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RESEARCH ARTICLE

A Prospective Observational Study of Antimicrobial Stewardship and De-escalation in a Tertiary Intensive Care Unit

Zunera Fatima[1], Syed Afzal Uddin Biyabani*[2], Pooja V Salimath[2], Vanishree P Babladi[2], Hafsa Naema[2], Sachin Patil[3]

[1] *Department of Pharmacy Practice, Deccan School of Pharmacy, Hyderabad, Telangana, India*
[2] *Department of Pharmacy Practice, Matoshree Taradevi Rampure Institute of Pharmaceutical Sciences, Kalaburagi, Karnataka, India*
[3] *Faculty of Pharmaceutical Sciences, Sharnbasva University, Kalaburagi. Karnataka, India*

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Abstract: Optimizing antimicrobial stewardship in intensive care settings remains a primary clinical imperative to mitigate the escalation of multi-drug-resistant pathogens and improve patient survival rates. This prospective observational investigation, conducted over a continuous four-month duration in a tertiary care multi-disciplinary critical care unit, evaluates the clinical impact of active stewardship interventions, de-escalation patterns, and pharmacological dose optimization among one hundred critically ill adults. Over the observation period, empirical regimens remained unmodified in 62% of cases, whereas active stewardship modifications were implemented in 38% of patients, consisting of treatment withdrawal (19%), therapeutic de-escalation (11%), and pharmacokinetic dose adjustments (8%). Favorable clinical endpoints of discharge and clinical recovery were documented in 77% of the study population, while adverse outcomes, including death and leaving against medical advice, occurred in 23%. Culture-guided interventions exhibited a statistically significant association with clinical recovery ($p = 0.041$). Therapeutic de-escalation was significantly associated with reduced hospital mortality, as no deaths occurred among patients who underwent de-escalation ($p = 0.048$). Multivariate logistic regression identified key independent clinical predictors of adverse outcomes, including multidrug-resistant infections (OR: 3.12, 95% CI: 1.22–7.96, $p = 0.017$), cumulative exposure to five or more distinct antimicrobial agents (OR: 2.76, 95% CI: 1.08–7.05, $p = 0.034$), and prolonged intensive care stay exceeding eight days (OR: 2.48, 95% CI: 1.01–6.08, $p = 0.047$). Implementing structured, microbiology-driven stewardship provides an essential mechanism to minimize poly-antibiotic exposure and improve patient survival.

Keywords: Antimicrobial stewardship; Therapeutic de-escalation; Intensive care unit; Clinical outcomes; Multidrug resistance.

1. Introduction

The immediate administration of empirical broad-spectrum antimicrobial therapy is important for early management in critically ill patients admitted to intensive care units [1]. In clinical scenarios involving severe sepsis or septic shock, delays in initiating appropriate antimicrobial agents are linked with progressive organ failure and escalating mortality rates [2]. Consequently, clinicians frequently employ broad-spectrum agents or multi-drug combinations as an empiric safety net to ensure coverage of all potential pathogens during the initial phases of acute illness [3]. Despite the short-term survival benefits of aggressive empiric treatment, the sustained and indiscriminate administration of broad-spectrum molecules generates profound biological and ecological consequences [4]. Prolonged exposure to wide-spectrum antimicrobials accelerates the selection pressure for multidrug-resistant pathogens, including carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* [5]. Apart from the development of resistance, extended therapeutic courses disrupt the protective host microbiome, predisposing critically ill individuals to opportunistic superinfections, such as *Clostridioides difficile*-associated diarrhea, and increasing the incidence of severe drug-induced toxicities, such as acute kidney injury and hepatotoxicity [6].

To balance the necessity of rapid infectious control with the preservation of antimicrobial efficacy, clinical institutions have established antimicrobial stewardship programs [7]. These structured, evidence-based frameworks are designed to optimize antimicrobial selection, dose, route, and duration of therapy [8]. In intensive care environments, critical components of these programs include the timely transition from empirical to targeted regimens, pharmacological dose modifications based on organ function, and the complete withdrawal of unnecessary agents [9]. Among these strategies, therapeutic de-escalation stands out as a critical practice [10]. De-escalation involves narrowing the antimicrobial spectrum by substituting broad-spectrum agents with

* Corresponding author: Syed Afzal Uddin Biyabani

narrower-spectrum alternatives or discontinuing redundant components of a combination regimen once microbiological data and clinical trajectories become clear [11]. This practice aims to limit unnecessary drug exposure and curtail resistance development without compromising clinical cure [12]. Similarly, pharmacokinetic and pharmacodynamic dose optimization ensures that critically ill patients, who often exhibit altered volumes of distribution and fluctuating renal clearance, receive drug concentrations that maximize bacterial killing while avoiding toxic accumulation [13]. Despite widespread clinical consensus regarding the theoretical benefits of antimicrobial stewardship, implementing these practices in real-world critical care settings is challenging [14]. Obstacles such as diagnostic delays, fear of clinical deterioration upon narrowing therapy, and deeply ingrained prescribing habits contribute to low de-escalation rates globally [15]. These challenges are particularly acute in resource-constrained healthcare settings, where access to rapid diagnostic tools, molecular resistance profiling, and dedicated infectious disease specialists may be limited [16].

While several retrospective studies have reported the general principles of stewardship, prospective data directly correlating specific stewardship interventions such as active withdrawal, de-escalation, and dose modification with clinical endpoints in resource-limited critical care units remain scarce [17]. To address this knowledge gap, this prospective observational study systematically analyzes the patterns of stewardship interventions in a tertiary care intensive care unit, evaluates their association with patient outcomes, and identifies clinical predictors of unfavorable hospital endpoints. Through these clinical observations, this work seeks to provide actionable insights to refine prescribing protocols and enhance the quality of care for critically ill patients [18].

2. Materials and Methods

2.1. Study Design

This study involved a prospective, observational cohort design to evaluate antimicrobial stewardship interventions and their relationship with clinical outcomes [10, 19]. The prospective design minimized selection and recall biases and permitted real-time, precise tracking of daily antibiotic prescriptions, microbiological culture reports, and clinical outcomes [20]. The study was conducted in the multi-disciplinary Critical Care Unit of a tertiary care teaching hospital over a continuous four-month period. This clinical environment serves a high-acuity patient population requiring advanced hemodynamic monitoring, mechanical ventilation, renal replacement therapy, and complex infectious disease management [21].

2.2. Study Population and Patient Selection

The study population consisted of adult patients admitted to the intensive care unit who required systemic antimicrobial therapy during their hospitalization.

2.2.1. Inclusion Criteria

Patients were eligible for inclusion in the study if they met all of the following criteria:

1. Adult status, defined as age equal to or greater than 18 years at the time of admission [22].
2. Active prescription and administration of at least one systemic antimicrobial agent (antibacterial, antifungal, or antiviral) during their intensive care stay [23].
3. Availability of complete electronic or paper-based medical charts, including daily medication administration records, clinical progress notes, and laboratory profiles [21].
4. Presence or absence of microbiological culture and sensitivity testing ordered during the infectious episode [24].

2.2.2. Exclusion Criteria

Patients were excluded from the study cohort if they met any of the following criteria:

1. Incomplete or missing clinical, microbiological, or pharmacological records that prevented the accurate determination of stewardship interventions or clinical outcomes [14].
2. Discharge, transfer to another facility, or death occurring within 24 hours of intensive care admission, as this window was deemed insufficient to evaluate the initiation or modification of stewardship activities [25].
3. Admission for non-infectious indications without the administration of systemic antimicrobial agents [21].
4. Duplicate patient records representing readmissions of a previously enrolled patient during the specified four-month study period, thereby ensuring that each patient was represented as a unique analytical unit [26].

2.3. Data Collection

Data collection was performed daily by trained clinical researchers who reviewed physical case sheets, electronic medical records, bedside nursing charts, and microbiology laboratory databases [10]. For each enrolled patient, a standardized data collection form was populated with key variables. Demographics and clinical baselines included age, biological sex, primary infectious diagnosis, and total duration of intensive care unit stay [20]. Pharmacological data tracked the specific antimicrobial agents prescribed, the route of administration, the daily dosing regimen, and the cumulative antibiotic burden, defined as the total number of distinct systemic antibiotics administered during the hospital stay [27]. This cumulative exposure was categorized into low-to-moderate exposure, representing one to four distinct antibiotics, and high exposure, representing five or more distinct antibiotics [28]. Microbiological data recorded the collection date of blood, urine, sputum, or wound cultures, the identified pathogens, and the associated antimicrobial susceptibility profiles, noting the presence of confirmed multidrug-resistant organisms [4].

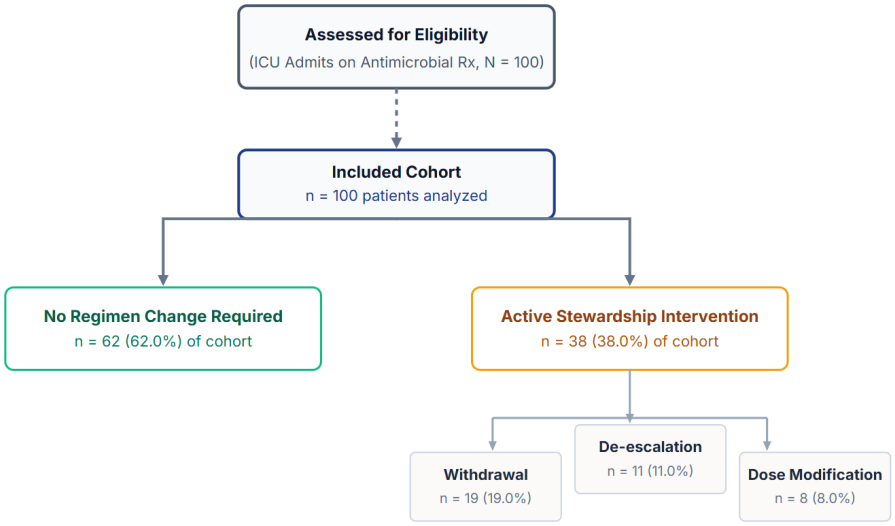

Figure 1. Cohort Enrollment and Allocation

2.4. Stewardship Interventions and Outcomes

Antimicrobial stewardship interventions were categorized into four mutually exclusive groups based on clinical actions taken within 72 hours of empirical treatment initiation or upon receipt of microbiological culture results [10].

1. *No change required:* The initial empirical antimicrobial regimen was continued without modification because it was clinically effective, microbiologically appropriate, or targeted to the identified pathogen [29].
2. *Withdrawal:* Active discontinuation of an antimicrobial agent without substitution, initiated when clinical signs of infection resolved, cultures returned negative, or an alternative non-infectious diagnosis was established [30].
3. *De-escalation:* The replacement of a broad-spectrum antimicrobial agent with an agent possessing a narrower spectrum of activity, or the discontinuation of one or more components of a combination empirical regimen based on culture sensitivity profiles and clinical stability [11].
4. *Dose modification:* Adjustment of the drug dose, dosing frequency, or infusion duration to align with renal function, hepatic function, body weight, or specific pharmacokinetic-pharmacodynamic targets [13].

Clinical outcomes were classified into favorable and unfavorable groups at the point of intensive care unit exit [20]. Favorable outcomes comprised patients who were clinically stable for discharge to general wards or home, and patients who achieved complete clinical recovery from the infectious episode. Unfavorable outcomes comprised patients who died during their intensive care stay, and those who left against medical advice due to clinical deterioration or palliative transition.

2.5. Statistical Analysis

All collected data were compiled and analyzed using IBM SPSS Statistics software [31]. Descriptive statistics summarized baseline demographic characteristics, clinical parameters, and stewardship intervention patterns. Quantitative continuous variables, such as age and length of stay, were expressed as means with standard deviations (± SD). Categorical variables, including sex, intervention categories, and clinical outcome frequencies, were presented as absolute numbers and percentages.

To determine the statistical significance of differences and associations, inferential tests were applied. Pearson's chi-square (χ^2) test of independence was used to analyze associations between categorical variables, including the relationship between antibiotic exposure categories and clinical outcomes, and the association between culture-guided interventions and treatment success [31]. Fisher's exact test was substituted for the chi-square test when individual cell frequencies fell below five. To explore linear relationships, Pearson correlation analysis evaluated the association between the cumulative number of antibiotics administered and the total length of intensive care unit stay, while Spearman's rank correlation assessed the connection between antibiotic burden and clinical outcome severity [32].

Multivariate logistic regression analysis was conducted to identify independent clinical predictors of unfavorable outcomes [31]. Variables demonstrating a clinical or univariate association with the outcome of interest specifically, microbiological confirmation of a resistant infection, high cumulative antibiotic burden ($\geq$ 5 antibiotics), prolonged intensive care hospitalization (> 8 days), and advanced age (> 60 years) were entered into the regression model. Odds ratios (OR) along with 95% confidence intervals (CI) were calculated for each covariate. For all statistical analyses, a two-tailed p-value of less than 0.05 ($p < 0.05$) was established as the threshold for statistical significance.

3. Results

3.1. Baseline Demographic and Clinical Characteristics

The baseline characteristics of the study cohort represent a clinical population with a mean age of 55.5 $\pm$ 13.2 years, which demonstrated a statistically significant distribution across the patient groups ($p = 0.021$). This age profile confirms a substantial representation of middle-aged to elderly individuals who are highly vulnerable to severe infections. A slight male predominance was observed, accounting for 54% of the cohort ($p = 0.038$). The mean length of intensive care unit hospitalization was 6.5 $\pm$ 2.8 days, which was also statistically significant ($p = 0.044$). These characteristics indicate that the evaluated cohort represented typical, high-acuity intensive care patients with significant baseline vulnerabilities. Table 1 shows the complete demographic and clinical baseline data.

Table 1. Baseline Demographic and Clinical Characteristics of Critically Ill Patients

Characteristic	Value	p-value
Total Patients (N)	100	
Mean Age (Years)	55.5 ± 13.2	0.021*
Male (n, %)	54 (54%)	0.038*
Mean ICU Stay (Days)	6.5 ± 2.8	0.044*

** indicates statistical significance at p < 0.05**

3.2. Distribution of Antimicrobial Stewardship Interventions

The pattern of stewardship activities during the study period reveals that for 62% of patients, no modification of the initial empiric therapy was required ($p < 0.001$), suggesting that empirical choices complied reasonably well with clinical indications or initial microbiologic trends. Active stewardship interventions were executed in the remaining 38% of the cohort ($p < 0.05$). Specifically, complete antibiotic withdrawal was performed in 19% of patients ($p = 0.012$), therapeutic de-escalation was successfully achieved in 11% ($p = 0.028$), and pharmacokinetic dose modifications were instituted in 8% ($p = 0.041$). The detailed distribution of these interventions is presented in Table 2.

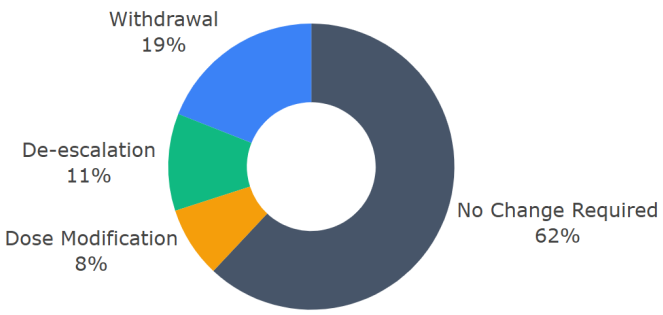

Figure 2. Distribution and Pattern of Antimicrobial Stewardship Interventions

Table 2. Distribution of Antimicrobial Stewardship Interventions in Critically Ill Patients

Intervention	Number of Patients (n)	Percentage (%)	p-value
No change required	62	62%	<0.001*
Withdrawal	19	19%	0.012*
De-escalation	11	11%	0.028*
Dose modification	8	8%	0.041*
Total	100	100%	

** indicates statistical significance at p < 0.05**

3.3. Clinical Outcomes and Association with Antibiotic Burden

Clinical endpoints documented at the time of intensive care unit exit showed that 65% of the patient population was discharged stable ($p < 0.001$), while 12% achieved complete clinical recovery ($p = 0.021$), culminating in an overall favorable outcome rate of 77%. Unfavorable outcomes occurred in 23% of patients, consisting of leaving against medical advice in 15% of cases ($p = 0.034$) and active hospital mortality in 8% ($p = 0.048$). When evaluating the impact of cumulative antibiotic exposure, patients receiving between one and four distinct antibiotics demonstrated a higher rate of favorable outcomes (40 out of 45 patients, 88.9%) compared to those exposed to five or more distinct antibiotics (25 out of 35 patients, 71.4%). In the unadjusted univariate analysis, this association did not cross the threshold for statistical significance ($p = 0.1715$). Table 3 shows the clinical outcomes and their relation to the antibiotic burden.

Table 3. Clinical Outcomes with Antibiotic Burden in Critically Ill Patients

Parameter	Category	n	Percentage (%)	Favorable Outcome	Unfavorable Outcome	p-value
Clinical Outcomes	Discharged	65	65%	-NA-	-NA-	<0.001*
	Recovered	12	12%	-NA-	-NA-	0.021*
	LAMA	15	15%	-NA-	-NA-	0.034*
	Death	8	8%	-NA-	-NA-	0.048*
Antibiotic Burden	1–4 antibiotics	-NA-	-NA-	40	5	0.1715
	≥ 5 antibiotics	-NA-	-NA-	25	10	

** indicates statistical significance at p < 0.05. LAMA: Left Against Medical Advice, -NA-: Not Applicable*

3.4. Culture-Guided Stewardship Intervention and Correlation Analysis

A highly significant clinical association was observed between the execution of culture-guided antimicrobial interventions and the achievement of favorable clinical outcomes ($p = 0.041$). Specifically, among patients who received culture-guided therapy, 87.9% (58 out of 66) experienced favorable clinical recovery, compared to only 55.9% (19 out of 34) of those whose therapy was not microbiologically guided. Correlation showed a moderate, highly significant positive correlation between the total number of antibiotics administered and the total duration of critical care stay ($r = 0.446$, $p < 0.001$), establishing that higher antibiotic exposure is strongly tied to prolonged hospitalization. A mild but statistically significant positive correlation was identified between antibiotic burden and overall outcome severity ($r = 0.287$, $p = 0.011$), showing a clear progression toward more severe clinical endpoints as antibiotic exposure increased. Table 4 shows these microbiological associations and correlative metrics.

Table 4. Culture-Guided Stewardship Intervention and Correlation

Parameters	Variable / Category	Favorable	Unfavorable	Correlation Coefficient (r)	p-value
Culture-Guided Intervention	Yes (n=66)	58	8	-NA-	0.041*
	No (n=34)	19	15	-NA-	
Correlation	Antibiotics vs. ICU stay	-NA-	-NA-	0.446	<0.001*
	Antibiotics vs. Severity	-NA-	-NA-	0.287	0.011*

** indicates statistical significance at p < 0.05, -NA-: Not Applicable*

3.5. Logistic Regression of Clinical Predictors

Multivariate logistic regression was conducted to identify independent predictors of unfavorable clinical endpoints. The model showed that the presence of a microbiologically confirmed multidrug-resistant infection was associated with a more than threefold increase in the risk of experiencing unfavorable outcomes (OR: 3.12, 95% CI: 1.22–7.96, $p = 0.017$). High cumulative antibiotic exposure (≥ 5 antibiotics) also emerged as a significant independent predictor of adverse outcomes (OR: 2.76, 95% CI: 1.08–7.05,

p = 0.034). Prolonged critical care stay exceeding eight days was similarly associated with a significantly higher risk of unfavorable clinical endpoints (OR: 2.48, 95% CI: 1.01–6.08, p = 0.047). Advanced age (> 60 years) did not show a statistically significant independent predictive value in this model (p = 0.31). The detailed multivariate regression results are given in Table 5.

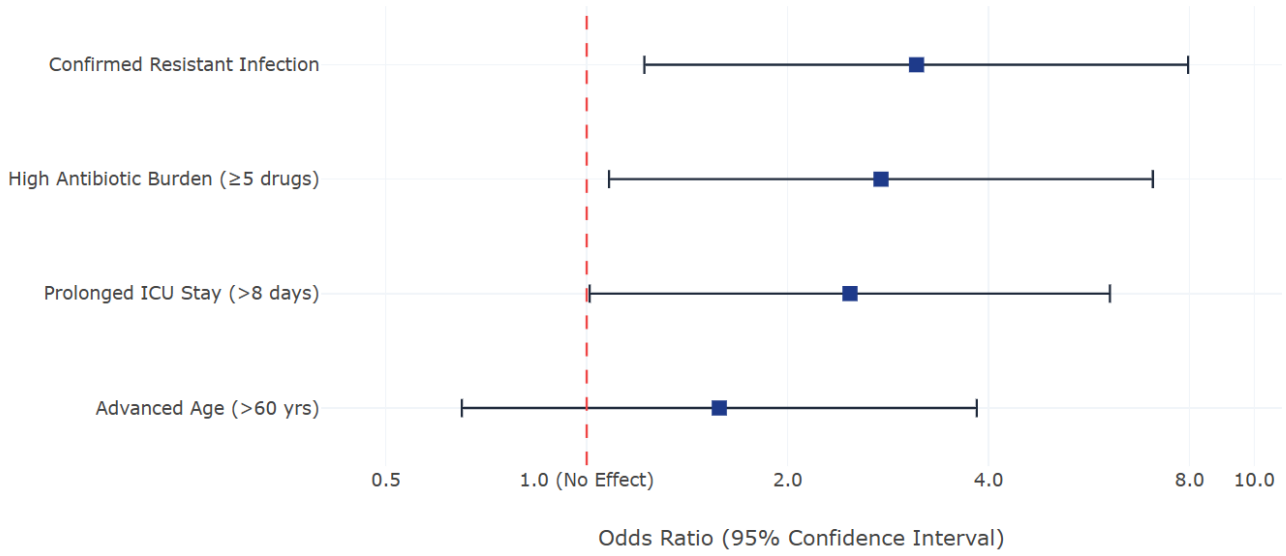

Figure 3. Forest Plot of Independent Predictors for Unfavorable Outcomes

Table 5. Logistic Regression of Predictors of Unfavorable Outcomes

Predictive Clinical Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Confirmed resistant infection	3.12	1.22–7.96	0.017*
High antibiotic burden (≥ 5 drugs)	2.76	1.08–7.05	0.034*
Prolonged ICU stay (> 8 days)	2.48	1.01–6.08	0.047*
Advanced age (> 60 years)	1.58	0.65–3.84	0.310

** indicates statistical significance at p < 0.05.*

3.6. Association Between De-escalation Practices and Mortality

The implementation of therapeutic de-escalation showed a significant protective association against hospital mortality (p = 0.048). Zero deaths occurred among the subset of patients (n = 11) who underwent successful de-escalation of their antimicrobial therapy. All eight recorded patient deaths took place within the non-de-escalation cohort (n = 89). Table 6 provides the comparative mortality distribution based on de-escalation status.

Table 6. Association Between De-escalation Practices and Mortality

De-escalation Executed	Hospital Deaths (n)	Hospital Survivors (n)	Total Patients (n)	p-value
Yes	0	11	11	0.048*
No	8	81	89	
Total	8	92	100	

** indicates statistical significance at p < 0.05.*

4. Discussion

The results of this prospective observational study show the current operational realities and therapeutic patterns associated with antimicrobial stewardship program execution within high-acuity critical care environments. The fact that the majority of patients (62%) required no active modification of their initial empirical regimens reflects a satisfactory level of concordance between initial clinician choices and subsequent clinical progression. This baseline appropriateness is crucial because the timely administration of proper empiric therapy is known to prevent clinical deterioration in severe infectious episodes [1, 20].

However, the active modifications implemented in 38% of patients emphasize the highly dynamic nature of infectious diseases in critically ill populations, where continuous re-evaluation is necessary to limit ecological damage [3, 10]. The withdrawal of unnecessary antimicrobials in 19% of cases indicates a growing clinical willingness to discontinue redundant agents when culture results are negative or when non-infectious etiologies are identified [14, 30]. Pharmacokinetic dose modifications (8%) reflect the clinical implementation of tailored dosing adjustments designed to match changing renal function, which is highly prevalent in severe sepsis [13]. The statistical significance linking culture-guided interventions with improved favorable outcomes ($p = 0.041$) reinforces the clinical value of objective microbiological evidence over prolonged empirical therapy. When clinicians transition from broad empirical coverage to targeted therapy based on identified culture profiles, patient safety is enhanced [20, 24]. This transition reduces the physiologic toxicity associated with broad-spectrum agents and targets the specific pathogen with optimized precision [7]. These findings align with contemporary critical care research establishing that culture-directed therapy minimizes the risk of superinfections and limits systemic inflammatory responses triggered by broad-spectrum agents [15, 29]. In resource-constrained settings, where diagnostic delays are common, establishing robust laboratory pathways and fast-tracking culture reports to bedside clinicians represents an essential intervention to improve recovery rates [16].

The moderate correlation observed between cumulative antibiotic burden and length of intensive care hospitalization ($r = 0.446$, $p < 0.001$) highlights the clinical costs of excessive prescribing. While severe infections inherently necessitate prolonged hospitalization, the direct relationship between high antibiotic exposure and outcome severity ($r = 0.287$, $p = 0.011$) indicates that poly-antibiotic exposure may introduce independent physiological risks. Exposure to multiple broad-spectrum agents disrupts the gut, respiratory, and skin microbiomes, eliminating competitive inhibition and predisposing patients to highly resistant opportunistic pathogens [4, 6]. Additionally, cumulative toxicities, particularly nephrotoxicity when aminoglycosides, glycopeptides, or polymyxins are combined, can prolong organ failure and extend hospital stay [6, 13]. Minimizing this poly-antibiotic burden through early, targeted stewardship interventions is a critical pathway to reduce hospitalization times and improve critical care outcomes [27]. The prospective observation that de-escalation was associated with zero mortality ($p = 0.048$) provides reassuring clinical evidence regarding the safety of this practice. Clinicians frequently hesitate to narrow antimicrobial regimens due to fear of clinical relapse or unrecognized secondary pathogens [11, 15]. However, the absence of deaths in the de-escalation group suggests that when de-escalation is carefully guided by objective microbiological profiles and clinical stability, it is highly safe and does not compromise clinical recovery. These results are consistent with multi-center clinical trials showing that de-escalation does not increase mortality or recurrent infection rates in septic populations [10, 12]. Implementing routine, protocol-driven clinical audits where de-escalation is actively discussed at the bedside every 48 to 72 hours can help overcome clinician hesitancy and reduce unnecessary broad-spectrum antibiotic exposure [25, 29].

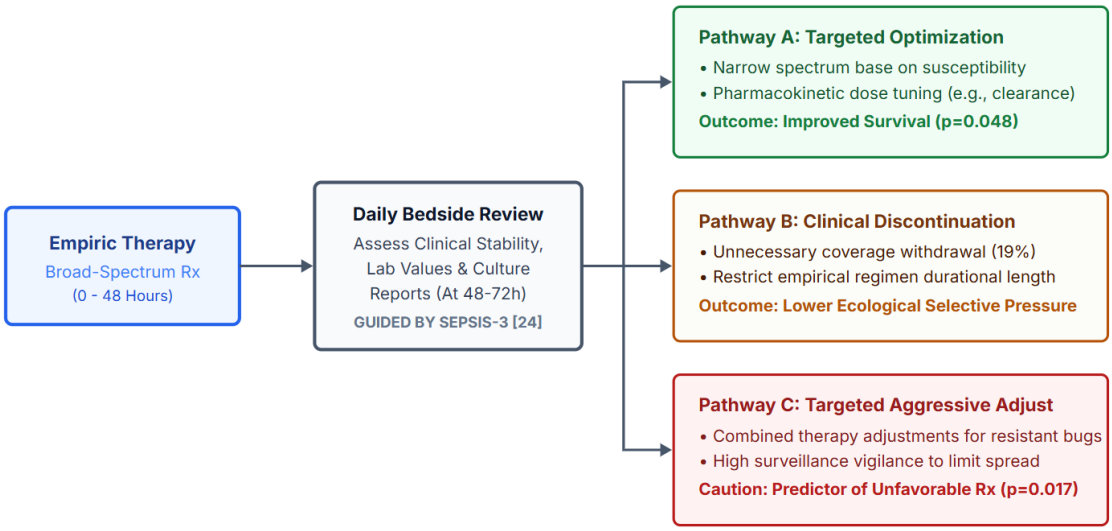

Figure 4. Stewardship-Driven De-escalation

The multivariate logistic regression analysis shows the primary clinical variables that drive adverse outcomes in critical care settings. The strong predictive capacity of multidrug-resistant infections (OR: 3.12, $p = 0.017$) emphasizes the severe clinical burden imposed by AMR [4]. Patients infected with resistant pathogens face higher rates of initial empirical therapy failure, which is a major driver of early mortality in severe sepsis [1, 20]. The independent predictive value of high cumulative antibiotic exposure (OR: 2.76, $p = 0.034$) highlights that excessive prescribing is not merely a marker of illness severity, but is independently associated with unfavorable outcomes. This independent risk may stem from severe drug-drug interactions, accumulated toxicity, or microbiological superinfections [6, 27]. The association between prolonged intensive care stay (> 8 days) and adverse outcomes (OR: 2.48, $p = 0.047$) reflects the accumulation of hospital-acquired complications, such as ventilator-associated pneumonia and catheter-related

bloodstream infections, which carry high mortality rates [2]. These results indicate that structured stewardship efforts must target modifiable risk factors such as cumulative antibiotic exposure to systematically improve ICU survival rates.

5. Conclusion

This prospective observational study indicated that structured antimicrobial stewardship interventions, particularly culture-guided therapy and therapeutic de-escalation, are strongly associated with improved clinical outcomes and reduced mortality in critically ill patients. Although a majority of patients required no modifications to their initial empirical treatments, active interventions such as treatment withdrawal, de-escalation, and pharmacokinetic dose optimization contributed significantly to refining therapy and preventing adverse events. Multidrug-resistant infections, excessive antibiotic burden (≥ 5 antibiotics), and prolonged intensive care hospitalization (> 8 days) were concluded as independent predictors of unfavorable clinical endpoints in this study.

Compliance with ethical standards

Acknowledgements

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Conflict of interest statement

All the authors declare that they have no competing interests, personal relationships, or financial conflicts of interest that could have inappropriately influenced, biased, or compromised the design, execution, statistical analysis, or reporting of this study.

Statement of ethical approval

This prospective observational study involving human subjects was conducted in strict compliance with the ethical guidelines of the Declaration of Helsinki (1964) and its subsequent amendments or comparable ethical standards. The clinical study design, data collection parameters, and research protocols were formally reviewed and approved by the Institutional Ethics Committee (IEC) of the participating tertiary care teaching hospital prior to study initiation and clinical patient enrollment.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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