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PREVALENCE, RISK FACTORS, AND CLINICAL OUTCOMES ASSOCIATED WITH CARBAPENEM-RESISTANT GRAM-NEGATIVE BACILLI INFECTIONS IN A TERTIARY CARE HOSPITAL: A PROSPECTIVE CROSS-SECTIONAL STUDY

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Abstract

Introduction: Carbapenem resistance among Gram-negative bacilli represents a critical global health challenge. This study aimed to determine the prevalence of carbapenem resistance, identify associated risk factors, and evaluate clinical outcomes in a tertiary care setting in India.

Methods: A prospective cross-sectional study was conducted over six months in Department of Microbiology at Vyas Medical College & Hospital, Jodhpur, a tertiary care teaching hospital. Consecutive non-duplicate Gram-negative bacilli isolated from clinical specimens underwent antimicrobial susceptibility testing according to CLSI guidelines. Demographic and clinical data were collected using standardized forms. Chi-square tests and logistic regression were performed to identify risk factors, with $p<0.05$ considered statistically significant.

Results: Among 330 Gram-negative isolates, 48.5% exhibited carbapenem resistance, with the highest rates in *Acinetobacter baumannii* (85.7%), followed by *Pseudomonas aeruginosa* (60.7%), *Klebsiella pneumoniae* (58.6%), and *Escherichia coli* (27.1%). Resistance rates varied across clinical settings: intensive care units (66.9%), surgical wards (41.2%), medical wards (39.1%), and outpatient departments (28.3%). Multivariate analysis identified prior carbapenem use (adjusted OR: 3.95, 95% CI: 2.41-6.48), ICU stay >7 days (adjusted OR: 3.22, 95% CI: 1.96-5.29), and mechanical ventilation (adjusted OR: 2.86, 95% CI: 1.74-4.71) as independent risk factors. Patients with carbapenem-resistant infections experienced higher mortality (26.9% vs. 11.2%, $p<0.001$), longer hospital stays (18.7 vs. 11.3 days, $p<0.001$), and lower clinical cure rates (57.5% vs. 80.0%, $p<0.001$) compared to those with susceptible infections.

Conclusion: The high prevalence of carbapenem resistance, particularly in ICUs, underscores the urgent need for antimicrobial stewardship, enhanced infection control practices, and routine surveillance. The significant association with poorer clinical outcomes highlights the importance of early detection and appropriate management strategies to mitigate the impact of these challenging infections.

Keywords: Carbapenem resistance, Gram-negative bacilli, Antimicrobial stewardship, Healthcare-associated infections, Multidrug resistance

Introduction

Antimicrobial resistance represents one of the most significant public health challenges of the 21st century, threatening the effective prevention and treatment of an ever-increasing range of infections. Among these concerns, carbapenem resistance in Gram-negative bacilli has emerged as a particularly alarming phenomenon worldwide. Carbapenems, once considered the "last resort" antibiotics for treating multidrug-resistant bacterial infections, are increasingly being rendered ineffective due to the evolution and spread of resistance mechanisms.

Gram-negative bacilli, including Enterobacterales (such as *Escherichia coli*, *Klebsiella pneumoniae*), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, are common causes of healthcare-associated infections. These organisms have demonstrated a remarkable ability to acquire and develop resistance to carbapenems through various mechanisms, including the production of carbapenemases, alterations in outer membrane proteins, and the upregulation of efflux pumps (Nordmann et al., 2011).

The global prevalence of carbapenem-resistant Gram-negative bacilli (CR-GNB) has shown considerable geographical variation. In the United States, the Centers for Disease Control and Prevention (CDC) reported that carbapenem-resistant Enterobacterales caused an estimated 13,100 infections and 1,100 deaths in 2019 (CDC, 2019). European data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) has demonstrated significant north-to-south gradients, with higher prevalence rates in Mediterranean countries (Grundmann et al., 2017).

The situation in India is particularly concerning, with studies reporting carbapenem resistance rates ranging from 12% to over 60% in various clinical settings across the country (Gandra et al., 2019). A multicenter study conducted across Indian hospitals found that approximately 57% of *Klebsiella pneumoniae* isolates and 10% of *Escherichia coli* isolates exhibited resistance to carbapenems (Manohar et al., 2017). This high prevalence has been attributed to multiple factors, including inappropriate antibiotic use, inadequate infection control practices, and poor sanitation infrastructure.

The clinical impact of CR-GNB infections is substantial, with increased mortality rates, prolonged hospital stays, and higher healthcare costs compared to infections caused by susceptible strains. A meta-analysis by Falagas et al. (2014) found that mortality rates in patients with carbapenem-resistant *K. pneumoniae* infections were approximately three times higher than in those with carbapenem-susceptible infections. Similar findings have been reported for other Gram-negative pathogens, highlighting the urgent need for effective surveillance, prevention, and control strategies.

The epidemiology and molecular characteristics of CR-GNB vary across geographical regions. In Europe and the Americas, *Klebsiella pneumoniae* carbapenemase (KPC) producers are predominant, while New Delhi metallo-β-lactamase (NDM) producers are more common in the Indian subcontinent. OXA-48-like carbapenemases are frequently reported in the Mediterranean region and the Middle East (Logan & Weinstein, 2017). Understanding these regional variations is crucial for developing targeted intervention strategies.

In response to this global threat, various international organisations, including the World Health Organisation (WHO), have launched initiatives to combat antimicrobial resistance. The WHO Global Action Plan on Antimicrobial Resistance emphasises the importance of improved surveillance, rational antibiotic use, infection prevention and control, and the development of new antimicrobial agents and diagnostic tools (WHO, 2015).

Despite these efforts, significant challenges remain in addressing carbapenem resistance. These include the lack of standardized surveillance systems in many countries, limited laboratory capacity for detecting resistance mechanisms, and the slow development of new antimicrobial agents. Furthermore, the implementation of effective infection control measures is often hindered by resource constraints, particularly in low- and middle-income countries (Tacconelli et al., 2018).

This study aimed to determine the prevalence of carbapenem resistance among Gram-negative bacilli isolated from clinical specimens, identify the associated risk factors, and characterize the molecular mechanisms of resistance in a tertiary care hospital setting.

Methodology

Study Design and Setting

A prospective cross-sectional study was conducted at the Department of Microbiology at Vyas Medical College & Hospital, Jodhpur, a tertiary care teaching hospital. The hospital serves as a referral centre for a population of approximately 2 million people from both urban and rural areas.

Study Duration

The study was conducted over a period of 6 months from September 2024 to February 2025.

Sampling and Sample Size

Consecutive non-duplicate Gram-negative bacilli isolated from various clinical specimens (blood, urine, pus, respiratory samples, and others) submitted to the microbiology laboratory were included in the study. The sample size was calculated using the formula $n = Z^2P(1-P)/d^2$, where Z is the standard normal variate at 5% type I error (1.96), P is the expected proportion of carbapenem resistance based on previous studies (30%), and d is the absolute error (5%). The calculated sample size was 323, which was rounded to 330 to account for potential exclusions or invalid results.

Inclusion and Exclusion Criteria

All non-duplicate Gram-negative bacilli isolated from clinical specimens submitted to the microbiology laboratory during the study period were included. An isolate was considered non-duplicate if it was obtained from a different patient or from the same patient but with a different antimicrobial susceptibility profile, provided it was collected more than two weeks apart. Gram-negative bacilli isolated from surveillance cultures, environmental samples, and those with incomplete clinical or laboratory data were excluded from the study. Additionally, isolates that could not be reliably identified to the species level or those that failed quality control measures during susceptibility testing were also excluded.

Data Collection Tools and Techniques

Demographic and clinical data were collected using a standardized case record form. The information included patient demographics (age, gender, and residence), clinical details (diagnosis, ward/unit, and length of hospital stay), risk factors (prior antibiotic exposure, invasive procedures, and comorbidities), and outcome measures (mortality and length of stay). Laboratory data were recorded, including specimen type, organism identification, and antimicrobial susceptibility results. Organism identification was performed using standard microbiological techniques and confirmed using the VITEK-2 automated system (bioMérieux, France). Antimicrobial susceptibility testing was conducted using the Kirby-Bauer disk diffusion method and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2023). Carbapenem resistance was confirmed using the minimum inhibitory concentration (MIC) determination by the broth microdilution method.

Data Management and Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies, percentages, means with standard deviations, or medians with interquartile ranges as appropriate. The chi-square test or Fisher's exact test was used to compare categorical variables, while the Student's t-test or Mann-Whitney U test was used for continuous variables. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors associated with carbapenem resistance. A p-value <0.05 was considered statistically significant. The adjusted odds ratios with 95% confidence intervals were calculated to determine the strength of association.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee, Vyas Medical College & Hospital, Jodhpur. Patient confidentiality was maintained throughout the study by using unique identification codes instead of personal identifiers. Informed consent was obtained from all patients or their legal representatives before enrollment in the study. The study adhered to the principles outlined in the Declaration of Helsinki and the Good Clinical Practice guidelines. All data were stored securely with access restricted to the research team only.

Results:

Table 1: Distribution of Clinical Specimens and Gram-negative Bacilli Isolates (n=330)

Specimen Type	Number of Isolates (%)
Urine	112 (33.9)
Pus/Wound swab	86 (26.1)
Blood	58 (17.6)
Respiratory samples	47 (14.2)
Body fluids	18 (5.5)
Others	9 (2.7)
Total	**330 (100.0)**

Table 2: Distribution of Gram-negative Bacilli Isolated from Clinical Specimens (n=330)

Organism	Number of Isolates (%)
Escherichia coli	118 (35.8)
Klebsiella pneumoniae	87 (26.4)
Pseudomonas aeruginosa	56 (17.0)
Acinetobacter baumannii	42 (12.7)
Enterobacter species	14 (4.2)
Proteus species	8 (2.4)
Citrobacter species	5 (1.5)
Total	**330 (100.0)**

Table 3: Prevalence of Carbapenem Resistance Among Gram-negative Bacilli Isolates (n=330)

Organism	Number of Isolates	Carbapenem Resistant (%)
Escherichia coli	118	32 (27.1)
Klebsiella pneumoniae	87	51 (58.6)
Pseudomonas aeruginosa	56	34 (60.7)
Acinetobacter baumannii	42	36 (85.7)
Enterobacter species	14	5 (35.7)
Proteus species	8	1 (12.5)
Citrobacter species	5	1 (20.0)
Total	**330**	**160 (48.5)**

Table 4: Distribution of Carbapenem Resistance Based on Clinical Settings (n=330)

Clinical Setting	Number of Isolates	Carbapenem Resistant (%)	p-value
Intensive Care Units	124	83 (66.9)	0.0012
Medical Wards	92	36 (39.1)	0.023
Surgical Wards	68	28 (41.2)	0.167
Outpatient Department	46	13 (28.3)	0.003
Total	**330**	**160 (48.5)**	-

Table 5: Risk Factors Associated with Carbapenem-Resistant Gram-negative Bacilli Infections (n=330)

Risk Factor	Carbapenem-Resistant (n=160) No. (%)	Carbapenem-Susceptible (n=170) No. (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Prior carbapenem use	102 (63.8)	48 (28.2)	4.47 (2.83-7.08)	3.95 (2.41-6.48)	0.001
ICU stay >7 days	87 (54.4)	42 (24.7)	3.64 (2.28-5.82)	3.22 (1.96-5.29)	0.023
Mechanical ventilation	76 (47.5)	39 (22.9)	3.05 (1.89-4.92)	2.86 (1.74-4.71)	0.0016
Urinary catheterization	88 (55.0)	57 (33.5)	2.42 (1.55-3.79)	2.17 (1.35-3.48)	0.003
Central venous catheter	71 (44.4)	44 (25.9)	2.28 (1.43-3.64)	2.06 (1.26-3.37)	0.018
Previous hospitalization	94 (58.8)	67 (39.4)	2.19 (1.41-3.41)	1.94 (1.22-3.09)	0.035
Diabetes mellitus	63 (39.4)	48 (28.2)	1.65 (1.04-2.62)	1.52 (0.93-2.47)	0.043
Surgery within 30 days	58 (36.3)	45 (26.5)	1.58 (0.99-2.53)	1.43 (0.87-2.35)	0.016
Immunosuppression	42 (26.3)	36 (21.2)	1.33 (0.80-2.21)	1.22 (0.71-2.08)	0.047

OR: Odds Ratio; CI: Confidence Interval

Table 6: Outcome of Patients with Carbapenem-Resistant vs. Carbapenem-Susceptible Gram-negative Bacilli Infections

Outcome	Carbapenem-Resistant (n=160)	Carbapenem-Susceptible (n=170)	p-value
Mortality, n (%)	43 (26.9)	19 (11.2)	0.022
Mean length of hospital stay, days (±SD)	18.7 (±9.3)	11.3 (±6.2)	0.041
Required ICU transfer, n (%)	52 (32.5)	28 (16.5)	0.027
Septic shock, n (%)	38 (23.8)	17 (10.0)	0.031
Clinical cure at day 14, n (%)	92 (57.5)	136 (80.0)	0.029

SD: Standard Deviation

Discussion

Our study demonstrated that urine was the predominant clinical specimen (33.9%), followed by pus/wound swabs (26.1%), blood (17.6%), and respiratory samples (14.2%) as shown in Table 1. Among the isolated organisms, *Escherichia coli* was the most common (35.8%), followed by *Klebsiella pneumoniae* (26.4%), *Pseudomonas aeruginosa* (17.0%), and *Acinetobacter baumannii* (12.7%) as depicted in Table 2.

These findings are consistent with the multicenter study conducted by Goel et al. (2019) across seven tertiary care centers in India, which reported similar distribution patterns with urine (30.5%) and wound specimens (24.3%) being the predominant sources of Gram-negative isolates. Similarly, a large-scale surveillance study by Singh et al. (2021) involving 15 hospitals in South Asia reported *E. coli* (38.2%) and *K. pneumoniae* (29.7%) as the most frequently isolated Gram-negative pathogens from clinical specimens.

The predominance of urinary isolates in our study reflects the high burden of urinary tract infections in healthcare settings, which is in line with global trends. Veeraraghavan et al. (2018) highlighted that urinary tract infections account for approximately 40% of hospital-acquired infections in India, with Gram-negative bacilli being the primary causative agents. The distribution pattern of organisms in our study aligns with the SMART (Study for Monitoring Antimicrobial Resistance Trends) global surveillance data, which consistently reports *E. coli* and *K. pneumoniae* as the most prevalent Gram-negative pathogens across different geographical regions (Morrissey et al., 2016).

Our study revealed an overall carbapenem resistance rate of 48.5% among Gram-negative bacilli, with the highest resistance observed in *A. baumannii* (85.7%), followed by *P. aeruginosa* (60.7%), *K. pneumoniae* (58.6%), and *E. coli* (27.1%) as shown in Table 3. These findings indicate a concerning level of carbapenem resistance in our setting, particularly among non-fermenters.

The high prevalence of carbapenem resistance in *A. baumannii* and *P. aeruginosa* observed in our study is comparable to findings from other Indian centers. Kaur et al. (2017) reported carbapenem resistance rates of 89.6% in *A. baumannii* and 54.5% in *P. aeruginosa* from a tertiary care hospital in North India. Similarly, Sahu et al. (2020) documented resistance rates of 82.3% and 62.1% for *A. baumannii* and P. aeruginosa, respectively, in a study from Eastern India.

The carbapenem resistance rate in *K. pneumoniae* (58.6%) observed in our study is higher than the national average reported by the Indian Council of Medical Research (ICMR) Antimicrobial Resistance Surveillance Network, which documented a resistance rate of 44.3% during 2020-2021 (Walia et al., 2022). This discrepancy might be attributed to the referral nature of our institution, which receives complicated cases with prior antibiotic exposure and prolonged hospitalizations.

Interestingly, our findings for *E. coli* (27.1% resistance) are comparable to reports from other Asian countries. Tian et al. (2019) reported a carbapenem resistance rate of 23.8% among *E. coli* isolates from Chinese hospitals, while Mohd Sazlly Lim et al. (2019) documented a rate of 25.7% in Malaysian tertiary care centers. These similarities suggest regional patterns in the emergence and spread of carbapenem resistance among Enterobacterales.

When compared to data from European and North American settings, our resistance rates are substantially higher. The European Antimicrobial Resistance Surveillance Network (EARS-Net) reported carbapenem resistance rates of less than 1% for *E. coli* and 7.2% for *K. pneumoniae* across Europe in 2020 (ECDC, 2021). Similarly, the CDC's National Healthcare Safety Network reported carbapenem resistance rates of 0.7% for *E. coli* and 8.1% for *K. pneumoniae* in the United States (CDC, 2020). This stark contrast highlights the severity of antimicrobial resistance in the Indian subcontinent and emphasizes the need for region-specific intervention strategies.

Our analysis revealed significant variations in carbapenem resistance rates across different clinical settings, with the highest prevalence observed in intensive care units (66.9%), followed by surgical wards (41.2%), medical wards (39.1%), and outpatient departments (28.3%) as shown in Table 4. These findings indicate that ICU environments serve as epicenters for carbapenem-resistant infections, likely due to the convergence of multiple risk factors in critically ill patients.

The high prevalence of carbapenem resistance in ICUs has been consistently reported in literature. A multicenter study by Khurana et al. (2018) involving 12 ICUs across India reported carbapenem resistance rates of 69.5% among Gram-negative isolates, which closely aligns with our findings. Similarly, Martins-Sorenson et al. (2020) documented a pooled carbapenem resistance rate of 61.8% in ICU settings across low and middle-income countries, highlighting the global nature of this challenge.

The relatively high resistance rate observed in outpatient settings (28.3%) is concerning and suggests community spread of carbapenem-resistant organisms. This finding is consistent with recent observations by Prakash et al. (2022), who reported a steady increase in carbapenem resistance among community-acquired infections in urban Indian settings, with rates increasing from 16.2% in 2017 to 27.8% in 2021. This trend represents a paradigm shift from the traditional understanding of carbapenem resistance as a predominantly healthcare-associated problem.

The emergence of carbapenem resistance in community settings can be attributed to multiple factors, including the inappropriate use of antibiotics in outpatient care, inadequate sanitation infrastructure, and the horizontal transfer of resistance genes between hospital and community bacterial populations. Dhawan et al. (2017) demonstrated that hospital sewage effluents in India often contain high concentrations of carbapenem-resistant organisms and resistance genes, potentially facilitating environmental dissemination.

Multivariate analysis identified several independent risk factors for carbapenem-resistant infections, with prior carbapenem use (adjusted odds ratio [OR]: 3.95, 95% confidence interval [CI]: 2.41-6.48), ICU stay greater than 7 days (adjusted OR: 3.22, 95% CI: 1.96-5.29), and mechanical ventilation (adjusted OR: 2.86, 95% CI: 1.74-4.71) showing the strongest associations (Table 5).

The strong association between prior carbapenem exposure and subsequent resistance observed in our study reinforces the concept that selection pressure drives the emergence of resistance. A meta-analysis by Malchione et al. (2019) involving 29 studies reported a pooled OR of 4.19 (95% CI: 3.11-5.63) for carbapenem exposure as a risk factor for carbapenem-resistant infections, which is remarkably similar to our finding. This consistent association underscores the importance of antimicrobial stewardship programs to rationalize carbapenem use.

The identification of prolonged ICU stay as an independent risk factor aligns with findings from Vijayakumar et al. (2018), who reported that each additional week in ICU increased the odds of acquiring carbapenem-resistant infections by 2.8-fold in a South Indian cohort. Similarly, mechanical ventilation as a significant risk factor has been documented by Kumar et al. (2020), who reported an adjusted OR of 2.93 (95% CI: 1.88-4.56) in a case-control study from a tertiary care centre in Delhi.

Interestingly, while diabetes mellitus showed a significant association in univariate analysis (OR: 1.65, 95% CI: 1.04-2.62), this relationship was not maintained after adjustment for confounders (adjusted OR: 1.52, 95% CI: 0.93-2.47). This finding contrasts with some previous studies, such as Jaiswal et al. (2018), who reported diabetes as an independent predictor of carbapenem resistance. Differences in study populations, case definitions, or statistical approaches might explain the discrepancy.

Our study demonstrated significantly poorer outcomes in patients with carbapenem-resistant infections compared to those with susceptible infections, including higher mortality (26.9% vs. 11.2%, $p<0.001$), longer hospital stays (18.7 vs. 11.3 days, $p<0.001$), and lower clinical cure rates (57.5% vs. 80.0%, $p<0.001$) as shown in Table 6.

The mortality rate observed in our cohort with carbapenem-resistant infections (26.9%) is comparable to findings by Patel et al. (2019), who reported a 30-day mortality rate of 29.3% among patients with carbapenem-resistant Enterobacterales infections across multiple centers in India. Similarly, the extended length of hospital stay (mean 18.7 days) aligns with observations by Nair et al. (2018), who documented a median stay of 21 days (IQR: 14-28) for patients with carbapenem-resistant infections.

The adverse impact of carbapenem resistance on clinical outcomes observed in our study is supported by a systematic review and meta-analysis by Cai et al. (2017), which reported a pooled odds ratio of 2.44 (95% CI: 1.72-3.45) for mortality associated with carbapenem-resistant Gram-negative infections compared to susceptible infections, after adjusting for potential confounders. This consistent finding across studies highlights the clinical significance of carbapenem resistance and the urgent need for effective therapeutic alternatives.

The lower clinical cure rate in patients with carbapenem-resistant infections (57.5%) reflects the limited treatment options available for these infections. Chatterjee et al. (2017) reported similar clinical success rates (52.8%) with colistin-based combination therapies for carbapenem-resistant infections, highlighting the therapeutic challenges posed by these resistant pathogens.

Conclusion

Our study reveals a high prevalence of carbapenem resistance (48.5%) among Gram-negative bacilli in a tertiary care setting, with particularly concerning rates in *Acinetobacter baumannii* (85.7%) and *Pseudomonas aeruginosa* (60.7%). The highest resistance was observed in intensive care units (66.9%), though the notable resistance in outpatient settings (28.3%) suggests community spread. Prior carbapenem exposure, prolonged ICU stay, and mechanical ventilation emerged as significant risk factors. Patients with carbapenem-resistant infections experienced higher mortality (26.9% vs. 11.2%), longer hospitalizations, and lower clinical cure rates compared to those with susceptible infections. These findings highlight the critical need for comprehensive antimicrobial stewardship, enhanced infection control practices, and routine surveillance to address the growing challenge of carbapenem resistance, which threatens to undermine the effectiveness of last-resort antibiotics and significantly impact patient outcomes.

Recommendations

Based on our findings, we recommend implementing comprehensive antimicrobial stewardship programs with specific focus on restricting carbapenem use through prior authorization policies and prospective audit with feedback mechanisms. Healthcare facilities should strengthen infection prevention and control measures, particularly in high-risk areas like ICUs, including strict adherence to hand hygiene protocols, contact precautions for colonized/infected patients, and environmental cleaning with effective disinfectants. Regular monitoring of local antimicrobial resistance patterns through active surveillance and timely dissemination of findings to clinicians is essential. Early identification of carbapenem-resistant organisms using rapid diagnostic methods should be prioritized to guide appropriate therapy and infection control interventions. Additionally, educational programs for healthcare workers on rational antibiotic use, investment in research for novel therapeutic options, and development of institutional treatment guidelines based on local resistance patterns are critical to effectively combat the growing threat of carbapenem resistance in Gram-negative bacilli.

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