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Original Article

Microbiology Section

Detection of Common Genotypes of Carbapenemase in Carbapenem-resistant Enterobacteriaceae Isolated from Lower Respiratory Tract Infections at a Tertiary Care Hospital in Southern India: A Cross-sectional Study

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ABSTRACT

Introduction: Lower Respiratory Tract Infections (LRTI) caused by Carbapenem-resistant Enterobacteriaceae (CRE) has emerged as a major threat to modern medicine and have limited treatment options available. Timely detection of genotypes of carbapenemases in the clinical laboratory is of paramount importance to give appropriate treatment.

Aim: To detect the proportion of common genes responsible for carbapenemase production (genotype) from CRE in a Tertiary Care Hospital in Southern India.

Materials and Methods: The present cross-sectional study was conducted in the Department of Microbiology, Believers Church Medical College Hospital, Thiruvalla, Kerala, India, from March 2025 to September 2025. The study included a total of 125 isolates obtained from patients with (LRTIs). CRE reported from aerobic bacterial culture and sensitivity testing of respiratory samples that show resistance to one or more carbapenems (meropenem, imipenem or ertapenem) was subjected to carbapenemase gene detection. The genes detected were NDM-1, OXA-48, KPC and VIM using a Polymerase Chain Reaction (PCR) assay. Bacterial identification and antibiotic susceptibility testing were performed using the VITEK® 2 Compact system. The statistical analysis was done in Statistical Package for Social Sciences (SPSS) version 21.0. The association between variables were tested using Pearson's Chi-Square Test. The p-value of <0.05 was considered statistically significant.

Results: Out of the total 125 CRE isolates tested, *Klebsiella pneumoniae* was isolated from 123 (98.4%) samples and *Enterobacter cloacae* from 2 (1.6%) samples. The most common genotype of carbapenemase observed was NDM-1+OXA-48 33 (26.4%), followed by NDM-1 alone 28 (22.4%) and OXA-48 alone 28 (22.4%). NDM-1 (alone and in combination with other genes) constituted about 83 (66.4%), and OXA-48 (alone and in combination with other genes) was present in 75 (60%) of the isolates.

Conclusion: The present study results indicate that NDM-1, followed by OXA-48, were responsible for carbapenemase production in more than 50% of CRE isolates tested. Among the total CRE isolates studied, 96.8% isolates were carbapenemase producers and 3.2% were non-carbapenemase producers. This high percentage of Carbapenemase-producing CRE is alarming. So, prompt detection of genotypes of CRE, strict anti-microbial stewardship practices, and infection control activities are absolutely essential in health care facilities to curtail CRE infections.

Keywords: Beta-lactamase, Drug resistance, *Klebsiella pneumoniae*

INTRODUCTION

The LRTI caused by CRE constitute a major health problem and cause significant mortality and morbidity. Among CRE, *Klebsiella pneumoniae* is the main pathogen causing LRTI [1]. The antimicrobial resistance of Enterobacteriaceae is influenced by regional antibiotic use and geographical location. The emergence of CRE is attributed to the widespread use of carbapenems [2].

The CRE is defined as Enterobacteriaceae that are resistant to any one of the carbapenem group of antibiotics, such as meropenem, imipenem or ertapenem [3]. The Carbapenem Resistance in CRE is due to acquisition of carbapenemase genes, altered porin expression, efflux pump mechanisms and decreased permeability [2]. Carbapenemases are a type of β-lactamase that can hydrolyse Carbapenems. Carbapenemases are divided into Class A, B and D according to the Ambler Classification method. Class A and Class D Carbapenemases are serine β-lactamases, which include KPC and OXA-48, respectively. Class B is Metallo-β-lactamases (MBL), which include NDM-1, VIM and IMP [4]. The main genes responsible for carbapenemase production are NDM-1, KPC, OXA-48 and VIM [5]. NDM-1 and OXA-48 are the most common genes prevalent in India, while KPC is the most common one in the United States of America [6,7].

Treatment options for LRTI caused by CRE are limited. Antibiotics that can be given for LRTI due to CRE are polymyxin B, tigecycline, aminoglycosides, ceftazidime-avibactam alone or in combination with aztreonam and high-dose meropenem [3]. For KPC and OXA-48-producing strains of Enterobacteriaceae, ceftazidime- avibactam alone can be used for treatment. But for strains bearing class B MBLs such as NDM and VIM, ceftazidime-avibactam should be combined with aztreonam [8]. There are different methods for the detection of carbapenemase enzyme production. They include phenotypic methods like Modified Hodge test, colorimetric test (Carba NP test), Modified Carbapenem Inactivation Method (m CIM), Spectrophotometric method, MALDI-TOF MS, rapid lateral flow assay and molecular methods [9,10].

Molecular methods are the gold standard tests for detecting carbapenemase genes and include multiplex real time PCR, loop-mediated isothermal amplification method with hydroxy naphthol blue dye (LAMP-HMB), microfluidic chip technology, BioFire-FilmArray Pneumonia Panel, BioFire blood culture identification panel, and whole genome sequencing. The advantage of the molecular methods is that it is time saving and can detect all types of carbapenemase genes. Though multiplex PCR and BioFire are the most commonly used genotypic methods in a hospital setting, whole genome sequencing is the most reliable method [9].

Indiscriminate use of antibiotics in clinical, veterinary, aquaculture and agricultural sectors has accelerated the emergence of antimicrobial resistance [11,12]. Carbapenemase-producing Enterobacteriaceae (CPE) can cause serious infections, increase mortality rates and lengthen hospital stay. Early efficient treatment should be done, but only a limited number of therapeutic options are available [13]. Early detection of genes responsible for carbapenemase production is essential to treat infections caused by CRE. There is a considerable knowledge gap regarding the proportion of genes responsible for carbapenemase production among CRE isolated from patients with LRTI in South India. The proportion of carbapenemase genes varies from region to region [1,2,10].

The study aimed to detect the proportion of common genes responsible for carbapenemase production (genotype) from CRE in a tertiary care hospital in South India. The primary objective of the study was to detect the proportion of genes responsible for carbapenemase production (genotype) among CRE in a tertiary care hospital in South India, and the secondary objective was to find out the association between prior meropenem usage, previous hospitalisation and the genotype of carbapenemase detected.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the department of Microbiology, in Believers Church Medical College Hospital, Thiruvalla, Kerala, India. The study was conducted from March 2025 to September 2025. Approval from the Institutional Ethics Committee, BCMCH, was obtained (IEC study No.-IEC/2025/06/491).

Inclusion criteria: The study population included all CRE reported from the respiratory samples, like sputum, which satisfied Bartlett's Criteria [14], Bronchoalveolar Lavage (BAL), bronchial wash and ET mini-BAL. Enterobacteriaceae resistant to any of the Carbapenems (Meropenem, Imipenem or Ertapenem) were included in the study.

Exclusion criteria: CRE isolates from a repeat sample from the patient during the same hospitalisation period, and isolates from samples like endotracheal aspirate, tracheostomy tube secretions and suction tip were excluded.

Sample size calculation: Sample size was calculated using the formula, n= {z2 p(1-p)}/d^2. After doing a pilot study in the Microbiology laboratory, BCMCH, the prevalence (p) was calculated as 45%, and the sample size was calculated as 122, which is approximated to 125.

Study Procedure

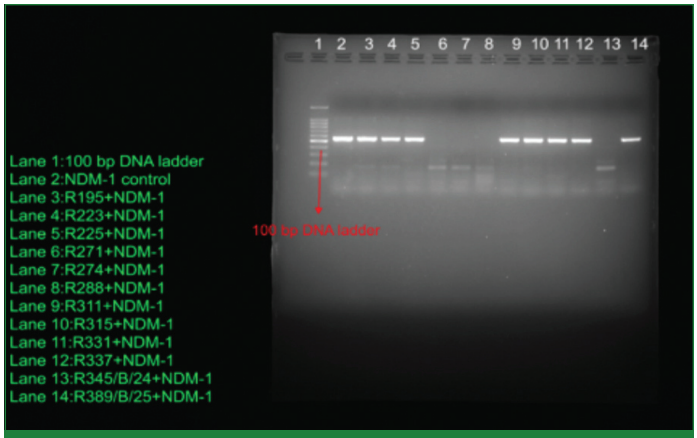
The study was done on CRE isolated from bacterial culture and sensitivity testing of respiratory samples of patients admitted to the Intensive Care Unit (ICU) and wards. Aerobic bacterial culture and sensitivity testing of respiratory samples were performed, and identification of the organism was done using the Vitek-2 compact system. Antibiotic sensitivity was interpreted using Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI M100-35th Edition) and carbapenem resistance was detected when Minimum Inhibitory Concentration (MIC) for meropenem or imipenem was ≥4 µg/mL or MIC for ertapenem is ≥2 µg/mL [15].

Genotypic method: The PCR assay detects four important genes producing carbapenemase, which include KPC, NDM-1, OXA-48, and VIM. DNA was extracted using the boiling method [16]. For each gene PCR mix was prepared as follows. 1 µL extracted bacterial Deoxyribonucleic Acid (DNA) was mixed with 1.5 µL forward primer (concentration -5 µm), 1.5 µL reverse primer (concentration -5 µm), 12.5 µL Taq PCR smart mix (that contains Taq DNA polymerase, dNTPs, Magnesium chloride and a PCR buffer), and 8.5 µL nuclease-free water. The primers used for the detection of carbapenemase genes [Table/Fig-1] [17].

Genotype	5'-3' sequence of primers	Amplicon size (bp)
NDM-1	F: CGACGATTGGCCAGCAAATG	551
	R: ACTTGGCCTTGCTGTCCTTG	
KPC	F: ATGTCACTGTATCGCCGTCT	893
	R: TTTTCAGAGCCTTACTGCCC	
VIM	F: AGTGGTGAGTATCCGACAG	261
	R: ATGAAAGTGCGTGGAGAC	
OXA-48	F: GCGTGTATTAGCTTATC	760
	R: CGCGGTTCGGTAGTGTGTTT	

[Table/Fig-1]: Primer sequences used for the detection of genotypes of carbapenemase and amplicon size.
F: Forward primer; R: Reverse primer

The PCR mix was loaded into the PCR machine and was programmed as follows. Initial denaturation at 95°C for five minutes, denaturation at 96°C for one minute, annealing at 56°C for 30 seconds, 35 cycles, extension at 72°C for one minute and final extension at 72°C for 10 minutes. PCR products were loaded after mixing with gel loading dye, along with a DNA ladder as a size marker and agarose gel electrophoresis was carried out. Electrophoresis was done at 120V for one hour, and the gel was viewed in Ultraviolet (UV) transilluminator, and the band pattern was observed. The image of the gel was interpreted, and the corresponding genotype was identified. Genotype was identified by visually comparing the molecular weight of the separated bands in the sample lanes to a DNA molecular weight ladder. Each test sample was run with a positive control for all the genes, and a non-template control was used as a negative control [Table/Fig-2,3].



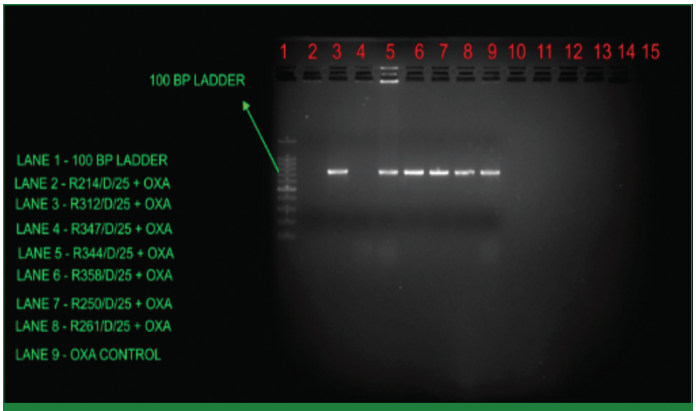
[Table/Fig-2]: The agarose gel electrophoresis showing a distinct band in the positive control (Lane 2), confirming the validity of the PCR assay. Presence of a corresponding band in test lane indicates NDM-1 positivity, while absence of a band indicates NDM-1 negativity.

STATISTICAL ANALYSIS

The data was collected, entered in Microsoft Excel 2019 and analysed using SPSS version 21.0. All variables were expressed as proportions and percentages. Associations were tested using Pearson's Chi-square test. The p-value of <0.05 was considered statistically significant.

RESULTS

Out of the total CRE isolated, 52 (41.6%) patients belonged to the 61-80 years age group. 111 (88.8%) patients were males, and 14 (11.2%) were females. 84 (67.2%) were admitted to the ICU, and 41 (32.8%) were admitted to wards and rooms [Table/Fig-4].



[Table/Fig-3]: The agarose gel electrophoresis shows a clear band in the positive control (Lane 2), confirming successful amplification of the OXA-48 gene. Presence of a similar band in test lanes indicates OXA-48 positivity, while absence of a band indicates OXA-48 negativity.

Variables	Age group (years)	Frequency (n)	Percentage (%)
Age (Years)	≤20	2	1.6%
	21-40	6	4.8%
	41-60	43	34.4%
	61-80	52	40%
	>81	22	17.6%
Gender	Female	14	11.2%
	Male	111	88.8%
Patient location	ICU	84	67.2%
	Wards and rooms	41	32.8%

[Table/Fig-4]: Demographic details of patients (n=125).

A total of 266 Enterobacteriaceae isolates were obtained from respiratory samples during the study period, of which 125 (47%) were CRE and constituted the study population. Among the 125 CRE isolates, *Klebsiella pneumoniae* was the predominant organism, accounting for 123 (98.4%) isolates, while *Enterobacter cloacae* were identified in 2 (1.6%) isolates [Table/Fig-5].

Organism isolated	Frequency (n)	Percentage (%)
Enterobacter cloacae	2	1.6%
Klebsiella pneumoniae	123	98.4%
Total	125	100.0%

[Table/Fig-5]: Shows the distribution of Carbapenem-resistant Enterobacteriaceae (CRE) (n=125).

Diabetes Mellitus (DM) was the most common comorbidity observed in this study population and was present in 30 (24%) patients, and 25 (20%) patients had Cerebrovascular Attack (CVA) [Table/Fig-6].

Co-morbidities	Frequency (n)	Percentage (%)
Diabetes Mellitus (DM)	30	24%
Cerebrovascular Attack (CVA)	25	20%
Chronic Kidney Disease (CKD)	18	14.4%
Chronic Liver Disease (CLD)	10	8%
Malignancy	12	9.6%
Chronic Obstructive Pulmonary Disease (COPD)	8	6.4%
Bronchial Asthma	2	1.6%
Tuberculosis (TB)	2	1.6%
Other pulmonary diseases	4	3.2%
No co-morbidity	14	11.2%

[Table/Fig-6]: Distribution of co-morbidities among Patients with Carbapenem-resistant Enterobacteriaceae (CRE) Infection (n=125).

Among the CRE isolates 121 (96.4%) were Carbapenemase producers. NDM-1 + OXA-48 were the most common genotype of carbapenemase detected and was found in 33 (26.4%) bacterial isolates. NDM-1 alone was detected in 28 (22.4%) isolates and OXA-48 alone was present in 28 (22.4%) isolates. NDM-1 + VIM were observed in 14 (11.2%) isolates. NDM-1 (alone and in combination with other genes) was found in 83 (66.4%) isolates. OXA-48 (alone and in combination with other genes) was present in 75 (60%) isolates. Only 4 (3.2%) of isolates showed no detectable carbapenemase gene [Table/Fig-7].

Carbapenemase gene detected in PCR	Frequency (n)	Percentage (%)
NDM-1	28	22.4%
NDM-1 and OXA-48	33	26.4%
NDM-1, OXA-48, KPC	2	1.6%
NDM-1, OXA-48, VIM	6	4.8%
NDM-1, VIM	14	11.2%
OXA-48	28	22.4%
OXA-48, VIM	6	4.8%
VIM	4	3.2%
Carbapenemase gene not detected	4	3.2%
Total	125	100.0%

[Table/Fig-7]: Types of carbapenemase gene detected in PCR (n=125).

Association between prior meropenem usage and the genotype of carbapenemase detected were not statistically significant [Table/Fig-8].

Gene detected in PCR	No previous use of Carbapenem (n=85)	Previous use of Carbapenem present (n=40)	Total (n=125)
NDM-1	22 (17.6%)	6 (4.8%)	28 (22.4%)
NDM-1 & OXA-48	19 (15.2%)	14 (11.2%)	33 (26.4%)
Carbapenemase	2 (1.6%)	2 (1.6%)	4 (3.2%)
NDM-1, OXA-48, KPC	2 (1.6%)	0 (0.0%)	2 (1.6%)
NDM-1, OXA-48, VIM	4 (3.2%)	2 (1.6%)	6 (4.8%)
NDM-1, VIM	8 (6.4%)	6 (4.8%)	14 (11.2%)
OXA-48	20 (16.0%)	8 (6.4%)	28 (22.4%)
OXA-48, VIM	4 (3.2%)	2 (1.6%)	6 (4.8%)
VIM	4 (3.2%)	0 (0.0%)	4 (3.2%)
Total	85 (68.0%)	40 (32.0%)	125 (100%)

[Table/Fig-8]: Association between previous use of carbapenems and carbapenemase genes detected by PCR among CRE isolates (n=125).
The Pearson Chi-square test was used; Chi-square value was 7.425, and the p-value was 0.492 (p-value >0.05)

There was no statistically significant association (p-value>0.05) between prior hospitalisation and the genotype of carbapenemase detected [Table/Fig-9].

Gene detected in PCR	No previous hospitalisation (n=48)	Previous hospitalisation present (n=77)	Total (n=125)
NDM-1	10 (8.0%)	18 (14.4%)	28 (22.4%)
NDM-1 & OXA-48	14 (11.2%)	19 (15.2%)	33 (26.4%)
NDM-1 & OXA-48 Not detected	2 (1.6%)	2 (1.6%)	4 (3.2%)
NDM-1, OXA-48, KPC	0	2 (1.6%)	2 (1.6%)
NDM-1, OXA-48, VIM	2 (1.6%)	4 (3.2%)	6 (4.8%)
NDM-1, VIM	8 (6.4%)	6 (4.8%)	14 (11.2%)
OXA-48	8 (6.4%)	20 (16.0%)	28 (22.4%)
OXA-48, VIM	4 (3.2%)	2 (1.6%)	6 (4.8%)
VIM	0 (0.0%)	4 (3.2%)	4 (3.2%)
Total	48 (38.4%)	77 (61.6%)	125 (100%)

[Table/Fig-9]: Association between previous hospitalisation and carbapenemase genes detected by PCR among CRE Isolates (n=125).
The pearson Chi-square test was used; Chi-square value was 9.594, and the p-value was 0.295 (p-value>0.5)

About 76 (60.8%) patients were discharged without much complications and 49 (39.2%) patients died while in the hospital.

DISCUSSION

The present study was conducted to further understand the different genotypes of carbapenemase produced by CRE causing LRTI, thereby guiding effective antimicrobial therapy. In the present study, a total of 266 isolates belonging to the family Enterobacteriaceae were isolated from respiratory samples, out of which 125 (47%) were CRE. This was concordant with the study done by Pawar SK et al., in 2018, where the percentage of CRE isolated from respiratory samples was 45% [18]. But in a study done by Thomas SK et al., in 2021, the percentage of CRE from respiratory samples was only 16.27% [19]. *Klebsiella pneumoniae* was the predominant isolate in this study and was detected in 123 (98.4%) samples, while *Enterobacter cloacae* were identified only in 2 (1.6%) isolates. This high percentage of *Klebsiella pneumoniae* was similar to a study done by Saeed NK et al., where the percentage was 87% [20].

In this study, among the total CRE isolated, 52 (41.6%) patients belonged to the age group of 61-80 years, and 43 (34.4%) belonged to the age group of 41-60 years. In a study done by Verma G et al., in Odisha, also similar result was obtained, where the majority of the CRE patients (38%) belonged to the age group of 66-80 years [21]. This finding indicates that CRE is predominantly observed in elderly patients. In this study, 111 (88.8%) patients were males, while 14 (11.2%) patients were females. This male predominance was also seen in a study done by Pawar SK et al., (65%) [18]. The male predominance may be due to other factors, like a higher incidence of comorbid conditions like CLD in male patients. In this study, 84 (67.2%) patients were admitted to the ICU, and 41 (32.8%) were admitted to wards and rooms. A similar observation was also seen in a study done by Pawar SK et al., where 60% of the CRE patients were admitted to the ICU [18]. There is a high chance of invasive procedures in the ICU, which would have contributed to the increased incidence of CRE in the ICU. DM was the most common co-morbidity and was observed in 34 (24%) study participants, and 25 (20%) patients had CVA. CKD was present in 18 (14.4%) patients. A similar observation was made in a study done in Palestine by Igbinosa O et al., in which DM was the most common co-morbidity (31.5%), followed by CKD (29.8%) [22]. DM and CKD can compromise a patient's immune system, making them vulnerable to severe infection from MDR organisms like CRE.

In this study, 121 (96.8%) CRE isolates were carbapenemase producers, and 4 (3.2%) were non-carbapenemase producers. This high percentage of Carbapenemase-producing CRE is alarming, due to their dissemination into various bacteria and the limited treatment options available. The most common genotype of carbapenemase observed in this study was NDM-1 + OXA-48 and was detected in 33 (26.4%) isolates, followed by NDM-1 alone 28 (22.4%) and OXA-48 alone 28 (22.4%). This was similar to a study done in South India by Appalaraju B et al., in which NDM-1 + OXA-48 genotype was the most predominant one (37%), followed by OXA-48 alone (31%) and NDM-1 (25%) [13]. According to a study done in China by Zhu X et al., KPC was the most predominant genotype (61.25%) while NDM (32.5%) was the second most common genotype.

. This finding was in contrast to the present study, and the reason may be due to the fact that the prevalence of genotypes varies with geographical location. NDM-1 (alone and in combination with other genes) was found in 83 (66.4%) isolates. OXA-48 (alone and in combination with other genes) was present in 75 (60%) isolates. This finding was slightly different from the study done by Joshi DN et al., in South India, in which OXA-48 (84.5%) was the most predominant genotype obtained, and NDM (58.6%) was the second most common genotype [5]. In another study done by Baran I and Aksu N in Turkey, OXA-48 was the most predominant genotype (47.5%), and NDM was seen in a very small percentage (3.33%) [24]. This shows the difference in the existence of genotypes of carbapenemase across different geographical areas. In 3.2% of isolates, there was no detectable carbapenemase gene, indicating that 3.2% of the isolates were non-carbapenemase producing CRE. The carbapenem resistance mechanism in this non-carbapenemase producing CRE may be due to altered porin expression, efflux pump mechanisms or decreased permeability of the cell membrane.

There are two main clinical implications and future perspectives for this study. One is that, based on the results of this study, further multicentric studies can be done in a region. After finding out the common genes responsible for carbapenemase production in a region, empirical treatment guidelines for CRE can be formulated. The other one was that by calculating the prevalence of CRE causing LRTI in different locations, like the ICU, and comparing with the previous data, infection control activities can be evaluated. Also, infection control measures can be revised whenever needed.

Limitation(s)

The main limitation of this study is that it is purely a hospital laboratory-based study. Since the patients coming to this hospital were not a representative sample of the overall population, the results obtained cannot be generalised. Another limitation of this study is that the authors have done a study on CRE isolated from respiratory samples only. So the results obtained will be different from other samples.

CONCLUSION(S)

Since CRE has become more common in hospitals in recent years, infection prevention and effective treatment depend on the prompt diagnosis of CRE, particularly carbapenemase-producing CRE. The high prevalence of CRE causing LRTI found in this study is alarming, which indicates infection control measures should be strengthened further. In this study, NDM-1 and OXA-48 genotypes were obtained in high percentages and this evidence can be useful for further studies. Thereby, formulation of effective empirical treatment guidelines can be done and ultimately reduce the adverse effects caused by these MDR organisms.

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