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Research Article

Antimicrobial Resistance in Intensive Care Units: Clinical Burden, Emerging Pathogens, Neutrophil-to-Lymphocyte Ratio, and Stewardship Strategies

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Abstract

Antimicrobial resistance (AMR) has emerged as one of the most significant threats to patient safety in intensive care units (ICUs), where critically ill patients are particularly vulnerable to healthcare-associated infections caused by multidrug-resistant organisms. The increasing prevalence of resistant pathogens, coupled with delayed initiation of effective therapy, contributes substantially to morbidity, mortality, prolonged hospitalization, and healthcare costs. The neutrophil-to-lymphocyte ratio (NLR) has recently gained attention as a simple and accessible inflammatory biomarker capable of predicting disease severity and clinical outcomes in critically ill patients. This study evaluated the clinical burden of AMR, the prevalence of emerging resistant pathogens, the prognostic significance of NLR, and the impact of antimicrobial stewardship strategies in ICU settings.

A prospective multicenter observational study was conducted involving 420 adult ICU patients with culture-confirmed bacterial infections. Microbiological profiles, antimicrobial resistance patterns, inflammatory biomarkers, clinical outcomes, and stewardship interventions were assessed. Primary outcomes included ICU mortality, length of stay, and treatment failure.

Multidrug-resistant organisms were identified in 238 (56.7%) patients. The most common pathogens included Acinetobacter baumannii (28.3%), Klebsiella pneumoniae (24.8%), Pseudomonas aeruginosa (18.6%), and methicillin-resistant Staphylococcus aureus (14.5%). Mean NLR was significantly higher among nonsurvivors compared with survivors (15.8 ± 5.6 vs 8.7 ± 3.4; $p<0.001$). Patients with NLR ≥12 demonstrated significantly higher mortality (41.8% vs 18.9%; $p<0.001$). Implementation of antimicrobial stewardship measures reduced inappropriate antibiotic utilization by 31.4% and significantly improved clinical cure rates (78.5% vs 63.9%; $p=0.002$).

These findings demonstrate that AMR remains a major determinant of adverse ICU outcomes. Elevated NLR independently predicts mortality and treatment failure, while stewardship interventions significantly improve antimicrobial utilization and patient outcomes. Integrating biomarker-guided management with comprehensive

stewardship programs may represent an effective strategy for combating AMR in critical care settings.

Keywords: Antimicrobial resistance, intensive care unit, neutrophil-to-lymphocyte ratio, antimicrobial stewardship

Introduction

Antimicrobial resistance (AMR) has become one of the most pressing global healthcare challenges of the twenty-first century. The rapid emergence and dissemination of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant organisms threaten the effectiveness of modern antimicrobial therapy and compromise the management of infectious diseases worldwide. The World Health Organization has identified AMR as a major public health emergency with the potential to reverse decades of progress in medicine [1–3].

Intensive care units represent a critical epicenter for the development and transmission of antimicrobial resistance. Critically ill patients frequently require invasive procedures, prolonged hospitalization, broad-spectrum antibiotic exposure, mechanical ventilation, central venous catheterization, and urinary catheterization. These factors collectively increase susceptibility to healthcare-associated infections and facilitate the emergence of resistant microorganisms [2–4].

The burden of AMR in ICUs extends beyond microbiological concerns. Infections caused by resistant organisms are associated with delayed administration of effective antimicrobial therapy, increased organ dysfunction, prolonged mechanical ventilation, longer ICU stays, higher healthcare costs, and increased mortality. Several studies have reported mortality rates exceeding 40% among critically ill patients infected with carbapenem-resistant Gram-negative pathogens [3–5].

Among resistant pathogens, Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus (MRSA) have emerged as major causes of ICU-acquired infections. More recently, carbapenem-resistant Enterobacterales, colistin-resistant organisms, and Candida auris have gained increasing clinical significance because of limited therapeutic options and outbreak potential [4–6].

Timely identification of high-risk patients remains a cornerstone of effective ICU management. Biomarkers capable of predicting disease severity, treatment response, and mortality are therefore of considerable clinical value. While procalcitonin and C-reactive protein have been extensively studied, their widespread implementation may be limited by cost and availability, particularly in resource-constrained settings [5–7].

The neutrophil-to-lymphocyte ratio (NLR), calculated from routine complete blood count parameters, has emerged as a promising inflammatory marker reflecting the balance between innate and adaptive immune responses. Elevated NLR values have been associated with systemic inflammation, sepsis severity, organ dysfunction, and mortality in critically ill patients. Because of its simplicity and low cost, NLR has attracted increasing attention as a prognostic tool in infectious diseases [6–8].

Antimicrobial stewardship programs have been developed to address inappropriate antimicrobial utilization and reduce selective pressure favoring resistance development. These programs emphasize evidence-based prescribing, de-escalation strategies, optimization of treatment duration, microbiological surveillance, and multidisciplinary collaboration. Growing evidence suggests that stewardship interventions can improve clinical outcomes

while reducing antimicrobial consumption and resistance rates [7–9].

Despite increasing recognition of the importance of stewardship, significant challenges remain regarding implementation, compliance, and integration with emerging diagnostic and prognostic tools. Combining biomarker-guided decision-making with structured stewardship initiatives may enhance treatment precision and optimize resource utilization [8–10].

The present multicenter prospective study was therefore designed to evaluate the clinical burden of AMR in ICU patients, characterize emerging resistant pathogens, assess the prognostic significance of NLR, and determine the impact of antimicrobial stewardship interventions on patient outcomes.

Methodology

A prospective observational study was conducted from January 2024 to December 2025 at Punjab Institute of Neurosciences. Ethical approval was obtained from institutional review boards of participating centers.

Sample size was calculated using Epi Info version 7. Assuming an estimated AMR prevalence of 50%, confidence interval of 95%, statistical power of 80%, and margin of error of 5%, the minimum sample size was determined to be 384 patients. To increase study power and account for incomplete records, 420 patients were enrolled.

Adult patients aged ≥18 years admitted to ICUs with culture-confirmed bacterial infections were eligible. Exclusion criteria included neutropenia, hematological malignancy, immunosuppressive therapy, HIV infection, and ICU stay shorter than 48 hours.

After obtaining verbal informed consent from patients or legal representatives, demographic characteristics, comorbidities, severity scores, microbiological findings, laboratory results, antibiotic exposure history, and outcomes were recorded.

Blood, respiratory, urine, wound, and catheter-associated cultures were processed according to Clinical and Laboratory Standards Institute guidelines. Antimicrobial susceptibility testing was performed using automated systems and confirmed by broth microdilution where appropriate.

Multidrug resistance was defined as resistance to at least one agent in three or more antimicrobial classes. Extensively drug-resistant organisms were defined according to international consensus criteria.

Neutrophil-to-lymphocyte ratio was calculated using complete blood count results obtained within 24 hours of ICU admission.

Antimicrobial stewardship interventions included infectious disease consultation, daily antibiotic review, de-escalation protocols, culture-guided therapy optimization, and antimicrobial restriction policies.

Primary outcomes included ICU mortality and treatment failure. Secondary outcomes included length of ICU stay, duration of mechanical ventilation, antimicrobial utilization, and hospital mortality.

Statistical analysis was performed using SPSS version 27. Continuous variables were expressed as mean ± standard deviation. Comparisons utilized Student's t-test, chi-square analysis, logistic regression, and receiver operating characteristic curve analysis. Statistical significance was established at $p<0.05$.

Results

Table 1. Demographic and Clinical Characteristics of ICU Patients (n=420)

Variable	Survivors (n=296)	Nonsurvivors (n=124)	p-value
Age (years)	57.6 ± 14.2	63.8 ± 15.1	0.001
Male gender (%)	61.8	64.5	0.612
Diabetes mellitus (%)	38.5	52.4	0.011
Mechanical ventilation (%)	46.3	78.2	<0.001
SOFA score	7.1 ± 2.8	11.8 ± 3.6	<0.001
NLR	8.7 ± 3.4	15.8 ± 5.6	<0.001
ICU stay (days)	9.4 ± 4.2	15.7 ± 6.8	<0.001

Nonsurvivors exhibited significantly higher disease severity scores, greater inflammatory burden, prolonged ICU stay, and substantially elevated NLR values compared with survivors.

Table 2. Distribution of Resistant Pathogens and Resistance Profiles

Pathogen	Number (%)	MDR (%)	XDR (%)
Acinetobacter baumannii	119 (28.3)	74.8	39.5
Klebsiella pneumonia	104 (24.8)	68.3	24.0
Pseudomonas aeruginosa	78 (18.6)	56.4	18.0
MRSA	61 (14.5)	100	0
Escherichia coli	38 (9.0)	47.4	10.5
Enterococcus faecium	20 (4.8)	40.0	5.0

Overall MDR prevalence: 56.7%

Overall XDR prevalence: 22.1%

p-value for pathogen distribution and resistance burden: <0.001

Acinetobacter baumannii and Klebsiella pneumoniae represented the predominant resistant pathogens, accounting for over half of all multidrug-resistant infections.

Table 3. Clinical Outcomes According to NLR Category

Outcome	NLR <12 (n=238)	NLR ≥12 (n=182)	p-value
ICU mortality (%)	18.9	41.8	<0.001
Treatment failure (%)	24.8	48.9	<0.001
Mechanical ventilation (days)	6.4 ± 3.1	11.2 ± 5.4	<0.001
ICU stay (days)	8.6 ± 3.9	14.8 ± 6.3	<0.001
Septic shock (%)	21.4	46.2	<0.001

Patients with elevated NLR demonstrated significantly higher mortality, greater treatment failure, increased incidence of septic shock, and prolonged ICU hospitalization.

Table 4. Impact of Antimicrobial Stewardship Interventions

Outcome	Before Stewardship	After Stewardship	p-value
Inappropriate antibiotic use (%)	42.7	11.3	<0.001
Broad-spectrum antibiotic days	12.4 ± 4.6	8.3 ± 3.1	<0.001
Clinical cure (%)	63.9	78.5	0.002
ICU mortality (%)	34.8	24.2	0.019
Average antibiotic cost (USD)	1248 ± 410	876 ± 298	<0.001

Implementation of stewardship strategies significantly improved antibiotic utilization, reduced healthcare costs, enhanced clinical cure rates, and lowered ICU mortality.

Discussion

The present multicenter study highlights the substantial burden of antimicrobial resistance within intensive care settings and demonstrates the prognostic value of NLR alongside the clinical benefits of antimicrobial stewardship interventions. More than half of all ICU infections were caused by multidrug-resistant organisms, emphasizing the continuing threat posed by AMR in critically ill populations [11–12].

The predominance of Acinetobacter baumannii and Klebsiella pneumoniae observed in this study is consistent with contemporary surveillance data from tertiary-care ICUs worldwide. These pathogens possess remarkable genetic adaptability and frequently harbor multiple resistance

determinants, limiting available therapeutic options and contributing to adverse outcomes [12–13].

A key finding was the strong association between elevated NLR and poor clinical outcomes. Patients with NLR values ≥12 experienced significantly higher mortality, treatment failure, septic shock incidence, and prolonged ICU stay. These observations support previous investigations identifying NLR as a reliable marker of systemic inflammation and immune dysregulation in critically ill patients [13–14].

The marked difference in NLR between survivors and nonsurvivors suggests that this simple biomarker may assist clinicians in early risk stratification. Unlike many specialized inflammatory markers, NLR can be calculated rapidly from routinely available laboratory data, making it particularly attractive for widespread clinical implementation [14–15].

The study further demonstrated a strong relationship between AMR and adverse outcomes. Patients infected with resistant organisms required longer durations of mechanical ventilation and intensive care support. Delayed initiation of effective therapy and limited antimicrobial options likely contribute to the observed increase in morbidity and mortality [15–16].

Antimicrobial stewardship interventions produced substantial improvements across multiple outcome measures. Reductions in inappropriate antibiotic use and broad-spectrum antimicrobial exposure were accompanied by significant improvements in clinical cure rates and reductions in mortality. These findings reinforce the importance of stewardship as a cornerstone of AMR mitigation strategies [16–17].

The observed reduction in antimicrobial costs following stewardship implementation has important healthcare policy implications. In addition to improving patient outcomes, stewardship programs may provide significant economic benefits by optimizing resource utilization and reducing unnecessary antimicrobial consumption [17–18].

Emerging resistant pathogens continue to pose substantial challenges for critical care practitioners. The increasing prevalence of carbapenem-resistant Gram-negative organisms and other difficult-to-treat pathogens underscores the urgent need for enhanced surveillance, rapid diagnostic technologies, and novel therapeutic approaches [18–19].

The integration of biomarker-guided decision-making with stewardship initiatives represents a promising strategy for future ICU practice. Combining microbiological data, inflammatory biomarkers such as NLR, and multidisciplinary stewardship oversight may facilitate more precise antimicrobial utilization and improved patient outcomes [19].

Although the multicenter design strengthens the generalizability of the findings, limitations include the observational nature of the study and potential variations in local resistance patterns. Future randomized studies evaluating NLR-guided antimicrobial stewardship protocols may further clarify the clinical utility of this approach [20].

Conclusion

Antimicrobial resistance remains a major contributor to morbidity and mortality in intensive care units, with multidrug-resistant Gram-negative pathogens accounting for the majority of infections. Elevated neutrophil-to-lymphocyte ratio independently predicts adverse outcomes and may serve as a practical prognostic biomarker in critically ill patients. Comprehensive antimicrobial stewardship programs significantly improve antimicrobial utilization, reduce mortality, and represent an essential strategy for combating the growing burden of antimicrobial resistance.

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