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Evaluation of Antibiotic Use in Pediatric Inpatients at One of Bandung Regional Hospitals in August 2023

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Abstract

Adverse Drug Reaction (ADR) is any unfavorable and unexpected drug response in paInfectious diseases are a major concern in the field of health, especially in developing countries like Indonesia. Children are vulnerable to infections because their immune systems are not fully developed. Proper management is necessary for the prevention and treatment of infectious diseases in pediatric patients. Antibiotics are the primary choice for addressing bacterial infections. However, the increased use of antibiotic can contribute to high levels of antimicrobial resistance (AMR), rendering infection treatment ineffective. The evaluation of antibiotic use can be conducted through the Anatomical Therapeutic Chemical (ATC) as the classification system and the Defined Daily Dose (DDD) measurement unit (ATC/DDD), which focuses on the quantity and types of antibiotics used. Although this method provides a quantitative overview, a qualitative approach using the Gyssens method and interviews with relevant parties are necessary for a more in-depth understanding of the rationality of antibiotic use. This study aims to comprehend the patterns of antibiotic use in pediatric inpatients at one of Bandung Regional Hospitals during August 2023. Using a retrospective observational approach, data were collected and processed using the ATC/DDD method. The evaluation results show that cephalosporins is the most commonly used antibiotic group, with cefotaxime being the dominant antibiotic administered intravenously. Quantitative evaluation indicates variations in DDD/100 patient days among different antibiotics, with ciprofloxacin having the highest value and amikacin the lowest. For a comprehensive understanding, qualitative research using the Gyssens method and interviews is necessary to strengthen the evaluation results of antibiotic use. Ultimately, this study provides a thorough perspective on antibiotic use in pediatric inpatients, supporting efforts to control antimicrobial resistance and promote more judicious antibiotic selection.

Keywords: Key words: Keywords: antibiotics; pediatrics; antibiotic use evaluation; WHO indicator ATC/DDD.

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Introduction

Infectious diseases are a major concern in the field of health, especially in developing countries like Indonesia. Children are more susceptible to infections due to their underdeveloped immune systems.[1] Study conducted by Djaja and Sulistiyowati, reveals that the highest mortality rates in infants and toddlers are caused by infectious diseases. Therefore, concerted efforts are needed for proper prevention and treatment of infectious diseases, especially in pediatric patients.[2]

The primary option to address the issue involves the use of antimicrobials, including antibiotics for bacteria, antifungal drugs, antivirals, and antiprotozoals. Generally, antibiotics are defined as the most commonly used drugs to fight bacterial infections and are considered a remarkable medical discovery of the 20th century. The introduction of antibiotics has transformed therapeutic paradigms, saving millions of lives from bacterial infections.[3,4]

The high rates of antibiotic use and prescription can be one of the contributing factors to the rose of antimicrobial resistance (AMR). AMR is a condition that occurs when bacteria is no longer responding to antibiotics, making treatments ineffective and difficult or not feasible to treat infections. The emergence and spread of antibiotic resistance are driven by various factors, including inherent microbial characteristics and numerous environmental factors involving both prescribers and patients. Factors contributing to antibiotic resistance include population and population's density, ineffective infection control programs, poor compliance, including inappropriate prescriptions and inadequate dosages.[5,6]

Drug Utilization Evaluation (DUE) is performed to assess whether the use of drugs, including antibiotics, is rational. The evaluation can be conducted qualitatively or quantitatively. Qualitative DUE is an approach used to assess the appropriateness of drug use based on predetermined criteria related to prescription and prescription indications. On the other hand, quantitative DUE is performed by classifying drugs based on the Anatomical Therapeutic Chemical (ATC) classification and drug usage in Defined Daily Doses (DDD).[7]

ATC is a classification system categorizing drugs based on therapeutic and pharmacological characteristics. Additionally, DDD is used as a measurement unit related to the ATC code. DDD represents the estimated average daily dose of a drug when used for its main indication in the adult population.[8,9] In pediatric patient groups' cases, DDD can serve as an overall measurement tool when it is difficult to identify warnings or limitations regarding the use of adult-based DDD.[8]

From those explanations above, an evaluation of antibiotic use in children is necessary to monitor and supervise appropriate and rational antibiotic usage. This study aims to understand the patterns of antibiotic use and conduct a quantitative evaluation using the ATC/DDD method in pediatric inpatients at one of Bandung Regional Hospitals in August 2023.

Methods

This study adopts an observational study approach, with data collection conducted retrospectively. The collected data originated from pediatric inpatients at one of the Regional General Hospitals (RSUD) in Bandung, West Java in August 2023, then categorized based on the type of antibiotic, the quantity and potency of antibiotics administered, as well as the total days of patient care. Inclusion criteria includes pediatric inpatients receiving

antibiotic therapy managed by the Pediatric Medical Staff Group (KSM), while exclusion criteria involves antibiotics without ATC codes. The collected data will be processed quantitatively using the ATC/DDD method. ATC codes and DDD values for antibiotics are obtained from the WHO website, which accessible through the link https://www.whocc.no/atc_ddd_index/. DDD calculations are performed for each ATC code, and the DDD calculation formula is as follows.[10]

Total Consumption in DDD[11]:

$$DDD = \frac{Number\ of\ item\ used\ x\ Amount\ of\ drug\ per\ item}{WHO\ recommended\ DDD\ of\ a\ drug\ (g)}$$

DDD/100 patient days is calculated using the formula[11]:

$$\frac{DDD}{100} Patient\ Days = \frac{Total\ Consumtion\ in\ DDD}{Total\ Days\ of\ care\ in\ the\ period} x100$$

Results and Discussion

The antibiotics use in pediatric inpatients were assessed using the ATC/DDD method. The evaluation is conducted by considering the Anatomical Therapeutic Chemical (ATC) codes and the standard Defined Daily Dose (DDD) values for each type of antibiotic. Subsequently, analysis and calculations are performed to obtain the DDD/100 patient-days value.

Table 2.1 shows that there are 10 antibiotic groups used in the treatment of pediatric inpatients at one of the Regional General Hospitals (RSUD) in Bandung, with cephalosporins being the most frequently prescribed category, accounting for 57.41% of the total prescriptions. Another study conducted at Dr. Soebandi Jember Regional General Hospital in the 2017 period indicated that cephalosporins was the most commonly prescribed antibiotic group, with a percentage of 46.22% in the treatment of pediatric inpatients.[12]

Meanwhile, at tertiary care hospital in Pune, Maharashtra for a period of 6 months (October 2018 to April 2019), the antibiotic group Cephalosporins was the most common class of antibiotic prescription (45%), followed by penicillins (27%) prescribed in pediatric wards.[13] Meanwhile, during a 6-month period (October 2018 to April 2019) at a tertiary care hospital in Pune, Maharashtra, cephalosporins were the most commonly administered antibiotic group (45%), followed by penicillins (27%), in pediatric wards.[13] This investigation was also carried out in Abu Dhabi, United Arab Emirates (UAE), a developed country on the West Asian continent. Cefaclor 130 (31.1%), Co-amoxiclav 103 (24.6%), and ceftriaxone 69 (16.9%) were the most commonly prescribed antibiotics in this study, whereas amoxicillin 1 (0.2%) and clarithromycin 2 (0.5%) were the least frequently prescribed.[14]

According to the majority of research, amoxicillin is the most commonly prescribed antibiotic, with broad-spectrum beta-lactams becoming increasingly popular.[15] Furthermore, another study discovered that amoxicillin prescriptions were significantly higher in both the United Kingdom and the Netherlands. [16] Nonetheless, multiple studies have shown that the beta-lactam family is still the most widely administered category of antibiotics. These patterns may be influenced by variations in patient characteristics, doctor prescription behaviors, pharmaceutical costs, and antibiotic prescribing guidelines for a variety of illnesses, including acute sinusitis, acute otitis media, and pharyngitis.[14]

A class of β-lactam antibiotics, Cephalosporins, are currently in their fifth generation. It is originally derived from the fungus Cephalosporium sp. which are a large group of bacterial antimicrobials that work through their β-lactam rings. Beta-lactam

Table 1. Antibiotic Profile Based on Number of Uses and Route of Administration

Class of Antibiotics	Type of Antibiotics	Number of Use	Route of Use (%)		Total Percentage
			Oral	Parenteral	
Cephalosporin	Cefotaxime	603		25.48	
	Ceftazidime	10		0.42	
	Ceftriaxione	376	12.72	15.89	57.41
	Cefixime	301			
	Cefoperazon	69		2.92	
Penicillin	Ampicillin	146		6.17	
	Amoxycillin	29	1.23		14.20
	Cloxacillin	161		6.80	
Carbapenems	Meropenem	243		10.27	10.27
Aminoglycosides	Gentamicin	183		7.73	9.80
	Amikacin	49		2.07	
Nitroimidazole	Metronidazole	71		3.0	3.0
Macrolides	Erythromycin	9	0.38		2.41
	Azithromycin	48	2.03		
Glicopeptide	Vancomycin	39		1.65	1.65
Fluroquinolones	Ciprofloxcacin	20	0.84		1.27
	Levofloxacin	10	0.42	0.42	
Total		2367	17.62	82.82	100

antimicrobials act on susceptible organism in two steps: in the first step, the antibiotic binds to a key receptor called membrane-bound penicillin-binding protein (PBP). This protein plays a vital role I the cell cycle, helping to build peptidoglycan structure of the cell wall. Therefore, inactivation of PBP by the bound antibiotic has an immediate effect in its function. The second steps involves the physiological effects of this receptor-ligand interaction. PBP acts in the cell wall's late phases of peptidoglycan production. As peptidoglycan maintains the integrity of the cell wall in a hypotonic environment, its disruption leads to lysis and cell death.[17–19]

Cephalosporins are divided into five generations based on their efficacy against gram-positive and gram-negative bacteria, as well as their discovery date. Cefazolin, cefadroxil, and cephalexin are first generation cephalosporins that are effective against most gram-positive cocci, such as *staphylococci* and *streptococci,* but have poor gram-negative coverage against *Proteus mirabilis*, *Escherichia coli*, and *Klabsiella pneumonia*. There are two types of second-generation cephalosporins: cefuroxime (cefprozil) and cephamycin (cefmetazole, cefotetan, cefoxitin).[19] In compared with the first generation, second-generation ceplaholsporins show lower action against gram-positive cocci but higher activity against gram-negative bacilli.[20]

Cefotaxime, ceftazidime, ceftriaxone, cefoperazone, and cefixime are third-generation cephalosporins that treat gram-negative infections resistant to prior generations or other β-lactam antimicrobials. Cefepime is a fourth-generation cephalosporin that covers *Streptococcus*

Table 2. Quantity Profile of Antibiotic Use based on the ATC/DDD Method

No	ATC Code	Antibiotics	Delivery Route	Total Grams	Standard DDD	Total DDD	Total LOS	DDD/ 100 *patient days**
1	J01MA02	Ciprofloxacin	O	10	1	10		76.92
2	J01DD04	Ceftriaxone	P	444	2	222		59.04
3	J01CF02	Cloxacillin	P	161	2	80,5		56.69
4	J01CA04	Amoxycillin	O	24.02	1.5	16.01		53.38
5	J01FA10	Azithromycin	O	26.6	0.3	88.67		46.67
6	J01DD08	Cefixime	O	126.5	0.4	310.5		45.39
7	J01DD01	Cefotaxime	P	603	2	150.75		27.162
8	J01DD02	Ceftazidime	P	10	4	2.5		22.73
9	J01MA12	Levofloxacin	P	5	0.5	10		21.28
10	J01DH02	Meropenem	P	243	3	81	2160	13.41
11	J01FA01	Erythromycin	O	21.6	1	21.6		12.71
12	J01DD12	Cefoperazon	P	69	4	19.75		10.23
13	J01XD01	Metronidazole	P	54.5	1.5	23.67		7.63
14	J01CA01	Ampicillin	P	146	6	35.33		5.56
15	J01XA01	Vancomycin	P	19.5	2	9.75		4.18
16	J01GB03	Gentamicin	P	7.32	0.24	30.5		3.76
17	J01GB06	Amikacin	P	12.25	1	12.25		3.21

pneumoniae (S. pneumoniae), methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Pseudomonas aeruginosa*.

This includes β-lactamase-producing gram-negative bacilli, as well as the gram-negative bacteria covered by the third generation. Despite its efficiency against both gram-positive and gram-negative bacteria, Cefepime is only used for severe systemic infections in individuals with multi-resistant pathogens.[21] Fifth-generation cephalosporins cover susceptible gram-positive and gram-negative pathogens, including MRSA and penicillin-resistant *S. pneumoniae*.[22–24]

Cephalosporins are widely used globally because of their broad antibacterial spectrum, low toxicity, and penicillinase resistance. They are frequently prescribed for both preventive and theurapeutic tratments of infections due to their safety in children, low allergenicity, and broad spectrum, which makes it effective against gram-positive and gram-negative bacteria. Cephalosporins are also commonly used as empiric therapy when the cause of illness is unknown, without any laboratory evidence, and often used as part of the initial treatment.[25,26]

In antibiotic prescriptions, there are 8 antibiotic groups consisting of 17 types of antibiotics. The most commonly prescribed antibiotic is cefotaxime (25.48%). Cefotaxime is a third-generation cephalosporin antibiotic widely used in the treatment of infections caused by both gram-negative and gram-positive bacteria, as well as penicillin resistance in pneumococcus. Additionally, cefotaxime can be used as empirical therapy for meningitis in infants and children, treatment of pneumonia, sepsis, and diseases susceptible to infection.[27,28] The use of cefotaxime is more recommended for children, especially neonates, compared to other cephalosporin group such as ceftriaxone because cefotaxime does not affect bilirubin metabolism. Moreover, cefotaxime has lower gastrointestinal side effects compared to ceftriaxone.[12]

In terms of antibiotic administration, the data shows that intravenous administration is the most commonly used route, reaching a percentage of 90.82%. The selection of the antibiotic administration route is based on the location of the infection and efficiency considerations. Intravenous antibiotics administration may be considered for patients with moderate to severe infection levels, in accordance with the guidelines of the Ministry of Health of the Republic of Indonesia in 2011. Intravenous administration is carried out to ensure that antibiotics directly enter the systemic circulation and evenly distribute to infected tissues, aiming for maximum antibiotic effects and optimal healing processes.[29]

The table 2.2 shows the calculation results of DDD/100 patient days indicate that ciprofloxacin has the highest percentage at 76.92%, while amikacin has the lowest percentage at 3.21%. The evaluation of DD/100 patient days for pediatric inpatients shows that antibiotic use is in line with WHO standards. If the DDD value exceeds the WHO standard, it indicates that the antibiotic use is less selective, raising concerns about irrational antibiotic use.[30] However, not all antibiotics with high usage rates have high DDD/100 patient- days values. For example, cefotaxime has the highest usage rate (see Table 2.1), but ciprofloxacin has the highest DDD/100 patient-days value (see Table 2.2).

The difference is affected by the total Length of Stay (LOS) and DDD values. A longer LOS for pediatric patients results in a lower DDD/100 patient-days value for each antibiotic, and vice versa. DDD values depend on the total grams of antibiotics used, determined by the doses given during the hospital stay, which vary in dosage, usage, and duration for each pediatric patient.

Additionally, varitions in WHO DDD standards for different antibiotics also impact DDD values.[8,31] For example, ceftriaxone and cefotaxime, where according to WHO DDDs standards, ceftriaxone has a standard DDD value of 2, and cefotaxime has a standard DDD value of 4 with a total of 603 grams, which is 159 grams more than ceftriaxone. Consequently, in the final results, the DDD value for ceftriaxone is larger than the DDD value for cefotaxime by 150.75.

The evaluation of DDD values doesn't fully explane the reasoning behind antibiotic use. DDD values can estimate the probable irrationality of antibiotic use (the rational parameters being the appropriate drug, indication and dose). To fully assess rational antibiotic use, further studies on other contributing factors are needed.

This study can provide information on the amount of antibiotics used in pediatric patients in one of the regional general hospitals in Bandung. Comparing these findings with similar studies in other hospitals, or even internationally, can provide a basis for considerations to help control antibiotic resistance, improve drug stock management, and develop hospital antibiotic use guidelines.[12,26] However, this method isn't a strict parameter for assessing the rationality of antibiotic use because ATC/DDD only measures the quantity and type of antibiotics used.[32]

A qualitative evaluation using the Gyssens method is needed to assess the appropriateness of antibiotic use, considering factors like indications, efficacy, toxicity, cost, spectrum, duration, dose, interval, rout, and timing of administration. This study has limitations, such as the lack of distribution of antibiotic use grouped by age and gender. Nonetheless, combining quantitative and qualitative

evaluations can provide a foundation for promoting intelligent and responsible antibiotic use in pediatric inpatients.

Recommendations include continuous monitoring and evaluation of drug use to enhance rational use, increased collaboration among healthcare professionals to improve antibiotic quality and prevent resistance, and the development and implementation of formulary system by the pharmacy and therapy committee to regular antibiotic use rationally.

Conclusion

Conclusion from the antibiotic usage profile indicates that cephalosporins (57.41%) and cefotaxime (25.48%) are the most widely used antibiotic groups and types, with the dominant route of administration is intravenous (82.82%). On the other hand, the evaluation of antibiotic usage quantity using the ATC/DDD method indicates that ciprofloxacin has the highest DDD/100 patient-days value at 76.92, while amikacin has the lowest value at 3.21. Interview with pertinent parties and qualitative research utilizing the Gyssens approach is required to obtain more comprehensive understanding of the rationale of antibiotic usage. This is done to strengthen the evaluation results of antibiotic usage in pediatric inpatients at one of Regional General Hospitals in Bandung during August 2023.

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Conflict of Interest

None declared.

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