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Pharmacoeconomic Analysis of Using Cephalosporin Group as Prophylatic Antibiotic in Appendicitis in Rumah Sakit Umum Daerah Subang
(Analisis Farmakoekonomi Penggunaan Golongan Cephalosporin sebagai Antibiotik Profilaksis pada Penderita Apendisitis di Rumah Sakit Umum Daerah Subang)

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Abstract: The administration of cephalosporin group antibiotics in patients with post-surgical appendicitis is necessary to prevent postoperative wound from infection. This pharmacoeoconomic study was conducted retrospectively in the period of 1 January to 31 December 2015 in RSUD Subang for the purpose of determining the effectiveness of drugs and the cost of antibiotic (ceftriaxone, cefotaxime, and ceftizoxime injection) by Cost Effectiveness Analysis method. The subject consisted of 78 appendicitis patients. Based on Average Cost Effectiveness Ratio (ACER), ceftriaxone is the most effective (IDR 729,124/day). While the result of cost effectiveness plane was with cefotaxime as standard drug, ceftriaxone occupies quadrant IV (otomatically the drug is not selected) and ceftizoxime occupies quadrant I (need to be calculated ICER). It was concluded that the Incremental Cost Effectiveness Ratio (ICER) of ceftizoxime against cefotaxime is IDR 106,347/day, it indicates that ceftizoxime is cost effective than cefotaxime but it needs consideration of resources especially funds owned and should be selected if sufficient resources are available.

Keywords: Cost effectiveness, prophylactic antibiotics, appendicitis.

Abstrak: Pemberian antibiotik golongan cephalosporin pada pasien dengan apendisitis pasca bedah diperlukan untuk mencegah luka pasca operasi dari infeksi. Penelitian farmakokonomi ini dilakukan secara retrospektif pada periode 1 Januari hingga 31 Desember 2015 di RSUD Subang untuk tujuan menentukan efektivitas obat dan biaya antibiotik (ceftriaxone, cefotaxime, dan ceftizoxime injection) dengan metode *Cost Effectiveness Analysis*. Subyek terdiri dari 78 pasien apendisitis. Berdasarkan Rasio Efektivitas Biaya Rata-rata (ACER), ceftriaxone adalah yang paling efektif (IDR 729.124/hari). Sementara hasil dari diagram efektivitas biaya dengan sefotaksim sebagai obat standar, ceftriaxone menempati kuadran IV (secara otomatis obat tersebut tidak dipilih) dan ceftizoxime menempati kuadran I (perlu dihitung ICER). Disimpulkan bahwa Rasio Efektivitas Biaya Tambahan (ICER) ceftizoxime terhadap cefotaxime adalah IDR 106.347/hari, ini menunjukkan bahwa ceftizoxime lebih efektif-biaya daripada sefotaksim tetapi perlu pertimbangan sumber daya terutama dana yang dimiliki dan harus dipilih jika sumber daya yang cukup tersedia.

Kata kunci: *Cost effectiveness, prophylactic antibiotics*, appendicitis.

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INTRODUCTION

THE APPENDICITIS is an acute inflammation of the appendicitis vermiformis. The vermiform appendicitis has a length that varies from 7 to 15 cm[1] and is the most common cause of acute abdominal pain and requires immediate surgical intervention to prevent generally dangerous complications[2].

Acute appendicitis is inflamation that requires surgical intervention, usually has a duration of no more than 48 hours, characterized by lower right quadrant, lower right abdominal pain with local tenderness and tenderness over, overlying muscle pain, and skin hyperesthesia[1].

The mortality rate of a caunted appendix is 22,000 inhabitants, where the male population is more than female. The incidence of appendicitis in Asia in 2004 was 4.8% of the population of the total population[3].

In 2006, appendicitis was ranked fourth most of the disease after dyspepsia, gastritis, and duodenitis with the number of inpatients as many as 28,040 in Indonesia. In addition, in 2008 the incidence of the appendicitis in Indonesia is highest rank among inter-abdominal cases[4].

Surveys in 12 provinces in Indonesia in 2008 showed the number of appendicitis patients treated in the hospital as many as 3,251 cases. This number increased dramatically compared to the previous year, which is 1,236 people. Beginning in 2009, there were 2,159 people in Jakarta who were hospitalized as a result of appendicitis[5]. The Ministry of Health considers the appendix a health priority issue at the local and national levels because it has a major impact on public health[4].

Cases of appendicitis that occurred in RSUD Subang every year has increased. In 2013 there were 45 cases, in 2014 occurred as many as 163 cases, and in 2015 as many as 209 cases[6].

In RSUD Subang various antibiotics are used as prophylactic for appendix surgery. The most commonly used antibiotics are ceftriaxone, cefotaxime and ceftizoxime. From the use of different antibiotics resulting in the cost of drugs issued by patients is varied. From the patient's perspective, the patient becomes burdened by the high cost of drug while from the hospital perspective provides its own advantages over the high cost of drug paid by the patient.

Therefore, it is necessary to conduct a pharmacoeconomic study considering clinical factors (effectiveness) as well as economic factors (cost) deadlock in Indonesia ranks the highest among inter-abdominal cases[4].

In Indonesia the implementation of health insurance policy continues to change for the for better health services which called the National Health Insurance (JKN) managed by BPJS. Implementation of the JKN system by BPJS this makes the researcher interested to conduct pharmacoeconomic studies as part from the perspective of the hospital and the need for this pharmacoeconomic program for BPJS as part of the evaluation by focusing more on what levers the community. Because from the perspective of the hospital there is an increase in the effectiveness of drug costs even at local hospitals at the end will have a significant impact on the efficiency of national health care costs.

In a pharmacoeconomic study one of the analytical methods that will be used by researchers is Cost Effectiveness Analysis (CEA). CEA is a method that compares two or more health interventions that provide different effects.

The purpose of the study is to determine the effectiveness of drugs and the cost of antibiotic (ceftriaxone, cefotaxime, and ceftizoxime injection) in RSUD Subang is pharmacoeconomic.

METHODS

METODE. Drug Criteria. The dosage of ceftriaxone is maximally administered intravenous dose of 1g/ day in a single dose, while the dose of cefotaxime administered 1 g injection of 1 g per 12 h, may be increased to 12 g per day in 3-4 administrations. ceftizoxime dose used intra-vena 0.5-2 grams per day divided into 2-4 doses.

Patient Criteria. The inclusion criteria in this study are: medical record data used is the data of inpatient class III patients with diagnosis appendicitis accompanied by surgery, the medical record data used are readable and identifiable data or unreadable but identifiable data and the medical record data used were patient data using prophylactic antibiotics for the diagnosis of appendicitis.

Exclusion criteria in this research are: medical record data outside the specified period, medical record data of patients with initial diagnosis of appendix, but final diagnosis is not written and unreadable medical record data.

Research Outcome. The outcome to be selected is the Length of Stay (LOS) of appendicitis patients who undergo surgery, due to missing data on laboratory results.

Assessment Perspective. The assessment perspective is important in the pharmacoeconomic review, since the selected perspective determines the cost components that should be included for analysis. Perspectives to be selected by the researchers is the perspective of BPJS for the hospital (claim hospital

to BPJS).

Cost Component. The cost components to be analyzed by researchers as follows: drug cost, room cost, general practitioner general visited cost, specialist doctor visited cost, action cost.

Pharmacoeconomic Analysis. This research used CEA method. On this method is calcualted Average Cost Efectiveness Ratio (ACER), statistical analysis, application of treatment alternative in Cost Effectivenee Plane, and ICER calculation. With ICER it is known that the additional cost for each one unit cost effectiveness change.

Sources of data in this study is patient data information derived from medical records (medical record) and financial records in surgical patients appendectomy who underwent hospitalization in third class RSUD Subang period January - December 2015.

Statistical hypothesis for outcome in this study is as follows: H0: there were no significant differences in medication using antibiotic injection against length of hospitalization; H1: there were significant differences in medication using antibiotic injection against length of hospitalization.

Decision making is determined if sig > 0.05 then H0 is accepted whereas if sig < 0.05 then H0 is rejected. From parametric statistic anova obtained sig < 0.05 then H0 rejected by conclusion that there is significant difference of medication use antibiotic injection to LOS.

Statistical hypothesis for cost in this study is as follows: H0: There were no significant differences in medication using antibiotic injection against cost; H1: There is a significant difference in medication using antibiotic injection against the length of the cost.

RESULT AND DISCUSSION

Based on the available data, patients diagnosed with acute appendicitis accompanied by surgery is 108 patients. From 108 patients, the most patients was BPJS class 3 patients (7.22%), therefore the patients selected for study were BPJS class 3 patients (Table 1).

More adult patients (60.26%) because they were not improper diet and decreased endurance (Table 2). While the result of patient grouping study based on the use of drugs obtained data as follows categories of children use ceftriaxone amounted to 6 frequency with percentage 85.71% from patient number 7 people, while the use of cefotaxime amounted to 1 frequency with percentage 14.29% and ceftizoxim in child category no (zero).

In the adolescent category the use of ceftriaxone amounted to 7 frequency with the percentage of 29.16%, the use of cefotaxime amounted to 13 frequency with the percentage 54.17% and the use of ceftizoxim amounted to 4 with a percentage of 16.67% of the number of patients 24 people. In the adult category, cefotaxim was more widely used (44.68%), because cefotaxim was first used in the hospital (Table 3).

Table 1. Distribution of appendicitis patients based on inclusion and exclusion criteria using ceftriaxone, cefotaxime, and seftizoxime injection period January - December 2015 in RSUD Subang.

Patient criteria	Frequency	Patient total	Percentage
Insurance	8	8	7.41
BPJS kelas 1	10	10	9.26
BPJS kelas 2	12	12	11.11
BPJS kelas 3	78	78	7.22
Total		108	100

Table 2. Distribution of appendicitis patients by age of use injection of Ceftriaxone, Cefotaxime, and Seftizoxim period January - December 2015 in RSUD Subang.

Age Category	Range (years)	Patient total	Percentage
Children	6 – 11	7	8.97
Teenager	12 – 25	24	30.77
Adult	26 – 45	47	60.26
Total		78	100

Table 3. Distribution of appendicitis patients by age and use of drugs using injection ceftriaxone, cefotaxime, and seftizoxim period January - December 2015 in RSUD Subang.

Usia	Ceftriaxone		Cefotaxime		Seftizoxim		Patient Total
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
Children	6	85.71	1	14.29	-	-	7
Teenager	7	29.16	13	54.17	4	16.67	24
Adult	13	27.66	21	44.68	13	27.66	47
Total	26	33.34	35	44.87	17	21.79	78

From the results of the study, the average LOS from the use of antibiotic treatment ceftriaxone injection is for 6 days, while the LOS use of cefotaxime injection antibiotics for 4 days and LOS of the use of antibiotic injection seftizoksim for 3 days. This may bed due to the longest half life of ceftriaxone in plasma (385-480 minutes) than others (60-70 minutes)[8] (Table 4).

Table 4. Average length of stay of inpatient patients using Ceftriaxone injection, Cefotaxime, and Seftizoxime the period of January-December 2015 in RSUD Subang.

	Ceftriaxone	Cefotaxime	Seftizoxime
Length of Stay (Days)	6	4	3

Ceftriaxone, cefotaxime and ceftizoxime are third generation cephalosporin antibiotics. Ceftriaxone and cefotaxime give an indication of Gram-positive and Gram-negative bacteria. Ceftriaxone activity is greater against Gram negative than against Gram positive. Single doses of maximal dose of intravenous administration of 1 g/day dose, while dose of cefotaxime administered injection of 1 g per 12 hours, may be increased to 2 g per day in 3-4 administrations.

Seftizoxim gives a strong indication of Gram positive bacteria, and gives an indication of anaerobic bacteria, the dose used intravena 0.5-2 grams per day divided into 2-4 doses. Compared with ceftriaxone, cefotaxime, and ceftizoxime, the new third-generation cephalosporin class of drugs automatically becomes the best ceftizoxime to supplement the previous generation of drug deficiency, ceftriaxone and cefotaxime.

From the research result, the average cost incurred for appendix patient is obtained by data as following appendix patients who use ceftriaxone medicine cost IDR 41,778, the cost of action is IDR 3,687,300, the cost of doctor visite is IDR 103,307, visite cost of specialist doctor IDR 129,134 and class 3 inpatient costs of IDR 413,230 resulting in an average total cost of IDR 4,374,751.

While appendicitis patients who used Cefotaxime drug cost IDR 77,236, the cost of action IDR 3,687,300, the cost of medical doctor visite Rp 69,943, specialist visite IDR 87,428 and the cost of inpatient class 3 of IDR 279,771 so the average total cost amounting to IDR 4,201,679. And appendicitis patients who use ceftizoxime drug cost amounted to IDR 450,046, the cost of action amounted to IDR 3,687,300, the cost of medical doctor visite IDR 55,000, visite cost of specialist doctor 68,750 and the cost of inpatient class 3 IDR 220,000 so the average total cost of IDR 4,481,096 (Table 5).

Based on Table 6, unit price of the cost component, seftriaxone injection drug is cheaper than cefotaxime injectable drug and ceftizoxime injectable drug. However, the average cost outcome in Table 7, of the most inexpensive therapeutic costs was obtained by cefotaxime injectable drugs when compared with seftriaxone and cftizoxime injectable drugs. This is due to the difference in outcomes obtained from any therapeutic drugs that affect other cost components such as hospitalization and physician visite.

Based on research results obtained from medical record data, all appendicitis patients using ceftriaxone, cefotaxime, and ceftizoxime injectable antibiotics may be discharged if the physician's physical examination results are not a complication such as bleeding, infection of the surgical wound, or a pocketing pus, and no intestinal paralytic (lazy bowel work), and the results of lab tests on the leucocyte value of the patient. The Kolmogorov-Smirnof Normality test was performed on the patient's long hospitalization data and the patient's average cost and the following results were obtained.

From the test results, the data normality was used Kolmogorov-Smirnof test (data count > 50) with the significance level of 0.05, indicating that the significance value of patient data using ceftriaxone, cefotaxime, ceftizoxime for ceftriaxone injection, p=0.117 (p > 0.05), p value of cefotaxime p=0.070 (p

Table 5. Unit cost components.

Drug	Unit cost				
	Drug	Physician visite cost	Specialist physician visite cost	Action cost	Room cost
Ceftriaxone	6.875	17.000	21.250	3.687.300	68.000
Cefotaxime	12.513	17.000	21.250	3.687.300	68.000
Ceftizoxime	99.361	17.000	21.250	3.687.300	68.000

value > 0.05) and p value of ceftizoxime p=0.061 (p > 0,05) indicate that data is normally distributed. As shown in the table below. The Kolmogorov-Smirnof test (data count > 50) with a 0.05 significance level indicates that the significance value of patient data using ceftriaxone, cefotaxime, ceftizoxime, antibiotics for the patient's average cost of p-ceftriaxone p= 0.121 (p > 0.05), p value of cefotaxime p=0.077 (p value > 0.05) and p value of Ceftizoxime p=0.117 (p > 0,05) indicates that the data is normally distributed. The data obtained is normally distributed and therefore ANOVA Parametric Statistic Test is used to test three or more samples.

Decision making is determined if Sig > 0.05 then H0 is accepted whereas if Sig < 0,05 then H0 is rejected. From ANOVA Parametric Statistic Result obtained Sig < 005 then H0 is rejected with the conclusion that there is significant difference of medication using antibiotic injection to cost. From the results of ACER research, it can be seen that the treatment of appendicitis patients using antibiotic injection ceftriaxone effectiveness cost of IDR 729,124, while the use of antibiotics cefotaxime injection cost effectiveness of IDR 1,050,419 and who use antibiotic injection seftizoksim cost effectiveness that is equal to IDR 1,493,698.

The effectiveness of the use of injection antibiotics was determined based on the duration of hospitalization. The total cost of ceftriaxone is higher (IDR 4,374,749) but less effective than cefotaxime, as standard drug (6 days), it causes ceftriazone to occupy in quadrant IV on cost effectiveness plane. While the total cost of ceftizoxime is higher (IDR 4,481,096) but more effective than cefotaxime, as standard drug (3 days), it causes ceftizoxime to occupy in quadrant I on cost effectiveness plane. Because it is in quadrant I, this intervention needs to be calculated ICER. If an intervention is in quadrant I then it can be chosen but requires consideration of resources (Figure 1).

Table 6. Table average cost of appendicitis patients using Ceftriaxone, Cefotaxime, and Ceftizoxime injection January - December 2015 in RSUD Subang.

Cost components / Drugs	Ceftriaxone	Cefotaxime	Ceftizoxime
Drug cost (Rupiah)	41.778	77.236	450.046
Action cost (Rupiah)	3.687.300	3.687.300	3.687.300
Physical visite costs (Rupiah)	103.307	69.943	55.000
Specialist physical visite Cost (Rupiah)	129.134	87.428	68.750
Room cost class 3 (Rupiah)	413.230	279.771	220.000
Average total cost (Rupiah)	4.374.751	4.201.678	4.481.096

Table 7. Average cost effectiveness ratio with appendicitis using Ceftriaxone, Cefotaxime and Seftizoxime in January - December 2015 in RSUD Subang.

Injection	Average total costs (Rp)	Length of stay (days)	ACER (Rp/day)
Ceftriaxone	4,374,749	6	729,124
Cefotaxime	4,201,678	4	1,050,419
Ceftizoxime	4,481,096	3	1,493,698

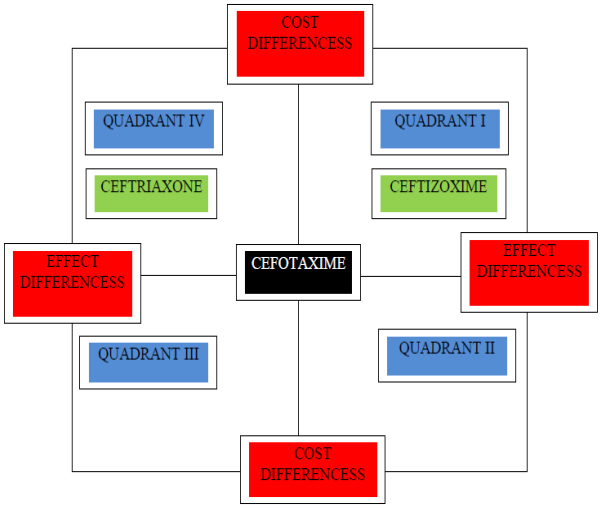

Figure 1. Cost effectiveness plane.

ICER = (Cost of Ceftizoxime - Cost of Cefotaxime)/ (Effectiveness of Seftizoxime-Effectiveness of Cefotaxime) = (4,481,096 – 4,374,749)/(3 - 4)
= IDR 106,347/day

Thus the cost to be added to switch from cefotaxime to ceftizoxime antibiotics is IDR 106,347/day. This cost is lower than the WHO Willingness to Pay ($ 12,000 or IDR 165,624,000, assuming the rupiah exchange rate against the dollar is IDR 13,802).

CONCLUSION

Ceftriaxone is less effective than cefotaxime. Ceftizoxime is more effective than cefotaxime but need to increase cost of IDR 106,347/day. It requires consideration of resources and should be selected if sufficient resources are available.

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