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# Faecal Carriage of Carbapenem-resistant *Enterobacterales* in a Tertiary Care Teaching Hospital in Mumbai

**Bhagyashree Kadam, Priyanka Sheshnath Prasad* and Gita Nataraj**

Department of Microbiology, Seth G.S. Medical College and KEM Hospital, Parel, Mumbai, Maharashtra, India.

## Abstract

**CRE colonization can act as a potential source for subsequent infection with high mortality rate. This study was to determine prevalence of faecal carriage of CRE among hospitalized patients and the associated risk factors for acquisition. A prospective cross-sectional study was carried over one year (August 2019-July 2020) on newly admitted indoor patients screened for CRE. Rectal swab/fecal specimen was collected, processed and interpreted as per CLSI standards. Of the 300 patients screened, 331 *Enterobacterales* were isolated of which 46 CRE strains were detected in 40 patients giving a prevalence 13.3% (40/300). Highest number of CRE were in the age group >60 years while among the CSE-positive patients, highest cases were in the age group 31-40 years. Males (62.5%) had a higher faecal carriage compared to females (37.5%). *E. coli* and *Klebsiella* species were predominant in both CRE and CSE groups (63% and 28.3% in CRE; 47.01% and 37.5% in CSE). Among the 46 CRE isolates, 25 (54.3%) were carbapenemase producers, of which 16 (64%) produced metallo-β-lactamases. Highest proportion of CRE cases were found among ICU patients (26.82%). Patients harbouring CSE had a mean length of stay (LOS) of 5.2 days while CRE patients had LOS of 15.4 days. On multivariate analysis, risk factors associated with CRE colonization were previous exposure to antibiotics, surgical intervention, and diabetes mellitus. Effective infection control measures, including early detection and isolation of CRE carriers are essential to prevent spread and improve patient outcomes.**

**Keywords:** Carbapenem-resistant *Enterobacteriaceae*, CRE, Fecal Carriage, Risk Factors, CRE Colonization

***Correspondence:** priyanka1975@gmail.com

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## INTRODUCTION

CRE (Carbapenem-resistant *Enterobacterales*) is defined as an organism belonging to *Enterobacterales* which is resistant to either imipenem or meropenem or both or the isolate showed the presence of a carbapenemase by a phenotypic method[1] as recommended by CLSI. Faecal carriage of CRE has been recognized as a significant reservoir for the dissemination of these bacteria in healthcare settings.[2] Gastrointestinal carriage of CRE varies from 0.3% to 18.3% worldwide including India as per various studies.[3,4] CRE colonizers can act as a potential source for subsequent infections, for themselves and as new infections for other susceptible individuals. These infections are associated with a high mortality rate of 22% to 72%.[1] Studies have demonstrated that colonization with CRE increases the risk of infection by the colonizing strain by at least 10.8-fold.[5] Understanding the epidemiology and risk factors associated with faecal carriage of CRE is important for implementing effective infection control measures and preventing the spread of these resistant strains.[6] WHO has also recommended routine surveillance of CRE in hospital settings to curb its spread.[1,7] Studies have shown that strict epidemiological interventions can help to control CRE infections in hospital settings.[2,8]

The primary objective of the present study was to determine the prevalence of faecal carriage of CRE among patients admitted to a tertiary care teaching hospital in different settings *i.e.* ward and ICU. The secondary objectives were to study the prevalence of carriage in different age groups, association with different co-morbidities and to analyse the risk factors associated with faecal carriage.

## MATERIALS AND METHODS

### Patients and setting

This was a prospective cross-sectional study conducted in a tertiary care teaching hospital over a period of one year from August 2019-July 2020. This is a 2250 bedded hospital with an annual OPD attendance of approximately 1.4 million patients and over 88,390 indoor admissions in 2019.

### Ethical approval

Institutional ethics committee permission (EC/158/2018) was obtained before commencing this study and only those patients who consented were enrolled. Procedures followed during the study were in accordance with ethical standards of the institutional ethics committee and with the Declaration of Helsinki of 1975, as revised in 2000.

### Sample size

A convenience sample size of 300 consecutive, non-duplicate, indoor patients admitted to medicine, general surgery, orthopaedics, obstetrics and gynaecology, paediatric wards and ICU's who fulfilled the inclusion criteria were enrolled for the study. Patients were screened for CRE after 48 hours of admission.

### Inclusion criteria

Hospitalized patients asymptomatic for CRE from all age groups consenting to the study were included.

### Exclusion criteria

Non-hospitalized patients and those already diagnosed with a CRE infection and those not consenting for the study were excluded.

Rectal swab/faecal specimen was collected from patients after 48 hours of admission and processed. This swab/sample was inoculated directly onto MacConkey's agar and incubated at 35 ± 2 °C in ambient air for 18-24 hours. Any growth was identified up to species level as per standard methods,[9] and only members of *Enterobacterales* were included in further study. If more than one type of *Enterobacterale* was isolated, each was sub-cultured separately and identified. Antibiotic susceptibility was performed for each isolate on Mueller-Hinton agar by Kirby Bauer disc diffusion method for the following groups of antibiotics and interpreted as per latest CLSI standards (2019 & 2020): Aminoglycosides, penicillins, cephalosporins, beta lactam-beta lactamase inhibitor combinations, tetracyclines, co-trimoxazole, chloramphenicol, fluoroquinolones and carbapenems.

In this study, the presence of a carbapenemase was detected by the mCIM test

**Table 1.** Species wise distribution of CRE & CSE isolates (n = 331)

| Species | CSE isolates n = 285 | Total CRE isolates n = 46 | Carbapenemase producing CRE n = 25 |
|---|---|---|---|
| *E. coli* | 134 (47.01%) | 29 (63%) | 12 (41.4%) |
| *Klebsiella* species | 106 (37.19%) | 13 (28.3%) | 9 (69.2%) |
| *Enterobacter* species | 18 (6.31%) | 1 (2.2%) | 1 |
| *Proteus* species | 10 (3.5%) | 1 (2.2%) | 1 |
| *Providentia* species | 11 (3.8%) | 1 (2.2%) | 1 |
| *Citrobacter* species | 5 (1.7%) | 1 (2.2%) | 1 |

(modified carbapenem inactivation method) as recommended by CLSI. Those strains showing susceptibility to both imipenem and meropenem and not demonstrating carbapenemase production phenotypically have been considered as carbapenem-susceptible *Enterobacterales*. For detection of metallo-β-lactamases, eCIM (EDTA-carbapenem inactivation method) test was carried out.

Risk factors for acquiring CRE carriage were noted. These include: age, gender, duration of stay in hospital, length of stay in ICU, previous history of hospitalization, intra-hospital transfer, history of prior surgery in past 3 months, mechanical ventilation, diabetes mellitus, hepatic disease, renal disease, CNS disease, malignancy, urinary catheterization, central venous catheterization, chronic heart disease, pulmonary disease and prior use of antibiotics for at least 3 days at the time when colonization was detected.[1,2,6,10-14]

**Statistical analysis**

To evaluate statistical significance, categorical variables were analysed using the Fisher's exact test. Continuous variables were analysed using the Student 't' test. For multivariate analysis, logistic regression model with odds ratio and 95% confidence interval were performed. All tests were two-sided and a p-value of <0.05 was deemed to be statistically significant. Statistical studies were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA).

## RESULTS

A total of 300 patients fulfilling inclusion criteria, admitted to various wards and ICUs were screened for carbapenem-resistant *Enterobacterales.*

From the 300 faecal specimens, 352 gram -negative bacilli were isolated, of which 21 were non-*Enterobacteriaceae* (*Pseudomonas* species, *Acinetobacter* species) and were excluded from the study. Of the 331 *Enterobacteriaceae* isolated, 46 were CRE strains. These 46 CRE strains were isolated from 40 patients and remaining 285 CSE strains were isolated from 260 patients (Table 1). The prevalence of CRE colonization among the screened patients was found to be 13.3% (40/300).

The age of patients ranged from 2-81 years with a mean of 45.87 years. The highest proportion of CRE cases were in the age group >60 years (27.5%), followed by the age group 51-60 years (17.5%) and 41-50 years (17.5%). Among the CSE patients, the age ranged from one year to 75 years, with a mean age of 36.62 years. The highest number of cases were in the age group 31-40 years (24.2%), followed by the age group 21-30 years (23.3%).

Males (25/40, 62.5%) had a higher faecal carriage of CRE compared to females (15/40, 37.5%) in all age groups.

*E. coli* and *Klebsiella* species were predominant in both CRE and CSE groups. (63% and 28.3% in CRE; 47.01% and 37.5% in CSE).

The 46 CRE isolates were screened for carbapenemase production using the modified carbapenem inactivation method (mCIM) test. Among these 46 isolates, 25 (54.3%, 25/46) were carbapenemase producers. Of these, 16 (64%, 16/25) were positive for metallo-β-lactamase while the remaining isolates were serine protease producers. 21 (45.7%) were carbapenem-resistant by other mechanisms.

**Table 2.** Univariate analysis of risk factors for CRE colonization (n = 300 patients)

| Risk factors | CRE (n = 40) | CSE (n = 260) | P-value |
|---|---|---|---|
| Age (mean) | 45.87 | 36.62 | 0.0029 |
| Sex: Male/Female | 25/15 | 139/121 | 0.2866 |
| Previous history of hospitalization | 19 | 142 | 0.4961 |
| Inter-hospital transfer | 5 | 20 | 0.3515 |
| History of surgical intervention | 23 | 74 | 0.0004 |
| Presence of wounds | 5 | 22 | 0.4092 |
| Mechanical ventilation | 7 | 27 | 0.1917 |
| Urinary catheter | 13 | 27 | 0.0003 |
| Central venous catheter | 9 | 27 | 0.0326 |
| Diabetes mellitus | 18 | 42 | <0.0001 |
| Renal disease | 7 | 9 | 0.0009 |
| Malignancy | 9 | 17 | 0.0017 |
| H/O Corticosteroids | 6 | 13 | 0.0215 |
| Chronic heart disease | 4 | 12 | 0.1689 |
| Pulmonary disease | 4 | 13 | 0.2122 |
| Hepatic disease | 3 | 7 | 0.1311 |
| **Previous exposure to antibiotics in last 3 months** | | | |
| Carbapenems | 8 | 21 | 0.0219 |
| Cephalosporins | 14 | 18 | <0.0001 |
| Fluoroquinolones | 5 | 12 | 0.0541 |
| Aminoglycosides | 7 | 11 | 0.0024 |

The distribution of CRE and CSE cases according to clinical setting was analysed. Of the 300 patients, 259 were from wards and 41 were from ICU's. The highest proportion of CRE cases were found in ICU patients (26.82%, 11/41 in ICU & 11.19%, 29/259 in wards). The majority of CRE cases were from the surgery department (45%, 18/40) followed by medicine department (32.5%, 13/40).

Overall, CSE strains were significantly more susceptible to all antimicrobial classes compared to CRE strains [Aminoglycosides (amikacin 87% v/s 21.73%, P < 0.0001; gentamicin 81.91% v/s 13%, P < 0.0001), penicillin's (ampicillin 31.92% v/s 0%, P < 0.0001; Piperacillin 21.75% v/s 0%, P = 0.0004), cephalosporins (ceftriaxone 61.1% v/s 0%, P < 0.0001; cefepime 57.89% v/s 17.39%, P < 0.0001), beta lactam-beta lactamase inhibitor combinations (piperacillin tazobactam 38.59% v/s 6.52%, P < 0.0001; cefoperazone-sulbactam 72.63% v/s 23.91%, P < 0.0001), fluoroquinolones (ciprofloxacin 54.38% v/s 13.04%, P < 0.0001; levofloxacin 85.96% v/s 15.21%, P < 0.0001), co-trimoxazole (49.12% v/s 0%), P < 0.0001] and carbapenems (imipenem 100% v/s 10.86%, P < 0.0001 and meropenem 100% v/s 6.52%, P < 0.0001).

**Table 3.** Multivariate analysis of risk factors for CRE colonization

| Risk factor | Odds ratio | P-value | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Previous exposure to cephalosporins | 7.2393 | <0.0001 | 3.2297 | 16.2266 |
| Previous exposure to aminoglycosides | 4.8017 | 0.0024 | 1.7404 | 13.2472 |
| History of surgical intervention | 3.4006 | 0.0004 | 1.718 | 6.7281 |
| Diabetes mellitus | 4.2468 | <0.0001 | 2.0982 | 8.5954 |

The length of hospital stay (LOS) for patients with CRE and CSE infection was compared. Patients harbouring CSE had a mean length of stay (LOS) of 5.2 days, whereas patients with CRE had a significantly longer mean LOS of 15.4 days (p < 0.0005).

By univariate analysis of risk factors (Table 2), CRE patients were significantly more likely than non-CRE (CSE) patients to have a higher age, history of surgical intervention (p = 0.0004), urinary catheter placement (p = 0.0003), a central venous line (p = 0.0326) diabetes mellitus (p < 0.0001), renal disease (p = 0.0009), malignancy (p = 0.0017), corticosteroid use (p = 0.0215), previous use of antibiotics especially belonging to carbapenem (p = 0.0219), cephalosporin (p ≤ 0.0001), aminoglycoside (p = 0.0024) groups.

On multivariate analysis (Table 3), only previous exposure to cephalosporins (OR = 7.2393, 95% CI = 3.23 to 16.23), aminoglycosides (OR = 4.8, 95% CI = 1.74 to 13.25) surgical intervention (OR = 3.4, 95% CI = 1.72 to 6.73), and diabetes mellitus (OR = 4.25, 95% CI = 2.1 to 8.6) were significantly associated.

## DISCUSSION

WHO has included CRE in its Indian list of antibiotic resistant 'priority pathogens' category which indicates that these are pathogens of serious concern.[15]

The present study was conducted to determine the prevalence and risk factors associated with faecal carriage of CRE in hospitalized patients in a tertiary care teaching institute through active surveillance in various wards and ICU's. Few studies from India have investigated CRE prevalence in faecal samples.[10,16]

The prevalence of CRE colonization among the enrolled patients was found to be 13.3%, indicating a significant burden of carbapenem resistance. This finding is consistent with previous studies that have reported high rates of CRE carriage in healthcare facilities i.e. 18.1% by Mohan et al. in 2012-2013, 51.85% by Saseedharan et al. in 2015 in ICU, 19.9% by Sharma et al. in 2019-2020.[1,10,16] Studies from some western countries show a much lesser prevalence as compared to the present study.[3,17] These low rates could be due to restricted availability of antibiotics, strict hospital infection protocols and antibiotic stewardship programmes. A high prevalence in this study may be due to greater exposure to antibiotics previously (carbapenems, cephalosporins, aminoglycosides) as this hospital is a tertiary care centre. CRE can be transmitted easily from person to person through the hands of health care workers (HCW's) or hospital equipment and patient devices.[6] CRE can also be acquired endogenously from the gut because of antibiotic selection pressure.[6] Knowledge of CRE carriage is essential as these asymptomatic colonizers can act as potential reservoirs for transmission of infections in the hospital environment.[1,6,18] Currently, there are no recommendations for CRE faecal carriage in India. Countries like Korea have declared CRE as a notifiable disease, especially in high-risk areas as per guidelines from WHO.[1,11]

This study revealed that patients in the higher age group, i.e. above 60 years and males, had the highest proportion of CRE colonization. These observations are in line with previous studies that have identified higher age and male gender as risk factors for colonization.[6,12,14,19,20] The higher prevalence of CRE in older individuals may be attributed to a higher frequency of hospitalizations, co-morbidities, antibiotic usage, and increased exposure to healthcare-associated risk factors.[20,21]

Species-wise distribution demonstrated that *E. coli* was the most common CRE species identified, followed by *Klebsiella* species. These findings are consistent with global trends where *E. coli* and *Klebsiella* species are the predominant CRE isolates.[1,16,19,20,22] The unique emergence of *E. coli* as the predominant CRE strain in this specific study diverges from some other studies that report higher percentages of *Klebsiella*, i.e. 87%, 42.2%, 39.3% and 70% as compared to *E. coli,* i.e. 7.9%, 24.3%, 21.97%, and 11.7%.[1,12,16,20,22] This might indicate a local increase in resistance among *E. coli* strains.

Though *E. coli* was the predominant CRE in the present study, a higher proportion of *K. pneumoniae* were found to be carbapenemase producers (69%) which is similar to other studies.[23] It is believed that the production of thick capsules and extensive ability to produce biofilms on indwelling foreign bodies like prosthetics give *Klebsiella* a survival advantage and it also has the capability of acquiring multiple multidrug-resistance plasmids.[24,25]

With regards to distribution of CRE in different clinical settings, higher proportion was observed in ICU patients, particularly in the surgical departments which was observed in other studies too.[1,16,20] Surgical patients have increased chances of colonization due to invasive procedures, catheter and other invasive devices in situ and longer hospital stay. ICU patients often have longer stay in the ward, even before being admitted to the ICU, more chances of mechanical ventilation and exposure to antibiotics, thus increasing their exposure to healthcare settings and potentially to resistant bacteria. There are studies that have demonstrated that CRE rates are higher in medical ICU's as compared to surgical ICU in contrast to the present study.[10] Medical ICU patients have been found to be older, have more carbapenem usage, longer hospital stay and more cases are bedridden ones.[10]

A significant proportion of isolates tested positive for carbapenemases (54.3%) of which 19.6% were serine carbapenemase producers. This may be useful as ceftazidime-

avibactam combination can be used to treat cases producing serine carbapenemases.[10] Other studies have also demonstrated high proportion of carbapenemase producers.[1,26] Epidemiological surveillance from India has confirmed NDM-1 to be widely disseminated in healthcare settings as well as in environment and is the predominant carbapenem-resistant mechanism in India.[27]

CRE strains exhibited decreased susceptibility to all tested antimicrobial classes compared to carbapenem-sensitive *Enterobacterales* (CSE) strains. CRE strains often possess various mechanisms such as efflux pumps, porin mutations, and acquisition of resistance genes on mobile genetic elements, contributing to resistance against multiple antibiotic classes.[28] Probable risk factors for faecal carriage of CRE by univariate logistic regression analysis demonstrated that history of surgical intervention ($p = 0.0012$), presence of urinary catheter ($p = 0.0018$) and central venous line ($p = 0.0308$), previous exposure to antibiotics like carbapenems ($p = 0.0239$), cephalosporins ($p = 0$) and aminoglycosides ($p = 0.0111$), H/o diabetes mellitus ($p = 0.0004$), renal disease ($p = 0.0057$), malignancy ($p = 0.0139$), corticosteroid use ($p = 0.0194$) were associated with increased risk of CRE colonization. Previous studies reported similar risk factors for acquiring faecal colonization with CRE infection.[1,2,26,29] Multivariate analysis done found four independent risk factors for colonization-history of surgical intervention, previous exposure to cephalosporins, previous exposure to aminoglycosides and diabetes mellitus.

On calculating the odds ratio, chance of CRE carriage in stool was found to be 7.54 times higher in patients with previous exposure to cephalosporins, 4.88 times higher with previous exposure to aminoglycosides, 4.35 times in diabetic patients and 3.42 times in patients having history of surgical intervention.

This study also identified chronic diseases like diabetes mellitus, malignancy, renal diseases as risk factors. Such patients could have had recurring admission as well as a relatively longer length of stay (mean days 15.4 v/s 5.2) ($p = 0.0005$) exposing them to greater risk than the general patient population.[1,10,20]

This study highlights the need for effective infection control measures, including early detection and isolation of CRE carriers to prevent the spread of these multidrug-resistant bacteria. Targeted infection control measures aimed at the identified risk factors, consistent antimicrobial stewardship initiatives, enhanced hand hygiene practices, and effective surveillance can aid in decreasing the transmission of CRE and stopping its further spread.

**Limitations of the study**

It is important to acknowledge certain limitations of this study. First, the study was conducted in a single tertiary care teaching hospital, which may limit the generalizability of the findings to other healthcare settings. Second, the study focused only on faecal carriage of CRE and did not assess the clinical impact of CRE colonization or infection. Thirdly, a study with a larger sample size could give better results but due to the ongoing COVID pandemic, patient reporting to the hospital were limited and therefore lesser number of enrolments could be done. Fourthly, all the tests used for detection of the resistance mechanism were phenotypic and were not confirmed by carrying out molecular detection of resistance genes.[30] Future studies should explore the clinical outcomes associated with CRE colonization to further understand the implications of these findings.

## CONCLUSION

This study highlights the high prevalence of CRE in hospitalized patients. The identification of risk factors, species distribution, antimicrobial susceptibility patterns, and mechanisms of resistance provides valuable insights for the development and implementation of effective infection control strategies. Understanding the epidemiology, trends, and associated factors of CRE colonization is crucial for preventing the transmission of these multidrug-resistant bacteria and improving patient outcomes.

## ACKNOWLEDGMENTS

None.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

PSP and BK conceptualized, designed the study and performed data collection. PSP and BK analysed the data. PSP, GN and BK wrote and revised the manuscript. All authors read and approved the final manuscript for publication.

## FUNDING

None.

## DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

## ETHICS STATEMENT

The study was approved by the Institutional Ethics Committee, Seth GS Medical College & KEM Hospital (EC/158/2018).

## INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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