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Cost-effectiveness analysis of the use of antibiotics for typhoid fever inpatients in RSUD Bayu Asih Purwakarta

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ABSTRACT: Typhoid fever is an infectious disease caused by *Salmonella typhi*, commonly treated with antibiotics to promote recovery and prevent complications. This study aimed to evaluate both the therapeutic effectiveness (clinical outcomes such as fever resolution and hospital stay duration) and the cost-effectiveness (economic efficiency of antibiotic use) in inpatients with typhoid fever at RSUD Bayu Asih Purwakarta (Bayu Asih District Hospital, Purwakarta) in 2023. A retrospective descriptive design was applied using 75 medical records from January to December 2023. Results showed that levofloxacin had the highest therapeutic effectiveness, reflected by the shortest hospitalization (3.5 days), whereas ceftriaxone was the most cost-effective, with an Average Cost-Effectiveness Ratio (ACER) of Rp. 194,858.78 per treatment. The Incremental Cost-Effectiveness Ratio (ICER) analysis indicated that the additional cost required for levofloxacin compared to ceftriaxone was disproportionate to the clinical benefit gained. In conclusion, while levofloxacin provides faster recovery, ceftriaxone remains the preferred option considering its superior cost-effectiveness. These findings emphasize the need to balance clinical outcomes and economic efficiency when determining antibiotic policies for typhoid management.

KEYWORDS: ACER and ICER Method; antibiotics; cost-effectiveness; therapeutic effectiveness; typhoid fever.

INTRODUCTION

Typhoid fever is a systemic infectious disease caused by *Salmonella typhi*, which continues to pose a significant public health problem in many developing countries, including Indonesia. The World Health Organization (WHO) estimates that more than 9 million typhoid fever cases occur annually worldwide, with approximately 110,000 deaths each year, particularly in regions with inadequate sanitation and limited access to clean water. In Indonesia (Jakarta), a recent study covering 2017-2023 found a cumulative incidence of 533.99 per 100,000 population for hospitalized typhoid fever cases [1]. The disease is transmitted primarily through the consumption of food or water contaminated by *S. typhi*, and without prompt and appropriate treatment, it can lead to serious complications such as intestinal perforation, peritonitis, and septicemia, thereby increasing morbidity and mortality rates [2], [3], [4].

The cornerstone of typhoid fever management is antibiotic therapy aimed at eradicating *S. typhi*, reducing the duration of illness, and preventing complications [5]. Historically, chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole were widely used as first-line antibiotics; however, the emergence of multidrug-resistant (MDR) *S. typhi* strains has substantially reduced their effectiveness [6]. This rising antibiotic resistance has encouraged the use of newer and more potent antibiotics such as third-generation cephalosporins (e.g., ceftriaxone, cefotaxime) and fluoroquinolones (e.g., levofloxacin) [7]. Nevertheless, the increased reliance on these antibiotics has resulted in higher treatment costs and potential resistance development, creating both clinical and economic challenges in hospital-based management of typhoid fever [8]. The use of ceftriaxone and azithromycin remains effective, but reports of decreased susceptibility highlight the need for careful antibiotic stewardship [9].

In resource-limited healthcare systems, the selection of antibiotic therapy should consider not only therapeutic effectiveness but also cost efficiency [10]. Cost-effectiveness analysis (CEA) provides a

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systematic approach to evaluate alternative treatment options by comparing clinical benefits relative to their associated costs [11]. Such evaluation helps policymakers and clinicians optimize resource allocation, particularly in public hospitals where healthcare budgets are constrained. Although several international studies have analyzed the cost-effectiveness of various antibiotics for typhoid fever, local data in Indonesia are still scarce (limited). Differences in patient demographics, hospital formularies, and local drug prices highlight the importance of conducting context-specific pharmacoeconomic evaluations [10], [12]. Recent analyses have also emphasized the importance of incorporating pharmacoeconomic evidence into antibiotic stewardship programs in Asia, particularly amid the rising cost of care and antimicrobial resistance trends observed in 2025 [13]-[15].

Despite the importance of balancing clinical and economic considerations, few studies have comprehensively assessed both therapeutic and cost-effectiveness aspects of antibiotic use for typhoid fever in Indonesian hospitals. RSUD. Bayu Asih Purwakarta, as a referral hospital in West Java, represents a crucial setting for evaluating antibiotic utilization due to its high patient volume and economic diversity. Therefore, this study aims to analyze the therapeutic effectiveness—based on fever resolution and hospitalization duration—and the cost-effectiveness—measured using the Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER)—of antibiotics used in the treatment of inpatients with typhoid fever at RSUD. Bayu Asih Purwakarta. The results are expected to support evidence-based decision-making for optimizing antibiotic selection and improving healthcare cost efficiency in Indonesia [16]-[18].

▪ MATERIALS AND METHODS

Study design

This study employed a retrospective descriptive design with a pharmacoeconomic cost-effectiveness analysis (CEA) approach. The design was chosen to evaluate both the therapeutic effectiveness and economic efficiency of antibiotic therapy in inpatients diagnosed with typhoid fever at Bayu Asih District Hospital, Purwakarta, West Java, Indonesia. This retrospective design enables analysis of real-world clinical data from patient medical records without affecting ongoing treatment. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and CHEERS 2022 (Consolidated Health Economic Evaluation Reporting Standards) guidelines to ensure transparency, reproducibility, and methodological rigor [19],[20].

Population, samples, and place and time of research

The sampling method was taken based on the number of cases of typhoid fever inpatients during 2023 at the Bayu Asih Purwakarta Regional General Hospital (RSUD). The number of samples taken was determined by the total sampling method in the form of medical records of typhoid fever inpatients who received antibiotic therapy at RSUD. Bayu Asih Purwakarta Hospital in the period January - December 2023.

Inclusion criteria were typhoid fever patients who were hospitalized, positive for typhoid fever, receiving antibiotic therapy, and all antibiotics with the trade name/generic name of the antibiotic used. While exclusion criteria were: incomplete medical records, patients who were forcibly discharged, and patients diagnosed with typhoid fever with other complications.

Data collection

The data used in this study were obtained retrospectively from secondary data using medical record data from patients who had laboratory test results indicating positive typhoid fever, used antibiotics, and patients had complete medical record data including: age, gender, fever-free time, length of hospitalization, antibiotics, and antibiotic prices. The medical record data used was from January to December 2023.

Processing and data analysis

After the data is collected, data processing is carried out using the following techniques:

Editing

The process of re-checking the completeness of data and removing data that does not meet the criteria so that it can be processed properly and facilitate the analysis process. Data errors can be corrected and data deficiencies can be supplemented by repeating data collection or by data insertion (interpolation).

Entry data

Data entry is an activity of processing data that has been previously grouped. The recapitulation of the medical record data is then input into a computer/laptop using the Microsoft Excel application to see the percentage that has been observed.

Tabulating

Data tabulation is carried out to detail research data by creating a data table.

Analysis of the effectiveness of therapy can be done by looking at the time free of fever and length of hospitalization. Data analysis is done using observation techniques from the data collection that has been obtained. Calculation of the cost-effectiveness ratio is done based on cost effectiveness [21]. Data processing was carried out using the SPSS version 24 program which uses descriptive statistics to determine the description of the characteristics of the treatment and a retrospective descriptive analysis was carried out. Furthermore, an analysis was carried out on the Microsoft Excel program to determine the cost-effectiveness of antibiotic use based on the ACER and ICER ratios. The ACER value will be known as the basis for research on the cost-effectiveness of therapy from the use of antibiotic therapy for typhoid fever patients at RSUD. Bayu Asih Purwakarta.

The ACER value is obtained by calculating the Average Cost Effectiveness Ratio (ACER) as follows:

$$\text{ACER} = \frac{\text{Direct medical costs (rupiah)}}{\text{Clinical outcome (percentage of effectiveness; \%)}}$$

The ICER value is obtained by calculating the Incremental Cost Effectiveness Ratio (ICER) as follows:

$$\text{ICER} = \frac{\text{Price of Drug A} - \text{Price of Drug B (Rupiah)}}{\text{Effectiveness of Drug A} - \text{Drug B Treatment (\%)}}$$

Information :
Drug A: a drug that has a higher cost than drug B
Drug B: a drug that has a lower cost than drug A

The ACER calculation results show effective results when they show the lowest cost (direct medical costs per day) per effectiveness obtained. A therapy can be said to be cost-effective if it has the same cost but with higher effectiveness or equivalent effectiveness but with lower costs and most importantly the lowest cost but high effectiveness [22]. If the ICER calculation shows negative or smaller results, then an alternative drug is more effective and cheaper, so that this therapeutic option is the best choice [23].

▪ RESULTS

Patient demographics and baseline characteristics

A total of 75 medical records of inpatients diagnosed with typhoid fever at RSUD. Bayu Asih Purwakarta during January–December 2023 were analyzed. The majority of patients were male (58.7%) and aged 6–11 years (17.3%), 17–25 years (17.3%), and 36–45 years (16.0%) (Table 1). Secondary diagnoses included mild dehydration (26.7%), gastritis (18.7%), and anemia (12.0%) (Table 2 and 3).

Table 1. Overview of characteristics of typhoid fever inpatients at RSUD. Bayu Asih Purwakarta in the period of January-December in 2023.

Characteristic	Number of respondents (n)	Percentage (%)
Gender		
Male	44	58.70
Female	31	41.30
Age (Year)		
Toddler (0-5)	9	12.00
Children (6-11)	13	17.30
Early adolescence (12-16)	11	14.70
Late teens (17-25)	13	17.30
Early adulthood (26-35)	10	13.30
Late adulthood (36-45)	12	16.00
Early elderly (46-55)	6	8.00
Late elderly (56-65)	1	1.30
Geezer (>65)	0	0
Total	75	100.00

Table 2. Overview of monotherapy and combination antibiotic use, route of antibiotic drug administration, and gender in inpatients with typhoid fever at RSUD. Bayu Asih Purwakarta Hospital in January-December 2023.

Use of antibiotics	Route of administration of antibiotic drug preparations	Gender (n)		Number of patients (n)	Percentage (%)
		Men	Women		
Monotherapy					
Ceftriaxone 1 g	Intravena	38	24	62	82.7
Cefotaxime 1 g	Intravena	1	2	3	4.0
Levofloxacin 500 mg	Intravena	1	1	2	2.6
Combination					
Ceftriaxone 1 g + Levofloxacin 500 mg	Intravena	2	3	5	6.7
Ceftriaxone 1 g + Ciprofloxacin 200 mg	Intravena	2	1	3	4.0
Total		44	31	75	100%

Table 3. Overview of the use of antibiotic drug types in inpatients with typhoid fever based on patient age at RSUD. Bayu Asih Purwakarta Hospital in the period January - December 2023.

age category (years)	types of antibiotics					number of patients (n)
	Ceftriaxone	Cefotaxime	Levofloxacin	Ceftriaxone + Levofloxacin	Ceftriaxone + Ciprofloxacin	
0 - 5	8	1	0	0	0	9
6 - 11	13	0	0	0	0	13
12 - 16	10	1	0	0	0	11
17 - 25	8	1	2	2	0	13
26 - 35	9	0	0	0	1	10
36 - 45	10	0	0	2	0	12
46-55	3	0	0	1	2	6
56-65	1	0	0	0	0	1
> 65	0	0	0	0	0	0
Total	62	3	2	5	3	75

Clinical outcomes of antibiotic therapy

The average hospitalization duration varied across antibiotics: levofloxacin 3.5 days, ceftriaxone 3.81 days, and cefotaxime 5 days (Table 4). Fever-free time was shortest with ceftriaxone (25.38 hours) and longest with ceftriaxone + ciprofloxacin (60.67 hours). All regimens achieved 100 % recovery with no reported relapse during hospitalization (Table 5).

Table 4. Analysis of the effectiveness of typhoid fever treatment therapy based on the average length of hospitalization and fever-free time at RSUD. Bayu Asih Purwakarta Hospital in the period January-December 2023.

Types of Antibiotics	Number of Patients (n)	Average Length of Hospitalization (Days)	Number of Patients Reaching Target If Length of Hospitalization is 3-5 Days (n)	Percentage of Effectiveness of Length of Hospitalization (%)	Average Fever-Free Time (Hours)	Number of Patients Who Reached the Fever-Free Target During Antibiotic Therapy, namely within the Range of 5-14 Days (n)	Effectiveness Percentage (%)
Monotherapy							
Ceftriaxone 1 g	62	3.81	54	87.10	25.38	62	100
Cefotaxime 1 g	3	5	2	66.67	31.67	3	100
Levofloxacin 500 mg	2	3.5	2	100	29	2	100
Combination							
Ceftriaxone 1 g + Levofloxacin 500 mg	5	5	4	80	33.8	5	100
Ceftriaxone 1 g + Ciprofloxacin 200 mg	3	6.67	2	66.67	60.67	3	100

Table 5. Average cost of treatment for typhoid fever patients at Bayu Asih Purwakarta Regional Hospital in January-December 2023.

Use of types of antibiotics	Total patients (n)	Total medication used (Blister/Strip)	Drug price per unit (Rp)	Total cost (Rp)	Average cost per inpatient (Rp)
Monotherapy					
Ceftriaxone 1 g	62	316	33.300	10.522.800	169.722
Cefotaxime 1 g	3	27	25.000	675.000	225.000
Levofloxacin 500 mg	2	4	98.200	392.800	196.400
Combination					
Ceftriaxone 1 g + Levofloxacin 500 mg	5	25 (C) + 10 (L)	33.300 + 98.200	1.814.500	362.900
Ceftriaxone 1 g + Ciprofloxacin 200 mg	3	10 (C) + 14 (C)	33.300 + 38.125	866.750	288.917
Total	75	406	274.385	12.676.570	1.072.859

*Information: C = Ceftriaxone
L = Levofloxacin

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Antibiotic usage patterns

Antibiotics used were ceftriaxone (82.7%), cefotaxime (4%), levofloxacin (2.6%), ceftriaxone + levofloxacin (6.7%), and ceftriaxone + ciprofloxacin (4%) (Table 6). All were administered intravenously with standard dosing: ceftriaxone 1–2 g/day, cefotaxime 1 g every 8 hours, levofloxacin 500 mg/day. The mean therapy duration was 4–6 days (Table 7).

Table 6. Results of cost effectiveness ratio (ACER) analysis of typhoid fever patient treatment based on length of hospitalization at RSUD. Bayu Asih Purwakarta Hospital in January-December 2023.

Types of antibiotics	Average cost (C; Rp)	Percentage of effectiveness of length of hospitalization (E; %)	ACER Value per inpatient (C/E; Rp)
Monotherapy			
Ceftriaxone 1 g	169.722	87.10	194,858.78
Cefotaxime 1 g	225.000	66.67	337.483.13
Levofloxacin 500 mg	196.400	100	196.400
Combination			
Ceftriaxone 1 g + Levofloxacin 500 mg	362.900	80	453.625
Ceftriaxone 1 g + Ciprofloxacin 200 mg	288.917	66.67	433.353.83

Information:
ACER = Average Cost-Effectiveness Ratio per clinical outcome
C = Average cost
E = Percentage of effectiveness of length of hospitalization

Table 7. Results of cost effectiveness ratio (ACER) analysis of typhoid fever treatment based on fever-free time at RSUD. Bayu Asih Purwakarta Hospital in the Period January-December 2023.

Types of Antibiotics	Average cost (C; Rp)	Fever-free time effectiveness percentage (E; %)	ACER Value per inpatient (C/E; Rp)
Monotherapy			
Ceftriaxone 1 g	169.722	100	169.722
Cefotaxime 1 g	225.000		225.000
Levofloxacin 500 mg	196.400	100	196.400
Combionation			
Ceftriaxone 1 g + Levofloxacin 500 mg	362.900	100	362.900
Ceftriaxone 1 g + Ciprofloxacin 200 mg	288.917	100	288.917

Information:
ACER = Average Cost-Effectiveness Ratio per clinical outcome
C = Average cost
E = Percentage of effectiveness of length of hospitalization

Cost analysis

The average direct medical cost per antibiotic therapy was Rp 169,722 for ceftriaxone, Rp 189,760 for cefotaxime, and Rp 362,900 for ceftriaxone+ levofloxacin (Table 8). The ACER for ceftriaxone (Rp 194,858.78 per treatment) was lower than levofloxacin (Rp 196,400). The ICER comparing levofloxacin and ceftriaxone was Rp 206,806.20, indicating that levofloxacin required a higher incremental cost for marginal improvement in effectiveness (Table 9).

Table 8. Comparative data of cost effectiveness between each treatment therapy for typhoid fever patients based on length of hospitalization at RSUD. Bayu Asih Purwakarta Hospital in the Period of January-December 2023.

Cost effectiveness	Lower cost	Same cost	Higher costs
Lower Effectiveness	A Ceftriaxone had lower costs and percentage effectiveness in terms of length of hospitalization compared to levofloxacin.	B	C - Cefotaxime has a higher cost compared to levofloxacin monotherapy and ceftriaxone monotherapy. - The combination of ceftriaxone + levofloxacin has the highest cost with a low percentage of effectiveness compared to levofloxacin monotherapy and ceftriaxone monotherapy.
Same Effectiveness	D	E	F The combination of ceftriaxone + ciprofloxacin has the same effectiveness but has a higher cost compared to cefotaxime (alone)
Higher Effectiveness	G Ceftriaxone has higher effectiveness than cefotaxime. But ceftriaxone has lower cost than cefotaxime.	H	I Levofloxacin has a higher cost and percentage of effectiveness than ceftriaxone monotherapy.

Table 9. ICER cost effectiveness analysis data of typhoid fever treatment based on length of hospitalization at RSUD. Bayu Asih Purwakarta Hospital in January-December 2023 Period.

Types of Antibiotics	Average Cost of Medicines (Rp)	Effectiveness of Length of Hospitalization (%)	ΔC	ΔE	ICER Value per Hospitalization (ΔC/ΔE; Rp)
Levofloxacin 500 mg	196.400	100	26.678	12.90	206.806.20
Ceftriaxone 1 g	169.722	87.10			

Information:
ICER = The difference in costs that must be added to produce a more cost-effective therapy in comparison to each drug (Incremental Cost-Effective Ratio)
ΔC = Average cost difference of levofloxacin versus ceftriaxone
ΔE = Difference in effectiveness of levofloxacin with ceftriaxone

▪ DISCUSSION

Interpretation of demographics and baseline data

The predominance of male and school-age patients aligns with national surveillance data indicating higher typhoid exposure in younger males due to outdoor activities and hygiene behaviors [3]. Comorbidities such as dehydration and anemia are consistent with systemic infection manifestations reported in Indonesian hospitals [24]. These baseline findings reflect typical clinical profiles of typhoid in endemic regions. The data collection method was carried out retrospectively based on the medical records of patients diagnosed with typhoid fever and receiving antibiotic therapy. The purpose of this study was to determine the effectiveness of therapy and the cost of using antibiotics in typhoid fever patients at RSUD. Bayu Asih Purwakarta. When viewed from the sociodemographic data of patients based on gender, inpatient typhoid fever patients at RSUD. Bayu Asih Purwakarta are more dominated by men than women. These results are in line with research conducted by Yunita and Soyata (2022) which showed that at RS. Islam At-Taqwa in Gumawang Belitang in the period January - December 2021, more male patients suffered from typhoid fever, 43 patients (53.75%) compared to female typhoid fever patients, 37 patients (46.25%) [18]. This can be influenced by men's activities outside the home and unhealthy behavior that is at high risk for typhoid fever. However, both men and women actually have the same risk factors, because factors that influence typhoid fever can be caused by the immune system, environmental conditions and the quality of food consumed by a person, especially in terms of cleanliness [25].

During childhood, children tend to have a lot of physical activity and pay less attention to their diet. This causes children to tend to prefer eating outside the home or buying snacks elsewhere, especially for school-age children whose level of cleanliness may still be lacking where *Salmonella thypimurium* bacteria

thrive in the food so that children are easily infected with typhoid fever. At school age, they tend to pay less attention to their personal hygiene which may be due to their ignorance that buying snacks carelessly can cause typhoid fever [26]. The results of this study are in accordance with research conducted by Oktaviana, et al. (2021) which showed that at the Kediri City Hospital, the age group most affected by typhoid fever was child patients aged 5-12 years with a percentage of 26.31% [27]. This typhoid fever disease is not only suffered by children, but also occurs in many late adolescents (17-25 years). This age group is a productive age where they often do activities outside the home/high mobility so that they are at high risk of being infected with *Salmonella typhi*. In addition, it can occur because late adolescent patients consume food that is not hygienic and poor personal sanitation so that they are easily infected with typhoid fever [28].

Effectiveness of antibiotic therapy

Levofloxacin demonstrated slightly shorter hospitalization and fever-free times, likely due to its high intracellular penetration and rapid bactericidal activity against *Salmonella typhi* [29], [30]. Nevertheless, ceftriaxone remained comparably effective, with differences not clinically significant. This supports WHO and Indonesian Ministry of Health guidelines recommending third-generation cephalosporins as empiric therapy in hospitalized typhoid cases [2]. The absence of therapeutic failure in this study indicates maintained sensitivity to ceftriaxone in the Purwakarta area, similar to reports from Yusransyah et al. (2023) and Restyana et al. (2023) [10], [16].

One of the treatments for typhoid fever is antibiotic therapy. Antibiotics have many types with various antibiotic groups that need to be selected appropriately as typhoid fever therapy. Choosing the right antibiotic is one of the important factors to achieve the target therapy in treating typhoid fever. In the treatment of typhoid fever, the choice of antibiotic depends on the sensitivity pattern of the local *Salmonella typhi* isolate. The emergence of *Salmonella typhi* strains that are resistant to many antibiotics (multidrug-resistant/MDR group) can reduce the choice of antibiotics to be given. Giving antibiotics for typhoid fever will reduce complications and mortality, shorten the course of the disease and improve the clinical picture, such as: a decrease in fever temperature [31].

The antibiotics of choice in treating typhoid fever patients at RSUD. Bayu Asih Purwakarta are ceftriaxone, cefotaxime, levofloxacin, a combination of ceftriaxone with levofloxacin, and a combination of ceftriaxone with ciprofloxacin. The results of the study in Table 2 show that the antibiotic ceftriaxone is the most widely used at RSUD. Bayu Asih Purwakarta with a percentage of 82.7%. In the treatment of typhoid fever in children, ceftriaxone and cefixime are the first line of antibiotic treatment. Despite antimicrobial resistance, ceftriaxone was given to 28 patients with an average duration of treatment of six days in another study [29]. At Hospital X in Yogyakarta, levofloxacin was the single antibiotic most widely used in the treatment of typhoid fever in adult patients, with 36% of cases using levofloxacin [32].

All antibiotics used in typhoid fever patients are through the intravenous route or injection preparation. This is because the intravenous route of administration is faster and more controlled in providing an indication effect in the body compared to oral. In addition, the intravenous route of administration can be given to patients who are uncooperative and unconscious, and can be used in emergencies. However, there are disadvantages that may arise due to this intravenous route of administration, namely the toxicity effect that easily occurs because high levels of drugs immediately reach the blood vessels and drug tissues so that the drug cannot be withdrawn [33]. Ceftriaxone is a third-generation cephalosporin with activity against a variety of aerobic and anaerobic infectors, gram-positive, and gram-negative pathogens. The advantage of ceftriaxone administration is its long elimination half-life, allowing it to be administered once or twice a day. The antimicrobial activity of cephalosporins is by inhibiting the synthesis of microbial cell walls in the third stage of the transpeptidase reaction in the series of cell wall formation reactions [34]. Administration of fluoroquinolone antibiotics to typhoid fever patients is quite effective, because isolates of *Salmonella typhi* bacteria are not resistant to fluoroquinolones. Until now, fluoroquinolones such as levofloxacin are considered optimal for the treatment of typhoid fever in adults. The use of levofloxacin was chosen because levofloxacin is a third-generation fluoroquinolone antibiotic that has a broad spectrum that is effective against gram-negative and gram-positive bacteria, although several studies have shown that fluoroquinolones are not always superior to other first-line antibiotics [35].

Several antibiotic options based on the Regulation of the Minister of Health of the Republic of Indonesia Number 28 of 2021 that are not used at RSUD. Bayu Asih Purwakarta, namely: chloramphenicol, amoxicillin, and cotrimoxazole. Since the late 1980s, the antibiotic chloramphenicol has been the therapeutic choice used in the treatment of typhoid fever. However, reports in the 1980s described a lot of research testing new drugs against *Salmonella typhi*. With this development, other antibiotics such as ampicillin and cotrimoxazole became the treatment of choice for typhoid fever, although their potential efficacy was lower than chloramphenicol. However, not long after the emergence of resistance to these two drugs was also reported worldwide with increased mortality in typhoid fever cases. This resulted in the use of fluoroquinolones such as ciprofloxacin and ceftriaxone which were then used to treat typhoid fever. So, from these several incidents, the antibiotics chloramphenicol, amoxicillin and cotrimoxazole are no longer used in the treatment of typhoid fever [36].

Combination antibiotic therapy is a change in antibiotic therapy from one type of antibiotic to a different type of antibiotic by considering improvements in clinical conditions. This change in antibiotic use is carried out on patients who do not respond to the first antibiotic given so that the use of the antibiotic is stopped and then replaced with another type of antibiotic adjusted to the bacteria causing the patient's disease. At the age of under 17 years, the antibiotics given are only cephalosporins and are given in the form of monotherapy. The choice of monotherapy antibiotics is partly to reduce drug interactions, be more economical for patients, and reduce the side effects of antibiotic use. At the age of under 17 years, the fluoroquinolone group (levofloxacin and ciprofloxacin) is not used because quinolones are not recommended as first-line agents by the FDA if there are other antibiotic options available with a lower potential for causing severe side effects. The use of quinolone drugs in pediatric patients is limited due to the possible side effects on immature cartilage [37], [38]. According to Sullivan, G. J., et al. (2020), giving combination antibiotics has more advantages than giving them alone, namely, it can increase antibiotic activity in specific infections (causing a synergistic effect), slow down the bacterial growth process, and reduce the risk of bacterial resistance [39].

Cost-effective analysis

Ceftriaxone achieved the lowest ACER, making it the most cost-effective regimen. Although levofloxacin produced slightly faster recovery, its higher cost and minimal incremental benefit (ICER>Rp200,000) reduced economic efficiency. These results agree with regional pharmacoeconomic analyses showing ceftriaxone's favorable cost-effectiveness compared to newer agents [22], [40], [41]. The findings imply that in resource-limited hospitals, ceftriaxone offers the best balance between clinical efficacy and financial sustainability.

Patients are said to have achieved the treatment target if the patient's hospitalization period is 3-5 days. In addition, the target or effective if the fever-free time when the patient receives antibiotic therapy is within 5-14 days. The use of antibiotics must be cost-effective and therapeutically effective. The therapeutic effectiveness of antibiotics in this study was seen from the use of antibiotics on fever-free time and length of hospitalization. The effectiveness of antibiotic use was seen from the length of hospitalization of typhoid fever patients, which indicates that the faster the patient goes home from the hospital because he is declared cured, it indicates that the antibiotic is more effective and faster to cure than other antibiotics [34].

Another parameter of the success of typhoid fever treatment is the fever-free time. If the body temperature of a typhoid fever patient decreases, it means that the treatment is successful, while if the temperature remains high, there is a possibility of another infection, complications, or multidrug resistance in *Salmonella thypi* bacteria. Normal body temperature ranges from 36.5-37.2 °C. The degree of body temperature that can be said to be feverish is rectal temperature (anus)≥38.0 °C, oral temperature (mouth)≥37.5 °C, or axillary temperature (armpit)≥37.2 °C [42],[43]. There are several factors that can influence clinical outcomes, such as the length of time it takes for fever symptoms to disappear, which can be influenced by the severity of the disease, the immune status of typhoid fever patients which differs for each individual, the provision of symptomatic therapy used to eliminate the symptoms of typhoid fever that arise, and the provision of supportive therapy used to restore the patient's comfort and optimal health [44]. Symptomatic therapy in reducing fever is by giving antipyretics to typhoid fever patients which aims to reduce the temperature from fever to normal temperature. Antipyretics commonly used in typhoid fever

are paracetamol. Supportive therapy in typhoid fever can be in the form of giving fluids with the aim of correcting electrolyte and fluid imbalances [45].

In the use of antibiotics must be cost-effective in achieving therapeutic treatment. Good antibiotics are those that have maximum effectiveness at low cost. The cost of antibiotics is the cost paid by patients for antibiotic therapy costs while the patient is in the healing process or the patient's condition is improving. The cost of antibiotics is taken from the average cost incurred by typhoid fever patients for one year consisting of the total number of patients, the total number and type of antibiotics used, the total cost of antibiotic therapy, and the average cost of antibiotics per patient/year. Based on research from Yusransyah, et. al. (2023) for the type of antibiotic ceftriaxone is more cost-effective than cefixime in the treatment of typhoid fever, with a lower ACER value. In addition, according to Restyana, A., et al. (2023) ceftriaxone is more cost-effective than chloramphenicol in treating pediatric patients with typhoid fever [10], [16].

Cost Effectiveness Analysis (CEA) is a pharmacoeconomic method for selecting and evaluating the best drug in several therapeutic options with the same goal, so that ACER and ICER calculations are required. This method is carried out to find out which treatment is more cost-effective than other selected treatment alternatives. ACER (Average Cost Effectiveness Ratio) describes the cost of alternative therapies divided by the specific clinical outcomes obtained [17]. A drug is said to be cost-effective if the ACER value of a drug of the two drugs being compared is the lowest of the drugs being compared [46]. After the ACER calculation was carried out, a comparison of the cost effectiveness between typhoid fever patient treatment therapies based on the length of hospitalization was carried out to determine which antibiotic was the main choice based on the high or low cost effectiveness obtained compared to other antibiotics. Based on the comparison of the cost effectiveness between typhoid fever patient treatment therapies based on the length of hospitalization, it was found that the antibiotic cefotaxime was in position C, where this position was included in the dominated column, meaning it did not need to be considered as an alternative in treatment (Table 8). Likewise, the combination of ceftriaxone and levofloxacin antibiotics was in position F, meaning it provided the same effectiveness at a higher cost than cefotaxime. While the antibiotic ceftriaxone in position G was included in the dominant position, where the effectiveness given by ceftriaxone was higher at a low cost compared to cefotaxime, which provided low effectiveness at a high cost. So that the antibiotic ceftriaxone was the chosen position as an alternative treatment. The monotherapy antibiotic ceftriaxone against levofloxacin is in position A, where in that position it requires consideration of cost effectiveness because the therapy of using the antibiotic has high effectiveness with high cost or low effectiveness with low cost by using the ICER value calculation. ICER calculation is also needed for antibiotics in position I, namely the monotherapy antibiotic levofloxacin against ceftriaxone, so the ICER calculation is carried out on the antibiotics ceftriaxone and levofloxacin.

The calculation of the ICER value is by comparing the costs of two treatment therapies with differences in effectiveness between antibiotic therapies used in typhoid fever patients, such as antibiotic therapy in typhoid fever inpatients at RSUD. Bayu Asih Purwakarta (Table 9), then a calculation is carried out to determine a measure of additional costs for each change in one unit of cost effectiveness. After calculating the ICER on the antibiotics ceftriaxone and levofloxacin, the ICER value was obtained, namely Rp. 206,806.20. This can be interpreted that when ceftriaxone antibiotic therapy wants to get an increase in effectiveness equivalent to levofloxacin, an additional cost of Rp. 206,806.20 is needed for each change in one unit of cost effectiveness [40], [47].

Adverse events or treatment limitations

No serious adverse reactions were documented in patient records, though the retrospective nature may underestimate mild events. Lack of microbiological confirmation and reliance on Widal test results are recognized limitations also noted by Kim et al. (2023) [4].

Strengths, limitations, and future directions

The main strengths are the real-world data and inclusion of cost analysis using ACER and ICER metrics. However, retrospective design limits control over confounding factors such as nutritional status and previous antibiotic use. Future prospective, multicenter studies with microbiological sensitivity testing are recommended to confirm and generalize these findings.

CONCLUSION

Levofloxacin therapy demonstrated the shortest hospitalization period and the fastest fever resolution among inpatients with typhoid fever at RSUD. Bayu Asih Purwakarta. However, ceftriaxone achieved comparable therapeutic outcomes with substantially lower treatment costs, resulting in a superior cost-effectiveness profile based on both Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER) analyses. Therefore, ceftriaxone remains the preferred antibiotic in this hospital setting, offering the optimal balance between clinical effectiveness and economic efficiency. From a practical standpoint, these findings support hospital formulary committees and clinicians in adopting cost-effectiveness principles when selecting antibiotics for typhoid fever management, particularly in resource-limited healthcare environments. Future studies are recommended to expand this analysis across multiple hospitals and employ prospective or multicenter study designs to validate and generalize these findings, as well as to explore the impact of antibiotic resistance patterns and patient-level factors on treatment outcomes.

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