

The Relationship Between Appropriateness of Antibiotic Use Based on the Gyssens Algorithm and Mortality: A Retrospective Cohort Study in Indonesian Tertiary Hospital

Fadrian^{1,2,3*}, Gestina Aliska^{3,4,5}, Widy Nur Utami³

¹ Division of Tropical and Infectious Disease, Department of Internal Medicine, Dr. M. Djamil Central General Hospital, Padang, Indonesia.

² Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Andalas, Padang, Indonesia.

³ Antimicrobial Resistance Stewardship Committee, Dr. M. Djamil Central General Hospital, Padang, Indonesia.

⁴ Department of Clinical Pharmacology, Dr. M. Djamil Central General Hospital, Padang, Indonesia.

⁵ Department of Clinical Pharmacology and Therapeutics, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

***Corresponding Author:**

Fadrian, MD. Division of Tropical and Infectious Disease, Department of Internal Medicine, Dr. M. Djamil Central General Hospital. Jl. Perintis Kemerdekaan, Padang, Indonesia. Email: fadrian@med.unand.ac.id.

ABSTRACT

Background: Some studies have reported that antibiotic use as therapy and prophylaxis in hospitals is inappropriate in approximately 9% to 64% of cases. The Gyssens algorithm is used for qualitative evaluation by assessing the appropriate antibiotic use. This study aimed to determine and evaluate the quality of antibiotic use in inpatients at Dr. M. Djamil Central General Hospital using the Gyssens algorithm. **Methods:** This was a retrospective cohort study at Dr. M. Djamil Central General Hospital from January to December 2021. We collected data from the medical records of inpatients who received antibiotics using a random sampling technique, and the number of patients from each department was calculated through a preliminary survey.

Results: There were three hundred and sixty samples from the population that met the inclusion criteria, adults (59.4%), patients treated for >14 days (38.9%), patients discharged with improvement (66.9%), and patients diagnosed with pneumonia (49.5%). Most antibiotics were appropriate (56.5%), with ceftriaxone being the most commonly used antibiotic (199 cases). Appropriate antibiotic use (Gyssens 0) is mostly found in the Internal Medicine Department. Meanwhile, antibiotic use without indications (Gyssens V) is mostly found in the Surgery Department. A significant correlation was found between the appropriateness of antibiotic administration and patient outcomes after discharge from the hospital ($p < 0.05$). There was an increase in the risk of death in inappropriate antibiotic use (Gyssens I-IV) and antibiotic use without indications (Gyssens V) by 1.96 and 4.05 times, respectively. **Conclusion:** There are many cases of inappropriate antibiotic use in Dr. M. Djamil Central General Hospital; therefore, education regarding appropriate antibiotic use is necessary.

Keywords: antibiotic use, Gyssens algorithm.

INTRODUCTION

In several studies, antibiotic use as a therapy and prophylaxis in hospitals showed an inappropriate indication in approximately 9% to 65% of cases.^{1,2} A study by Luciana et al., in Indonesia reported that 44% to 97% of patients in hospitals were prescribed antibiotics unnecessarily.³ Inappropriate use of antimicrobials can increase morbidity, mortality, health care costs, the emergence or selection of resistant microorganisms, and *Clostridium difficile* infection rates. In addition, it can cause antimicrobial drug toxicity and can increase drug interactions, catheter-related infections associated with intravenous antimicrobial administration, and other nosocomial infections that prolong hospitalization.⁴

Appropriate antibiotic use was evaluated qualitatively using the Gyssens algorithm. This algorithm can be used to evaluate the accuracy of antibiotic use selected as initial or empirical therapy in cases of infection. Evaluation of antibiotic use is conducted not only to identify the amount and quality of antibiotic use in the hospital but also to serve as a fundamental step in establishing surveillance of antibiotic use in a systematic and standardized manner as an indicator of the quality of hospital services.⁵ A study by Hadi et al., divided the appropriateness of antibiotic use into 3 groups, including appropriate antibiotic use (Gyssens 0), inappropriate antibiotic use (Gyssens I-IV), and antibiotic use without indications (Gyssens V).⁶ This study aims to identify and assess the quality and the outcome due to the appropriateness of antibiotic use in patients at Dr. M. Djamil Central General Hospital using the Gyssens algorithm.

METHODS

This was a retrospective cohort study with data collection from the medical records of all patients who were treated with antibiotics at Dr. M. Djamil Central General Hospital from January to December 2021. Patients who received antibiotics for empirical and definitive indications were included in the study. Patients were selected using a random sampling technique in each department. In the sampling selection, a random sampling technique was used in each department and then the number of patients

from each department was calculated through a preliminary survey. The preliminary survey was conducted in two phases. The first phase was conducted at the antimicrobial stewardship committee of Dr. M. Djamil Central General Padang. In the first phase, it was found that there were 11 appropriate uses of antibiotics from 30 patients, thus obtaining a total minimal sample size of 356 patients. After that, the second phase of the preliminary survey recorded the usage of antibiotics from all departments of Dr. M. Djamil Central General Padang in one week. The calculation of the proportion of patients in each department was carried out with a preliminary survey for one week, the results per department were as follows: pediatric (34 patients), surgery (102), cardiovascular care unit (14), the ICU (37), internal medicine (91), cardiology (18), ophthalmology (2), OB-GYN (9), pulmonology (24), intensive observation room (2), neurology (16), and ENT (11). Demographic data (age, gender, body weight, number of medical records, and dates of admission and discharge), diagnosis, admission and discharge conditions, laboratory test results, chest X-rays, and antibiotic treatments were collected. An evaluation was conducted using the Gyssens algorithm by classifying each antibiotic administration into six categories, category VI (inappropriate use because the medical record was incomplete for evaluation), category V (inappropriate use because it was not as indicated), category IVa (inappropriate use because there were more effective antibiotics), category IVb (inappropriate use because there were safer antibiotics), category IVc (inappropriate use because there were cheaper antibiotics), category IVd (inappropriate use because there were other antibiotics with a narrower or more specific spectrum), category IIIa (inappropriate use because of very long administration), category IIIb (inappropriate use because of very short administration), category IIa (inappropriate use of administration dose), category IIb (inappropriate use of administration interval), category IIc (inappropriate use of administration procedure), category I (inappropriate administration time), and category 0 (appropriate antibiotic use or not included in categories I-VI).^{7,8} Patients who were in Gyssens category VI were excluded

from this study. The appropriateness of antibiotic use in this study will be divided into 3 groups, including appropriate antibiotic use (Gyssens 0), inappropriate antibiotic use (Gyssens I-IV), and antibiotic use without indications (Gyssens V). Data on the characteristics of the patients and the quality profile of antibiotic use were presented as descriptive statistics. Patient outcome was a dichotomous variable, documented as either recovery or dead state. An analysis of the relationship between the appropriateness of antibiotic use and the patient's outcome was carried out by using the chi-square method. The collected quantitative data were processed and analyzed by computerization.

RESULTS

According to the inclusion and exclusion criteria based on the proportion in each department, the number of patients in this study was 360. Out of a total of 360 patients, there were 608 antibiotics used.

Table 1 presents the characteristics of the subjects. The majority of the patients in this study were male (59.2%), adults (59.4%), patients who had a length of stay >14 days (38.9%), and patients who had an improved or recovered outcome (66.9%) after antibiotic administration. Out of a total of 360 patients, there were 278 infectious diseases and 100 without diagnosis of infections in the medical record. Pneumonia

Table 1. Characteristics of the subjects.

Characteristics	Distribution (n = 360)	Frequency (%)
Gender		
Male	213	59.2
Female	147	40.8
Age Category		
Children	51	14.2
Adult	214	59.4
Elderly	95	26.4
Department/Room		
Pediatric	34	9.4
Surgery	102	28.3
CVCU ¹	14	3.9
ICU ²	37	10.3
Internal Medicine	91	25.3
Cardiology	18	5.0
Ophthalmology	2	0.6
OB-GYN ³	9	2.5
Pulmonology	24	6.7
Intensive Observation Room	2	0.6
Neurology	16	4.4
ENT ⁴	11	3.1
Length of Stay		
0-7 days	102	28.3
7-14 days	118	32.8
>14 days	140	38.9
Outcome		
Recovery	241	66.9
Dead	119	33.1
Infectious Disease (n=378)		
Pneumonia	188	49.7
Skin and soft tissue infection	23	6.1
Urinary tract infection	16	4.2
Intra-abdominal infection	15	4.0
CNS ⁵ infection	12	3.2
Other infections	24	6.3
No diagnosis of infections in medical record	100	26.5

¹CVCU, cardiovascular care unit; ²ICU, intensive care unit; ³OB-GYN, obstetrics and gynecology; ⁴ENT, ear, nose throat;

⁵CNS, central nervous system

was the most common infectious disease (49.5%) observed in this study. There were 100 patients without a diagnosis of infection who received antibiotics from medical records. This is generally found in postoperative patients who receive antibiotics without infection.

Figure 1 shows that antibiotic use at Dr. M. Djamil General Hospital was appropriate (Gyssens 0) in 344 cases (56.5%), followed by antibiotic use without indications (Gyssens V) in

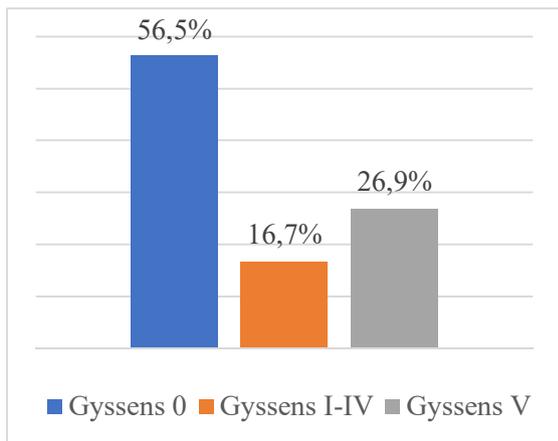


Figure 1. Appropriateness of Antibiotic Use. The use of antibiotics at Dr. M. Djamil General Hospital was appropriate (Gyssens 0) in 56.5% of cases, 26.9% of cases without indications (Gyssens V), and inappropriate (Gyssens I-IV) in 16.7% of cases.

164 cases (26.9%), and inappropriate antibiotic use (Gyssens I-IV) in 100 cases (16.7%).

The details and appropriateness of the antibiotics used in 608 cases can be seen in **Figure 2**. Based on the results presented in **Figure 2**, ceftriaxone and levofloxacin were the two most commonly used antibiotics, with 199 and 142 of the total 608 antibiotics used, respectively. Appropriate antibiotic use (Gyssens 0) was found to be 344, with ceftriaxone and levofloxacin accounting for 120 and 99 of the total antibiotics used in the Gyssens 0 category, respectively. In terms of antibiotic use without indications (Gyssens V), ceftriaxone and levofloxacin were found in 68 and 29 out of 164 antibiotics used in the Gyssens V category, respectively.

The Gyssens categories based on departments are presented in **Figure 3**. Antibiotic use without indications (Gyssens V) was mostly found in the Surgery Department (59 cases), followed by the Internal Medicine Department (22 cases), and the ICU (17 cases). The appropriate antibiotic use (Gyssens 0) was found in the Internal Medicine Department (108 cases), followed by surgery (95 cases) and the ICU (29 cases).

Table 2 shows that there was a significant relationship between the appropriateness of

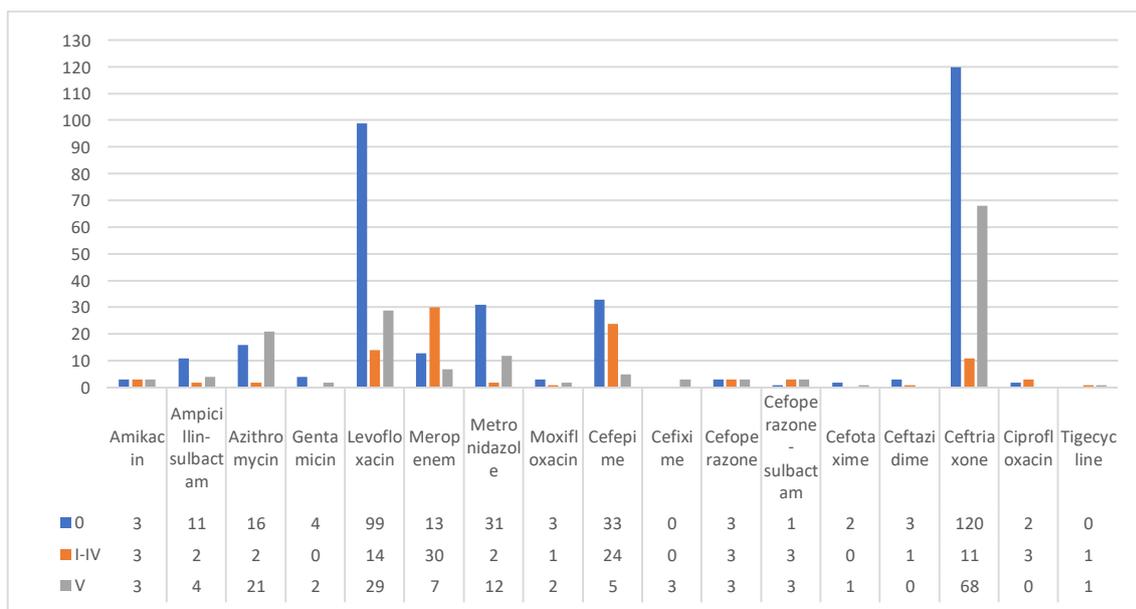


Figure 2. Types of Antibiotics Based on Gyssens Categories. Ceftriaxone and levofloxacin were the two most commonly used antibiotics. Appropriate antibiotic use (Gyssens 0) was found to be 344, with ceftriaxone as much as 120 and levofloxacin as much as 99 of the total antibiotics in the Gyssens 0 category used. While for antibiotics use without indications (Gyssens V), ceftriaxone was found to be 68 and levofloxacin was 29 out of a total of 164 antibiotics in the Gyssens V category. The use of inappropriate antibiotics (Gyssens I-IV), such as meropenem, had a fairly high distribution, which was 30 out of a total of 100 antibiotics.

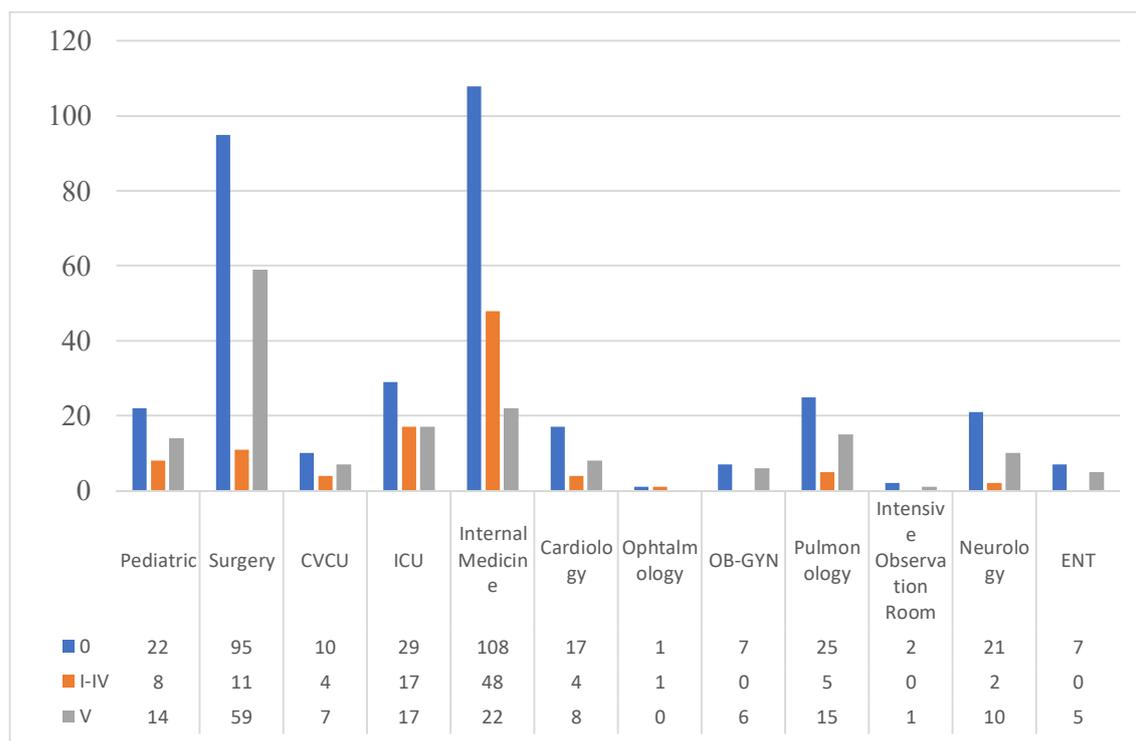


Figure 3. Gyssens categories based on the department. The use of antibiotics without indications (Gyssens V) was mostly found in the surgery department, internal medicine, and the ICU. Rational and appropriate antibiotic use (Gyssens 0) was found in internal medicine, surgery, and the ICU. Inappropriate antibiotic use (Gyssens I-IV) was mostly found in internal medicine, the ICU, and surgery

Table 2. Outcome of hospital discharge based on appropriateness of antibiotic use.

Gyssens Category	Patient's Outcome		Total	p-value	Odds ratio (95% CI)
	Recovery n (%)	Dead n (%)			
0	216 (62.8)	128 (37.2)	344 (100)	Ref ¹	Ref ¹
I-IV	45 (45)	55 (55)	100 (100)	0.002	1.965 (1.286-3.001)
V	126 (76.8)	38 (23.2)	164 (100)	0.000	4.053 (2.372-6.923)
Total	387 (63.7)	221 (36.3)	608 (100)		

¹Ref, Reference

antibiotic use and the patient’s condition upon discharge from the hospital. The analysis also showed that patients with inappropriate antibiotic use (Gyssens I-IV) had increased mortality risk by 1.96 times, and patients with antibiotic use without indication (Gyssens V) had increased by 4.05 times mortality risk.

DISCUSSION

This study showed that male patients were more common (59.2%) than female patients. This finding is similar to that of a study by Rohmah et al., which showed that the patients were mostly male (62.5%). This could be due to the differences in the lifestyle and behavior

of women and men who are at risk.⁹ Contrary to the study by Masyrifah et al., which showed that the patients were predominantly female (52.7%). Based on the age group, most patients in this study were adults. Masyrifah et al., also showed that the largest patients of the study were patients in the age group of 19-65 years (66.4%).⁹ The differences in the results of this study are thought to be caused by the total sampling technique and different inclusion criteria. There were differences in the length of hospitalization between this study and previous observational studies at Fatmawati General Hospital Jakarta. Most of the patients in this study spent more than 14 days of hospitalization, whereas in the

study at Fatmawati General Hospital Jakarta, most of the patients only spent less than 14 days of hospitalization (85.5%).¹⁰ The reason for this difference may be that Dr. M. Djamil Central General Hospital is the only final referral hospital for the West Sumatra region. Thus, generally, the patients treated are those with multiple comorbidities that require longer treatment. This is supported by Fadrian et al., research in 2022 showed that many patients treated at Dr. M. Djamil Central General Hospital with more than one comorbidity, with the highest presentations such as chronic kidney disease (28%), type 2 diabetes mellitus (19.2%), and malignancy (12.4%).¹¹ Another research in 2021 regarding comorbidities and outcomes in patients also showed that the percentage of patients with comorbidities >1 had poor outcomes with deaths of 93.1%, compared to only 6.9% who lived (OR = 10.97, 95% CI 2.19-54.96).¹²

Most of the patients in this study were discharged from the hospital in an improved condition after receiving antibiotics, which is in contrast to the results of a study by Chen et al., which showed that the study patients were more likely to die (63.8%) than to recover (36.2%).¹³ A similar finding was also reported by Masyrifah et al., who showed that patients who used antibiotics according to the Gyssens algorithm had a higher mortality rate (71.8%) than those who recovered (28.2%). The high mortality in the study by Masyrifah et al. was due to various causative factors, including the number of comorbid diseases that the patient had, the source of infection, the use of ventilators, and other causative factors.¹⁰ However, this study is in line with another study in 2023 which showed that patients who were given antibiotics were more likely to recover (95.8%) than die (4.2%).⁹

In terms of infectious diseases, the majority of the patients in this study were diagnosed with pneumonia. The results of this study are in line with a study in 2022 that reported that the patients were more likely to have a diagnosis of pneumonia (66.4%), followed by intra-abdominal infections (10%), and skin and soft tissue infections (8.2%).¹⁰

Furthermore, this study showed that antibiotic use was appropriate. Meanwhile,

research by Ma'rifah et al., in the internal medicine department, found that there was 40% appropriate use of antibiotics (Gyssens 0), 7.27% inappropriate use (Gyssens I-IV), and 52.73% use of antibiotics without indication (Gyssens V).¹⁴ Different result can happen because the study only focuses in two departments. The study by Sukmawati et al. showed that 40% of the study patients in the Gyssens 0 category received intravenous ceftriaxone, intravenous levofloxacin, and oral levofloxacin antibiotics and those in the Gyssens I-IV categories were 60% of the study patients, dominated by those in category IIIA (40%).¹⁵ The antibiotics most commonly used in this study were ceftriaxone and levofloxacin. Fadrian et al., also found that ceftriaxone was the most commonly used initial empirical antibiotic alone, followed by cefepime and meropenem.¹⁶ This is due to the most common disease in those study was pneumonia. Ceftriaxone is recommended as first-line antibiotic treatment with the addition of fluoroquinolone /macrolides for pneumonia.^{17,18}

Patients referred to Dr. M. Djamil Central General Hospital were clinically severe with significant comorbidities, making it a consideration for clinicians to provide early antibiotic therapy for better patient outcomes. In addition, the risk of nosocomial bacterial infection in hospitals is another factor that needs to be considered by clinicians when providing antibiotic therapy to patients. The antibiotic use policy is a strategy of the Antibiotic Resistance Control Program. Appropriate antibiotic use can reduce the risk of antibiotic resistance in patients which has an impact on patient outcomes.¹⁹

This study showed that antibiotic use without indication (Gyssens V) is common in the surgical department. This is likely due to the large number of cases of postoperative antibiotic use in patients without a diagnosis of infection. Appropriate antibiotic use (Gyssens 0) was most prevalent in the Internal Medicine Department, and inappropriate antibiotic use (Gyssens I-IV) was most prevalent in the Internal Medicine Department. A study by Hadi et al., of 999 patients who used appropriate

antibiotics (Gyssens 0) was predominantly found in the Internal Medicine Department (49 cases). Inappropriate antibiotic use (Gyssens I-IV) was found mostly in the pediatric department (48 cases).⁶ The difference in the results of this study is considered because there are only 4 departments used for the study. In contrast, our study includes all departments and uses a preliminary proportion system, so there were differences in the proportion of the pediatric department.⁶

In this study, 241 patients who used 387 antibiotics were discharged after improvement. This was also consistent with the statistically significant relationship ($p < 0.05$) between the appropriateness of antibiotic use and the patient's condition at discharge. Patients with inappropriate antibiotic use (Gyssens I-IV) had increased mortality risk by 1.96 times, and those with antibiotic use without indication (Gyssens V) had increased mortality risk by 4.05 times. A study by Adani et al., on 48 sepsis patients in the ICU of Dr. Hasan Sadikin Hospital showed 81.3% of death cases, and most of them (56.3%) had a history of inappropriate antibiotic use (Gyssens I-IV).²⁰ Another study by Masyrifah et al., also reported that inappropriate antibiotic use had a high mortality rate, which was 80.6%.¹⁰ In addition, Dhillon et al., who conducted a study at the Persahabatan Central General Hospital, found that there was a statistically significant relationship between inappropriate empirical antibiotic use, which could increase the risk of mortality by 4.2 times, and patient outcomes.²¹ In those studies that have carried out inappropriate antibiotic use, Gyssens I-V is not described more specifically. Therefore, our study divides Gyssens I-IV and Gyssens V because there is more antibiotic use without indication at 26.9% (Gyssens V) than those with inappropriate antibiotic use at 16.7% (Gyssens I-IV). Although our study provides the same results as several previous studies regarding increased mortality, we described 2 groups to see the differences in mortality between groups with inappropriate antibiotic use (Gyssens I-IV) and antibiotic use without indication (Gyssens V).

CONCLUSION

Antibiotic use at Dr. M. Djamil General Hospital was appropriate (Gyssens 0) in 343 cases (56.5%). On the other hand, we found antibiotic use without indications (Gyssens V) in 164 cases (26.9%), and inappropriate antibiotic use (Gyssens I-IV) in 101 cases (16.7%). The analysis also showed that patients with inappropriate antibiotic use (Gyssens I-IV) had an increased mortality risk of 1.96 times and patients with antibiotic use without indication (Gyssens V) had an increased by 4.05 times mortality risk. The increased risk of death from inappropriate and the usage of antibiotics without indication should be a concern. Therefore, education regarding appropriate antibiotic use is necessary.

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REFERENCES

1. Afekouh H, Baune P, Abbas R, De Falvelly D, Guermah F, Haber N. Antibiotic prescription evaluation in the rehabilitation ward of a geriatric hospital. *Med Mal Infect.* 2015;45(11-12):427-35.
2. Cusini A, Rampini SK, Bansal V, et al. Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: A prevalence survey. *PLoS One.* 2010;5(11):e14011.
3. Luciana T, Andrajati R, Rianti A, Khan A. Rational antimicrobial use in an intensive care unit in Jakarta, Indonesia: A Hospital-Based, Cross-Sectional Study. *Tropical Journal of Pharmaceutical Research.* 2015 May 6;14(4):707.
4. Katarnida SS, Murniati D, Katar Y. Evaluasi penggunaan antibiotik secara kualitatif di RS Penyakit Infeksi Sulianti Saroso, Jakarta. *Sari Pediatri.* 2016 Nov 9;15(6):369.

5. Sihite EN, Ramadhan AM, Samsul E. Evaluasi penggunaan antibiotik secara kuantitatif dan kualitatif pada pasien bedah digestif di RSUD Abdul Wahab Sjahranie Samarinda. *Proceeding of Mulawarman Pharmaceuticals Conferences*. 2021;14:214–21.
6. Hadi U, Duerink DO, Lestari ES, Nagelkerke NJ, Keuter M, In't Veld DH, Suwandojo E, Rahardjo E, van den Broek P, Gyssens IC. Audit of antibiotic prescribing in two governmental teaching hospitals in Indonesia. *Clinical microbiology and infection*. 2008;14(7):698-707.
7. Sundariningrum RW, Setyanto DB, Natadidjaja RI. Evaluasi kualitatif antibiotik metode gyssens dengan konsep regulasi antimikroba sistem prospektif RASPRO pada pneumonia di Ruang Rawat Intensif Anak. *Sari Pediatri*. 2020;22(2):109.
8. Sitompul F, Radji M, Bahtiar A. Evaluasi penggunaan antibiotik dengan metode Gyssens pada pasien stroke rawat inap di RSUD Koja secara retrospektif (Periode KJS Dan BPJS). *Indonesian Pharmaceutical Journal*. 2016;6(1):30–8.
9. Rohmah SD, Andrajati R, Yudhorini LT. Qualitative evaluation of antibiotic use in bacterial meningitis patients using the Gyssens method. *Jurnal Aisyah: Jurnal Ilmu Kesehatan*. 2023;8(S1):169–78.
10. Masyrifah M, Andrajati R, Yudhorini LT. Qualitative evaluation of antibiotics use with Gyssens method in sepsis patients at Fatmawati Central General Hospital Jakarta. *Pharmaceutical Sciences and Research*. 2022;9(2).
11. Chen LK, Nathanael J, Shakinah S, et al. Association between early antibiotic administration and in-hospital mortality in moderate and severe COVID-19 patients. *Jurnal Penyakit Dalam Indonesia*. 2022;9(4).
12. Fadrian F, Linosefa L, Ridhwan F. M, Hasnah H, Syafa Ayuni A. Multidrug-resistant organisms and determinant factors in sepsis patients. *Iran J Med Microbiol*. 2023;17(5):596-605.
13. Elly U, Yusticia K. The role of age and comorbidities on the outcome of confirmed clinically critical Covid-19 patients treated with Remdesivir At Indonesia's National Referral Hospital. *Afr J Infect Dis*. 2022;17(1):55-59.
14. Ma'rifah N, Hasmono D, Hadi U, Kuntaman K. Analysis of quality of antibiotic usage on patient with internal and surgical service. *FMI*. 2021;57(1):1-5.
15. Sukmawati IGAND, Adi Jaya MK, Swastini DA. Evaluasi Penggunaan antibiotik pada pasien tifoid rawat inap di salah satu rumah sakit pemerintah Provinsi Bali dengan metode Gyssens dan ATC/DDD. *Jurnal Farmasi Udayana*. 2020;26:37.
16. Fadrian F, Chen K, Kumalawati J, Rumende CM, Shatri H, Nelwan EJ. The validation of drug resistance in pneumonia (DRIP) score in predicting infections due to drug-resistant pathogens in community-acquired pneumonia at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. *Acta Med Indones*. 2021;53(4):416–22.
17. Barcha M, Steinberg Y, Kozlovsky D, Gvili AG. Ceftriaxone versus ampicillin for the treatment of community-acquired pneumonia. A propensity-matched cohort study. *Clin Microbiol Infect*. 2023;29(1):70-6.
18. Metlay JP, Watere GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):45-67.
19. Ibrahim AM, Widyati W, Prasetyadi FOH. Analisis Kualitatif penggunaan antibiotik pada pasien rujukan dengan metode analisis alur Gyssen di RSPAL Dr. Ramelan Surabaya. *MPI (Media Pharmaceutica Indonesiana)*. 2020 Dec 22;3(2):88–95.
20. Adani SD, Zulfariansyah A, Santoso PTR. Quality assessment of antibiotic prescription for sepsis treatment in intensive care unit at top referral hospital in West Java, Indonesia. *Althea Medical Journal*. 2017 Jun;4(2):286–92.
21. Dhillon J, Agustin H, Burhan E, et al. Evaluation of antibiotics use based on gyssens method and their relationship to the outcome of hospitalized community-acquired pneumonia patients in Persahabatan General Hospital Jakarta. [Jakarta]: Universitas Indonesia; 2020.