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EVALUATION OF THE QUANTITY AND QUALITY OF ANTIBIOTIC USE IN INPATIENT PEDIATRIC URINARY TRACT INFECTION (UTI) PATIENTS AT RSUD KRMT WONGSONEGORO SEMARANG

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ABSTRACT

Background: Antibiotics are the main drug in treating various infectious diseases. The high use of antibiotics can cause bacterial resistance to antibiotics. Hence, it is necessary to evaluate antibiotics in quantity (amount of antibiotics used) and quality (accuracy of antibiotic use). **Objective:** This study was conducted to determine the quantity and quality of antibiotic use in pediatric urinary tract infection (UTI) patients hospitalized at KRMT Wongsonegoro Hospital Semarang. **Methods:** This study was a retrospective cross-sectional study. The study materials were medical records of pediatric UTI patients who were hospitalized at KRMT Wongsonegoro Hospital Semarang. Analysis was performed qualitatively using the Gyssens method and quantitatively using the ATC/DDD and DU90% methods. **Results:** There were 46 prescriptions from 43 pediatric UTI patients. The most commonly used single antibiotic was ceftriaxone (47.73%). Evaluation of the quantity of antibiotic use obtained the total DDD (Defined Daily Dose) value of pediatric UTI patients in the 2019-2022 period was 40.39 DDD/100 patient-days. Antibiotics that fall into the DU90% segment are ceftriaxone and cefotaxime. Evaluation of the quality of antibiotic use obtained 8 of antibiotic use is appropriate/wise. **Conclusion:** There is still inappropriate antibiotic use in pediatric UTI patients at KRMT Wongsonegoro Hospital in 2019-2022.
Keywords: *Antibiotics, Pediatrics, Urinary Tract Infection*

INTRODUCTION

UTI is an infectious disease due to the proliferation of pathogenic microorganisms in the ureters and kidneys[1]. World Health Organization (WHO) says that UTI is in second place as an infectious disease with the highest prevalence after Upper Respiratory Tract Infections (URIs)[2]. UTI sufferers in Indonesia are estimated to reach 90-100 cases per 100.000 population or around 180.000 new cases each year. This number of cases makes UTI the second cause of childhood morbidity with a prevalence ranging from 3-10% in girls and 1-3% in boys[3,4]. Antibiotics are the main drug in the treatment of UTIs. Antibiotics are defined as chemical substances that can inhibit or kill other types of microorganisms[5]. Their success in curing various infectious diseases has led to the stigma that antibiotics can kill all kinds of germs. This has resulted in high rates of inappropriate and irrational use of antibiotics, which has an impact on the occurrence of the resistance of microorganisms to antibiotics[6]. Changes in the pattern of resistance of microorganisms that cause UTIs are known to be faster than other infectious diseases[7]. The incidence of antibiotic resistance in microorganisms that cause UTIs is increasing causing the need for appropriate use of antibiotics, thus supporting the success of therapy. Bacteria that cannot be treated by antibiotics due to improper use can rise and enter the kidneys, causing patients to experience kidney infections and permanent kidney damage[8]. The use of antibiotics can be evaluated qualitatively from the accuracy of their use and quantitatively from the amount of antibiotics used. Therefore, a study was conducted on the quantity and quality of the use of antibiotics in pediatric UTI patients at KRMT Wongsonegoro General Hospital, Semarang. This study aims to determine the profile, quantity, and quality of antibiotic use in inpatient pediatric UTI patients at KRMT Wongsonegoro Hospital Semarang in 2019-2022.

METHODS

The research was conducted in February - April 2023 at KRMT Wongsonegoro Hospital Semarang. This type of research is retrospective. The population in this study were all pediatric patients with a diagnosis of UTI who were hospitalized at KRMT Wongsonegoro Hospital Semarang in 2019-2022. Exclusion criteria for this study were incomplete medical records, patients died, patients stopped treatment at their request, and patients had

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other infections. The samples used were 43 samples taken by the total sampling method. The independent variable in this study was the use of antibiotics in inpatient pediatric UTI patients, while the dependent variable in this study was the quantity and quality of antibiotic use in inpatient pediatric UTI patients. This study was approved by the Health Research Ethics Committee of KRMT Wongsonegoro Semarang Hospital and the director of KRMT Wongsonegoro Hospital Semarang. Data collection includes demographic and clinical data: medical record number, age, gender, diagnosis, date of admission and discharge of inpatient installation, laboratory examination, urinalysis examination, radiological examination, name, type, dose, route, interval, time and duration administration of antibiotics and other drugs. The analysis was carried out qualitatively using the Gyssens method and quantitatively using the ATC/DDD and DU90% methods.

RESULTS

The results of research that was conducted at the KRMT Wongsonegoro Hospital Semarang in 2019-2022 showed that there were 43 samples of pediatric inpatients as a reachable population.

Sample Characteristics

The characteristics of the sample in this study were translated into age, age, presence of comorbidities, length of stay, and type of UTI can be seen in Table 1

Table 1. Sample characteristics

Characteristics		Total (n=43)*	Percentage (%)
Age	0-28 days (neonates)	0	0
	1 month-2 years (infant)	8	18.6
	2-11 years (children)	22	51.16
	12-18 years (adolescent)	13	30.23
Gender	Woman	33	76.74
	Man	10	23.26
Presence of comorbidities	Presence	11	25.58
	Absence	32	74.42
Length of Stay (LOS)	≤3 days	16	37.21
	>3 days	27	62.79
Type of UTI	Pyelonephritis	0	0
	Cystitis	3	6.98
	Site not specific	43	93.02

*Total sample

Of the 43 samples analyzed, there were 46 prescriptions for antibiotics due to changes in prescriptions such as changing antibiotics, changing intervals for giving antibiotics, and changing single antibiotic prescriptions to prescribing combination antibiotics. Types of antibiotics used in inpatient pediatric UTI patients at KRMT Wongsonegoro Hospital in 2019-2022 can be seen in Table 2.

Table 2. Type of Antibiotics Prescription

Types of Antibiotic	Frequency	Percentage (%)
Single Antibiotic Type		
Cephalosporins		
Cefotaxime	17	36.96
Ceftriaxone	20	43.48
Quinolones		
Pipemidic acid	2	4.35
Penicillin		
Ampicillin	4	8.7
Amoxicillin	1	2.17
Nitroimidazole		
Metronidazole	1	2.17
Combination Antibiotics Type		
Gentamicin-Ceftriaxone	1	2.17
Total	46	100

*Total use of antibiotics

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Quantity of Antibiotic

Table 3. Quantity of Antibiotic Use

No	ATC Code	Antibiotics	Total Usage (grams)	Definitive DDD (grams)	DDD/100 patient days	Percentage (%)	Segmen DU90%
1	J01DD04	Ceftriaxone	98.24	2	27.75	68.71	90.00
2	J01DD01	Cefotaxime	62.27	4	8.8	21.79	
3	J01MB04	Pipemidic Acid	2	0.8	1.41	3.49	
4	J01CA01	Ampicillin	12.38	6	1.17	2.90	
5	J01XD01	Metronidazole	1.4	1.5	0.53	1.31	10.00
6	J01GB03	Gentamicin	0.24	0.24	0.56	1.39	
7	J01CA04	Amoxicillin	0.9	3	0.17	0.42	
Total			**177.43**	**17.54**	**40.39**	**100**	

The total use of antibiotics based on Table 3 is 177.43 grams with a definitive total DDD value of 17.54 grams so the total value of DDD/100 patient-days of using all antibiotics is 40.39 DDD/100 patient-days. The antibiotic with the highest DDD/100 patient-days was ceftriaxone (27.75 DDD/100 patient-days). The antibiotic with the lowest DDD/100 patient-days was amoxicillin (0.17 DDD/100 patient-days). Antibiotics included in 90% DU are ceftriaxone and cefotaxime.

Quality of Antibiotic

Of the 46 prescriptions of antibiotics, 69 categories of assessment results were obtained. One prescription can produce several category results so that the category assessment results are collected greater than the number of antibiotic prescriptions. The results showed that 8 antibiotic prescribing was included in the appropriate/wise use of antibiotics (category 0) and 37 use of antibiotics included in 61 categories were inappropriate/wise using antibiotics (category I-V) which can be seen in Table 4

Table 4. Quality of Antibiotic Use

No	Antibiotics	Gyssens Category													Total
		0	I	IIA	IIB	IIC	IIIA	IIIB	IVA	IVB	IVC	IVD	V	VI	
Single Antibiotics															
1	Ceftriaxone	1	2	0	15	0	0	0	0	18	0	0	0	0	36
2	Cefotaxime	7	2	9	0	0	0	0	0	0	0	0	0	0	18
3	Ampicillin	0	0	2	0	0	0	0	4	0	0	0	0	0	6
4	Amoxicillin	0	0	0	0	0	0	0	1	0	0	0	0	0	1
5	Pipemidic Acid	0	0	0	0	1	0	1	2	0	0	0	0	0	4
6	Metronidazole	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Combination Antibiotics															
1	Gentamicin-Ceftriaxon	0	0	1	1	0	0	0	0	1	0	0	0	0	3
Total		8	4	12	16	1	0	1	8	19	0	0	0	0	69

DISCUSSION

Age, sex, and presence of comorbidities are risk factors for UTI4. This study shows that pediatric patients are dominated by patients aged 2-11 years (children). Age 2-11 years is an active period for children. The large number of activities outside the home makes children of this age susceptible to infectious agents, one of which is UTI. Infection can also be caused by lack of and difficulty maintaining personal hygiene in children. Other factors such as how to rinse, shower, soap, and anatomical abnormalities can trigger UTIs[9,10]. In this study, the number of female patients (74.74%) was greater than that of male patients. Women are generally more prone to UTIs because they have a shorter urethra, which is about 4 cm than men. The location of the female bladder which is closer to the rectum also makes it easier for microorganisms from outside to enter the bladder, making it easier for UTIs to occur[11]. The presence of co-morbidities is associated with the length of stay (LOS) of UTI patients. UTI patients who are hospitalized >3 days mostly have comorbidities, whereas patients with length of stay ≤3 days do not have comorbidities and go home with a cured condition or continue outpatient therapy.

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Almost all types of UTIs in this study were UTIs with unknown locations. Determining the location of the UTI is critical to selecting the most appropriate antibiotic management for patients. Therapeutic guidelines refer to the location where infection occurs. Cystitis patients can be treated with the antibiotic ceftriaxone which is the antibiotic of choice for cystitis in children according to the therapy guidelines because of its good activity against gram-negative uropathogenic bacteria, while pyelonephritis is treated with regimens such as third-generation cephalosporins, ampicillin, and aminoglycosides[12,13]. Pyelonephritis is treated with regimens such as third-generation cephalosporins, ampicillin, and aminoglycosides.12 The duration of antibiotic therapy is related to the type of UTI. Simple cystitis can be treated with 3-5 days of therapy, whereas in pyelonephritis giving parenteral antibiotics for 7-14 days is effective for treating acute pyelonephritis[14,15].

The most used antibiotics in this study were ceftriaxone with 20 prescriptions (43.48%) and cefotaxime with 17 prescriptions (26.96%). Ceftriaxone and cefotaxime are antibiotics of the cephalosporin class and belong to the third generation. These two antibiotics are widely prescribed because they are the first-line therapy for UTI in children with fever[11].

The antibiotic with the highest DDD/100 patient-days value was ceftriaxone at 27.75 DDD/100 patient-days. This means that in 100 days of hospitalization, the ceftriaxone antibiotic used in UTI patients is 27.75. The highest DDD/100 patient-days value was followed by cefotaxime of 8.8 DDD/100 patient-days. This is following a study conducted at a hospital in Kebumen, where the highest DDD/100 patient-days value was ceftriaxone of 33.85 DDD/100 patient-days[16]. The large difference in DDD/100 patient-days values can be caused by differences in restrictions or differences in medical problems[17]. Ceftriaxone has the highest DDD/100 patient-days values because it is widely used as a first-line treatment for UTI in children. 18 Ceftriaxone is a broad-spectrum antibiotic that is stable against many bacterial ß-lactamases compared to previous generations. Ceftriaxone has broader activity against gram-negative bacteria which are often found in the urine of UTI patients. Ceftriaxone is the first line of empirical antibiotic therapy used in pediatric UTI patients. The DDD/100 patient-days value is influenced by the total LOS and DDD value. The higher the DDD value, the higher the DDD/100 patient-days value, while the higher the LOS means the opposite. The high DDD value is influenced by the total number of grams of antibiotic used with different doses, rules of use, and duration of use for each child[18].

The antibiotic with the lowest DDD/100 patient-days was amoxicillin (0.17 DDD/100 patient-days). The reason for the low DDD/100 patient-days value of amoxicillin is that amoxicillin is not the first-line therapy for inpatient UTIs in children. E. Coli bacteria as one of the main causes of UTI have high resistance to amoxicillin antibiotics, so antibiotics with a wider spectrum such as third-generation cephalosporins are more often used to treat child UTIs[19].

In previous research conducted at RSUP Dr. Sardjito Yogyakarta, it was found that 84.3% of the use of antibiotics was in category 0, and 15.7% of other uses were in categories IIIB and IIA[20]. This study shows that 8 antibiotic prescriptions (17.78%) fall into category 0 (appropriate/wise use of antibiotics) and 37 antibiotic prescriptions (82.22%) fall into category I-V (inappropriate/wise use of antibiotics). The results of evaluating the use of antibiotics using the Gyssens method showed that 8 uses of antibiotics were included in the IVA category. The existence of other antibiotics that are more effective is defined when the antibiotics used are not first-line therapy antibiotics according to the guidelines and if the antibiotics do not match the results of laboratory tests, urinalysis, or culture results. enter into empiric therapy. Based on the 2015 Guidelines on Urological Infections, the antibiotics used are not the first line of empiric therapy for pediatric UTIs. The first-line empirical therapy recommended by the 2015 Guidelines on Urological Infections is a cephalosporin (third generation) such as ceftriaxone or cefotaxime[12].

There are 19 uses of antibiotics that fall into the IVB category. The IVB category (other antibiotics are safer/non-toxic) is evaluated from the presence of contraindications, drug interactions, and side effects caused by antibiotics. Antibiotics that fall into this category are ceftriaxone with problems of interaction with other drugs. Ceftriaxone interacts with lactated Ringer's fluid therapy. Ringer's lactate may increase the adverse effects of ceftriaxone. Ceftriaxone can

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bind to calcium in Ringer's lactate to form precipitates that do not dissolve in the blood. Precipitates that do not dissolve can cause reduced drug levels and blockages in blood vessels. This interaction is included in risk category X, so it is better to avoid giving ceftriaxone and Ringer's lactate simultaneously. The choice of third-generation cephalosporin antibiotics that can be used is cefotaxime[21].

Based on a qualitative evaluation using the Gyssens method conducted on pediatric UTI patients at KRMT Wongsonegoro Hospital, it was found that there was 1 use of antibiotics that was included in category IIIB. Use of antibiotics too short is the use of antibiotics with a duration of use that is less than recommended by the guidelines. This category is evaluated by looking at whether the duration of antibiotic use in pediatric UTI patients is too short or less than recommended. One patient received oral antibiotics with a duration of use of only one day. Based on the 2015 Guidelines on Urological Infections, pediatric patients with mild UTIs should be treated with oral antibiotics for up to 5-7 days. 18 The lack of duration of therapy in pediatric UTI patients can lead to recurrence of infection due to the bacteria that cause UTIs and increase the potential for antibiotic resistance[22].

The use of inappropriately dosed antibiotics means that the dose given is not following the guideline recommendations. Calculation of the dose given to UTI patients takes into account the patient's age, weight, and kidney and liver function[12]. The results of the evaluation showed that 12 antibiotics were used in category IIA, namely underdose. Dosage accuracy can affect the success of antibiotic therapy in children. The effectiveness of antibiotics is determined by the level of the drug at the target of its action. Administering antibiotics at doses that are too high can increase the risk of toxic effects, while administration at lower doses can reduce the therapeutic effect of antibiotics, which can lead to therapy failure. Not only that, the use of irrational doses can increase the risk of developing antibiotic resistance in children[23].

The results of evaluating the quality of antibiotic use in pediatric UTI patients using the Gyssens method showed that 16 antibiotics were used in category IIB. Category IIB (incorrect use of antibiotics at intervals) was evaluated by looking at the suitability of the intervals of antibiotic administration with the recommendations from the guidelines. In this study, there were 15 uses of ceftriaxone antibiotics given at intervals of every 12 hours and 1 use of ceftriaxone antibiotics given at intervals of every 8 hours. The time interval for administering ceftriaxone for UTIs in children recommended by the Guidelines on Urological Infections 2015 and the Pedoman Penatalaksanaan Urologi Anak di Indonesia 2016 is every 24 hours[12,24].

Based on the results of evaluating the quality of the use of antibiotics with the Gyssens method, 1 use of antibiotics was found in an inappropriate way/route of use (category IIC). The route of administration of antibiotics in UTI patients is chosen based on several considerations such as the patient's age, nausea, vomiting, and the severity of the disease[12]. The inpatient oral route of administration can be used in patients who are not nauseated and able to swallow the drug. Patients under 3 years of age who have difficulty swallowing medication, nausea, vomiting, and need rapid onset, may be given parenteral antibiotics.[15] The patient received oral antibiotics, while the patient experienced nausea and vomiting, so this method of administration was inappropriate.

The results showed that there were 4 use of antibiotics that were included in category I. Category I occurs if the administration of antibiotics does not match the time that should be based on the diagnosis or if use every day is not appropriate and consistent. Time to use antibiotics needs to be considered related to the availability of drugs in the blood which has an impact on the effectiveness of the resulting therapy[25].

The use of antibiotics is considered appropriate/wise if it passes category I-VI based on the Gyssens flow. In this study, category 0 was obtained for 8 uses. Appropriate use of antibiotics can prevent and reduce the incidence of antibiotic resistance, thereby shortening the length of stay and reducing patient care costs, as well as improving the quality of hospital services[26].

CONCLUSIONS

The total use of antibiotics in pediatric UTI patients was 177.43 grams. Ceftriaxone became the antibiotic with the largest DDD/100 patient-days of 27.75 DDD/100 patient-days. The results of the evaluation of the quality of the use of antibiotics were

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that 8 uses of antibiotics (17.38%) were included in the appropriate/wise category while the other 37 uses (82.61%) were included in categories I-V. The most widely used antibiotic in this study was ceftriaxone because it is the first line of treatment for UTIs in children.

ETHICAL APPROVAL

Ethical Clearance for this study was obtained with the approval and consideration of the Health Research Ethics Commission (KEPK) KRMT Wongsonegoro Hospital Semarang with number B/070/590/IV/2023.

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