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Monitoring the Use of Antibiotics in Children Patients Acute Respiratory Infection Using ATC/DDD Method

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Abstract: The use of antibiotics needs to be monitored because it is known that excessive use of antibiotics can increase resistance in the community and this has become a focus both nationally and globally. This study aims to evaluate the use of antibiotics in patients with acute respiratory infection at Hasanuddin University Hospital using the ATC/ DDD analysis method. The research design used a cross-sectional study design with retrospective data collection. The sample in this study was patient medical record data from January-December 2021, taken from total sampling and met the inclusion and exclusion criteria. Descriptive statistics are used to present and analyze data. Evaluation of the use of antibiotics by quantitative methods ATC/DDD (Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD), DDD/1000/ patient/day. The results showed that the most widely used antibiotic was ampicillin (280 mg) 32.96 DDD/1000 patients/day and the lowest was cefadroxil (150 mg) 1.45 DDD/1000 patients/day. Antibiotics with the highest DDD / 100-patient days value and exceeding the WHO DDD standard were ampicillin antibiotics from the penicillin group with a DDD / 100 patient-day value of 32.96 DDD /100 patient-days.

Keywords: Acute respiratory infection; Antibiotics; Children; DDD/ATC

Introduction

Sustainable Development Goals or commonly known as Sustainable Development Goals (SDGs) are the achievements of development targets related to international development agreed upon by more than 190 countries replaced the Millennium Development Goals (MDGs) at the end of 2015. The SDGs contain 17 goals that were agreed upon and apply to all nations without exception, one of which is to guarantee a healthy life and promote prosperity for all people at all ages. To achieve this goal, there are 13 targets that must be achieved. Some of these targets are by 2030 ending the AIDS epidemic, tuberculosis, malaria and neglected tropical diseases, as well as fighting hepatitis, waterborne diseases and other infectious diseases (Kementrian Kesehatan Republik Indonesia, 2015), (Kementerian Perencanaan Pembangunan Nasional/ Badan Perencanaan Pembangunan Nasional, 2023).

Acute respiratory tract infection (ARI) is the major cause of death and morbidity in low- and middle-income countries (LMICs) (Boloursaz et al., 2013; Ramanathan et al., 2020), in all age groups and genders (Kassebaum et al., 2019). Until now, infectious diseases in Indonesia are still included in the top ten diseases, one of which is respiratory tract infection. Acute Respiratory Infection (ARI) is an acute infection of the airway structures that interfere with the gas exchange process from the nose to the alveoli including the adnexes (sinuses, middle ear cavity, pleura) (Moiseeva, 2019). Upper respiratory tract infections can be defined as self-limited irritation and swelling of the upper airways with associated cough with no proof of pneumonia, lacking a separate condition to account for the patient symptoms, or with no history of COPD/emphysema/chronic bronchitis (Kinkade & Long, 2016; Kinkade & Long, 2016; Ramanathan et al., 2020).

Antibiotics are the most widely used drugs for infections caused by bacteria. The relatively high

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intensity of antibiotic use causes Acute Respiratory Infections problems and is a global threat to health, especially bacterial resistance to antibiotics and the emergence of unwanted drug effects. This occurs due to the unwise use of antibiotics and improper application of standard precautions in health care facilities (Riskesdas, 2018). The use of antibiotics needs to be monitored because it is known that excessive use of antibiotics can increase resistance in the community and this has become a focus both nationally and globally (Adebisi, 2023). According to resistance data, as many as 70% of bacteria have been resistant to antibiotics that are often used in hospitals (Blair et al., 2015). In addition, the impact of misuse of antibiotics can lead to treatment failure, superinfection, increased risk of death, increased side effects, unnecessary prescribing of drugs and increased medical costs (Llor & Bjerrum, 2014). In one study reported by World Health Organization (WHO), it was found that more than 50% of antibiotics prescribed were ineffective and/or unnecessary (Kon, 2016).

Various efforts have been made by the WHO to control resistance globally. WHO has created global action plan to combat antibiotic resistance by increasing wise use of antibiotics and by evaluating the use of antibiotics (World Health Organization, 2016). Evaluation of the use of antibiotics can be done quantitatively or qualitatively. The ATC/DDD Anatomical Therapeutic Chemical (ATC) Defined Daily Dose (DDD) method is one of the methods recommended by the World Health Organization (WHO) and the Ministry of Health of the Republic of Indonesia (Kementrian Kesehatan Republik Indonesia, 2011). Quantitative assessment using the ATC/DDD method is to determine the amount of antibiotics used. The ATC / DDD method was assumed to be the average daily dose for the drug used for the main indication for adult treatment. Information on the quantity of drug use can predict the rationality/irrationality of drug use (Hollingworth & Kairuz, 2021). The values obtained from the results of DDD/100 patient-days were compared with WHO standards. If the DDD value obtained is greater than the WHO standard value, the use of antibiotics is estimated to be less selective, so it is feared that there is irrationality in the use of antibiotics (Hollingworth & Kairuz, 2021).

The define daily dose/DDD value of antibiotics is determined after tracing the Anatomical Therapeutic Chemical/ATC code. This ATC code consists of 5 levels, where each level indicates a large group of antibiotics starting from the main group to the chemical compound. This DDD method can be used to determine whether the level of drug use is excessive or underused (Pani et al., 2015), besides that it can be used in drug planning because it looks at drug use in one year. DDD is a unit of measurement that does not always reflect the recommended or prescribed daily dose. The DDD value only provides a rough estimate of consumption and is not an exact reflection of actual usage (WHO, 2023). The DDD value can be used as a reference to assess the amount of antibiotic use in one agency compared to other agencies. The smaller the DDD/100 patient days value, the smaller the quantity of antibiotics used, which correlates with the rationality of using these antibiotics. On the other hand, a high DDD value indicates excessive use of antibiotics (Hutchinson et al., 2004).

This study aims to evaluate the use of antibiotics in patients with Acute Respiratory Infections at Hasanuddin University Hospital using the ATC / DDD analysis method. This research is expected to increase awareness of the use of antibiotics for health workers and the local government in an effort to increase rationality in the use of antibiotics in the community.

Method

The research design used a observational study design with retrospective data collection. Data on the quantity of antibiotic use with the ATC code was taken and processed using the ATC / DDD method with units of DDD/1000 patients/day. Descriptive statistics are used to present and analyze data. The inclusion criteria in this study were all data of inpatients with Acute Respiratory Infection who received antibiotic therapy with an age of 2-10 years, while the exclusion criteria were patients who ended their hospitalization period at their own request or died and patients with a history of other infectious diseases. The research was conducted at Hasanuddin University Hospital. The sample in this study was taken by total sampling in the January-December 2021 period. The data obtained were displayed descriptively including the demographic characteristics of the patient (age, gender, type of antibiotic used in Acute Respiratory Infection patients). Evaluation of the use of antibiotics by quantitative methods ATC/DDD (Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD), DDD/1000 /patient /day.

Result and Discussion

A total of 37 samples met the inclusion criteria in this study. Data on the characteristics of research subjects can be seen in table 1. Based on table 1, patient characteristics based on gender indicate that the prevalence of Acute Respiratory Infection is more common in male. This is in accordance with the results of the basic health research (RISKESDAS) of the Indonesian Ministry of Health in 2018 Boys are usually

more active and often do activities outside than girls so the possibility of exposure and infection in boys is greater (Maakh et al., 2017; Grassella et al., 2018; Jadhav & Khanwelkar, 2018).

Table 1. Characteristics of patients

Characteristics	(n=37)	Percentage (%)
Gender		
Male	20	54
Female	17	46
Age (years)		
2-5	29	78.37
6-10	8	21.63

Patient characteristics based on age indicate that the prevalence of 2-5 years of age is greater than those of 6-10 years of age. This is also in accordance with the results of the RISKESDAS which showed that ages 1-4 years were 13.7%, then ages 5-14 years were 10.6% (Riskesdas, 2018). Infant age with ARI incidence. The existence of a relationship between a baby's age and a low incidence of ARI is easy to understand, because the younger the baby, the more immune it is (Rogan, 2016). It is reported that the highest incidence of ARI and pneumonia is at the age of 6 months to less than 12 months due to a decrease in maternal antibodies, immaturity. immune adaptation system, when breastfeeding stops and the child goes to a health service facility (Imran et al., 2019).

Based on table 2, it is known that the administration of antibiotics in patients with Acute Respiratory Infection includes the use of monotherapy and combination antibiotics. The highest use of antibiotics was β-lactam monotherapy antibiotics, namely ampicillin as many as 7 people with a percentage of 18.9%. Ampicillin is widely used as the antibiotic of choice for the treatment of infectious diseases, because of its wide spectrum, relatively cheap price and relatively lower toxicity compared to other types of antibiotics (Eyler & Shvets, 2019). The mode of action of beta-lactam antimicrobials on sensitive organisms can be thought of as a two-step process: In the first step, the drug binds to a primary receptor called membrane-bound penicillin-binding protein (PBP). This protein plays an important role in the cell cycle; the formation of the peptidoglycan structure of the cell wall. Therefore, inactivation of PBP by the bound antimicrobial immediately affects its function (Peechakara et al., 2023). The second stage consists of physiological effects caused by this receptor-ligand interaction. PBPs are involved in the final stage of cell wall peptidoglycan synthesis. Since peptidoglycan maintains the integrity of the cell wall, which is in a hypotonic environment, its disruption leads to cell lysis and death (Tipper, 1979). Then the use of antibiotics is small, namely the use of the antibiotic monotherapy cefadroxil and several other antibiotic combinations, where the number of patients who use it is only 1 person.

Table 2. Type of Antibiotics

Types of antibiotics	(n=37)	Percentage (%)
Ampicillin	7	18.90
Cefixime	2	5.40
Cefadroxil	1	2.70
Ceftriaxone	3	8.10
Cefotaxime	5	13.50
Ampicillin + Cefixime	4	10.80
Ampicillin + Cefadroxil	1	2.70
Ampicillin + Gentamycin	2	5.40
Ampicillin + Erythromycin	1	2.70
Ampicillin + Cefotaxime	1	2.70
Cefixime + Cefotaxime	3	8.10
Cefixime + Ceftriaxone	1	2.70
Cefotaxime + Cotrimoxazole	1	2.70
Ceftriaxone + Gentamycin	1	2.70
Cefotaxime + Cefadroxil	2	5.40
Ampicillin + Gentamycin + Cefotaxime	1	2.70
Ampicillin + Gentamycin + Cefadroxil	1	2.70

The results of the study on the duration of use indicate that the duration of use of 1 to 5 days is the time to use antibiotics which is often encountered with a percentage of 81.08%. Duration of antibiotic use is grouped based on a literature study conducted where the duration of antibiotics for most infectious diseases is 3-7 days (Kementrian Kesehatan Republik Indonesia, 2011). There are several possible factors regarding the magnitude of the findings regarding the duration of antibiotic use from 1 to 5 days including that many antibiotics are prescribed for the purpose of empiric therapy. According to research results from the PPRA (Antibiotic Resistance Control Program) Ministry of Health (2010) in the case of empirical therapy, broad-spectrum antibiotics were used, such as penicillin and cephalosporin antibiotics with a duration of 2 to 3 days of antibiotics. The findings of this study showed that penicillin and cephalosporin classes were the most widely used antibiotics, contributing to the large number of antibiotics used with a duration of 1 to 5 days (Kementrian Kesehatan Republik Indonesia, 2011).

For the number of days of care for all patients each month during the period January-December 2021, the most were in June, which was 26 days with 4 patients, and the number of patient days was very few, namely in July, which was 7 days with the number of patients. 2 persons (table 3).

Data on the number of days of stay is needed to calculate the use of antibiotics in Acute Respiratory Infections patients with DDD units/100 patient-days. LOS is the length of the patient's hospitalization days

since the patient is admitted to the hospital. The total number of days of care for all Acute Respiratory Infections patients during the January-November 2021 period was 162 days (table 4).

Table 3. Number of Days of Patient Care for the Period January-December 2021

Months	n	LOS (Days)	Average (Days)
January	4	16	4.0
February	5	18	3.6
March	2	10	5.0
April	3	13	4.30
May	2	16	8.0
June	5	26	5.20
July	2	7	3.50
August	6	25	410
September	5	19	3.80
October	3	12	4.0
November	-	-	-
December	-	-	-
Total	37	162	4.37

Table 4. Length of Stay in Patients

Length of Stay (LOS)	n (37)	Percentage (%)
1-5	30	81.08
6-10	7	18.92

Based on table 5, the most widely used antibiotic class is the penicillin (ampicillin) group with a total usage of 106.795 grams. Ampicillin is still widely used as the antibiotic of choice for the treatment of infectious diseases, including Acute Respiratory Infection. Ampicillin is an antibiotic that is often used by clinicians as initial therapy for the management of Acute Respiratory Infection cases of infection. Ampicillin has become the main choice due to its wide spectrum (can be used for gram-positive and negative bacterial infections), low cost and relatively less toxicity for pediatric patients compared to other types of antibiotics such as gentamicin and ciprofloxacin (Eyler & Shvets, 2019; Bezuidenhout, 2023).

Table 5. Results of DDD / 100 Day-Patient Calculations

Antibiotics	Type of Antibiotics (ATC Code)	Total usage (gram)	WHO DDD standard value (gram)	DDD/100 Patient days
β-Lactam (Penicilin)	Ampisilin J01CA01	106,795	2	32.96
Sefalosporin First generation	Cefadroxil J01DB05	4.71	2	1.45
Cephalosporin	Cefotaxime J01DD01	59.7	4	9.21
third generation	Ceftriaxone J01DD04	33.0	2	10.18
	Cefixime J01DD08	11.73	0,4	18.10
Combination TMP-SMX	Cotrimoxazole J01EE01	4.80	1,92	1.54
Macrolide	Erythromycin J01FA01	4.0	1	2.46
Aminoglycoside	Gentamycin J01GB05	1.04	0,24	2.66

Based on the DDD/100-patient days calculation, it was found that the largest use of antibiotics based on the DDD/100-patient days was ampicillin from the penicillin group with a DDD/100 patient-day value of 32.96 DDD / 100 patient-days, while the lowest, namely the cefadroxil antibiotic from the first generation cephalosporin group of 1.45 DDD/100 patient-days. This is supported by the results of previous studies by Carolina, et all (2014) where the highest DDD/100 patient-days values obtained were Ampicillin from the penicillin group of 10.33 DDD/100 patient days (Carolina & Widayati, 2014).

Based on the results of DDD / 100 patient-days calculations, it is known that several antibiotics have DDD / 100 patient-days values higher than the standard DDD values set by WHO and the Ministry of Health Republic Indonesia, these antibiotics include: ampicillin, cefixime, ceftriaxone, cefotaxime, gentamicin, and erythromycin. When the quantity of antibiotic use stated in the DDD value is higher and does not match the standards set by the WHO and Ministry of Health Republic Indonesia DDD standard values, this indicates that the prescribing and use of antibiotics in patients may not be selective, so it is feared that there will be many prescriptions and use of antibiotics that are not the indication is right so that this will affect the rationality of the use of antibiotics in patients, especially on the rationality of the accuracy of the indication (Kementrian Kesehatan Republik Indonesia, 2011; Limato et al., 2022). In addition, the high DDD value of several types of antibiotics that exceeded the WHO standard value is also an early prediction of the possibility of giving antibiotics in excessive doses. The high DDD value was influenced by the amount (g) of antibiotics used, which was determined by the number of doses used by the patient during the patient's hospitalization. If the dose is given excessively, the DDD value will tend to be higher than the predetermined standard value (WHO, 2023; Montecatine-Alonso et al., 2023).

In this study, the increase in the number (gram) of antibiotic use was also thought to be due to the frequency with which it was administered, mostly more than once a day. This assumption is supported by the results obtained in this study, whereas some of the

antibiotics used in this study tended to be prescribed more than once a day. The evaluation of the use of the DDD method cannot fully illustrate the rationale for the use of antibiotics. The results obtained from the DDD value provide an estimate of the irrationality of the use of antibiotics (in this case the rational parameters that can be estimated are the right drug, indication and the right dose). There needs to be further research on the rationality parameters of the use of other antibiotics (the right patient, the right drug, and the drug side effect alert) so that the rationality of using antibiotics can be fully described.

DDD values obtained cannot accurately judge the accuracy of indication and dose. Further research is needed to determine the accuracy of indications and the accuracy of using antibiotic doses in patients. This can be done by comp Acute Respiratory Infectioning the DDD value with the Prescribed Daily Dose value (the actual dose used each day) so that it can be seen whether there is an inaccuracy in the dosage used in pediatric patients (WHO, 2023; Montecatine-Alonso et al., 2023). Further matching between the applied diagnosis and the antibiotics given as well as consideration of the patient's clinical condition can be made so that the real situation can be found from the accuracy of the indication for antibiotic administration.

Conclusion

Antibiotics with the highest DDD/100-patient days value and exceeding the WHO DDD standard were ampicillin antibiotics from the penicillin group with a DDD/100 patient-day value of 32.96 DDD / 100 patient-days.

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Author Contributions
Conceptualization: all authors; Data curation: F; Formal analysis: W, Z; Investigation: all authors and Enumerator; Methodology: F, AA; Project administration: F ; Resources: F ; Validation: F; Writing–original draft: F ; Writing–review & editing: all authors.

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Conflicts of Interest
The authors declare no conflict of interest.

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