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Evaluation of the Rationality of Antibiotic Use Among Typhoid Fever Patients at Hospital X in Surakarta: An Analysis Using Gyssens Method

Evaluasi Rasionalitas Penggunaan Antibiotik pada Pasien Demam Tifoid di Rumah Sakit X di Surakarta: Sebuah Analisis Diagram Gyssens

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ABSTRACT

S. typhi bacteria cause typhoid fever and ranks as the 15th deadliest disease in Indonesia. In Central Java, the incidence of typhoid fever reached 244,071 cases. One of the problems in managing typhoid fever is bacterial resistance due to the irrational use of antibiotics. So, it is vital to ensure the rational use of antibiotics. One of the efforts to control antibiotic resistance is to evaluate the rationality of antibiotic use. The Gyssens method was chosen to evaluate antibiotic rationality because it is more accurate, specific, and follows a systematic assessment flow. This study is descriptive, observational, and cross-sectional. This study examined the medical records of typhoid fever patients who received treatment at Surakarta "X" Hospital in 2021. A total of 84 inpatients of "X" Hospital who were diagnosed with typhoid fever and received antibiotic therapy rationally (category 0) amounted to 29.76%. Antibiotic irrationality was found in categories IVA (21.43%), IV B (9.52%), IIIA (3.57%), III B (55.95%), IIA (40.47%), and II B (32.14%).

Kata kunci
Demam Tifoid
Rasionalitas
Antibiotik
Diagram gyssens

ABSTRAK

Demam tifoid disebabkan oleh bakteri *S. typhi* dan menempati urutan ke 15 penyakit mematikan di Indonesia. Di Jawa Tengah kejadian demam tifoid mencapai 244.071 kasus. Salah satu permasalahan dalam penanganan demam tifoid adalah resistensi bakteri akibat penggunaan antibiotik yang irrasional. Sehingga penting untuk memastikan penggunaan antibiotik yang rasional. Salah satu upaya pengendalian resistensi antibiotik adalah dengan mengevaluasi rasionalitas penggunaan antibiotik. Diagram gyssens dipilih untuk mengevaluasi rasionalitas antibiotik karena lebih akurat, lebih spesifik, dan mengikuti alur penilaian yang sistematis. Penelitian ini bersifat deskriptif dan observasional, serta *cross-sectional*. Penelitian ini mengkaji rekam medis pasien demam tifoid yang mendapat perawatan di RS "X" Surakarta pada tahun 2021. Sebesar 84 pasien rawat inap RS "X" yang terdiagnosis demam tifoid dan menerima terapi antibiotik secara rasional (kategori 0) sebesar 29,76%. Ketidakrasionalan antibiotik ditemukan pada kategori IVA (21,43%), IV B (9,52%), IIIA (3,57%), III B (55,95%), IIA (40,47%), dan II B (32,14%).

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1. INTRODUCTION

Infection with Salmonella typhi (S. typhi) bacteria in the digestive system will cause typhoid fever, a type of enteric fever. This bacterium contaminates food and water with poor sanitation and hygiene. Worldwide, typhoid fever causes 11-21 million illnesses and 128,000-161,000 deaths per year [1] [2]. Data from the Ministry of Health of the Republic of Indonesia states that there are 81.7 cases of typhoid fever for every 100,000 people, and 20-40% of those who contract the disease require hospitalization [3]. These figures make typhoid fever rank fifth as an incurable disease and fifteenth as a deadly disease in Indonesia [4]. Based on data from the Ministry of Health's Early Vigilance and Response System (SKDR) in 2016, typhoid fever cases increased in Central Java between 2015 and 2016, with 13,397 cases, and 244,071 cases, respectively [5].

Typhoid fever is commonly treated using antibiotics such as Ampicillin/ Amoxicillin, Trimethoprim/ Sulfamethoxazole, Chloramphenicol, Ciprofloxacin, Orofloxacin, Cefixime, Azithromycin and Ceftriaxone [6]. However, high antibiotic use will increase the risk of irrational antibiotic use which has the potential to cause antibiotic resistance [7]. This is in line with a literature review on antibiotic sensitivity testing in Salmonella thypi which showed resistance to ceftriaxone, cefuroxime, amoxicillin, ampicillin, ciprofloxacin, augmentin, fluoroquinolones, azithromycin and nalidixic acid [8]. Bacterial resistance is now a major health problem worldwide that requires immediate action. Using antibiotics appropriately and conducting systematic, long-term and consistent monitoring and evaluation of antibiotic use in hospitals or public health facilities are two strategies to combat this resistance [9].

Previous studies provide a comprehensive picture of the reasons behind the use of antibiotics in the treatment of typhoid fever in various hospitals in Central Java. Based on Purwaningsih's (2015) research, typhoid fever is the most common disease suffered by pediatric patients treated at Sultan Agung Islamic Hospital, which is 210 out of 385 cases, while the rate of rational use of antibiotics is only 23.9% [10]. A study conducted by Hanifah et al (2018) showed there were 98 cases of typhoid fever with a rationality rate of 20.4%. According to additional research by Yualta (2018), only 5.12% of typhoid fever patients used antibiotics rationally [11].

Based on the above description, it is known that the frequency of typhoid fever in Central Java continues to increase. The data shows that many studies have been conducted on the rationality of antibiotics in typhoid fever which results show a low level of rationality. Evaluation of the rationality of antibiotic use is not a new study, but this study has an important role to control antibiotic use and increase caution and awareness about rational antibiotic treatment [12]. Data searches conducted by researchers showed that there were no studies that assessed the effectiveness of antibiotics for typhoid fever therapy conducted at related facilities.

2. METHODS

This study used descriptive observational methodology and was cross-sectional in nature. The data used were medical records of patients diagnosed with typhoid fever at Surakarta "X" Hospital from January to December 2021. Data were collected in May 2022 with the sampling method, namely total sampling. The study inclusion criteria were typhoid fever patients who were admitted to Hospital X between January and December 2021. Conversely, patients who did not receive antibiotic therapy and whose medical records were incomplete or unreadable, met the exclusion criteria of this study. There were 84 samples that met the inclusion criteria in this study. This study has obtained the

approval of the Ethics Committee for Health Assessment of the Faculty of Medicine, Universitas Muhammadiyah Surakarta with number 4685/C.2/KEPK-FKUMS/XI/2022.

Data analysis was conducted using the SPSS 26 program, descriptively by entering data, gender, age, comorbidities, and antibiotic use and then statistically analyzed to see the frequency or prevalence, then the results were presented in tables and percentages. Rationality data using the Gyssens diagram to qualitatively examine the use of antibiotics used for typhoid fever patients compared to the Guidelines for the Control of Typhoid Fever by the Ministry of Health of the Republic of Indonesia in 2006. Gyssens diagram has the advantage of having high accuracy, where antibiotic rationality is divided into each category based on the type of rationality. In addition, the Gyssens diagram has a systematic flow that is suitable for use in this study. Furthermore, the data were statistically processed using descriptive analytic cross-tabulation to describe information about the rationality of antibiotic use. The results of further analysis were presented in the form of a table of percentage of antibiotic rationality.

3. RESULTS

3.1. Patient Characteristics

Of the total 96 typhoid fever patients, 84 patients met the inclusion criteria, while 12 people were not given antibiotics so they were included in the exclusion criteria. Data on patient characteristics are shown in Table I, grouped by age and gender.

Table 1. Characteristics of Typhoid Fever Patients in Surakarta X Hospital

Characteristics	Number (Percentage)
Gender	
Male	32 (38,1)
Female	52 (61,9)
Age	
Gender	

3.2. Drug Usage

Table II displays information related to the use of antibiotics for typhoid fever patients.

Table II. Antibiotic Prescribing Patterns in Typhoid Fever Patients at Hospital X Surakarta

Antibiotik	Frekuensi (Persentase)
Sefalosporin	
Seftriakson	**49 (58,33)**
Sefotaksim	**8 (9,52)**
Sefiksim	**8 (9,52)**
Penisilin (Beta-Laktam)	
Ampisilin	**1 (1,2)**
Kuinolon	
Levofloksasin	**10 (11,9)**
Siprofloksasin	**1 (1,2)**
Fenikol	
Kloramfenikol	**3 (3,57)**
Tiamfenikol	**4 (4,76)**
Total	**84 (100.0)**

3.3. Antibiotic Rationality

Antibiotic rationality assessment was performed with a Gyssens diagram using categories 0-VI. Definitions for each category can be found in table III.

Table III. Gyssens Categories for Antibiotic Rationality

Category	Description
0	Antibiotics can be used appropriately for prophylaxis or therapy, including at the right time (rational)
I	Administration of antibiotics not at the right time
IIA	Using antibiotics not in the right amount
IIB	Using antibiotics at inappropriate intervals
IIC	Using antibiotics that are inappropriate for the route of administration
IIIA	Using antibiotics for a long period of time
IIIB	Using antibiotics for an insufficient period of time
IVA	There are more efficient substitute drugs
IVB	There are less harmful substitute drugs
IVC	There are substitute drugs that are not too expensive
IVD	Other antibiotics with a more limited scope are also available
V	Using antibiotics for treatment without complaints
VI	Medical records are not complete enough to be evaluated

Furthermore, to measure the level of rationality, the treatment data of typhoid fever patients was analyzed using the Gyssens diagram.

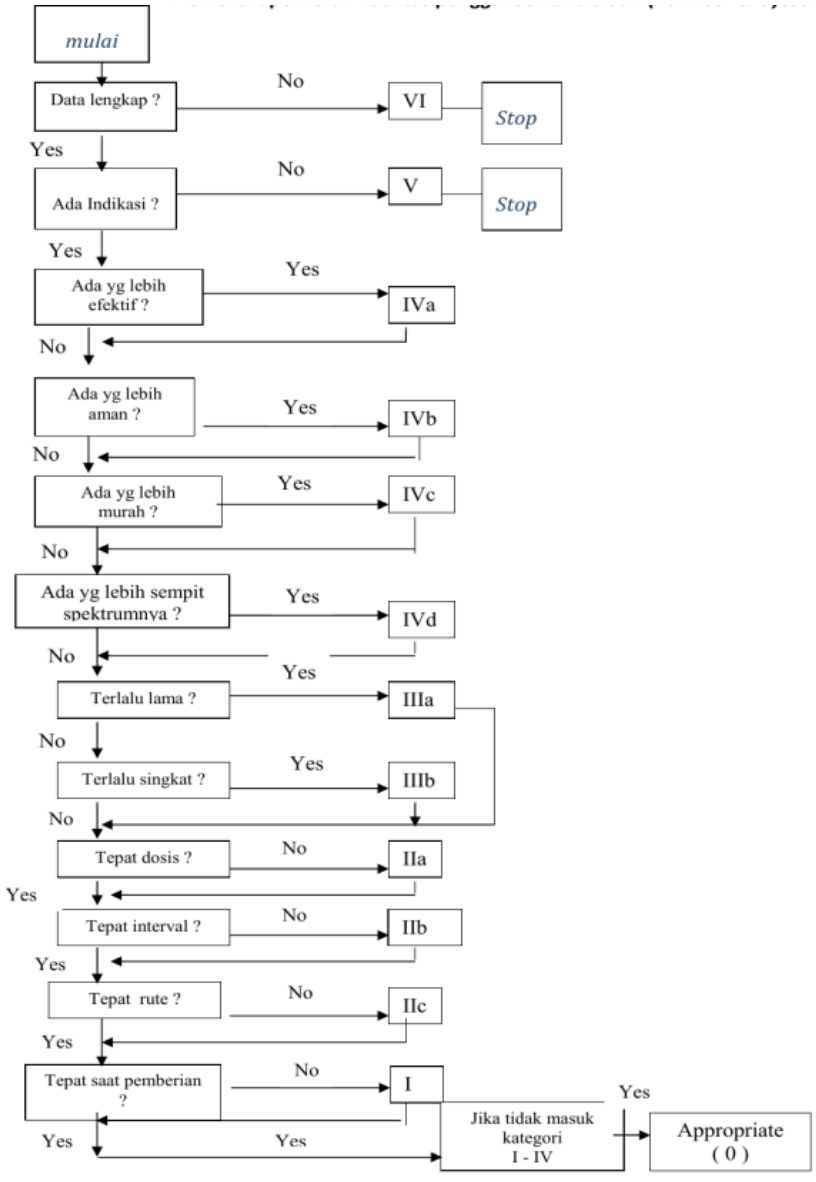

Figure I. Flow of antibiotic rationality analysis with Gyssens diagram.

Table IV shows the results of the analysis of the rationality of antibiotic therapy in typhoid fever patients, and the categorization of rationality using the Gyssens diagram is presented in table V.

Table IV. Results of Analysis of Prescribing Rationality in Typhoid Fever Patients at Hospital X Surakarta

		Rationality		Total
		Rational	Not Rational	
Antibiotik	Seftriakson	22	27	49
	Sefotaksim	0	8	8
	Sefiksim	0	8	8
	Ampisilin	0	1	1
	Levofloksasin	0	10	10
	Siprofloksasin	1	0	1
	Kloramfenikol	0	3	3
	Tiamfenikol	2	2	4
Total		**25 (29,76%)**	**59 (70,24%)**	**84 (100,0%)**

Table V. Results of Analysis of Prescribing Rationality in Typhoid Fever Patients Using the Gyssens Diagram.

		Rationality Category												
		VI	V	IV A	IV B	IV C	IV D	III A	III B	II A	II B	II C	I	0
Antibiotik	**Seftriakson**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**20**	**23**	**22**	**0**	**0**	**22**
	Sefotaksim	**0**	**0**	**8**	**0**	**0**	**0**	**0**	**4**	**0**	**1**	**0**	**0**	**0**
	Sefiksim	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**8**	**7**	**1**	**0**	**0**	**0**
	Ampisilin	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**0**	**0**
	Levofloksasin	**0**	**0**	**10**	**8**	**0**	**0**	**0**	**9**	**0**	**0**	**0**	**0**	**0**
	Siprofloksasin	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**
	Kloramfenikol	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**1**	**3**	**0**	**0**	**0**
	Tiamfenikol	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**2**
Total		**0**	**0**	**18**	**8**	**0**	**0**	**3**	**47**	**34**	**27**	**0**	**0**	**25**

4. DISCUSSION

A total of 84 medical records of patients hospitalized with typhoid fever were used in this study. The data obtained were analyzed based on patient characteristics and rationality.

4.1. Patient Characteristics

Table I shows that more patients were female than male. The high prevalence of typhoid fever is not significantly correlated with gender, according to several studies. Hormonal imbalances are thought to be the cause of the high prevalence of typhoid fever in women, especially anti-inflammatory steroid hormones during pregnancy, which trigger a decrease in the immune system against infections including Salmonella thypi infection [13]. Previous research stated that there was no relationship between gender as a cause of typhoid fever, contact with typhoid fever sufferers, low knowledge about typhoid fever and living in an inadequate environment [14].

Another characteristic in this study is the age grouping based on Permenkes No.25 of 2014, which divides two age groups, first under 18 years of age totaling 45 and second over 18 years of age totaling 39. Hanifah's research (2018) shows that weak immunity and consumption of food contaminated with Salmonella typhi bacteria cause children to be more susceptible to typhoid fever [11].

4.2. Drug Usage

Table II provides an overview of the use of antibiotics given to patients with typhoid fever. The data shows the highest level of antibiotic use is cephalosporin group antibiotics (ceftriaxone) as much as 58.33%, followed by quinolone group (levofloxacin) as much as 11.9%. Ceftriaxone and quinolones have the same effectiveness on Salmonella typhi bacteria, Ceftriaxone shows a higher level of safety compared to quinolones which tend to give side effects, namely bone growth in children [17] and better than amphenicol group antibiotics, which cause side effects of spinal cord aplasia in children [18]. According to various studies, Chloramphenicol is no longer the first-line treatment, replaced by third-generation cephalosporin antibiotics such as cefixime and ceftriaxone [19]. This is because, although S. typhi showed sensitivity to chloramphenicol in vitro, patient reactions were not appropriate. Chloramphenicol in use shows a slower response. As a result, the duration of treatment becomes longer and potentially causes side effects of chloramphenicool, namely bone marrow suppression. In contrast, ceftriaxone showed a faster reduction in fever by the third day of therapy and has been shown to provide a superior clinical response [19].

Quinolones are the second most commonly prescribed class of antibiotics. Since chloramphenicol is ineffective in treating typhoid fever, levofloxacin (fluoroquinolone) is used instead. In the 1980s there was a sharp increase in resistance of S. typhi to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. Due to plasmid exchange between S. typhi bacteria, this strain was dubbed multidrug resistant Salmonella typhi (MDRST). The blaTEM-1, catA, dhfr1b, sul1, sul2, and integron class 1 genes are responsible for S. typhi resistance. In addition, fluoroquinolone antibiotics were used in 1985. These antibiotics inhibit the action of DNA gyrase and DNA topoisomerase type II. These inhibitors effectively treat MDRST by damaging bacterial DNA [20].

4.3. Antibiotic Rationality

In table III describes the categorization of antibiotic rationality while figure I shows the flow of analysis of the rationality of antibiotic use, patient treatment data is analyzed starting from data completeness (category VI), indicated antibiotic use (category V), antibiotic effectiveness and safety and price (categories IVa, IVb and IVc), treatment duration (categories IIIa and IIIb), dose, distance and route of administration (categories IIa, IIb and IIc), when the drug is given (category I), if treatment with antibiotics is appropriate based on categories VI to I then the use of antibiotics is rational (category 0).

a. Analysis of the Rationality of Prescribing in Typhoid Fever Patients at Hospital X Surakarta

Table IV shows that out of 84 prescriptions in typhoid fever patients, 25 prescriptions (29.76%) were included in the rational category, where rational antibiotics consisted of ceftriaxone as much as 22 prescriptions, ciprofloxacin as much as 1 prescription and tiamfenikol as much as 2 prescriptions while the remaining 59 (70.24%) were in the irrational category, where irrational antibiotics were dominated by ceftriaxone as much as 27 prescriptions and levofloxacin as much as 10 prescriptions. Pediatric patients in this study often experience irrationality in the use of ceftriaxone. Doses that are too low, time of use that is too short, or inappropriate use intervals are some of the common causes of this irrationality. In the typhoid fever control guidelines, the recommended use of ceftriaxone in children is 80mg/KgBB/day with a single dose for 5 days [17]. However, the prescription of ceftriaxone antibiotics in this study was not in accordance with the recommendations where the use of ceftriaxone in patients was 2 times a day and only 3 to 4 days. As is known that the nature of antibiotics is divided into 2 categories, namely time dependent and dose dependent.

Ceftriaxone and other beta lactam antibiotics are examples of time dependent antibiotics, meaning that their effectiveness is determined by the percentage of time the antibiotic concentration is above the minimum inhibitory concentration (MIC). Therefore, it is more effective to use longer dosing intervals and duration of administration than doses that increase concentrations beyond the MIC. The irrational use of antibiotics risks causing incomplete treatment of infection and resulting in decreased antibiotic sensitivity [21]. The irrational use of levofloxacin is because fluoroquinolone class antibiotics can interfere with bone growth where this situation will greatly affect the condition of child development/growth, so it is recommended to use third-generation cephalosporin antibiotics that are safer for children, including ceftriaxone and cefixime [17].

b. Analysis of the Rationality of Prescribing in Typhoid Fever Patients Using the Gyssens Diagram

Based on Table V, Antibiotics used to treat typhoid fever are included in category 0 (zero) or rational as many as 25 prescriptions (29.76%) and irrational as many as 59 prescriptions (70.24%) consisting of category IV A as many as 18 prescriptions (21,43%), IV B as many as 8 prescriptions (9.52%), III A as many as 3 prescriptions (3.57%), category III B as many as 47 prescriptions (55.95%), II A as many as 34 prescriptions (40.47%) and II B as many as 27 prescriptions (32.14%). The irrational use of antibiotics is dominated by categories III B, II A and II B. Category III B means that the antibiotics used have a duration that is too short, category II A means that the antibiotics used have an inappropriate dose and category II B means that the antibiotics used have an inappropriate interval or frequency. When an inappropriate dose of antibiotic is given, for a short period of time, or even an inappropriate interval, it can result in a decrease in the bioavailability of the antibiotic in the body, meaning that the drug will not function as long as expected. Administering antibiotics with microorganism resistance can make selecting antibiotics for subsequent therapy difficult [22].

5. CONCLUSION

Findings from an assessment conducted at X Surakarta Hospital from January and December 2021 regarding the rational administration of antibiotics for use by typhoid fever patients, rational antibiotic use (category 0) as many as 25 prescriptions (29.76%) and irrational as many as 59 prescriptions (70,24%) consisting of category IV A as many as 18 prescriptions (21.43%), IV B as many as 8 prescriptions (9.52%), III A as many as 3 prescriptions (3.57%), category III B as many as 47 prescriptions (55.95%), II A as many as 34 prescriptions (40.47%) and II B as many as 27 prescriptions (32.14%).

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