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Cost Effectiveness Analysis of Antibiotics in Appendicitis Surgery Patients at Kediri City Hospital

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ABSTRACT

Pre and post-appendicitis guideline therapy include broad-spectrum antibiotics before surgery, appendectomy (laparoscopic or open), and follow-up antibiotics post-surgery in complicated cases of appendicitis. The incidence of appendicitis is estimated to be around 100 cases per 100,000 people per year, with a consistent incidence rate in Western countries and an increasing trend in developing regions. In Indonesia, there are 24.9 cases of acute appendicitis per 10,000 people. The use of antibiotics in appendicitis surgery has been widely used. In most studies, it is known that the most widely used types of prophylactic antibiotics are second or third generation cephalosporins or a combination of metronidazole, either given as a single dose, two or three doses. However, there has been no research on direct comparisons between antibiotics. Most studies have not found significant differences in the incidence of SSI. In Indonesia, health financing uses the National Health Insurance system which requires cost-effective therapy. This study aims to determine the cost-effectiveness between the use of cefoperazone-metronidazole and ceftriaxone. The perspective in this study uses the perspective of health care facilities. Costs are observed in two classes of care and effectiveness is measured through the incidence of Surgical Wound Infection. The results of cefoperazone-metronidazole antibiotic therapy compared to ceftriaxone in insurance patients obtained an ICER value of Rp 94,380.68,-. So the use of cefoperazone-metronidazole antibiotics will incur additional costs of Rp 94,380.68,- per increase in therapy outcomes. While in the analysis of the cost-effectiveness of cefoperazone-metronidazole antibiotic therapy compared to ceftriaxone in non-insured patients, the average cost was lower with higher effectiveness with cefoperazone-metronidazole antibiotic therapy than using therapy with ceftriaxone antibiotics. Thus, cefoperazone-metronidazole antibiotics can be considered as the main choice in non-insured patient therapy. In this study, no relationship was found between demographic factors, type of appendicitis and class of care on the incidence of surgical wound infections.

Keywords : Cost-effective, Appendicitis, Cefoperazone-Metronidazole, Ceftriaxone

INTRODUCTION

Inflammation of the vermiform appendix is known as appendicitis. This disease usually appears suddenly within 1 x 24 hours after it occurs, but can also develop into a more severe condition. Causing acute abdominal pain and requiring immediate surgery to prevent complications that are generally dangerous such as gangrenous, perforation, or even generalized peritonitis (Amalina, 2018).

The incidence of appendicitis is estimated to be approximately 100 cases per 100,000 people per year, with a consistent incidence rate in Western countries and an increasing trend in developing regions. The condition commonly affects people between the ages of 5 and 45 years. The incidence of morbidity and mortality associated with appendicitis varies by demographic factors, with a higher prevalence observed in the pediatric population and a peak in adolescents (Echevarria *et al.*, 2023).

In Indonesia there are 24.9 cases of acute appendicitis per 10,000 people. Men and women can suffer from this appendicitis, with the risk of suffering during their lifetime reaching 7-8%. The highest prevalence occurs at the age of 20-30 years, with perforated appendicitis occurring between 20-30% and increasing to 32-72% of all cases of appendicitis over 60 years (Wijaya, 2020).

Initial management of acute appendicitis usually includes preoperative antibiotics to reduce perioperative infections, antibiotics are given before surgery. Broad spectrum antibiotics such as ceftriaxone + metronidazole or ciprofloxacin + metronidazole are often used. Post-Operative Antibiotic Therapy Patients with uncomplicated

appendicitis may not require further antibiotics after surgery. However, in complicated appendicitis (perforation or abscess), continued antibiotics are recommended for 3-5 days, depending on the clinical response. Frequently used antibiotics include piperacillin-tazobactam or a combination of metronidazole with ceftriaxone or ciprofloxacin (Di Saverio *et al*, 2020).

A Cochrane meta-analysis indicated that cephalosporins and imidazole derivatives are the most frequently used antibiotics for prophylaxis before appendectomy. Various studies have endorsed this combination for preventive treatment. A similar combination of imidazole and cephalosporin antibiotics (metronidazole 500 mg + cefazolin 1 g) is listed in the local guidelines of Salmanya Medical Complex, Bahrain, yet was found not to be consistently followed in the current study (Alanzi A, *et al,* 2023).

Antibiotic therapy is often recommended as a bridge before surgery in patients with suspected appendicitis without an obvious cause, such as evidence of perforation or peritonitis. The majority of patients with uncomplicated acute appendicitis worldwide still undergo appendectomy. In the US, only 6% of patients with uncomplicated appendicitis receive conservative treatment with antibiotics. The majority of patients undergo laparoscopy (Alajaimi *et al*., 2023). The postoperative antibiotic regimen consists of cefuroxime (1500 mg three times daily) or ceftriaxone (2000 mg once daily) in combination with metronidazole (500 mg three times daily), given intravenously (De Wijkerslooth *et al*., 2024).

In most studies, the most commonly used prophylactic antibiotics were second or third generation cephalosporins or a combination of metronidazole, either given as a single dose, two or three doses. Although direct comparisons were not made, most studies found no significant difference in the incidence of SSI after appendectomy between single-dose and multidose prophylactic antibiotics (Putri Nadila Sari, 2024).

Previous research results show that giving antibiotics can handle complaints, is safe and practical, is associated with reduced complications, reduces pain and treatment time, and is more economical, but failure and recurrence make surgery the gold standard of treatment for acute appendicitis. Surgical procedures for appendicitis are at risk of Surgical Wound Infection effects so that prophylactic antibiotics are required (Kurniadi *et al*., 2023). Recent studies have shown that the use of antibiotics can provide significant reductions in hospitalization costs without compromising patient safety. Its potential effects on social costs are still underexplored. (De Wijkerslooth *et al*., 2024).

In many high-income countries, health care expenditure has exceeded 10% of gross domestic product (data available online in the WHO Global Health Observatory repository). This requires a critical review of cost-effectiveness across all areas of medicine to identify opportunities for cost reduction. Given the high annual number of patients treated for acute appendicitis, reducing indirect costs could have a large impact (De Wijkerslooth *et al*., 2024).

In Indonesia, health care facilities must consider financing for national health insurance patients. Health care facilities must make efficiency in the management of acute appendicitis cases in national health insurance patients. In addition to controlling the cost of case management, health care facilities must also consider the length of patient care. The longer a patient receives treatment in the hospital, the greater the costs incurred by the hospital (Tri Widiyantara and Dewi, 2016).

The aim of this study was to evaluate the cost-effectiveness of cefoperazone-metronidazole and ceftriaxone antibiotics in appendicitis surgery. The study is urgent due to the need for effective and economical antibiotic regimens to prevent complications in appendicitis surgery, particularly for patients with national health insurance. Optimizing antibiotic use could help reduce healthcare costs and shorten hospital stays, addressing financial constraints in Indonesia's healthcare system. Additionally, the study provides critical insights into cost-effective management strategies for appendicitis, which is especially relevant given the high incidence of the condition and its burden on healthcare resources.

RESEARCH METHOD

This study observed the cost-effectiveness of cefoperazone-metronidazole antibiotic therapy and ceftriaxone antibiotic therapy in inpatient appendicitis surgery at Hospital A, Kediri City in the period 2023. Data collection was carried out retrospectively using patient medical record documents and cost data. Data were obtained for 12 patients with cefoperazone-metronidazole antibiotic therapy and 20 for patients with ceftriaxone antibiotic therapy.

This study used a cross-sectional research design. Sampling was done by purposive sampling. The inclusion criteria for the sample in this study were the type of appendectomy selected as laparotomy, patients with the most single and combination antibiotic therapy. Patients with

incomplete medical records were the exclusion criteria. Data were analyzed quantitatively. The treatment class was divided into insurance patients and insurance patients. The perspective in this study was the perspective of health service provider facilities.

Tools

Medical record data collection sheets, ACER and ICER calculation sheets and calculation tools in statistical analysis.

Materials

Research materials in the form of secondary data, namely medical record data and direct medical cost data as a whole.

Research process

Preparation (permit application): the first stage is to create and submit a letter of request for research implementation which is submitted to the Hospital supported by the Faculty of Pharmacy Study Program, Strada Indonesia University, Kediri.

Data collection

After receiving confirmation from the hospital, the researcher collects data according to the desired criteria, after which the researcher will carry out documentation for the continuation of the research.

Data processing

The last stage is data processing, where the author will use several stages. First, the researcher will check the data that has been documented. This stage can be called a correction because the researcher makes corrections to the data to take important data and group it based on its variables. The next stage is entering data into the program. The last stage is the checking stage where in this last stage the author will re-check the data to see if it is correct or ready to be processed.

Data analysis or the process of determining and compiling data used in research through field notes or documentation during research, in this study the researcher utilized patient medical record data and used descriptive statistical data analysis which aims to determine the characteristics of each variable to be studied descriptively by involving the collection, presentation and implementation of data related to drug use and surgical wound infections (SWI). Calculation of therapeutic effectiveness:

$$\frac{\text{Total patient who did not have SWI}}{\text{Total patient with current antibiotics}} \text{x } 100\ \%$$

Calculation of cost effectiveness of therapy:

This is done using the Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER) values.

$$\text{ACER} = \frac{\text{average cost of therapy}}{\text{effectivity (\%)}}$$

$$\text{ICER} = \frac{\text{cost of antibiotic A-cost of antibiotic B}}{\text{effectivity ofantibiotic A-effectivity of antibiotic B}}$$

Statistical Analysis

On demographic data, a chi square statistical test was performed. This aims to determine the relationship between demographic factors and the incidence of SWI. On the type of appendicitis, a statistical test was also performed to determine the relationship between the type of appendicitis and the incidence of SWI. Meanwhile, to determine the relationship between the class of care and the incidence of SWI, a chi square statistical test was also performed. The results obtained are concluded to have a relationship if the p value <0.05.

RESULT AND DISCUSSION

The population of appendicitis patients in January-December 2023 at Hospital X, Kediri City was 76 patients. After going through the inclusion-exclusion process, the number of patients obtained was 32 patients who met the inclusion and exclusion criteria. Patient characteristics can be described in this study including age and gender. The results of this study obtained the characteristics of respondents in the form of demographic distribution as follows Table 1.

Based on table 1, data obtained from patients with cefoperazone-metronidazole antibiotics were 75% male patients and 25% female patients. Meanwhile, patients with ceftriaxone antibiotics, men and women have the same percentage. Several authors have reported a tendency for gender with all ages slightly higher among men, with a lifetime incidence of 8.6% for men and 6.7% for women. However, women tend to have higher rates of appendicitis due to various gynecological conditions (Echevarria† et al., 2023). Then a statistical test was carried out between gender and the incidence of SSI. Based on the statistical test, the p result was 0.307 (>0.05). This means that statistically gender has no relationship with the incidence of SWI.

In terms of age, most patients with appendicitis are aged 15-64 years. This is in line with research showing that the frequency distribution of the age of the research subjects with the largest number is 26-45 years, which is 15 people (40.5%) (Caesarridha et al., 2021). This study is also in line with research by Sani N et al in 2020, which found that the age of 26-45 years is the age group with the highest incidence of

appendicitis and decreases at ages> 65 years. This data was then subjected to statistical tests between age and the incidence of SSI. Based on the statistical test, a p value of 0.300 (> 0.05) was obtained. This means that statistically there is no relationship between age and the incidence of SWI.

Table 1. Demographic Distribution of Appendicitis Patients

No.	Demographic Characteristics	Number	%	*p-value*
1	Gender			
2	Man	19	59	0,307
3	Woman	13	41	
4	Age			
5	<15 years	6	19	0,300
6	15-64 years	22	69	
7	>65 years	4	12	

This study obtained a classification pattern of the severity of appendicitis. The highest case was acute appendicitis. This was also found in Anharuddin's study (2023) that the most common type of appendicitis was acute appendicitis (53.1%) followed by chronic appendicitis as many as 11 people (17.2%), and the least perforated appendicitis as many as 19 people (29.7%) (Muhammad Anharuddin, 2023).

Table 2. Appendicitis Severity Pattern

No.	Appendicitis severity	cefoperazone + metronidazole	%	ceftriaxone	%	*p-value*
1	Acute	10	83,33	16	80	0,185
2	Perforation	2	16,66	4	20	

Statistical tests have been conducted on the data on the severity of appendicitis and the incidence of SWI. The statistical test obtained a p value of 0.185 (>0.05). This means that the severity of appendicitis is not related to the incidence of SWI. The pattern of antibiotic therapy in patients with appendicitis in the hospital is shown in Table 3.

The pattern of antibiotic use in hospitals shows that ceftriaxone antibiotics are the most widely used and cefoperazone + metronidazole antibiotics are the second highest after ceftriaxone. In a study conducted by Crisin (2024) from 32 samples there were 2 types of antibiotics used, namely ceftriaxone (78.1%) and a combination of ceftriaxone and metronidazole (21.9%).

This is in line with the study by Billah et al (2024) where the results of their study showed that the prophylactic antibiotic used was ceftriaxone antibiotics in 92 patients (97.87%) (Billah, Tazkia Hasna Ilham Alifiar, 2024). The results of this study support therapeutic guidelines where cefoperazone + metronidazole and cetriaxone are broad spectrum antibiotics. where the guideline therapy states that the therapy guidelines before and after appendicitis include extensive antibiotics before surgery, appendectomy (laparoscopic or open), and continued antibiotics after surgery in cases of complicated appendicitis.

The outcome of appendicitis was obtained from the length of stay (LoS) value and the probability of Surgical Wound Infection (SWI). It was obtained that the average LoS of patients with cefoperazone + metronidazole antibiotic therapy was 4.58 ± 1.56 days. The length of stay of 3.5 and 6 days had the same percentage, namely 25% of patients (Table 4).

Appendicitis outcome with ceftriaxone antibiotic therapy obtained an average LoS of 4.2±1.28 days. As many as 45% of patients with ceftriaxone antibiotic therapy had a length of stay of 3 days (Table 5).

One researcher hypothesized that direct healthcare costs would be lower for patients in the 2-day LoS group but productivity costs would be similar, as efficacy outcomes in both trial arms were comparable (De Wijkerslooth et al., 2024).

In insurance patients with cefoperazone-metronidazole antibiotic therapy, no SWI incidence was found. In ceftriaxone antibiotic therapy, 17.65% of patients experienced SWI. In non-insurance patients with cefoperazone-metronidazole antibiotic therapy, 25% of patients experienced SWI and

inceftriaxone antibiotic therapy, 33.33% of patients experienced SWI (Table 6).

Table 3. Antibiotic Therapy Pattern for Appendicitis Patients

No.	Antibiotics	Number	Precentage
1	Cefoperazone	2	4,5 %
2	Ceftriaxone	17	38,6 %
3	Cefuroxime	1	2,3 %
4	Cefuroxime + Ceftriaxone	1	2,3 %
5	Cefoperazone + Metronidazole	10	22,8 %
6	Ceftriaxone + Metronidazole	2	4,5 %
7	Cefuroxime + Ceftriaxone	2	4,5 %
8	Cefuroxime + Cefoperazone	2	4,5 %
9	Cefoperazone + Metronidazole	3	6,8 %
10	Cefuroxime + Metronidazole, Ceftriaxone	1	2,3 %
11	Ceftriaxone + Metronidazole, Metronidazole	1	2,3 %
12	Metronidazole, Metronidazole + Ceftriaxone	1	2,3 %
13	Cefoperazone + Metronidazole, Ceftriaxone + Metronidazole	1	2,3 %

Table 4. Length of Stay (LoS) of patients with Cefoperazone + metronidazole Antibiotic Therapy

No.	Length of Stay (days)	Number	Precentage (%)
1	2	1	8,3
2	3	3	25
3	4	1	8,3
4	5	3	25
5	6	3	25
6	7	1	8,3
	Average length of stay	4,58±1,56	

Tabel 5. Length of Stay (LoS) of patients with Ceftriaxone Antibiotic Therapy

No.	Length of Stay (days)	Number	Precentage (%)
1	2	0	0
2	3	9	45
3	4	2	10
4	5	6	30
5	6	2	10
6	7	1	5
	Average length of stay	4,2±1,28	

Table 6. Probability of Surgical Wound Infection (SWI)

No.	Parameter	Probability (%) (Insurance Patients)	Probability (%) (Non Insurance Patients)
1	ceftriaxone	17,65	33,33
2	cefoperazone-metronidazole	0	25
3	*p value*	0,286	

Based on previous studies, it was reported that most ILOs occur in men and this may be due to differences in colonies and growth on men's skin, which makes them more at risk (Kurniadi *et al*., 2023). Effectiveness is measured based on the frequency of non-occurrence of SWI. Table 6 shows that in ceftriaxone antibiotics, the probability of non-occurrence of SWI in insurance patients is 82.35% and in non-insurance patients is 66.67. While the effectiveness of combination antibiotic therapy, the probability of non-occurrence of SWI in insurance patients is 100% and in non-insurance patients is 75%.

Based on the statistical test between the incidence of SWI and the treatment class, a p-value of 0.286 (>0.05) was obtained. This means that no relationship was found between the treatment class and the incidence of SWI.

This study also obtained table 7 about patient costs based on insurance and non-insurance treatment classes. Based on treatment class, patients who use cefoperazone + metronidazole antibiotic therapy with insurance class produce lower average costs than patients with non-insurance treatment classes.

Table 7. Patient Costs With Antibiotic Therapy Cefoperazone + Metronidazole

	Insurance	Non insurance
Total cost	Rp94.310.315	Rp63.238.350
Average of total cost	Rp11.788.789	Rp15.809.588

Table 8 shows that the average cost of patients with ceftriaxone antibiotic therapy with insurance class of care was lower than that of non-insured patients on ceftriaxone antibiotics.

Table 8. Patient costs with ceftriaxone Antibiotic Therapy

	Insurance	Non insurance
Total cost	Rp172.090.490	Rp61.267.435
Average of total cost	Rp10.122.970	Rp20.422.478

Several studies have reported that the main factors affecting the cost of hospitalization for appendicitis are length of hospitalization (LoS), whether or not surgery is performed, having comorbidities, age, and severity of appendicitis, level of surgery and payment method (Peng *et al*., 2023).

Table 9. ACER Value Of Patients With Antibiotic Therapy Cefoperazone + Metronidazole

	Average cost	Effectivity	ACER
Insurance	Rp11.788.789	100	Rp 117.887,89
Non Insurance	Rp15.809.588	75	Rp 210.794,51

The ACER value in patients with cefoperazone-metronidazole antibiotic therapy was obtained from the average cost and its effectiveness value. Table 9 shows that the ACER in insurance patients is lower than in non-insured patients.

Table 10. ACER Value of Patients with Ceftriaxone Antibiotic Therapy

	Average cost	Effectivity	ACER
Insurance	Rp10.122.970	82,35	Rp 122.926,17
Non Insurance	Rp20.422.478	66,67	Rp 306.321,85

Table 10 shows that the ACER value for ceftriaxone therapy in insurance patients is lower than ceftriaxone therapy in non-insured patients.

Table 11. Nilai ACER Pasien Asuransi

No.	Antibiotics	Average cost	Effectivity	ACER
1	cefoperazone + metronidazole	Rp11.788.789	100	Rp 117.887,89,-
2	ceftriaxone	Rp10.122.970	82,35	Rp 122.926,17,-

Table 12. Nilai ACER Pasien Non Asuransi

No.	Antibiotics	Average cost	Effectivity	ACER
1	cefoperazone + metronidazole	Rp15.809.588	75	Rp 210.794,51,-
2	ceftriaxone	Rp20.422.478	66,67	Rp 306.321,85,-

Based on the treatment class, the ACER value of a therapy group is declared the most cost-effective if it has the lowest ACER value compared to the ACER value in other therapy groups. The smaller the ACER value of a therapy group, the more cost-effective it is (Agustin, Dewi and Hanifah, 2023). In the ACER table for insurance patients, the ACER value of the antibiotic cefoperazone + metronidazole is lower than the antibiotic ceftriaxone. Likewise, the ACER value of non-insured patients, the use of the antibiotic cefoperazone + metronidazole resulted in a lower ACER than patients using the antibiotic ceftriaxone.

The average cost and effectiveness in insurance patients with cefoperazone-metronidazole antibiotics were higher than in insurance patients with ceftriaxone antibiotics. Based on the cost-effectiveness table, this condition is included in quadrant I. This means that this condition requires consideration of the available resources, by considering the ICER value. Table 13 shows the ICER value of IDR 94,380.68 which was spent in achieving an increase per unit outcome.

Table 13. ICER Value On Insured Patients

No.	Antibiotic	Average cost	Effectivity	ICER
1	Cefoperazone-metronidazole	Rp11.788.789	100	Rp 94.380,68
2	Ceftriaxone	Rp10.122.970	82,35	

Table 14. ICER Value For Non-Insured Patients

No.	Antibiotics	Average cost	Effectivity	ICER
1	Cefoperazone + metronidazole	Rp15.809.588	75	-
2	Ceftriaxone	Rp20.422.478	66,67	

Table 14 shows that non-insured patients with cefoperazone-metronidazole antibiotic therapy have an average cost lower than ceftriaxone antibiotics. While the effectiveness of cefoperazone-metronidazole antibiotics shows a higher value than ceftriaxone antibiotics. Based on the cost-effectiveness table (Indonesia, 2013), if a health intervention offers lower costs that result in higher effectiveness, then this condition falls into area G (dominant).

This means that it is definitely selected so that there is no need to calculate the cost-effectiveness analysis. Thus, cefoperazone-metronidazole antibiotics can be considered as the main choice for therapy for non-insured patients.

CONCLUSION

1. Cost-effectiveness analysis of cefoperazone-metronidazole antibiotic therapy compared to ceftriaxone in insurance patients with cefoperazone-metronidazole antibiotics obtained an ICER value of IDR 94,380.68, meaning that the use of cefoperazone-metronidazole antibiotics will incur additional costs of IDR 94,380.68 per increase in therapeutic outcome.
2. Cost-effectiveness analysis of cefoperazone-metronidazole antibiotic therapy compared to ceftriaxone in non-insured patients obtained lower average costs with higher effectiveness with cefoperazone-metronidazole antibiotic therapy than using ceftriaxone antibiotic therapy. Thus, cefoperazone-metronidazole antibiotics can be considered as the main choice in non-insured patient therapy.

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AUTHOR CONTRIBUTION

All authors have contributed to the conceptualization, design, analysis and interpretation of data in this research and writing of this manuscript.

ETHICS

This research has been approved by the Health Research Ethics Committee of the STRADA Indonesian Institute of Health Sciences as stated in

the Certificate of Passing Research Ethics Eligibility number001.302/EC/KEPK/I/05/2024

CONFLICT OF INTEREST

There is no conflict of interest in this research.

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