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Evaluation of Antibiotics Appropriateness in the Treatment of Typhoid Fever in Pediatric Outpatient at Gondosari Gebog Kudus Health Center

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ABSTRACT

Background: Typhoid fever is an acute bacterial infection in the human digestive tract caused by *Salmonella typhi* bacteria. Typhoid fever is treated with antibiotics. However, inappropriate use of antibiotics can lead to resistance.

Aim: To evaluate the appropriateness of using antibiotics in outpatient pediatric typhoid fever at the Gondosari Gebog Kudus Health Center in 2021-2022.

Methods: Non-experimental research with retrospective data collection and descriptive analysis. Parameters in this study for evaluating the antibiotics appropriateness are 7 parameters (right diagnosis, right patient, right indication, right drug, right dose, right way of administration, and right duration) based on the Rational Drug Use module according to Indonesian Ministry of Health (2011).

Results: The samples obtained in this study were 40 patients. The results of evaluating the appropriate use of antibiotics in pediatric typhoid fever in this study were 100% right diagnosis, 100% right patient, 100% right indication, 100% right drug according to WHO (2011), 100% right drug according to Indonesian Ministry of Health (2006), 85% right dose according to WHO (2011), 100% right dose according to Indonesian Ministry of Health (2006), 100% right method of administration, 20% right duration according to WHO (2011), and 80% right duration according to Indonesian Ministry of Health (2006).

Conclusion: The results of the evaluation of the appropriate use of antibiotics at the Gondosari Health Center are appropriate based on 7 parameters (right diagnosis, right patient, right indication, right drug, right dose, right way of administration, and right duration).

Keywords: Typhoid fever, Antibiotics, Appropriateness of treatment

INTRODUCTION

Typhoid fever is an acute infectious disease which is a serious problem in the world. Typhoid fever is an endemic disease in most countries caused by *Salmonella typhi* and only humans are the reservoir for this bacterium ¹. Until now, typhoid fever is still a health problem in developing countries, especially countries with poor sanitation, including Indonesia. It is estimated that the incidence of typhoid fever worldwide reaches 11-21 million cases with 128.000-161.000 deaths every year of all ages, most cases are in South Asia and Southeast Asia ². According to Basic Health Research (Riskesdas) data in 2007, the prevalence of typhoid fever in Indonesia reached 1,7%. The prevalence of typhoid fever in Central Java Province is 1,6%, while in Semarang is 1,2% ³.

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Typhoid fever is generally treated with antibiotics. Improper use of antibiotics can cause losses such as antibiotic resistance⁴. According to WHO (2013), as many as 23.000 people died and there were 2.049.442 cases of disease caused by antibiotic resistance. The slow development of new antibiotic treatments for typhoid can further exacerbate the threat of typhoid that is resistant to certain antibiotics⁵.

Research conducted by Abdurrachman & Febrina (2018) regarding the rational use of antibiotics in pediatric typhoid fever patients at Al Islam Bandung Hospital in 2017 showed the percentage of right patients was 100%, right indication was 100%, right medication during hospitalization was 100%, right medication 95% for outpatient care, 30% for inpatient doses, and 17,5% for outpatient care⁶. From the results of the study (Hasyul *et al.*, 2019), an evaluation of drug use at the Cibatu Tarogong Cisurupan Health Centers in Garut Regency for the January-December 2017 period, the results obtained were 96,68% of patients had the right indication for giving antibiotics, 58,27% were right drug, as much as 63,32% right dose, and 49,75% right time of administration⁷. Quantitative evaluation of the use of antibiotics in the internal medicine ward of a hospital Dr. H. Abdul Moeloek Lampung Province obtained 166 cases (98,8%) right indication, 168 cases (100%) right patient, 150 cases (89,29%) right drug, and 89 cases (52,97%) right dose⁸.

Based on the statement above, there are still many cases of inappropriate antibiotic therapy for typhoid fever in Indonesia, so it is necessary to manage appropriate antibiotic therapy for typhoid fever patients. In addition, it is necessary to increase the role of pharmacists in monitoring and evaluating antibiotic therapy in cases of typhoid fever in order to achieve maximum therapeutic effect and not cause adverse effects on patients. Thus, this study aims to evaluate the appropriateness of antibiotics based on the 7 parameters (right diagnosis, right patient, right indication, right drug, right dose, right way of administration, and right time of administration) in typhoid fever patients at the Gondosari Health Center in the period 1 January 2021 - December 2022.

METHODS

This research is a descriptive analytic non-experimental study using a cross-sectional study design where data was collected from medical records retrospectively on cases of patients diagnosed with typhoid fever who received antibiotic treatment at Gondosari Health Center for the period 2021 - 2022. Sampling technique carried out by purposive sampling method based on inclusion and exclusion criteria. Inclusion criteria in this study were patients with the main diagnosis of typhoid fever, age 5 – 11 years, positive widal test results, receiving antibiotic therapy for at least 48-72 hours, complete and/or legible medical records. While the exclusion criteria in this study were patients with the main diagnosis of typhoid fever accompanied by other infectious diseases. The data analysis technique uses univariate analysis, namely the analysis is carried out on each variable and the study results are presented in the form of a percentage distribution of the data obtained.

RESULTS AND DISCUSSION

Based on the results of the study, data obtained from outpatient pediatric typhoid fever patients at the Gondosari Health Center during January 2021 - December 2022 with total of 40 cases.

Patient Characteristics

Characteristics of typhoid fever patients in this study are distinguished by gender and age. Based on gender, the results showed that there were more male typhoid fever patients than female patients, namely 24 male patients (60%) and 16 female patients (40%). In this study, there were more men than women because boys tend to less cleaner than girls. In addition, boys tend to prefer to play outside the home, thus allowing children to often eat snacks at random because of the playmate factor. The results showed that there were 40 patients with typhoid fever in Gondosari Health Center for the period 2021 – 2022 aged 5 – 11 years. Age 5 - 11 years is the age of school children. School-age children generally tend to pay less attention to personal hygiene which can lead to the risk of developing typhoid fever. Typhoid fever transmission can occur anywhere & anytime, generally occurs through consumption of food outside the home or in public places that do not maintain cleanliness⁹. In addition, the incidence of typhoid fever can also be caused by a lack of awareness of food vendors to maintain food hygiene. Characteristics of outpatient typhoid fever at the Gondosari Health Center can be seen in the following table.

Table 2. Characteristics of Typhoid Fever Patients

Patient Characteristics		n	%
Gender	Male	24	60
	Female	16	40
Age	5 year	8	20
	6 year	9	22.5
	7 year	6	15
	8 year	6	15
	9 year	3	7.5
	10 year	5	12.5
	11 year	3	7.5

Gender and age do not affect the incidence of typhoid fever but typhoid fever is influenced by the personal hygiene of each individual. Ulfa & Handayani (2018) research, states that there is no relationship between the age and gender of the respondent with the incidence of typhoid fever¹⁰. However, there is a relationship between eating habits outside the home and personal hygiene with cases of typhoid fever.

Drug Characteristics

Medicines given to outpatient pediatric typhoid fever patients at the Gondosari Health Center consist of main therapy and supporting therapy. The main therapy for typhoid fever patients is antibiotics. Antibiotics are used to kill and stop the spread of *Salmonella typhi* bacteria. Based on the results of the study in Table 2, the antibiotics given to outpatient typhoid fever patients at the Gondosari Health Center were Thiamphenicol for 19 patients (47.5%), Amoxicillin for 13 patients (32.5%), and Co-trimoxazole for 8 patients (20%).

Table 2. Characteristics of Typhoid Fever Drugs

Group	Drug	n	%
Antibiotic	Thiamphenicol	19	47.5
	Amoxicillin	13	32.5
	Co-trimoxazole	8	20
Analgesic-Antipyretic	Paracetamol	40	100
Supplement	Multivitamins	22	55
Antiulcer	Ranitidine	10	25

Supportive therapy is a non-antibiotic drug given to support healing and reduce symptoms or complaints felt by patients, as well as prevent complications. Supportive therapies provided at the Gondosari Health Center are analgesic-antipyretic, supplements, and antiulcer. Analgesic-antipyretics are a class of drugs that can reduce pain without losing consciousness and can reduce fever. This drug is given to patients with typhoid fever because one of the symptoms that appears in patients is fever and headache. The analgesic-antipyretic given at the Gondosari Health Center was Paracetamol in 40 patients (100%). Supplements are used to support the needs of vitamins and nutrients also to increase immune. Supplements are given to patients with typhoid fever because when the patient has an infection there will be a deficiency of vitamins and the body's nutritional needs increase, while the patient experiences symptoms of nausea and vomiting which can cause decreased appetite. The supplements given at the Gondosari Health Center were multivitamins for 22 patients (55%). Giving antiulcer is used to relieve symptoms of digestive problems such as nausea, vomiting, and abdominal pain experienced by patients. The given at the Gondosari Health Center was Ranitidine in 10 patients (25%). One of the most widely used H-2 receptor antagonists in children as a standard treatment for peptic ulcers is ranitidine ¹¹.

Evaluation of Antibiotics Appropriateness

Evaluation of the appropriateness of using antibiotics in this study was evaluated from several indicators in Indonesian Ministry of Health (2011). The following is a table of results of evaluating the use of antibiotics in outpatient pediatric patients at the Gondosari Health Center for the period January 2021 - December 2022.

Table 3. Results of Antibiotic Appropriateness Evaluation

Indicators	Correct		Incorrect	
	n	%	n	%
Right diagnosis	40	100	0	0
Right patient	40	100	0	0
Right indication	40	100	0	0
Right drug				
- Based WHO (2011)	40	100	0	0
- Based Indonesian Ministry of Health (2006)	40	100	0	0
Right dose				
- Based WHO (2011)	34	85	6	15
- Based Indonesian Ministry of Health (2006)	40	100	0	0
Right way of administration	40	100	0	0
Right duration				
- Based WHO (2011)	8	20	32	80
- Based Indonesian Ministry of Health (2006)	32	80	8	20

Right diagnosis is the appropriateness of establishing the diagnosis of the disease suffered by the patient. The diagnosis is made by a doctor based on a physical examination, patient symptoms/complaints, and laboratory test results. The parameters for the right diagnosis in this study were typhoid fever patients who had received the right diagnosis in the medical records according to the clinical symptoms experienced and were positive on the Widal test. All patients at the Gondosari Health Center who had a high fever for more than 3 days immediately underwent two laboratory tests, namely test for Dengue Hemorrhagic Fever (DHF) and widal test for typhoid fever. In this study, the results obtained were that outpatient pediatric typhoid fever patients at the Gondosari Gebog Kudus Health Center had a 100% right diagnosis.

Right patient is a drug that is given according to the patient's condition so that it does not cause contraindications. The patient's right parameters in this study were the antibiotic drugs given to the patients according to whether or not they had drug allergies, age, co-morbidities other than typhoid fever, and history of diseases such as kidney or liver disorders. There were no outpatient pediatric patients at the Gondosari Health Center who had co-morbidities or a history of severe illness. There were 3 patients with a history of allergy to penicillin who were not given amoxicillin. For patients with severe typhoid fever or complications, they are immediately referred to the hospital because the Gondosari Health Center does not provide inpatient care. Based on the results of the study, the antibiotics given to outpatient pediatric typhoid fever patients at the Gondosari Public Health Center were all in accordance with the patient's condition and there were no contraindications. So it can be concluded that the evaluation of the accuracy of antibiotics at the Gondosari Gebog Kudus Public Health Center is 100% right patient.

The right indication is the suitability between the patient's diagnosis and the drug given. In this study, patients were said to have the right indication if they received antibiotic therapy with clear indications after being diagnosed with typhoid fever based on clinical symptoms and laboratory results. The diagnosis of typhoid fever can be made if the patient is positive on supporting laboratory tests including examination of blood cultures, widal, salmonella IgM, and tubex ⁶. In this study, all patients diagnosed with typhoid fever based on the results of the Widal test received antibiotic therapy. Antibiotics are drugs indicated for diseases caused by bacterial infections. Typhoid fever is caused by an infection with the *Salmonella typhi* bacteria in the intestine. Based on the results of the study, all of the antibiotic drugs given to outpatient pediatric typhoid fever patients at the Gondosari Public Health Center were 100% right indication. The antibiotics given have the right indications for typhoid fever patients based on therapy guidelines according to WHO (2011) and Indonesian Ministry of Health (2006).

The right drug is a drug that is prescribed must have a therapeutic effect that is in accordance with the diagnosis that has been established. The right drug parameter in this study was that patients with a diagnosis of typhoid fever received antibiotics according to the therapy guidelines according to WHO (2011) and Indonesian Ministry of Health (2006). In this study, 40 cases (100%) obtained the right drug results according to WHO (2011) and Indonesian Ministry of Health (2006).

According to WHO therapy guidelines (2011), based on the results of culture and antibiotic sensitivity tests, it is shown that fluoroquinolone (Ciprofloxacin) is the optimal choice for the treatment of typhoid fever at all ages. In 2016, the *American Academy of Pediatrics* stated that fluoroquinolone is quite safe for use in children and can be used for gastrointestinal infections caused by *Salmonella* in children ¹⁴. However, in the therapy guidelines according to WHO (2011) it is also stated that chloramphenicol, amoxicillin, and co-trimoxazole are traditional first-line drugs that can be used for the treatment of typhoid fever in areas where the bacteria are still fully sensitive to these drugs and if the use of fluoroquinolones is limited in areas (WHO, 2011). Antibiotics of the fluoroquinolone class in Indonesian Ministry of Health's therapeutic guidelines (2006) are not

recommended for children because they can cause side effects on bone growth. The first-line therapy for typhoid fever according to Indonesian Ministry of Health's therapeutic guidelines (2006) uses chloramphenicol, amoxicillin and co-trimoxazole.

Thiamphenicol is an antibiotic derived from chloramphenicol and is effective against *Salmonella* bacteria¹⁵. Thiamphenicol can be used as first-line therapy to replace chloramphenicol because of haematological side effects, recurrence rates, and lower carrier rates compared to chloramphenicol¹⁵. Thiamphenicol has the side effect of causing bone marrow suppression but almost never has the side effect of aplastic anemia¹⁵. Thiamphenicol does not cause side effects of aplastic anemia and gray baby syndrome because it does not have an aromatic nitro group¹⁶.

Dose is one of the most important aspects in determining drug efficacy. Doses that are too high can be at risk of causing side effects, while doses below the therapeutic range do not guarantee the desired therapeutic effect¹⁷. The dose of a drug is adjusted according to the patient's clinical condition because not every patient can receive the same dose. The right dose parameter in this study was the appropriation of drug dose based on age, weight, and chronology of the patient's disease as stated in the medical record compared to the standard reference dose of WHO (2011) and Indonesian Ministry of Health (2006). In this study, the right dose results were obtained in 34 cases (85%) according to WHO (2011) and 40 cases (100%) according to the Indonesian Ministry of Health (2006). In this study, there were 6 cases of incorrect dose according to WHO (2011). According to WHO (2011), there was an incorrect dose because 6 patients received co-trimoxazole at a dose below the dose range (underdose) according to WHO (2011).

The right parameter for the way of administration in this study is if the drug dosage form and route of drug administration are in accordance with the patient's condition. Gondosari Health Center only provides outpatient care so that all drugs are administered to patients by the oral route. Pediatric patients who are unable to swallow tablet or capsule are given drugs in the form of powder, syrup, or suspension. The typhoid fever drugs used are Thiamphenicol, Amoxicillin, and Co-trimoxazole which according to the WHO (2011) and the Indonesian Ministry of Health (2006) therapy guidelines, these drugs can be administered orally. Therefore, it can be said that the results of the evaluation were 100% right way of administration.

The duration of drug administration is determined by the type of disease and condition of each patient. The parameters for the right duration in this study were patients with a diagnosis of typhoid fever who received antibiotic drug therapy with the duration of use in accordance with the guidelines for the treatment of typhoid fever according to WHO (2011) and Indonesian Ministry of Health (2006). At the Gondosari Health Center, antibiotics are given to patients for use every 5 days, then the patient is required to come back to the Gondosari Health Center on the 5 day for control and drug collection. Thiamphenicol was given for 10 days, amoxicillin for 10 days, and co-trimoxazole for 14 days.

In this study, results obtained on the right duration were 8 patients (20%) according to WHO (2011) and 40 patients according to Indonesian Ministry of Health (2006). In this study, there were 32 cases of inappropriate duration according to WHO (2011) and 8 cases according to Indonesian Ministry of Health (2006). According to WHO (2011) there was an inappropriate duration because 13 patients received Amoxicillin therapy with duration of 10 days while according to WHO (2011) therapy guidelines it was 14 days. In addition, 19 patients received Thiamphenicol therapy with a duration of 10 days, while according to WHO (2011) therapy guidelines, it is 14-21 days for chloramphenicol class drugs. There was inappropriateness according to the Indonesian Ministry of Health (2006) because as many as 8 patients received co-trimoxazole for 14 days while according to the Ministry of Health (2006) it was 10 days.

Based on therapy guidelines according to the Indonesian Ministry of Health (2006), Thiamphenicol is given for 5-7 days free of fever. Fever-free time is the time from drug administration until body temperature drops to less than 37.5°C and lasts at least 48 hours¹⁸. The fever-free time needed for typhoid fever patients for the antibiotic thiamphenicol is 5 days¹⁹.

CONCLUSION

The result of evaluation of the appropriateness use of antibiotics in pediatric typhoid fever in this study were 100% right diagnosis, 100% right patient, 100% right indication, 100% right drug according to WHO (2011), 100% right drug according to Indonesian Ministry of Health (2006), 85 % right dose according to WHO (2011), 100% right dose according to Indonesian Ministry of Health (2006), 100% right method of administration, 20% right duration according to WHO (2011), and 80% right duration according to Indonesian Ministry of Health (2006).

ACKNOWLEDGEMENT

We would like to thank Gondosari Health Center for supporting this study.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

AUTHOR DETAILS

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