

The Association between Resistance of Sepsis-Inducing Bacteria to First-Line Antibiotics and Sepsis Outcome: A Retrospective Cross-Sectional Study

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Submitted : 05-02-2026

Revised : 01-03-2026

Accepted : 05-03-2026

Keywords: antibiotic resistance, first-line antibiotics, sepsis.

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Abstract

Background: Sepsis is a significant infectious disease linked to high mortality rates. Several bacterial pathogens that cause sepsis have shown resistance to first-line antibiotics. This resistance in sepsis-causing bacteria to initial antibiotic agents threatens treatment success, elevating mortality risk, healthcare costs, and prolonged hospital stays.

Objective: This study aimed to investigate the relationship between the resistance of sepsis-causing bacteria to first-line antibiotics and sepsis treatment outcomes.

Methods: This cross-sectional study was a single-center retrospective study. Data were collected from sepsis patients admitted to the intensive care unit of a general hospital in Bali between 2022 and 2023. The patients included in this study were those with a positive bacterial infection, as provided in culture result. Therapy outcomes were evaluated based on discharge status: improved or unimproved (deceased). The resistance of sepsis-causing bacteria to first-line antibiotics, including fluoroquinolones, third- and fourth-generation cephalosporins, piperacillin-tazobactam, and vancomycin, was assessed through blood cultures. The relationship between antibiotic resistance and therapy outcomes was analyzed using the Gamma correlation coefficient. This study included 57 of 108 sepsis patients, primarily male (57.89%) and older than 60 years (57.89%).

Results: A strong, significant positive correlation was observed between the resistance of sepsis-causing bacteria to third-generation cephalosporins and therapy outcomes ($p=0.001$; $r=0.637$). In contrast, resistance to fluoroquinolones ($p=0.108$; $r=0.387$), fourth-generation cephalosporin ($p=0.377$; $r=-0.199$), piperacillin-tazobactam ($p=0.816$; $r=-0.060$), and vancomycin ($p=0.911$; $r=0.030$) did not significantly impact therapy outcomes. The outcome of sepsis therapy is associated with resistance of sepsis-causing bacteria to third-generation cephalosporins but not to fluoroquinolones, fourth-generation cephalosporins, piperacillin-tazobactam, or vancomycin. This study uses a relatively small sample size, which precludes subgroup analyses.

Conclusion: Non-significant findings for some antibiotics may reflect insufficient power; further study is needed to assess the correlation between resistance of sepsis-causing bacteria to fluoroquinolones, fourth-generation cephalosporins, piperacillin-tazobactam, and vancomycin.

How to Cite: (citation style AMA 11th Ed.)

Meriyani H, Sanjaya DA, Juanita RA, Siada NB, Yudiarta IWM, Suryawan K. The Association between Resistance of Sepsis-Inducing Bacteria to First-Line Antibiotics and Sepsis Outcome: A Retrospective Cross-Sectional Study. *J. Ilm. Medicam.*, 2026;12(1): 71-80.
<https://doi.org/10.36733/medicamento.v12i1.13597>

INTRODUCTION

Sepsis is a life-threatening clinical syndrome characterised by dysregulated host responses to infection, leading to organ dysfunction and high mortality. Globally, sepsis remains a major public health challenge, with an estimated 48.9 million cases and 11 million deaths in 2017, representing nearly 20% of all global deaths.^{1,2} According to the Global Burden of Disease study, sepsis-related disease increased in 2021 to 166 million sepsis cases and 21.4 million sepsis-related deaths.³ Despite advances in critical care, early recognition, and antimicrobial therapy, sepsis continues to impose substantial clinical and economic burdens on healthcare systems. Timely initiation of effective antimicrobial therapy is a cornerstone of sepsis management, as delays in appropriate treatment significantly increase the risk of progression to septic shock, multiorgan failure, and death.^{4,5}

The effectiveness of empirical antibiotic therapy, particularly first-line regimens, is increasingly threatened by the global rise of antimicrobial resistance (AMR). AMR has been described as an escalating pandemic that complicates the management of bacterial infections, including sepsis, and contributes to prolonged hospitalisation and increased

mortality.⁶⁻⁸ In many hospital settings, especially in low- and middle-income countries, multidrug-resistant organisms (MDROs) such as extended-spectrum β -lactamase (ESBL)-producing organisms, carbapenem-resistant Gram-negative bacteria, and methicillin-resistant *Staphylococcus aureus* (MRSA) are increasingly prevalent. These resistance patterns reduce the likelihood that first-line empirical antibiotics will effectively target the causative pathogens.⁹⁻¹¹

Recent clinical studies underscore the critical importance of aligning empirical antibiotic therapy with local resistance profiles. An extensive retrospective study demonstrated that early administration of broad-spectrum antibiotics significantly increased the odds of survival among hospitalised sepsis patients (OR $\approx$ 4.94).¹² However, the benefit of early broad-spectrum therapy depends on the susceptibility of the infecting organisms. When empirical therapy fails to cover resistant pathogens, patients experience delays in receiving adequate treatment, which is strongly associated with adverse outcomes.^{13,14} Evidence from a prospective cohort study further shows that, although mortality differences may not always reach statistical significance, patients treated with antibiotics to which the pathogens were sensitive had significantly shorter hospital stays than those receiving ineffective therapy.^{1,7}

The relationship between AMR and sepsis outcomes is further complicated by the increasing prevalence of MDRO-associated sepsis in hospital settings. A recent analysis of sepsis cases in internal medicine wards found that MDRO-positive sepsis was associated with more extended hospitalisation and higher mortality compared to drug-sensitive infections. These findings highlight the need for continuous surveillance of resistance patterns and for integrating such data into empirical treatment protocols.^{1,15,16}

Despite extensive evidence linking antimicrobial resistance (AMR) to adverse outcomes in sepsis, an important knowledge gap remains regarding how resistance to commonly used first-line antibiotics—particularly third-generation cephalosporins, which constitute the empirical backbone of sepsis management in many hospitals—relates to patient outcomes. Most available studies evaluate broad patterns of AMR or overall treatment success but do not specifically examine the association between pathogen resistance to first-line agents and clinically relevant outcomes such as survival. Because resistance profiles vary substantially across hospitals and regions, generating local evidence on the relationship between first-line antibiotic resistance and sepsis outcomes is essential to support antimicrobial stewardship efforts and to refine empirical treatment guidelines.¹⁷⁻¹⁹

Therefore, this study aims to investigate the correlation between bacterial resistance to first-line antibiotics and sepsis treatment outcomes in a hospital setting. By analysing pathogen susceptibility profiles alongside clinical outcomes, this research aims to provide evidence-based insights to support the refinement of empirical antibiotic protocols, enhance antimicrobial stewardship, and ultimately improve patient outcomes.

METHODS

Study Design

This study employed a retrospective cross-sectional design conducted at a public general hospital in Bali. The study uses medical record data from all sepsis patients admitted to the intensive care unit (ICU) between January 2022 and December 2023. The design was selected to evaluate the association between bacterial resistance to first-line antibiotics and sepsis outcomes at the time of hospital discharge. The collected data includes patients' demographic characteristics, antibiotic types used in sepsis patients, treatment duration, bacterial cultures, including pathogens' sensitivity to sepsis first-line therapy, and treatment outcomes.

Setting

The study was conducted in the ICU of one of the public general hospitals in Bali. All data were obtained from the hospital's medical records and microbiology laboratory databases. The antibiotic susceptibility results were obtained from blood culture data, and the outcome assessment was determined by discharge status recorded at the end of hospitalisation.

Participants

Participants were selected using a total sampling approach. All adult patients (≥ 19 years) diagnosed with bacterial sepsis and admitted to the ICU during the study period were screened. Inclusion criteria were: (1) age ≥ 19 years; (2) diagnosis of bacterial sepsis supported by a SOFA (Sequential Organ Failure Assessment) score ≥ 2 ; (3) Positive bacterial culture result; and (4) complete medical record data. Exclusion criteria were: (1) ICU stay; (2) transfer to another hospital; (3) pregnant or breastfeeding patients; and (4) patients with incomplete data/ missing key variables (culture results, antibiotic susceptibility, or outcome). The study size was determined by the total number of eligible

sepsis cases during the study period. No sample size calculation was performed because the study used all available cases.

Variables

Sepsis outcomes were classified as *improved* (discharged alive) or *unimproved* (deceased). This binary outcome reflects the final clinical status at discharge and is commonly used in sepsis outcome research. Bacterial resistance to first-line antibiotics, categorised as sensitive, resistant or Unknown (no susceptibility test available or incomplete antibiogram). The first-line sepsis antibiotics evaluated included fluoroquinolones, third- and fourth-generation cephalosporins, piperacillin–tazobactam, and vancomycin. Other Variables observed were: demographics data (age group, sex); clinical variables (type of antibiotic therapy (monotherapy, combination, sequential)); microbiological variables (bacterial species isolated from blood culture). Potential confounders such as comorbidities, infection source, and SOFA score dynamics were not included due to incomplete documentation in the retrospective dataset.

Research Procedure

The research followed a systematic workflow, starting with securing institutional research permission and ethical approval to ensure ethical compliance. Once approved, data were collected from the medical records department, where patient records fitting the study's timeframe and diagnostic criteria were accessed. All cases were then screened based on predefined inclusion and exclusion criteria to select eligible participants. Relevant variables—including demographic details, microbiological results, antibiotic susceptibility patterns, and clinical outcomes—were carefully extracted using a standardized form. The assembled dataset was then analyzed with suitable statistical techniques to examine the relationship between bacterial resistance and sepsis outcomes. In the end, the results were compiled and reported following scientific standards to emphasize their clinical relevance.

Data Sources and Measurement

All variables were extracted from the hospital's electronic and paper-based medical records. Antibiotic susceptibility was obtained from microbiology laboratory reports using standard disc diffusion or automated systems following CLSI guidelines. Outcome data were taken from discharge summaries. Demographic and clinical data were extracted from admission notes and treatment records. All data were extracted using a standardised data collection form to ensure consistency. Because all participants were from a single ICU, measurement methods were comparable across the entire cohort.

Several steps were taken to minimize bias were: selection bias was reduced by including all eligible patients during the study period (total sampling); information bias was minimized by using laboratory-confirmed culture and susceptibility results; misclassification bias may have occurred due to the presence of “unknown” susceptibility categories; these were retained as a separate category to avoid data loss. Confounding could not be fully addressed due to the limited availability of clinical covariates in the retrospective dataset.

Data Analysis

The patients' demographic characteristics are presented in the descriptive table. The association between the resistance of sepsis-inducing bacteria to first-line antibiotics and the outcome of sepsis treatment was assessed using the Gamma correlation. The association between bacterial resistance and sepsis outcomes was analysed using the Gamma correlation coefficient, as both exposure and outcome variables were ordinal, with asymmetric distributions of categories, and Gamma is appropriate for assessing directional associations in ordinal data. No subgroup or interaction analyses were performed due to the limited sample size. Missing susceptibility data were handled by retaining “unknown” as a separate analytical category. Sensitivity analyses were not conducted due to the small sample size and limited availability of covariates. All analyses were performed using standard statistical software, and significance was set at $p < 0.05$.

Ethical consideration

This research was approved by the Institutional Review Board (IRB) of RSUD Sanjiwani (Approval No. 02/PEPK/1/2025). All procedures adhered to the ethical principles outlined in the World Medical Association's Declaration of Helsinki for studies involving human participants. All collected data will remain strictly confidential.

RESULT AND DISCUSSION

The total number of sepsis patients admitted to the ICU during the 2022-2023 period was 108 patients. Of 108 patients, only 57 met the research criteria. The patient characteristics are presented in **Table 1**. Most of the patients

were elderly (>60 years). The finding that most sepsis patients are elderly (≥ 60 years) is strongly supported by current epidemiological evidence. Age is one of the most significant risk factors for sepsis due to immunosenescence, reduced physiological reserve, and a higher burden of chronic comorbidities, all of which increase susceptibility to severe infection and organ dysfunction.²⁰ Elderly individuals constitute the majority of sepsis cases in hospital settings and highlight the need for age-focused prevention and management strategies.²¹

Table 1. Patients Characteristic

Characteristics	Number	Percentage (%)
Age		
Elderly (>60 years)	33	57.89
Middle age (45-59 years)	15	26.32
Adults (19-44 years)	9	15.79
Total	57	100.0
Gender		
Male	33	57.89
Female	24	42.11
Total	57	100.0

Table 2. Antibiotics profile

Type of Antibiotics	Number	Percentage (%)
Monotherapy		
Levofloxacin	6	10.53
Ceftriaxone	6	10.53
Cefoperazone	3	5.26
Cefepime	2	3.51
Moxifloxacin	1	1.75
Ceftazidime	1	1.75
Meropenem	1	1.75
Total monotherapy	20	35.09
Antibiotic Combination		
Ceftriaxone + Metronidazole	3	5.26
Levofloxacin + Cefoperazone	3	5.26
Levofloxacin + Metronidazole	2	3.51
Levofloxacin + Ceftriaxone + Cefixime	2	3.51
Amikacin + Ceftazidime	1	1.75
Moxifloxacin + Cefepime	1	1.75
Ceftriaxone + Ciprofloxacin	1	1.75
Moxifloxacin + Metronidazole	1	1.75
Ceftriaxone + Cefixime	1	1.75
Cefoperazone + Cefixime	1	1.75
Ceftriaxone + Levofloxacin	1	1.75
Moxifloxacin + Cefotaxime	1	1.75
Moxifloxacin + Ceftazidime + Metronidazole	1	1.75
Cotrimoxazole + Levofloxacin + Cefoperazone -Sulbactam	1	1.75
Cefoperazone + Ciprofloxacin + Gentamicin	1	1.75
Ceftazidime + Gentamicin + Cefixime	1	1.75
Moxifloxacin + Meropenem + Ceftriaxone + Metronidazole	1	1.75
Moxifloxacin + ampicillin sulbactam + Ceftazidime	1	1.75
Moxifloxacin + Cefoperazone + Cotrimoxazole + Cefotaxime	1	1.75
Ceftriaxone + Moxifloxacin + Cefepime + Metronidazole	1	1.75
Ampicillin Sulbactam + Gentamicin + Amoxicillin-Clavulanate	1	1.75
Moxifloxacin + Cefoperazone + Cefixime + Ceftriaxone	1	1.75
Levofloxacin + Ceftazidime + Ceftriaxone + Metronidazole	1	1.75
Total antibiotic combination	30	52.63
Sequential Antibiotic Treatment		
Levofloxacin → Meropenem	1	1.75
Ceftriaxone → Cefepime	1	1.75
Ceftriaxone → Cefixime	1	1.75
Levofloxacin → Ceftriaxone	1	1.75
Ciprofloxacin → Ceftriaxone → Cefixime	1	1.75
Levofloxacin → Cefoperazone-Sulbactam → Cefuroxime	1	1.75
Ceftriaxone → Levofloxacin → Ceftazidime → Amikacin → Meropenem → Cefixime	1	1.75
Total Sequential Antibiotic Treatment	7	12.28
Total	57	100

According to **Table 1**, most of the sepsis patients are male patients (57.89%), which aligns with emerging epidemiological evidence showing that men have a higher incidence of sepsis than women. A large prospective cohort study using UK Biobank data reported that the age-standardized risk of incident sepsis hospitalization was higher in men than in women (40.2 vs 31.2 per 10 000 person-years; HR 1.26, 95% CI 1.23–1.29), indicating that male sex is associated with a greater likelihood of developing sepsis.²² Other large cohort analyses have shown that men are more likely to develop sepsis than women. A population-based cohort study from Germany, including 159,684 sepsis patients, reported that 52.5% were male, confirming a male predominance in sepsis incidence. Biological mechanisms also contribute to this pattern.²³ A 2024 review on sex differences in sepsis explains that estrogen enhances inflammatory and immune responses, whereas testosterone exerts immunosuppressive effects, thereby influencing susceptibility to infection. These hormonal differences shape how males and females respond to pathogens and help explain why men are more frequently affected by sepsis.²⁴

Table 2 shows that most sepsis patients in the ICU received combination therapy (52.63%), followed by monotherapy (35.09%) and a smaller proportion undergoing sequential antibiotic changes (12.28%). The dominant agents across all groups are third- and fourth-generation cephalosporins (ceftriaxone, cefoperazone, cefepime, ceftazidime, cefotaxime, cefixime), fluoroquinolones (levofloxacin, moxifloxacin, ciprofloxacin), and a limited use of carbapenems (meropenem). This pattern suggests an empirical strategy centred on broad-spectrum β -lactams and fluoroquinolones, with carbapenems reserved mainly for escalation rather than first-line use. Combination therapy is usually chosen to broaden the spectrum of coverage during polymicrobial infections. However, the recent evidence showed that there was no significant difference in clinical cure at day 7 or in mortality at days 7 and 28 between empirical combination and monotherapy.²⁵

The clinical benefit of empirical combination therapy in sepsis is limited compared with appropriately selected monotherapy. Recent analyses in critically ill populations show that combination regimens do not consistently reduce mortality and may offer no advantage when the initial agent is active against the causative pathogen. Instead, outcomes are strongly influenced by the appropriateness of empirical coverage, defined by concordance with local susceptibility patterns.^{26,27} A 2024 ICU cohort study reported that patients receiving appropriate empirical antibiotic therapy experienced better early clinical improvement and lower short-term mortality than those receiving inactive regimens, particularly in infections caused by multidrug-resistant organisms.⁷ These findings align with updated expert guidance emphasising that the timely administration of an active agent, rather than the use of multiple antibiotics, is the primary determinant of survival in sepsis.²⁶ Consequently, in settings where resistance to first-line agents such as ceftriaxone or fluoroquinolones is high, empirical monotherapy that appears guideline-concordant may still be microbiologically inadequate, and treatment outcomes will depend more on initial susceptibility than on whether monotherapy or combination therapy is used.⁷

According to **Table 2**, 12.28% of patients received sequential antibiotic treatment, which often involves stepwise escalation from first-line cephalosporins or fluoroquinolones to broader-spectrum agents such as meropenem, with some multiple switches. Moreover, sequential antibiotic therapy refers to stepwise modification or escalation of antibiotics due to inadequate clinical or microbiological response. Recent ICU studies and expert reviews consistently indicate that sequential antibiotic therapy often reflects initial treatment failure attributable to antimicrobial resistance. When empirical therapy is inactive against the causative pathogen, particularly in settings with high resistance, patients frequently require escalation or sequential switching. This pattern has been documented in contemporary ICU cohorts, where MDR/XDR organisms are strongly associated with the need to modify therapy, and is reinforced by expert guidance emphasising that sequential changes are a clinical consequence of initial microbiological inadequacy.^{7,25,28}

Table 3. Sepsis Induces-bacteria

	Bacteria	Number	Percentage (%)
Gram-Negative Bacteria			
1	<i>Burkholderia cepacia</i>	8	14.03
2	<i>Escherichia coli</i>	6	10.53
3	<i>Klebsiella pneumoniae</i> ss. <i>pneumoniae</i>	5	8.77
4	<i>Proteus mirabilis</i>	3	5.26
5	<i>Achromobacter xylosoxidans</i> ss. <i>denitrificans</i>	2	3.51
6	<i>Serratia marcescens</i>	2	3.51
7	<i>Salmonella</i> sp.	2	3.51
8	<i>Pseudomonas aeruginosa</i>	1	1.75
9	<i>Enterobacter cloacae</i>	1	1.75

	Bacteria	Number	Percentage (%)
10	<i>Acinetobacter baumannii</i>	1	1.75
11	<i>Acinetobacter lwoffii</i>	1	1.75
13	<i>Pseudomonas mendocina</i>	1	1.75
Total Gram-Negative Bacteria		37	64.91
Gram-Positive Bacteria			
1	<i>Staphylococcus aureus ss. aureus</i>	10	17.54
2	<i>Streptococcus suis</i>	4	7.02
3	<i>Staphylococcus epidermidis</i>	4	7.02
4	<i>Enterococcus faecalis</i>	2	3.51
Total Gram-Positive Bacteria		20	35.09
Total		57	100.0

The bacterial profile (**Table 3**) shows a clear predominance of Gram-negative pathogens (64.91%), with *Burkholderia cepacia*, *Escherichia coli*, and *Klebsiella pneumoniae* as the most frequent isolates. Gram-positive organisms accounted for 35.09%, led by *Staphylococcus aureus* and *Streptococcus suis*. This distribution aligns with contemporary epidemiological patterns in critical care settings, where Gram-negative bacteria consistently account for the aetiology of severe infections, particularly in low and middle-income countries (LMICs). Recent ICU surveillance studies confirm that Gram-negative organisms, especially *K. pneumoniae*, *A. baumannii*, *E. coli*, and *P. aeruginosa*, remain the leading causes of ICU infections and are frequently multidrug-resistant. (MDR).²⁹ The high proportion of Gram-negative isolates in this study is clinically significant, as these organisms often exhibit complex resistance mechanisms, including extended-spectrum β -lactamase (ESBL) production, carbapenem resistance, and efflux-pump-mediated fluoroquinolone resistance. A recent ICU analysis from China (2019–2024) reported substantial resistance among *K. pneumoniae* and *A. baumannii* to third-generation cephalosporins and carbapenems, underscoring the global challenge of treating Gram-negative sepsis in critical care settings.²⁹

According to **Table 3**, the Gram-positive isolates, particularly *Staphylococcus aureus* (17.54%) and *Staphylococcus epidermidis*, align with global ICU trends. Although Gram-positive infections are less prevalent than Gram-negative infections, they remain clinically important because of their association with catheter-related bloodstream infections and the potential presence of methicillin-resistant strains. Recent reviews highlight that Gram-positive pathogens continue to contribute significantly to ICU morbidity, especially in patients with invasive devices or prolonged hospitalisation.³⁰

Table 4. The Correlation Between The Resistance Of Sepsis-Inducing Bacteria To First-Line Antibiotics And The Outcome Of Sepsis Treatment

Resistance to		Treatment Outcome		Correlation Coefficient (r)	p
		Recover	Death		
Fluoroquinolones	Sensitive	18	17	0.387	0.108
	Unknown	1	1		
	Resistant	8	17		
Third Generation of Cephalosporin	Sensitive	20	12	0.637	0.001*
	Unknown	6	17		
	Resistant	1	6		
Fourth Generation of Cephalosporin	Sensitive	12	21	-0.199	0.377
	Unknown	11	9		
	Resistant	4	5		
Piperacillin-Tazobactam	Sensitive	10	14	-0.060	0.816
	Unknown	16	20		
	Resistant	1	1		
Vancomycin	Sensitive	13	16	0.030	0.911
	Unknown	14	19		
	Resistant	0	0		

*) statistically significant

According to **Table 4**, among the antibiotics evaluated, resistance to third-generation cephalosporins was strongly and significantly associated with mortality ($r = 0.637$, $p = 0.001$). This finding is clinically meaningful, as third-generation cephalosporins remain widely used empirically for severe infections in many hospital settings, including in Indonesia.^{1,31} This finding is also in line with regional and global data. A systematic review from sub-Saharan Africa reported a high prevalence of third-generation cephalosporin resistance among Enterobacteriaceae in bloodstream

infections and emphasised that such resistance is likely to increase mortality in settings where ceftriaxone is the mainstay of empiric sepsis management.³² Similarly, clinical data from Malawi demonstrated that third-generation cephalosporin resistance in bloodstream infections was associated with increased mortality and prolonged hospitalisation, highlighting the substantial morbidity burden of third-generation cephalosporin-resistant pathogens.³³ More recently, a 2023 study of Enterobacterales bloodstream infections found that even when isolates were categorised as susceptible, definitive treatment with third-generation cephalosporins was associated with higher in-hospital mortality and longer length of stay than alternative regimens, suggesting that functional or inducible resistance may compromise outcomes.³⁴ The higher mortality in patients infected with bacteria resistant to third-generation cephalosporins is related to the fact that most of these bacteria are Gram-negative and to the ability of some Gram-negative bacteria to produce AmpC β -lactamase.³⁴

AmpC β -lactamase is a class C β -lactamase enzyme produced by several Gram-negative bacteria (e.g., *Enterobacter cloacae*, *Klebsiella aerogenes*, *Citrobacter freundii*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *E. coli* and *Klebsiella pneumoniae*). This type of enzyme hydrolyses a wide range of β -lactam antibiotics, including third-generation cephalosporins (3GCs) such as ceftriaxone, cefotaxime, and ceftazidime; penicillin; β -lactam; and cephamycin (e.g., ceftiofex). AmpC enzymes break the β -lactam ring of third-generation cephalosporins, rendering them inactive. This leads to failure of some β -lactam antibiotics to inhibit cell wall synthesis, persistent bacterial growth despite therapy, and increased risk of progression to bacteraemia and septic shock.^{35,36}

In this study, resistance to fluoroquinolones, fourth-generation cephalosporins, piperacillin–tazobactam, and vancomycin did not show a statistically significant association with sepsis mortality. Several methodological and clinical factors explain these findings. First, contemporary sepsis literature consistently shows that mortality is driven primarily by discordant therapy to the main empiric backbone agents (often third-generation cephalosporins such as ceftriaxone), rather than by resistance to all individual classes. A 2024 modelling study demonstrated that the excess risk of death in septic shock was substantially higher for ceftriaxone resistance than for cefepime resistance (4.53% vs 0.60%), indicating that resistance to some agents has a smaller, and sometimes statistically undetectable, impact on mortality at the individual-patient level.³⁷ Second, recent systematic reviews emphasise that timing and appropriateness of initial therapy—early administration of any active broad-spectrum regimen—are stronger predictors of outcome than resistance to a specific non-backbone agent.⁸ Thus, if clinicians rapidly escalated or adjusted therapy when resistance was suspected (for example, switching from fluoroquinolones or piperacillin–tazobactam to carbapenems or other active agents), the potential mortality signal of resistance to these drugs would be attenuated. Third, vancomycin is primarily active against Gram-positive pathogens, whereas the dominant burden of sepsis in many settings is due to Gram-negative organisms; as a result, vancomycin resistance patterns may have limited influence on overall mortality in a Gram-negative–predominant study, leading to a non-significant association. Finally, the relatively small number of resistant isolates and the high proportion of “unknown” susceptibility categories for some agents in this dataset likely reduced statistical power, making it more difficult to detect modest effect sizes.³⁸

The generalisability of these findings is influenced by the single-centre design and the specific resistance patterns observed in this ICU population. Resistance profiles vary widely across regions, and hospitals with different empirical therapy protocols or pathogen distributions may observe different associations. For example, the MBIRA multicentre cohort demonstrated substantial heterogeneity in resistance patterns and mortality across eight hospitals in Africa, underscoring the importance of local epidemiology in shaping clinical outcomes.³⁹ Therefore, while the findings provide valuable insight into the local burden of resistance and its clinical implications, broader multicentre studies with larger sample sizes are needed to enhance external validity and support generalisation to other settings.

Limitation

This study has some limitations, including a relatively small sample size, which precludes subgroup analyses. In addition, the high proportion of “unknown” susceptibility categories reduces the study's statistical power. Non-significant findings for some antibiotics may reflect insufficient power; further study is needed to identify the correlation of the resistance of sepsis-causing bacteria to fluoroquinolones, fourth-generation cephalosporins, piperacillin–tazobactam, and vancomycin⁴⁰. In addition, this study did not adjust for potential confounders such as SOFA score, comorbidities, or infection source, which may influence mortality outcomes.

CONCLUSION

The outcome of sepsis therapy is associated with resistance of sepsis-causing bacteria to third-generation cephalosporins, but not with resistance to fluoroquinolones, fourth-generation cephalosporins, piperacillin-tazobactam, or vancomycin. This study uses a relatively small sample size, which precludes subgroup analyses. Non-significant findings for some antibiotics may reflect insufficient power; further study is needed to assess the correlation between resistance of sepsis-causing bacteria to fluoroquinolones, fourth-generation cephalosporins, piperacillin-tazobactam, and vancomycin. Although the result of this study shows that resistance to other first-line agents was not significantly associated with mortality, this likely reflects variation in pathogen distribution, treatment adjustments during clinical care, and limited statistical power rather than a lack of clinical relevance. Collectively, these findings emphasize the urgent need for robust antimicrobial stewardship, continuous surveillance of local resistance patterns, and the integration of rapid microbiological diagnostics to optimize empiric therapy and improve sepsis survival. Future research should explore predictive models and targeted interventions that can further reduce delays in appropriate therapy and mitigate the impact of antimicrobial resistance on sepsis outcomes.

FUNDING

This study was supported by the Faculty of Pharmacy, Universitas Mahasaraswati Denpasar (Grant Number: 1119.22/E.003/FF-UNMAS/XII/2024).

GENERATIVE AI DISCLOSURE STATEMENT

An artificial intelligence tool (Microsoft Copilot, 2026) was used to assist in language refinement, grammar correction, and paraphrasing during manuscript preparation. All content, interpretations, analyses, and conclusions were generated, reviewed, and verified entirely by the authors, who take full responsibility for the accuracy and integrity of the work. No AI tool was used for data analysis, data interpretation, or the generation of scientific content.

AUTHOR CONTRIBUTION STATEMENT

Herleeyana Meriyani: Conceptualisation, Methodology, original draft preparation; **Dwi Arymbhi Sanjaya:** Software, Validation, Formal Analysis, Review and Editing; **Rr. Asih Juanita:** Investigation, Project Administration, Review and Editing; **Nyoman Budiarta Siada:** Visualisation, Supervision; **I Wayan Maysa Yudiarta:** Investigation, Writing - Original Draft; **Kadek Suryawan:** Resources and Investigation.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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