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Cost-Effectiveness Analysis Of Ceftriaxon And Chloramphenicol In Pediatric Patients With Tyfoid Fever In Hospital X, Jombang Regency

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ABSTRACT

Typhoid fever is a disease caused by infection by the bacterium Salmonella typhi which infects the human digestive tract. Typhoid fever is spread all over the world, it is estimated that the incidence is between 11-21 million cases per year with a death rate reaching 215,000 (Rampengan, 2016). The main treatment for typhoid fever is by administering antibiotics and also bed rest. The first antibiotic administered as therapy for typhoid fever was chloramphenicol. But along with technological developments which affect the drug development as well, many new antibiotics for typhoid fever have been discovered, such as ceftriaxone antibiotic (Rampengan, 2016). This study aims to find out a more cost-effective therapy for the treatment in pediatric patients with typhoid fever in Jombang Public Hospital. This study used a cross-sectional research design with retrospective data collection. The samples in this study were 31 pediatric patients with typhoid fever with 16 patients were administering ceftriaxone injection antibiotic therapy and 15 patients were administering chloramphenicol injection antibiotic therapy. Data were identified using the cost-effectiveness analysis of ACER and ICER calculations with the long-of-stay therapy outcome. The results showed that ceftriaxone had a lower ACER value of IDR 1,687,279.88 with an effectiveness of 100%, compared to the ACER of chloramphenicol which had value of IDR 2,336,405.29 with an effectiveness of 86.67%. From these results it was concluded that ceftriaxone is more cost-effective than chloramphenicol.

Keywords : Ceftriaxone, Chloramphenicol, Cost Effectiveness Analysis, Typhoid Fever

INTRODUCTION

Typhoid fever is an infectious disease spread throughout the world, it is estimated that the incidence happens between 11-21 million cases per year with a death rate reaching 215,000 (Rampengan, 2016). The prevalence of typhoid fever in Indonesia is also quite high, reaching 500 cases per 100,000 population per year (Health Ministry of Indonesia Republic, 2006). Based on WHO, the number of typhoid fever sufferers in Indonesia reaches 81% per 100,000 population with the most age group being suffered is 2-15 years (DEPKES RI, 2013).

The main treatment for typhoid fever is by administering antibiotics and also bed rest. The first antibiotic administered as therapy for typhoid fever was chloramphenicol. However, along with technological developments which influences drug development, many new antibiotics have been discovered for typhoid fever, such as third-generation cephalosporin antibiotics (cefataxime, ceftriaxone, cefixime) (Rampengan, 2016).

Chloramphenicol is the first choice in the treatment of typhoid fever because it is effective, inexpensive and easy to obtain. Chloramphenicol can inhibit bacterial protein synthesis in the peptidyl transferase enzyme which acts as a catalyst to form peptide bonds in the bacterial protein synthesis process. But many cases of resistance, bone marrow suppression and aplastic anemia are found in the use of chloramphenicol (Rampengan, 2016). Apart from chloramphenicol, the third generation of cephalosporins such as ceftriaxone has also become an option. Because ceftriaxone is a potent antibiotic, the therapy takes shorter time, the side effects are milder, the recurrence rate due to resistance is low, it is effective for the short term treatment of typhoid fever because it can damage the germ structure and does not interfere with the human body's cells, has a broad spectrum, and the tissue penetration is quite good, but the price is quite expensive when compared to chloramphenicol (Cita, 2011).

However, another problem arises, such as the increase of quite expensive health costs for the payers such as the government, insurers, and patients. Especially in impatients with typhoid fever who require greater direct medical costs (Rosinta L, 2014). The right solution is to conduct a pharmacoeconomic study in the form of a Cost Effectiveness Analysis (CEA), an analytical method to identify drugs which offer higher effectiveness at a minimum cost so that they can be used in therapy recommendations (Andayani, 2013).

Based on the description above, researchers are interested in conducting research on typhoid fever at Jombang District General Hospital in BPJS (Social Security Agency of Health) therapy class. The hospital is a type B hospital which is referred to by most residents as a means of treatment hospital, and BPJS class 3 therapy was chosen because it has lower premiums than equivalent therapeutic drugs to other BPJS classes.

METHODS

1. Research Instruments

   Instruments are in the form of medical record data and details of BPJS costs of inpatients with typhoid fever at Jombang District Public Hospital which meet the inclusion criteria. Furthermore, it will be recorded on the data collection sheet.

   The inclusion criteria in this study were:

   a. Pediatric patients with typhoid fever without comorbidities.
   b. Pediatric patients with typhoid fever who administer single antibiotic treatment with *ceftriaxone*. or *chloramphenicol*
   c. Pediatric patients with typhoid fever with complete medical record data and medical financing details.
   d. Pediatric patients with typoid fever with Class 3 BPJS.

Exclusion criteria in this study were patients with typhoid fever who died and were forcely discharged; Typhoid fever patients who received replacement of antibiotics during hospitalization

2. Research Design

   This study was a descriptive study with a cross-sectional approach and data collection was carried out retrospectively based on medical records and financial administration of pediatric patients with typhoid fever who were hospitalized at Jombang General Hospital.

3. Research Subject

   The population of this study were pediatric patients with typhoid fever for the year of 2020 period.

4. Data Collection Procedure

   Data collection was carried out by taking the patients' medical records and financial administration data by using data collection sheets which were then presented in the form of *Excel* tables.

5. Data Analysis

   The Average Cost Effectiveness Ratio (ACER) method describes the total cost of a program or alternative divided by the clinical outcome, presented as several rupiahs per specific clinical outcome produced, regardless of the comparison (Andayani, 2013).

$$\text{ACER} = \frac{\bar{x}\ \text{Direct Medical Expenses}}{\text{Drug effectiveness}}$$

Note:

Drug Effectiveness:

Length of stay in Incremental Cost Effectiveness Ratio (ICER) is defined as the ratio of the difference between the costs of the 2 alternatives with the difference in effectiveness between the alternatives and ICER shows the additional cost to produce each one unit of outcome

$$\text{ICER} = \frac{\text{Cost of new drugs} - \text{Cost of comparison}}{\text{New drug effectiveness} - \text{Comparator effectiveness}}$$

Note:

Cost:

The difference in direct medical costs for injection of *ceftriaxone-chloramphenicol* antibiotic therapy

Effectiveness:

The differences in the effectiveness of *ceftriaxone-chloramphenicol* therapy

RESULTS

Based on the research, the result obtained 31 samples that met the inclusion criteria with patients characteristics as shown in table 1.

Table 1. Characteristic Distribution of Typhoid Fever Patients at Jombang Public Hospital for the 2020 Period

Patient Characteristics	Number of Patients	Percentage (n=33; 100%)
Age		
0-5 years	6	19,35%
6-11 years	16	51,62%
12-18 years	9	29,03%
Gender		
Male	17	55%
Female	14	45&
Therapeutic Administration		
Ceftriaxon	16	51%
Chloramphenicol	15	48%

Based on table 1 for the pediatric patient age group, the most patients were in the age group of 6-11 years with a total of 16 patients and with a percentage of 51.62%, while the age group 0-5 years had the least number of patients, which was 6 patients and with a percentage of 19.35%. Based on the number of typhoid fever patients based on gender distribution indicated that male suffered more with total number of 17 male patients with a percentage of 55%, while there were 14 female patients with a percentage of 45%. The number of typhoid fever patients based on the characteristics of the the therapeutic antibiotics administration, there were 16 (51.61%) patients with ceftriaxone antibiotic therapy and 15 (48.39%) patients with chloramphenicol antibiotics, out of a total of 31 patient samples (table 1).

Table 2. Data on the Length of Hospitalization of Patients with Typhoid Fever

Therapeutic Administration	Length of Hospitalization	Number of Patients	%
Ceftriaxon	≤7 days	16	100
	≥7 days	0	0
Total		**16**	**100**
Chloramphe nicol	≤7 days	13	86,67
	≥7 days	2	13,33
Total		**15**	**100**

Based on Table 2, total of 16 (100%) pediatric patients with typhoid fever data with ceftriaxone injection therapy with length of stay ≤7 was obtained, and and total of nil (0%) patients with length of stay ≥7 days out of total of 16 patients. While there were 13(86.67%) pediatric patients with chloramphenicol injection therapy with length of stay ≤7 days and 2 (13.33%) pediatrics patients with length of stay ≥7 days.

Table V.3 Average Length of Days of Fever Dropping Therapy

Therapy Antibiotics	Number of patients	x̄ The length of fever dropping
Ceftriaxon	16	3,06 days
Chloramphenicol	15	4,27 days

Based on Table V.3, the average length of days for dropping fever in patients treated with ceftriaxone injection was 3.06 days and with chloramphenicol injection was 4.27 days.

Table 4. Recapitulation of Direct Medical Costs for Patients with Typhoid Fever at Jombang Public Hospital (Total Cost & x̄ Cost of *Ceftriaxon*)

Cost Types	Total Cost & x̄ Cost of *Ceftriaxon*	
	Total cost	Cost x̄
Cost of Antibiotics	687.843	42.990,19
Cost of supporting drugs & medical devices	6.620.485	413.780,31
Hospitalization costs	13.407.400	837.962,5
Medical Support Costs	6.280.750	392.546,88
Total Medical Cost	**26.996.478**	**1.687.279,88**
Σ Patients	16	

Table 5. Recapitulation of Direct Medical Costs for Patients with Typhoid Fever at Jombang Public Hospital (Total Cost & x̄ *Chloramphenicol* Cost)

Cost Types	Total Cost & x̄ *Chloramphenicol* Cost	
	Total Cost (IDR)	Cost x̄ (IDR)
Cost of Antibiotics	381.710	25.447,33
Cost of supporting drugs & medical devices	8.159.529	543.968,6
Hospitalization costs	14.929.600	995.306,67
Medical Support Costs	7.019.250	467.950
Total Medical Cost	**30.490.089**	**2.032.672,6**
Σ Patients	15	

Based on table V.4 data, it can be seen that the recapitulation of costs spent by patients with ceftriaxone injection therapy on 16 patients was totaling IDR. 26,996,478 and with chloramphenicol injections on 15 patients was totalling IDR. 30,490,089. The average cost for ceftriaxone injection was IDR 1,687,279.88/patient and chloramphenicol injection was IDR 2,032,672.6/patient.

Table 6 Percentage of Effectiveness of Therapy Based on Length of Hospitalization Using *Ceftriaxone* and *Chloramphenicol* in Patients with Typhoid Fever at Jombang Public Hospital in 2020

Therapeutic Administration	Σ Patients	Σ Patients Who Reach the Target	Effectiveness (%)
Ceftriaxon	16	16	100%
Chloramphenicol	15	13	86,67%

Data table V.5 shows the percentage of effectiveness of therapy based on length of stay for the administering of ceftriaxone injection was 100% and for injection of chloramphenicol was 86.67%

Table 7 Calculation of ACER and ICER of *Ceftriaxone* Therapy administration in Patients with Typhoid Fever at Jombang Public Hospital for the 2020 Period Based on Clinical Outcomes of Length of Days of Treatment

Therapeutic Administration of Ceftriaxone			
x̄ Total medical cost	**Probability**	**ACER**	**ICER**
Rp 1.897.279,88	1	1.687.279,88	-

Table 8 Calculation of ACER and ICER of ***Chloramphenicol*** Therapy administration in Patients with Typhoid Fever at Jombang Public Hospital for the 2020 Period Based on Clinical Outcomes of Length of Days of Treatment

Therapeutic Administration of *Chloramphenicol*			
x̄ Total medical cost	**Probability**	**ACER**	**ICER**
Rp 2.032.672,60	0,87	2.336.405.29	2.656.867,07

DISCUSSION

This research was conducted by analyzing the cost-effectiveness of Inpatients with typhoid fever who administered *ceftriaxone* injection drug therapy or *chloramphenicol* injection. The total population of pediatric inpatients with typhoid fever in 2020 at Jombang Public Hospital was 143 patients, with a sample was 31 patients who met the inclusion criteria in the study.

Based on the samples that met the study criteria, the results of characteristics of patients who received *ceftriaxone injection* or *chloramphenicol injection* therapy were obtained. Anyone can experience typhoid fever, but in this study the patients studied were those in the pediatric age group. Pediatric patients then were regrouped into 3 subgroups, namely the toddler group (0-5 years), the children group (6-11 years), and the adolescent group (12-18 years). Data on the age distribution, patients with the most frequent typhoid fever in this study were in the 6-11 year age group, there were 16 patients with a percentage of 51.62. These result is in line with Nurvina's 2013 study, which said that the highest cases of typhoid fever was at the age of 6-11 years because this age is the school period age where children usually like to buy food and drink in the school environment or on the side of the road where the hygiene is not maintained well which plays a major role in the spread of S. .Tiphy. In this case, the lowest cases were found in the ages of 0-5 years, because this age group tends to consume food that comes from homes with a fairly good level of hygiene.

This study reveals that boys have a higher incidence of cases than girls. This is because boys more often consume the less hygienic food, while girls pay more attention to the food hygiene. These results are in line with Nuraini's 2015 study which showed that there were more male patients than female patients because of the habit regarding food hygiene. This habit causes boys to be more susceptible to cases of typhoid fever than girls.

The antibiotics administered in pediatric patients with typhoid fever in this study were *ceftriaxone* injection or *chloramphenicol* injection. Administering antibiotic therapy aims to kill the infecting bacteria. A total of 16 (51%) patients used *ceftriaxone* injection, and 15 (49%) used *chloramphenicol* injection. The choice of first-line antibiotic drugs for typhoid fever in developing countries is based on factors of efficacy, availability, and cost. Based on this, *chloramphenicol* is bacteriostatic and still remains as the main drug for typhoid fever. But many cases of resistance have occurred in administration of *chloramphenicol*, besides that *chloramphenicol* also has some side effects. *Ceftriaxone* is an alternative bacteriocidal antibiotic option because *ceftriaxone* is a potent antibiotic, has shorter duration of therapy, milder side effects, lower recurrence rate due to resistance, is effective for treating short term typhoid fever because it can damage the structure of the germs and does not disrupt human body cells, has a broad spectrum, and the tissue penetration is quite good (Rampengan, 2016).

The effectiveness of the administering antibiotics in this study can be seen from the length of stay parameters. Where the length of treatment is the number of days needed by inpatients while undergoing treatments for typhoid fever until they are discharged by the doctor (cured, improved, not forcely discharged) (Siagian, 2011). The percentage of effectiveness was calculated by comparing the number of patients who reached the target length of stay with the number of patients who administered antibiotic injections. The length of stay according to WHO 2011 is the duration of antibiotics for treating typhoid fever with an average of 5-14 days, depending on the type of antibiotic used. Whereas in the standard of care (clinical pathway) at Jombang Public Hospital for inpatient with typhoid fever is ≥7 days.

Based on the standard length of treatment days, *ceftriaxone antibiotic* injection was shown to be more effective because the *ceftriaxone* injection group all achieved the target duration of the therapy, which was less than or equal to 7 days, with a total of 16 out of 16 patients who administered *ceftriaxone* injections achieved the target with an effectiveness percentage of 100% Whereas in the *chloramphenicol* injection group there were 2 patients who did not reach the target of the therapy or the length of stay was more than 7 days, the number of patients who administered *chloramphenicol* injection that achieved the target of therapy was 13 out of 15, with an effectiveness percentage of 86.67%.

One indicator of recovery from typhoid fever is also seen from the length of days the fever drops. In this study, it was obtained that the average length of days for the fever to drop for patients with *ceftriaxone* injection was 3.06 days and for patients with *chloramphenicol* injection was 4.27 days. *Ceftriaxone* injection therapy is faster to drop fever compared to *chloramphenicol* injection. These result is comparable to Amalia's 2018 study which showed that the average length of days to drop fewer by administering *ceftriaxone* lower than *chloramphenicol*.

There are several cost components in calculating the direct medical costs of inpatient of typhoid fever in pediatric at the Jombang Public Hospital which include: the cost of antibiotic drugs, the cost of supporting drugs, the cost of treatment and the cost of medical support.

The average cost of *ceftriaxone* injection antibiotics therapy for typhoid fever was higher, which was IDR 42,990.19 compared to *chloramphenicol* injections with an average of

IDR 25,447.33, this was because the price of each antibiotic was different. *Ceftriaxone* antibiotic is more expensive, by IDR 6,489, and *chloramphenicol* is cheaper by IDR 2,009.

The average cost of supporting drugs was obtained by using *ceftriaxone* injection of IDR 413,780.31 lower than *chloramphenicol* injection of IDR 543,968.6. The average cost of hospitalization resulted in an average cost of administering *ceftriaxone* injection of IDR 837,962.5 lower than the average cost of administering *chlorampenicol* injection of IDR 995,306.67. The average medical support cost for *ceftriaxone* injection was IDR 392,546.88, lower than the average *chloramphenicol* injection, which was IDR 467,950.

The price difference in the average cost of supporting drugs, the average cost of treatment, and the average cost of medical support, shows that the cost of administering chloramphenicol injection is higher than that of ceftriaxone injection. This was influenced by the length of stay in the *chloramphenicol* injection group which was longer than the *ceftiaxone* injection group, the longer the patient's hospitalization is, the more costs the patients need to pay. This result is in line with Amalia's 2018 study which showed the average cost of *ceftriaxone* antibiotics was higher than the average cost of *chloramphenicol* antibiotics and the average cost of medical support drugs, the average cost of treatment, and the average cost of medical support in the therapy group *ceftriaxone* injection was lower than the *chloramphenicol* injection therapy group.

The component of direct medical costs for pediatric patients with typhoid fever administering *ceftriaxone* injection, the smallest cost for patients administering *ceftriaxone* injection was IDR1,378,305 and the highest cost was IDR 2,06,723. The total of medical costs for all patients administering *ceftriaxone* injection therapy was IDR 26,996,478, with an average direct medical cost per patient was IDR 1,687,279.88. In the group of patients who administered *chloramphenicol* injection therapy, the smallest cost was Rp. 1,566,986 and the lowest cost was Rp. 2,765,918. The total medical costs for all patients administering *chloramphenicol* injection therapy was IDR 30,490,089 with an average direct medical cost was IDR 2,032,672.6. Differences in direct medical costs from patients and treatment groups are due to differences in the length of time of hopitilization because the longer the patient is hospitalized, the higher cost they need to spend (Haluang et al, 2015).

Cost-effectiveness results are expressed in terms of ACER and ICER. The Average Cost Effectiveness Ratio (ACER) was calculated for each alternative therapy and the comparison was obtained from the relative differences between the new therapy and the comparators. The results are interpreted as the average cost per unit effectiveness. Incremental Cost Effectiveness Ratio (ICER) is defined as the ratio of the difference between the costs of the 2 alternatives with the difference in effectiveness between the alternatives and ICER shows the additional cost to produce each one unit of outcome and is calculated (Andayani, 2013).

In this study, the ACER value was lower in the *ceftriaxone injection* group with an ACER value of IDR 1,687,279.88, compared to the ACER result of *chloramphenicol injection* which was IDR 2,336,405.29. From the results of ACER, effectiveness, and total medical costs, it can be seen that *ceftriaxone* injection is more cost-effective due to the lower ACER value, higher effectiveness, and lower total medical costs when it is compared to *chloramphenicol* injection. This result was due to the higher effectiveness of *ceftriaxone* and the lower total medical costs compared to *chloramphenicol* which had lower effectiveness and higher total medical costs. This result is in line with Eva's 2019 study, although the price of *ceftriaxone* is more expensive but its effectiveness is higher, which affects the length of stay of *ceftriaxone* users. The length of hospitalization will greatly affect the costs spent, because the longer the patient is hospitalized, the more direct medical costs they will spend. In the ICER calculation, the ICER result obtained in this study was IDR 2,656,867.07, if the

ICER calculation shows a negative value then the new therapeutic drug is cheaper than the comparator drug.

CONCLUSION

Based on the calculation of the effectiveness, ACER and ICER of the administering of antibiotics in pediatric patients with typhoid fever who were hospitalized at Jombang Public Hospital, it can be concluded that *ceftriaxone* is more cost effective than *chloramphenicol*.

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