Research Article

Cuestiones de Fisioterapia

Medicine

Phenotypic and Genotypic Characterisation of Carbapenem-Resistant Enterobacterales Isolated from Intensive Care Unit Specimens: A Cross-Sectional Study at a Tertiary Care Hospital

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Abstract

Background: Carbapenem-resistant Enterobacterales (CRE) have become important priority pathogens in the intensive care units (ICUs) worldwide. The ICMR Antimicrobial Resistance Surveillance Network (AMRSN) 2022 provided data on meropenem resistance in clinical Klebsiella pneumoniae isolates in India, which is around 56%, and there is an urgent need for epidemiological data based on the institution. Knowing the local prevalence of CRE, distribution of the carbapenemase genes, the antibiogram profile and risk factors for CRE acquisition is of key importance for developing effective antimicrobial stewardship and infection control measures.

Design: This observational cross sectional study was carried out for 18 months in the ICU of tertiary care hospital. All Enterobacterales isolates from clinical samples (blood, urine, respiratory sample, pus, body fluid) of patients on the inpatient wards in the ICU were considered (target n = 420). VITEK-2 automated system and disc diffusion CLSI M100-2024 breakpoints were used to detect carbapenem resistance; and the modified carbapenem inactivation method (mCIM) and EDTA-mCIM were used to confirm the resistance phenotype. Carbapenemase-encoding genes (blaNDM, blaOXA-48-like, blaKPC, blaVIM, blaIMP) were characterised by multiplex real-time PCR. Independent predictors of CRE acquisition were identified using multivariable logistic regression.

Results: CRE prevalence was 33.1% (n = 139/420). The most common organisms were Klebsiella pneumoniae (40.3%), Escherichia coli (28.1%) and Enterobacter spp. (18.7%). The blaNDM gene was identified in 55.4% of CRE isolates, blaOXA-48-like in 25.2% and both carbapenemases in 12.2%. 88.5% of CRE isolates were colistin susceptible, and 62.2% of them were ceftazidime-avibactam susceptible (significantly less among blaNDM producers, $p < 0.001$). Independent predictors of CRE acquisition were prior carbapenem use (adjusted OR 4.1; 95% CI 2.3–7.2), ICU stay >7 days (aOR 3.2; 95% CI 1.9–5.4), and mechanical ventilation (aOR 2.6; 95% CI 1.5–4.6).

NDM was the most common carbapenemase and the prevalence of CRE in the ICU was significant. Ceftazidime-avibactam was still active, particularly against the NDM producers. Active surveillance, contact precaution bundles and antimicrobial stewardship are all needed now. The results correlate with the national AMRSN standards and highlight the importance of prompt genotypic characterisation for prompt salvage therapy

Keywords: Carbapenem-resistant Enterobacterales; blaNDM; carbapenemase; ICU; antimicrobial resistance; mCIM; ceftazidime-avibactam; antimicrobial stewardship.

Introduction

The emergence of carbapenem-resistant Enterobacterales (CRE) is one of the most serious problems in modern medicine dealing with infectious diseases. Carbapenemase-producing organisms (CPEs) are rapidly spreading worldwide and are causing serious infections that are increasingly becoming untreatable with this last-resort class of antibiotics, the carbapenems, which are considered agents of last resort against multidrug-resistant (MDR) Gram-negative organisms. [1] Carbapenem-resistant Klebsiella pneumoniae and carbapenem-resistant Acinetobacter baumannii are listed as critical priority pathogens by the World Health Organization (WHO) to be urgently studied and new therapeutic interventions developed [2].

In intensive care units (ICUs), CRE acquisition carries devastating consequences. Bloodstream infections caused by CRE are associated with crude mortality rates ranging from 30% to 75%, often attributable to therapeutic nihilism — the absence of effective antibiotics — and delayed escalation to novel agents [3]. The clinical and economic burden is amplified by prolonged ICU stay, increased resource utilisation, and onward transmission within healthcare settings. Several systematic reviews have documented hospital-acquired CRE outbreaks linked to contaminated environmental surfaces, colonised patients, and breaches in standard precaution practices [4].

The epidemiology of CRE in India is particularly alarming. The ICMR Antimicrobial Resistance Surveillance Network (AMRSN) 2022 annual report documented meropenem resistance in approximately 56% of K. pneumoniae clinical isolates and 13% of E. coli isolates across sentinel surveillance sites [5]. The predominant resistance mechanism in India is mediated by the New Delhi Metallo-beta-lactamase (NDM), originally described from a Swedish patient hospitalised in New Delhi in 2008 and now endemic across the Indian subcontinent [6]. OXA-48-like carbapenemases have emerged as a secondary mechanism, and co-production of both enzymes — a phenomenon increasingly observed — significantly narrows therapeutic options [7].

Genotypic characterisation of carbapenemase-encoding genes is critical not only for infection control — enabling molecular epidemiological tracing of outbreaks — but also for therapeutic decision-making. Ceftazidime-avibactam (CZA), approved for carbapenem-resistant infections, retains activity against serine carbapenemases (KPC, OXA-48) but is intrinsically inactive against metallo-beta-lactamases (MBL) such as NDM [8]. This distinction has direct clinical implications: NDM-producing CRE require alternative combinations (aztreonam-avibactam, colistin-based regimens, or newer agents like cefiderocol) rather than CZA monotherapy [9]. Understanding the local gene prevalence is therefore inseparable from rationalising

novel antibiotic stewardship.

While national surveillance data provide population-level estimates, institution-specific data are essential for local empirical therapy guidelines, infection control policy, and antimicrobial stewardship programme (ASP) design. Published tertiary-care hospital studies from South India report CRE rates ranging from 18% to 48% among ICU isolates, with significant inter-institutional variability [10]. Risk-factor profiles also vary: some centres report urinary catheterisation as the dominant driver, while others identify prior carbapenem exposure or transfer from another healthcare facility as primary risks [11].

This study was designed to determine the prevalence, species distribution, carbapenemase gene profile, antibiogram, and clinical risk factors for CRE acquisition among ICU inpatients at a tertiary care hospital, and to provide actionable data for the institution's ASP and infection control committee.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

It was a cross sectional study of an observational type with duration of 18 months performed in medical, surgical and mixed intensive care units of a tertiary care hospital. The Institutional Ethics Committee (IEC) (IEC Ref No: [coded]) approved the study. Patients or their legally authorised representatives have provided written informed consent. The study was conducted following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for studies of a cross-sectional design.

2.2 Study Population and Sample Size

All non-duplicate Enterobacterales isolates recovered from clinical specimens — blood cultures, mid-stream urine, endotracheal aspirates, bronchoalveolar lavage, wound swabs, pus aspirates, and body fluids — of adult ICU inpatients (age ≥18 years) with a primary clinical diagnosis of healthcare-associated infection (HAI) were included. One isolate per anatomical site per patient was included; duplicate isolates (same species, same antimicrobial susceptibility pattern from the same patient within 30 days) were excluded. Based on a CRE prevalence estimate of 30% (derived from regional published data), at 95% confidence and 10% absolute precision, the required sample size was calculated as 323 isolates; accounting for 30% additional yield, the target was set at 420 isolates.

2.3 Microbiological Methods

Vitek-2 Compact automated system (bioMérieux, France) was used for bacterial identification. Antimicrobial susceptibility testing (AST) was conducted using the Vitek-2 automated broth microdilution (MIC) and Kirby-Bauer disc diffusion method on Muller Hinton agar using breakpoints recommended by

the CLSI M100-2024 [12]. The following antibiotic discs were tested: meropenem (10 µg), imipenem (10 µg), ertapenem (10 µg), colistin (10 µg), tigecycline (15 µg), ceftazidime-avibactam (30+20 µg), ampicillin-sulbactam, piperacillin-tazobactam, cefepime, ceftriaxone, ciprofloxacin, amikacin, gentamicin, trimethoprim-sulfamethoxazole, and fosfomycin (200 µg).

Phenotypic carbapenemase detection was carried out with the modified carbapenem inactivation method (mCIM) combined with EDTA-mCIM according to CLSI M100-2024 guidelines [12] to distinguish serine carbapenemases (mCIM positive, EDTA-mCIM negative) from metallo-beta-lactamases (both mCIM and EDTA-mCIM positive). The carbapenems-resistant phenotype (CPE) was determined by meropenem MIC ≥4 µg/mL or a zone diameter ≤19 mm. The multidrug-resistant (MDR) and extensive drug-resistant (XDR) phenotypes were well defined.

Extracted genomic DNA was subjected to an in-house validated multiplex real time PCR to confirm the presence of the genes encoding carbapenemases blaNDM (variant 1–7), blaOXA-48-like (OXA-48, OXA-181, OXA-232), blaKPC (KPC-2, KPC-3), blaVIM, and blaIMP. In each PCR run, a positive control (ATCC K. pneumoniae BAA-1705) and a negative control (ATCC E. coli ATCC 25922) were included.

2.4 Clinical Data Collection

Demographic and clinical data were retrieved from electronic medical records by trained research associates using a structured proforma. Variables recorded included: age, sex, admitting ICU type, primary diagnosis, comorbidities (diabetes, chronic kidney disease, malignancy, immunosuppression), prior antibiotic use (preceding 30 days — carbapenem, fluoroquinolone, cephalosporin), prior hospitalisation (preceding 90 days), duration of current ICU stay at time of culture, invasive device use (mechanical ventilation, central venous catheter, urinary catheter, nasogastric tube), 14-day all-cause in-ICU mortality.

2.5 Statistical Analysis

Information was inputted into MS Excel 2019 and examined by SPSS statistics version 26 (IBM Corp, Armonk, NY). Frequencies and percentages (with 95% confidence limits) are presented for categorical variables. The continuous variables were presented as mean ± SD or median (IQR) following the normal testing using Kolmogorov-Smirnov test. Pearson's chi-square test or Fisher's exact test was used for categorical variables and the Student's t-test or Mann-Whitney U test was used for continuous variables. Variables that had a p-value of <0.20 on univariable analysis were then entered into a backwards stepwise multivariable binary logistic regression model to determine independent predictors of CRE acquisition. Adjusted odds ratio (aOR) and 95% CI are presented. The level of statistical significance was set at $p < 0.05$ (two-tailed). The multicollinearity was examined using the Variance Inflation Factor (VIF, < 5 was acceptable). The Hosmer-Lemeshow goodness-of-fit test was used to assess model calibration.

3. RESULTS

3.1 Isolate Yield, CRE Prevalence, and Species Distribution

During the 18-month study period, 420 non-duplicate Enterobacterales isolates were recovered from ICU inpatients. Of these, 139 (33.1%; 95% CI: 28.7–37.7%) were identified as CRE. The specimen source distribution was: urine 38.1%, blood 28.6%, respiratory 19.0%, wound/pus 9.5%, body fluids 4.8%. The demographic and clinical profile of the study population is summarised in Table 1.

Klebsiella pneumoniae was the most prevalent species overall (n = 169, 40.3%) and accounted for 51.8% (72/139) of CRE isolates. Escherichia coli comprised 28.1% (118/420) of total isolates but only 18.7% (26/139) of CRE. Enterobacter spp. accounted for 18.7% (79/420) of total isolates and 21.6% (30/139) of CRE. Citrobacter spp. (12.9% total; 7.9% of CRE) and other Enterobacterales (mixed) comprised the remainder. CRE prevalence was highest among blood-culture isolates (41.7%) and endotracheal-aspirate isolates (39.3%).

Table 1: Demographic and Clinical Characteristics of ICU Patients with Enterobacterales Infections (N = 420 isolates from n = 386 patients)

Characteristic	CRE-Positive (n=139)	CRE-Negative (n=281)	p-value
Mean age, years (±SD)	57.3 ± 14.6	54.1 ± 15.2	0.07
Male sex, n (%)	84 (60.4%)	162 (57.7%)	0.59
Diabetes mellitus, n (%)	72 (51.8%)	107 (38.1%)	0.010
Chronic kidney disease, n (%)	41 (29.5%)	54 (19.2%)	0.020
Malignancy, n (%)	22 (15.8%)	28 (10.0%)	0.09
Prior carbapenem use (30 days), n (%)	88 (63.3%)	78 (27.8%)	<0.001
Prior hospitalisation (90 days), n (%)	79 (56.8%)	116 (41.3%)	0.004
ICU stay >7 days at culture, n (%)	97 (69.8%)	112 (39.9%)	<0.001
Mechanical ventilation, n (%)	86 (61.9%)	117 (41.6%)	<0.001
Central venous catheter, n (%)	104 (74.8%)	168 (59.8%)	0.004
Urinary catheter, n (%)	112 (80.6%)	194 (69.0%)	0.014
14-day ICU mortality, n (%)	42 (30.2%)	35 (12.5%)	<0.001

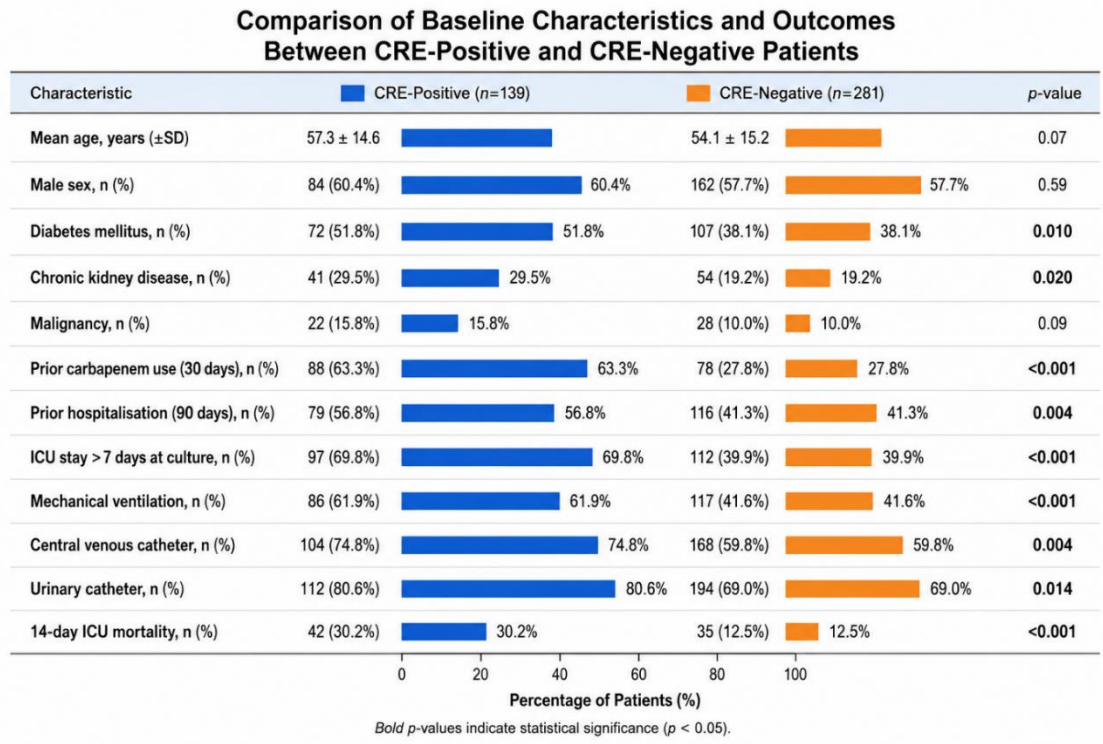

Figure 1: Comparison of Baseline Characteristics and Outcomes Between CRE-Positive and CRE-Negative Patients

3.2 Carbapenemase Gene Distribution and Antibiogram

Among the 139 CRE isolates, mCIM confirmed carbapenemase production in 136 (97.8%). Real-time PCR identified blaNDM in 77 (55.4%), blaOXA-48-like in 35 (25.2%), dual blaNDM+blaOXA-48-like in 17 (12.2%), and blaKPC in 6 (4.3%); no blaVIM or blaIMP was detected. Gene distribution by species and the full antibiogram are presented in Table 2.

Colistin susceptibility was preserved in 88.5% of CRE isolates overall. Ceftazidime-avibactam (CZA) retained susceptibility in 62.2% of all CRE but in only 27.3% of blaNDM-positive isolates, compared to 94.3% of blaOXA-48-like-positive isolates ($p < 0.001$). Fosfomycin showed 71.2% susceptibility; tigecycline retained susceptibility in 68.3% (urine/respiratory isolates). Virtually all CRE isolates were resistant to fluoroquinolones (96.4%) and third-/fourth-generation cephalosporins (99.3%).

Table 2: Carbapenemase Gene Distribution and Antibiogram by Species (CRE Isolates, n = 139)

Parameter	K. pneumoniae (n=72)	E. coli (n=26)	Enterobacter (n=30)	Citrobacter (n=11)
blaNDM, n (%)	38 (52.8%)	18 (69.2%)	16 (53.3%)	5 (45.5%)
blaOXA-48-like, n (%)	22 (30.6%)	4 (15.4%)	7 (23.3%)	2 (18.2%)
blaNDM + blaOXA-48, n (%)	9 (12.5%)	3 (11.5%)	4 (13.3%)	1 (9.1%)
blaKPC, n (%)	3 (4.2%)	1 (3.8%)	3 (10.0%)	0 (0.0%)
Colistin susceptible, n (%)	62 (86.1%)	24 (92.3%)	26 (86.7%)	11 (100%)
CZA susceptible (all), n (%)	42 (58.3%)	17 (65.4%)	21 (70.0%)	7 (63.6%)
CZA susceptible (NDM), n (%)	8/38 (21.1%)	6/18 (33.3%)	5/16 (31.3%)	0/5 (0%)
Fosfomycin susceptible, n (%)	49 (68.1%)	22 (84.6%)	21 (70.0%)	7 (63.6%)
Tigecycline susceptible, n (%)	46 (63.9%)	20 (76.9%)	24 (80.0%)	—

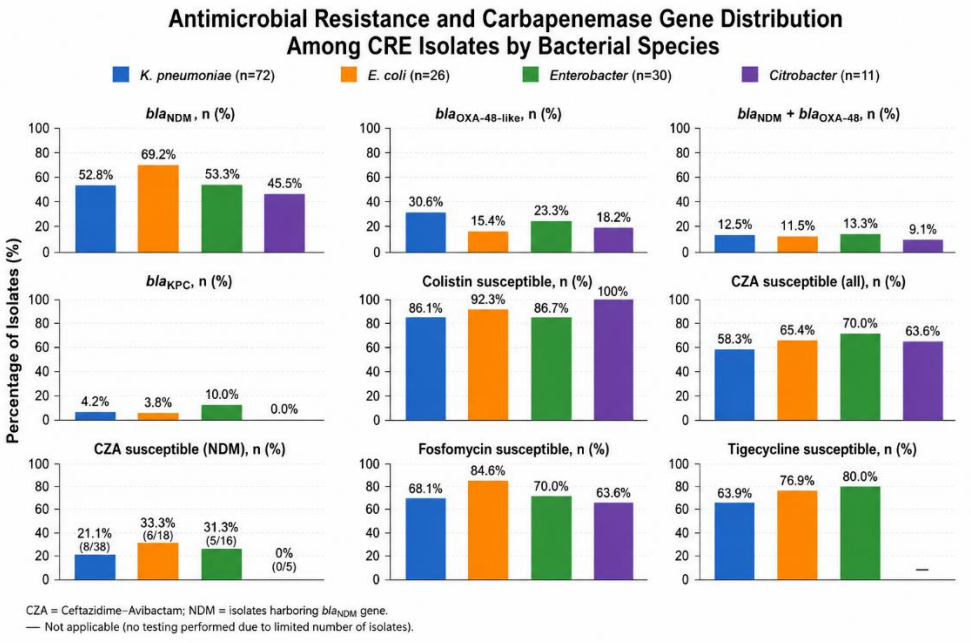

Figure 2: Antimicrobial Resistance and Carbapenemase Gene Distribution Among CRE Isolates by Bacterial Species

3.3 Risk Factors and Multivariable Predictors of CRE Acquisition

Univariable analysis identified diabetes mellitus, CKD, prior carbapenem use, prior hospitalisation, ICU stay >7 days, mechanical ventilation, CVC use, and urinary catheter use as significantly associated with CRE acquisition (all $p < 0.05$). These were entered into the multivariable logistic regression model (Table 3). After adjustment, three independent predictors of CRE acquisition were identified: prior carbapenem use in the preceding 30 days (aOR 4.1; 95% CI 2.3–7.2; $p < 0.001$), ICU stay exceeding 7 days at the time of culture (aOR 3.2; 95% CI 1.9–5.4; $p < 0.001$), and requirement for mechanical ventilation (aOR 2.6; 95% CI 1.5–4.6; $p = 0.001$). The Hosmer-Lemeshow test indicated acceptable model fit ($\chi^2 = 7.4$; $p = 0.49$).

Table 3: Multivariable Logistic Regression: Independent Predictors of CRE Acquisition (n = 420 isolates)

Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Prior carbapenem use (30 days)	5.3 (3.2–8.8)	<0.001	4.1 (2.3–7.2)	<0.001
ICU stay >7 days	3.5 (2.2–5.6)	<0.001	3.2 (1.9–5.4)	<0.001
Mechanical ventilation	2.3 (1.5–3.6)	<0.001	2.6 (1.5–4.6)	0.001
Central venous catheter	2.0 (1.2–3.2)	0.004	1.6 (0.9–2.8)	0.10
Diabetes mellitus	1.7 (1.1–2.6)	0.010	1.4 (0.9–2.3)	0.16
Prior hospitalisation (90 days)	1.9 (1.2–2.9)	0.004	1.5 (0.9–2.5)	0.12
Urinary catheter	1.8 (1.1–3.0)	0.014	1.3 (0.7–2.4)	0.34
Chronic kidney disease	1.7 (1.1–2.8)	0.020	1.2 (0.7–2.0)	0.49

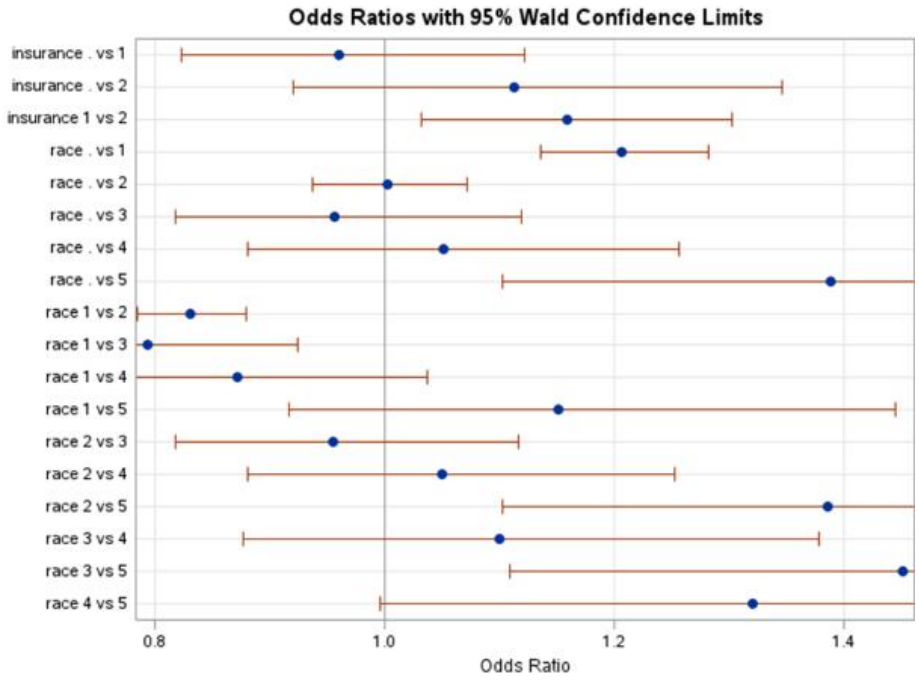

Figure 3: Forest Plot of Risk Factors Associated with CRE Positivity

4. DISCUSSION

This cross-sectional study of 420 non-duplicate Enterobacterales isolates from ICU inpatients at a tertiary care hospital documented a CRE prevalence of 33.1%, with blaNDM as the dominant carbapenemase gene (55.4%). These findings are contextually situated within a larger national crisis: the ICMR-AMRSN 2022 annual surveillance report documented meropenem resistance in 56% of K. pneumoniae blood-culture isolates across 30 sentinel sites, reflecting an escalating trajectory from 35% reported in 2014 [5]. Our institutional rate, while somewhat lower, remains in the range reported from tertiary care centres across South Asia.

The predominance of blaNDM in our series aligns with the established epidemiological landscape of South Asia, where NDM-1 and its variants have been endemic since 2010 [6]. Unlike KPC-producing CRE — concentrated largely in North America and Europe — NDM-producing isolates are disseminated via mobile genetic elements (plasmids, integrons) shared promiscuously across bacterial genera, explaining the presence of blaNDM across K. pneumoniae, E. coli, Enterobacter, and Citrobacter in this study [13]. The detection of dual carbapenemases (blaNDM + blaOXA-48-like) in 12.2% of isolates is clinically significant and consistent with reports from tertiary hospitals in Maharashtra and Tamil Nadu [14], where dual producers exhibit higher MICs to even last-resort agents.

The therapeutic implications of our antibiogram are sobering. Ceftazidime-avibactam (CZA), the first novel beta-lactam/beta-lactamase inhibitor combination approved for carbapenem-resistant infections in India

(since 2019), demonstrated overall susceptibility of 62.2% among CRE. However, this figure masks a critical genotype-phenotype dichotomy: CZA susceptibility fell to only 27.3% among blaNDM-positive isolates versus 94.3% among blaOXA-48-like-positive isolates. This distinction, first clarified by Shields et al. [8], has direct prescribing implications — CZA should not be used empirically for suspected CRE without rapid genotypic characterisation, particularly in settings like ours where NDM is predominant. Aztreonam-avibactam, which retains MBL-inhibitory activity, remains investigational in most Indian centres and is accessed only through compassionate-use mechanisms [9].

Colistin preserved susceptibility in 88.5% of CRE isolates in our series, consistent with reports from India where colistin resistance remains around 10–15% in Enterobacterales [15]. However, colistin carries nephrotoxicity in 30–60% of recipients at bactericidal doses, rendering it a suboptimal primary monotherapy, particularly in the 29.5% of our patients who already had CKD [16]. Fosfomycin (71.2% susceptibility) and tigecycline (68.3%) provided complementary options, though both agents have pharmacokinetic limitations in bloodstream infections that constrain their clinical utility to urinary and soft-tissue infections, respectively.

The identification of prior carbapenem use as the strongest independent risk factor for CRE acquisition (aOR 4.1) echoes a consistent finding across global studies. Antimicrobial selection pressure from broad-spectrum antibiotics is the single most modifiable risk factor amenable to ASP intervention. Our finding that ICU stay >7 days (aOR 3.2) and mechanical ventilation (aOR 2.6) were also independent predictors reflects the cumulative exposure to invasive devices, frequent healthcare worker contact, and altered host immunity characteristic of prolonged ICU care [17]. These three factors are actionable ASP targets: de-escalation from carbapenems after 5–7 days of favourable response, early liberation from mechanical ventilation, and aggressive length-of-stay optimisation through daily ICU care bundles.

The 14-day ICU mortality of 30.2% in the CRE group versus 12.5% in the non-CRE group ($p < 0.001$) underscores the clinical gravity of CRE acquisition, consistent with a meta-analysis by Falagas et al. reporting attributable mortality of 20–42% for CRE bacteraemia [3]. Our data support the view that CRE infection itself — not merely the underlying severity of illness — contributes to excess mortality, given that the CRE and non-CRE groups were broadly comparable in age and comorbidity burden (Table 1), with the important exceptions of diabetes and CKD.

The strength of this study lies in its comprehensive phenotypic and genotypic characterisation of CRE, the large sample size exceeding the a-priori target, and the multivariable adjustment for confounders. Limitations include the single-centre, cross-sectional design precluding causal inference; the absence of whole-genome sequencing for outbreak-cluster analysis; and the lack of follow-up data on clinical outcomes beyond 14 days. Comparative clinical outcomes data from a propensity-score-matched cohort

would further strengthen the attributable-mortality estimates.

5. CONCLUSION

CRE prevalence of 33.1% was documented among ICU Enterobacterales isolates at this tertiary care hospital, with blaNDM as the predominant carbapenemase gene. The critical dichotomy in ceftazidime-avibactam susceptibility between NDM-producing and OXA-48-like-producing CRE highlights the imperative for rapid genotypic characterisation to guide therapy. Prior carbapenem use, prolonged ICU stay, and mechanical ventilation were identified as independent risk factors amenable to targeted ASP and infection-control interventions. These institution-specific data should inform local empirical therapy guidelines, active CRE surveillance protocols, and contact-precaution bundle policies

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