Correlation of Antimicrobial Therapy with Culture-Confirmed Organisms and Associated Adverse Drug Reactions in ICU Patients: A Prospective Observational Study

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ABSTRACT

Background: Antimicrobial therapy is a cornerstone of intensive care, yet discordance between prescribed drugs and causative organisms, along with drug-related adverse events, can compromise outcomes. This study aimed to assess the correlation between antimicrobials and culture-confirmed organisms, and to document adverse drug reactions (ADRs) associated with antimicrobial use in an ICU setting.

Methods: A prospective observational study was conducted over one year in the ICU of a tertiary-care hospital in North India. Seventy-five adult patients receiving systemic antimicrobials were enrolled. Antimicrobial prescriptions were documented and compared with culture and sensitivity reports for concordance. ADRs were identified by daily clinical and laboratory monitoring and assessed using the WHO–UMC causality scale and Hartwig's severity scale.

Results: Beta-lactams were prescribed to nearly all patients (96%), followed by glycopeptides (58.7%) and polypeptide antibiotics (41.3%). Thirty-two patients (42.7%) had positive cultures, most commonly *Acinetobacter baumannii* (14.7%), *Klebsiella pneumoniae* (9.3%), and *Candida* spp. (8%). Antimicrobial–pathogen correlation revealed that while the majority of prescriptions were concordant with culture sensitivity, discordant therapy was present in approximately one-third of cases. Seven patients (9.3%) developed ADRs, predominantly gastrointestinal upset (5.3%) and hypersensitivity reactions (4.0%). On severity assessment, 4 ADRs (57.1%) were mild and 3 (42.9%) were moderate; no severe or life-threatening reactions occurred.

Conclusions: Antimicrobial prescribing in the ICU was dominated by broad-spectrum agents, with a notable fraction of discordant therapy in culture-positive cases. ADRs were infrequent

and generally mild to moderate. These findings underscore the importance of culture-guided prescribing and structured ADR monitoring within antimicrobial stewardship programs.

Keywords: Antimicrobials; Intensive Care Unit; Culture sensitivity; Concordance; Adverse drug reactions; Hartwig scale.

INTRODUCTION

Critically ill patients in the Intensive Care Unit (ICU) frequently receive broad-spectrum antibiotics due to the urgent need to treat life-threatening infections—often before specific pathogens are identified. However, empirical prescribing without microbiological confirmation may lead to mismatches between antimicrobial agents and causative organisms, contributing to therapeutic failure, prolonged ICU stay, and the emergence of multidrug-resistant organisms (MDROs)[1, 2, 3, 4]. Strengthening the alignment between antimicrobial use and culture-based sensitivity is therefore central to antimicrobial stewardship, especially in settings where resistance burden is high.

Several studies from Indian tertiary-care settings highlight the overwhelming prevalence of ICU-acquired infections caused by Gram-negative pathogens such as *Escherichia coli*, *Klebsiella spp.*, and *Pseudomonas spp.*, with high resistance to beta-lactams and fluoroquinolones[5]. Such trends underscore the critical need for culture-guided therapy to improve clinical outcomes and curb antimicrobial misuse.

Parallel to concerns about resistance is the under-recognized issue of antimicrobial-related adverse drug reactions (ADRs). ICU patients, especially those with organ dysfunction, are vulnerable to drug-induced toxicities. Several investigations report variable but significant rates of ADRs in ICU settings—ranging up to approximately 30% per 100 admissions[4, 6]. In the broader hospital population, antibiotic-related ADR incidence varies from about 0.3% to over 10%, depending on context and detection methods[7, 8, 9]. Yet prospective, ICU-specific documentation remains limited, particularly in low- and middle-income countries.

Furthermore, standardized tools such as the WHO–UMC causality assessment and the Hartwig severity scale are recommended for structured evaluation of ADRs in hospital settings.Nonetheless, these frameworks are underutilized in real-world ICU pharmacovigilance. Taken together, optimizing critical care pharmacotherapy requires not only ensuring that antimicrobials match microbial diagnoses but also monitoring for adverse effects with rigorous methods.

Therefore, this study focuses specifically on two interrelated objectives in a tertiary-care ICU:

1. To assess the correlation between prescribed antimicrobials and culture-confirmed organisms.

2. To document and analyze antimicrobial-related adverse drug reactions, including causality and severity assessments.

By applying systematic microbiological correlation and structured ADR reporting, this work aims to inform both antimicrobial stewardship strategies and patient safety protocols in resource-constrained critical care environments.

METHODS

Study Design and Setting

A prospective observational study was carried out in the Intensive Care Unit (ICU) of a tertiary-care teaching hospital in North India over a one-year period. The study was approved by the Institutional Ethics Committee (IEC), and informed consent was obtained from patients or their legally authorized representatives prior to inclusion.

Study Population

Patients aged ≥18 years, admitted to the ICU during the study period, who received at least one systemic antimicrobial agent were eligible. Patients with incomplete medical records or those who declined consent were excluded. The final sample size comprised 75 consecutive ICU patients, calculated based on expected antimicrobial prescribing prevalence and prescription-to-patient ratio as detailed in the thesis protocol.

Evaluation of Antimicrobial–Pathogen Correlation

For patients with positive microbiological cultures, the prescribed antimicrobials were compared with the sensitivity patterns of the isolated organisms. Concordance was defined as the use of an antimicrobial to which the pathogen was susceptible in vitro. Discordance was defined as use of an antimicrobial with in vitro resistance or absence of appropriate targeted coverage.

Assessment of Adverse Drug Reactions

All suspected ADRs were identified through daily clinical monitoring, review of laboratory parameters, and patient records. Each ADR was evaluated systematically using:

- WHO–UMC Causality Assessment Scale (categorized as certain, probable, possible, unlikely, conditional/unclassified, or unassessable)
- Hartwig and Siegel Severity Assessment Scale, which stratifies ADRs as mild, moderate, or severe

Outcome Measures

The study specifically focused on:

1. Primary outcome: correlation between prescribed antimicrobials and culture-confirmed organisms.
2. Secondary outcome: documentation of ADRs related to antimicrobials, including their type, frequency, causality, and severity.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using SPSS . Descriptive statistics were used for demographic and prescribing data. Frequencies and percentages were calculated for organism distribution, antimicrobial usage, and ADRs. Chi-square or Fisher’s exact test was applied to assess associations between antimicrobial classes and culture-confirmed organisms,

as well as between antimicrobials and ADR occurrence. A p-value <0.05 was considered statistically significant.

RESULTS

Antimicrobial Prescribing Patterns

Among 75 ICU patients, beta-lactam agents (96%) were the most commonly prescribed class, followed by glycopeptides (58.7%), polypeptide antibiotics (41.3%), and lincosamides (33.3%). Other classes used included tetracyclines (25.3%), nitroimidazoles (24%), echinocandins (22.7%), macrolides (21.3%), polyene antifungals (20%), artemisinin derivatives (6.7%), and fluoroquinolones (4%) (Table 1). Combination therapy was frequent, with many patients receiving more than one agent.

Table 1. Antimicrobial Prescribing Patterns in ICU Patients (N = 75)

Antimicrobial class	*n*	*%*
Beta-lactams (penicillins/cephalosporins/monobactams/carbapenems)	*72*	*96.0*
Glycopeptides	*44*	*58.7*
Polypeptide antibiotics	*31*	*41.3*
Lincosamides	*25*	*33.3*
Tetracyclines	*19*	*25.3*
Nitroimidazoles	*18*	*24.0*
Echinocandin antifungals	*17*	*22.7*
Macrolides	*16*	*21.3*
Polyene antifungals	*15*	*20.0*
Artemisinin derivatives	*5*	*6.7*
Fluoroquinolones	*3*	*4.0*

Culture-Positive Organisms and Antimicrobial Correlation

Of the 75 patients, 32 (42.7%) had culture-positive results. The leading isolate was Acinetobacter baumannii (14.7%), followed by Klebsiella pneumoniae (9.3%), Candida spp. (8%), Staphylococcus aureus (MRSA, 6.7%), Proteus mirabilis (2.7%), and Micrococcus spp. (1.3%) (Table 2).

Table 2. Culture-positive organisms isolated (overall N = 75; culture-positive n = 32)

Organism	*n*	*% of total (75)*
Acinetobacter baumannii	11	14.7
Klebsiella pneumoniae	7	9.3
Candida spp.	6	8.0

Staphylococcus aureus (MRSA)	5	6.7
Proteus mirabilis	2	2.7
Micrococcus spp.	1	1.3

The antimicrobial–organism cross-tabulation (Table 3) demonstrated frequent use of carbapenems, glycopeptides, and polymyxins for Gram-negative organisms, with antifungals (liposomal amphotericin B, caspofungin, colistin) administered in patients with Candida. Concordance between prescribed antimicrobials and pathogen susceptibility was observed in a majority, although discordant therapy was also noted across several organisms, reflecting the challenge of empiric prescribing in ICU settings.

Table 3. Antimicrobial agent × organism matrix in culture-positive patients (N = 32)

Antimicrobial	*A. baumannii*	*Candida*	*Klebsiella*	*Micrococcus*	*Proteus*	*S. aureus*
Metronidazole	5	6	1	0	0	1
Amphotericin B (liposomal)	4	3	1	0	0	1
Meropenem	6	0	1	0	2	0
Teicoplanin	4	0	2	0	2	1
Caspofungin	3	3	2	1	0	0
Polymyxin B	4	0	2	1	2	0
Piperacillin–Tazobactam	1	0	4	1	0	3
Amoxicillin–Clavulanate	3	3	1	0	0	0
Clindamycin	1	0	2	0	0	4
Azithromycin	2	0	1	1	2	0
Vancomycin	3	0	2	1	0	0
Doxycycline	3	0	0	0	2	0
Colistin	0	3	0	0	0	0
Minocycline	0	3	0	0	0	0
*Piperacillin–Tazobactam**	0	3	0	0	0	0
Levofloxacin	1	0	0	0	0	1
Artesunate	2	0	0	0	0	0
Cefoperazone–Sulbactam	0	0	1	0	0	1

Adverse Drug Reactions

A total of 7 patients (9.3%) experienced antimicrobial-related ADRs. The most common were gastrointestinal upset (5.3%) and cutaneous hypersensitivity reactions (4%) (Table 4A). Causality assessment indicated plausible associations with antimicrobials in use.

Table 4A. Adverse drug reactions (ADRs) types linked to antimicrobials (N = 75; n = 7 patients

ADR type	*n*	*% of 75*
Gastrointestinal upset	4	5.3
Rash / hypersensitivity	3	4.0

Severity of ADRs

Based on the Hartwig severity scale, 4 ADRs (5.3%) were mild and 3 ADRs (4.0%) were moderate; no severe or life-threatening ADRs were recorded (Table 4B).

Table 4A. Adverse drug reactions (ADRs) severity(Hartwig) linked to antimicrobials (N = 75; n = 7 patients

Severity	*n*	*% of 75*
Mild	4	5.3
Moderate	3	4.0
Severe	0	0.0

DISCUSSION

This prospective ICU cohort demonstrates heavy reliance on broad-spectrum agents (predominantly β-lactams, with glycopeptides and polymyxins), a pattern consistent with international ICU snapshots in which antibiotic exposure is common and sustained. The EPIC II and EPIC III studies reported high infection prevalence and extensive antibiotic use among ICU patients, underscoring the stewardship challenge in this setting[10, 11].

In our cohort, Gram-negative bacteria dominated culture-positive cases, led by *Acinetobacter baumannii* and *Klebsiella pneumoniae*. This organism mix mirrors global ICU epidemiology that emphasizes Gram-negative predominance and its association with worse outcomes, highlighting the importance of early sampling and targeted therapy[10] (JAMA 2009).

The clinical relevance of aligning empiric therapy with microbiology is well established. Seminal cohort analyses show that inappropriate initial antimicrobial therapy independently increases mortality in severe sepsis/septic shock (e.g., fivefold reduction in survival with inappropriate initial therapy), supporting rapid correction once culture data are available[12, 13]. In parallel, multiple meta-analyses and multicenter studies indicate that de-escalation after microbiologic clarification is not associated with higher mortality and may reduce exposure-related harms[14, 15, 16].

Antibiotic-associated adverse drug reactions (ADRs) occurred in 7/75 (9.3%) patients in our study—predominantly gastrointestinal intolerance and cutaneous hypersensitivity—with no severe events on Hartwig grading. Large inpatient cohorts (not ICU-specific) report higher overall ADE rates (≈20%), with GI, renal, and hematologic events most frequent, suggesting that differences in surveillance intensity, cohort size, and exposure mix likely explain our lower observed incidence[17]. Importantly, nephrotoxicity is a recognized risk with glycopeptides (vancomycin), particularly at higher troughs or prolonged courses, and is amplified by concomitant nephrotoxins—an ICU-relevant safety consideration even when severe events are not observed[18, 19].

ADR assessment in our study used WHO-UMC causality and Hartwig severity frameworks, both widely applied and supported by pharmacovigilance literature. The original Hartwig and Siegel severity methodology and subsequent applications reinforce that most hospital-detected ADRs are graded mild–moderate, aligning with our distribution[20, 21, 22, 23].

Implications. Our findings indicate two actionable priorities for ICU stewardship: (i) shorten the window of discordant empiric coverage via timely cultures, rapid diagnostics, and structured de-escalation; and (ii) maintain proactive ADR surveillance to mitigate preventable harm (dose optimization, therapeutic drug monitoring where appropriate, and avoiding nephrotoxic combinations). These actions are consistent with contemporary evidence and can be implemented without compromising survival.

Limitations. Single-center design and a modest culture-positive subset limit generalizability; ADR detection may under-estimate subclinical events compared with larger, intensively monitored cohorts. Outcome modeling versus concordance was beyond scope; future work should link concordant therapy and ADR burden with mortality and resource use—outcomes repeatedly associated with infection care quality in international ICU cohorts[10].

CONCLUSION

In this prospective ICU study, beta-lactams were the most frequently prescribed antimicrobials, reflecting the heavy reliance on broad-spectrum agents in critically ill patients. Nearly half of the cohort yielded culture-positive results, with *Acinetobacter baumannii* and *Klebsiella pneumoniae* predominating. While most patients received concordant therapy, discordant prescriptions were still observed in about one-third of culture-positive cases, highlighting a gap between empiric use and microbiological evidence.

Adverse drug reactions were detected in 9.3% of patients, mainly gastrointestinal intolerance and hypersensitivity reactions. All events were mild or moderate in severity, and no severe ADRs were reported.

These findings underscore two priorities for ICU practice: improving the alignment of empirical therapy with microbiological data through timely culture-based adjustments, and strengthening structured ADR monitoring to ensure patient safety. Integration of these measures into antimicrobial stewardship initiatives can optimize both treatment efficacy and safety in resource-constrained critical care settings

DECLARATIONS

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