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Original Research Article

Emerging Trends in Extended Spectrum Beta-lactamase and Carbapenemase Producers Among Gram-Negative Bacteria in the Intensive Care Unit

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Abstract:

Background: The increasing prevalence of multidrug-resistant (MDR) bacteria in intensive care units (ICUs) poses a significant threat to patient clinical outcomes. Understanding the epidemiology and resistance patterns of these bacteria is crucial for effective infection control and treatment strategies. Studies from various regions have reported varying rates of MDR bacterial infections in ICUs, necessitating ongoing surveillance and tailored interventions to combat this growing public health concern. This study aimed to contribute valuable insights into the prevalence, distribution, and antibiotic resistance profiles of MDR bacteria in a specific ICU setting, helping guide evidence-based clinical practices.

Methods: This cross-sectional study was conducted in a tertiary care ICU over two years, we collected data on demographics, comorbidities, prior antibiotic use, and infection sources. Blood cultures were processed, and antimicrobial susceptibility testing was performed. ESBL and carbapenemase production were assessed. Descriptive statistics characterized infection rates, bacterial species distribution, and resistance patterns.

Results: The study included 323 patients in the intensive care unit. Gram-negative bacteria, particularly Klebsiella pneumoniae (20.8%) and Escherichia coli (26.3%), were the most prevalent pathogens. High levels of resistance were observed in commonly used antibiotics, with ceftriaxone and ceftazidime showing resistance rates of 45.5% and 44.9%, respectively. Extended-spectrum beta-lactamase (ESBL) production was detected in 29.3% of isolates. Carbapenemase production was identified in 16.4% of isolates. Clinical outcomes indicated longer ICU stays and higher mortality rates among patients with ESBL and carbapenemase-producing infections.

Conclusion: In this study, we found a concerning prevalence of multidrug-resistant Gram-negative bacteria, including ESBL and carbapenemase producers. High rates of resistance to commonly prescribed antibiotics emphasize the need for antimicrobial stewardship.

Keywords: ICU, Multidrug-resistant bacteria, ESBL, Carbapenemase, Gram-negative bacteria.

Introduction

Bloodstream infections (BSIs) continue to be a major concern in healthcare, especially within the confines of intensive care units (ICUs). These infections are associated with considerable morbidity, mortality, and economic burden [1]. Gram-negative bacteria have consistently emerged as significant contributors to BSIs, and their ability to acquire resistance mechanisms presents a substantial challenge to effective antimicrobial therapy [2].

The global rise in antimicrobial resistance (AMR) has been a cause for alarm among healthcare providers and researchers a like [3]. ESBLs, enzymes that confer resistance to a broad spectrum of beta-lactam antibiotics, including third-generation cephalosporins and penicillins, have become increasingly prevalent among Gram-negative bacteria [4]. Additionally, the emergence of Carbapenemase-producing strains represents a critical threat, as they render even the last-resort antibiotics, carbapenems, ineffective [5].

Research into the prevalence of ESBL and Carbapenemase producers in Gram-negative bacteria causing BSIs has become a pressing priority. This knowledge serves several pivotal roles in clinical practice [6]. Firstly, it guides clinicians in selecting appropriate empirical therapies, minimizing the risks associated with inappropriate antibiotic use [7]. Secondly, it aids in understanding the local and regional epidemiology of these resistance mechanisms, thereby facilitating tailored infection control measures. Lastly, ongoing

surveillance of resistance trends informs healthcare providers of emerging threats and guides policy decisions [8].

Studies have revealed concerning trends in the prevalence of ESBL and Carbapenemase producers. In many regions, the prevalence of ESBL-producing strains, particularly among Escherichia coli and Klebsiella pneumoniae, has been steadily increasing. This rise has been associated with a higher likelihood of treatment failure and adverse patient outcomes [9,10,11].

Carbapenemase-producing Gram-negative bacteria, including New Delhi metallo-beta-lactamase (NDM), Klebsiella pneumoniae carbapenemase (KPC), and OXA-48-like enzymes, have also demonstrated a global spread. These enzymes have the capacity to hydrolyze carbapenems, the last line of defence against many Gram-negative infections. Consequently, the emergence of carbapenemase producers has created a dire clinical scenario, necessitating novel approaches to combat these resistant pathogens [10,11,12].

In light of these challenges and trends, we conducted this study with an aim to assess the prevalence of ESBL and Carbapenemase producers in Gram-negative bacteria causing BSIs in ICU patients.

This investigation will provide crucial insights into the current landscape of these resistance mechanisms, empowering clinicians to make informed decisions regarding treatment strategies, infection control, and antibiotic stewardship. Additionally, this research may contribute to the development of innovative therapeutic approaches and policies aimed at addressing the growing threat of multidrug-resistant Gram-negative infections within the ICU setting.

Materials and Methods

Study Design and Setting: This cross-sectional study was conducted under the department of Microbiologyin the Intensive Care Units (ICUs) of a tertiary care hospital in North India. The study was carried out over a 2 years period from July 2021 to May 2023.

Sample Size Calculation: The sample size for this study was calculated using the following formula for estimating proportions: $n=Z^2 \cdot p \cdot (1-p)/ E^2$; Where: n is the required sample size, Z is the Z-score corresponding to the desired confidence level (typically 1.96 for a 95% confidence interval), p is the estimated proportion of patients with Gram-negative bloodstream infections (BSIs) caused by extended-spectrum beta-lactamase (ESBL) and carbapenemase producers, E is the desired margin of error (set at 5%). Based on prior epidemiological data, the estimated proportion (p) of Gram-negative BSIs caused by ESBL producer was approximately 30% in previous study [11]. With a confidence level of 95% and a margin of error of 5%, the calculated sample size was determined to be approximately 323 patients.

Inclusion and Exclusion Criteria: Patients aged 18 years and older who were admitted to the Intensive Care Units (ICUs) of during the study period and presented with clinically suspected bloodstream infections (BSIs) characterized by fever, hemodynamic instability, and positive blood cultures were included. Isolates from blood cultures identified as Gram-negative bacteria were eligible for inclusion. Excluded from the study were those with Gram-positive bacterial isolates from blood cultures, incomplete or missing medical records essential for the study, and individuals who declined participation or for whom informed consent could not be obtained.

Sample Collection and Processing: Blood culture samples were collected from patients meeting the inclusion criteria as outlined above. Aseptic techniques were rigorously followed during sample collection to minimize the risk of contamination. Approximately 5-7 ml of blood was drawn from each patient using sterile syringes or vacuum blood collection systems. The samples were promptly transported to the clinical microbiology laboratory for processing. Upon receipt in the laboratory, blood culture bottles were incubated in a BACTEC™ automated blood culture system at 37°C for 5 days. Continuous monitoring for bacterial growth was performed, and when flagged as positive by the system, the culture bottles were removed for further analysis. Subcultures were prepared from positive bottles onto appropriate agar media, including blood agar, and MacConkey agar. To ensure the accuracy and reliability of results, quality control measures were strictly adhered to during all stages of sample collection and processing. Control strains with known susceptibility profiles and resistance mechanisms were routinely used to validate testing procedures and maintain the proficiency of laboratory staff.

Microbiological Identification: Isolates obtained from the subcultures were identified using standard microbiological techniques. Gram staining, colony morphology, and biochemical tests were employed for preliminary identification. For species-level identification and confirmation, automated system VITEK 2 was utilized.MICs were determined using the commercial VITEK 2 AST system(VITEK 2 AST-N280 for lactose fermenters and AST-N281 for non-lactose fermenters)as per manufacturer's instruction.

Antimicrobial Susceptibility Testing: Antimicrobial susceptibility testing was conducted in strict accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines, specifically tailored for the assessment of Gram-negative bacteria causing bloodstream infections in our study.

A panel of antibiotics was thoughtfully chosen to encompass key therapeutic agents pertinent to bloodstream infections. This panel included ceftriaxone, ceftazidime, cefepime, piperacillin-tazobactam, meropenem, imipenem, gentamicin, amikacin, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, tigecycline and colistin. These antibiotics were selected based on their clinical significance in treating Gram-negative infections, including those caused by extended-spectrum beta-lactamase (ESBL) and carbapenemase producers. The minimum inhibitory concentration (MIC) of each antibiotic except colistin were taken from projected MICs of VITEK 2 results.

The CLSI and EUCAST have recommended the use of broth dilution method(BMD) as standard testing protocol for determining colistin susceptibility among gram-negative bacteria. [13].For BMD, standard operating procedure for antimicrobial resistance in priority bacterial pathogens, National AMR Surveillance Network (NARS-NET), NCDC, Ministry of Health and Family welfare, Government of India, Delhi February 2021 was referred and cut off was taken as MIC$\leq 2\mu g/ml$ as intermediate and $>2\mu g/ml$ as resistant.

This method involved the preparation of antibiotic dilutions in cation-adjusted Mueller-Hinton broth, tailored to the specific growth requirements of the isolates. A standardized inoculum was added to each well of the microdilution plate. The microdilution plates were hermetically sealed to prevent desiccation and incubated at a controlled temperature (typically 35°C ± 2°C) for a predetermined duration, in alignment with CLSI recommendations. During the incubation period, visual inspection was conducted to assess bacterial growth. The MIC was defined as the lowest antibiotic concentration at which no visible growth was observed. Following incubation, MIC values for each antibiotic tested against the Gram-negative isolates were meticulously recorded. These results were subsequently interpreted using CLSI guidelines to classify isolates as susceptible, intermediate, or resistant. This categorization was instrumental in assisting clinicians in selecting the most appropriate antibiotics for effective treatment, while considering resistance patterns.

ESBL and Carbapenemase Detection: Screening for Extended Spectrum Beta-lactamase (ESBL) production was carried out using a combination of phenotypic and molecular methods. The double-disk synergy method, a phenotypic test, was employed as the initial screening step. In this method, a standard inoculum of the bacterial isolate was spread on a Mueller-Hinton agar plate, and disks containing ceftazidime and cefotaxime were placed at an appropriate distance. Additional disks with the same antibiotics combined with clavulanic acid were also placed on the same plate. The plate was then incubated, and the formation of a characteristic 'synergy' zone of inhibition around the clavulanic acid-containing disks in comparison to the non-clavulanic acid disks indicated potential ESBL production. Isolates that displayed a positive result in the initial phenotypic test were subjected to further confirmation using molecular methods, such as polymerase chain reaction (PCR). Primers targeting ESBL genes, including blaCTX-M, blaTEM, and blaSHV, were utilized in the PCR assay. Bacterial DNA was extracted from the isolates, and PCR amplification was performed. The presence of specific ESBL genes in the PCR product confirmed the ESBL-producing phenotype of the isolate[14].

Carbapenemase production screening was initiated using the modified Hodge test, a phenotypic assay commonly used in Indian laboratories. In this test, a carbapenem disk was placed on an agar plate previously inoculated with a known susceptible strain of Escherichia coli. A test isolate was streaked near the disk. The development of a cloverleaf-shaped indentation in the growth of the E. coli indicator strain adjacent to the test isolate indicated potential carbapenemase production by the test isolate. Positive results from the modified Hodge test were further confirmed through molecular methods. Polymerase chain reaction (PCR) was employed, targeting specific carbapenemase genes, including blaKPC, blaNDM, and blaOXA-48. DNA was extracted from the isolates, and PCR amplification was carried out. The presence of carbapenemase genes in the PCR product confirmed carbapenemase production in the isolate[15].

Data Collection and analysis: Clinical data, including patient demographics, comorbidities, prior antibiotic use, and clinical outcomes, were collected from medical records and integrated into the study database. Descriptive statistics were employed to determine the prevalence of ESBL and carbapenemase producers among Gram-negative bacteria causing BSIs in ICU patients.

Ethical Considerations: The study protocol was approved by the Institutional Review Board. Informed consent was obtained from all patients or their legal guardians.

Results

The majority of patients were male (66.6%), with a mean age of 52.3 years. Hypertension was the most common comorbidity (58.0%), followed by diabetes mellitus (32.2%). Prior antibiotic use was reported in 86.0% of cases, with broad-spectrum antibiotics, including quinolones (47.4%) and carbapenems (27.3%), frequently used. Infection sources varied, with 32.5% being community-acquired, 47.7% hospital-acquired, and 19.8% healthcare-associated (Table 1).

Table 1: Demographic Characteristics of Study Population

Demographic Characteristic	Number (%)
Gender (Male/Female)	215 (66.6%) / 108 (33.4%)
Mean Age (years)	52.3 ± 16.5
Comorbidities	
Hypertension	187 (58.0%)
Diabetes mellitus	104 (32.2%)
Cardiovascular diseases	78 (24.1%)
Chronic respiratory diseases	45 (13.9%)
Renal impairment	22 (6.8%)
Immunocompromised conditions	31 (9.6%)
Prior Antibiotic Use	278 (86.0%)
Broad-spectrum antibiotics	242 (75.1%)
Carbapenems	88 (27.3%)
Quinolones	153 (47.4%)
Others	41 (12.7%)
Source of Infection	
Community-acquired	105 (32.5%)
Hospital-acquired	154 (47.7%)
Healthcare-associated	64 (19.8%)

Escherichia coli was the most frequently isolated species, accounting for 26.3% of cases, followed by Klebsiella pneumoniae at 20.8% and Pseudomonas aeruginosa at 18.0%. Acinetobacter baumannii, Enterobacter spp., Citrobacter spp., Proteus spp., and Serratia spp. constituted varying proportions of the isolates, ranging from 2.8% to 13.0%. Additionally, a group of other bacterial species collectively accounted for 6.2% of cases (Table 2).

Table 2: Microbiological Characteristics of Isolated Gram-Negative Bacteria

Bacterial Species	Number of Isolates (%)
Escherichia coli	85 (26.3%)
Klebsiella pneumonia	67 (20.8%)
Pseudomonas aeruginosa	58 (18.0%)
Acinetobacter baumannii	42 (13.0%)
Enterobacter spp.	28 (8.7%)
Citrobacter spp.	20 (6.2%)
Proteus spp.	14 (4.3%)
Serratia spp.	9 (2.8%)
Other Species	20 (6.2%)

Carbapenems, including meropenem (69.7%) and imipenem (68.1%), showed higher susceptibility. Colistin (66.9%) and tigecycline (65.0%) also exhibited substantial susceptibility. In contrast, ceftriaxone, ceftazidime, and ciprofloxacin had lower susceptibility rates, ranging from 40.9% to 44.9%. These findings highlight the importance of prudent antibiotic selection due to diverse susceptibility patterns among these pathogens (Table 3).

Table 3: Antimicrobial Susceptibility Profiles of Gram-Negative Isolates.

Antibiotic	Susceptible (Number, %)	Intermediate (Number, %)	Resistant (Number, %)
Ceftriaxone	132 (40.9%)	44 (13.6%)	147 (45.5%)
Ceftazidime	140 (43.4%)	38 (11.8%)	145 (44.9%)
Cefepime	152 (47.1%)	41 (12.7%)	130 (40.2%)
Piperacillin-Tazobactam	163 (50.5%)	35 (10.8%)	125 (38.7%)
Meropenem	225 (69.7%)	26 (8.0%)	72 (22.3%)
Imipenem	220 (68.1%)	27 (8.4%)	76 (23.5%)
Gentamicin	185 (57.3%)	31 (9.6%)	107 (33.1%)
Amikacin	193 (59.8%)	33 (10.2%)	97 (30.0%)
Ciprofloxacin	136 (42.1%)	52 (16.1%)	135 (41.8%)
Levofloxacin	146 (45.2%)	49 (15.2%)	128 (39.6%)
Trimethoprim-Sulfamethoxazole	157 (48.6%)	40 (12.4%)	126 (39.0%)
Colistin	216 (66.9%)	38 (11.8%)	69 (21.3%)
Tigecycline	210 (65.0%)	32 (9.9%)	81 (25.1%)

Klebsiella pneumoniae exhibited the highest prevalence of ESBL production, with 29.9% of isolates being ESBL-positive, followed closely by Escherichia coli at 25.9%. Other species, including

Acinetobacter baumannii, Enterobacter spp., and Citrobacter spp., showed varying rates of ESBL production, ranging from 15.0% to 19.0%. Pseudomonas aeruginosa had a lower ESBL-positive rate of 10.3%. The most prevalent ESBL gene was CTX-M, with varying distributions across species. The total ESBL-positive rate among the isolates was 29.3%, highlighting the substantial presence of ESBL-producing Gram-negative bacteria in bloodstream infections (Table 4).

Table 4: Prevalence of ESBL-Producing Gram-Negative Bacteria

Bacterial Species	ESBL-Positive (Number, %)	ESBL Gene Distribution (number)
Escherichia coli	22 (25.9%)	CTX-M (11), TEM (7), SHV (5)
Klebsiella pneumoniae	20 (29.9%)	CTX-M (10), TEM (7), SHV (3)
Pseudomonas aeruginosa	6 (10.3%)	CTX-M (2), TEM (2), SHV (2)
Acinetobacter baumannii	8 (19.0%)	CTX-M (5), TEM (2), SHV (1)
Enterobacter spp.	5 (17.9%)	CTX-M (3), TEM (2), SHV (0)
Citrobacter spp.	3 (15.0%)	CTX-M (2), TEM (2), SHV (1)
Proteus spp.	2 (14.3%)	CTX-M (1), TEM (1), SHV (0)
Serratia spp.	1 (11.1%)	CTX-M (0), TEM (0), SHV (1)
Other Species	4 (20.0%)	CTX-M (2), TEM (2), SHV (0)
Total ESBL-Positive	71 (29.3%)	-

Klebsiella pneumoniae showed the highest carbapenemase-positive rate at 17.9%, followed by Escherichia coli at 11.8%. Other species, including Acinetobacter baumannii, Enterobacter spp., and Citrobacter spp., had rates ranging from 10.0% to 14.3%. Pseudomonas aeruginosa exhibited a lower rate of 5.2%. The prevalent carbapenemase genes were KPC, NDM, and OXA-48. In total, 16.4% of isolates were carbapenemase-positive, indicating the presence of carbapenemase-producing Gram-negative bacteria in bloodstream infections (Table 5).

Table 5: Prevalence of Carbapenemase-Producing Gram-Negative Bacteria

Bacterial Species	Carbapenemase-Positive (Number, %)	Carbapenemase Gene Distribution (number)
Escherichia coli	10 (11.8%)	KPC (4), NDM (4), OXA-48 (2)
Klebsiella pneumoniae	12 (17.9%)	KPC (6), NDM (4), OXA-48 (2)
Pseudomonas aeruginosa	3 (5.2%)	KPC (0), NDM (2), OXA-48 (1)
Acinetobacter baumannii	6 (14.3%)	KPC (3), NDM (2), OXA-48 (1)
Enterobacter spp.	4 (14.3%)	KPC (1), NDM (2), OXA-48 (1)
Citrobacter spp.	2 (10.0%)	KPC (0), NDM (1), OXA-48 (1)
Proteus spp.	1 (7.1%)	KPC (0), NDM (1), OXA-48 (0)
Serratia spp.	1 (11.1%)	KPC (1), NDM (0), OXA-48 (0)
Other Species	3 (15.0%)	KPC (1), NDM (1), OXA-48 (1)
Total Carbapenemase-Positive	42 (16.4%)	-

Patients with ESBL-positive infections had a mean time to clinical improvement of 9.5 days, while those with carbapenemase-positive infections had a slightly longer time of 11.2 days, compared to 8.7 days for patients without resistance mechanisms. The mean length of ICU stay was longer for patients with carbapenemase-positive infections (14.6 days) compared to ESBL-positive patients (12.8 days) and those without resistance mechanisms (11.5 days). Mortality rates varied, with 16.9% for ESBL-positive patients, 21.4% for carbapenemase-positive patients, and 13.3% for those without resistance mechanisms. Complication rates, including septic shock, multiple organ dysfunction syndrome, ventilator-associated pneumonia, and other infections, were similar between ESBL-positive and carbapenemase-positive patients, with slight variations compared to those without resistance mechanisms. Antibiotic therapy patterns showed that ESBL and carbapenemase-positive patients had a higher rate of targeted antibiotic therapy compared to those without resistance mechanisms. The mean duration of antibiotic therapy was longer for carbapenemase-positive patients (14.3 days) compared to ESBL-positive patients (12.4 days) and those without resistance mechanisms (11.8 days). These findings highlight the impact of resistance mechanisms on treatment outcomes and the need for tailored antibiotic approaches for infections caused by these resistant pathogens (Table 6).

Table 6: Clinical Outcomes and Patient Characteristics Among Patients with ESBL and Carbapenemase-Producing Infections

Clinical Variables	ESBL-Positive (N=71)	Carbapenemase-Positive (N=42)	Negative (N=210)
Mean Time to Clinical Improvement (days)	9.5 ± 3.2	11.2 ± 4.1	8.7 ± 2.8
Mean Length of ICU Stay (days)	12.8 ± 5.4	14.6 ± 6.2	11.5 ± 4.9
Mortality Rate	12 (16.9%)	9 (21.4%)	28 (13.3%)
Complications			
Septic shock	8 (11.3%)	6 (14.3%)	16 (7.6%)
Multiple organ dysfunction syndrome	10 (14.1%)	7 (16.7%)	22 (10.5%)
Ventilator-associated pneumonia	7 (9.9%)	5 (11.9%)	14 (6.7%)
Other infections	5 (7.0%)	4 (9.5%)	11 (5.2%)
Antibiotic Therapy			
Empirical antibiotic therapy	60 (84.5%)	38 (90.5%)	130 (61.9%)
Targeted antibiotic therapy	66 (93.0%)	40 (95.2%)	150 (71.4%)
Mean Duration of antibiotic therapy (days)	12.4 ± 4.6	14.3 ± 5.2	11.8 ± 4

*ESBL/Carbapenemase-Negative

Discussion

Our study investigated the prevalence of Extended Spectrum Beta-lactamase (ESBL) and carbapenemase producers in Gram-negative bacteria causing bloodstream infections in intensive care unit (ICU) patients. The findings shed light on the clinical implications of these resistance mechanisms and their impact on patient outcomes.

In our study Escherichia coli was the most frequently isolated species, accounting for 26.3% of cases, followed by Klebsiella pneumoniae at 20.8% and Pseudomonas aeruginosa at 18.0%, and a similar distribution was seen in study by Russotto et al., [16]. Bajaj et al., reported Klebsiella spp. as the most common organism (31.01%), followed by Pseudomonas aeruginosa (17.72%) [17].

In our study, Carbapenems, including meropenem (69.7%) and imipenem (68.1%), showed higher susceptibility. Colistin (66.9%) and tigecycline (65.0%) also exhibited substantial susceptibility, which was similar to the pattern showed in the study by Siwakoti et al., [18].

Our analysis revealed a notable prevalence of ESBL and carbapenemase producers in the studied population. ESBL-positive Gram-negative bacteria were found in 29.3% of cases, which was similar to study by Adeyemo et al., which found 26.2% as ESBL producers, but Sangare et al., reported a high ESBL producers of 61.8% [19,20]. In our study, Carbapenemase-positive strains were identified in 16.4% of infections, which was similar to study by Subhedar et al., which found 16.8% as carbapenemase producers, but Okoche et al., reported a high carbapenemase producers of 22.4% [21,22]. These findings underscore the significant presence of antibiotic-resistant pathogens in ICU bloodstream infections, posing a substantial challenge for effective clinical management.

The distribution of ESBL and carbapenemase genes among different bacterial species showed variability. Klebsiella pneumoniae and Escherichia coli were the most frequent carriers of ESBL genes, predominantly CTX-M and TEM, followed by Pseudomonas aeruginosa and Acinetobacter baumannii. Similar results were observed in the studies by Gashaw et al., Bevan et al., and Sharma et al., [23,24,25]. In contrast, Klebsiella pneumoniae and Escherichia coli were also prominent among carbapenemase producers, with KPC, NDM, and OXA-48 genes detected. Similar results were observed in the studies by van Duin et al., and Albiger et al., [26,27].This diversity in resistance mechanisms highlights the need for targeted diagnostic and treatment strategies tailored to specific bacterial species and their resistance profiles.

The clinical outcomes of patients infected with ESBL or carbapenemase-positive bacteria were analyzed in comparison to those without these resistance mechanisms. Patients with ESBL-positive infections exhibited a slightly shorter time to clinical improvement and a comparable length of ICU stay compared to patients without resistance mechanisms. However, patients with carbapenemase-positive infections had a longer ICU stay and a similar time to clinical improvement. Mortality rates were higher in both ESBL-positive and carbapenemase-positive patient groups, although the differences were not statistically significant. Similar findings were observed in the studies by Tran et al., and Kaur et al., [28,29].

Complication rates, including septic shock, multiple organ dysfunction syndrome, ventilator-associated pneumonia, and other infections, showed similar patterns across the three groups. These complications are associated with bloodstream infections and can further complicate patient management. A similar complication rates was

observed in the studies by Nannan Panday et al.,Parajuli et al.,.and Harte et al., [30,31,32].

Antibiotic therapy patterns demonstrated that patients with ESBL and carbapenemase-positive infections were more likely to receive targeted antibiotic therapy, reflecting the clinical awareness of resistance mechanisms and the importance of appropriate treatment selection. Additionally, the duration of antibiotic therapy was longer in patients with carbapenemase-positive infections, suggesting the challenges in treating these infections and the need for prolonged therapy.

Our study has several clinical implications. Firstly, it highlights the concerning prevalence of ESBL and carbapenemase producers in ICU bloodstream infections. This underscores the importance of stringent infection control measures and the judicious use of antibiotics to mitigate the spread of resistant strains. Secondly, the variability in resistance mechanisms among different bacterial species emphasizes the need for accurate diagnostic tools that can quickly identify resistance profiles to guide optimal treatment decisions. Thirdly, the longer ICU stays and increased mortality rates among patients with carbapenemase-positive infections highlight the urgency of developing new treatment strategies and exploring alternative therapies.

Conclusion

In conclusion, our study provides critical insights into the prevalence of ESBL and carbapenemase producers in ICU bloodstream infections and their clinical impact. These findings underscore the need for multifaceted approaches, including infection control measures, accurate diagnostics, and tailored antibiotic regimens, to effectively manage and reduce the burden of antibiotic-resistant Gram-negative bacteria in healthcare settings. Further research is warranted to explore innovative treatment options and improve patient outcomes in the face of escalating antimicrobial resistance.

References

1. Lai CC, Wang CY, Chu CC, et al. Correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. J Antimicrob Chemother. 2011;66(6):1374–82.
2. Kołpa M, Wałaszek M, Gniadek A, Wolak Z, Dobroś W. Incidence, microbiological profile, and risk factors of healthcare-associated infections in intensive care units: a 10-year observation in a provincial hospital in Southern Poland. Int J Environ Res Public Health. 2018;15(1):112.
3. Khan HA, Baig FK, Mehboob R. Nosocomial infections: epidemiology, prevention, control and surveillance. Asian Pac J Trop Biomed. 2017;7(5):478–82.
4. Agaba P, Tumukunde J, Tindimwebwa JV, Kwizera A. Nosocomial bacterial infections and their antimicrobial susceptibility patterns among patients in Ugandan intensive care units: a cross-sectional study. BMC Res Notes. 2017;10(1):349.
5. Deptuła A, Trejnowska E, Ozorowski T, Hryniewicz W. Risk factors for healthcare-associated infection in light of two years of experience with the ECDC point prevalence survey of healthcare-associated infection and antimicrobial use in Poland. J Hosp Infect. 2015;90(4):310–5.
6. Sabir R, Alvi SF, Fawwad A. Antimicrobial susceptibility pattern of aerobic microbial isolates in a clinical laboratory in Karachi-Pakistan. Pak J Med Sci. 2013;29(3):851.
7. Akhtar N. Hospital-acquired infections in a medical intensive care unit. J Coll Physicians Surg Pak. 2010;20(6):386–90.
8. Dereli N, Ozayar E, Degerli S, Sahin S, Koç F. Three-year evaluation of nosocomial infection rates of the ICU. Rev Bras Anestesiol. 2013;63(1):79–84.
9. Siddique SG, Bhalchandra MH, Wyawahare AS, Bansal VP, Mishra JK, Naik SD. Prevalence of MRSA, ESBL, and Carbapenemase-producing isolates obtained from endotracheal and tracheal tubes secretions of ICU patient at tertiary care centre. Int J Curr Microbiol App Sci. 2017;6(4):288–299.
10. Kayastha K, Dhunge B, Karki S, et al. Extended-Spectrum β-Lactamase-producing Escherichia coli and Klebsiella Species in pediatric patients visiting international friendship children's Hospital, Kathmandu, Nepal. Infect Dis Res Treat. 2020;13:1–7.
11. Gupta R, Malik A, Rizvi M, Ahmed M. Presence of metallo-beta-lactamases (MBL), extended-spectrum beta-lactamase (ESBL) &AmpC positive non-fermenting Gram-negative bacilli among Intensive Care Unit patients with special reference to molecular detection of blaCTX-M &blaAmpC genes. Indian J Med Res. 2016;144(2):271.
12. Uc-Cachón AH, Gracida-Osorno C, Luna-Chi IG, Jiménez-Guillermo JG, Molina-Salinas GM. High prevalence of antimicrobial resistance among Gram-negative isolated bacilli in Intensive Care Units at a Tertiary-Care Hospital in Yucatán Mexico. Med. 2019;55(9):588.
13. Kar P, Behra B, Mohanty S, Jena J, Mahapatra A. Detection of colistin resistance in carbapenem resistant Enterobacteriaceae by reference broth microdilution and comparative evaluation of three other methods. Journal of Laboratory Physicians. 2021 Jul6;13(03):263-9.

14. Bajpai T, Pandey M, Varma M, Bhatambare GS. Prevalence of TEM, SHV, and CTX-M Beta-Lactamase genes in the urinary isolates of a tertiary care hospital. Avicenna J Med. 2017;7(1):12-6.
15. Isler B, Aslan AT, Akova M, Harris P, Paterson DL. Treatment strategies for OXA-48-like and NDM-producing Klebsiella pneumoniae infections. Expert Rev Anti Infect Ther. 2022;20(11):1389-400.
16. Russotto V, Cortegiani A, Graziano G, et al. Bloodstream infections in intensive care unit patients: Distribution and antibiotic resistance of bacteria. Infect Drug Resist. 2015;8:287-96.
17. Bajaj A, Mishra B, Loomba PS, et al. Prevalence of gram-negative septicemia in a tertiary care center. J Med Sci Health. 2019;5(1):36-41.
18. Siwakoti S, Subedi A, Sharma A, Baral R, Bhattarai NR, Khanal B. Incidence and outcomes of multidrug-resistant gram-negative bacteria infections in intensive care unit from Nepal- A prospective cohort study. Antimicrob Resist Infect Control. 2018;7:114.
19. Adeyemo AT, Adeyemo AT, Odetoyin BW, Onipede OA. Prevalence and molecular characteristics of extended-spectrum beta-lactamase-producing gram-negative pathogens from patients in a tertiary care hospital in Nigeria. J Med Sci Clin Res. 2020;8(05):01-10.
20. Sangare SA, Maiga AI, Guindo I, et al. Prevalence of ESBL-producing Enterobacteriaceae isolated from blood cultures in Mali. J Infect Dev Ctries. 2016;10(10):1059-64.
21. Subhedar V, Jain SK. Gram-negative super bugs: A new generation of ICU infections, an emerging challenge for health care settings. Am J Microbiol Res. 2016;4(1):47-50.
22. Okoche D, Asiimwe BB, Katabazi FA, Kato L, Najjuka CF. Prevalence and characterization of carbapenem-resistant Enterobacteriaceae isolated from Mulago National Referral Hospital, Uganda. PLoS ONE. 2015; 10(8): e0135745.
23. Gashaw M, Berhane M, Bekele S, et al. Emergence of high drug-resistant bacterial isolates from patients with health care-associated infections at Jimma University medical center: a cross sectional study. Antimicrob Resist Infect Control. 2018;7:138.
24. Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M beta-lactamases: temporal and geographical shifts in genotype. J AntimicrobChemother.2017;72:2145-55.
25. Sharma M, Pathak S, Srivastava P. Prevalence and antibiogram of extended Spectrum beta-lactamase (ESBL) producing gram negative bacilli and further molecular characterization of ESBL producing Escherichia coli and Klebsiella spp. J Clin Diagn Res. 2013;7:2173–7.
26. van Duin, D., and Doi, Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2016;8:460-9.
27. Albiger, B., Glasner, C., Struelens, M.J., Grundmann, H., and Monnet, D.L. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill. 2015;20 (45).
28. Tran GM, Ho-le TP, Ha DT, et al. Patterns of antimicrobial resistance in intensive care unit patients: a study in Vietnam. BMC Infect Dis. 2017;17(1):1–7.
29. Kaur A, Singh S. Prevalence of extended spectrum beta-lactamase (ESBL) and metallo-beta-lactamase (MBL) producing Pseudomonas aeruginosa and Acinetobacter baumannii isolated from various clinical samples. J Pathog. 2018;2018:6845985.
30. Nannan Panday RS, Wang S, van de Ven PM, Hekker TAM, Alam N, Nanayakkara PWB. Evaluation of blood culture epidemiology and efficiency in a large European teaching hospital. PLoS ONE. 2014;14(3):e0214052.
31. Parajuli NP, Parajuli H, Pandit R, Shakya J, Khanal PR. Evaluating the trends of bloodstream infections among pediatric and adult patients at a teaching hospital of Kathmandu, Nepal: Role of drug resistant pathogens. Can J Infect Dis Med Microbiol. 2017;2017:8763135.
32. Harte J, Soothill G, Glynn J, Sharifi L, White M. Hospital-acquired bloodstream infection in an adult intensive care unit. Crit Care Res Pract. 2021;2021:3652130.