Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 34–43

OPEN ACCESS

Original Article

Evaluation of Definitive Antibiotic Therapy Effectiveness in Sepsis Patients at Tabanan Hospital, Indonesia

Luh Rai Maduretno Asvinigita[1,5], Ketut Tunas[2], Ida Ayu Alit Widhiartini[3], Agata Widatama[4], Rini Noviyani[1]

[1]Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Udayana University, Bali, Indonesia
[2]Program of Health Information Management, Faculty of Health Science, Bali Internasional University, Bali, Indonesia
[3]Department of Pharmacology and Therapy, Faculty of Medicine, Udayana University, Bali, Indonesia
[4]Installation of Pharmacy, Tabanan Hospital, Bali, Indonesia
[5]Apotek Bhakti Widya Farma (BWF), Bali, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1210

Accepted: October 07th, 2024
Approved: March 13th, 2025

Author Affiliation:
Department of Pharmacy,
Faculty of Mathematics and Natural Sciences,
Udayana University, Bali, Indonesia

Author Correspondence:
Rini Noviyani
Raya Kampus Unud street,
Bukit Jimbaran 80361, Indonesia

E-mail:
rini.noviyani@unud.ac.id

Abstract

Background : The study evaluated the use of definitive antibiotics and examined the association between the causative bacteria, resistance patterns, and antibiotic regimens with clinical outcomes in sepsis. This study was aimed to assess the suitability of definitive antibiotics in sepsis patients at Tabanan Hospital, focusing on the correlation between bacterial type, antibiotics, and resistance profiles with clinical outcomes, aiming to improve sepsis management and reduce antibiotic resistance.
Methods : The observational cross-sectional study analyzed data descriptively to evaluate antibiotic-pathogen compatibility retrospectively. Chi-square tests were used for bivariate analysis of mortality-related variables. Survival analysis employed the Kaplan-Meier method.
Results : Among 112 sepsis patient records (Jan 2020 – Dec 2022), 62% received antibiotics based on bacterial sensitivity test contradiction to another 38% who were given inappropriately antibiotic. Empiric antibiotic treatment was associated with increased mortality (OR=4.379; CI 95% 1.274-15.052; *p*=0.022). Bacterial type and resistance status showed no significant association with mortality (OR=0.417; CI 95% 0.030–5.708; *p*=1.000 and OR=1.500; CI 95% 0.156–14.420; *p*=1.000, respectively).
Conclusion : Definitive antibiotic use for sepsis patients at Tabanan Hospital was mostly appropriate, and the empiric antibiotics treatment was associated with mortality, while the causal bacteria and resistance status were not significantly associated with mortality. Findings highlight the importance of transitioning from empiric to targeted therapy to potentially reduce mortality in sepsis management.

Keywords: antimicrobial stewardship, clinical outcomes, definitive antibiotics, empiric antibiotics, sepsis.

INTRODUCTION

Sepsis, as defined by the World Health Organization, represents a critical, life-threatening medical condition characterized by a dysregulated and excessive immune response to infection, culminating in potentially devastating organ dysfunction.[1] This aberrant immune response precipitates a cascade of tissue and organ damage, potentially culminating in shock, multisystem organ failure, and mortality if not promptly identified and treated. The global burden of sepsis is substantial, with an annual incidence of 731 cases per 100,000 individuals. Notably, sepsis-associated mortality rates surpass those of several other significant health conditions, including heart failure, breast cancer, colorectal cancer, and AIDS.[2] This underscores the critical nature of sepsis as a public health concern and emphasizes the urgency for improved diagnostic and therapeutic strategies.

This study aims to assess the congruence between definitive antibiotic selection and causative pathogens in sepsis cases, while also examining the relationships between bacterial species, antibiotic classes, resistance patterns, and clinical outcomes at Tabanan Hospital. The findings are intended to provide valuable insights to clinicians and hospital administrators, informing evidence-based practices for optimal definitive antibiotic utilization in sepsis management.

Healthcare institutions in developing nations frequently face significant infrastructural and resource constraints, impeding their capacity to deliver optimal care to their populations. Existing facilities often operate under suboptimal conditions, characterized by inadequate sanitation, poor ventilation, unreliable electrical supply, and insufficient lighting.[3] These deficiencies not only compromise patient safety but also create an environment conducive to the proliferation of healthcare-associated infections. Such systemic challenges can significantly impede the implementation of appropriate treatment protocols and exacerbate the risk of adverse outcomes. In Indonesia, the burden of sepsis remains particularly pronounced, with incidence rate of 30.29% and a mortality rate from 11.56% to 49%.[4] These statistics highlight the critical importance of implementing focused interventions and enhancing sepsis management protocols within Indonesia's healthcare infrastructure. The data emphasizes the pressing need for strategic improvements to address the significant burden of sepsis in the country.

According to the Surviving Sepsis Campaign (SSC) guidelines,[5] which align with the protocol at Tabanan Hospital, the primary treatment for sepsis is administering antibiotics within the first hour of diagnosis. Tabanan Hospital is a teaching hospital with 160 beds located in the district of Tabanan in Bali, Indonesia, which provides healthcare services to patients, especially treatment for sepsis. Antibiotics are one of the most important therapies in managing sepsis cases and are an effective intervention to reduce mortality.[5] Sepsis patients should be given antibiotics immediately within the first 3 hours after the diagnosis of sepsis. The effectiveness of antibiotics for sepsis patients is that it can prevent the severity of sepsis from turning into septic shock.[6] There are still many incidences of antibiotic resistance caused by the use of antibiotics in cases of sepsis. A study by Legese in 2022 reveals that there was a high incidence of multidrug resistance in Enterobacteriaceae bacteria (83.3%) and K*lebsiella pneumonia* (>80%) in several hospitals in Ethiopia on October 2019 – September 2020.[7] A study by Pradipta in 2013 found that of 25 types of antibiotics used in sepsis patients at hospitals in Bandung on May – August 2012, there was ≥ 50% resistance to 14 types of antibiotics.[8] In Bali, Multi Drug Resistant (MDR) was also found in 33 pediatric sepsis patients (52.4%) at the PICU (Pediatric Intensive Care Unit) at Sanglah General Hospital from January 2015 to April 2017.[9] Consequently, the appropriate use of antibiotics plays a very important role in preventing the occurrence of antibiotic resistance. Managing suspected sepsis requires personalized care. Immediate empiric therapy is crucial for patients with a high likelihood of infection, severe illness, or shock. The choice of empiric antimicrobials should consider infection sites, common pathogens, patient-specific resistance risk factors, and local antibiogram data.[10] The first antibiotic therapy given based on the management of SSC while waiting for culture results is empirical or broad-spectrum antibiotics.[5] Definitive antibiotics were administered once the culture results were available. The bacteria causing sepsis are also identified through a culture sampling procedure.[11]

The judicious application of definitive antibiotic therapy is important to reduce mortality rates and facilitate treatment de-escalation based on culture results and ongoing clinical laboratory data. This de-escalation process, which involves narrowing the antibiotic spectrum in response to definitive microbiological findings, is crucial in mitigating the emergence of antimicrobial resistance.[10] The selection of definitive antibiotics is contingent upon the identified pathogen and its specific resistance profile in each patient. However, discrepancies between antibiotic administration and sensitivity test results are not uncommon, potentially leading to suboptimal treatment outcomes. Inappropriate definitive antibiotic use can exacerbate antimicrobial resistance, consequently prolonging hospitalization and escalating healthcare costs.[12] Moreover, resistant infections in sepsis patients can double mortality rates, underscoring the critical nature of this issue. Therefore, a comprehensive evaluation of definitive antibiotic appropriateness in sepsis management is imperative[13] to reduce the

resistance to sepsis which can double the death rate.[14]

METHODS

Study Design and Setting

An observational research study was designed with a cross sectional performed at Tabanan Hospital from April to June 2023. The population used in this study included medical records of sepsis patients at Tabanan General Hospital who received empirical and definitive antibiotic therapy from January 2020 to December 2022. This study included sepsis patients at Tabanan General Hospital who met the inclusion and exclusion criteria. Total sampling was applied, with purposive sampling method. The research received approval from the ethical commission of Tabanan Hospital with reference number 445/220/TIMKORDIK/RSUD/2023.

Inclusion and Exclusion Criteria

The inclusion criteria of this study are all sepsis patients' medication records at Tabanan Hospitals documented thoroughly the patients' demography, diagnosed with sepsis who received empirical and definitive antibiotics, had microbiological culture sensitivity tests, and completed outcome therapy successively between January 2020 and 2022 were included as criteria. Incomplete and illiterate patient medication records were excluded from the study. All the comorbidities were documented as supporting data.

Data Analysis

The antibiotic's appropriateness was evaluated descriptively based on the culture sensitivity microbiological test result and the antibiotic use. The recommended antibiotic use is defined as a definitive antibiotic and another as an empirical antibiotic. The correlation of bacteria species, sensitivity or resistance status on the test result, and antibiotics use to the clinical outcome of the sepsis patients were analysed. Bivariate analysis was performed to determine the relationship between the variables related to mortality using the Chi-Square test. Survival analysis was conducted using the Kaplan-Meier test. The software used for the statistical test was SPSS version 29. A 95% confidence interval (CI) and p-values less than < 0.05 were considered significant. The results were presented in tables, figures, and narratives.

RESULTS

The research conducted at Tabanan Hospital from January 2020 to December 2022 involved a sample of 112 sepsis patients. After the inclusion criteria were applied, a total of 84 patients were identified, of which 71 patients received empirical antibiotic therapy and 13 patients received definitive antibiotic therapy.

The demographic and clinical characteristics of these sepsis patients are detailed in Table 1. The majority of patients were male, accounting for 48 cases (57.14%), compared to 36 female patients (42.86%). The age distribution was as follows: 9 patients (10.71%) were under 45 years old, 24 patients (28.57%) were between 45 and 60 years old, 40 patients (47.62%) were between 61 and 80 years old, and 11 patients (13.10%) were over 80 years old. Regarding comorbidities, anemia was the most prevalent, affecting 22 patients (22.62%).

Out of the 84 sepsis patients, 13 underwent culture tests. As shown in Table 2, infections caused by Gram-negative bacteria were more common, occurring in 9 patients (63.23%), compared to Gram-positive bacterial infections, which were observed in 4 patients (30.77%). This finding aligns with the general trend where the predominant cause of sepsis is Gram-negative bacteria which were about 62.2% of patients exhibiting positive blood cultures, while Gram-positive bacteria are responsible for infection in 46.8% of cases.[15]

Furthermore, in 13 patients who received definitive antibiotics, the most frequently prescribed antibiotic type was meropenem, which is a carbapenem class (Table 3). Meropenem is a broad spectrum carbapenem class of antibiotics because it works effectively on Gram-negative and Gram-positive bacteria.

Moreover, in this study, antibiotic sensitivity tests were performed on the group of patients receiving definitive antibiotics. Antibiotic sensitivity to bacteria was categorized into 3 parts, namely susceptible (S), intermediate (I), and resistant (R). Susceptible means that antibiotics can inhibit bacteria optimally, so they are effective for treatment. Intermediate means that antibiotics are less than optimal in inhibiting bacterial growth, so they are less effective for treatment, and resistance means that antibiotics are unable to inhibit bacterial growth and cannot be used for treatment. In addition, we also categorized antibiotic resistance into MDR and non-MDR; MDR if resistance occurs to three or more classes of antibiotics while if resistance occurs to less than three types of antibiotics it is classified as non-MDR. The results, based on antibiotic sensitivity to bacteria and MDR and non-MDR, all Gram-negative bacteria found as bacteria causing sepsis were sensitive to meropenem antibiotics (100%) with 6 patients categorized as MDR (Table 4), while Gram-positive bacteria were most sensitive to linezolid and vancomycin (Table 5) with only 1 patient categorized as MDR.

We also conducted an assessment of the appropriateness of the use of definitive antibiotics (Figure 1), which was seen by comparing the definitive antibiotics given to patients with the sensitivity of the

TABLE 1
Characteristics of sepsis patients using definitive antibiotics

Patients Characteristics	Number of Patients (N=84)	Percentage (%)
Gender		
Male	48	57.14
Female	36	42.86
Age		
< 45 years	9	10.71
45 – 60 years	24	28.57
61 – 80 years	40	47.62
> 80	11	13.10
Type of comorbidities*		
Anemia	19	22.62
Chronic Kidney Failure	18	21.43
Diabetes Mellitus	17	20.24
Hyperkalemia	12	14.28
Hypovolemia	9	10.71
Hyponatremia	7	8.33
Pneumonia	5	5.95
Encephalopathy	5	5.95
Heart Failure	5	5.95
Hypertension	3	3.57

*1 patient can suffer from > 1 co-morbidity

bacteria that cause sepsis, where the appropriate administration of definitive antibiotics is the administration of antibiotics that are included in the type of antibiotics that are sensitive based on the results of the sensitivity test, while the administration of definitive antibiotics is inappropriate if there is at least one antibiotic that is not included in the type of antibiotics that are sensitive based on the results of the sensitivity test. As a result, based on Figure 1, it can be seen that there were 8 patients whose used definitive antibiotics matched with sensitivity of the bacteria based on culture results (62%), obtaining that antibiotics were susceptible to bacteria. While there were 5 patients whose used definitive antibiotics did not match with the culture results (38%).

According to the Chi Square analysis, as shown in Table 6, it can be seen that the type of bacterial infection is not related to the impact of mortality (OR=0.417; 95% CI 0.030–5.708; p=1.000), and also does not show any relationship between resistance status and mortality risk in sepsis patients (OR=1.500; 95% CI 0.156–14.420; p=1.000). However, the type of antibiotic treatment is related to the clinical outcome of sepsis patients, namely alive or dead (OR=4.379; 95% CI 1.274–15.052; p=0.022).

Finally, we analyzed survival time using the Kaplan-Meier test, with the results showing that the median survival time due to sepsis in the empirical antibiotic group was 3.77 days (95% CI 2.820–5.180) and the definitive antibiotic group was 13.77 days (95% CI 9.182–14.818) (Figure 2).

DISCUSSION

Sepsis is a critical global healthcare that demands careful antimicrobial stewardship to prevent resistance. This study found a higher prevalence in males, particularly among those aged 61–80 years, highlighting a notable gender disparity.[15] This disproportionate distribution can be attributed to the differential immunomodulatory effects of sex hormones. Estrogen, predominant in females, enhances immune function, conferring a more

TABLE 2
Types of bacteria infecting sepsis patients receiving definitive antibiotic

Type of Bacteria	Specimen Used	Number of patients (N=13)	Percentage (%)
Gram-Negative			
Escherichia coli	Pus	2	15.39
Proteus mirabilis	Pus	2	15.39
Pseudomonas stutzeri	Pus	1	7.69
Enterobacter cloaceae complex	Blood	1	7.69
Providencia rettgeri	Pus	1	7.69
Klebsiella pneumoniae	Pus	1	7.69
Pseudomonas aeruginosa	Urine	1	7.69
Sub-Total		9	63.23
Gram-Positive			
Enterococcus faecalis	Blood	1	7.69
Enterococcus faecalis	Urine	1	7.69
Kocuria kristinae	Pus	1	7.69
Staphylococcus epidermidis	Pus	1	7.69
Sub-Total		4	30.77
Total		13	100

TABLE 3
Definitive antibiotics received by sepsis patients

Class of Antibiotics	Number of patients (N = 13)	Type of Antibiotics	Number of patients (N = 13)
Carbapenem	4	Meropenem	4
Glycopeptide	2	Vancomycin	2
Quinolones	2	Levofloxacin	1
		Moxifloxacin	1
Cephalosporins & Cephalosporins	1	Ceftriaxone + Cefotaxime	1
Cephalosporins & Nitroimidazoles	1	Ceftriaxone + Metronidazole	1
Cephalosporins & Aminoglycosides	1	Ceftriaxone + Amikacin	1
Quinolones & Nitroimidazoles	1	Levofloxacin + Metronidazole	1
Glycopeptide a & Aminoglycosides	1	Vancomycin + Amikacin	1
Total	13		13

robust immune response.[16] Conversely, testosterone, the primary male hormone, exhibits immunosuppressive properties, potentially predisposing men to a higher susceptibility to infections and sepsis.[17] This study also found that the most common comorbidity of sepsis patients was anemia, occuring due to inflammation, iatrogenic blood loss, and depression of serum iron levels.[17]

TABLE 4

Antibiotic sensitivity test to gram-negative bacteria based on culture results from sepsis patients given definitive antibiotics at the Tabanan Hospital in the period January 2020 – December 2022

Cultured Bacteria	Types of Antibiotics Tested																																		Type of Antibiotics used	Suitability	Multi Drug Resistant (MDR)
	CX			CP			CD			EM			MM			AM			AC			GC			CF			TG			NF			AP			TS			MD			LF			PT					
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R			
Eschericia coli	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	Ceftriaxone & Metronidazole	Not Appropriate	Non MDR
Eschericia coli	–	–	1	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	1	–	–	1	–	–	–	–	1	1	–	–	1	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	Meropenem	Appropriate	MDR
Pseudomonas stutzeri	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	–	–	1	–	–	1	1	–	–	Ceftriaxone & Cefotaxime	Not Appropriate	Non MDR
Enterobacter cloaceae complex	–	–	1	–	–	1	–	–	1	1	–	–	1	–	–	–	1	1	1	–	–	–	–	1	–	–	1	1	–	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	Vancomycin	Not Appropriate	MDR
Proteus mirabilis	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	–	–	1	1	–	–	–	–	–	–	–	–	–	1	–	–	Levofloxacin & Metronidazole	Not Appropriate	MDR
Proteus mirabilis	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	–	–	1	1	–	–	–	–	1	–	–	1	–	–	–	–	–	1	1	–	–	–	–	–	–	–	–	–	–	–	–	Amikacin & Ceftriaxone	Appropriate	MDR
Providencia rettgeri	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	Meropenem	Appropriate	MDR
Klebsiella pneumoniae	–	–	1	1	–	–	–	–	1	1	–	–	1	–	–	–	–	1	1	–	1	1	–	–	–	–	1	1	–	–	–	–	–	–	–	1	–	–	1	–	–	–	–	–	1	–	–	Meropenem	Appropriate	MDR
Pseudomonas aeruginosa	–	–	–	1	–	–	–	–	1	–	–	–	1	–	–	1	–	–	–	–	–	1	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	Meropenem	Appropriate	Non MDR

Abbreviations : S = *Susceptible*, I = *Intermediate*, R= *Resistant*, MDR = *MultiDrug-Resistant*;
CX = Ceftriaxone; CP = Cefepime; CD = Ceftazidime; EM = *Ertapenem*; EM = Meropenem; AM = Aztreonam; AC = Amikacin; GC = Gentamycin; CF = Ciprofloxacin; TG = Tigecycline;
NF = Nitrofurantoin; AP = Ampicillin; TS = Trimethoprim Sulfamethoxazole; MD = Metronidazole; LF = Levofloxacin; PT = Piperacillin Tazobactam

TABLE 5

Antibiotic sensitivity test to gram-positive bacteria based on culture results from sepsis patients given definitive antibiotics at the Tabanan Hospital in the period January 2020 – December 2022

Cultured Bacteria	Types of Antibiotics Tested																																		Type of Antibiotics used	Suitability	Multi Drug Resistant (MDR)
	TC			CF			MC			GC			CM			MD			MM			LF			LZ			AP			MF			AZ			SC			VM			NF			EC					
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R			
Kocuria kristinae	–	–	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	1	1	–	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	–	–	1	–	–	–	–	–	1	–	Moxifloxacin	Appropriate	MDR
Enterococcus faecalis	–	–	1	–	–	1	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	Amikacin & Vancomycin	Not appropriate	Non MDR
Enterococcus faecalis	1	–	–	1	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	1	–	–	1	–	–	–	–	1	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	Levofloxacin	Appropriate	Non MDR
Staphylococcus epidermidis	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	Vancomycin	Appropriate	Non MDR

Abbreviations : S = *Susceptible*, I = *Intermediate*, R= *Resistant*, MDR = *MultiDrug-Resistant*;
TC = Tetracycline, CF = Ciprofloxacin, MC = Methicillin, GC = Gentamycin, CM = Cefixime, MD = Metronidazole, MM = Meropenem, LF = Levofloxacin, LZ = Linezolid, AP = Ampicillin,
MF = Moxifloxacin, AZ = Azithromycin, SC = Streptomycin, VM = Vancomycin, NF = Nitrofurantoin, EC = Erythromycin

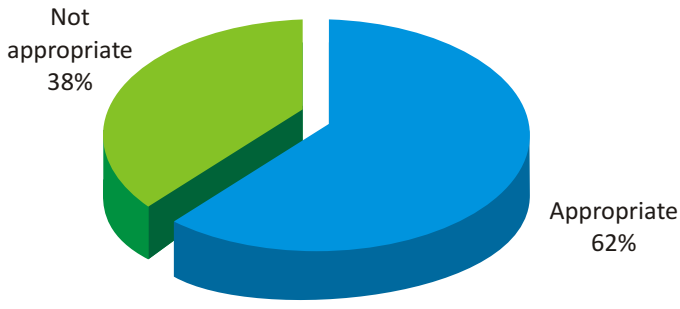

Figure 1. Appropriateness of the use of definitive antibiotics for the culture results of sepsis patients

TABLE 6
The association between bacteria types, resistance status, and antibiotic treatment type with clinical outcome of the sepsis patients

Variable	Clinical Outcome		OR	CI 95%	*p-value*
	Died	Live			
Type of Bacteria			0.417	0.030 – 5.708	1.000
Gram-positive	1 (25%)	3 (75%)			
Gram-negative	4 (44.4%)	5 (55.6%)			
Resistance Status			1.500	0.156 – 14.420	1.000
MDR	3 (42.85%)	4 (57.15%)			
Non-MDR	2 (33.33%)	4 (66.67%)			
Type of Antibiotic Treatment			4.379	1.274 – 15.052	0.022
Empiric	52 (73.24%)	19 (26.76%)			
Definitive	5 (38.46%)	8 (61.54%)			

Abbreviations: CI= Confidence Interval; OR= Odds Ratio; MDR= Multi Drug Resistant

Gram-negative bacteria are the leading cause of sepsis, responsible for 60–70% of cases, while Gram-positive bacteria account for 20–40%.[18] This aligns with research conducted in Prof. Dr. Margono Soekarjo Hospital, Purwokerto, Indonesia in 2018 identified Gram-negative bacteria in 13 patients and Gram-positive bacteria in 9 patients.[19] However, another study in Semarang, Indonesia, found that Gram-positive bacteria were the predominant cause in 83.32% of sepsis cases.[4] The most common Gram-negative bacteria at Tabanan General Hospital were *Escherichia coli* and Proteus mirabilis (15.39% each), while *Enterococcus faecalis* was the most common Gram-positive bacterium (15.39%). Similarly, a study in a Central Java hospital found *Escherichia coli* to be a prevalent cause of sepsis, and at Dr. Soetomo Hospital, Surabaya identified it as a common Gram-negative pathogen, with *Staphylococcus hominis* being the most frequent Gram-positive pathogen.[13,14]

At Tabanan Hospital, wound bed pus was the most common specimen for bacterial sensitivity testing in sepsis patients with skin infections, whereas sputum was more frequently used at Dr. Moewardi Hospital, Solo, Indonesia.[20] Definitive antibiotics are administered after identifying the causal bacteria through culture procedures, to specifically eradicate or inhibit the growth of the infectious bacteria.[11] Meropenem is a widely used definitive antibiotic for severe infections due to its broad-spectrum efficacy and minimal adverse effects, similar findings in Dr. Moewardi Hospital have been noted on frequent use of Meropenem in sepsis patients.[20,21] Meropenem, a broad-spectrum carbapenem, is effective against both Gram-negative and Gram-positive bacteria and is a preferred choice for treating severe sepsis and

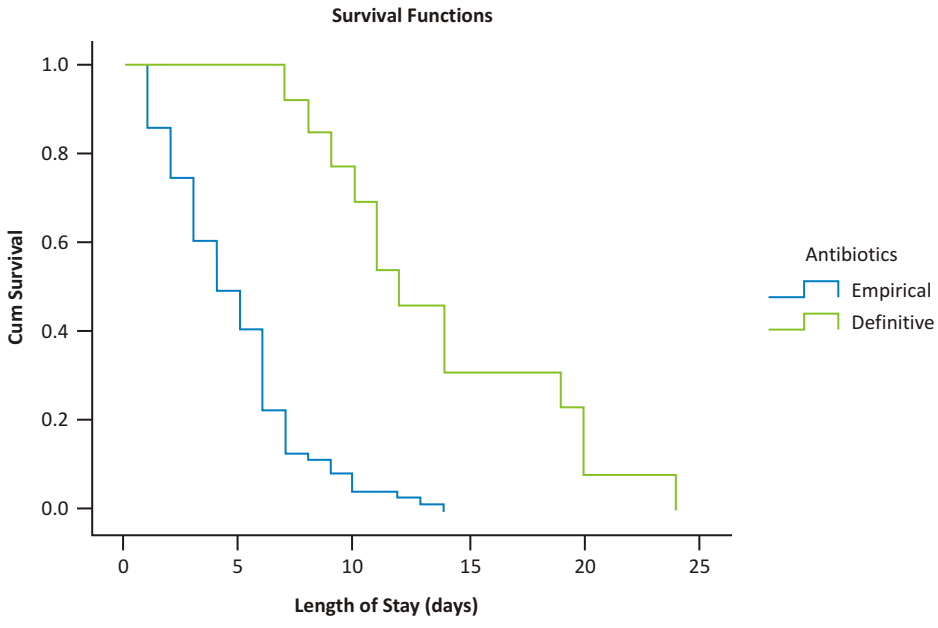

Figure 2. Kaplan Meier curves of mortality patterns in empirical and definitive antibiotic treatment of sepsis patients at Tabanan hospital in the period January 2020 - December 2022

septic shock due to its broad-spectrum efficacy and low toxicity.[21]

For antibiotic selection after culture, sensitive antibiotics are chosen based on susceptibility criteria, while bacteria classified as intermediate or resistant are considered non-sensitive. A bacterium is said to still be sensitive to antibiotics if it is included in the susceptibility criteria, and is said to be resistant if it is included in the intermediate and resistant criteria.[22] Based on the bacterial patterns found in this study, it is also known that all Gram-negative bacteria found as sepsis-causing bacteria are sensitive to meropenem antibiotics (100%). This is different when compared to research by Ramita *et al*. (2018) [23] in several hospitals, the sensitivity of sepsis-causing bacteria to meropenem was only 16.67%. Research by Ekayana *et al*. (2019)[11] showed that the highest sensitivity of sepsis-causing bacteria at Haji Adam Malik General Hospital, Medan, was to amikacin and meropenem antibiotics. Meanwhile, the highest resistance of Gram-negative bacteria occurred to ciprofloxacin. Ciprofloxacin is a type of antibiotic that quickly loses its effectiveness due to resistance problems. In addition, long-term use of ciprofloxacin antibiotics results in the growth of more resistant bacteria.[22] The highest resistance occurs in ampicillin (100%).

There was inappropriate use of antibiotics in this study. This could occur because there were patients who received combination antibiotics, where one antibiotic was in accordance with the culture results, while the other antibiotic was not in accordance with the culture results. This inaccuracy could also occur due to allergies in patients or potential drug interactions with prescribed drugs. Based on research by Sijbom *et al*. (2022),[24] allergic reactions occurred in the administration of antibiotics in the penicillin group (45%), nitrofuran (10.3%), tetracycline (7.7%), macrolide (6.7%), fluoroquinolone (5.4%), and other groups (24.9%). However, due to the limited data available in this study, this could not be traced.

The type of bacteria could be related to the clinical outcomes of sepsis patients. A cohort study by Morgan *et al*. (2016)[25] found that 90-day mortality of first-hit sepsis patients who developed a gram-negative infection was 43.6% following elective surgery and 27.9% following trauma (p<0.01), which compared with 25.6% and 20.6%, respectively, in gram-positive (p<0.05). However, there was an inverse relationship in second-hit infection. Gram-negative had a 90-day mortality of 40.4% (p<0.01), compared with 43.6% (p<0.05) in gram-positive infections. Then, Guo *et al*. (2023)26 showed sepsis patients with gram-positive infection had a higher rate of 28-day mortality (17.7% vs 15.4%; p<0.001) and in-hospital mortality (18.0% vs 15.8%; p<0.001) than gram-negative infection group. Those previous studies border with our study which indicates type of bacterial infection was not associated with mortality impact. Nowadays, the harmfulness of sepsis caused by gram-negative bacteria and gram-positive bacteria is still controversial along with pathogen-associated molecular evolution and geographic differences. So, it impacts on clinical heterogeneity of the affected individuals and the host's immune system has a crucial role in determining sepsis

prognostic.[27,28]

Increasing use of antibiotics for bacterial infections has led to the global spread of MDR. Some risk factors for the development of MDR are represented by previous exposure to broad-spectrum antibiotics, initial inappropriate antibiotic use, and colonization of resistant bacteria.[29] MDR status often causes higher morbidity and mortality. An observational study found there was significantly higher in-hospital mortality among sepsis patients with MDR than among non-MDR bacteria (40.2% vs 23.1%, p=0.001).[30] In contrast, this study showed no association between resistance status with risk of mortality in sepsis patients. Further research is needed to analyze other factors, such as inflammatory response, comorbidities, and multiple organ dysfunction, that may influence prognosis.

The bacteria type with the most MDR in this study was *Enterobacter cloacae complex*. A study by Legese *et al*. (2022),[7] showed Enterobacter cloacae complex that infects sepsis patients had the highest resistance to ampicillin, whereas most others were resistant to amikacin, ampicillin-sulbactam, aztreonam, ceftazidime, cefotaxime, ceftriaxone. It is similar to this study where the bacteria had resistance against aztreonam, ampicillin, ceftriaxone, cefepime, ceftazidime, ciprofloxacin, trimethoprim, sulfamethoxazole, and gentamicin.

Furthermore, early administration of antibiotics treatment was linked with the clinical outcomes of patients. Empiric antibiotic treatment has been shown effective for the initial treatment of sepsis.[31] Besides that, sepsis patient's treatment with a narrower antibiotic spectrum according to culture, known as definitive antibiotics, also reduces the mortality rate. A previous study showed hospitality mortality rate was 24.6% in sepsis patients in whom therapy was de-escalated and 32% in the no change of adequate empirical antibiotic group (p=0.008). De-escalation therapy also was a protective factor regarding 90-day mortality.[32] De-escalation refers to the reduction of one or more components of empirical therapy or through the switching to a narrower spectrum. In this study, type of antibiotic treatment was associated with the clinical outcomes of sepsis patients. Sepsis patients with empiric antibiotics or who did not perform a culture test have a higher mortality than the definitive antibiotic group. It is important to be aware that optimal management includes empiric therapy should be together with reassessment and subsequent definitive therapy based on cultures and antibacterial susceptibility tests.

Antimicrobial treatment impacts mortality rates, making careful prescribing essential. Strategies such as accurate diagnosis, distinguishing empiric from definitive therapy, de-escalating broad spectrum antibiotics, and identifying MDR bacteria can improve clinical outcomes and prevent worsening sepsis prognosis.

CONCLUSION

The use of definitive antibiotics for sepsis patients at Tabanan Hospital was appropriate, with the causative bacteria by 62% (8 patients) and 38% (5 patients), which was inappropriate. Sepsis patients with empiric antibiotics treatment were associated with mortality, meanwhile, the type of causal bacteria and resistance status were not significantly associated with mortality. Future sepsis research should focus on long-term antibiotic resistance trends, the impact of patient factors like comorbidities and gender on outcomes, and the effectiveness of rapid diagnostics and early treatment protocols. Collaborative multicenter studies are also crucial to gain broader insights into bacterial etiology and resistance patterns across diverse populations and healthcare settings.

Acknowledgment

Thank you to the Tabanan Hospital Medical Record Installation and all parties who have assisted in this research.

Conflict of Interest

All authors declare that they have no conflict of interest.

Abbreviations

AIDS (acquired immunodeficiency syndrome); CI (Confidence Interval); MDR (Multi Drug Resistant); OR (Odds Ratio); SSC (Surviving Sepsis Campaign).

REFERENCES

1. M. Singer, C. S. Deutschman, C. W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, *et al*. 2016. "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)." *JAMA* 315(8):801–810. Retrieved (https://doi.org/10.1001/jama.2016.0287).
2. K. Grozdanovski, Z. Milenkovikj, H. Demiri, K. Spasovska, M. Cvetanovska, V. Saveski, *et al*. 2018. "Epidemiology of Community-Acquired Sepsis in Adult Patients: A Six Year Observational Study." *Sciendo* 39:59–66. Retrieved (https://doi.org/10.2478/prilozi-2018-0024).
3. K. E. Rudd, N. Kissoon, D. Limmathurotsakul, S. Bory, B. Mutahunga, C. W. Seymour, *et al*. 2018. "The Global Burden of Sepsis: Barriers and Potential Solutions." *Crit Care* 22(1):232. Retrieved (https://doi.org/10.1186/s13054-018-2157-z).
4. M. Batara, S. Darmawati, M. E. Prastiyanto. 2018. "Keanekaragaman dan Pola Resistensi Bakteri pada Pasien yang Terdiagnosa Sepsis." *Journal Labora Medika* 2:1–5. Retrieved (https://doi.org/10.26714/jlabmed.2.2.2018.1-5).
5. L. Evans, A. Rhodes, W. Alhazzani, M. Antonelli, C. M. Coopersmith, C. French, *et al*. 2021. "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock." *Intensive Care Med* 47:1181–1247. Retrieved (https://doi.org/10.1097/CCM.0000000000005337).

6. M. L. Martínez, E. P. Plata-Menchaca, J. C. Ruiz-Rodríguez, R. Ferrer. 2020. "An Approach to Antibiotic Treatment in Patients with Sepsis." *Journal Thorac Dis* 12(3):1007–1021. Retrieved (https://doi.org/10.21037/jtd.2020.01.47).
7. M. H. Legese, D. Asrat, G. Swedberg, B. Hasan, A. Mekasha, T. Getahun, *et al*. 2022. "Sepsis: Emerging Pathogens and Antimicrobial Resistance in Ethiopian Referral Hospitals." *Antimicrob Resist Infect Control* 11(83):1–16. Retrieved (https://doi.org/10.1186/s13756-022-01122-x).
8. I. S. Pradipta, D. C. Sodik, K. Lestari, I. Parwati, E. Halimah, A. Diantini, *et al*. 2013. "Antibiotic Resistance in Sepsis Patients: Evaluation and Recommendation of Antibiotic Use." *North Am J Med Sci* 5(6):344–352. Retrieved (https://doi.org/10.4103/1947-2714.114165).
9. N. M. A. Agustini, D. K. Wati, I. B. G. Suparyatha, I. N. B. Hartawan, I. M. G. D. L. Utama, N. N. S. Budayanti, *et al*. 2018. "The Relationship Between Bacterial Types and Antibiotic Resistance with The Clinical Outcomes of Sepsis Patients in Pediatric Intensive Care Unit at Sanglah Hospital Denpasar, Bali-Indonesia." *Indones J Biomed Sci* 12(1):13–18. Retrieved (https://doi.org/10.15562/ijbs.v12i1.144).
10. M. S. Niederman, R. M. Baron, L. Bouadma, *et al*. 2021. "Initial Antimicrobial Management of Sepsis." *Crit Care* 25:307. Retrieved (https://doi.org/10.1186/s13054-021-03736-w).
11. E. Ekayana, A. Fithrie, I. K. Nasution. 2019. "Gambaran Bakteri dan Sensitivitas Antibiotik pada Pasien Stroke dengan Sepsis di Ruang Neurology RSUP Haji Adam Malik Medan." *Neurona* 36:106–112. Retrieved (https://doi.org/10.52386/neurona.v36i2.62).
12. Sugiyono, Padmasari. 2019. "Hubungan Kesesuaian Antibiotik Definitif dengan Clinical Outcome pada Pasien Ulkus Diabetik di RSUD Kota Yogyakarta." *Fitofarmaka* 9(1):56–63. Retrieved (https://doi.org/10.33751/jf.v9i1.1261).
13. I. D. Toyyibah, M. Rusli, Juniastuti. 2022. "Bacterial Pattern among Sepsis Patients in Internal Medicine Inpatient Ward Dr. Soetomo General Academic Hospital, Surabaya, Indonesia." *Majalah Biomorfologi* 32(2):52–58. Retrieved (https://doi.org/10.20473/mbiom.v32i2.2022.52-58).
14. A. Y. Nugraheni, M. S. Putri, A. Y. Saputro. 2021. "Evaluasi Ketepatan Antibiotik pada Pasien Sepsis." Pharmacon: *Jurnal Farmasi Indonesia* 18(2):194–207. Retrieved (https://doi.org/10.23917/pharmacon.v18i2.16635).
15. L. Gay, C. Melenotte, I. Lakbar, S. Mezouar, C. Devaux, D. Raoult, *et al*. 2021. "Sexual Dimorphism and Gender in Infectious Diseases." *Front Immunol* 12:698121. Retrieved (https://doi.org/10.3389/fimmu.2021.698121).
16. E. Quiros-Roldan, A. Sottini, P. G. Natali, L. Imberti. 2024. "The Impact of Immune System Aging on Infectious Diseases." *Microorganisms* 12:775. Retrieved (https://doi.org/10.3390/microorganisms12040775).
17. Y. Jiang, F. Q. Jiang, P. Kong, M. An, B. Jin, D. Cao, *et al*. 2019. "Inflammatory Anemia-Associated Parameters are Related to 28-Day Mortality in Patients with Sepsis Admitted to The ICU: A Preliminary Observational Study." Ann Intensive Care 9:1–11. Retrieved (https://doi.org/10.1186/s13613-019-0542-7).
18. F. B. Mayr, S. Yende, D. C. Angus. 2014. "Epidemiology of Severe Sepsis." *Virulence* 5:4–11. Retrieved (https://doi.org/10.4161/viru.27372).
19. W. Siswandari, R. A. N. Hestiyani, V. Indriani, I. D. S. A. P. Peramiarti. 2018. "Profil Bakteri Penyebab Sepsis di Ruang Perawatan Intensive RSUD Prof Dr. Margono Soekarjo Purwokerto." *Prosiding Seminar Nasional dan Call for Papers* 14:340–347. Available at: http://jurnal.lppm.unsoed.ac.id/ojs/index.php/Prosiding/article/view/828. Date accessed: 9 Jan. 2024.
20. F.N. Maliza, A. P. Gonibala. 2023. "Pola Penggunaan Antibiotik Pada Pasien Sepsis Rawat Inap di RSUD Dr. MOEWARDI." *J Pharm Sci Med Res* 6(1):11–20. Retrieved (https://doi.org/10.25273/pharmed.v6i1.15759).
21. Y. Sun, Y. Liu, J. Wang, C. Cui. 2023. "The Effect of Meropenem versus Piperacillin-Tazobactam in Critically Ill Patients with Sepsis and Septic Shock." *Heliyon* 9(6). Retrieved (https://doi.org/10.1016/j.heliyon.2023.e16542).
22. Safitri, Y., Rohmi, Gede, LS. 2017. "Identifikasi Jenis Sampel (Bakteri Murni dan Campuran Bakteri) Penyebab ISK terhadap Hasil Uji Sensitivity Antibiotik Ciprofloxacin". Jurnal Analis Medika Bio Sain 4(1):12–16. Retrieved (https://doi.org/10.32807/jambs.v4i1.78).
23. Ramita, GR, Gama, SI, Ramadhan, AM. 2018. "Hubungan Ketepatan Pemilihan Antibiotik Empiris dengan Outcome Terapi pada Pasien Sepsis di Instalasi Rawat Inap Beberapa Rumah Sakit". Proceeding of the 8th Mulawarman Pharmaceuticals Conferences, Samarinda, November 2018 220–228. Retrieved (https://doi.org/10.25026/mpc.v8i1.327).
24. M. Sijbom, K. K. Braun, F. L. Buchner, L. B. Vos, B. J. C. Hendriks, M. G. J. Boer, *et al*. 2022. "Cues to Improve Antibiotic-Allergy Registration: A Mixed-Method Study." *PLoS One* 17(4):1–13. Retrieved (https://doi.org/10.1371/journal.pone.0266473).
25. M. P. Morgan, T. Szakmany, S. G. Power, P. Olaniyi, J. E. Hall, K. Rowan, *et al*. 2016. "Sepsis Patients with First and Second-Hit Infections Show Different Outcomes Depending on the Causative Organism." *Front Microbiol* 7:1–7. Retrieved (https://doi.org/10.3389/fmicb.2016.00207).
26. Q. Guo, P. Qu, W. Cui, M. Liu, H. Zhu, W. Chen, *et al*. 2023. "Organism Type of Infection is Associated with Prognosis in Sepsis: An Analysis from The Mimic-IV Database." *BMC Infect Dis* 23:1–11. Retrieved (https://doi.org/10.1186/s12879-023-08387-6).
27. Tang, A., Shi, Y., Dong, Q., Wang, S., Ge, Y., Wang, C., Gong, Z., Zhang, W., Chen, W. 2023. "Prognostic Differences in Sepsis Caused by Gram-Negative Bacteria and Gram-Positive Bacteria: A Systematic Review and Meta-Analysis". *Crit Care* 27:1–12. Retrieved (https://doi.org/10.1186/s13054-023-04750-w).
28. Dyck, B., Unterberg, M., Adamzik, M., Koos, B. 2024. "The Impact of Pathogens on Sepsis Prevalence and Outcome". *Pathogens* 13:1–10. Retrieved (https://doi.org/10.3390/pathogens13010089).
29. S. Busani, G. Serafini, E. Mantovani, C. Venturelli, M. Giannella, P. Viale, *et al*. 2019. "Mortality in Patients With Septic Shock by Multidrug Resistant Bacteria: Risk Factors and Impact of Sepsis Treatments." *J Intensive Care Med* 34:48–54. Retrieved (https://doi.org/10.1177/0885066616688165).
30. N. Capsoni, P. Bellone, S. Aliberti, G. Sotgiu, D. Pavanello, B. Visintin, *et al*. 2019. "Prevalence, Risk Factors and Outcomes of Patients Coming from the Community with Sepsis Due to Multidrug-Resistant Bacteria." *Multidiscip Respir Med* 14:1–11. Retrieved (https://doi.org/10.1186/s40248-019-0185-4).
31. Ferrer R, Martin-Loeches, I., Phillips, G., Osborn, TM, Townsend, S., Dellinger, RP, Artigas, A., Schorr, C., Levy, MM. 2014. "Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock from the First Hour: Results From a Guideline-based Performance Improvement Program". Crit Care Med. 42(8):1749–55. Retrieved (10.1097/CCM.0000000000000330. PMID: 24717459).
32. J. Garnacho-Montero, A. Gutierrez, A. Escoresca, Y. Corcia, I. Herrera, C. Ortiz, *et al*. 2014. "De-escalation of Empirical Therapy is Associated with Lower Mortality in Patients with Severe Sepsis and Septic Shock." *Intensive Care Med* 40(1):32–40. Retrieved (https://doi.org/10.1007/s00134-013-3077-7).