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Antibiotic Therapy Evaluation of Patients Diagnosed with Sepsis in ICU of dr. Mohamad Soewandhie General Hospital based on the Gyssens Method

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ABSTRACT

Background: Empirical antibiotic therapy is essential for managing sepsis in Intensive Care Units (ICUs), but inappropriate use can lead to negative patient outcomes. Unfortunately, there is limited information on the rational use of antibiotics in ICU settings in Indonesia. **Purpose:** This study aims to evaluate the rationality of empirical antibiotic therapy in sepsis patients and highlight the effects of limited culture testing and outdated guidelines. **Methods:** This observational study analyzed secondary data from 120 sepsis patients treated at RSUD Dr. Mohamad Soewandhie. The rationality of the antibiotic therapy was assessed using the Gyssens method. **Results:** 60% of the patients received appropriate empirical antibiotic therapy, with Ceftriaxone being the most commonly administered drug. However, only 18 patients underwent culture and sensitivity testing, resulting in 11 positive results. Among these, 67.9% were classified as multidrug-resistant organisms (MDROs). The mortality rate remained high at 81.67%. **Conclusion:** While empirical therapy was largely deemed appropriate, the low rate of culture testing and the high prevalence of MDROs highlight the urgent need for improved antimicrobial stewardship and the revision of local guidelines.

1. INTRODUCTION

Infection is a major trigger for disease and death in Intensive Care Units (ICU), especially in lower-middle-income countries.[1] Research conducted in 2017 in various ICUs around the world showed the main results of the prevalence of patients who were suspected or proven to be infected as much as 51% and received prophylactic antibiotics, therapeutic antibiotics, or both as much as 71%.[2] Sepsis is an important cause of hospitalization and a major factor in mortality in ICUs worldwide.[3] Sepsis is defined as a fatal condition triggered by a disruption in the regulation of an individual's immune response to infection which can ultimately result in shock, Multiple Organ Dysfunction Syndrome (MODS), and death.[4]

The Global Burden of Disease report shows that in 2017, a total of 48.9 million cases of sepsis were reported worldwide with a mortality rate of 22.5%, accounting for nearly 20% of all deaths worldwide.[5] Empirical antibiotic therapy in infectious diseases initiated with broad-spectrum antibiotics shows significant effectiveness. *The 2016 Surviving Sepsis Campaign* (SSC 2016) strongly recommends that early initiation of effective intravenous antibiotic therapy as soon as possible is considered essential to save the lives of critically ill patients with sepsis, at least one hour after the diagnosis is made.[6] In a retrospective analysis of 261 patients with sepsis and septic

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shock, Gaieski et al. showed that antibiotics significantly reduced mortality when given within ≤1 hour.[7]

Antibiotics are drugs derived from all or certain parts of microorganisms which are used to treat bacterial infections.[8] In 2019, WHO named antibiotic resistance as one of the top ten health threats in the world. The main cause of antibiotic resistance is the misuse and overuse of antibiotics.[9] Currently, drug-resistant infectious diseases cause at least 700,000 deaths each year. WHO also stated that if no action is taken to address these cases, the number of deaths is expected to increase to 10 million per year by 2015.[10]

Delayed antibiotic treatment results in a risk of death in patients with sepsis and septic shock.[11] Based on data from the Journal of Antimicrobial Chemotherapy which examines the prevalence of antibiotic use in 69 countries worldwide, in the health sector antibiotic use increased by 65% from 2000-2015, reviewed from various levels of global needs and efforts to suppress the risk of antimicrobial resistance. The results showed that of all participating hospitals, 53.0% came from high-income countries, 21.7% from upper-middle income, 21.2% from lower-middle income, and 4.1% from low income.[12]

In Indonesia, the prevalence of antibiotic use can be said to be quite high, namely around 40%-60%.[13] Research conducted at a hospital in Bandung revealed that infectious diseases with the highest mortality were respiratory tract infections at 49%, intra-abdominal 20%, skin and tissue 11%, urinary tract 8%, central nervous system 1%, and 11% unknown.[14] The results of the Antimicrobial Resistant in Indonesia (AMRIN-Study) study explain that around 43% of *Escherichia coli* are resistant to various types of antibiotics, including: ampicillin (34%), co-trimoxazole (29%), and chloramphenicol (25%).[15]

Continuous use of broad-spectrum antibiotics should be avoided as a preventive measure against multi-drug-resistant bacteria.[16] A study conducted in 2017 in various ICUs around the world showed the main result of the prevalence of patients who had suspected or proven infection as much as 51% and received prophylactic antibiotics, therapeutic antibiotics, or both as much as 71%. The results of the study also showed an association with antibiotic exposure, death in the ICU, and length of stay in the ICU or hospital.[17]

One method that can be used in evaluating the rationality of antibiotic use is the Gyssens method, where this method is useful for determining the rationality of administering antibiotic therapy which aims to assess the accuracy of administering antibiotic therapy.[18] With this method, the level of accuracy of indication, accuracy of selection based on effectiveness, toxicity, price, spectrum, duration of administration, dose, interval, route, and time of administration, will be divided into 0-6 category groups. The Gyssens method has been used generally throughout the world.[19]

This study was conducted to measure the rationality of antibiotic use using the Gyssens method in the population of sepsis patients in the ICU of Dr. Mohamad Soewandhie Hospital. Unlike previous studies, which have largely focused on antibiotic resistance patterns or general prescribing trends, this research specifically applies the Gyssens method to critically ill sepsis patients, providing a structured and comprehensive evaluation of antibiotic use in a real-world ICU setting. By assessing the accuracy of indication, selection, dosage, and administration timing, this study aims to generate evidence-based insights that can guide more rational antibiotic prescribing practices, ultimately contributing to efforts in antimicrobial stewardship. The findings will be particularly relevant for hospitals in Indonesia, where data on the rationality of antibiotic use in ICU settings remains limited. Additionally, as Dr. Mohamad Soewandhie Hospital serves as both a community referral and a teaching hospital, the results of this study can have a broader impact on medical education and clinical decision-making in the country. The objective of this study is to assess the rationale of antibiotic therapy in patients diagnosed with sepsis in the ICU of Dr. Mohamad Soewandhie General Hospital using the Gyssens Method, with the goal of improving antibiotic stewardship and optimizing patient outcomes.

2. METHOD

The research design used was a retrospective method by studying secondary data. Data were taken from medical records of 120 sepsis patients who received antibiotic therapy who were treated in the Intensive Care Unit (ICU) of Dr. Mohamad Soewandhie Hospital. Sample collection was carried out by consecutive sampling of all adult sepsis patients who were hospitalized in the ICU from January 2021 to September 2024. Qualitative evaluation was carried out to see the accuracy of empirical antibiotic administration according to the Gyssens method which is categorized into 0-6 groups, namely:

Category 0 (Rational): Cases where antibiotics are appropriate.
Category I (Timing Issues): Errors related to the timing of administration.
Category IIa (Wrong Dose): Incorrect antibiotic dose.
Category IIb (Incorrect Interval): Incorrect dosing interval.
Category IIc (Wrong Route): Wrong route of administration.
Category IIIa (Too Long Duration): The duration of antibiotics is too long.
Category IIIb (Too Short Duration): The duration of antibiotics was too short.
Category IVa (More Effective Alternative): There are other antibiotics that are more effective.
Category IVb (Less Toxic Alternatives): There are other antibiotics that are less toxic.
Category IVc (Cheaper Alternatives): There are other antibiotics that are cheaper.
Category IVd (Narrower Spectrum Alternatives): There are other antibiotics that have a narrower spectrum.
Category V (No Indication): There is no indication for antibiotic use.
Category VI (Incomplete Data): Incomplete data.

3. RESULTS

Patient characteristics were evaluated based on age, gender, patient origin when initially hospitalized, referral status, source of health financing, and duration of ICU stay.

Table 1.
Patient Characteristics (N= 120)

Patient Demographics	n	%
Age		
25-40	12	10
41-55	30	25
>55	78	65
Gender		
Male	57	47.5
Female	63	52.5
Origin of Room		
Emergency unit	114	95
Non-Emergency unit	6	5
Patient Origin		
Inpatient	49	40.8
Outpatient	71	59.2
Length of stay in ICU		
<1-3 days	41	34.17
4-7 days	37	30.83
8-14 days	27	22,5
>14 days	15	12,5

Table 2.
Source of Infection in Patients with Sepsis Diagnosis in ICU (N = 120)

Source of Infection	n	%
Source of Infection Known		
Respiratory Tract Infection		
Community Acquired Pneumonia	58	48.3
Health Care Associated Pneumonia	6	5
Mycobacterium tuberculosis	2	1.7
Leptospirosis	1	0.8
Skin/Adnexal Infection		
Chronic infected wounds (Diabetic ulcers, Gangrene Pedis, Decubitus, etc.)	5	4.2
Cellulitis (cruris, pedis)	3	2.5
Gastrointestinal Infection		
Spontaneous Bacterial Peritonitis (Postoperative, Appendix Perforation)	4	3.3
Gastrointestinal bleeding (Gastroenteritis, Colon Carcinoma)	3	2.5
Acute cholangitis	1	0.8
Urinary Tract Infection		
Urinary Tract Infection (e.g. Urinary Tract Stones)	9	7.5
Urosepsis (proven by Urine Culture+)	3	2.5
No Indication for Antibiotics		
Suspected Misdiagnosis		
Viral Infection (Acute Viral Hepatitis, DHF)	2	1.7
Hypovolemic Shock	3	2.5
Cardiogenic Shock	2	1.7
Source Of Infection Unknown		
(The cause of infection is unknown even in discharged patients)	18	15

There were variations of the diagnosis of comorbid disease groups in sepsis patients in this study.

Table 3.
Diagnosis List of Comorbid Diseases (N=120)

Diagnosis of Comorbid Disease Groups	**n**	**%**
Acid Base Disorders, Fluid & Electrolyte Imbalance	63	52.5
Blood and/or Plasma Protein Disorders	73	60.8
Cardiovascular Disorders/Underlying Heart & Vascular Diseases	31	25.8
Gastrointestinal Disorders	30	25
Respiratory Tract Diseases	89	74.2
Liver Diseases	27	22.5
Urinary Tract Diseases	31	25.8
Skin Wound Infection	18	15
Renal Disorder	27	22.5
T2DM & T2DM related disorders	46	38.3
Neurological Disorders	34	28.3
Malignancy	4	3.3
History of Trauma	3	2.5

In this study, 22 types of antibiotic therapy were found, namely 3 types of monotherapy antibiotics and 19 types of combination therapy. The most common antibiotic use was intravenous cephalosporin injection with the choice of 2x1 gram ceftriaxone injection antibiotics. In this study, 10 patients (8.3%) received definitive antibiotic therapy (antibiotic therapy based on culture and sensitivity test results), while 110 (91.7%) patients received empirical antibiotic therapy.

Table 4.
Types of Antibiotic Therapy Combinations Used in Sepsis Patients in ICU (N=120)

Types of Antibiotic Combinations	**Number of Patients who received Therapy**	**Rationality of Antibiotic Therapy**		***Outcome***	**%**
		Appropriate (Category 0)	**Inappropriate (Category I-VI)**		
Cephalosporin iv monotherapy	47 patient[1]	18	29	33 patients died, 14 patients alive	39.2
Cephalosporin i.v+carbapenem i.v	3 patients[2]	2	1	Died	2.5
Cephalosporin i.v+penicillin iv	1 patient[3]		1	Died	0.83
Cephalosporin i.v+aminoglioside i.v	1 patient[4]		1	Died	0.83
Cephalosporin i.v+carbapenem i.v+quinolone i.v +imidazole i.v+beta lactam i.v.	3 patients[5]	3		Died	2.5
Cephalosporin i.v+quinolone i.v.+imidazole i.v+penicillin i.v	2 patients[6]	2		Died	1.67
Cephalosporin i.v + carbapenem i.v + quinolone i.v + imidazole i.v	1 patient[7]	1		Died	0.83
Cephalosporin i.v+imidazole iv	8 patients[8]	4	4	6 patients died, 2 patients alive	6.67
Cephalosporin i.v+imidazole i.v+tetracycline i.v	1 patient[9]	1		Died	0.83
Cephalosporin i.v+imidazole i.v+aminoglycoside i.v	1 patient[10]		1	Died	0.83
Cephalosporin i.v+imidazole i.v+carbapenem i.v	4 patients[11]	4		Died	3.3
Cephalosporin i.v+quinolone iv	11 patients[12]	8	3	9 patients died, 2 patients alive	9.17
Cephalosporin i.v+quinolone i.v+imidazole i.v	7 patients[13]	6	1	Died	5.83
Cephalosporin i.v+quinolone i.v+penicillin i.v	1 patient[14]	1		Died	0.83
Cephalosporin i.v+quinolone i.v+carbapenem i.v	1 patient[15]	1		Died	0.83
IV quinolone monotherapy	20 patients[16]	17	3	16 patients died, 4 patients alive	16.7
Quinolone i.v+RHZE+imidazole iv	1 patient[17]	1		Died	0.83
Quinolone i.v+carbapenem iv	2 patients[18]	2		Died	1.67
Quinolone i.v+aminoglycoside iv	1 patient[19]	1		Died	0.83
Quinolones i.v+imidazoles i.v+carbapenems i.v	2 patients[20]	2		Died	1.67
Carbapenem monotherapy	1 patient[21]		1	Died	0.83
Carbapenem i.v+tetracycline i.v+aiminoglycoside i.v	1 patient[22]		1	Died	0.83
Total	120 patients	74	46	22 patients alive, 98 patients died	18.3 81.7 100.0

Notes:
[1]Ceftriaxone IV 2x1 g
[2]Ceftriaxone IV 2x1 g +Meropenem IV 3x1 g
[3]Cefoperazone Sulb 2x2 g IV + Ampicillin Sulb 3x1.5 g IV
[4]Cefoperazone Sulb 2x1 g IV + Gentamicin 5g Topical
5Ceftriaxone 3x1 g IV + Levofloxacin 1x375 mg IV (48 hours), Ceftazidime 3x195 mg IV + Levofloxacin IV 1x750 mg (6 days), Ampicillin Sulbactam 3x1.5 g IV (3 days) in combination with Moxifloxacin 1x400 mg IV (7 days) + Cefoperazone Sulb 2x1 g IV (2 days) + Meropenem 2x1 g IV (3 days)
[6]Levofloxacin IV injection 1x500 mg combination +Cotrimoxazole 2x960 mg IV, Ampicillin Sulb 3x1 g IV, Ciprofloxacin 2x400 mg IV + Metronidazole IV injection 3x500 mg + Ceftriaxone IV injection 3x1 g
[7]Levofloxacin 1x750 mg (3 days), Ceftriaxone 2x1 g IV (4 days), Metronidazole 3x500 mg (4 days) + Meropenem 3x1 g IV (4 days)

[8]Ceftriaxone 2x1 g IV + Metronidazole 3x500 mg IV
[9]Ceftriaxone 2x1 g IV (8 days), Cefoperazone Sulb 3x1 g IV (8 days), Fluconazole 1x400 mg IV (6 days), Tigecycline 1x100 mg IV (initial) continued 2x50 mg IV (4 days)
[10]Cefoperazone Sulb 2x1 g IV (10 days), Fluconazole 1x200 mg IV (20 days) + Amikacin 1x250 mg IV (20 days)
[11]Ceftriaxone 2x1 g IV (1 day) + Metronidazole 3x500 mg IV (2 days), Meropenem 3x1 g IV (1 day)
[12]Ceftriaxone 2x1 g IV + Moxifloxacin 1x400 mg IV
[13]Moxifloxacin 1x400 mg IV (14 days) + Fluconazole 1x400 mg IV (10 days), Metronidazole 3x500 mg IV (6 days) + Cefoperazone Sulb 3x1 g IV (3 days)
[14]Levofloxacin 1x750 mg IV (2 days) + Ampicillin Sulb 4x1 g IV (2 days) + Ceftazidime 3x2 g IV (5 days)
[15]Moxifloxacin 1x400 mg IV (7 days), Meropenem 2x1 g IV (14 days), Ceftazidime 3x1 g IV (14 days)
[16]Moxifloxacin 1x400 mg IV
[17]Levofloxacin 1x750 mg IV (12 days) + Isoniazid 1x300 mg Oral (6 days) + Rifampicin 1x400 mg Oral (6 days) + Pyrazinamide 1x1.5 g Oral (6 days) + Streptomycin 1x1 g IV (6 days), Fluconazole 1x200 mg IV (2 days)
[18]Moxifloxacin 1x400 mg IV, Meropenem 3x1 g IV
[19]Ciprofloxacin 2x200 mg + Gentamicin 2x80 mg IV
[20]Levofloxacin 1x750 mg IV (9 days), Fluconazole 1x200 mg IV (2 days) + Meropenem 3x1 g IV (2 days)
[21]Meropenem 3x1 g IV (6 days)
[22]Meropenem 3x1 g IV (8 days), Tigecycline 1x100 mg IV (8 days) + Amikacin 2x250mg IV (8 days), Mycamin 1x100 mg IV (8 days)

Table 5.1
Gram-Positive and Negative Bacteria Isolates and Antibiotic Sensitivity Patterns in ICU Patients (2021-2024)

Species	Specimens				Recommended Antibiotics	Antibiotics that should be avoided
	Blood	Urine	Pus	Sputum		
Gram-Positive Bacteria						
Streptococcus pseudoporcinus (1 of 120, 0.8%)	1				Cefotaxime, Ceftriaxone, Chloramphenicol, Gentamicin, Erythromycin, Linezolid, Tigecycline, Rifampicin, Trimethroprim/Sulfamethoxazole, Levofloxacin, Moxifloxacin.	Benzylpenicillin, Oxacillin, Vancomycin, Clindamycin, Tetracycline, Penicillin G, and Erythromycin. (This is due to low sensitivity and even some gram-positive bacterial isolates are already resistant)
Staphylococcus aureus (6 of 120, 5%)	1	1		4		
Gram-Negative Bacteria						
Acinetobacter baumannii (7 of 120, 5.8%)		1		6	Piperacillin/Tazobactam, Amikacin, Ceftazidime, Cefepime, Aztreonam, Gentamicin, Ciprofloxacin, Meropenem, Imipenem, and Ertapenem.	Amoxicillin, Ampicillin, Ceftriaxone, Cefotaxime, Cefazoline, Tetracycline. (This is due to low sensitivity and even some gram-negative bacterial isolates are already resistant)
Escherichia coli (4 of 120, 3.3%)		3		1		
Pseudomonas aeruginosa (2 of 120, 1.7%)	1			1		
Morganella morganii (2 of 120, 1.7%)			2			
Stenotrophomonas maltophilia (2 of 120, 1.7%)				2		
Proteus mirabilis (1 of 120, 0.8%)			1			
Klebsiella pneumoniae (1 of 120, 0.8%)				1		

Table 5.2
Multidrug-Resistant Organism (MDRO) Isolates and Antibiotic Sensitivity in ICU Patients (2021-2024)

Most common MDRO isolates in the ICU		
Species	**Number of Isolates**	**Recommended Antibiotics**
Acinetobacter baumannii	7	Meropenem, Ertapenem, Tigecycline, Erythromycin, Clindamycin.
Staphylococcus aureus	2 of 6 isolates +MRSA	
Escherichia coli	1 of 4 isolates +ESBL	
Klebsiella pneumoniae	1 isolate +ESBL	

Researchers evaluated the rationality of administering antibiotic therapy to sepsis patients in the ICU with the assistance of three reviewers who were experts in the Gyssens method, with the dominant review results after analysis by the three reviewers which would be taken to decide whether the patient received rational or irrational antibiotic therapy.

Likewise, the selection of respondents in this study was patients with a diagnosis of sepsis who were treated in the ICU of Dr. Mohamad Soewandhie Hospital. The diagnosis of sepsis has been determined by the doctor treating the patient (based on medical records) where the medical record data must be complete (in accordance with what is required in the Case Record Form which includes: patient identity, date of admission and discharge from the hospital, diagnosis and health status, physical and supporting examinations, and history of antibiotic use) and the respondents studied were only adult patients (>20 years).

Table 6
Allocation of The Number of Patients Based On The Rationality of Antibiotic Therapy and Outcomes (N = 120)

Rationality of Antibiotics Therapy	**Patients' Outcomes**		**Total**
	Alive	**Died**	
	n	n	
Appropriate Therapy	11	63	74
Inappropriate Therapy	11	35	46
	22	98	120

Table 6 Explanations:
1. Risk of death in the appropriate therapy group : 63/74 ≈ 0.851 (or 85.1%)
2. Risk of death in the inappropriate therapy group : 35/46 ≈ 0.761 (or 76.1%)
3. Absolute Risk Reduction (ARR):
   ARR measures the absolute difference in risk between two groups.
   ARR = Rappropriate – Rinappropriate = 0.851−0.761 = 0.090 or 9%
4. Relative Risk Reduction (RRR):
   RRR is the proportional reduction in risk between two groups.
   RRR = ARR/Rappropriate = 0.090/0.851 ≈ 0.106 (or 10.6%)
5. Number Needed to Treat (NNT):
   NNT indicates how many patients need to receive the "appropriate" therapy to prevent one additional death.
   NNT = 1/ARR = 1/0.090 ≈ 11.1 (rounded to 11 patients)
6. Attributable Risk (AR):
   AR reflects the excess risk attributed to exposure to inappropriate therapy.
   AR = Rinappropriate−Rappropriate = 0.761−0.851 = −0.090 or −9%
7. Attributable Risk Percent (AR%):
   AR% shows the percentage of risk in the inappropriate group attributable to receiving inappropriate therapy.
   AR%= (Rinappropriate/AR)×100 = (−0.090/0.761) × 100 ≈ −11.8%
8. PR (Prevalence Ratio) calculation : (Rappropriate/Rinappropriate)
   = 0.851/0.761 ≈1.12
9. OR (Odds Ratio) calculation : (11x35)/(11x63) ≈ 0.56

4. DISCUSSION

In the ICU, 52 of 120 sepsis patients (43.33%) received combination antibiotic therapy. Of the 52 patients, only 20 patients (16.7%) underwent culture tests to determine the type of infecting microorganism and ensure the accuracy of antibiotic selection. As many as 35 of 52 patients (67.3%) received empirical antibiotic combinations without bacterial culture results. This was likely due to the patients' critical condition upon arrival, necessitating immediate empirical therapy, as well as the prolonged time required to obtain culture test results.The most common use of combination antibiotics was a combination of ceftriaxone (33 combination therapies) with other antibiotics such as metronidazole, levofloxacin, and meropenem. Ceftriaxone is also the most widely used empirical antibiotic, both as single therapy and in combination.[20]

Our data revealed that although a high proportion of patients received “appropriate” antibiotic therapy, overall mortality remained elevated (81.7%). In fact, the calculated prevalence ratio (PR) indicated that patients receiving appropriate therapy had a 12% higher risk of death compared with those receiving inappropriate therapy (PR = 1.12, 95% CI: 0.93–1.35). In parallel, the odds ratio (OR) for survival was 0.56 (95% CI: 0.22–1.42). These seemingly paradoxical findings underscore that while antibiotic choice is crucial, other factors—such as timeliness of administration, severity of illness, and comorbidities—likely contribute substantially to the outcome.

The high number of death outcomes in most sepsis patients in the ICU is generally caused by the patient's poor condition when they are admitted to the hospital, so that many patients undergo a very short duration of treatment and culture results are not yet available. In addition, other causes found from the outcome of death in patients include the selection of empirical antibiotics that are less effective in sepsis with certain types of comorbid diseases, elderly patients, the occurrence of co-infections during treatment, and comorbid diseases owned by patients (DM, hypertension, cancer, metabolic disorders, organ and organ system failure, etc.) are considered to have a significant influence on the poor outcome of sepsis patients in the ICU.

Most of the patient deaths were dominated by septic shock cases (87 patients), but not all of them were purely due to septic shock alone. As many as 18 patients died due to respiratory failure, and a small portion (7 patients) experienced hypovolemic shock, in addition, electrolyte imbalance and metabolic disorders accompanying the patient were important causes of poor outcomes and even death. So that the patient's comorbid diseases greatly affect the number of poor patient outcomes.

These results revealed a paradoxical finding: despite 61.7% of patients receiving “appropriate” antibiotic therapy, overall mortality remained strikingly high (81.7%). A closer examination of the calculated indicators, including the Prevalence Ratio (PR), Odds Ratio (OR), Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), Number Needed to Treat (NNT), and Attributable Risk (AR), sheds light on the complexities underlying these outcomes. The calculated PR of 1.12 (95% CI: 0.93–1.35) indicated that the risk of death was 12% higher in patients who received “appropriate” therapy compared to those who received “inappropriate” therapy, though this finding was not statistically significant. The OR for survival was 0.56 (95% CI: 0.22–1.42), suggesting that patients who received appropriate therapy had lower odds of survival. These results align with previous studies that highlight the multifactorial nature of sepsis outcomes, where factors beyond antibiotic selection, such as delays in administration and comorbidities, play crucial roles.[21,22]

The ARR of 9% implies that appropriate therapy was associated with a 9% higher absolute risk of death compared to inappropriate therapy. Similarly, the RRR of 10.6% suggests that the relative risk of death increased by 10.6% in the appropriate therapy group. These findings may reflect confounding by indication — sicker patients or those presenting with more severe forms of sepsis likely received broader-spectrum antibiotics deemed "appropriate" according to the Gyssens method. This phenomenon has been documented in previous research, where patients at higher risk of mortality were more likely to receive appropriate therapy, potentially biasing the observed associations.[7,23,24]

The calculated NNT was 11, meaning that 11 patients needed to receive appropriate therapy to prevent one additional death. However, given the high overall mortality rate, this number may indicate that antibiotic appropriateness alone was insufficient to counteract the severity of illness in these patients. Other interventions, such as source control and early hemodynamic support, may have been underutilized.[22,25,26]

The negative AR of -9% and AR% of -11.8% further support the notion that factors outside antibiotic appropriateness contributed to mortality. Inappropriate therapy may not have been the primary driver of poor outcomes — instead, advanced age, multi-organ dysfunction, and delays in initiating therapy could have outweighed the benefits of appropriate antibiotic selection. These results echo findings from other studies indicating that even when antibiotics are correctly chosen, survival is strongly influenced by the timing of administration, fluids administration, use of vasopressors. patient comorbidities, and the rapid progression of sepsis.[21,27–29]

The use of antibiotics for patients is reviewed by three observers, comprising two internal medicine specialists and one pulmonologist, all of whom are highly experienced in infectious diseases and the Gyssens method. The inter-rater agreement between these three reviewers was assessed using Cohen's kappa statistic, which indicated a good level of agreement ($\kappa = 0.75$, $p < 0.05$). Two out of three reviewers' assessments were considered final in determining the appropriate antibiotic therapy group. One of the guidelines used by reviewers to determine the rationality of antibiotic therapy given to sepsis patients in the ICU is the Panduan Praktis Klinis Penyakit Dalam Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia (PPK PAPDI).[30] The large number of Gyssens IVa categories (less effective) is mostly dominated by the use of IV ceftriaxone injection in sepsis patients with pneumonia, which, according to the reviewers, is considered less effective and not in accordance with the guidelines for the management of sepsis with pneumonia.

One reviewer also stated that the appropriate empirical therapy for sepsis with pneumonia when adjusted to the guidelines for the management of sepsis is the use of levofloxacin injection or the second option, namely ceftriaxone combined with the macrolide group. Based on *Panduan Praktis Klinis Penyakit Dalam Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia* (PPK PAPDI) that used by the reviewers, which recommend the use of class III cephalosporin antibiotics as empirical therapy in sepsis. However, the main problem encountered was that many patients with a history of respiratory tract infection (especially pneumonia) were given antibiotic therapy that was less appropriate (such as ceftriaxone) with the clinical guidelines.[7,31,32] This was considered as one of the causes of inappropriate therapy, which contributed to poor outcomes, including death in the majority of patients (98 of the total 120 patients).

The quality of antibiotic use from January 2021 to September 2024 in all patients in this study was mostly (60%) categorized as rational (category 0). The use of antibiotics that were categorized as inappropriate (categories I-IV) and no indication (category V) were 39.2% and 0.8%, respectively. These results are better than the study by Ibrahim et al. (2020)[14] who also researched a similar topic at RSPAL Dr. Ramelan Surabaya, which obtained the results of the rationality of category 0 antibiotic therapy of 44.05% of the total population of 84.

Some gram-negative bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*, show resistance to ceftriaxone antibiotics, so cephalosporins may be less effective in treating these microorganisms. Researchers found that the high use of ceftriaxone in sepsis patients with gram-negative infections, even though it is known that high levels of resistance, can be caused by the determination of broad-spectrum antibiotics that follow trends (commonly used), hospital policies, and/or the use of guidelines that have not been updated. In addition, it can also be caused by the suboptimal use or procurement of germ maps in local hospitals is also an important point that can be the main cause of the many cases of resistance in sepsis patients. Even though several types of antibiotics found from culture results are not available at the hospital, the hospital always has alternative antibiotics that are in accordance with the culture results obtained, so that all patients who have culture results can be assessed as having received appropriate (definitive) antibiotic therapy.

A total of 45 patients received empirical antibiotic therapy with intravenous cephalosporin monotherapy. Bacterial findings showed a prevalence of MDRO of 67.9% in the ICU, with 19 of 28

isolates testing positive for MDRO. Of the total 120 patients, only 18 patients had culture results, which is very unfortunate for the provision of appropriate antibiotic therapy and patient outcomes. However, most patients who did not have culture results were patients who came in very severe conditions so that culture tests were likely to have been performed, but the patient in question was no longer able to survive. Because almost all of the patient's medical record data was found to have been proposed by the doctor in charge to perform blood culture tests and/or other specimens on the patient.

Comparison with Previous Studies

Our findings resonate with recent literature indicating that the management of sepsis is multifactorial. For example, Evans et al. (2021)[26] emphasized that prompt initiation of effective antimicrobial therapy is essential; however, they also noted that even early treatment might not overcome the effects of severe organ dysfunction or high bacterial loads. Similarly, [27,28,33]demonstrated that while early and appropriate antibiotic therapy is associated with improved outcomes, the overall prognosis in sepsis is significantly influenced by the patient's underlying condition and the rapid progression of the disease. In our study, the higher mortality observed in the "appropriate" therapy group may reflect a selection bias where sicker patients—those with multiple comorbidities and advanced disease severity—are more likely to be managed with what is deemed "appropriate" therapy according to the Gyssens method. This interpretation is supported by several recent investigations that highlight the interplay between antimicrobial stewardship and the patient's baseline severity of illness.[34]

In settings with a high prevalence of the outcome, as seen in our cohort, the risk ratio (or prevalence ratio) is a more intuitive measure than the odds ratio. Our PR of 1.12 suggests that mortality risk was 12% higher in the appropriate therapy group, although this counterintuitive result likely reflects confounding factors such as delayed antibiotic administration or higher initial severity of sepsis in this group. On the other hand, the OR of 0.56 for survival—while informative for comparative purposes—may overestimate associations when outcomes are common.[35] Reporting both measures enriches the discussion by providing a dual perspective on the association, while also emphasizing the need for cautious interpretation in retrospective, cross-sectional studies.

Although the Gyssens method classified the majority of antibiotic treatments as "appropriate" (Category 0), the overall mortality remained high (98 of 120 patients, approximately 81.7%). This paradox may be explained by several factors that extend beyond antibiotic selection:

a. Delay in Antibiotic Initiation:

Even when the choice of antibiotics is optimal, delayed administration can critically worsen outcomes. Studies have demonstrated that every hour's delay in effective therapy is associated with increased mortality in sepsis.[7,27,35]

b. Severity of Illness and Organ Dysfunction:

Sepsis is a complex syndrome characterized by a dysregulated host response that can lead to shock and multiple organ dysfunction. Patients presenting with severe sepsis or septic shock—regardless of receiving "appropriate" therapy—may have an inherently poor prognosis.[27,28,34,36]

c. Patient Characteristics and Comorbidities:

Factors such as advanced age, underlying chronic conditions (e.g., cardiovascular, respiratory, renal disorders), and a high burden of comorbidities (as shown in Table 2 above) may further impair the response to treatment. Such patient-related factors have been repeatedly linked to worse outcomes in sepsis.[22,34,36–38]

d. Infection Source and Bacterial Load:

The type of sepsis (for instance, pulmonary versus abdominal) and the extent of the infection may also influence mortality. It is possible that, even with appropriate therapy, patients with high

bacterial loads or infections originating from difficult-to-treat sites might experience treatment failure.[7,39]

e. Alternative or Adjunctive Therapies:

In cases where patients worsen despite receiving guideline-adherent antibiotics, the consideration of adjunctive measures (such as source control, hemodynamic support, or immunomodulatory therapies) is crucial. The data may suggest that in some patients, the progression of sepsis occurred too rapidly or was compounded by other complications, thereby negating the potential benefits of the selected antibiotic regimen.

In summary, the high death rate may be a reflection not solely of antibiotic choice but of delays in treatment, severe underlying pathophysiology, and complex patient comorbidities that collectively drive poor outcomes in the ICU.

While this study provides valuable insights into the relationship between antibiotic appropriateness and outcomes in sepsis patients, several limitations should be acknowledged. The retrospective cross-sectional design of our study precludes us from establishing causality between the observed associations, and unmeasured variables such as time to antibiotic initiation and overall severity of patients' conditions may have confounded our results. Furthermore, the single-center setting of our study, conducted in a tertiary care hospital, may limit the generalizability of our findings to other regions with different local protocols, microbial flora, and patient demographics. Additionally, the retrospective nature of our study design may have introduced incomplete data and misclassification bias, particularly in assigning the rationality of antibiotic therapy using the Gyssens method, which could have impacted the accuracy of our results.

Despite these limitations, our study provides valuable insights into the complex relationship between antibiotic stewardship and sepsis outcomes. By employing the Gyssens method, we offer a structured evaluation of antibiotic appropriateness in a critically ill population. This approach not only reinforces the importance of rapid, guideline-adherent antibiotic administration but also highlights the need for integrated strategies that address other determinants of sepsis mortality, such as early source control and comprehensive supportive care. Our findings contribute to the growing body of evidence aimed at optimizing sepsis management, which may ultimately inform future clinical protocols and antimicrobial stewardship programs in similar resource-limited settings.

5. CONCLUSION

Based on the Gyssens method, 60% of antibiotic use in sepsis patients at Dr. Mohamad Soewandhie Hospital was classified as rational (Category 0), though irrational use (Category IVa) was common in pneumonia cases treated with ceftriaxone monotherapy. Poor outcomes (98 deaths out of 120) were influenced by delayed appropriate therapy and outdated sepsis management guidelines. Key recommendations include updating antibiotic protocols based on resistance patterns, conducting antimicrobial sensitivity testing, ensuring cultures are performed before antibiotic administration in severe cases, and optimizing germ maps through the *Program Pengendalian Resistensi Antimikroba (PPRA)*.

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