Original Article

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Microbiology Section

Antimicrobial Resistance in Gram-negative Pathogens Isolated from Blood Cultures of Intensive Care Unit Patients: A Hospital-based Cross-sectional Study

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ABSTRACT

Introduction: Intensive Care Units (ICUs) are considered the "epicentre of infections." In developing countries, Antimicrobial Resistance (AMR) has emerged as a major healthcare concern. Infections, including bloodstream infections caused by Gram-Negative Bacteria (GNB), are usually higher among ICU patients. Owing to their distinctive cell wall structure, GNB are often more resistant to antimicrobial agents compared to their Gram-positive counterparts.

Aim: To determine the pattern of AMR among GNB, isolated from blood cultures of patients admitted to ICUs of a tertiary care hospital.

Materials and Methods: This cross-sectional study was conducted over a period of two years (January 2023-December 2024) in the Department of Microbiology, Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital, Pune, Maharashtra, India. A total of 247 GNB isolated from positive blood cultures were included in the study. These isolates were identified up to the species level using standard microbiological procedures, including Gram staining, motility testing, and biochemical tests. Antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method. Patients' demographic details were recorded and analysed. Results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (2023, M100). Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM, USA), and a p-value <0.05 was considered as statistically significant.

Results: Out of the 247 GNB, *Klebsiella pneumoniae* (68; 27.5%), followed by *Escherichia coli* (51; 20.6%), were the most common pathogens isolated from blood cultures. Isolation of *K. pneumoniae* was significantly higher in the Medical ICU (MICU) compared to other ICUs. *K. pneumoniae* demonstrated high resistance to almost all classes of antimicrobials. Colistin resistance was observed in two isolates of *K. pneumoniae* and in one isolate each of *Pseudomonas aeruginosa* and *Acinetobacter* spp. GNB pathogens from blood cultures of MICU patients showed significantly high resistance to different classes of antimicrobial agents.

Conclusion: AMR among GNB isolated from bloodstream infections in ICU patients is alarmingly high. As AMR rates vary widely based on geographical region and healthcare settings, it is essential for each healthcare facility to determine its own AMR patterns. This will enable the implementation of appropriate strategies to prevent and control the emergence and spread of drug-resistant pathogens, particularly among critically ill patients.

Keywords: Bloodstream infections, *Escherichia coli, Klebsiella pneumoniae*

INTRODUCTION

Over the past few decades, there has been a shift from antimicrobial-susceptible species to increasingly resistant pathogens. Even among previously susceptible species, a notable transition toward AMR strains has been observed. This trend can be attributed partly to the ability of pathogens to accumulate AMR determinants and partly to the widespread and injudicious use of antimicrobial agents [1]. Despite numerous global awareness programmes, the rising trend of AMR remains largely unchecked. If this trend continues, many common infections may become untreatable, ushering in a "post-antibiotic era" [2]. The emergence of Pan-drug-resistant (PDR) bacteria, which are resistant to all classes of available antimicrobial agents, represents a worrisome endpoint in the fight with bacterial infections [3]. These infections are especially serious in critically ill patients, as drug resistance limits therapeutic options, leading to increased morbidity, mortality, prolonged hospital stays, and higher healthcare costs [4].

Several factors contribute to the increased isolation of MDR pathogens from ICU patients, including indiscriminate antimicrobial use, prolonged ICU stays, presence of indwelling medical devices, multiple underlying co-morbidities, poor adherence to standard and transmission-based precautions, and lack of effective isolation protocols [5]. In ICU settings, GNB are responsible for severe infections such as pneumonia, urinary tract infections, bacteraemia, and septicaemia [6]. Among these, bacteraemia due to GNB is a major cause of morbidity and mortality in Indian hospitals [7]. The incidence of GNB infections in ICU patients is two to five times higher than in patients admitted to general wards. These infections are of particular concern due to the global dissemination of drug resistance among GNB [8]. Bacteraemia caused by drug-resistant GNB-including carbapenem-resistant organisms- along with complicated infections, persistent positive blood cultures, multiorgan failure, septic shock, and inappropriate antimicrobial therapy, have been identified as major risk factors for increased mortality [9,10]. GNB may utilise multiple mechanisms targeting a single antimicrobial agent or a single mechanism conferring resistance to multiple antimicrobial classes [11].

Several factors like overcrowding in ICUs, high disease severity, and close patient proximity in confined specialised care areas, increases the risk of person-to-person transmission [11,12]. Studies evaluating resistance patterns of ICU pathogens vary widely in design, healthcare

setting, geographic location, patient population, and associated risk factors [13,14]. Therefore, it is essential to generate local AMR data to guide institution-specific corrective and preventive strategies.

According to the World Health Organisation (WHO) list of antibiotic-resistant "priority pathogens," bacteria are categorised into critical, high, and medium priority groups based on the urgency of need for new antimicrobial agents. Gram negative pathogens such as *Acinetobacter*, Pseudomonas, and Enterobacterales are included in the critical priority group, particularly carbapenem-resistant and Extended-Spectrum Beta-Lactamase (ESBL)-producing strains. These organisms are responsible for serious and often life-threatening healthcare-associated infections [15]. In contrast to developed countries, the AMR surveillance network in India has limited coverage. Therefore, institutional studies play a crucial role in providing valuable insights into emerging resistance patterns, thereby aiding clinicians and infection control teams.

The present study was undertaken to determine the pattern of AMR among GNB isolated from blood cultures of ICU patients in a tertiary care academic hospital. The primary objective was to assess the AMR patterns of GNB isolated from ICU blood cultures, while the secondary objective was to analyse the ICU-wise distribution of Gram negative pathogens.

MATERIALS AND METHODS

This hospital-based, cross-sectional study was conducted in the Department of Microbiology, Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital, Pune, Maharashtra, India. The study period extended over two years, from January 2023 to December 2024.

Inclusion criteria: GNB isolated from blood cultures of ICU patients were included in the study.

Exclusion criteria: Blood culture samples from non ICU patients and growths other than Gram negative bacteria from ICU blood cultures were excluded from the study.

Study Procedure

A total of 7,158 blood culture bottles were received from ICUs during the study period and were processed. Samples from positive blood culture bottles were subcultured on blood agar, MacConkey agar, and chocolate agar for isolation of bacterial growth. Gram-negative isolates were identified up to the species level using standard microbiological protocols, including Gram staining, motility testing, and biochemical tests such as catalase, oxidase, and IMViC tests (Indole, Methyl Red, Voges- Proskauer, and Citrate). *Acinetobacter* spp. were identified based on biochemical reactions including gelatin liquefaction and Oxidative-fermentative (OF) tests. Antimicrobial susceptibility testing for GNB was performed using the Kirby- Bauer disc diffusion method on Mueller-Hinton agar. Results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (2023, M100) [16].

The antibiotic discs used included amikacin (30 µg), amoxicillin-clavulanic acid (20/10 µg), cefotaxime (30 µg), cefepime (30 µg), ceftazidime (30 µg), ciprofloxacin (5 µg), co-trimoxazole (25 µg), ceftazidime-avibactam (30/20 µg), ertapenem (10 µg), imipenem (10 µg), meropenem (10 µg), and piperacillin–tazobactam (100/10 µg). All antibiotic discs were procured from HiMedia Laboratories Pvt. Ltd., Mumbai, India.

Colistin susceptibility testing was performed using the broth microdilution method. The Colistin HiMIC plate kit (HiMedia Laboratories Pvt. Ltd., Mumbai) was used, which determines the Minimum Inhibitory Concentration (MIC) of colistin against test organisms (200 µL of 10^6 CFU/mL) in a concentration range of 0.25 µg/mL to 16 µg/mL. The test was performed as per the manufacturer's instructions, and plates were incubated at 35°C for 24 hours. After incubation, a visible colour change from purple to pink was observed. The MIC was defined as the lowest concentration of colistin showing no colour change (first purple-coloured well).

STATISTICAL ANALYSIS

Data obtained from the study were entered into Microsoft® Excel spreadsheets. Statistical analysis was performed using SPSS version 24.0 (IBM, USA). Descriptive statistics such as frequencies and percentages were calculated and presented in the form of tables and graphs. The Chi-square test was used to analyse associations between variables, and a p-value <0.05 was considered statistically significant.

RESULTS

A total of 247 GNB were isolated during the study period. The species-wise distribution of GNB is shown in [Table/Fig-1], with *Klebsiella pneumoniae* (68; 27.5%) followed by *Escherichia coli* (51; 20.6%) being the most common pathogens isolated from blood cultures.

Isolate	Number (%)
Klebsiella pneumoniae	68 (27.5)
E. coli	51 (20.6)
Pseudomonas aeruginosa	36 (14.6)
Acinetobacter spp.	32 (13)
Enterobacter spp.	30 (12.1)
Citrobacter spp.	30 (12.1)
Total	247 (100)

[Table/Fig-1]: Species wise distribution of Gram-Negative Bacteria (GNB).

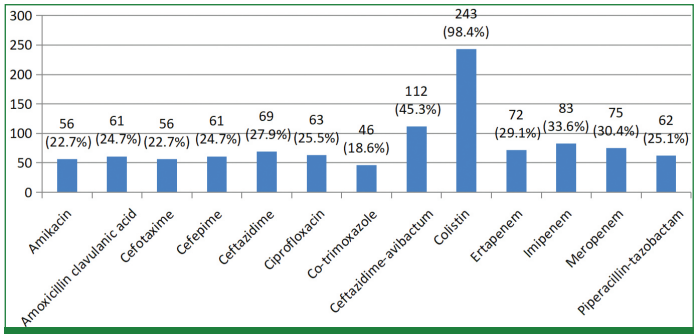
The ICU-wise distribution of GNB from blood cultures is depicted in [Table/Fig-2]. *Klebsiella pneumoniae* was the predominant GNB in all ICUs except the Surgical ICU (SICU), where *E. coli* was the most common isolate. The Chi-square test revealed that isolation of *K. pneumoniae* was significantly higher in the Medical ICU (MICU) compared to other ICUs (p-value <0.05). However, no significant association was observed between other GNB and the type of ICU.

Isolate	Medical ICU (%)	Surgical ICU (%)	Paediatric ICU (%)	Neonatal ICU (%)	Total (%)
Klebsiella pneumoniae	29 (25)	12 (15.4)	08 (36.4)	19 (61.3)	68 (27.5)
E. coli	23 (19.8)	17 (21.8)	06 (27.3)	05 (16.1)	51 (20.6)
Pseudomonas aeruginosa	19 (16.4)	14 (17.9)	02 (9.1)	01 (3.2)	36 (14.6)
Acinetobacter spp.	14 (12.1)	12 (15.4)	04 (18.2)	02 (6.4)	32 (13)
Enterobacter spp.	15 (12.9)	12 (15.4)	01 (4.5)	02 (6.4)	30 (12.1)
Citrobacter spp.	16 (13.8)	11 (14.1)	01 (4.5)	02 (6.4)	30 (12.1)
Total	116	78	22	31	247

[Table/Fig-2]: The ICU-wise distribution of Gram-negative pathogens from blood culture.
Chi-square test was used; Chi-square value=29.72; p value=0.01298

The overall antimicrobial susceptibility profile of GNB isolated from blood cultures is presented in [Table/Fig-3]. Among the penicillin group, 62 (25.1%) isolates were susceptible to piperacillin-tazobactam, while 61 (24.7%) were susceptible to amoxicillin-clavulanic acid. High resistance rates were observed against second- and third-generation cephalosporins. Among carbapenems, resistance to meropenem (69.6%) was higher compared to imipenem (66.4%) and 29.1% were susceptible to ertapenem. A total of 112 (45.3%) isolates were susceptible to the Ceftazidime-avibactam (Caz-Avi) combination.

Pathogen-wise antimicrobial susceptibility patterns are shown in [Table/Fig-4]. *K. pneumoniae* demonstrated resistance to almost all antimicrobial classes, including aminoglycosides,



[Table/Fig-3]: The antimicrobial susceptibility profile of Gram-negative pathogens from blood culture.

penicillins, cephalosporins, sulfonamides, and carbapenems. Colistin resistance, as determined by broth microdilution, was observed in two isolates of *K. pneumoniae* and one isolate each of *Pseudomonas aeruginosa* and *Acinetobacter* spp. Upon testing the ceftazidime-avibactam combination, 53 (77.9%) of the 68 *K. pneumoniae* isolates were resistant. Among *Acinetobacter* spp., 16 (50%) isolates were susceptible to the ceftazidime-avibactam combination.

Owing to their distinctive cell wall structure, GNB are often more resistant to antimicrobial agents than their Gram-positive counterparts. In GNB, AMR mechanisms involve both enzymatic inactivation of antimicrobial agents and non enzymatic pathways resulting from increased intrinsic resistance due to chromosomal gene mutations. These mechanisms include increased production of antimicrobial-inactivating enzymes, overexpression of efflux pumps, and alterations in membrane permeability or drug targets [23].

AMR may also be acquired through the horizontal transfer of mobile genetic elements carrying resistance genes, such as plasmids encoding β-lactamases, aminoglycoside-modifying enzymes, or non enzymatic mechanisms like qnr (plasmid-mediated quinolone resistance genes) conferring resistance to fluoroquinolones in Enterobacterales [24].

Among Enterobacterales, the rampant spread of Extended-Spectrum β-Lactamase (ESBL)-producing strains has resulted in resistance to third-generation cephalosporins in more than 10% of isolates, while carbapenem resistance has been reported in 2-7% of isolates. In contrast, carbapenem resistance is observed in nearly 40% of *Pseudomonas aeruginosa* isolates and in 40-70% of

Antimicrobial class	Antimicrobial agent	*K. pneumoniae* (68)	*E. coli* (51)	*P. aeruginosa* (36)	*Acinetobacter* spp. (32)	*Enterobacter* spp. (30)	*Citrobacter* spp. (30)
Aminoglycosides	Amikacin	9 (13.24%)	18 (35.3%)	5 (13.8%)	2 (6.25%)	11 (36.6%)	11 (36.6%)
Penicillin	Amoxicillin clavulanic acid	12 (17.6%)	15 (29.4%)	*Intrinsically resistant	11 (34.4%)	12 (40%)	11 (36.6%)
	Piperacillin tazobactam	11 (16.17%)	14 (27.5%)	9 (25%)	9 (28.1%)	10 (33.3%)	9 (30%)
Cephalosporins (3rd generation)	Cefotaxime	12 (17.6%)	15 (29.4%)	*Intrinsically resistant	9 (28.1%)	11 (36.6%)	9 (30%)
	Ceftazidime	12 (17.6%)	16 (31.4%)	10 (27.7%)	9 (28.1%)	11 (36.6%)	11 (36.6%)
Cephalosporins (4th generation)	Cefepime	12 (17.6%)	15 (29.4%)	8 (22.2%)	07 (21.9%)	10 (33.3%)	9 (30%)
Sulfonamides	Co-trimoxazole	6 (8.8%)	17 (33.3%)	*Intrinsically resistant	1 (3.1%)	11 (36.6%)	11 (36.6%)
Carbapenems	Imipenem	12 (17.6%)	19 (37.3%)	16 (44.4%)	12 (37.5%)	13 (43.3%)	11 (36.6%)
	Meropenem	12 (17.6%)	19 (37.3%)	10 (27.7%)	11 (34.3%)	12 (40%)	11 (36.6%)
	Ertapenem	14 (20.6%)	22 (43.1%)	*Intrinsically resistant	12 (37.5%)	13 (43.3%)	11 (36.6%)
Polymyxin	Colistin	66 (97.1%)	51 (100%)	35 (97.2%)	31 (96.9%)	30 (100%)	30 (100%)
	Ceftazidime-avibactam	15 (22.1%)	26 (50.9%)	21 (58.3%)	16 (50%)	18 (60%)	16 (53.3%)

[Table/Fig-4]: Pathogen wise sensitivity to various classes of antimicrobial agents.
*Intrinsically resistant: inherent non-susceptibility as per CLSI guidelines

DISCUSSION

Bloodstream infections, both community-acquired and hospital-acquired, are common complications among ICU patients [17]. These infections significantly contribute to increased morbidity, mortality, and healthcare costs, making early diagnosis and appropriate antimicrobial therapy essential [18]. In ICU settings, more than half of bloodstream infections are caused by GNB. Although the aetiology of bloodstream infections may vary depending on the healthcare setting, Enterobacterales predominate in most centres [19]. *Acinetobacter* spp. and *Pseudomonas aeruginosa* are the next most common GNB causing bloodstream infections in ICU patients [20]. Similar findings were observed in the present study, wherein Enterobacterales (*K. pneumoniae*, *E. coli*, *Citrobacter* spp., and *Enterobacter* spp.), followed by *Pseudomonas* spp. and *Acinetobacter* spp., were the most common GNB isolated from bloodstream infections in ICU patients. Borcan A et al., reported that *Pseudomonas aeruginosa* is the third most common isolate from bloodstream infections and is associated with high mortality rates ranging from 21% to 62% [21].

Klebsiella pneumoniae was the predominant cause of bloodstream infections in all types of ICUs except the Surgical ICU (SICU). *Escherichia coli* was the most commonly isolated organism in the SICU. This may be attributed to the fact that patients admitted to the SICU are frequently exposed to invasive surgical interventions, which may facilitate the translocation of *E. coli*- a gut commensal- into the bloodstream [22].

Acinetobacter baumannii isolates from ICU patients [25]. Consistent with these findings, the present study demonstrated high resistance to almost all classes of antimicrobial agents among GNB.

To address the challenge of AMR and treatment failure, several novel antimicrobial agents and combination therapies have been introduced in recent years [26]. Ceftazidime-avibactam (Caz-Avi) is one such combination and has demonstrated good activity against β-lactamase-producing organisms, including ESBLs, AmpC β-lactamases, and class D carbapenemases. However, it is ineffective against Metallo-β-lactamase (MBL)-producing organisms [27].

Resistance to the ceftazidime–avibactam combination has been increasingly reported in Asian countries, particularly among Carbapenem-resistant Enterobacterales (CRE) [19]. In the present study, 53 (77.9%) of the 68 *K. pneumoniae* isolates exhibited resistance to the Caz-Avi combination. Additionally, 50% of *Acinetobacter* spp. isolates were resistant to Caz-Avi. Similar findings of high resistance to the Caz-Avi combination in *Acinetobacter* spp. have been reported by Xu T et al., [27].

The study also revealed that AMR was more prevalent among GNB isolated from patients admitted to the Medical ICU (MICU) compared to other ICUs. This may be attributed to the generally longer duration of hospital stay in the MICU. Furthermore, MICU patients are frequently exposed to invasive medical devices such as mechanical ventilators, urinary catheters, and central venous lines. Increased use of drugs such as sedatives and muscle relaxants in

MICU patients may also predispose them to infections caused by drug-resistant pathogens [28,29].

Limitation(s)

This was a single-centre study; therefore, the findings are primarily applicable to the institute and the surrounding region and cannot be directly extrapolated to a larger population.

CONCLUSION(S)

The present study concludes that Enterobacterales, particularly *Escherichia coli* and *Klebsiella pneumoniae*, are major causative agents of bloodstream infections in ICU patients. AMR among GNB isolated from bloodstream infections in ICU patients is alarmingly high. As AMR rates vary widely across geographical regions and healthcare settings, it is essential for each healthcare facility to generate and regularly update its local AMR data. This will enable timely and targeted interventions to prevent and control the emergence and dissemination of drug-resistant pathogens, especially among critically ill patients who are at high-risk of developing multiple infections. The study also underscores the critical importance of strict adherence to infection prevention and control policies and the implementation of robust antimicrobial stewardship programs. In addition, ensuring proper cleaning and disinfection of the patient environment is essential to minimise cross-contamination. Greater emphasis should also be placed on improving awareness among all stakeholders regarding antimicrobial resistance.

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