*Original Article*

# Assessing the Impact of Antimicrobial Stewardship on Antibiotic Rationality in a Tertiary Hospital Setting

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***Abstract***

***Introduction:*** *Irrational use of antibiotics can lead to antibiotics resistance, necessitating efforts for prevention. The implementation of an Antimicrobial Stewardship Program aims to mitigate inapproriate antimicrobial prescribing. This study aims to compare antibiotic rationality based on quantity, quality, and total cost of antimicrobial utilization following the Antimicrobial Stewardship Program in a tertiary hospital setting.*
***Methods:*** *This was a cross-sectional study. Data were obtained from the medical record of 120 patients hospitalized in the pediatrics ward and classified into two groups: post-program and control. The quantity of antibiotic utilization was measured using Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD). Antibiotic rationality was assessed using Gyssens modified category. Normality was evaluated using the Kolmogorov-Smirnov test and analyzed with an independent t-test.*
***Results:*** *There was 10% increase of prudent antibiotic use and a 30.61% reduction in total cost in the post-program study group. However, there was no significant difference in the quantity of antimicrobial utilization in both groups (p=0.06).*
***Conclusion:*** *The program improves the rationality of prudent antibiotic prescription and reduces the total cost of antimicrobial utilization.*

***Keywords****: Antibiotic rationality, Antimicrobial stewardship, Antibiotic resistance, Gyssens modified category.*

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**Penilaian Dampak Pengelolaan Antimikroba terhadap Rasionalitas Antibiotik di Rumah Sakit Tersier**

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***Abstrak***

***Pendahuluan:*** *Penggunaan antibiotik yang tidak bijak dapat mengakibatkan perkembangan resistensi antibiotik, sehingga langkah-langkah pencegahan diperlukan. Tujuan dari Penerapan Program Penatagunaan Antimikroba adalah untuk mengurangi peresepan antibiotik yang tidak rasional. Penelitian ini bertujuan untuk membandingkan tingkat rasionalitas penggunaan antibiotik berdasarkan aspek kuantitas, kualitas, dan total biaya setelah Pelaksanaan Program Penatagunaan Antimikroba di rumah sakit tingkat lanjutan.*
***Metode:*** *Penelitian ini merupakan studi cross-sectional. Data dikumpulkan dari rekam medis 120 pasien yang dirawat di unit pediatrik dan dibagi menjadi dua kelompok: kelompok post-program dan kelompok kontrol. Kuantitas penggunaan antibiotik diukur dengan Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD). Rasionalitas antibiotik dievaluasi berdasarkan kategori modifikasi Gyssens. Normalitas data diperiksa menggunakan uji Kolmogorov-Smirnov dan dianalisis dengan uji t independen.*
***Hasil:*** *Terdapat peningkatan penggunaan antibiotik yang bijak sebesar 10% dan pengurangan total biaya sebesar 30,61% pada kelompok setelah program diimplementasikan. Namun, tidak terdapat perbedaan signifikan dalam kuantitas penggunaan antimikroba antara kedua kelompok (p=0,06).*
***Kesimpulan:*** *Program ini berhasil meningkatkan rasionalitas penggunaan antibiotik dan mengurangi total biaya penggunaan antimikroba.*

***Kata kunci:*** *Rasionalitas antibiotik, Program Penatagunaan Antimikroba, Resistensi antibiotik, Gyssens modified category.*

## Introduction

Irrational and unnecessary use of antimicrobials create resistant microbes throughout the universe.[1] A literature study in Malaysia revealed that ten developing countries in Asia have high levels of irrational and excessive antimicrobial prescribing.[2] Improper use of antimicrobials is a major driver of antimicrobial resistance. According to the latest 2019 Antibiotic Resistance Surveillance conducted by the Centers for Disease Control and Prevention (CDC), more than 2.8 million cases of antibiotic resistance occur and 35,000 people die annually.[3] Moreover, they are related to increased mortality and cause a significant economic burden, estimated at over 20 billion dollars per year in the United States.[4] Given the significant impact of rational antimicrobials utilization, it becomes imperative to prioritize it, along with enhancing antimicrobial stewardship program implemented worldwide to curb irrational antimicrobial prescribing. An antimicrobial stewardship program is a coordinated intervention designed to assess and enhance the rational use of antimicrobial.[5] The policy promotes the responsible use of antimicrobials in primary health care, and its effectiveness appears to be well-established.[6]

Therefore, this study was conducted to evaluate the effectiveness of the antimicrobial stewardship program. The evaluation encompassed the quantity, quality, and total cost of antimicrobial utilization. To our knowledge, this study is the first research endeavor to assess antibiotic rationality after the implementation of antimicrobial stewardship program, based on the quantity, quality of antimicrobial use, and the total cost, in a tertiary hospital setting in Indonesia.

## Methods

We conducted a cross-sectional study to evaluate antibiotic rationality in Prof. Dr. Margono Soekarjo Hospital from 2017 to 2019 after the antimicrobial stewardship program based on the quantity, quality, and total cost of antimicrobial use.

The subjects were patients aged 1-14 years old who were hospitalized in the pediatric ward at Prof. Dr. Margono Soekarjo Hospital during both the pre- and post-implementation periods of the antimicrobial stewardship program (2017-2019). We recruited 120 patients hospitalized in pediatric ward and were divided into two groups, post-program and control study group. The patients who lived and treated around those periods, expected to dwell in the pediatric ward for more than 48 hours and obtained antibiotics therapy, were qualifying to be registered in this study. The patients, whose medical record was incomplete, were excluded from this study. The data were taken from medical records. Patient characteristics, including demographic such as age, sex, and body weight, as well as the length of hospital stay, were documented. Information regarding the administration of antibiotic drugs and associated costs were also extracted from medical records.

The quantity of antimicrobial usage was assessed using by Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system, which serves as both a classification method and a unit of measure.[7] The quantity was reported as usage density, representing the daily doses per 100 patient-days. This information is to be collected on an annual basis and reported by the pharmacist. DDD/100 patients-days denotes the defined daily dose per the total length of stay of all patients. The data encompasses both the institution-wide and pediatric department scopes. It is imperative that the data be disaggregated to the agent level and made available to the research team.

The rationality of antimicrobial utilization, assessed for quality, was determined using Gyssens' modified method, which categorizes into six groups:[8]

- Gyssens category 0: appropriate antibiotics utilization.
- Gyssens category I: antibiotics utilization is not at the right time.
- Gyssens category IIA: antibiotic utilization is not in the right dose.
- Gyssens category IIB: antibiotic utilization is not given at the right interval.
- Gyssens category IIC: antibiotic utilization is given not in the right route.
- Gyssens category IIIA: the duration of the antibiotic utilization is too long.
- Gyssens category IIIB: the duration of the antibiotic utilization is too short.
- Gyssens category IVA: there is a more effective antibiotic than the antibiotic used in this case.
- Gyssens category IVB: there was another more safe antibiotic.
- Gyssens category IVC: there was another cheaper antibiotic.
- Gyssens category IVD: there was another narrower spectrum antibiotic.
- Gyssens category V: there was no indication to give an antibiotic.
- Gyssens category VI: the medical record is incomplete.

Of these categories, I to VI represent irrational antibiotic use, while category 0 reflects prudent antibiotic use. The total cost of antimicrobial use in this study was measured in Indonesian currency (Rp). This cost was calculated based on the daily pharmacy prices of the hospital.

The data analysis for this research encompassed both univariate and bivariate analyses. The demographic information and length of stay for patietns were subject to univariate analysis. Within this, descriptive statistics was employed. Regarding the quantity and total cost of antimicrobial utilization, normality was innitially assessed using the Kolmogorov-Smirnov test, followed by an independent t-test. All reported p values are two-sided, with the threshold of statistical significance set at $<0.05$. This study received ethical approval from Ethical Committee of Prof. Dr. Margono Soekarjo General Hospital with reference number 420/12262/X/2019.

## Results

Out of the total 120 research subjects, 60 patients who met the eligible criteria were non-randomized taken from the medical record of pediatric ward patients who were hospitalized prior the implementation of antimicrobial stewardship program. This group was classified as the control study group. The post-program study group comprised 60 non-randomized selected patients who met the eligible criteria from the medical records of pediatric ward patients hospitalized after the implementation of antimicrobial stewardship program. The characteristics of these patients are detailed in Table 1.

**Table 1. The Characteristics of the Subjects**

| Characteristics | Post-Program Group | Control |
|---|---|---|
| Gender (n,%) | | |
| Male | 28 (46.67) | 32 (53.33) |
| Female | 32 (53.33) | 28 (46.67) |
| Age (n,%) [years old] | | |
| 0-5 | 52 (86.67) | 55 (91.67) |
| 6-10 | 5 (8.33) | 5 (8.33) |
| 11-14 | 3 (5) | 0 (0) |
| Body Weight (n,%) [Kg] | | |
| 0-10 | 30 (50) | 29 (48.33) |
| 11-20 | 24 (40) | 28 (46.67) |
| 21-30 | 5 (8.33) | 4 (6.67) |
| >30 | 1 (1.67) | 0 (0) |
| Length of stay (mean±SD) | 6.71±4.54 | 5.32±3.37 |

Table 2 presents data on the seven types of antimicrobials observed over the course of a year in the control study group. Out of the 100 antimicrobials administered, all were categorized as empiric therapy, constituting 100% of the total usage. As per the ATC/DDD system, the mean quantity of antimicrobial utilization in this group was 4.74±4.79 DDD/100 patients-day. In the post-program study group, a wider range of antimicrobials types were administered over the five-month observation period. Out of the 114 antibiotics utilized, 95.61% were categorized as empiric therapy, while 4.39% were classified as definitive therapy. The mean quantity of antimicrobial utilization in the post-program study group was 2.58±3.58 DDD/100 patients-day. There was no significant difference in the quantity of antimicrobial utilization between both groups (p=0.06).

The rationality of antimicrobial utilization was assessed by two reviewers using the Modified Gyssens category. In the control study group, a total of 100 antimicrobials were evaluated, while in post-program study group, 114 antimicrobials were assessed. Table 3 displays the rationality of antimicrobial utilization, revealing a noteworthy 10% improvement in prudent antimicrobial use in the post-program study group.

**Table 2. Antibiotics Utilization with ATC/DDD System**

| Antibiotics | DDD/100 Patients-Day | |
|---|---|---|
| | Post-Program Study Group | Control |
| Ceftriaxone | 12.37 | 6.49 |
| Cefixime | 1.56 | 0.55 |
| Ampicillin | 8.09 | 13.05 |
| Gentamicin | 4.66 | 8.50 |
| Cefotaxime | 3.15 | 1.98 |
| Chloramphenicol | 1.39 | 2.45 |
| Amoxicillin | 0.74 | 0 |
| Cefadroxil | 0.06 | 0 |
| Ceftazidime | 0.06 | 0 |
| Ampicillin-Sulbactam | 0.06 | 0 |
| Vancomycin | 0.04 | 0 |
| Meropenem | 0.50 | 0 |
| Amikacin | 0.25 | 0 |
| Erythromycin | 1.19 | 0 |
| Cotrimoxazole mixt | 0.04 | 0.13 |
| Mean±SD* | 2.54±3.54 | 2.21±3.98 |

**Independent t-test showed p-value 0.06*
*Anatomical Therapeutic Chemical (ATC) / Defined Daily Dose (DDD) System.*

In Table 4, the total cost of antibiotic use was computed using the daily pharmacy prices of the hospital, denoted in Indonesian currency (Rp). Interestingly, the mean total cost of antimicrobial use exhibited a reduction in the post-program study group. Specifically, there was a noteworthy 30.61% decrease in total cost in this group. However, it is important to note that no significant difference was observed in the total cost of antimicrobial use between both groups (p=0.28).

## Discussion

Given the substantial benefits antibiotics offer in treating infectious disease among hospitalized patients, it is crucial to administer them appropriately. Inappropriate use of antibiotics can lead to significant risks, including the development of antibiotic resistance. This has emerged as a critical issue, posing threats to both publish health and the economy. Consequently, the adoption of Antimicrobial Stewardship programs has seen a global surge. This program encompassed three key aspects: the quantity of antimicrobial utilization, the rationality of antimicrobial use, and the total cost of antimicrobial utilization.

**Table 3. The Rationality of antibiotic use with Modified Gyssens Category**

| Gyssens Category | Post-program Group (n,%) | Control (n,%) |
|---|---|---|
| VI | 1 (0.9) | 0 (0) |
| V | 18 (16) | 31 (31) |
| IVA | 10 (8.8) | 10 (10) |
| IVB | 0 (0) | 0 (0) |
| IVC | 4 (3.5) | 1 (1) |
| IVD | 0 (0) | 0 (0) |
| IIIA | 3 (2.6) | 4 (4) |
| IIIB | 6 (5.3) | 4 (4) |
| IIA | 4 (3.5) | 2 (2) |
| IIB | 6 (5.3) | 3 (3) |
| IIC | 0 (0) | 0 (0) |
| I | 0 (0) | 1 (1) |
| 0 | 62 (54) | 44 (44) |

*VI: the medical record is incomplete, V: no indication to give an antibiotic , IVA: there is another more effective antibiotic, IVB: there is another more safe antibiotic, IVC: there is another cheaper antibiotic, IVD: there is another narrower spectrum antibiotic, IIIA: the duration of antibiotic utilization is too long, IIIB: the duration of the of antibiotic utilization is too short, IIA: the antibiotic utilization is not in the right dose, IIB: the antibiotic utilization is not given at the right interval, IIC: the antibiotic utilization is given not in the right route, I: the antibiotic utilization is not at the right time, 0: the appropriate antibiotic utilization. Category I-VI show an irrational use of antibiotic and category 0 shows a rational use of antibiotic.*

**Table 4. Total Cost of Antibiotic Use***

| | Post-Program Study Group | Control |
|---|---|---|
| Total | 696,979,704.00 | 1,004,428,090.00 |
| Mean | 36,683,242.32±42,097,733.70 | 55,801,560.56±68,639,690.13 |

**All value in Rupiah (Rp.)*

## Quantity of Antimicrobial Utilization

This study reveals that ampicillin, gentamicin, and ceftriaxone were the most frequently prescribed antimicrobials in both groups. However, there was a notable difference in their usage. In control group, ampicillin was the most utilized with 13.05 DDD/100 patients-day, indicating its administration to 13.05% of pediatric ward patients in 2017. Conversely, in the postprogram group, ceftriaxone took precedence with 12.37 DDD/100 patients-day, indicating its administration to 12.37% of pediatric ward patients over five months in 2019. This shift in antimicrobial trends could be attributed to the fact that 33.3% of patients in the post-program group, who were initially administered the 1st line empirical antibiotic treatment, did not show improvement. It's plausible that some patients had already received this treatment in a previous hospital or were initially given inappropriate antibiotic prescriptions. It's worth noting that a study by Herawati, et al.[9] similarly identified Ampicillin as the most prescribed antimicrobial for pediatric wards in a secondary hospital setting. In contrast, a tertiary hospital in southwest Ethiopia predominantly used gentamicin, crystalline penicillin G, and ampicillin.[10]

The total antibiotic utilization increased by 1.01 DDD/100 patients-day after the program. The independent t-test yielded a p-value of 0.06, indicating that the program did not lead to a reduction in antimicrobial usage of the post-program study group might be a contributing factor, but further evaluation is warranted.

The findings of our current study contradict those of Le Corvoisier, et al.[11] Their study reported a notable reduction in antibiotic prescription over a 30-months period following an educational seminar, similar to the Antimicrobial Stewardship Program Seminar in our study. Additionally, studies by Altiner, et al.[12] and Enriquez-Puga, et al.[13] also showed a significant decrease in the antibiotic prescription, but the intervention of those studies was an educational outreach.

Interventions targeting antibiotic resistance reduction come in various forms, including norms and standards, knowledge enhancement, decision support, supply chain improvements, economical measures, and management strategies. Wilkinson, et al.[14] highlighted that knowledge intervention as yielding the most favorable outcomes. Nevertheless, it's worth noting that multifaceted interventions tend to have a more significant impact compared to single intervention.[14]

## The Quality of Antibiotic Use

Physicians can mitigate these potential disadvantages through formal training to optimize antibiotic prescriptions for patient treatment. An analysis of antibiotic utilization quality was undertaken to enhance clinical outcomes and avoid antibiotic misuse. Qualitatively, antibiotic utilization is assessed by examining the rationality of use and prescription. Notably, approximately half of prescribed antibiotics are deemed irrational, and 50% of patients had inadequate reconciliation.[15]

The analysis revealed that in the control study group, 44% of antibiotics were used prudently, while 66% were used irrationally. Conversely, in the post-program study group, 54% of antibiotics were used prudently, and 46% were used irrationally. This indicates a 10% increase in prudent antibiotic use following the implementation of the antimicrobial stewardship program.

The assessment of antimicrobial utilization rationality, as determined by the Gyssens modified category, shows a 10% increase in the percentage of Gyssens 0 criteria in the post-program group compared to the control group (54% vs. 44%) (refer to Table 3). These findings closely mirror those of a study by Murni, et al.[16] where the use of rational antibiotics increased by up to 79.4% following an antibiotic stewardship program. This rise in Gyssens 0 criteria percentage can be attributed, in part, to an emerging adherence among clinicians to empirically guided antibiotic therapy.

The percentage of antibiotics prescribed without indication was notably higher before program implementation, accounting for 31%. Despite this relatively high figure, it's worth noting that the rate of antibiotics administered without indication at Prof. Dr. Margono Soekarjo Hospital is still lower than the 41.9% observed in the Korea National Patients Database.[17] Following the implementation of antibiotic stewardship, there was a significant decrease in the prescribing of antibiotics without indication, resulting in a reduction of 15%. This reduction is anticipated to contribute to a lower incidence of antibiotic resistance in the future.

The inappropriate use of antibiotics has emerged as a significant concern in developing nations, where antibiotic resistance poses substantial economic and health burdens.[16] Our study underscores the effectiveness of antimicrobial stewardship, guided by the WHO Hospital Care for Children guidelines, in setting a standard to curb inappropriate antibiotic prescriptions. This aligns with the findings of Balinskaite, et al.[18], who demonstrated a substantial reduction in irrational antimicrobial use through a similar program. On average, their implemented program led to an 11.6% reduction in antimicrobial prescriptions, with significant decreases in both overall antimicrobial and broad-spectrum antibiotic prescriptions.[18]

The need for rational antibiotics prescribing underscores the ongoing responsibility of healthcare providers. Emphasizing continuous education and promotion of antibiotic stewardship is crucial, requiring commitment from all stakeholders. Rational use means avoiding side effects and ensuring cost-effectiveness. This involves considering factors like diagnosis appropriateness, patient condition, infection site, pathogen sensitivity, and cost.[19]

## Total Cost of Antibiotic Use

The study's results indicate a notable 30.61% decrease in the total cost of antibiotic utilization after the program. This finding aligns with a study by Zhang, et al.[20], which reported a significant reduction in the average antibiotic cost following a real-time monitoring and control intervention. Similarly, a study by Xin, et al.[21] observed a significant decrease in the total cost of carbapenems after implementing medication order monitoring and an educational group intervention. The lack of a significant difference between both groups in our study may be attributed to three cases involving the definitive prescription of costly antibiotics: amikacin, meropenem, and vancomycin. These particular antibiotics are among the most expensive ones according to in our study.

Inappropriate antibiotic prescriptions not only contribute to antibiotic resistance, but also result in unnecessary cost. The Organization for Economic Co-operation and Development (OECD) has highlighted that curbing antibiotic overuse and promoting hospital hygiene could lead to annual savings of up to US$ 4.8 billion per year across 33 OECD countries.[22] Therefore, the financial implications of antibiotic use and the potential burden due to antibiotic resistance should be a factor considered by physicians when making prescription decisions.

## Strength and Limitation

This study comprehensively assessed the rationality of antibiotic use across various dimensions, including quantity, quality (prudent use), and cost burden, within a tertiary hospital setting in Indonesia. However, it's important to note that this study did not conduct a cost-effectiveness analysis due unavailability of cost details for patients covered by the National Health Insurance. Moreover, for more robust findings, future studies may require an extended study period and an increased sample size. Additionally, conducting a cost-effectiveness analysis with a different patient population or those not covered by insurance over a longer duration could offer valuable insights.

## Conclusion

The implementation of antimicrobial stewardship program led to an enhancement in the rationality of prudent antibiotic prescription and a reduction in the overall cost of antimicrobial utilization.

## Conflict of Interest

There was no conflict of interest in this study and manuscript.

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