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Cost effectiveness analysis of ceftriaxone with cefoperazon in thypoid patients at x mataram hospital

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ABSTRACT:

Typhoid is the third most common cause of hospitalisation in Indonesia, affecting 100,000 people every year. Typhoid fever, with an average case fatality rate of 2.45% at X Mataram Hospital, was among the top 10 most common inpatient illnesses in 2019 and 2020. Antibiotics are effective in reducing typhoid infection, lowering body temperature, shortening the length of hospitalisation, and reducing mortality. The aim study to determine the cost-effectiveness of using ceftriaxone and cefoperazone antibiotics for typhoid patients at X Mataram Hospital. Method a compares two groups of antibiotics and evaluates direct costs and clinical outcomes clinic (length of stay and time free of fever). This research is using ACER's cost-effectiveness analysis. The study included 63 samples with an average direct cost of IDR 3,645,106 for cefoperazon and IDR 3,168,106 for ceftriaxone. According to the ACER analysis results, hospitalisation with ceftriaxone is more cost-effective a lower cost of IDR 704,023 and based on fever-free time, cefoperazone is more cost-effective at IDR 1,024,094. No correlation between antibiotic effectiveness and fever-free time, no correlation between antibiotic effectiveness and length of hospitalisation (p-value >0.05).

KEYWORDS: Typhoid; antibiotic; ACER.

INTRODUCTION

The incidence of typhoid tends to increase each year in Indonesia, based on case studies in hospitals, with an average population morbidity and mortality of about 0.6 to 5% [1]. According to WHO, in 2018, 11-21 million typhoid cases and 128,000-161,000 deaths were reported [2]. In Indonesia, typhoid is the third leading cause of hospitalisation, with 100,000 cases [3]. Typhoid fever is an infectious disease. It is a major public health problem in several countries, particularly in tropical and subtropical countries with low levels of sanitation [4]. Typhoid fever is an acute febrile illness caused by gram-negative Salmonella enterica bacteria, particularly Salmonella typhi and paratyphi A, B and C [5]. According to medical record data from X Mataram Hospital typhoid is one of the top 10 most common inpatient diseases in 2019 and 2020, with an average case fatality rate of 2.45%,

Ceftriaxone is a powerful and effective antibiotic used to treat typhoid fever. Ceftriaxone has a broad spectrum, good tissue penetration, limited bacterial resistance, but high cost [6]. Third-generation cephalosporins, such as ceftriaxone or cefoperazone, are indicated for the treatment of chloramphenicol-resistant typhoid fever. Even in cases of fluoroquinolone resistance, ceftriaxone is considered sensitive and is effective when used as an alternative therapy with azithromycin and cefixime [7]. Treating typhoid fever in hospitalised patients is rather expensive because it involves the payment of the main antibiotic and supportive drugs, with the average length of stay of typhoid patients, which is considered to be effective with the use of antibiotics, ranging from 4-14 days, so is very important that we conduct farmakoekonom research [8].

Data on the procurement of antibiotics at the IFRS (hospital pharmacy installation) Hospital X Mataram, the average demand for antibiotics is increasing by ± 5% every year. The procurement of ceftriaxone injection was recorded at 29,000 vials in 2018 and increased to 31,400 vials in 2019; cefoperazon injection was 30,000 vials in 2018 and increased to 31,800 vials in 2019. Cost analysis in pharmacoeconomics is used to compare the cost-effectiveness of using alternative medicines for specific conditions. The aim is to find out which medicines are more cost-effective. The cost of drug therapy is a cost concept that provides data sources for goods or

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services. For this reason, pharmacoeconomic analysis is carried out, a comprehensive way of evaluating the economic impact of alternative drug therapies using cost effectiveness analysis (CEA), which is an economic evaluation method that can be used for decision making in choosing the best alternative [9].

The cost-effectiveness of antimicrobials in typhoid treatment at X Mataram Hospital should be evaluated by a pharmacoeconomic evaluation of costs, health care interventions and clinical results in terms of length of hospital stay and free of fever, to determine which antibiotic therapy is more cost-effective, and the accuracy of antibiotic selection based on hospital treatment guidelines using medical record data.

MATERIALS AND METHODS

Materials

The materials used in this study were secondary data from the medical records of patients diagnosed with typhoid fever based on ICD-10 with code A01.0, who were hospitalised between June 2019 and December 2020 and received antibiotic therapy with ceftriaxone and cefoperazon, and details of the patient's hospital bill. A case report form was used to collect subjective and objective data, and the Statistical Package for Social Sciences (SPSS) was used. Inclusion criteria patients aged 12 years and older up to 45 years with a diagnosis of typhoid fever and having received antibiotic therapy with ceftriaxone and cefoperazone, with Social health insurance administration (BPJS) or non-BPJS payment status, having routine blood laboratory test results, Salmonella IGM test or Widal test, having complete medical record data according to the Case Report Form and being allowed to go home with the permission from doctor.

Methods

The design of the study is crossectional study using secondary data to compare ceftriaxone and cefoperazone. Direct costs were assessed from the hospital perspective in the finance and audit department, while effectiveness was assessed from the length of hospital stay and fever-free time based on medical record data. Pharmacoeconomic studies were then performed using cost-effectiveness analysis to obtain the ACER (Average Cost-Effectiveness Ratio), which is used to determine which antibiotic is more cost-effective. Data is analyzed using statistics Man Whitney to compare two groups non parametrics.

RESULTS

Characteristic patients

This study has obtained a research ethics permit from the ethics commission of the NTB Provincial Hospital with number 080.1/1/KEP/2022. The characteristics of the sample in this study were seen based on: Gender, age, and payment status. Patients met the inclusion criteria were 63. Data on characteristics were analysed using frequency distribution and proportion. Table 1 showed that there were 24 (38.1%) female patients and 39 (61.9%) male patients, and the most typhoid patients were in the 12-16 years age group with 29 patients. According to Table 1, the most frequently used antibiotics were ceftriaxone (38 patients) and cefoperazone (25 patients).

Table 1. Antibiotic distribution based on characteristics

Characteristics	Ceftriaxone (n = 38)		Cefoperazone (n = 25)	
	n	(%)	n	(%)
Gender				
Male	22	57.9	17	68
Female	16	42.1	8	32
Age (years)				
12 - 16	24	63.2	5	20
17- 25	11	28.9	4	16
26 - 35	0	0	6	24
36 - 45	3	7.9	10	40
Payment				
BPJS	24	63.2	8	32
Non BPJS	14	36.8	17	68

Direct medical cost

From Table 2, mean distribution of direct costs by type of antibiotic the highest direct costs is cefoperazone comparing ceftiaxone were drug costs.

Table 2. Mean distribution of direct costs by type of antibiotic

Direct medical cost	Ceftriaxone (Rp)	Cefoperazone (Rp)	*p value (T-test)*
Drugs	994,629	1,374,290	0.049*
Medical equipment	115,529	103,860	0.249
Visite	166,842	165,600	0.596
Laboratory	522,815	569,699	0.658
Room	639,473	566,000	0.729
Care treatment	728,818	866,327	0.833
Total	3,168,106	3,645,775	0.03*

Notes: *has a significant difference between the drugs used

Outcome clinic

Based on Table 3, the fastest average length of stay was cefoperazon with 4.2 days compared to ceftriaxone with 4.5 days lenght of stay. From the results of SPSS output on effectiveness based on fever-free time, a p-value of 0.156> 0.05 means that there is no difference in the effectiveness of ceftriaxone and cefoperazon with fever-free in typhoid patients.

Table 3. Effectiveness test of fever free time and length of hospitalisation

Variabel		Antibiotics		*p-value (Mann Whitney)*
		Ceftriaxone n = 38	Cefoperazone N=25	
Length of stay	Total days Length of Hospitalisation	171	105	0.156
	Average length of stay	4.5	4.2	
Free-fever time	Total days of fever-free time	103	89	0.293
	Average fever-free time	2.71	3.56	

Table 3 shows that the fastest mean fever-free time was ceftriaxone at 2.71 days, followed by cefoperazon at 3.56 days. In the effectiveness of fever-free time and length of hospitalisation, a p-value of 0.293> 0.05 means that there is no difference in the effectiveness of ceftriaxone and cefoperazon fever-free time with length of hospitalisation in typhoid patients.

Study pharmacoeconomics

In the cost-effectiveness analysis method, the effectiveness of the treatment of length of stay and fever-free time on direct medical costs can be compared. Figure 1. Describes the cost effectiveness of ceftriaxone and cefoperazon antibiotics, Ceftriaxone with almost the same effectiveness at a lower cost goes into Quadrant II, while cefoperazon with almost the same effectiveness at a higher cost goes into Quadrant IV.

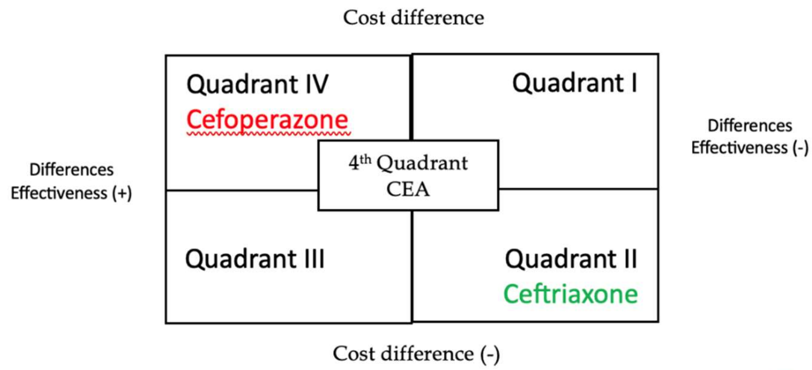

Figure 1: Cost-effectiveness diagram of ceftriaxone and cefoperazone

The results of the ACER calculation for ceftriaxone and cefoperazon are presented in Table 4. The ACER value of cefoperazon is lower than that of ceftriaxone for the fever-free period, which is IDR 1,024,094.. Meanwhile, based on the effectiveness of length of hospital stay, cefriaxon is more cost-effective because it has a lower cost of IDR 704,023. If the lowest ACER value is the more cost-effective option, then the antibiotic with the lowest ACER value is the one that should be the choice of therapy.

Table 4. ACER calculation result

Antibiotics	Cost (IDR)	Mean fever-free time	Mean lenght of stay	ACER fever-free time (IDR)	ACER lenght of stay (IDR)
Ceftriaxone	3,168,106	2.71	4.5	1,169,042	704,023
Cefoperazone	3,645,775	3.56	4.2	1,024,094	868,041

▪ DISCUSSION

The results of this study are in line with previous research conducted at the Bali Provincial government hospital in 2019, where female patients had a percentage of 66.7% higher than male patients at 33.3%. This may be influenced by the immune system of women who are more likely to be affected by complications from typhoid [10]. Based on these results, ceftriaxone therapy is the most dominant therapy when compared with the other types of therapy cefoperazone, because ceftriaxone is empiric antibiotic of choice in X Mataram Hospital. Ceftriaxone is a third-generation cephalosporin with bactericidal activity which inhibits bacterial cell wall synthesis by binding to one or more penicillin-binding proteins. This interferes with the synthesis of peptidoglycan (the major structural component of the bacterial cell wall), which ultimately leads to lysis of the bacteria, as the cell wall autolytic enzymes continue to function while the cell wall synthesis is inhibited [11].

The age distribution is consistent with a previous 2014 study from Sanglah Hospital, Denpasar, which found that 11 to 25 year olds accounted for 55.7% more typhoid cases than any other age groups (12). Typhoid can occur at any age, as the incidence of typhoid is highly dependent on an individual's level of hygiene. Young adolescents (12-16 years) are more likely to consume food and drink which is less sanitary and therefore more likely to be contaminated with Salmonella typhi. This could explain why typhoid is more common in this age group [10].

The results of this study are similar to research conducted at Sanglah General Hospital in 2020, where 60% of antibiotic therapy for typhoid cases was ceftriaxone [12]. Ceftriaxone as empirical therapy for typhoid fever has been shown to reduce the duration of treatment, have low side effects and relapse rates, and reduce fever more rapidly [13].

Direct costs are costs that are directly related to health care, including the cost of drugs and medical supplies, doctor consultation fees, nurse service fees (care treatment), use of hospital facilities, laboratory tests, informal service fees and other health costs [14]. The cost of health care, and in particular the cost of medicines, has risen significantly in recent decades and this trend is likely to increase. The discovery of new drugs, drug resistance and the increasing complexity of disease symptoms are factors that contribute to the increase in medical costs [15]. Previous research by Dr Soedarso Pontianak at RSUD Inpatient Facility found that the highest direct costs for typhoid cases were hospitalisation (41.9%), followed by drugs (22.77%). It also concluded that typhoid treatment costs were still below national reimbursement rates [16]. The variation in the results of this study is highly dependent on hospital charges, therapeutic guidelines, severity of symptoms and disease, and the brand of drugs and medical devices used. Table 2 describes the costs grouped by type of antibiotic, with the highest average direct drug cost being cefoperazone.

Clinical outcome is a very important aspect in evaluating the effectiveness of an intervention. In this study, treatment effectiveness was assessed by length of stay and fever-free time. Length of hospitalisation is an endpoint outcome, while fever-free time is an intermediate outcome. Fever-free time is calculated when the patient is given antibiotics and then a decrease in body temperature occurs, but an increase in body temperature may increase again. Based on the hospital's perspective, the normal temperature range is 35.8°C to 37.5°C. Statistical data that can be used to measure the quality of health care services are usually available for every hospital that provides inpatient services. One indicator of the quality of hospital services is the Average Length of Stay (AVLOS), or the average time a patient needs to stay [4]. Length of stay may be calculated from admission to hospital until leaving hospital, when the patient is discharged by the doctor. The results of measuring the length of stay can be used as a key indicator to evaluate the efficiency of implementing operational and clinical performance improvements, where the average efficient length of stay according to medical service standards is 3-5 days [3].

The results of the SPSS output homogeneity test on the length of hospitalisation, obtained a significance value of 0.550> 0.05 which means the variance of the length of hospitalisation data on each antibiotic is homogeneous. In the homogeneity test on fever-free time, a significance value of 0.065 > 0.05 was obtained, which means that the variance of fever-free time data on each antibiotic is homogeneous. The length of time free from fever is strongly influenced by the supportive therapy given, the severity of symptoms, nutrition and individual immunity factors. For the normality test, the data distribution of the average fever-free time and length of hospitalisation for each type of antibiotic was not normally distributed because the significance value was <0.05.

According to Table 3, the results of this study are rather similar to previous studies, where the ceftriaxone group had an equivalent average day of care of 4.96 [4]. Cephalosporin (ceftriaxone, cefotaxime, cefoperazone) and fluoroquinolone (levofloxacin, ciprofloxacin) antibiotics are currently recommended because of the high level of multidrug resistance in first-line antibiotics such as penicillin, chloramphenicol and trimethoprim-sulfamethoxazole [17].

Fever-free time is one of the parameters of success in typhoid treatment; if the temperature decreases, the treatment is considered successful. Temperature monitoring should be a priority for the management of typhoid fever and should be included as part of the medical history to obtain data on clinical improvement [18]. Based on the results of the fever-free, the results of the study are in line with previous studies where ceftriaxone provides efficacy for faster fever-free time than cefotaxime in children with typhoid [19].

The cost-effectiveness analysis method describes the ratio between cost and effectiveness in natural units. This method is suitable if the alternative therapies being compared have different outcomes. The results of the analysis can help decision-makers to choose treatment therapies that are effective in terms of benefits and costs. The initial stage of cost-effectiveness analysis is to create a cost consequence table. The cost consequence table can help to facilitate further calculations and analyses.

The calculation of the Average Cost-Effectiveness Ratio (ACER) value is used to determine the cost per day that must be incurred by the patient compared to the effectiveness that will be obtained [22]. The treatment therapy that has the lowest ACER value is the treatment therapy that is considered more cost-effective [23].

Based on figure 1, the alternative cost-effectiveness in this study, the position of the Seftriaxone regimen is in window D (dominant), so theoretically there is no need for ICER calculations to make decisions. It is clear that the seftriaxone regimen is the first-line alternative. However, this still needs to be based on the results of patient screening, taking into account the clinical condition of the patient.

CONCLUSION

The effectiveness of the therapy was measured by the length of the hospital stay and the fever-free time.There was no difference in the average length of the hospital stay and the fever-free time for each type of therapy. The highest average direct costs were found for drugs, and the lowest for medical devices. Results of the ACER analysis: Cefoperazone was more cost-effective based on fever-free time (IDR. 1,024,094) and cefriaxone was more cost-effective based on length of stay (IDR. 704,023).

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