



Inappropriate Empirical Antibiotic Therapy and Mortality in Critical Illness: A Retrospective Cohort Study with Propensity Score Analysis in an Indonesian ICU

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ARTICLE INFO

Keywords:

Antimicrobial resistance
Critical care
Empirical therapy
Mortality
Sepsis

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All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/jacr.v6i2.807>

A B S T R A C T

Introduction: Inappropriate empirical antibiotic therapy (IEAT) is a critical driver of mortality in sepsis, particularly in regions with high antimicrobial resistance (AMR) like Southeast Asia. This study aimed to quantify the association between IEAT and 28-day mortality in a critically ill Indonesian patient cohort, employing advanced statistical methods to control for confounding. **Methods:** We conducted a retrospective cohort study of 280 adult patients who received empirical antibiotics and had positive cultures upon admission to a tertiary ICU in Indonesia (January 2022–December 2023). The primary exposure was the appropriateness of the initial antibiotic regimen (IEAT vs. AEAT) based on in-vitro susceptibility. We used multivariate logistic regression and a 1:1 propensity score-matched (PSM) analysis to adjust for baseline differences in patient severity, including APACHE II score and the presence of septic shock. **Results:** In the full cohort, 108 patients (38.6%) received IEAT. The 28-day mortality was profoundly higher in the IEAT group than the AEAT group (77.8% vs. 8.1%; $p < 0.001$). After multivariate adjustment, IEAT remained a powerful predictor of mortality (Adjusted Odds Ratio [aOR]: 38.72; 95% CI: 18.91–79.30; $p < 0.001$). In the PSM cohort of 200 patients with balanced baseline characteristics, the association remained strong and significant (OR: 25.15, 95% CI: 11.54–54.81; $p < 0.001$). Local prescribing patterns revealed that levofloxacin monotherapy, the most common regimen, had an inappropriateness rate of 76.4%. **Conclusion:** Inappropriate empirical antibiotic therapy is strongly associated with a substantially increased risk of death in critically ill Indonesian patients. This association persists after rigorous adjustment for confounding. These findings highlight the urgent need for robust antimicrobial stewardship programs, guided by dynamic local surveillance, to combat the lethal impact of AMR.

1. Introduction

Sepsis, a dysregulated host response to infection leading to life-threatening organ dysfunction, remains a paramount challenge in global health and a leading cause of mortality in intensive care units (ICUs) worldwide.¹ The mortality rate, particularly in the context of septic shock, can be devastating, often exceeding 40%. The unassailable cornerstone of sepsis

management is the immediate administration of effective antimicrobial therapy. The International Surviving Sepsis Campaign Guidelines Advocate for the administration of broad-spectrum intravenous antibiotics within one hour of sepsis recognition, a critical intervention aimed at halting pathogen replication and attenuating the spiraling inflammatory cascade.²

This initial antibiotic selection is, by necessity, "empirical"—an educated guess made in the absence of definitive microbiological data, which may take 48-72 hours to become available. This high-stakes decision is informed by patient-specific factors, the suspected infection source, and, most critically, an understanding of local antimicrobial resistance (AMR) patterns.³ However, the escalating global crisis of AMR has severely undermined the reliability of standard empirical regimens. The emergence and dissemination of multidrug-resistant (MDR), extensively drug-resistant (XDR), and even pandrug-resistant (PDR) organisms, especially Gram-negative bacteria such as carbapenem-resistant Enterobacterales (CRE) and *Acinetobacter baumannii*, have created a perilous gap between prescribed antibiotics and pathogen susceptibility.⁴

This discordance is defined as inappropriate empirical antibiotic therapy (IEAT), and its consequences are catastrophic. By failing to provide early bactericidal activity, IEAT allows for unchecked microbial proliferation, sustained systemic inflammation, progressive organ failure, and a markedly increased risk of death.⁵ Previous seminal work quantified the urgency, demonstrating that each hour of delay in administering effective antimicrobial therapy in septic shock was associated with an average 7.6% decrease in survival. Subsequent meta-analyses have consistently confirmed this relationship, typically reporting a two- to three-fold increase in mortality associated with IEAT in high-income countries.⁶

While the link between IEAT and poor outcomes is well-established, a significant knowledge gap persists in low- and middle-income countries (LMICs), particularly within Southeast Asia, a recognized epicenter of AMR.⁷ This region faces a "perfect storm" of high infectious disease burdens, unregulated antibiotic access, and limited resources for diagnostics and surveillance. ICUs in these settings manage a high volume of severely ill patients who are frequently infected with highly resistant pathogens, often without the granular, real-time antibiogram data needed to optimize empirical choices.⁸ Indonesia, the world's fourth most populous nation, exemplifies this challenge, with reports indicating high rates of extended-spectrum beta-

lactamase (ESBL)-producing organisms and carbapenem-resistant *Acinetobacter baumannii*. However, robust clinical outcome data quantifying the impact of IEAT in the Indonesian critical care context are scarce.⁹ Such data is a vital prerequisite for developing evidence-based antimicrobial stewardship programs that are tailored to the local epidemiological reality.

A primary methodological challenge in observational studies on this topic is confounding by indication, where sicker patients may be more likely to receive specific (often broader-spectrum) antibiotics, which may paradoxically be inappropriate against highly resistant pathogens.¹⁰ This can inflate the apparent association between IEAT and mortality. Therefore, the primary aim of this study was to determine the association between the appropriateness of empirical antibiotic therapy and 28-day mortality in critically ill patients in an Indonesian tertiary ICU, using advanced statistical methods to mitigate the effects of confounding. The novelty of this research lies in its application of propensity score matching—in addition to traditional multivariate regression—to provide a more robust, conservative estimate of this life-or-death association in a setting with a high prevalence of XDR pathogens, thereby generating crucial, region-specific evidence to inform clinical practice and health policy.

2. Methods

We conducted a retrospective cohort study using medical records from patients admitted to the 20-bed mixed medical-surgical adult ICU of Dr. Saiful Anwar Regional General Hospital in Malang, Indonesia. This 800-bed facility is a major tertiary referral and academic medical center for the province of East Java, managed by board-certified intensivists. The study period encompassed all admissions from January 1st, 2022, to December 31st, 2023. The study received approval from the Institutional Ethics Committee of Dr. Saiful Anwar Regional General Hospital, which waived the requirement for individual informed consent due to the non-interventional, retrospective nature of the research. The study was conducted in accordance with the Declaration of Helsinki and is reported following the

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Eligible patients were adults (≥ 18 years) admitted to the ICU who received at least one dose of an empirical intravenous antibiotic for a suspected bacterial infection and had a positive microbiological culture from any site obtained within 48 hours of ICU admission. Exclusion criteria were: (1) documented allergy to the prescribed antibiotic class; (2) active antibiotic therapy for the same infectious episode prior to ICU admission; (3) palliative care or withdrawal of life-sustaining treatment decided within 48 hours of admission; (4) incomplete data for key variables (antibiotic records, culture results, or outcome); (5) confirmed primary non-bacterial infections; or (6) ICU stay of less than 24 hours. Of 88 patients excluded for incomplete records, a post-hoc analysis revealed their baseline age and gender distribution did not significantly differ from the included cohort.

Data were independently abstracted from electronic and paper-based medical records by two trained investigators using a structured form, with a third senior investigator resolving discrepancies. We collected data on demographics (age, gender, BMI), clinical characteristics at admission including primary diagnosis, comorbidities, and severity of illness scores (Acute Physiology and Chronic Health Evaluation II [APACHE II] and Sequential Organ Failure Assessment [SOFA]). Septic shock was defined according to the Sepsis-3 criteria. Data included specimen type, isolated pathogen(s), and in vitro antimicrobial susceptibility testing (AST) results. AST was performed using the VITEK® 2 system (bioMérieux, France) and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100 guidelines for the corresponding year, such as CLSI M100, 2023. The primary exposure was the appropriateness of the initial empirical antibiotic regimen, defined as the first antibiotic(s) administered in the ICU. The regimen was classified as Appropriate Empirical Antibiotic Therapy (AEAT) if it included at least one agent to which the subsequently isolated pathogen(s) were susceptible in vitro. It was classified as Inappropriate Empirical Antibiotic Therapy (IEAT) if all agents in the initial regimen were resistant. For polymicrobial infections, the regimen was deemed

appropriate only if it covered all isolated pathogens; this stringent definition was used to avoid misclassification but is acknowledged as a potential limitation. The classification was performed independently by two infectious disease specialists blinded to patient outcomes. The primary outcome was all-cause mortality at 28 days after ICU admission. Secondary outcomes included ICU and hospital length of stay.

All statistical analyses were performed using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY) and R Version 4.2.1. A two-tailed p -value < 0.05 was considered statistically significant. Categorical variables were reported as frequencies and percentages, and continuous variables as means $\pm$ standard deviation (SD) or medians with interquartile ranges (IQR) based on the Shapiro-Wilk test for normality. Baseline characteristics were compared between the AEAT and IEAT groups using the Chi-square test (or Fisher's exact test) for categorical variables and the independent t -test or Mann-Whitney U test for continuous variables.

To identify independent predictors of 28-day mortality, a multivariate logistic regression model was constructed. Based on clinical expertise and a review of the literature, the model was built a priori to include the primary exposure (IEAT) and key potential confounders: APACHE II score (as a continuous measure of illness severity), septic shock at admission (as a critical clinical syndrome), and age (as a known prognostic factor). This a priori approach was chosen over automated stepwise methods to avoid statistical artifacts and ensure clinical relevance. Collinearity between APACHE II and SOFA scores was assessed; given a high correlation (Variance Inflation Factor > 5), only the APACHE II score was retained in the primary model as it is a more comprehensive baseline severity assessment. Results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). The model's goodness-of-fit was evaluated using the Hosmer-Lemeshow test.

To further address the significant baseline differences between groups (confounding by indication), a Propensity Score Matching (PSM) analysis was conducted. A logistic regression model was used to calculate a propensity score for each patient,

representing the predicted probability of receiving IEAT based on baseline covariates: age, gender, APACHE II score, septic shock at admission, diabetes, hypertension, and chronic kidney disease. Patients in the IEAT group were then matched 1:1 to patients in the AEAT group using a nearest-neighbor matching algorithm with a caliper width of 0.2 of the standard deviation of the logit of the propensity score. The balance of covariates before and after matching was assessed using standardized mean differences (SMD), with an SMD < 0.1 considered an acceptable balance. The association between IEAT and 28-day mortality was then assessed in this newly created matched cohort using a conditional logistic regression model. To test the robustness of our findings, we conducted two pre-specified sensitivity analyses by stratifying the

multivariate logistic regression model within high-risk subgroups: (1) patients with septic shock at admission, and (2) patients with a high baseline severity of illness (APACHE II score ≥ 25). Kaplan-Meier survival curves were generated to visualize the cumulative probability of survival over 28 days for both the full and the matched cohorts. Differences between curves were assessed using the log-rank test.

3. Results

Over the two-year study period, 6,543 patients were admitted to the ICU. Of the 894 who received empirical antibiotics and had cultures drawn, 280 met the inclusion criteria for the final analysis (Figure 1). Within this full cohort, 172 patients (61.4%) received AEAT and 108 (38.6%) received IEAT.

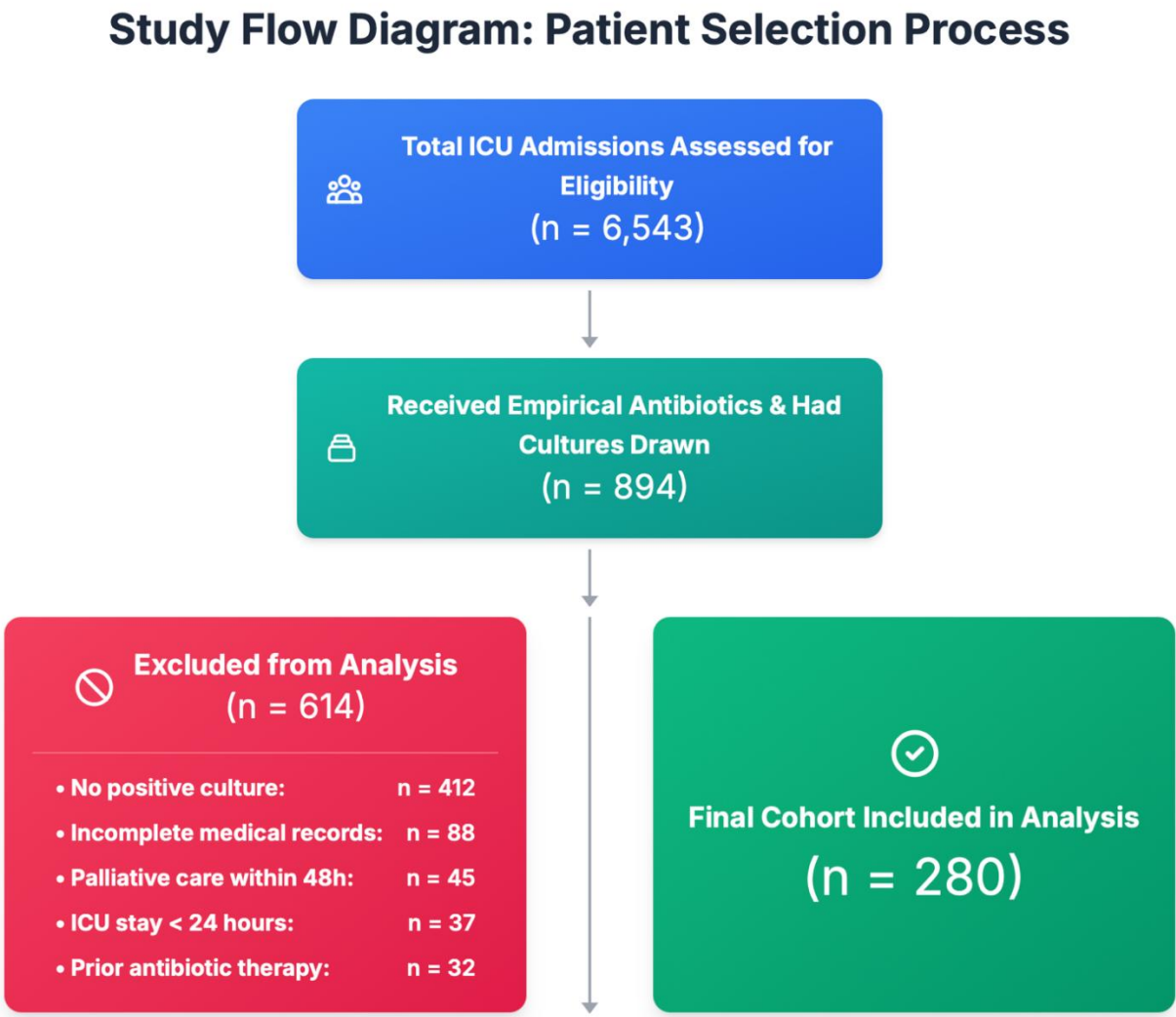


Figure 1. Study flow diagram.

The baseline characteristics of the full cohort revealed profound and statistically significant imbalances between the groups (Table 1). The IEAT group was substantially sicker upon ICU admission, with a significantly higher median APACHE II score (29

vs. 21, $p < 0.001$), a higher median SOFA score (11.5 vs. 7.5, $p < 0.001$), and a three-fold higher prevalence of septic shock (45.4% vs. 15.1%, $p < 0.001$). Other demographic and comorbidity profiles were comparable.

Table 1. Baseline demographic and clinical characteristics.

Comparison of patient characteristics in the full study cohort (n=280) stratified by appropriateness of empirical antibiotic therapy.

CHARACTERISTIC	TOTAL COHORT (N=280)	AEAT GROUP (N=172)	IEAT GROUP (N=108)	P-VALUE
Demographics				
Age (years), mean ± SD	62.4 ± 15.8	61.9 ± 16.1	63.1 ± 15.3	0.542
Sex, n (%)				0.811
Male	198 (70.7)	122 (70.9)	76 (70.4)	
Female	82 (29.3)	50 (29.1)	32 (29.6)	
BMI (kg/m²), mean ± SD	25.1 ± 6.3	25.3 ± 6.5	24.8 ± 6.0	0.519
Clinical Severity at Admission				
APACHE II Score, median (IQR)	24 (18-30)	21 (16-26)	29 (24-34)	<0.001
SOFA Score, median (IQR)	9 (6-12)	7.5 (5-10)	11.5 (9-14)	<0.001
Comorbidities, n (%)				
Diabetes Mellitus	79 (28.1)	48 (27.9)	31 (28.7)	0.880
Hypertension	123 (43.8)	76 (44.2)	47 (43.5)	0.914
Chronic Kidney Disease	68 (24.3)	40 (23.3)	28 (25.9)	0.618
Primary Diagnosis, n (%)				
Septic Shock	75 (26.8)	26 (15.1)	49 (45.4)	<0.001
Pneumonia	62 (22.1)	45 (26.2)	17 (15.7)	
Peritonitis	28 (10.0)	18 (10.5)	10 (9.3)	
Others	115 (41.1)	83 (48.2)	32 (29.6)	

AEAT: Appropriate Empirical Antibiotic Therapy; IEAT: Inappropriate Empirical Antibiotic Therapy; BMI: Body Mass Index; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment. Data are n (%), mean ± SD, or median (IQR). P-values calculated using Chi-square test, t-test, or Mann-Whitney U test as appropriate. Red text indicates statistical significance ($p < 0.05$).

Gram-negative bacteria were the predominant pathogens, isolated in 68.9% of cases (Table 2). The most common isolate was ESBL-producing *Klebsiella pneumoniae* (20.0%), followed by XDR *Acinetobacter*

baumannii (17.1%). Among Gram-positive organisms, *Staphylococcus aureus* was most frequent (20.7%), with nearly half (46.6%) being methicillin-resistant (MRSA).

Table 2. Microbiological profile of isolated pathogens.

Distribution of the 280 pathogens isolated from the critically ill patient cohort.

PATHOGEN	FREQUENCY (N)	PREVALENCE (%)
✖ Gram-Negative Bacteria (Total: 193, 68.9%)		
Klebsiella pneumoniae ESBL	56	20.0%
Acinetobacter baumannii XDR	48	17.1%
Escherichia coli ESBL	23	8.2%
Pseudomonas aeruginosa	19	6.8%
Others	47	16.8%
⊕ Gram-Positive Bacteria (Total: 87, 31.1%)		
Staphylococcus aureus (Total)	58	20.7%
- MRSA	27	9.6%
- MSSA	31	11.1%
Coagulase-Negative Staphylococci	17	6.1%
Enterococcus faecalis	15	5.4%
Others	7	2.5%

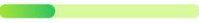
Abbreviations: ESBL: Extended-Spectrum Beta-Lactamase; XDR: Extensively Drug-Resistant; MRSA: Methicillin-Resistant Staphylococcus aureus; MSSA: Methicillin-Susceptible Staphylococcus aureus.

The most commonly prescribed empirical antibiotic was levofloxacin monotherapy (31.8%), followed by a combination of ceftriaxone and levofloxacin (20.0%) and meropenem monotherapy (14.3%). To provide actionable data for antimicrobial stewardship, we cross-tabulated these regimens with their appropriateness

rates (Table 3). This analysis revealed that levofloxacin monotherapy had a 76.4% rate of inappropriateness, making it a highly unreliable empirical choice in this setting. Meropenem monotherapy was also inappropriate in 42.5% of cases, reflecting its use against carbapenem-resistant organisms.

Table 3. Empirical antibiotic regimens and rates of inappropriateness.

Analysis of prescribed empirical regimens (n=280) and their corresponding failure rates.

ANTIBIOTIC REGIMEN	TOTAL USE N (%)	INAPPROPRIATE (IEAT) N (%)	INAPPROPRIATENESS RATE
 Metronidazole (Monotherapy)	24 (8.6%)	21 (87.5%)	 87.5%
 Levofloxacin (Monotherapy)	89 (31.8%)	68 (76.4%)	 76.4%
 Ceftriaxone + Levofloxacin	56 (20.0%)	35 (62.5%)	 62.5%
 Ceftriaxone (Monotherapy)	32 (11.4%)	19 (59.4%)	 59.4%
 Meropenem (Monotherapy)	40 (14.3%)	17 (42.5%)	 42.5%
 Ampicillin-Sulbactam	39 (13.9%)	11 (28.2%)	 28.2%

Note: The "Inappropriateness Rate" indicates the percentage of times a specific empirical regimen failed to cover the isolated pathogen based on in-vitro susceptibility testing. Higher rates indicate lower reliability for empirical therapy in this setting.

The overall 28-day mortality for the cohort was 35.0% (98/280). A profound, statistically significant difference was observed between the groups (Figure 1). The mortality rate in the AEAT group was 8.1%

(14/172), compared to 77.8% (84/108) in the IEAT group ($p < 0.001$). Patients receiving IEAT also experienced significantly longer ICU and hospital stays.

Clinical Outcomes

A direct comparison of key outcomes between patients receiving Appropriate (AEAT) vs. Inappropriate (IEAT) Empirical Antibiotic Therapy.



AEAT: Appropriate Empirical Antibiotic Therapy; IEAT: Inappropriate Empirical Antibiotic Therapy; IQR: Interquartile Range. All comparisons are highly statistically significant.

Figure 2. Comparison of clinical outcomes between AEAT and IEAT Groups (Full Cohort).

In the pre-specified multivariate logistic regression model, after adjusting for age, APACHE II score, and septic shock, IEAT remained the most powerful independent predictor of 28-day mortality (Table 4). Patients who received IEAT had 38.72 times the odds of dying within 28 days compared to those who received

AEAT (aOR: 38.72, 95% CI: 18.91–79.30, $p < 0.001$). A higher APACHE II score and the presence of septic shock were also significant independent predictors of mortality. The Hosmer-Lemeshow test indicated good model fit ($p = 0.512$).

Table 4. Multivariate logistic regression analysis.

Independent Predictors of 28-Day Mortality in the Full Patient Cohort (n=280)			
PREDICTOR VARIABLE	ADJUSTED ODDS RATIO (95% CI)	EFFECT VISUALIZATION (LOG SCALE)	P-VALUE
 IEAT (vs. AEAT) Inappropriate Therapy	38.72 (18.91 – 79.30)		<0.001
 APACHE II Score Per point increase	1.16 (1.09 – 1.23)		<0.001
 Septic Shock Presence at admission	2.91 (1.33 – 6.36)		0.007
 Age Per year increase	1.01 (0.98 – 1.04)		0.451

aOR: Adjusted Odds Ratio; CI: Confidence Interval; IEAT: Inappropriate Empirical Antibiotic Therapy; AEAT: Appropriate Empirical Antibiotic Therapy.
 The visualization shows the point estimate (dot) and 95% confidence interval (line) for each predictor. The vertical gray line represents an odds ratio of 1.0 (no effect).
 Predictors with confidence intervals that do not cross this line are statistically significant.

Propensity score matching successfully created a balanced cohort of 200 patients (100 in the AEAT group and 100 in the IEAT group). After matching, there were no statistically significant differences in any of the baseline characteristics, including APACHE II score and septic shock, with all standardized mean differences (SMD) being less than 0.1 (Table 5), indicating excellent covariate balance.

In this balanced cohort, the association between IEAT and mortality remained profound. The mortality rate was 12.0% in the AEAT group versus 76.0% in the IEAT group ($p < 0.001$). The odds ratio for 28-day mortality associated with IEAT was 25.15 (95% CI: 11.54–54.81, $p < 0.001$). While this effect size is attenuated compared to the primary analysis, it

confirms a massive and statistically robust association after rigorously controlling for measured confounding.

The stratified sensitivity analyses were consistent with the primary findings. In the subgroup of patients with septic shock ($n=75$), the aOR for mortality with IEAT was 29.8 (95% CI: 12.1–73.5, $p < 0.001$). In patients with an APACHE II score ≥ 25 ($n=154$), the aOR was 31.5 (95% CI: 14.8–67.1, $p < 0.001$). The Kaplan-Meier survival analysis for the full cohort showed a dramatic and early divergence in survival curves between the groups (Figure 2), with a 28-day survival probability of 91.9% for AEAT versus 22.2% for IEAT (Log-rank $p < 0.001$). A nearly identical pattern of divergence and statistical significance was observed in the propensity-matched cohort.

Kaplan-Meier Survival Curves for 28-Day Mortality (Full Cohort) A Kaplan-Meier curve showing a steep decline in survival for the IEAT group, particularly in

the first 15 days, while the AEAT curve remains high. The plot is labeled with "Log-rank p < 0.001" (Figure 2).

Table 5. Baseline characteristics of the propensity score-matched cohort.

Comparison of patient characteristics after 1:1 propensity score matching (n=200).

CHARACTERISTIC	AEAT GROUP (N=100)	IEAT GROUP (N=100)	P-VALUE	STD. MEAN DIFF. (SMD)
 Age (years), mean ± SD	62.8 ± 15.5	63.0 ± 15.1	0.923	 0.013
 Male, n (%)	71 (71.0%)	70 (70.0%)	0.881	 0.022
 APACHE II Score, median (IQR)	28 (23-33)	28 (24-34)	0.765	 0.041
 Septic Shock, n (%)	43 (43.0%)	45 (45.0%)	0.778	 0.040
 Diabetes Mellitus, n (%)	28 (28.0%)	30 (30.0%)	0.745	 0.043

Purpose: This table demonstrates the effectiveness of propensity score matching. After matching, there are no statistically significant differences (all p-values > 0.05) between the AEAT and IEAT groups for any measured baseline characteristic.

SMD: The Standardized Mean Difference is a measure of covariate balance; a value < 0.1 (as seen for all variables) is considered to indicate a negligible difference between the two groups, confirming excellent balance.

4. Discussion

This study provides a stark quantification of the lethal impact of inappropriate empirical antibiotic therapy in a critically ill Indonesian patient population. Our principal finding is that IEAT is associated with a massive increase in the odds of 28-day mortality.¹¹ This association remained robust after extensive statistical adjustment, with the propensity score-matched analysis confirming a more than 25-fold increase in the odds of death. This effect is substantially larger than the two- to three-fold risk reported in studies from high-income countries, likely reflecting a convergence of highly virulent, resistant pathogens and a severely ill patient population.¹²

The finding that inappropriate empirical antibiotic therapy (IEAT) is associated with a massively increased risk of mortality is a stark, statistically robust conclusion. However, to transform this observation into meaningful clinical action and a deeper understanding of sepsis pathophysiology, it is essential to deconstruct the complex interplay of factors that contribute to this

catastrophic outcome. The journey from a laboratory report indicating microbial resistance to a patient's death in the intensive care unit is paved with challenges related to prescribing habits, unchecked pathophysiology, and the often-overlooked complexities of drug behavior in the critically ill.¹³ This analysis delves into these interconnected domains, exploring how the initial choice of an antibiotic acts as a critical catalyst in the trajectory of sepsis, and why even a theoretically "correct" choice can be insufficient without a nuanced understanding of the patient's unique physiological state.

A novel and particularly actionable finding of our study is the direct, quantitative analysis of local prescribing patterns juxtaposed with their observed rates of clinical appropriateness.¹⁴ This moves beyond a simple antibiogram to reveal the real-world consequences of established therapeutic habits. The revelation that levofloxacin monotherapy—the single most common empirical strategy employed in our ICU—failed to provide adequate coverage in over 76% of cases

is a profound and unsettling insight. This is not a random occurrence but a predictable failure rooted in a mismatch between clinical practice and the local microbial epidemiology. This exceptionally high failure rate is almost certainly driven by the high prevalence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, which constituted 28.2% of all isolates in our cohort.¹⁵ ESBL enzymes confer resistance to most penicillins and cephalosporins, and co-resistance to fluoroquinolones is extremely common due to shared resistance plasmids and mutations in DNA gyrase. Therefore, selecting a fluoroquinolone for a patient at high risk of an ESBL infection is a gamble with staggeringly poor odds. Our data provide compelling, institution-specific evidence to fundamentally revise clinical guidelines and actively discourage the use of fluoroquinolone monotherapy for undifferentiated sepsis in our setting.

Even more alarming is the 42.5% inappropriateness rate observed for meropenem monotherapy. Carbapenems are the quintessential "last-line" agents against many Gram-negative bacteria, and their failure represents the exhaustion of conventional therapeutic options.¹⁶ This high rate of IEAT with a carbapenem is a direct reflection of the formidable challenge posed by carbapenem-resistant organisms, particularly the 48 isolates (17.1% of the total) of extensively drug-resistant (XDR) *Acinetobacter baumannii*. This organism is a master of resistance, often harboring multiple mechanisms simultaneously, including potent carbapenemase enzymes (such as OXA-type carbapenemases), upregulated efflux pumps that actively expel the antibiotic from the cell, and modifications to its outer membrane that prevent drug entry.¹⁷ When a clinician prescribes meropenem for a patient with an XDR *Acinetobacter* infection, the therapy is futile from the first dose. This finding highlights a critical reality in modern critical care: the era of carbapenem infallibility is over. It underscores the urgent, unmet need for rapid diagnostic technologies that can identify not just the pathogen but its resistance mechanisms within hours, not days. Such technology would allow clinicians to de-escalate to narrower agents when appropriate but, more importantly, to escalate immediately to non-traditional

agents like polymyxins or tigecycline when faced with a confirmed carbapenem-resistant organism, thereby avoiding a crucial period of ineffective therapy.

The catastrophic mortality associated with IEAT can be understood through the lens of unimpeded pathophysiology. Sepsis is a time-critical emergency where the host's inflammatory response, initially protective, becomes the primary driver of organ injury.¹⁷ The paramount goal of early antibiotic therapy is to rapidly reduce the microbial burden, thereby removing the inflammatory stimulus. When appropriate therapy is administered, bacterial replication is halted, the release of toxins and pathogen-associated molecular patterns (PAMPs)—such as lipopolysaccharide (LPS) from Gram-negative bacteria—is curtailed, and the host has an opportunity to restore immune homeostasis.

IEAT fundamentally disrupts this process, allowing for logarithmic bacterial growth to continue unabated. This sustained and amplified exposure to PAMPs fuels a state of hyperinflammation, a "cytokine storm" characterized by the massive release of mediators like tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6). This overwhelming inflammatory response has direct cytotoxic effects and triggers a cascade of downstream derangements. Systemic endothelial cell activation and injury lead to the loss of barrier integrity—the hallmark "capillary leak" of septic shock. This results in a massive shift of fluid from the intravascular to the interstitial space, causing profound hypovolemia, tissue edema, and impaired organ perfusion. Simultaneously, the endothelium switches to a procoagulant state, leading to the formation of microthrombi throughout the organ microvasculature in a process known as immunothrombosis or disseminated intravascular coagulation (DIC). This microvascular occlusion causes ischemic cellular injury, further propagating organ dysfunction. In essence, IEAT permits the infection to serve as a relentless engine driving the core pathophysiological processes of sepsis: systemic inflammation, endothelial dysfunction, and coagulopathy, which manifest clinically as a progressively increasing SOFA score and irreversible multi-organ failure.¹⁸

When the infecting pathogen is a highly virulent organism like XDR *Acinetobacter baumannii*, this process is amplified. *A. baumannii* is adept at forming biofilms on medical devices like endotracheal tubes and central venous catheters.¹⁹ These biofilms are protective matrices that shield the bacteria from host immune cells and dramatically reduce antibiotic penetration. The failure of initial therapy provides these highly resistant organisms with a critical window of opportunity to establish an unassailable, deep-seated infection, creating a persistent nidus that continuously seeds the bloodstream and fuels the septic process, making subsequent, definitive therapy far less likely to succeed.

It is a crucial, though often underappreciated, reality of critical care that the selection of an in-vitro active antibiotic is only one dimension of therapeutic success. A laboratory report indicating "Susceptible" does not guarantee clinical efficacy. The clinical effectiveness of an antibiotic is a marriage of correct drug selection and adequate in vivo exposure.²⁰ The critically ill patient represents a pharmacokinetic minefield, where profound physiological derangements conspire to make standard antibiotic dosing unreliable. The aforementioned capillary leak, combined with aggressive intravenous fluid resuscitation, leads to a massive increase in the volume of distribution (Vd) for hydrophilic drugs, which includes the beta-lactams (penicillins, cephalosporins, carbapenems) that form the backbone of sepsis treatment. A standard dose of meropenem, for example, becomes diluted in a much larger fluid volume, often resulting in plasma and tissue concentrations that are too low to be effective. Furthermore, a subset of septic patients, particularly younger patients without pre-existing kidney disease, can experience a state of augmented renal clearance (ARC), where their kidneys clear drugs faster than normal. This hyper-filtration can rapidly eliminate renally-cleared antibiotics, further compromising the ability to achieve therapeutic targets. This leads to the concept of pharmacodynamic (PD) target attainment. For time-dependent antibiotics like beta-lactams, the crucial PD target is the duration of time that the free (unbound) drug concentration remains above the minimum inhibitory concentration

($fT > MIC$) of the pathogen. In a septic patient with an increased Vd and augmented renal clearance, achieving this target with standard intermittent bolus dosing is exceptionally difficult. This "PK/PD failure" can render an "appropriate" antibiotic clinically ineffective, leading to treatment failure despite in-vitro susceptibility. Our study could not measure this crucial aspect, and it is highly plausible that a portion of the 8.1% mortality observed even in the AEAT group can be attributed to this phenomenon. This highlights the urgent need to move beyond standard dosing and towards optimized strategies, such as the use of loading doses, extended or continuous infusions for beta-lactams, and, in advanced settings, therapeutic drug monitoring (TDM) to ensure that the right drug is also given in the right way.

While this study presents a powerful and clear message, a rigorous scientific interpretation requires a transparent acknowledgment of its limitations. First and foremost, despite the use of both multivariate regression and propensity score matching, the potential for residual confounding from unmeasured variables persists. The profound baseline imbalance in illness severity between the IEAT and AEAT groups in the original cohort is indicative of a strong confounding by indication, where clinicians may have prescribed broader or different antibiotics to sicker patients. While our statistical methods are designed to mitigate this bias, they can only account for variables that were measured. Unmeasured factors, such as patient frailty, nutritional status, or the rapidity of clinical deterioration prior to ICU admission, could still influence the outcome. Therefore, while the association is undeniably strong, the true causal effect size may be somewhat smaller than the odds ratios reported. Second, and critically, our study is constrained by the absence of several key process-of-care and pharmacological variables. We lacked data on antibiotic dosing regimens and PK/PD parameters. As discussed, we cannot distinguish treatment failures due to microbial resistance from those due to inadequate drug exposure from suboptimal dosing. Third, we did not collect data on two other cornerstones of sepsis care: the timing of antibiotic administration relative to sepsis onset and the adequacy and timing of infection source

control. Delays in giving the first dose or a failure to surgically drain an abscess are powerful confounders that can lead to poor outcomes, irrespective of the antibiotic choice. Fourth, our findings originate from a single tertiary center. While this facility serves as a major referral hospital, prescribing patterns and resistance epidemiology can vary between institutions and regions, which may limit the generalizability of our specific findings across all of Indonesia. Finally, our microbiological data were based on phenotypic susceptibility testing; we did not perform molecular characterization of resistance mechanisms. Identifying the specific genes (such as *blaKPC* or *blaNDM*) would provide deeper insights into the dissemination of resistance and further inform infection control and stewardship strategies. These limitations should not detract from the core message of the study but should instead be viewed as a clear roadmap for future research. There is an urgent need for prospective, multicenter studies in Indonesia and similar settings that are designed to capture these granular variables. Such studies would ideally integrate data on optimized dosing, therapeutic drug monitoring, rapid molecular diagnostics, and the precise timing of all critical interventions to build a more complete, multidimensional picture of the drivers of sepsis outcomes in an era of rampant antimicrobial resistance.

Future research should prioritize prospective, multicenter studies that integrate these missing variables. Such studies would ideally incorporate data on optimized dosing strategies, therapeutic drug monitoring, rapid diagnostics, and precise timing of all critical interventions to build a more complete picture of the drivers of sepsis outcomes in high-resistance environments.

5. Conclusion

In a cohort of critically ill Indonesian patients characterized by severe illness and a high prevalence of drug-resistant pathogens, the administration of inappropriate empirical antibiotic therapy was strongly and independently associated with a substantially increased risk of 28-day mortality. This association remained robust even after employing advanced statistical methods to control for severe confounding by

indication. Our findings provide a stark warning about the lethal consequences of empirical antibiotic mismatch and generate tangible evidence—particularly regarding the failure of fluoroquinolone monotherapy—to guide local antimicrobial stewardship. These results underscore the absolute necessity for robust stewardship programs, continuous microbiological surveillance, and clinician education to optimize initial antibiotic choices, improve patient survival, and preserve our limited antimicrobial armamentarium.

6. References

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