Analysis Cost Effectiveness of Antibiotic Usage in Typhoid Fever Patients in Hospital Royal Prima Medan

Agung Haganta Pinem[1], Rapael Ginting[2], Ali Napiah Nasution[3], Ermi Girsang[4]

[1, 2,3 4]Master Public Health Faculty of Medical, Universitas Prima Indonesia, Medan, North Sumatera, Indonesia

Abstract— *Typhoid fever is an acute infection of the gastrointestinal tract caused by Salmonella Typhi. There are various studies on the cost-effectiveness of antibiotics in patients with typhoid fever, but research is still limited to pediatric patients. Therefore, this study analyzes the cost-effectiveness of antibiotic therapy in patients with Typhoid Fever at the Royal Prima General Hospital, Medan, from November – December 2019. This study was an observational study with a cross-sectional approach. Sampling in this study was carried out using the saturated sampling method on all medical records of inpatients diagnosed with typhoid fever at the Royal Prima General Hospital in November-December 2019. The results showed that in patients with typhoid fever at the Royal General Hospital Prima in November-December 2019 showed the ACER value of ceftriaxone and levofloxacin, respectively, was Rp. 1,297,286.73 and Rp. 1,400,804.65. Meanwhile, ICER analysis shows the ICER value is Rp. 962.215.58. So it can be concluded that therapy with ceftriaxone is more cost-effective than levofloxacin.*

Keywords— *Typhoid fever, ceftriaxone, levofloxacin, cost-effectiveness analysis.*

I. INTRODUCTION

Typhoid fever is an acute infection of the gastrointestinal tract caused by Salmonella Typhi. Another terminology used is typhoid fever, paratyphoid fever, Typhus, and paratyphus abdominals or enteric fever. Pierre Louis first introduced this term from France in 1829. Typhoid or Typhus comes from the Greek typos, which means fever sufferers with impaired consciousness (Widoyono, 2011).

This infectious disease is a public health problem with 22 million cases per year globally and causes 216,000-600,000 deaths. Studies conducted in urban areas in several Asian countries in children aged 5-15 years showed that the incidence with positive blood cultures reached 180-194 per 100,000 children; it was 400-500 per 100,000 population, in South Asia at the age of 5-15 years it was 400-500 per 100,000 population, in Southeast Asia 100-200 per 100,000 population, and in Northeast Asia less than 100 cases per 100,000 population (Ochiai et al., 2007).

Case Fatality Rate (CFR) is estimated at 1-4%, with a ratio ten times higher in older children (4%) than children aged < 4 years (0.4%). Serious complications can occur up to 10%, especially in individuals who suffer from typhoid for more than two weeks and do not receive adequate treatment. In cases that do not get treatment, CFR can increase up to 20% (Nuraini, Garna, and Respati, 2015).

In Indonesia, typhoid must receive serious attention from various parties because this disease is endemic and threatens public health. The problem is increasingly complex with the increase in cases of carrier or relapse and resistance to the drugs used, making it difficult for treatment and prevention efforts (Minister of Health, 2006).

The results of case studies in large hospitals in Indonesia show a tendency to increase the number of typhoid cases from year to year with an average illness of 500/100,000 population and an estimated death of 0.6-5%. Based on the Basic Health

Research (RISKESDAS) results in 2007, the prevalence of typhoid fever in Indonesia reached 1.7%. The highest prevalence distribution was at age 5-14 years (1.9%), age 1-4 years (1.6%), age 15-24 years (1.5 %), and age <1 year (0.8 %).

The incidence of antibiotic resistance in typhoid fever patients has been reported in various studies, including Sur et al. (2018). They said that from 267,536 total blood samples taken from 5 hospitals in India, 44% confirmed S. Typhi and 35% confirmed S. parathyroid infection, of which 82% showed resistance to quinolones and 1% to quinolones. Cephalosporins and 9% were resistant to macrolides, so that the appropriate administration of antibiotics must be done to reduce the incidence of resistance from typhoid fever.

In addition to giving the right thing, price considerations are also a must. Several studies in Indonesia have been conducted to assess the cost-effectiveness of administering antibiotics in typhoid fever patients. One of them is the research undertaken by Beatrix et al. (2018), who reported that Cefixime was more cost-effective than cefotaxime in pediatric patients at Pancaran Kasih General Hospital GMIM Manado ICER of IDR 1,592,700 per day free of fever. Another research is research conducted by Rosyid et al. (2015) at the Sultan Agung Islamic Hospital in Semarang in pediatric patients, Sari's research (2017) on pediatric patients, and the research of Nurmainah et al. (2015) at RST TK II Kartika Husada Kubu Raya (Rosyid and Timur, 2015; Nurmainah, Syabriyantini, and Susanti, 2017; Permana Sari, 2017; Meiryna et al., 2018).

The selection of cost-effective antibiotics is limited to pediatric patients, so it is necessary to conduct research that analyzes the cost-effectiveness of antibiotics in typhoid fever patients, not only in pediatric patients but also in adult patients.

II. LITERATURE REVIEW

2.1. Typhoid Fever

Salmonella is a gram-negative facultative anaerobic bacillus that does not form spores and measures 2-3 times 0.4-0.6 m. Therefore, early identification of Salmonella in clinical microbiology laboratories is based on growth characteristics. Salmonella, like other Enterobacteriaceae, produces acid on glucose fermentation, reduces nitrate, and does not produce cytochrome oxidase. In addition, all salmonellae except S. gallinarum-pullorum can move using peritrichous flagella, and all but S. Typhi have gas (H2S) on sugar fermentation (Pegues and Miller, 2014).

This germ has three antigens that are important for laboratory examination, namely: O antigen (somatic), H antigen (flagellate), and K antigen (membrane). According to the new terminology, Salmonella is distinguished according to its DNA linkage, so that now there are only two species of Salmonella, namely Salmonella bongori and Salmonella enterica. The original name S.typhi became S.enterica serovar Typhi, shortened to S.Typhi (note that the name typhi is no longer italicized and uses a capital T). Salmonella that attacks humans is referred to as strains in subspecies I and S. enterica (Widoyono, 2011).

The clinical manifestations of typhoid fever depend on virulence and body resistance. An experiment in adult humans showed that 107 microbes could cause 50% of volunteers to become sick, although 1000 microbes could also cause disease. The incubation period is 10-20 days, although some say 8-14 days. As for the symptoms of gastroenteritis caused by paratyphoid, the incubation period is faster, namely 1-10 days (Widoyono, 2011).

Figure 1. Mikroskopik *Salmonella Typhi.*

2.2. Clinical Overview

Untreated typhoid fever is often a severe illness that lasts for four weeks or more.
a. First week: increasing fever, headache, malaise, constipation, nonproductive cough, relative bradycardia.
b. Second week: persistent fever, apathy, diarrhea, abdominal distension, "rose spot" (in 30%), splenomegaly (in 75%).
c. Third week: persistent fever, delirium, drowsiness, massive abdominal distension, pea soup diarrhea.
d. Fourth week: gradual improvement in all symptoms (Mandal et al., 2008).

The clinical symptoms of typhoid fever vary from mild clinical symptoms and do not require special treatment to be severe to be treated. This symptom variation is caused by the

Salmonella strain, nutritional status, host immunologic, and length of illness at home (Soedarmo et al., 2015).

All patients with typhoid fever always suffer from fever at the beginning of the disease. In the era of antibiotic use, the appearance of fever in cases of typhoid fever has a particular term, namely, the step ladder temperature chart, which is characterized by fever arising insidiously then rising gradually every day and reaching its highest point at the end of the first week, after which the fever will persist. High and at week four, the fever decreases slowly by lysis; unless there is a focus of infection such as cholecystitis, the fever will last. Many parents of typhoid fever patients report that the fever is higher in the afternoon and evening than in the morning. At the time of high fever in cases of typhoid fever can be accompanied by foggy consciousness or delirium and even decreased consciousness to coma (Soedarmo et al., 2015).

Other systemic symptoms that accompany the onset of fever are headache, malaise, anorexia, nausea, myalgia, abdominal pain, and sore throat. In severe cases, hypovolemic shock may be present. Gastrointestinal symptoms that can be found are diarrhea, constipation, diarrhea; in some patients the tongue looks dirty with white in the middle, the edges and ends are reddish. Hepatomegaly is more common than splenomegaly (Soedarmo et al., 2015). Rose spot, a red maculopapular rash with a size of 1-5 mm often found on the abdomen, thorax, extremities, and back in white people, has never been reported in Indonesian children. This rash appears on days 7-10 and lasts 2-3 days (Soedarmo et al., 2015).

Figures 2. Rose spot

III. METHOD OF RESEARCH

This research is an observational study with a cross-sectional approach where this research is carried out to get a picture of a phenomenon, situation, problem in a population in one point of time (cross-sectional), not in one time period (Kumar, 2011; Widiana, 2011). 2015).

The target population of this study is all medical records of inpatients with a diagnosis of Typhoid Fever in 2019. Meanwhile, the affordable population of this study is all medical records of inpatients with a diagnosis of typhoid fever at the Royal Prima General Hospital in November-December 2019.

Data analysis in this study was carried out using the IBM SPSS 25 program. First, data on sample characteristics, types of antibiotics, direct medical costs, and length of stay were analyzed using descriptive statistics. Then the analysis was continued to assess the effectiveness of direct medical costs of each type of antibiotic by measuring the ICER and ACER values with the following formula.

ACER=(Treatment Cost (IDR))/(Treatment Effectiveness (%))
ICER = (Treatment Cost (A)-Treatment Cost (B))/(Treatment Effectiveness (A)-Treatment Effectiveness (B))

The ACER value is the average of the direct treatment costs of each antibiotic divided by the effectiveness of the therapy, namely the length of stay of the patient. Meanwhile, ICER is used to determine the increase in the cost of treatment by adding or replacing treatment which may increase the cost of treatment, but with the increase in financing for these patients, it will have a better effect on the drug, patients get other benefits or better patient outcomes.

IV. ANALYZE AND RESULT

The characteristics of inpatients with a diagnosis of typhoid fever at the Royal Prima General Hospital in November-December 2019 as respondents assessed in this study were age, gender, choice of supporting examination, severity of typhoid fever, type of antibiotic used, and length of stay.

An overview of the frequency distribution of inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 based on age can be seen in the table below.

TABLE 1. Frequency Distribution of Inpatients with Typhoid Fever at Royal Prima General Hospital in November-December 2019 by Age.

Ages	Frequency	Percentage
≤ 20 Years	11	27.5
21-25 Years	11	27.5
26-30 Years	10	25.0
> 31 Years	8	20.0
Total	**40**	**100.0**

From the table data above, it can be seen that the majority of patients with typhoid fever who were hospitalized at the Royal Prima Public House in November-December 2019 were aged 20 years and 21-25 years, namely 11 people (27.5%), followed by the 26-40 age group. years as many as 10 people (25%), and the least are from the age group > 30 years.

An overview of the frequency distribution of inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 by gender can be seen in the table below.

TABLE 2. Frequency Distribution of Inpatients with Typhoid Fever at Royal Prima General Hospital in November-December 2019 by Type

Gender	Frequency	Percentage
Man	24	60
Woman	16	40
Total	**40**	**100.0**

From the table data above, it can be seen that typhoid fever patients who were hospitalized at the Royal Prima General Hospital in November-December 2019 were primarily men, namely 24 people (60%) and the remaining 16 people (40%) were women.

An overview of the frequency distribution of inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 based on supporting examinations can be seen in the table below.

TABLE 3. Frequency Distribution of Inpatients with Typhoid Fever at Royal Prima General Hospital in November-December 2019 Based on Supporting Examinations

Supporting investigation	Frequency	Percentage
Full blood	40	22.0
Tubex Test	40	22.0
Antibody Rapid Test	40	22.0
Thorax Photo	36	20.0
Blood Sugar Level	13	7.3
Regular Stool	9	5.1

Inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019, the majority came from 25 years, as many as 22 people (55%). The results of this study are in line with the results of research conducted where the majority of typhoid fever patients at Pirngadi Hospital Medan in 2016 the majority came from the age group 17-45 years as many as 47 people (57%).

Inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 were reported to be more common in men, namely as many as 24 people (60%) than women, which were only 16 people (40%). The results of this study are in line with the results of research conducted on pediatric typhoid fever patients at Deli Serdang Hospital in January – December 2019. Rahayu et al. (2021) reported that there were more patients with typhoid fever with male sex, namely 25 people (55.81%), and the remaining 19 people (44.19%) were women.

All inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 underwent routine blood tests, tube tests, and rapid antibody tests. The difference in the results of this study may be due to differences in the location of the analysis and the considerations of medical personnel related to the sensitivity, specificity, positive precision value, and negative precision value of the two types of examinations.

Inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 showed as many as 35 people (90%) had positive results on tube examinations.

This could be due to differences in the location of the current research study with previous research. In this study, the tubes examination was carried out based on doctors, general practitioners, and specialists at the Royal Prima General Hospital, while in the previous study, the tube test was based on reviews by one practicing doctor who was on duty at the laboratory.

The results of this study indicate that in patients with typhoid fever at the Royal Prima General Hospital in November-December 2019 used antibiotics in the form of ceftriaxone or levofloxacin. The use of these two types of antibiotics in inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 was 20 people (50%) on every kind of antibiotic. Agnes et al. reported that the choice of antibiotic in patients with typhoid fever at Bhayangkara Hospital Manado was cefotaxime, as many as 12 people, while the other option was ceftriaxone as many as 16 people. Another study conducted by Rahayu et al. (2021) in pediatric typhoid fever patients at Deli Serdang Hospital in January - December 2019 reported that the choice of antibiotic in typhoid fever patients was ceftriaxone.

The results showed that about 50% of inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 had a length of stay between 6-8 days and tended to stay in hospital for seven days. In pediatric typhoid fever patients at Deli Serdang Hospital in January - December 2019, most patients were treated for between 5-6 days. Namely, 32 people (74.43%) of the total 43 patients were treated.

V. CONCLUSION

The conclusions that can be drawn from the results of this study are as follows:

a. Inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 who received ceftriaxone tended to have a longer length of stay of 8 days than the group of patients who received levofloxacin, which was six days.

b. Inpatients with typhoid fever at the Royal Prima General Hospital in November-December 2019 showed the ACER value of ceftriaxone and levofloxacin, respectively, was Rp. 1,297,286.73 and Rp. 1,400,804.65. Meanwhile, ICER analysis shows the ICER value is Rp. 962.215.58.

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