used as the main indication in adults.(Putri et al., 2019; World Health Organization, 2019b, 2024) This unit is internationally standardized, providing a parameter for comparison (Nasution et al., 2023).

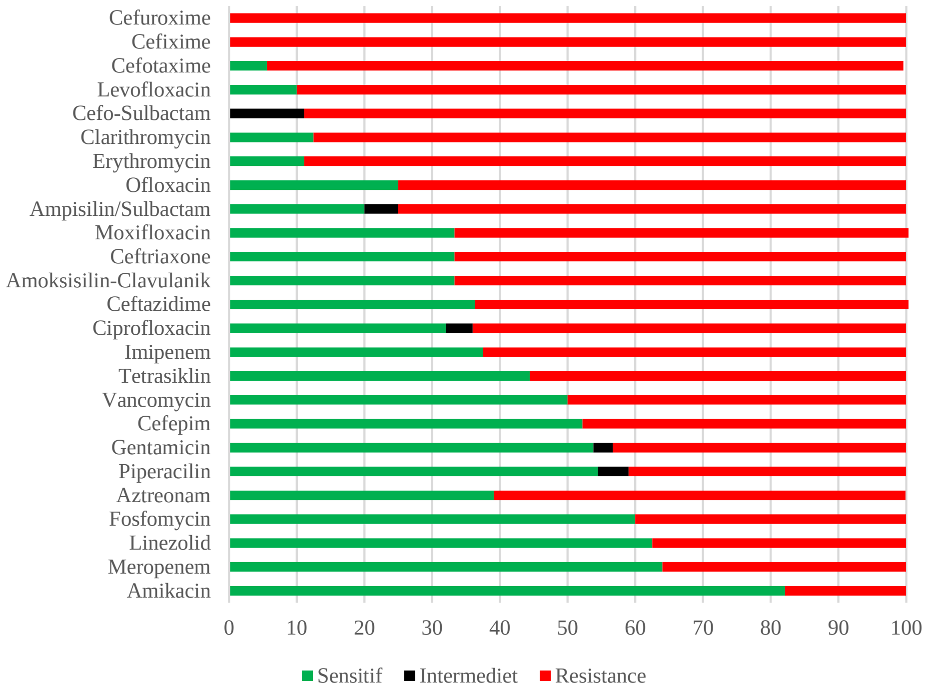

Figure 1. Antibiotic Resistance Pattern of Microorganism Isolated from Sample

Table 4. ATC/DDD Method for Quantitative Analysis Antibiotic Usage

NO	ANTIBIOTICS	ATC CODE	DDD Standard Value (WHO)	DDD	DDD 100 Patient-Days	% DDD	% Cumulative	DU 90%
1	Ceftriaxone	J01DD04	2 g	219.00 g	63.11	55.47	55.47	DU 90%
2	Levofloxacin	J01MA12	0.5 g	57.00 g	16.43	14.44	69.91	
3	Metronidazole	J01XD01	1.5 g	31.33 g	9.03	7.94	77.84	
4	Meropenem	J01DH02	3 g	28.50 g	8.21	7.22	85.06	
5	Moxifloxacin	J01MA14	0.4 g	15.0 g	4.32	3.80	88.86	
6	Cefo-sulbactam	J01DD62	4 g	14.5 g	4.18	3.67	92.53	
7	Ceftazidime	J01DD02	4 g	10.5 g	3.02	2.66	95.19	
8	Cefotaxime	J01DD01	4 g	9.50 g	2.74	2.41	97.60	
9	Amikacin	J01GB06	1 g	5.50 g	1.58	1.39	98.99	
10	Cefepime	J01DE01	4 g	3.00 g	0.86	0.76	99.77	
11	Gentamicin	J01GB03	0.24 g	1.00 g	0.29	0.25	100	
	TOTAL		24.64 g	394.83 g	113.78			

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Table 5. Gyssens method for analysis of qualitative antibiotic usage

Category	Gyssens Category	Percentage
VI	Incomplete Data	0 (0%)
V	Antibiotic not indicate	0 (0%)
IV A	There is a more effective alternative	1(1,1%)
IV B	There is a non-toxic alternative	0 (0%)
IV C	There is a cheaper alternative	0 (0%)
IV D	There is a narrow spectrum of alternative	2 (2,2%)
III A	Antibiotic administration is too long	2 (2,2%)
III B	Administering antibiotics is too short	2(2,2%)
II A	Inappropriate dose	3 (3,3%)
II B	Inappropriate interval	5 (5,5%)
II C	Inappropriate routes of administration	0 (0%)
I	Inappropriate timing	1 (1,1%)
0	Rational use of antibiotic	75 (82,4%)
	Total	91(100%)

The total quantity of antibiotics administered in this study was 394.83 DDD, with a DDD/100 patient-day value of 113.78. Ceftriaxone was the most frequently administered antibiotic, accounting for 219 DDD, whereas gentamicin had the lowest usage, at 1 DDD. The DDD/100 patient-days for ceftriaxone was 63.11, indicating that 63 of the 100 patients received 2 g of this antibiotic daily. The antibiotics included in the 90% Drug Utilization (DU) segment were ceftriaxone, levofloxacin, metronidazole, meropenem, and moxifloxacin. The results of the quantitative analysis of antibiotics are presented in Table 4.

The consumption of antibiotics in this study was found to be lower than the national estimate of 134.8 DDD/100 bed-days.(Limato et al., 2022) However, there was considerable variation in comparison to the results of other regional studies. For example, a comparison with studies of ICU patients at West Nusa Tenggara Provincial Hospital revealed a total DDD value of 829.67, with a DDD/100 patient-days of 133.60. The mean length of hospital stay was six days. The most frequently administered antibiotics were ceftriaxone, levofloxacin, meropenem, metronidazole, and amikacin, with respective usage rates of 60.71, 29.15, 16.10, 11.00, and 6.24.(Qonita et al., 2023)

Other investigations have demonstrated that levofloxacin and ceftriaxone are the most commonly used antibiotics in the ICU at Universitas Sumatra Utara Hospital, with DDD values of 45.62 and 28.25 per 100 patient days, respectively. The mean length of stay in this hospital is 5.4 days, with a total DDD/100 patient-days of 93.96.(Nasution et al., 2023) In comparison to the initial study conducted in the ICU, the DDD/100 patient-days value is lower, while in contrast, it is higher than the second study.

The factors that may influence the consumption of antibiotics include hospital policies regarding the use of antibiotics, the condition of the patient, and the preferences of the prescribing physician.(Limato et al., 2022; Nasution et al., 2023; Tan et al., 2022) A rational prescription of antibiotics is indicated by lower usage rates, whereas higher DDD values may be indicative of irrational use.(Hanifah et al., 2022)

The Gyssens method is employed to evaluate antibiotics from various perspectives, including the accuracy of indications and efficacy of antibiotic selection based on factors such as toxicity, cost, spectrum, duration of administration, dosage, interval, route, and timing of administration. In this study, the qualitative analysis revealed that 17.6% of the cases exhibited irrational use. Irrational antibiotic use was observed in categories IV A (1.1%), IV D (2.2%), III A (2.2%), III B (2.2%), IIA (3.3%), IIB (5.5%), and I (1.1%) (Table 5).

Within the category of inappropriate antibiotic use, this is defined as the use of an antibiotic that is not the most effective in the treatment of infection (Category IV A). During this study, one instance of inappropriate antibiotic use was identified. Patients with code 9 in Table 3 who had undergone craniotomy and developed

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acute kidney injury (AKI) were administered meropenem intravenously at a dosage of 500 mg/day. The results of the patient's culture on January 5, 2023, revealed that the patient was infected with *Klebsiella pneumoniae*, which demonstrated resistance to meropenem, sensitivity to amikacin, and intermediate resistance to tigecycline. The patient was administered meropenem from January 6 to January 10, 2023.

Meropenem is typically employed as a last resort for the treatment of multidrug-resistant gram-negative bacterial infections with multidrug resistance (MDR). However, in recent years, the resistance of gram-negative bacteria to carbapenems has increased. A combination of meropenem with other antibiotics may be employed if the isolate exhibits a minimum inhibitory concentration (MIC) of ≤ 8 mg/L.(Gan et al., 2023; Shortridge et al., 2023) In light of the culture results, the patient was advised to receive a single dose of amikacin. In accordance with the guidelines set forth by Johns Hopkins, tigecycline (I) can be employed as a therapeutic option in cases of multidrug-resistant (MDR) infections. (ASHP Therapeutic Guidelines, 2008; The Johns Hopkins Hospital Antimicrobial Stewardship Program, 2015; Tim Program Pengendalian Resistensi Antimikroba, 2022)

In Category IV D, inappropriate use of antibiotics was observed owing to the presence of narrower antibiotics with a more limited spectrum of activity. This finding indicates that the two antibiotics were used inappropriately an within this category. In the patient with code 41 in Table 3, who had undergone craniotomy and developed sepsis, the culture results indicated a gram-negative infection, namely, *Pseudomonas stutzeri*, *Proteus mirabilis*, and *Acinetobacter baumannii*. The patient was found to be sensitive to amikacin. Subsequently, the patient was administered the intravenous antibiotic moxifloxacin at a dosage of 400 mg per day in accordance with the results of the culture examination. It is a broad-spectrum antibiotic. In accordance with the ARCP guidelines, amikacin, including the aminoglycoside group, is effective against gram-negative bacteria.(Tim Program Pengendalian Resistensi Antimikroba, 2022) It is, therefore, recommended that patients be treated with amikacin antibiotics with a narrower spectrum.

Furthermore, the patient with code 48 in Table 3, who had undergone a craniotomy and was diagnosed with pneumonia, was found to have *Klebsiella pneumoniae* present in their system. It is a Gram-negative bacterium. Metronidazole was administered intravenously at a dose of 500 mg every eight hours. Metronidazole is indicated for the treatment of vaginal infections caused by *Trichomonas*, *Giardia lamblia*, *Entamoeba histolytica*, *Clostridium difficile*, *Helicobacter pylori* and anaerobic bacteria.(Cereulos et al., 2019) In accordance with the ARCP guidelines and the Johns Hopkins guidelines, amikacin represents an efficacious option for the treatment of Klebsiella pneumoniae infections.(The Johns Hopkins Hospital Antimicrobial Stewardship Program, 2015; Tim Program Pengendalian Resistensi Antimikroba, 2022) The results of the patient's culture demonstrated that amikacin was a sensitive antibiotic.

The prolonged use of antibiotics is classified as Category III A. In the course of this study, two antibiotics were identified as having been administered for an excessive duration. Patients with Code 9 in Table 3 who had undergone craniotomy and acute kidney injury and received ceftriaxone intravenously at a dose of 1 g every 12 hours for eight days, from December 30, 2022, to January 6, 2023. Patient culture results were obtained on January 5, 2023. In another patient, classified as Code 41 in Table 3, with post craniotomy and sepsis, ceftriaxone was administered intravenously at a dose of 1 g every 12 hours for a period of 10 days, commencing on January 11 and concluding on January 20. The culture results were obtained on January 17, 2023, in accordance with the National Formulary, the antibiotic ceftriaxone may be employed as empirical therapy for a period of up to seven days.(Keputusan Menteri Kesehatan Republik Indonesia, 2017) It is advised that the definitive antibiotic be replaced following the availability of culture results on the seventh day.

Category IIIB encompasses the use of antibiotics that are insufficiently prolonged during administration. This evaluation identified two antibiotics within this category. In patients with code 30 Table 3 and a post-craniotomy diagnosis of pneumonia, antibiotics were administered: cefepime i.v. 1 g/8 h and gentamicin i.v. 80 mg/8 h for one day following the achievement of bacterial culture results. In accordance with the Johns Hopkins guidelines, the administration of antibiotics (cefepime and gentamicin) to patients with pneumonia should be continued for a period exceeding 48 h. In accordance with the ARCP guideline, the administration of antibiotics to patients with a *Pseudomonas* infection should last between seven and ten days(Tim Program Pengendalian Resistensi Antimikroba, 2022).

Category IIA involves evaluation of inappropriate antibiotic doses. The present study included three antibiotics in this category. A high creatinine clearance

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(CrCl) indicates a reduction in renal function. An increase in drug clearance results in a reduction in drug concentration, whereas a decrease in drug clearance leads to an increase in the drug concentration. In patients with a high CrCl, the dosage of drugs eliminated by the kidneys should be reduced, particularly in those with renal disease.(Stefani et al., 2019) This finding is in accordance with the ARCP guideline, which recommends adjustments to the dosage and interval of antibiotic administration for this condition (Tim Program Pengendalian Resistensi Antimikroba, 2022).

In the case of a patient with code 4 in Table 3, the patient was diagnosed with chronic kidney disease (CKD) and sepsis while undergoing dialysis. The patient was administered 750 mg/day of levofloxacin. Levofloxacin is a class of antibiotics eliminated by the kidneys. In accordance with the ARCP guideline, the dose must be adjusted.(Tim Program Pengendalian Resistensi Antimikroba, 2022) Therefore, in the event that the patient is administered a dose of 750 mg per day, the subsequent dose should be reduced to 500 mg over a period of 48 hours.(Van Der Meer & Gyssens, 2001)

Inpatient code 9, Table 3, which pertains to a patient who had undergone post-craniotomy and acute kidney injury (AKI), was administered amikacin at a dosage of 500 mg per day. The data laboratory demonstrated that the creatinine value was 3.44 mg/dL with a body weight of 70 kg, indicating a CrCl of 19.78. Aminoglycoside antibiotics are drugs with a narrow therapeutic index and a high potential for toxicity. For patients with a CrCl value of less than 20, the recommended dosage is 3 mg per body weight (BW) administered once. In this instance, amikacin is advised to be administered at a dosage of 210 mg.(Khilnani et al., 2019) Similarly, the patient identified as code 42 in Table 3, with a CrCl of 19.8, received meropenem at a dosage of 1 g per day. In accordance with the ARCP guidelines, patients with a CrCl of 10-25 are advised to receive a reduced dose of meropenem, namely 500 mg every 12 h (Khilnani et al., 2019; Tim Program Pengendalian Resistensi Antimikroba, 2022).

The second category, IIB, pertains to the accuracy of the antibiotic administration interval. This category encompasses five cases. In patients with code 1 (Table 3) presenting with sepsis, pneumonia, and AKI, ceftriaxone (1 g/12 h), levofloxacin (750 mg/24 h), and cefepime (1 g/8 h) were administered. In patients with a CrCl value of 30.8, as per existing guidelines, a levofloxacin dose of 750 mg/24 hours is administered on the first day, followed by 750 mg/48 hours on the subsequent day.(Wargo et al., 2005) Cefepime is eliminated by the kidneys; thus, in patients with a CrCl of 30-60, a dose of 1 g/12 hours is administered.(Lindsay et al., 2017)

In the case of patient code 4, Table 3 shows the diagnosis of sepsis and CKD with hemodialysis, for which the patient was prescribed levofloxacin 750 mg/day. In this case, if the patient was taking a dose of 750 mg/day, the subsequent dose is recommended to be administered at 500 mg/48 hours.(Stefani et al., 2019; Wargo et al., 2005) Inpatient code 42, Table 3, with a CrCl of 19.8, the antibiotic meropenem 1 g/8 hours was administered. The ARCP guidelines recommend meropenem 500 mg/12 h for patients with CrCl values of 10-25. Patient code 9 (Table 3), who had undergone craniotomy and developed AKI, received amikacin 500 mg/day for a period of three days. In patients with a CrCl of 6.09 and a body weight of 70 kg, the recommended dose is 3 mg/kg to be administered on a single occasion. Therefore, 210 mg is recommended to be administered on a single occasion (The Johns Hopkins Hospital Antimicrobial Stewardship Program, 2015; Tim Program Pengendalian Resistensi Antimikroba, 2022).

The final case identified an irrational antibiotic, which was classified as Category I with a single instance. This category assesses the inappropriate timing of antibiotic administration. Inpatient code 1 (Table 3) included patients with sepsis, pneumonia, and AKI who were administered levofloxacin at a dosage of 750 mg per 24 h. The patients were administered the therapy on 23rd-25th January 2023 at 12:00, and on 26th-30th January 2023, they received therapy at 24:00. The initial administration, occurring between 12:00 and 24:00 the following day, represents a 36-hour administration interval. The recommended dosage and time interval for levofloxacin were every 24 h, in accordance with relevant guidelines.

A qualitative evaluation conducted at a tertiary care general hospital in Medan revealed a lower percentage of irrational antibiotic use compared to this study, with 8.63% of cases identified as irrational.(Limbong et al., 2023) In contrast, another study at a hospital in Semarang using qualitative evaluation reported a 17.38% rate of irrational antibiotic use, a finding closely aligned with this study's results. (Gusa et al., 2024) However, significantly higher percentages were observed at RSUP Dr Kariadi Hospital in Semarang (84.48%) and RSUP Dr M. Djamil Hospital in Padang (43.5%), underscoring the variability in irrational antibiotic use across healthcare facilities.(Arief & Rahmania Eka Dini, 2024; Fadrian et al., 2024)

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Evaluation results from RSUD Abdul Moeloek in Lampung Province, although showing a lower percentage compared to other studies, confirm the presence of irrational antibiotic use. The irrational use of antibiotics is a significant contributor to antimicrobial resistance (AMR), highlighting the urgent need for preventive measures. The Antimicrobial Stewardship Program (ASPs) is a cornerstone of healthcare systems aimed at optimizing antibiotic use.(World Health Organization, 2019a) In 2014, the Centers for Disease Control and Prevention (CDC) recommended the implementation of ASPs in hospitals. The ASPs framework includes seven core elements: hospital leadership commitment, accountability, pharmacy expertise, actionable interventions, tracking, reporting, and education.(Centers for Disease Control and Prevention, 2019)

Implementing ASPs is crucial for improving patient outcomes, reducing the transmission of multidrug-resistant organisms, and mitigating microbial resistance.(Centers for Disease Control and Prevention, 2019; Dyar et al., 2017) Literature reviews from several Asian countries demonstrate that ASP implementation not only avoids negative impacts on patient outcomes but also improves them, reduces AMR, and significantly lowers healthcare costs associated with antibiotic use.(Setiawan et al., 2019) In Indonesia, some hospitals have successfully implemented ASPs, while others face challenges, such as limited access to antimicrobial resistance data.(Lutfiyati et al., 2022; Manurung & Andriani, 2022) At a tertiary hospital in Banyumas, ASP implementation led to a 10% increase in rational antibiotic use and reduced overall antimicrobial costs.(Nursyamsi Agustina et al., 2023)

At RSUD Abdul Moeloek, the presence of an Antibacterial Resistance Control Program (ARCP), guidelines for antibiotic use, and existing data on antimicrobial resistance patterns create a strong foundation for implementing ASPs. However, this study did not evaluate the implementation of ASPs at this facility, highlighting a critical gap in understanding and practice. Assessing ASPs implementation at RSUD Abdul Moeloek is essential for optimizing antibiotic use and effectively addressing resistance.

This study has certain limitations, including the small sample size and restricted reference for analyzing antibiotic rationality. Future research should examine the broader impact of ASPs implementation on hospital management, patient outcomes, and associated costs to strengthen further efforts to combat AMR.

CONCLUSION

The quantitative evaluation in this study revealed that the total antibiotics administered amounted to 394.83 Defined Daily Doses (DDD), with a DDD/100 patient-day value of 113.78. Ceftriaxone was the most frequently prescribed antibiotic, accounting for 219 DDD, whereas gentamicin was the least utilized antibiotic, with only one DDD. Qualitative evaluation showed that 17.6% of cases involved irrational antibiotic use. These cases were distributed across categories IV A (1.1%), IV D (2.2%), III A (2.2%), III B (2.2%), II A (3.3%), II B (5.5%) and I (1.1%). This finding highlights the continued use of irrational antibiotics by RSUD Dr H. Abdul Moeloek. Antimicrobial stewardship programs play a vital role in monitoring and promoting the rational use of antibiotics, and evaluations such as these are integral components of the program. The active involvement of all healthcare professionals is critical, as irrational antibiotic use involves multiple levels within the hospital system. Collaborative efforts within the ASP framework can significantly reduce the prevalence of irrational antibiotic use, enhance patient outcomes, and combat antimicrobial resistance.

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AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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