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Original Article

Pharmacology Section

Antimicrobial Utilisation and Resistance Patterns in Critically-ill ICU Patients with Multidrug-resistant Infections: A Retrospective Study

AKHILA CHAGALAMARI[1], DEBABRATA DASH[2], UPPARA KADIYALA RAKESH[3], MADHAV RAO[4], SUSHIL SHARMA[5], GAURAV M RANGARI[6], G HEMANTH KUMAR[7], MOHAMMED SIBGATULLAH[8]

ABSTRACT

Introduction: Multidrug-resistant (MDR) infections are increasingly prevalent in critically-ill patients in Intensive Care units (ICUs), complicating empirical antimicrobial choices. Antimicrobial Resistance (AMR) surveillance through antibiograms and outcome analysis is vital to guide stewardship.

Aim: To analyse empirical antimicrobial utilisation patterns and AMR patterns in ICU patients with MDR infections and to assess concordance with department-level antibiogram data.

Materials and Methods: A single-centre retrospective observational analysis was conducted at Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India, between January 2021 and December 2023, including 92 ICU patients with culture-confirmed MDR infections. A total of 683 urine, 92 blood, 185 respiratory and 50 pyogenic isolates were analysed. Antimicrobial utilisation, resistance patterns and recorded clinical outcomes were evaluated. Descriptive statistics were used; categorical variables were expressed as percentages and continuous variables as mean±SD or median {Interquartile Range (IQR)}. A p-value <0.05 was considered statistically significant.

Results: Among ICU isolates, Methicillin-Resistant *Staphylococcus Aureus* (MRSA) constituted 7/15 (46.7%) of pyogenic *S. aureus* isolates, while Vancomycin-Resistant *Enterococcus* (VRE) was identified in 3/48 (6.3%) isolates. Among Bloodstream *Enterobacterales*, carbapenem susceptibility was observed in 79/92 (86.5%) isolates and piperacillin-tazobactam susceptibility in 71/92 (76.9%) isolates. Respiratory isolates (*Acinetobacter baumannii* and *Klebsiella pneumoniae*, n=185) demonstrated susceptibility rates below 70% for most tested agents, with colistin susceptibility preserved in the majority of isolates. In respiratory isolates of *A. baumannii* and *K. pneumoniae*, carbapenem showed modest activity, with susceptibility observed in 79/185 isolates (42.8%). Clinical outcomes were assessed descriptively, with variability observed according to organism type and empirical antimicrobial coverage.

Conclusion: Empirical antibiotic strategies informed by local antibiogram trends improve outcomes in critically-ill MDR-infected patients. Continuous resistance surveillance and stewardship-driven de-escalation are critical to optimising ICU antimicrobial protocols and combating AMR.

Keywords: Anti-bacterial agents, Antimicrobial stewardship, Cross infection, Drug resistance, Hospital mortality, Intensive care unit

INTRODUCTION

The AMR is a major global health threat, arising when microorganisms develop mechanisms to withstand previously effective antimicrobial agents [1,2]. The World Health Organisation (WHO) has warned that AMR jeopardises routine medical procedures and critical care interventions [3]. In 2019, approximately 1.27 million deaths were directly attributed to resistant bacterial infections, with nearly five million deaths associated with AMR globally [4]. Projections estimate a substantial rise in mortality and economic burden if effective containment strategies are not implemented [5]. Low- and middle-income countries, including India, face a disproportionate burden due to high infectious disease prevalence and challenges in antibiotic regulation and stewardship [6].

India has reported widespread irrational antibiotic prescribing, over-the-counter antimicrobial availability and suboptimal infection control practices [7-9]. ICUs are particularly vulnerable to the emergence and spread of MDR organisms due to invasive procedures, prolonged hospitalisation and frequent exposure to broad-spectrum antibiotics [9]. Gram-negative pathogens such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Escherichia coli* commonly exhibit resistance to β-lactams, carbapenems and aminoglycosides [10], while Gram-positive organisms including Vancomycin-Resistant *Enterococci* (VRE) and MRSA further complicate therapy [11]. These pathogens form part of the *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* (ESKAPE) group, known for their ability to evade multiple antimicrobial classes [12].

Delayed or inappropriate empirical therapy in critically-ill patients is associated with increased mortality, particularly in septic shock [13,14]. Accordingly, international and national guidelines advocate early empirical therapy followed by de-escalation guided by microbiological data and institutional antibiograms [8,15-17]. Despite this, many studies from India have examined resistance patterns or antimicrobial consumption independently, with limited integrated ICU-based analyses linking empirical antimicrobial utilisation, resistance patterns and concordance with institutional antibiogram data.

In this context, the present study was undertaken to evaluate antimicrobial utilisation patterns and AMR patterns among critically-ill ICU patients with culture-confirmed MDR infections at a tertiary care centre. The primary objective was to descriptively analyse empirical antimicrobial prescribing patterns and antimicrobial susceptibility

profiles. Secondary objectives included assessing concordance between empirical antimicrobial therapy and department-level antibiogram data and descriptively examining recorded clinical outcomes, including mortality and ICU course, without formal comparative outcome modelling. A clinical outcome in ICU patients with MDR infections was also assessed.

MATERIALS AND METHODS

The present study was designed as a single-centre retrospective observational analysis conducted at the All India Institute of Medical Sciences (AIIMS), Mangalagiri, a tertiary care teaching hospital in South India. Clinical and microbiological data of critically-ill patients admitted to the ICU between January 2021 and December 2023 were retrospectively reviewed. The patients included in the study had undergone treatment and completed follow-up as part of routine standard clinical care during the study period, and no prospective recruitment or intervention was performed for research purposes. The study protocol, retrospective data retrieval, analysis, and interpretation were carried out between January 2024 and November 2024. The study was approved by the Institutional Ethics Committee of the All India Institute of Medical Sciences (AIIMS), Mangalagiri (IEC Approval No.: AIIMS/MG/IEC/2025-26/337), dated 23 June 2025, in accordance with institutional requirements for retrospective record-based studies. Given the retrospective observational design and use of anonymised patient data, the requirement for informed consent was waived by the Ethics Committee.

Sample size: During the study period (January 2021 to December 2023), a total of 92 ICU patients with culture-confirmed MDR infections met the inclusion criteria and were included in the analysis. These patients yielded 683 urine isolates, 92 blood isolates, 185 respiratory isolates and 50 pyogenic isolates, all of which were analysed. As this was a retrospective observational study, no formal sample size calculation was performed. All consecutive eligible cases during the defined study period were included to minimise selection bias and maximise representativeness of ICU AMR patterns.

Inclusion criteria:

- Adult patients (≥18 years) admitted to the ICU during the study period;
- Patients with culture-confirmed MDR bacterial infections from blood, urine, respiratory, or pyogenic specimens;
- Availability of complete microbiological and prescription records for the infection episode.

Exclusion criteria:

- Patients aged <18 years;
- Patients with non bacterial infections (e.g., isolated fungal or viral infections);
- Duplicate isolates from the same patient during the same infection episode (only the first isolate was included);
- Patients with incomplete medical or microbiological records.
- Patients with mixed cultures without clinical correlation.

Study Procedure

Microbiological data collection: Clinical specimens were processed in the Department of Microbiology according to Clinical and Laboratory Standards Institute (CLSI) guidelines for isolation and identification of pathogens [18]. Bacterial identification was performed using an automated system (VITEK 2, bioMérieux). Where required, conventional biochemical tests were conducted to support automated identification. These included Gram staining, catalase and oxidase tests, motility testing, indole production, citrate utilisation, urease testing, Triple Sugar Iron (TSI) reactions, methyl red-Voges Proskauer (MR-VP) tests, coagulase testing (slide and tube), bile esculin hydrolysis, Pyrrolidonyl Arylamidase (PYR) test, haemolysis pattern on blood agar, 6.5% Sodium Chloride (NaCl) growth test, Oxidative-Fermentative (OF) glucose test and carbohydrate fermentation reactions, following standard microbiological identification algorithms.

For gram-negative bacilli isolated from urine and blood specimens (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacterales* group organisms), oxidase, catalase, indole, citrate, urease, TSI, MR-VP, motility testing and lactose fermentation were performed. Respiratory isolates including *Acinetobacter baumannii* and *Klebsiella pneumoniae* were further characterised using oxidase, catalase, OF glucose testing and motility assessment. Gram-positive cocci such as *Enterococcus faecalis* and *Enterococcus faecium* were identified using bile esculin hydrolysis, 6.5% NaCl growth and PYR testing. *Staphylococcus aureus* (including MRSA) from pyogenic specimens was confirmed using catalase tests, slide and tube coagulase tests and mannitol fermentation.

Antimicrobial Susceptibility Testing (AST) was performed using the Kirby-Bauer disk diffusion method and automated systems, with interpretation according to CLSI M100 standards (31st edition) [19]. Quality control strains {*Escherichia coli* American Type Culture Collection (ATCC) 25922, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 25923 and *Enterococcus faecalis* ATCC 29212} were used to ensure accuracy of results [20].

Antibiotics studied: The antimicrobial panel included agents commonly used in ICU practice. AST was performed using commercially available antibiotic discs with the following potencies: ceftriaxone (30 µg), cefepime (30 µg), piperacillin-tazobactam (100/10 µg), meropenem (10 µg), imipenem (10 µg), amikacin (30 µg), gentamycin (10 µg), vancomycin (30 µg), teicoplanin (30 µg), linezolid (30 µg), colistin (10 µg), polymyxin B (300 units) and fosfomycin (200 µg with 50 µg glucose-6-phosphate).

Susceptibility interpretation was performed according to CLSI M100 guidelines (31st edition) [19]. Susceptibility to fosfomycin was specifically assessed for *Escherichia coli* and *Enterococcus faecalis* urine isolates, given its emerging role in treating MDR urinary tract infections [21].

Antimicrobial utilisation data: Medical Drug Records (MRD) were reviewed to document antimicrobial prescriptions among ICU patients during the study period. Antimicrobial utilisation was analysed by recording the number of patients receiving each antibiotic and calculating the proportion of total ICU patients exposed to that agent. Utilisation percentages were derived as the number of prescriptions for a given antibiotic divided by the total number of included ICU patients, expressed as n (%). Prescriptions were further categorised as empirical or culture-guided based on timing relative to microbiological reporting.

Assessment of concordance with department-level antibiogram: Concordance between empirical antimicrobial therapy and department-level antibiogram data was assessed descriptively. For each patient, the initial empirical antimicrobial regimen initiated at ICU admission was recorded from prescription charts. These agents were then cross-referenced with the department-level antibiogram generated during the same study period.

Empirical therapy was considered concordant if at least one antimicrobial agent included in the initial empirical regimen demonstrated susceptibility ≥70% against the corresponding organism group as reported in the institutional antibiogram. Empirical regimens that did not include any agent meeting this criterion were considered non concordant.

This assessment was performed at the organism-group level rather than individual isolate level and was intended to evaluate alignment between prescribing practices and institutional resistance patterns. No inferential statistical testing was performed for concordance assessment and findings are reported descriptively.

Combination antibiogram analysis: Combination antibiograms were constructed to descriptively evaluate the potential incremental coverage offered by commonly used dual empirical antimicrobial

regimens, particularly for *Enterobacterales* isolates in the ICU. By examining cross-susceptibility patterns to agents such as amikacin and meropenem, these analyses demonstrate how the addition of a second antimicrobial may increase the likelihood of initial in-vitro coverage in settings with high baseline resistance.

From a clinical perspective, the combination antibiogram does not imply routine dual therapy for all patients; rather, it provides a data-driven framework to support empirical decision-making in critically-ill patients at high risk for MDR infections. In real-world ICU practice, these findings can assist clinicians in selecting empirical regimens that align with local resistance patterns while awaiting culture and susceptibility results, thereby balancing early adequate coverage with antimicrobial stewardship principles.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarise antimicrobial utilisation patterns and antimicrobial susceptibility profiles across different clinical specimens. Categorical variables were expressed as frequencies and percentages, while continuous variables were reported as mean±standard deviation where applicable. Data completeness was assessed prior to analysis. Variables with missing or inconsistently recorded values were excluded from analysis and no imputation methods were applied, given the retrospective nature of the study. No formal inferential statistical comparisons or pooled significance testing across specimen types were performed. Statistical analyses were carried out using Statistical Packages for Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY).

RESULTS

Study population and isolates: A total of 683 urine isolates, 50 pyogenic isolates, 92 blood culture isolates and 185 respiratory specimens were analysed from critically-ill ICU patients, yielding a cumulative 1,010 clinical isolates during the study period. The mean age of patients was 52.6±14.8 years, with a male-to-female ratio of 1.6:1. The median duration of ICU stay was 11 days (interquartile range: 8-15 days).

Across specimen types, Gram-negative bacilli predominated, particularly Carbapenem-Resistant *Acinetobacter Baumannii* (CRAB) and Carbapenem-Resistant *Enterobacterales* (CRE), as reflected in the ICU isolate dataset. Among Gram-negative organisms, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were the most frequently encountered pathogens. Among Gram-positive organisms, *Enterococcus faecalis*, *Enterococcus faecium* and *Staphylococcus aureus* were identified, including MRSA cases documented in the ICU dataset.

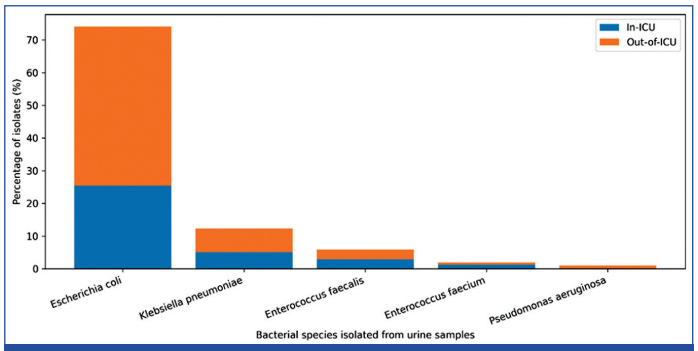
Clinical outcomes in ICU patients with Multidrug-resistant (MDR) infections: A total of 92 ICU patients with culture-confirmed MDR infections were included in the outcome analysis. Mortality was documented in 14 patients (15.2%) during the ICU stay. Among the deceased patients, infections were predominantly caused by CRAB {n=4/14 (28.57%)} and CRE {n=5/14 (35.7%)}. Fatal outcomes were more frequently observed in patients with bloodstream and ventilator-associated respiratory infections caused by these organisms {n=8/9 (88.9%)}.

Concordance analysis between empirical antimicrobial therapy and institutional antibiogram data was performed descriptively for all 92 ICU patients. However, due to the absence of a predefined binary concordance variable in the retrospective dataset, exact concordant versus non concordant counts could not be reliably extracted. Therefore, concordance findings are presented descriptively without numerical stratification or inferential comparison.

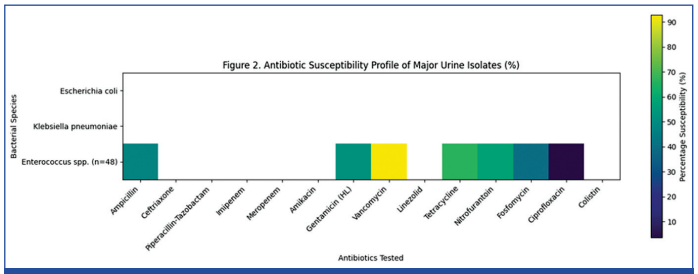
Urine isolates: Of the 683 urine samples, *E. coli* was the most frequently isolated pathogen. Amikacin demonstrated the highest in-vitro susceptibility among urine isolates {507/683 (74.3%)}, while resistance to ceftriaxone was observed in 473/683 isolates (69.2%).

Fosfomycin showed preserved activity against *Escherichia coli* {564/683 (82.5%)} and *Enterococcus faecalis* {29/37 (78.4%)}. VRE were identified in 3/48 (6.3%) *Enterococcus* isolates.

The distribution of urine isolates by organism and location is presented in [Table/Fig-1]. *Escherichia coli* was the predominant uropathogen, followed by *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium* and *Pseudomonas aeruginosa*. Antibiotic susceptibility patterns of urine isolates are presented in [Table/Fig-2].



[Table/Fig-1]: Distribution of urine isolates by organism and location (N=683).

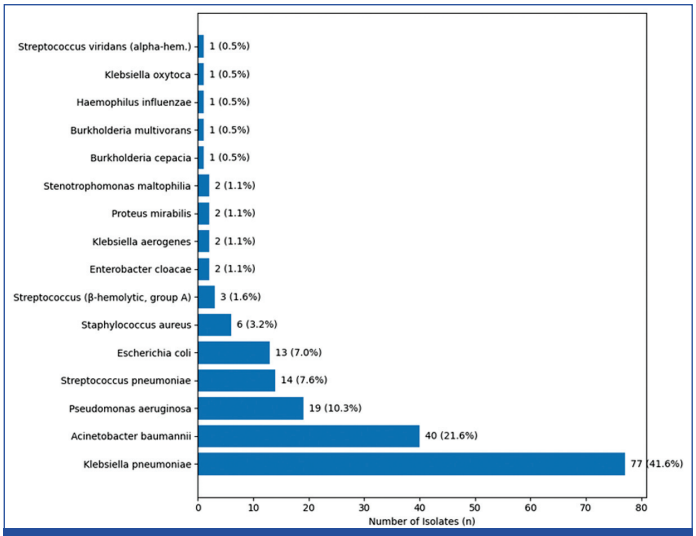


[Table/Fig-2]: Antibiotic susceptibility profile of major urine isolates (Jan 2023-Nov 2024).

Bar graph showing the proportional distribution of major bacterial pathogens isolated from urine samples (N=683), stratified by in-ICU and out-of-ICU locations. Values are expressed as percentages (%) of total urine isolates within each location category. *Escherichia coli* (n=564; ICU=141, Non ICU=423); *Klebsiella pneumoniae* (n=67; ICU=27, Non ICU=40), *Enterococcus faecalis* (n=37; ICU=18, Non ICU=19), *Enterococcus faecium* (n=11; ICU=5, Non ICU=6) and *Pseudomonas aeruginosa* (n=4; ICU=1, Non ICU=3).

Heatmap depicting percentage susceptibility (%) of major bacterial pathogens isolated from urine specimens during the study period [Table/Fig-2]. Data for *Enterococcus* spp. (n=48) are shown based on institutional antibiogram findings. Enterococcus isolates demonstrated susceptibility to vancomycin 45/48 (93.8%), high-level gentamycin 25/48 (52.1%), ampicillin 23/48 (47.9%), tetracycline 32/48 (66.7%), nitrofurantoin 28/48 (58.33%), fosfomycin 9/48 (39.6%) and ciprofloxacin 2/48 (4.2%). Blank cells indicate antibiotics not routinely tested or species-specific data not available in the consolidated dataset. Colour intensity corresponds to percentage susceptibility.

Respiratory isolates: Respiratory pathogens were predominantly *A. baumannii* and *K. pneumoniae* (total respiratory specimens analysed: n=185; *Acinetobacter baumannii* n=40/185 (21.6%) and *Klebsiella pneumoniae* n=77/185 (41.6%). Both organisms demonstrated high resistance to third-generation cephalosporins and piperacillin-tazobactam, with susceptibility rates below 30% (i.e., 56/185 isolates). Meropenem showed modest activity, with susceptibility observed in 79/185 isolates (42.8%). In contrast, colistin and polymyxin B retained activity in 167/185 of isolates (90% isolates). These findings can be seen in [Table/Fig-3] and reflect the significant burden of CREs and MDR *A. baumannii* in the ICU setting.



[Table/Fig-3]: Distribution of bacterial pathogens isolated from respiratory specimens (n=185).

Respiratory pathogens were dominated by *Acinetobacter baumannii* {n=40/185 (21.6%)} and *Klebsiella pneumoniae* {n=77/185 (41.6%)}. The detailed antibiotic susceptibility patterns of these two predominant respiratory isolates are illustrated in [Table/Fig-4]. As shown in the heatmap, both organisms demonstrated extensive resistance to third-generation cephalosporins (cefotaxime, ceftriaxone), cefepime and piperacillin-tazobactam, with susceptibility rates generally below 30%. Carbapenem susceptibility was markedly reduced, particularly in *A. baumannii*, indicating a high burden of carbapenem-resistant isolates. Aminoglycoside susceptibility was variable, with relatively better activity observed for amikacin compared to gentamicin. Fluoroquinolones and cotrimoxazole exhibited limited effectiveness. In contrast, colistin demonstrated preserved activity (>90% susceptibility) against both organisms, while minocycline retained moderate in-vitro activity. These findings highlight the MDR phenotype of major respiratory Gram-negative pathogens in the ICU setting.

Distribution of bacterial pathogens isolated from respiratory specimens (n=185). Horizontal bar chart depicting the distribution of bacterial species isolated from respiratory specimens during the study period. *Klebsiella pneumoniae* was the most frequently isolated organism {77/185 (41.6%)}, followed by *Acinetobacter baumannii* {40/185 (21.6%)}, *Pseudomonas aeruginosa* {19/185 (10.3%)} and *Streptococcus pneumoniae* {14/185 (7.6%)}.

Antibiotic susceptibility profile of respiratory isolates of *Acinetobacter baumannii* (n=40) and *Klebsiella pneumoniae* (n=77) as shown in [Table/Fig-4]. Heatmap illustrating antimicrobial susceptibility patterns of the two predominant respiratory pathogens isolated during the study period (total respiratory isolates = 185). Susceptibility results are expressed as n/total isolates tested (% susceptible) for each antibiotic. *Acinetobacter baumannii* (n=40) and *Klebsiella pneumoniae* (n=77) were selected for detailed depiction due to their predominance and high MDR burden among respiratory isolates. Colour intensity represents the proportion of susceptible isolates.

Blood isolates: A total of 92 culture-positive blood isolates were analysed. Combination antibiogram analysis of bloodstream infections demonstrated that 62 isolates (67.3%) were susceptible to both meropenem and amikacin, 12 isolates (13.0%) were resistant to amikacin but susceptible to meropenem and nine isolates (9.8%) were resistant to meropenem but susceptible to amikacin.

Staphylococcus aureus was infrequently isolated from blood cultures. Among blood-derived *S. aureus* isolates (n=9), MRSA accounted for 3 (33.3%) and all MRSA isolates 3/3 (100%) were susceptible to vancomycin and linezolid.

The susceptibility profile of Enterobacterales bloodstream isolates is presented in [Table/Fig-5]. A total of 92 blood culture isolates were analysed, of which *Escherichia coli* {n=30/92 (32.6%)} and *Klebsiella pneumoniae* {n=28/92 (30.4%)} were the predominant Gram-negative organisms. Susceptibility testing was consistently available for four key agents-piperacillin-tazobactam, meropenem, amikacin and chloramphenicol-representing commonly used empirical and targeted therapies for bloodstream infections in the ICU.

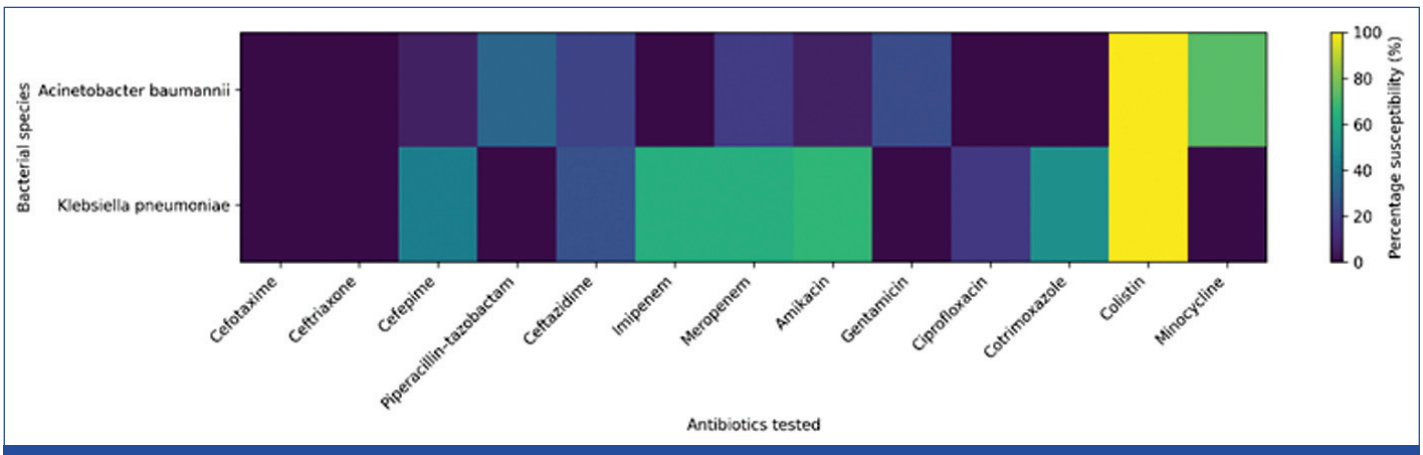
Among *E. coli* isolates (n=30), susceptibility to meropenem was observed in 26/30 (86.7%), amikacin in 24/30 (80.0%), piperacillin-tazobactam in 23/30 (76.7%) and chloramphenicol in 27/30 (90.0%).

Among *K. pneumoniae* isolates (n=28), meropenem susceptibility was 17/28 (60.7%), amikacin 18/28 (64.3%), piperacillin-tazobactam 15/28 (53.6%) and chloramphenicol 14/28 (50.0%).

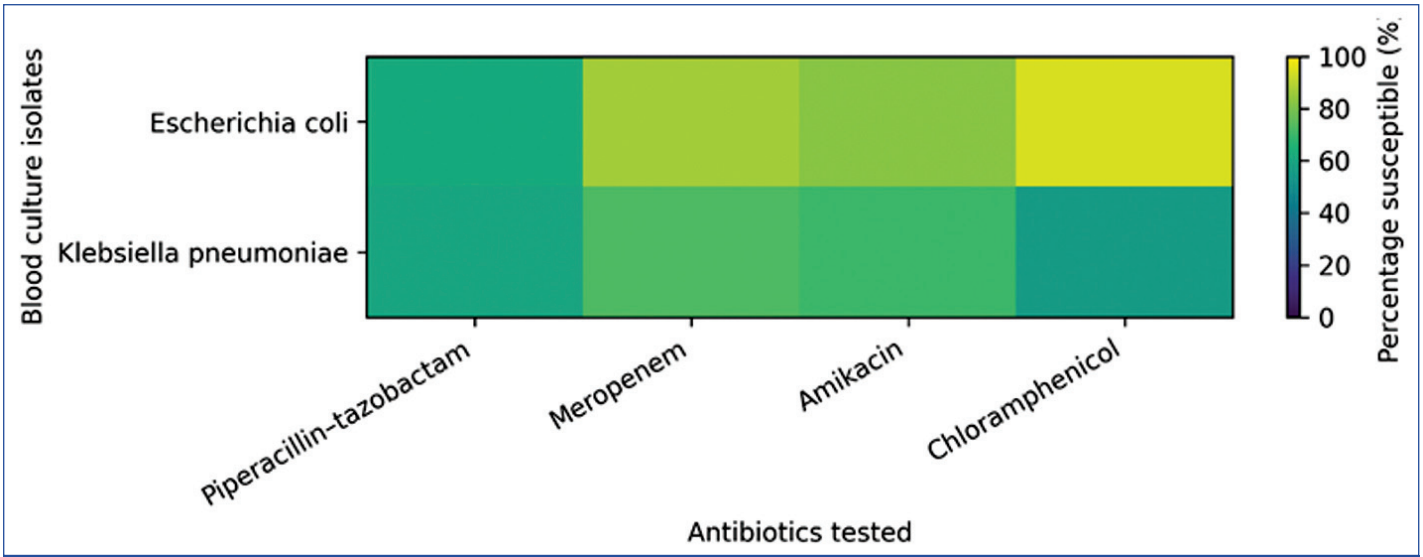
Overall, carbapenem susceptibility was higher in *E. coli* compared to *K. pneumoniae*, whereas aminoglycosides demonstrated relatively preserved activity across both organisms. The combination antibiogram findings are shown in [Table/Fig-6a-c].

The map illustrating antimicrobial susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* (n=30) and *Klebsiella pneumoniae* (n=28) isolated from blood cultures (total blood isolates=92) is given in [Table/Fig-5]. Susceptibility results are expressed as n/total isolates tested (% susceptible) for each antibiotic. The four antibiotics shown-piperacillin-tazobactam, meropenem, amikacin and chloramphenicol-were selected because they were consistently tested across bloodstream *Enterobacterales* isolates and represent commonly used empirical and targeted therapies for Gram-negative bloodstream infections in the ICU setting. Colour intensity represents the percentage of susceptible isolates.

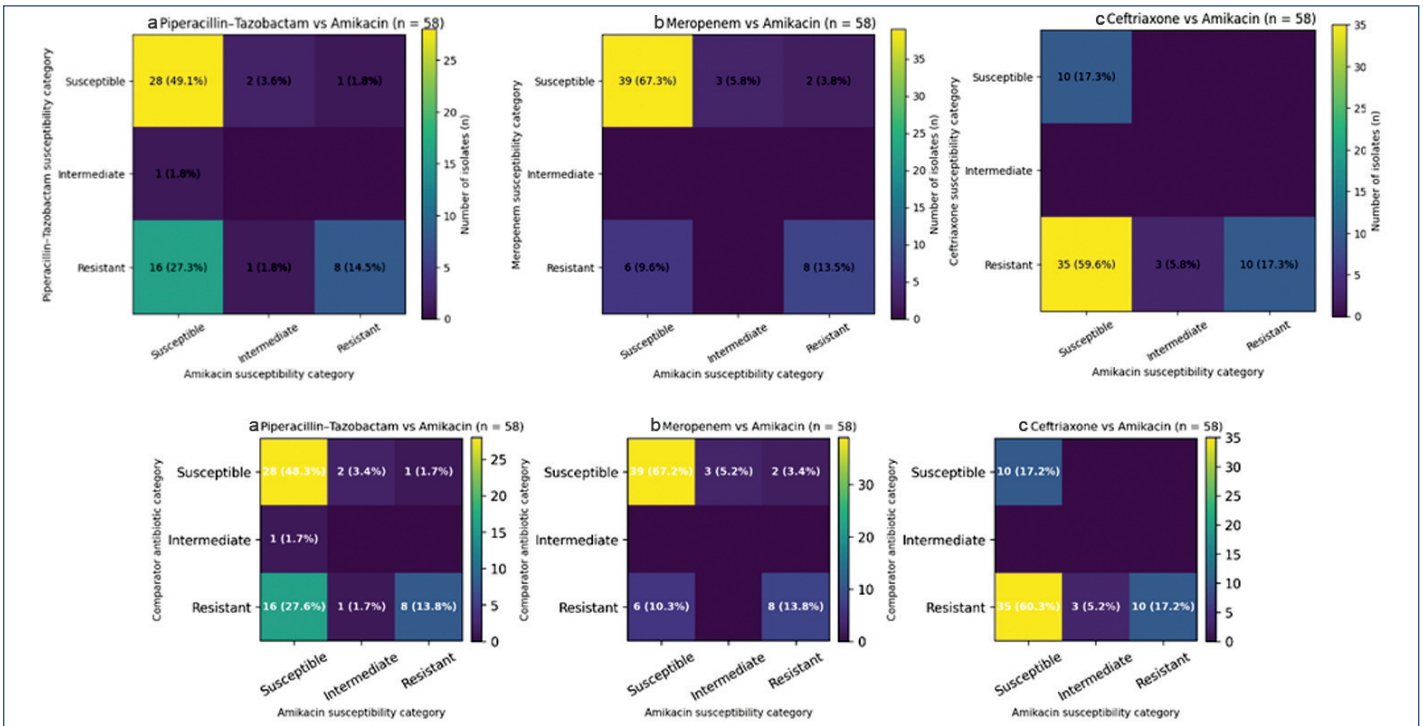
The cross-susceptibility patterns between amikacin and selected β-lactam antibiotics among *Enterobacterales* isolated from blood cultures as illustrated [Table/Fig-6]. Each heatmap cell displays the number of isolates and corresponding percentage {n (%)} based on the total number of *Enterobacterales* bloodstream isolates (n=58).



[Table/Fig-4]: Antibiotic susceptibility patterns of *Acinetobacter baumannii* and *Klebsiella pneumoniae* from respiratory specimens.



[Table/Fig-5]: Antibiotic susceptibility profile of ICU and inpatient blood isolates.



[Table/Fig-6]: Combination antibiogram of Enterobacterales blood isolates. a) Demonstrates the combination antibiogram for piperacillin-tazobactam versus amikacin; b) Depicts meropenem versus amikacin cross-susceptibility; c) Presents ceftriaxone versus amikacin cross-susceptibility.

Pyogenic isolates: Among the 50 pyogenic isolates {n=50 (100%)}, *S. aureus* accounted for 15/50 isolates {n=15 (30.0%)} and *Escherichia coli* accounted for 9/50 isolates {n=9 (18.0%)}, making them the predominant organisms.

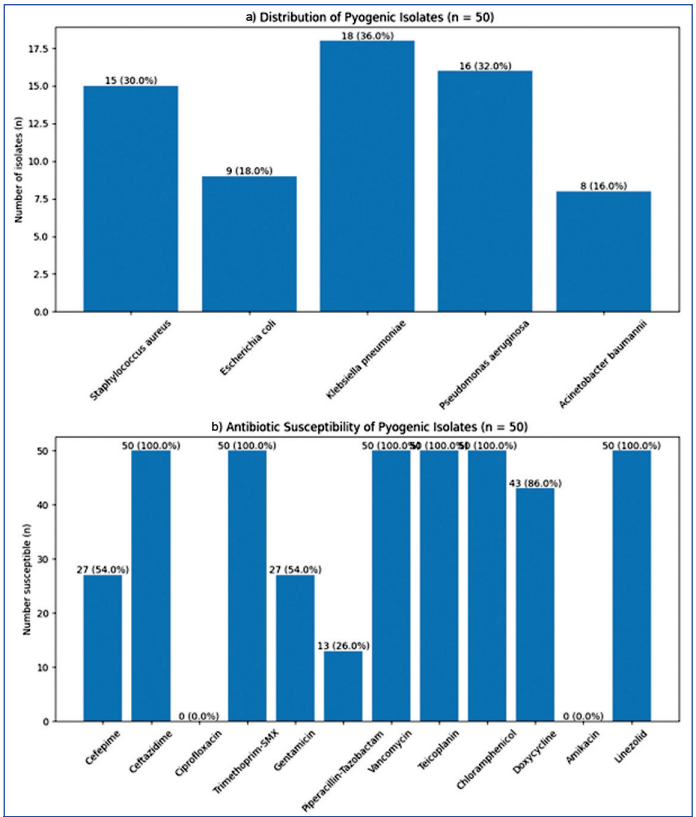
High resistance to ceftriaxone was observed in 34/50 isolates {n=34 (68.0%)} and ciprofloxacin resistance was noted in 31/50 isolates {n=31 (62.0%)}.

Amikacin demonstrated susceptibility in 29/50 isolates {n=29 (58.0%)}, while piperacillin-tazobactam showed activity in 26/50 isolates {n=26 (52.0%)}, indicating moderate in-vitro effectiveness.

Among Gram-positive pyogenic isolates (n=18), linezolid retained excellent activity, with susceptibility observed in 18/18 isolates {n=18 (100%)}. Among the 15 *S. aureus* isolates, 7/15 {n=7 (46.7%)} were MRSA, consistent with the departmental antibiogram. The distribution and antimicrobial susceptibility patterns of pyogenic isolates are illustrated in [Table/Fig-7] with all values expressed as n (%).

Distribution and antibiotic susceptibility patterns of pyogenic isolates (n=50): (a) Distribution of bacterial species isolated from pyogenic specimens; (b) Antibiotic susceptibility profile of pyogenic isolates.

Combination antibiogram analysis: The combination antibiogram analysis evaluated the incremental in-vitro coverage achieved with dual empirical regimens among bloodstream isolates (n=92) and major respiratory pathogens. Among isolates from blood cultures (n=92), dual susceptibility to meropenem and amikacin was observed in 62 (67.3%) isolates. Susceptibility to meropenem with resistance to amikacin was seen in 12 (13.0%) isolates, while susceptibility to amikacin with resistance to meropenem was observed in 9 (9.8%) isolates; the remaining isolates were resistant to both agents. These findings indicate that the addition of amikacin to meropenem, or vice versa, increases the probability of achieving initial empirical in-vitro coverage compared with monotherapy alone. Cross-susceptibility patterns were similarly assessed for piperacillin-tazobactam and ceftriaxone in combination with amikacin, with matrix heatmaps illustrating the distribution of isolates across susceptibility categories (susceptible, intermediate and resistant), thereby allowing estimation of expanded empirical coverage with combination therapy. Among respiratory isolates, which included *Acinetobacter baumannii* (n=40) and *Klebsiella pneumoniae* (n=77), overall meropenem susceptibility was observed in 61/117 (52.14%) isolates. Combination susceptibility to piperacillin-tazobactam



[Table/Fig-7]: Distribution and antibiotic susceptibility patterns of pyogenic isolates (n=50).

coverage expressed as n (%). Combination regimens demonstrate incremental in-vitro coverage compared to single-agent therapy.

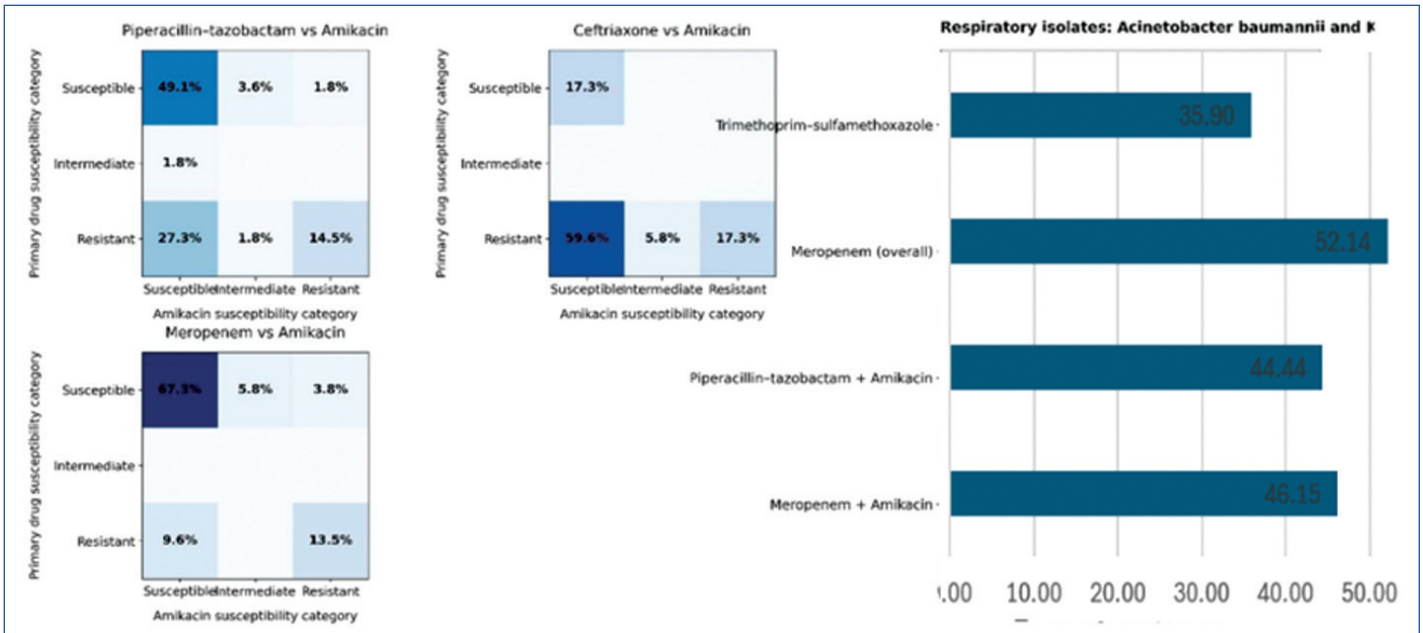
Abbreviations: AMK=Amikacin; MEM=Meropenem; TZP=Piperacillin-tazobactam; CRO=Ceftriaxone.

Antimicrobial utilisation: Analysis of ICU prescription records showed frequent use of broad-spectrum antibacterial agents, predominantly carbapenems, piperacillin-tazobactam and aminoglycosides. Meropenem and amikacin were the most commonly prescribed agents based on Defined Daily Dose (DDD) frequency counts within the cohort.

Empirical carbapenem therapy was initiated in 31 of 92 patients (34%) in whom no pathogen was subsequently isolated on culture. Antimicrobial use in these cases was therapeutic rather than prophylactic and was guided by clinical suspicion of severe sepsis or septic shock at presentation.

Antifungal therapy was administered to 11 of 92 ICU patients {11/92 (12.0%)}, predominantly using fluconazole and voriconazole. Documented fungal isolates were uncommon in the cohort and antifungal therapy was largely empirical, initiated in patients with prolonged ICU stay or multiple clinical risk factors for invasive fungal infection. On descriptive assessment, no consistent relationship was observed between antifungal administration {11/92 (12.0%)} and bacterial resistance patterns across the analysed specimens.

Cross-specimen resistance patterns: Across specimen types (urine n=683, blood n=92, respiratory n=185 and pyogenic n=50), broadly consistent resistance patterns were observed,



[Table/Fig-8]: Combination antibiogram analysis of bloodstream isolates (n=92) and major respiratory pathogens {n=177 (40+77)}.

plus amikacin was noted in 52/117 (44.44%) isolates and to meropenem plus amikacin in 54/117 (46.15%) isolates, while trimethoprim-sulfamethoxazole susceptibility was seen in 42/117 (35.9%) isolates. Collectively, these findings suggest that dual-drug strategies may provide incremental in-vitro coverage in high-resistance ICU settings. All values presented in [Table/Fig-8] are expressed as n (%).

Heatmap matrices (left panels) demonstrate cross-susceptibility patterns between amikacin and piperacillin-tazobactam, ceftriaxone and meropenem among isolates from blood cultures (n=92). Each cell represents the number of isolates expressed as n (%), stratified by susceptibility category (susceptible/intermediate/resistant).

The right panel summarises susceptibility patterns among major respiratory pathogens, including *Acinetobacter baumannii* (n=40) and *Klebsiella pneumoniae* (n=77), showing overall and combination

particularly among Gram-negative organisms. High resistance to third-generation cephalosporins and carbapenems was noted across multiple specimen categories, especially among *Klebsiella pneumoniae* and *Acinetobacter baumannii*. In contrast, agents such as amikacin, colistin and linezolid retained activity in selected settings. These findings were consistent with organism-specific susceptibility profiles described in the respective sections above.

DISCUSSION

The present study provides an integrated evaluation of AMR patterns and antimicrobial utilisation in a tertiary-care ICU setting, contextualised within national and global resistance trends. The high burden of MDR Gram-negative organisms observed in this cohort mirrors findings from recent Indian surveillance data, where carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter*

baumannii have emerged as dominant ICU pathogens [22-24]. Similar resistance patterns have been reported in multicentric Indian studies demonstrating carbapenem resistance rates exceeding 60% among *Enterobacterales*, particularly in critically-ill populations [24]. These findings align with the WHO priority pathogen list, which categorises CRE and *A. baumannii* as urgent threats requiring intensified surveillance and stewardship efforts [23].

Among Gram-positive organisms, the detection of VRE at rates comparable to or slightly higher than previous Indian reports (4-6%) suggests an evolving resistance landscape in tertiary centres [25]. The sustained susceptibility of *Staphylococcus aureus* isolates to vancomycin and linezolid is reassuring and consistent with global ICU surveillance data [26,27], although vigilance is warranted given reports of emerging linezolid resistance in high-consumption settings [28,29]. Importantly, these observations reinforce the concept that resistance epidemiology is dynamic and must be interpreted in the context of local antimicrobial prescribing patterns.

Patterns of antimicrobial utilisation in this cohort reflect a broader global concern regarding empirical broad-spectrum prescribing in culture-negative sepsis [30]. Indian hospital-based studies have previously linked high carbapenem consumption to the increasing prevalence of CRE [30,31]. Although the WHO ATC/DDD framework was applied to describe relative utilisation in this study, normalisation to DDD per 1,000 ICU-days was not feasible, which limits direct comparison with surveillance datasets. Nevertheless, the observed prescribing trends underscore the need for strengthened Antimicrobial Stewardship Programs (ASPs), structured de-escalation protocols and improved diagnostic stewardship. Rapid molecular diagnostics and shorter turnaround times for culture reporting have been shown to reduce inappropriate empirical exposure and improve antimicrobial optimisation [32,33].

Although formal comparative outcome modelling was beyond the scope of this retrospective design, the descriptive association between MDR infections and adverse clinical outcomes is consistent with international data demonstrating higher mortality in infections caused by carbapenem-resistant organisms [34,35]. Most importantly, outcomes in patients with MRSA and VRE infections appeared comparatively more favourable, likely reflecting the availability of reliably active agents such as vancomycin and linezolid. This observation supports the principle that timely administration of effective therapy, rather than resistance status alone, is a critical determinant of survival [36].

From a clinical perspective, these findings reinforce the importance of institution-specific antibiograms in guiding empirical therapy in ICU settings. The integration of resistance surveillance with antimicrobial utilisation analysis provides actionable data for stewardship committees. Future research should focus on prospective multicentric surveillance, incorporation of molecular resistance profiling and structured evaluation of empirical therapy concordance with clinical outcomes. Additionally, implementation studies assessing the real-world impact of combination antibiogram-guided protocols on mortality, antimicrobial consumption and resistance trends would further strengthen evidence-based ICU practice.

A notable aspect of the present study is the application of combination antibiograms to evaluate the potential incremental coverage offered by dual-agent empirical regimens in the ICU setting. In the present cohort, combination antibiogram analysis demonstrated broader in-vitro coverage of *Enterobacterales* isolates when amikacin was combined with meropenem, compared with either agent alone.

These findings are consistent with antimicrobial stewardship literature suggesting that combination antibiograms can support empirical decision-making in critically-ill patients with suspected sepsis, particularly in settings with a high prevalence of MDR pathogens [37]. Although underutilised in routine practice, combination antibiograms may assist clinicians in selecting empirical regimens that balance early adequate coverage with avoidance of unnecessary broad-spectrum exposure [38].

The observed combination antibiogram patterns in bloodstream infections further highlight the potential role of dual-agent empirical therapy in high-resistance settings, as supported by prior studies [39]. Similarly, the preserved susceptibility of MRSA to vancomycin and linezolid observed in this study is consistent with published literature [40].

Pharmacy data highlighted the extensive use of carbapenems, often in culture-negative sepsis. This pattern reflects a common global issue where broad-spectrum agents are initiated empirically and continued unnecessarily [29]. Overuse of carbapenems has been directly linked to the rise of CRE in Indian hospitals [30]. The WHO ATC/DDD methodology used in this study confirmed disproportionate utilisation of meropenem, echoing findings from other Indian ICUs [31].

The high reliance on empirical therapy underscores the urgent need for rapid diagnostic stewardship. Molecular diagnostics and rapid culture techniques can significantly shorten the time to pathogen identification and susceptibility reporting, thereby reducing inappropriate empirical coverage [32]. Furthermore, ASPs should reinforce de-escalation protocols, ensuring that broad-spectrum therapy is narrowed or discontinued once culture results are available [33].

Clinical outcomes and mortality impact: Although the present study was not designed to perform formal comparative outcome analysis, the descriptive observation of adverse outcomes in patients with MDR infections highlights the clinical challenges posed by resistant pathogens in the ICU setting. Prior studies have consistently shown that inappropriate or delayed antimicrobial therapy is associated with increased mortality in septic shock [34].

In particular, infections caused by carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* have been associated with poorer outcomes in published literature, emphasising the need for continued development of novel therapeutic strategies, including next-generation β-lactam/β-lactamase inhibitor combinations and alternative approaches such as phage therapy [35]. These considerations underscore the importance of early adequate empirical coverage and antimicrobial stewardship in critically-ill patients.

Interestingly, outcomes in patients with VRE and MRSA infections were comparatively better, likely because effective agents such as linezolid and vancomycin were readily available and initiated early. This highlights that availability of active agents at the right time is the key determinant of outcome, not resistance per se [36].

Limitation(s)

The strengths of the present study include its comprehensive inclusion of multiple specimen types (urine, blood, respiratory and pyogenic) and the integration of AMR patterns with antimicrobial utilisation data, providing a holistic assessment of AMR in the ICU setting. The application of combination antibiograms adds a clinically relevant dimension to empirical therapy guidance in high-resistance environments.

However, several limitations must be acknowledged. The retrospective design limits the ability to establish causal associations between antimicrobial utilisation and resistance outcomes. As a single-centre study conducted in a tertiary care teaching hospital, the findings may not be generalisable to other healthcare settings, particularly secondary or rural hospitals. Molecular characterisation of resistance mechanisms (e.g., carbapenemase gene profiling) was not performed, which could have provided deeper insights into the underlying epidemiology of MDR organisms. Additionally, although the WHO ATC/DDD methodology was used to describe

relative antimicrobial utilisation, calculation of standardised DDD per 1,000 ICU-days was not feasible due to variability in individual ICU length of stay and incomplete aggregation of daily bed-occupancy data across the study period. Consequently, antimicrobial consumption could not be normalised to ICU-days, which limits direct comparison with surveillance studies reporting standardised DDD metrics.

The ICU length-of-stay data were recorded descriptively in patient charts; however, consistent numeric ICU stay duration (in days) was not uniformly available across all cases, which precluded robust comparative statistical analysis of ICU stay outcomes. Consequently, ICU stay outcomes could not be reliably reported as mean or median differences across patient groups. Additionally, antimicrobial escalation or de-escalation decisions after receipt of culture results were clinician-directed and not governed by a predefined institutional antimicrobial stewardship protocol during the study period. These factors represent methodological constraints and highlight the need for prospectively designed studies with structured outcome variables and standardised stewardship frameworks.

Despite these limitations, the findings have important clinical implications. ICU physicians should rely on local antibiogram data to guide empirical therapy and adopt combination antibiograms to optimise initial coverage. ASPs must prioritise carbapenem-sparing regimens and promote timely de-escalation. National guidelines, such as those from the NCDC, should integrate combination antibiogram reporting into routine practice to support clinicians in high-resistance settings [37].

CONCLUSION(S)

The present study highlights a significant burden of MDR organisms in the ICU, particularly among Gram-negative pathogens such as *Klebsiella pneumoniae* and *Acinetobacter baumannii*, which demonstrated limited susceptibility to commonly used antibiotics. The findings underscore the critical importance of integrating local antibiogram data into empirical treatment decisions and using combination antibiograms to optimise early antimicrobial coverage in critically-ill patients.

Strengthening ASPs, promoting carbapenem-sparing strategies and encouraging timely de-escalation based on culture results are essential to improving patient outcomes. Continuous surveillance of resistance trends coupled with rapid diagnostics and disciplined prescribing practices, remains crucial for mitigating the progression of AMR in ICU settings.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
2. Associate Professor, Department of Microbiology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
3. Associate Professor, Department of General Medicine, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
4. Additional Professor, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
5. Professor and Head, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
6. Associate Professor, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
7. Junior Resident, Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh, India.
8. Assistant Professor, Department of Pharmacology, PSP Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Akhila Chagalamari,
Senior Resident, Department of Pharmacology, All India Institute of Medical Sciences, Atmakur, Mangalagiri-522503, Andhra Pradesh, India.
E-mail: akhilachagalamari03@gmail.com

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