Original Article

Clinical pharmacist participation improved the cost-effectiveness of antibiotic treatment in a pediatric intensive care unit

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ABSTRACT

Based on a survey conducted by the Antibiotics Control Program of the Department of Pediatrics, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, the use of antibiotics and evidence of antibiotic resistance in the Pediatric Intensive Care Unit (PICU) was found to be worse than average. This study aimed to evaluate the cost-effectiveness of the participation of clinical pharmacists in the PICU. A non-parallel experimental study cost-effectiveness. The study population consisted of two groups: those who received a recommendation from a clinical pharmacist (R group, n=51) and those who did not (NR group, n=42). The direct medical costs measured were the cost of the anti-bacterial agent, hospital administration, physician visits, and microbial laboratory tests. ACER and ICER were calculated using the proportion of patients with length of stay (LOS) of < = 3 days. Within the three months of the study, 120 recommendations were made. There were no significant differences in characteristics between the two groups. The effectivity of the R group (35.83%) was significantly higher than the NR group (30.26%) ($p < 0.05$), and the cost was also significantly lower in the R group ($p < 0.05$). It was also cost-saving, as shown by the ICER of the R group relative to the NR group minus IDR 395,095/effectivity-gained. Sensitivity analysis confirmed the robustness of these results. The participation of clinical pharmacists in prescription review and giving recommendations on antibiotic therapy can reduce costs and LOS of pediatric patients in PICU.

Keywords: Anti-bacterial agents, Clinical pharmacist, Cost-effectiveness analysis, Pediatric, Pharmacoeconomics

Introduction

Since 2002, the use of clinical pharmacy services has grown worldwide; clinical pharmacists now play a significant role in rationalizing drug therapy in hospitals. Collaboration among health practitioners, including medical doctors, pharmacists, and nurses, can optimize the efficiency, effectiveness, and safety of drug therapies. Clinical pharmacist services include accompanying doctors on their rounds, medication reconciliation, initial drug assessment, minimizing drug side effects, preventing medication errors, managing drug-related problems, and improving drug administration. These services are achieved through providing information on drugs to patients, as well as through ensuring the appropriateness of treatments [1, 2]. Some studies have shown that pharmaceutical care from clinical pharmacists not only improves patient outcomes but can also reduce costs [3-5].

One of the clinical pharmacy services provided in hospitals is the qualitative and quantitative evaluation of drug use [1]. Currently, one of the biggest drug problems in the world is antibiotic resistance [6]. Based on a survey conducted from June to November 2011 by the Antibiotics Control Program of the Department of Pediatrics, Dr. Cipto Mangunkusumo Hospital (RSCM), Jakarta, the national referral center for government hospitals in Indonesia, use of antibiotics and evidence of antibiotic resistance in the Pediatric Intensive Care Unit (PICU) was found to be worse than average. Evaluation is therefore necessary to

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Sauriasari R, Rizkyani NA, Tambunan T. Clinical pharmacist participation improved the cost- effectiveness of antibiotic treatment in a pediatric intensive care unit. J Adv Pharm Educ Res. 2023;13(4):93-8. https://doi.org/10.51847/8k1tg176ra

control the use of antibiotics, including the types used and their cost.

There are still very few studies on the role of clinical pharmacists in reducing medical costs and improving patient outcomes in Indonesia, and the paradigm that the pharmacist position does not deliver any economic benefits is still prevalent. However, many studies abroad mention the impact of clinical pharmacist participation in reducing costs and improving patient outcomes, including in PICUs [3, 4, 7-12]. A pharmacoeconomic study in Indonesia is needed to determine the effect of clinical pharmacists participation in the interdisciplinary team on antibiotic therapy in PICUs, beginning with the Dr. Cipto Mangunkusumo Hospital as a national referral hospital with a large number of PICU patients.

Materials and Methods

Study design

The study was conducted using a non-parallel experimental study design with total sampling. The study site is the 10-bed PICU of Dr. Cipto Mangunkusumo Hospital (RSCM), a national referral hospital in Indonesia. The study subjects were divided into a control group and a study group. The control group contained patients who did not receive a recommendation from a clinical pharmacist (NR group) on their antibiotic prescriptions, while the study group was the group of patients who did receive a recommendation from a clinical pharmacist (R group). In the R group, the clinical pharmacist gave a recommendation to health practitioners (clinician and nurse) based on both clinical data about antibiotic therapy held in medical records and the real clinical condition of patients.

Sample and data collection

The intervention phase was carried out between August to October 2014. Pediatric patients who were hospitalized at the PICU of Dr. Cipto Mangunkusumo Hospital (RSCM) from August to October 2014 were subjected to clinical pharmacist evaluation for their antibiotic prescriptions and were observed prospectively (R group). Those hospitalized from May to July 2014 were treated without involving clinical pharmacist for antibiotic prescription evaluation; these patients provided baseline information, and their data were extracted retrospectively from medical records (NR group). The inclusion criteria were pediatric patients (aged 1–18 years) who were hospitalized in the PICU of RSCM from May to October 2014, received antibiotics and were diagnosed with an infection as a result of clinical examination by a physician. All of the study subjects were covered by Indonesian national health insurance (JKN). Exclusion criteria were incomplete medical records for antibiotics, patients who died or were forced to go home, and those patients whose diagnosis was unclear.

Data analysis

The characteristics of the control (NR) and study (R) group patients were analyzed according to sex, age, body mass index (BMI), severity, and type of underlying disease. Grouping of the patients based on the type of underlying disease was performed by physician diagnosis. The characteristics of the patients in the NR and R groups were compared using statistical tests. Logistic regression analysis was performed with patients' LOS as the binary outcome. Subsequent statistical analysis to compare clinical variables of patients from the control and the study group was performed using chi-square testing (nominal and ordinal scale) for gender, type of comorbidities, and BMI category. Unpaired t-testing was used to determine the age and BMI of the patients on numerical scales. The Mann–Whitney test was performed for age and number of comorbidities.

Cost-effectiveness analysis

Effectiveness

In this study, the effectivity (outcome) was measured as the proportion of patients with LOS of ≤ 3 days.

Costs

Total direct medical costs were derived from the sum of all antibiotics costs, maintenance costs, and doctor-visit costs in the NR and R groups. For the R group, there was an additional cost for the laboratory testing of microbial cultures.

Data analysis

The study results were analyzed using the cost-effectiveness analysis (CEA) method. The average cost-to-effectiveness ratio (ACER) was calculated based on the total cost incurred for antibiotic use, represented by the formula ACER = total cost/effectivity. Sensitivity analysis in this study was conducted to test the robustness of the CEA results. Drug costs were increased by 5%, 10%, and 15% and the new cost and ACER were recalculated. All calculations and results used Microsoft Excel 2007 (Microsoft Corp., Redmond. WA) and SPSS® statistical software, version 22 (IBM®, SPSS Inc. Chicago. IL).

Results and Discussion

Selection of study subjects

This study was approved by the Ethics Committee, Faculty of Medicine, Universitas Indonesia–Dr. Cipto Mangunkusumo Hospital (No. 508/H2.F1/ETIK/2014). The Ethics Committee waived the need for consent since there were no direct interventions to the patients but to the clinician and nurse as part of the implementation of the standard of pharmaceutical care practice that is supposed to be implemented according to Ministry of Health, Republic of Indonesia regulation (MoH Regulation No. 72/2016) and has not been implemented before in the study site. The researcher in this study was a clinical pharmacist staff member of PICU, Cipto Mangunkusumo Hospital, who directly conducted the study interventions. However, all of the patients were verbally informed about the participation of the clinical pharmacist in their treatment, and they accepted it.

There were 220 patients in the PICU of the RSCM from May to October 2014. A total of 123 patients were excluded due to several reasons, consisting of 22 patients who died, 13 patients

who were forced to go home, 78 patients under the age of one year (neonates), and 10 patients with incomplete data. During the collection and retrieval of data from August to October 2014, a further two patients could not be analyzed further because their diagnosis was still under medical team discussion and unclear. Thus, 93 patients remained as eligible study subjects, consisting of 51 patients in the R group and 42 patients in the NR group and all the patients in the was provided informed consent prior to data collection. We found no significant differences between the two groups in terms of basic characteristics ($p > 0.05$) **(Table 1)**.

Table 1. Characteristics of the patients

Characteristic	NR (n = 42)	R (n = 51)	p-value
Sex			0.840
Male	23 (55%)	29 (57%)	
Female	19 (45%)	22 (43%)	
Age (years)	7.74 ± 5.52	8.17 ± 5.34	0.536
BMI (kg/m^2)	16.74 ± 1.93	16.90 ± 1.88	0.781
Severity of infection			0.675
Mild	26 (61.9%)	29 (69.04%)	
Severe	16 (38.1%)	22 (30.96%)	

NR: group of patients who did not receive a recommendation from the clinical pharmacist; R: group of patients who received a recommendation from the clinical pharmacist

Number of recommendations and response rate

Table 2 gives an overview of the patient's clinical conditions and the types of recommendations provided by the clinical pharmacist. Within the three months of the study, 120 recommendations were made to 51 patients, composed of 107 laboratory evaluation recommendations, six antibiotics recommendations, and seven dosage recommendations. The response rate, as evidenced by the responses of physicians and nurses, was 100%, indicating that all the recommendations given were accepted.

Table 2. Type of recommendation given by the clinical pharmacist

Type of recommendation	Patient's condition before given recommendations	Recommendations provided	Clinical impact
Laboratory evaluation (n = 107)	Patients who had antibiotics for a long period had not been examined for fungal cultures, and patients with high procalcitonin values had not had swabs from other sources to determine the cause of infection (n = 37).	Check for cultures of other sources of infection when the PCT is still high, not only bacterial cultures but also fungal cultures. The fastest culture results were taken from the results of Gram staining. After 5 days, the culture and sensitivity of new antibiotics can be seen.	Increased laboratory cost.
	Patients received antibiotics but were not cultured (n = 20).		Decrease in the number of antibiotics given per patient.
	Gram staining was not performed to determine the type of bacteria (n = 50).		Decreased use of broad-spectrum antibiotics.
	The antibiotics given did not fit the culture results (n = 1).		
Antibiotic recommendation (n= 6)	Antibiotics were no longer compatible with the latest culture results (n = 2).	Selection of suitable antibiotics according to culture results, at least in terms of Gram staining. Drug screening for availability, potency, and price. Determination of escalation/de-escalation based on patients' clinical condition.	Decrease in the cost and number of antibiotics.
	Some antibiotics did not have data on efficacy and safety for children, such as tigecycline (n = 3).		
Dosage recommendation (n = 7)	Not yet given the correct number of doses for sepsis (two times the normal dose) (n = 2).	The dosage of meropenem was increased from 500 mg to 1g.	Increased cost of antibiotics. Decrease in the cost of reconstitution services.
	Incorrect frequency of antibiotics (n = 5).	Cefotaxime replacement frequency every 12 hours.	Increased cost of antibiotics.

Cost-effectiveness analysis

The total direct medical cost in the R group (IDR 349,302,060) was lower than in the NR group (IDR 427,805,134) ($p < 0.05$) **(Table 3)**. Average LOS per patient was lower in the R group (4.5 days) than in the NR group (6.4 days) ($p < 0.05$). Effectivity was better in the R group (47%) than in the NR group (33%) ($p< 0.05$). In the NR group, ACER was IDR 12,963,792 per effectivity, whereas in the R group, ACER was IDR 7,431,959 per effectivity. Thus, it was also cost-saving or cost-effective (ICER of the R group relative to the NR group was minus IDR 395,095/effectivity-gained). Sensitivity analysis showed the robustness of the results **(Table 4)**, indicating that even when acquisition costs were increased by 15%, overall outcomes did not change.

Table 3. Cost-effectiveness analysis between NR and R groups

Description	NR (n = 42)	R (n = 51)	p-value
Costs			
Antibiotic cost	IDR 92,805,134	IDR 34,877,060	

Hospital administration cost	IDR 281,400,000	IDR 239,400,000	
Physician visit cost	IDR 53,600,000	IDR 45,600,000	
Bacterial culture test cost	-	IDR 29,425,000	
Total costs	IDR 427,805,134	IDR 349,302,060	
Total costs per patient **(B)**	IDR 10,185,837	IDR 6,849,060	$p < 0.05$
Effectivity			
Total LOS (days)	268	228	
Average LOS per patient (days)	6.4 (58.72%)	4.5 (41.28%)	
Proportion of patients with LOS < = 3 days (%) **(E)**	33%	47%	$p < 0.05$
ACER (B/E) (IDR/% effectivity)			
ICER for the R relative to NR (Cost R- Cost NR/Effectivity R- Effectivity NR) (IDR/% effectivity-gained)	12,963,792	7,431,959 (395,095)	

NR: a group of patients who did not receive a recommendation from the clinical pharmacist; R: a group of patients who received a recommendation from the clinical pharmacist; ACER: average cost- to-effectiveness ratio; ICER: incremental cost-to-effectiveness ratio.

Table 4. Results of the sensitivity analysis

Description	NR (n = 42)	R (n = 51)
Cost-to-effectiveness (B) in increments of:		
5% of acquisition cost	IDR 10,695,128	IDR 7,191,513
10% of acquisition cost	IDR 11,204,420	IDR 7,533,966
15% of acquisition cost	IDR 11,713,712	IDR 7,876,419
Effectivity (E)		
Proportion of patients with LOS <= 3 days (%)	33%	47%
ACER (B/E) in increments of:		
5% of acquisition cost	324,094.79	153,010.92
10% of acquisition cost	339,527.88	160,297.15
15% of acquisition cost	354,960.97	167,588.38
Position	Dominated	Dominant

NR is a group of patients who did not receive a recommendation from the clinical pharmacist; R is a group of patients who received a recommendation from the clinical pharmacist; ACER is the average cost-to-effectiveness ratio.

The problem of non-compliance with the antibiotic management guidelines is still a common issue in Indonesia, not only at primary health centers [13-16] but also at tertiary hospitals [17]. In this study, the clinical pharmacist reviewed antibiotic prescriptions to minimize drug-related problems according to the 'Use of Antibiotics Guidelines' (PPAB) [18, 19], the guidelines implemented at the study site. The guidelines were used as a tool to select the antibiotic used, as well as give information about the dose, frequency, duration, and route of administration of the antibiotic recommended. The types of recommendations given by the clinical pharmacist after evaluation included dosage adjustments, antibiotic selections, and suggestions for laboratory evaluations. The most frequent recommendation was laboratory evaluation. These recommendations were delivered to other health practitioners, such as physicians and nurses who worked in the PICU. The response rate was 100%, meaning that all recommendations were accepted. For dosage recommendations, increasing or decreasing dosage or frequency of administration to optimize the therapy outcomes and/or minimize the incidence of adverse drug reactions was determined based on the patient's condition. Antibiotic recommendations were based on their spectrum, and the steps required for antibiotic escalation or de-escalation were according to the guidelines [18, 20-22]. Another recommendation was to perform laboratory evaluations such as bacterial, fungal, or pericyte cultures to assist in the selection of antibiotics so that the antibiotics used could be narrowed down and targeted. At the RSCM, culture, and antibiotic sensitivity test results are typically completed within five days. Therefore, Gram staining results were also requested to accelerate the selection of antibiotics, and this additional laboratory test increased the medical costs incurred. However, the cost of antibiotics could be reduced as a result, and costs related to treatment failure and adverse drug reactions would be reduced or avoided. Moreover, the use of antibiotics could be controlled, and the possibility of antibiotic resistance reduced [23-25].

Examples of the recommendations given include increasing Meropenem dosage from 500 mg to 1–2 g for resistance to severe sepsis and amending the cefotaxime regimen from every 12–24 hours to every 6–8 hours. Dosage adjustments made by physicians for hemodialysis patients were already appropriate because physicians in the PICU at RSCM are well-educated, and therapeutic dose tabulation guidelines for hemodialysis patients are already in place to minimize mewell-educatedrs. Another type of recommendation was antibiotic selection based on the results of culture and antibiotic sensitivity testing, or at least on Gram staining testing. Escalation or de-escalation suggestions were also given by considering patients' clinical condition and indicators of sepsis from laboratory results, such as procalcitonin and leucocyte counts, according to the guidelines. Tigecycline and vancomycin antibiotics were only given to patients according to the results of culture and antibiotic sensitivity tests. If patients showed a good response to the therapy, the administration was continued, and the patient's clinical conditions continued to be monitored.

Within the three months of the study, 120 recommendations were given by the clinical pharmacist to the 51 patients in the R group. The number of recommendations given in this study is more than in other studies, for example, the research by LaRochelle into 159 PICU patients [10, 24, 26]. Another study in Thailand reported a

98.4% acceptance rate from 127 recommendations [11, 27, 28]. The total costs of the R and NR groups were direct costs consisting of antibiotics, reconstitution service costs, maintenance costs (the cost of hospitalization in PICU), doctor-visit costs, and the additional cost of laboratory testing for the R group. The costs of the antibiotics used were the prices charged to the patients covered by JKN. Inflation as a potential confounder did not apply due to the short-term nature of this study (May to October 2014). As the inflation rate was below 5% per year, according to central bank inflation data for that year, it was assumed that there would be no change in the price of antibiotics. The total cost of the NR group was IDR 427,805,134 and this was greater than the R group cost of IDR 349,302,060 ($P < 0.001$). This finding shows that by adding laboratory evaluations the cost of antibiotics can be reduced by decreasing the number and types used.

This study also assessed the effect of clinical pharmacist intervention on the LOS of patients in the PICU. The average LOS of R group patients (4.5 days) was significantly shorter than for the NR group (6.4 days). Effectivity for the R group (47%) was significantly higher than the NR group (33%) ($p < 0.05$). It was also cost-saving or cost-effective (ICER of the R group relative to the NR group was minus IDR 395,095/effectivity- gained). Previous studies have shown different results regarding the benefit of clinical pharmacist intervention. In a Thai study, pharmacist interventions did not significantly reduce the cost of drug therapy or LOS in an intensive care unit [11, 23]. Conversely, a study in the USA showed that clinical pharmacist interventions within two years could reduce antibiotics costs by 31%, length of stay by 2.4 days, and mortality by 1.67% [3, 25, 29, 30]. In the present study, decreases in mortality were not investigated because the APACHE (Acute Physiology and Chronic Health Evaluation) data required to assess organ dysfunction in patients in the PICU were not available. However, within three months, there was a decrease in the total cost per patient of 32.75% and a decrease in LOS of 1.9 days per patient. In the present study, the ACER of group R (IDR 7,431,959) was lower than the NR group (IDR 12,963,792).

The results of the sensitivity analysis are shown in **Table 4** and indicate that even when acquisition costs were increased by 15%, overall outcomes did not change, and the NR group's results were still better than those of the R group. In other words, it could be concluded that the results of the CEA in this study were robust in relation to the uncertainty of drug costs.

The calculation of the effectiveness of monetary value assumes that the savings earned are IDR 78,503,074 (total cost in NR group – total cost in R group), with savings in medical costs of IDR 42,000,000, doctor-visit costs of IDR 8,000,000, and antibiotics costs of IDR 57,928,074. These savings can reduce the government and hospital budgets required for paying for the care of national health insurance patients.

The limitation of this study was that the physicians who were in charge between May to July and August to October 2014 were different. The patients also did not have the same diagnoses on the type of seandis and comorbiditands. However, the severity of infection between the two groups was not significantly different **(Table 1)**. At the sample selection step, we also made relatively strict inclusion and exclusion criteria and only patients with a complete medical data were included in this experimental study.

Conclusion

The participation of clinical pharmacists in prescription review and giving recommendations on antibiotic therapy can reduce costs and LOS of pediatric patients in PICU. This finding could reduce government and hospital budgets required for health payments. With the development of medicine and the update of expert consensus and guidelines on antibiotics, clinical pharmacists may give more suggestions to complete similar studies under the current situation so as to benefit critically ill children.

Acknowledgments: The authors are grateful to the patients and staffs at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, for their great contribution to this study.

Conflict of interest: None

Financial support: This study was supported by PDUPT Grant, Ministry of Research and Technology/National Agency for Research and Innovation, Republic of Indonesia No. NKB-93/UN2.RST/HKP.05.00/2020 and Addendum No. NKB-2692/UN2.RST/HKP.05.00/2020.

Ethics statement: This study was approved by the Ethics Committee, Faculty of Medicine, Universitas Indonesia–Dr. Cipto Mangunkusumo Hospital (No. 508/H2.F1/ETIK/2014).

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