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by Teti Sutriyati Tuloli

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THE RATIONALITY OF ANTIBIOTICS THERAPY TOWARD CHILDREN WITH TYPHOID FEVER AT M.M. DUNDA HOSPITAL

TETI SUTRIYATI TULOLI*, DEWI R MOO

Department of Pharmacy, Faculty of Sport and Health, State University of Gorontalo, Indonesia. Email: tetisutriyati@gmail.com

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ABSTRACT

Objectives: Typhoid fever is an acute systemic infectious disease in the small intestine caused by *Salmonella enterica* serotype typhi (*Salmonella typhi*) having the symptoms of fever a week or more with impairment of the gastrointestinal tract with or without impaired consciousness. The purpose of this study was to determine the rationality of antibiotic therapy in pediatric patients at M.M Dunda Limboto Hospital.

Methods: This research belongs to non-experimental descriptive with retrospective data retrieval. The data used were obtained from 83 medical records of childhood typhoid patients during 6 months (June–November 2016) at the regional general hospital of M.M Dunda Limboto. These data were analyzed using the Gyssens criteria.

Results: The results showed that the most antibiotics used by physicians were ceftriaxone 39% of the use of antibiotic quality which was category IIB 9%, category IIA 13%, and category 0 (rational) 52%.

Conclusion: The rationality of antibiotic therapy in children with typhoid fever at M.M Dunda Limboto Hospital was 52% of the most antibiotics used, i.e. ceftriaxone (39%).

Keywords: Antibiotic, Dunda limboto, Rationality, Typhoid, Therapy.

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INTRODUCTION

Typhoid fever is a global problem, especially in developing countries. The main cause is *Salmonella typhi* that contaminates food and drink and poor environmental sanitation system [1,2]. Globally, it has been recorded that there are 17 million cases of typhoid with a total of 600,000 death cases from typhoid. In Asia, more than 13 million people are infected by typhoid, a systemic and endemic disease [3].

The incidence of typhoid fever in Indonesia is still very high, ranging between 358 and 810 per 100,000 population, as well as from cases of typhoid fever in major hospitals in Indonesia, indicating that the rate of typhoid fever tends to increase every year with the average of 500/100,000 inhabitants. The typhoid fever death rate is estimated to occur around 0.6–2% as a result of delayed treatment and the high cost of treatment [4].

Based on the health profile of Indonesia people in 2010 by the Ministry of Health of the Republic of Indonesia showed typhoid fever ranked the third of 10 inpatient diseases in hospitals in Indonesia as many as 41,081 cases of 274 people died. The highest incidence rates of typhoid fever occurred in children and young adults in the 5–34 years' age range [5]. The highest morbidity rate was the age of 5–19 years with mild clinical manifestations. In pediatric patients with this typhoid, diagnosis was used antibiotics and other supporting drugs as typhoid therapy [6].

In a study of pediatric patients suffering from typhoid fever at Fatmawati Hospital, Jakarta, in 2001–2002, it was found that chloramphenicol was still the primary choice used in childhood typhoid fever. Meanwhile, ceftriaxone was the second choice antibiotic which used by physician. In December 2002 based on the results of preliminary observation at M.M Dunda hospital, data obtained from June–November 2016 about typhoid fever occupied the first position of 10 the most diseases in hospitalization M.M Dunda with the number of patients as many as 628 patients who given cephalosporin antibiotics

The antibiotic prescription in Indonesia is quite high which is likely to trigger a rise in cases of antibiotic resistance. The impact of antibiotics resistance is the increase in patient morbidity and mortality. In the past decade, many microorganisms have been resistant to antibiotics that exist in some therapeutic standards. This is a phenomenon occurring almost all over the world caused by excessive abuse and antibiotics use [7]. Based on the above description, the researcher felt that it was necessary to evaluate the rationality of antibiotic therapy in child fever at M.M Dunda to support the success of typhoid therapy and reduce the appearance of resistant microorganisms against antibiotics.

METHODS

This research was conducted in Medical Record Room at Regional General Hospital of M.M Dunda Limboto. The study was conducted in January–May 2017. This type of research is analytical descriptive with the retrospective approach.

The population in this study was all pediatric typhoid children using antibiotic therapy during June–November 2016 at The Regional General Hospital of M.M Dunda Limboto. Data collected from the medical record included the name of antibiotics, diagnosis, dosage, frequency, administration duration, route of administration, number of antibiotic combinations, demographic data, and clinical data.

The data obtained were analyzed qualitatively using the Gyssens category [8]. This category consisted of 12 categories such as category 0: Appropriate/rational antibiotic use, category I: Irrational due to inappropriate timing, category IIA: Irrational due to inaccurate dosage, category IIB: Irrational due to incorrect interval, category IIC: Irrational due to wrong way of giving, category IIIA: Irrational due to prolonged giving, category IIIB: Irrational due to too short giving, category IVA: Irrational due to other more antibiotics effective, category IVB: Irrational due to other antibiotics less toxic, category IVC: Irrational because of other antibiotics cheaper, category IVD: Irrational because

of other antibiotics more specific, and category V: Irrational due to the absence of indications for antibiotics use. The results of the analysis will be presented in the form of a percentage of the accuracy or the absence of antibiotics. This research has obtained the recommendation of ethical approval No. 017/KEPK/SG/02/2018 from the Health Research Ethics Commission of Yogyakarta Health Sciences College.

RESULTS

This study obtained 83 medical records at M.M Dunda Hospital which met the criteria for inclusion with the prescription of antibiotics 90 items of antibiotics. Demographic characteristics of study respondents can be seen in Table 1.

Based on Table 1, it was known that the respondents of pediatric patients with female sex were more dominant (64%) than the number of respondents of child patients of male sex (36%). Based on the age group showed that the incidence of typhoid infections were the highest at the age of 5-10 years about 54% and the lowest at the age of 11-14 years around 8%. The results of this study indicated that as children age, the incidence of infection decreases. Children are infected 3-6 times a year although some children were infected more often than children of 2-3 years age range, and the incidence of infection in children of this age occurred because the immune system in this child was not fully developed to prevent infection [9].

This study showed that there are four types of antibiotics that have been prescribed in patients with typhoid fever with the number of antibiotics classified as dominant were ceftriaxone (39%) and cefotaxime (32%). The dominant use of the third-generation cephalosporin class (ceftriaxone) in typhoid fever was due to a faster cure rate in ceftriaxone therapy than on chloramphenicol therapy of 7 days and the absence of a relapse possibility for patients with ceftriaxone therapy for 8-14 day [10]. Surveys of several strains of bacteria in several South Asian countries between 2002 and 2004 revealed that 23% of bacterial strains have been resistant to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole [11]. Yet, other studies also showed that the prevalence of resistance to some antibiotics varied from 0% to 50% [12].

Pediatric patients in this study also received a number of different antibiotics such as patients with single antibiotics 85.5% and patients who get two combinations of antibiotics 14.5% and this is shown in Table 2. The purpose of the use of this antibiotics combination is to increase the efficacy of antibiotics in typhoid infections.

The rationality assessment of the use of antibiotics qualitatively in this study was conducted using the criteria of Gyssens (Table 3). The highest analysis result was the category 0 (rational) of 52% followed by the category IIIB (administration of antibiotics too short) of 26%, followed by the category IIA (13% unnecessary administration of antibiotics).

Meanwhile, the data also showed that there were no antibiotics therapy in typhoid fulfilled category V (antibiotics without indication), IVD (more specific antibiotics), IVC (cheaper antibiotics), IVB (more toxic), IIIA (long administration), IIC (not exact way of administration), and I (time is not appropriate). So that in all of these categories got 0. In category IIIB, there were 23 (26%) antibiotic treatments which considered to be overvalued assuming. This could lead to ineffective therapy. For category IIB, there was eight antibiotic therapies (9%) which were assessed not exactly the interval, while category IIA gave 12 antibiotic therapies (13%) which assessed not exactly dose. For category 0, there was 47 antibiotics therapies (52%) that were considered rational both in terms of administration time, dose, interval, and the way of antibiotics.

DISCUSSION

Demographic characteristics of respondents in this study were assessed by sex and age range of children with typhoid at M.M. Dunda. In this study, it was found that pediatric patients with female sex (64%) had

Table 1: The characteristic of respondents

The characteristic	N (%)
Gender	
Female	53 (64)
Male	30 (36)
Total	83 (100)
Age	
1-4 years	30 (36)
5-10 years	45 (54)
11-14 years	8 (10)
Total	83 (100)

Table 2: The therapy of antibiotics on children thypoid patients

Variable	N (%)
Antibiotics	
Vicilin	17 (19)
Cefotaxime	29 (32)
Cefixime	9 (10)
Ceftriaxone	35 (39)
Total	90 (100)
Antibiotics combination	
Single	77 (85.5)
Double	13 (14.5)
Total	90 (100)

Table 3: The rationality of antibiotics therapy based on Gyssens category (2001)

The category of therapy rationality	Total
	N (%)
0=Rational	47 (52)
I=Not on time	0 (0)
II A=Not exactly dose	12 (13)
II B=Not exactly interval	8 (9)
II C=Not exactly administration	0 (0)
III A=Giving too long	0 (0)
III B=Giving too short	23 (26)
IV A=More effective antibiotics	0 (0)
IV B=More toxic antibiotics	0 (0)
IV C=Cheaper antibiotics	0 (0)
IV D=More specific antibiotics	0 (0)
V=Antibiotics without indication	0 (0)
Total	90 (100)

more numbers than the number of male children (36%). Typhoid fever disease can affect anyone, and there is no difference between sex and female.

In general, the typhoid disease was more common in children suffering than adults, in adulthood, often experience symptoms that are not typical, and then disappear or heal itself [10]. The results of this study were not in line with previous research, stating that children diagnosed with typhoid fever were more common in male sex (58%). This was partly due to the type of activity, living habits, and physiological conditions of each individual [13].

Based on data showed that the incidence of typhoid fever was in the range of age varying with the highest number existed at the age of 5-10 years (54%) and the lowest at the age range 11-14 years (10%). This study showed that the increase of children age of the incidence of typhoid fever was reduced. This was in line with previous research findings that the rate of infection in children decreased on age [7].

It can be seen that antibiotics often prescribed in the treatment of typhoid fever were ceftriaxone (39%), cefotaxime (32%), vicilin (19%), and cefixime (10%). Pediatric patients also received a combination

of two antibiotics (14.5%) and a single antibiotic (85.5%). The most commonly prescribed antibiotic combination was vicilin-cefotaxime (7.8%). Both of these antibiotics have the same characteristics that are equally bactericidal, having the same mechanism of action that inhibits the synthesis of bacterial cell walls, as well as both of these antibiotics having lactam beta rings on their molecular structure. In general, both antibiotics are active against Gram-positive and Gram-negative bacteria. The choice of cefotaxime to be combined with vicilin is caused by cefotaxime which is a third-generation cephalosporin and tends to be more active against Gram-negative bacteria such as *S. typhi* so that if both these antibiotics are combined, it will obtain synergistic results in overcoming the bacteria causing typhoid fever. However, the use of cefotaxime to be combined with vicilin which is advisable to do a skin test in advance to avoid the possibility of cross-reactivity due to the use of cephalosporin in patients hypersensitive to beta-lactam antibiotics.

The use of a single antibiotic, the administration of ceftriaxone in the treatment of typhoid fever is more preferable than chloramphenicol because ceftriaxone is not easy to cause resistance having minimal side effects and clinical efficacy. Ceftriaxone can decrease fever more quickly causing the duration of therapy was shorter than chloramphenicol. This is assumed to cause ceftriaxone more preferred than other reasons that the possibility of multidrug-resistant *S. typhi* (MDRST). MDRST is the preferred resistance of antibiotics in the treatment of typhoid fever which caused by the use of irrational antibiotics and intrinsic factor changes in microbes. Ceftriaxone is the preferred antibiotic used in the event of MDRST. In addition, chloramphenicol also has side effects such as bone marrow suppression and aplastic anemia [14].

The second sequence, the most widely used antibiotics for typhoid therapy, is cefotaxime [15]. Cefotaxime is used in patients with severe typhoid fever who are quinolone-resistant. Cefotaxime and ceftriaxone are effective for the treatment of Gram-negative bacteria such as *S. typhi* [16]. This reason allows ceftriaxone and cefotaxime to be used at M.M. Dunda Limboto. The results of this study were related to cefotaxime which was the most widely used antibiotic for the treatment of typhoid fever in pediatric patients. Cefotaxime is class III cephalosporin group that has a very wide spectrum, its antibacterial activity is stronger, and side effects are relatively lower [17].

Viciline is also used for the treatment of typhoid fever of inpatients. Besides that, amoxicillin and ampicillin have the same spectrum and antibacterial activity. However, in terms of the ability to reduce fever, the effectiveness of amoxicillin and ampicillin is smaller than chloramphenicol [18]. Finally, cefixime is an antibiotic that is also used to treat therapies in patients with typhoid fever at M.M. Dunda. Cefixime is a third-generation cephalosporin antibiotic that is stable against the β -lactamase enzyme produced by organisms such as *Streptococcus* strains, *Haemophilus influenza*, *Neisseria gonorrhoeae*, and the majority of Enterobacteriaceae. This antibiotic is bactericidal with a broad spectrum of Gram-positive bacteria (*Streptococcus* sp. and *Streptococcus pneumonia*) and Gram-negative (*E. coli*, *Proteus* sp., and *Haemophilus influenza*). The cefixime activity decreases against *Staphylococcus aureus*, *Enterococci*, *Listeria monocytogenes*, and *Pseudomonas* spp. The incidence of cefixime-resistant bacteria is reported to be very low. Cefixime may be used as an alternative medicine for the treatment of typhoid fever, especially unless chloramphenicol cannot be given (e.g., leukocyte count) [19].

Assessment of rationality level of antibiotics in this study uses Gyssens criteria. This Gyssens method takes into account several components: Therapeutic indications, antibiotic characteristics (efficacy, safety of use, price, and spectrum), dose, interval, and time of administration. After the assessment with criteria, Gyssens obtained the results of the use of antibiotics for the therapy of child on typhoid fever which can be seen in Table 3. A total of 47 prescriptions (52%) fall into category 0, i.e., the rational use of antibiotics in which antibiotics are given a clear indication relating to the patient's needs (assessed for efficacy, safety, suitability and cost), dose, appropriate intervals and delivery routes

and time. Meanwhile, the previous studies showed 32% of children with typhoid receiving rational antibiotic therapy [7].

The use of antibiotics for the treatment of childhood typhoid fever was 13% of the category IIA, which is the dose used was not appropriate well beyond the maximum dose or below the maximum dose. Based on clinical practice guidance of child health sciences of M.M. Dunda was the doses of ceftriaxone should be given 50 mg/kg BW, ampicillin 200 mg/kg BW and amoxicillin 100 mg/kg BW, cefixime 20 mg/kg BW, chloramphenicol 75 mg/kg BW. Doses may be under maximum doses such as the use of ceftriaxone which is dose for children 50 mg/kg BW but body weight 19 kg of children should be given ceftriaxone with a dose of 950 mg/day and 475 mg for single dose because ceftriaxone is given every 12 hours but in the treatment is given only 380 mg/day and 190 mg for single dose. The condition is also adjusted to the form of antibiotic preparations used to suppress the cost of patient therapy. The results obtained in the study were high category which compared with previous studies obtaining the results that the use of antibiotics for Bengkulu hospital 0.6% belonging to not exactly dose [7].

The study showed that there were eight prescribers (9%) who entered in the category IIB having the inappropriate antibiotics interval. Based on the clinical practice guidelines of children's health sciences of M.M. Dunda stated that ceftriaxone 50 mg/kg BW which given 2 times daily or 80 mg/kg BW, once daily intravenously for 5-7 days. Meanwhile, we obtained the example of ceftriaxone which was given 3 times a day in children weighing 19 kg. The results of this study in the IIB category were judged to be greater when compared with previous studies, showing that 6.8% of prescribed antibiotics were not used properly, in part, because of incorrect therapy duration or incorrect dose intervals [20].

Based on the Gyssens criteria used in this study described there were 23 prescriptions (26%) belonging to IIIB criteria (giving too short). This is related to the clinical practice guidelines of children's health sciences of M.M. Dunda. Whereas, according to the WHO, it is stated that the use of ceftriaxone to achieve optimal therapy was 10-14 days [8], for example, for giving too short of administration of antibiotics ceftriaxone 2 times a day with a dose of 225 mg in patients having body weight 9 kg and given only for 2 days. In Indonesia, the use of antibiotics is in the range of 3-7 days to kill disease-causing microbes [7,21]. If the treatment was done too short, the therapy will not be optimal and in the long run which will cause the resistance of antibiotics.

CONCLUSION

The rationality of antibiotics therapy in childhood typhoid fever at M.M. Dunda Limboto Hospital was 52% of the most antibiotics use, i.e., ceftriaxone (39%).

AUTHORS' CONTRIBUTION

Mrs. Teti ST - Review of literature and Data analysis. Mrs. Dewi RM - Data Collection.

CONFLICTS OF INTEREST

All authors have none to declare.

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