Journal of Disease and Global Health

Volume 17, Issue 1, Page 15-22, 2024; Article no.JODAGH.12152
ISSN: 2454-1842, NLM ID: 101664146

Screening of Carbapenem-Resistant Enterobacteriaceae (CRE) in Stool Samples in Hospitalized Patients: A Study from a Tertiary Care Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.56557/jodagh/2024/v17i18722

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://prh.ikprress.org/review-history/12152

Original Research Article

Received: 26/03/2024
Accepted: 31/05/2024
Published: 06/06/2024

ABSTRACT

Background: Infection with Carbapenem-Resistant Enterobacteriaceae (also known as CRE) is being more recognized as a significant obstacle in healthcare settings and is a global cause for worry.

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Cite as: *Kashyap, Sanchi, Monika Matlani, Santhosh Rajan, Divya, and Vinita Dogra. 2024. "Screening of Carbapenem-Resistant Enterobacteriaceae (CRE) in Stool Samples in Hospitalized Patients: A Study from a Tertiary Care Hospital". Journal of Disease and Global Health 17 (1):15-22. https://doi.org/10.56557/jodagh/2024/v17i18722.*

Aims: This surveillance study was undertaken to investigate the prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) in the faecal samples of inpatients admitted to a tertiary care hospital in Delhi, India.

Methods: In this prospective study, which was carried out over the course of 8 months (from February 2019 to September 2019), we screened 398 Enterobacteriaceae isolates for carbapenemase from the stool samples of 353 inpatients admitted to a tertiary care hospital in Delhi.

Results: Of the total of 398 Enterobacteriaceae isolates screened, 56 (14.08%) of the isolates demonstrated carbapenemase activity. The prevalence of CRE was found to be highest in *E.coli* (15.23%) followed by *Klebsiella pneumoniae* (13.71%).

Conclusions: Screening for the presence of CRE in the faeces of patients can serve as a helpful guide for doctors in determining whether or not a patient's gut is colonized by multidrug-resistant Enterobacterales. This is especially important in patients who are at possible endogenous infection risk. This includes patients who are undergoing any gastrointestinal surgical process, patients with haematological malignancies who are receiving chemotherapy, and patients who have had a bone marrow transplant planned for them.

Keywords: Carbapenem-resistant enterobacteriaceae; carbapenem; carbapenemase; haematological malignancies.

ABBREVIATIONS

CAZ : Ceftazidime
CRE : Carbapenem-Resistant Enterobacteriaceae
CP-CRE : Carbapenemase Producing-CRE
CDC : Centre for Disease Control and Prevention
CDST : Combined disk synergy test
DDST : Double disk synergy test
eCIM : EDTA-modified carbapenem inactivation method
ICU : Intensive Care Unit
IPM : Imipenem
IPM-EDTA : Imipenem- Ethylenediamine tetra acetic acid
mCIM : Modified Carbapenem Inactivation Methods
MBL : Metallo-beta-lactamase
VMMC : Vardhman Mahavir Medical College

1. INTRODUCTION

CRE are being increasingly being reported throughout the world. They cause significant problems in patient treatment and hospital infection control [1-3]. Enterobacteriaceae that the has determined to be resistant to at least one of the carbapenem antibiotics (Meropenem, Ertapenem, Imipenem, or Doripenem) or that produce a carbapenemase are classified as CRE (CDC) [4].

The development and spread of carbapenem resistance among Enterobacteriaceae possess a significant risk to the general population's health. These organisms are the root cause of diseases that carry a high risk of mortality & morbidity and have the capacity to quickly spread to a wide variety of environments. Because of the potential impact of these organisms on hospital patients, a concerted effort and the participation of all relevant stakeholders, including healthcare institutions, healthcare professionals, the public healthcare system, and the pharmaceutical sector, will be required.

Enterobacteriaceae is a family of bacteria that most commonly colonises the normal human intestines but can also colonise other parts of the body. In immunocompromised patients, particularly children, colonization of the gastrointestinal tract with CRE strains can be a risk factor for bacterial translocation, which can result in subsequent endogenous infections [3].

The global spread of CRE has led to an increase in the number of seriously ill patients with multiple risk factors like continuous intravenous catheter, admission to intensive care units (ICU), and the presence of malignancies and has left us

with minimal therapeutic options. This results in the building up of a potentially endogenous reservoir in the human gut with simultaneous resistance to carbapenems which poses a serious threat to the inhabitants [3,5-7]. In the last 10 to 15 years, it has been seen that asymptomatic faecal carriage of CRE leads to the introduction and beginning of many nosocomial infections [8,9]. A long-term exposure to antibiotics, a protracted hospital stay, the use of a continuous intravenous catheter, admission to intensive care units (ICU), and the presence of malignancies are all factors that have been linked to CRE faecal carriage [3,8-11].

Antibiotic abuse as well as poor hygiene as well as sanitation in the areas of urban slums can cause the fast proliferation and broad-scale carriage of multidrug-resistant or pan-drug-resistant isolates in the gut microbiota, which could represent a possible source of both infections of exogenous as well as endogenous [12-29].

Thus, this prospective surveillance study was performed over a period of eight months to calculate the carriage of CRE isolates through sampling of the stool of admitted patients from a tertiary care centre of New Delhi, India. Carbapenemase carriage by CRE isolates was determined irrespective of the symptoms of the patient or any type of history of taking antibiotic therapy in the present or in the past.

2. MATERIALS AND METHODS

i. Study Design

This prospective laboratory investigation was carried out over the course of eight months, beginning in February 2019 and continuing till September 2019, at the Microbiology Laboratory of VMMC and Safdarjung Hospital, located in New Delhi.

ii. Sample Size

A total of 353 in-patients admitted to the hospital from Feb to Sep 2019 have been taken up for the research.

The sample size has been calculated based on the formula

$$S = \frac{1.96 \times 1.96\ P\ (1\text{-}P)}{L^2}$$

Where

S=Sample size
P = Estimated prevalence
L = Margin of error at 5%
Taking P = 35 % [7]

Sample size was calculated as ~ 350, we are taking sample size as 353.

iii. Inclusion Criteria

Patients of all age groups who were admitted in the ICU and gave informed written consent (self/attendant) were included in the study.

iv. exclusion Criteria

Patients who were unable to have stool samples collected, including paediatric patients (<5 years), post-operative patients, and patients in the Surgical ICU, were not included in the study.

V. Definition of CRE

CRE refers to a group of Enterobacterales that either has been shown to be resistant to at least one of the carbapenem antibiotics (Meropenem, Ertapenem, Imipenem, or Doripenem) or form a carbapenemase [4].

Vi. Specimen Collection and CRE Screening

To collect stool samples, a universal container with a wide mouth and a screw top was used. The samples were then transported to the microbiology laboratory within 2 hours of collection. A gross examination of the samples of stool was done to rule out the presence of any parasitic infestation. Saline and Lugol's iodine mounts were made for stool sample microscopy. The samples of stool have been cultured on MacConkey agar (HiMedia, India) and Deoxycholate citrate agar (HiMedia, India). The culture plates have been incubated at 37°Celsius for the time of 18-24 hours [13].

A total of 398 isolates were identified as a member of the Enterobacteriaceae family by conventional methods. The various gram-negative bacteria of the Enterobacteriaceae family which were isolated from a single faecal sample were included in the study. Subsequently, 1 to 3 various Enterobacterales isolates per sample have been screened for carbapenem resistance. The Kirby Bauer disc diffusion method was utilized in order to

determine whether or not the isolates exhibited antibiotic resistance for Meropenem (10μg), Ertapenem (10μg), Imipenem (10μg), or Doripenem (10μg). Isolates resistant to one or more carbapenems disks were considered CRE screen positive.

Vii. CRE Confirmatory Test

Carbapenemase activity was determined by Modified Carbapenem Inactivation Methods (mCIM) as per Clinical and Laboratory Standards Institute M100 document [14].

Viii. Differentiation Between Serine and MBL Carbapenemase

The activity of carbapenemase was evaluated using Modified Carbapenem Inactivation Methods (mCIM), and EDTA-modified carbapenem inactivation method (eCIM) which was performed in the Clinical and Laboratory Standards Institute M100 guideline [15].

i. Imipenem- EDTA Combined disk synergy test (CDST-IPM) [15]

2 IPM (10μg) disks have been placed on an agar plate surface and 10 EDTA solution has been added to one of them to attain the required concentration of 750μg. At a 35°C temperature, the plates were kept warm for 16 to 18 hours. It is determined to have MBL if the inhibition zone of the IPM-EDTA disc was at least ≥ 7 mm greater than a disc of Imipenem alone.

ii. "**Imipenem- EDTA Double disk synergy test (DDST-IPM)** [15]

An IPM (10μg) disc was placed 20 mm center to center from a blank disc containing 10 μL EDTA (750μg). At a temperature of 35°C, the plates were kept warm for 16" to 18 hours. It was determined to be positive for MBL if there had been an improvement of the inhibition zone among the IPM and the EDTA disc.

Interpretation: DDST-IPM: Improvement of the zone of IPM towards EDTA.

iii. Ceftazidime- EDTA Combined disk synergy test (CDST-CAZ) [15]

The methods and explanation are the same as the CDST-IPM technique, with the exception that ceftazidime (30 μg) discs is used instead of imipenem.

Interpretation: CDST-CAZ: The zone of inhibition of CAZ+EDTA disc is ≥ 7mm than that of the CAZ disc alone.

iv. Ceftazidime - EDTA Double disk synergy test (DDST-CAZ) [15]

Methods and explanation are similar to the DDST-IPM technique except utilizing a Ceftazidime (30 μg) discs in place of IPM.

Interpretation: DDST-CAZ: Enhancement of zone of CAZ towards EDTA.

3. RESULTS

A total of 353 patients admitted in wards and ICU were screened for CRE carriage over a period of 8 months. Of the 353 stool samples cultured, a total of 398 Enterobacteriaceae isolates have been acknowledged using conventional approaches. A total of 56 CRE isolates have been obtained giving a CRE faecal carriage rate of 14.08 %. The majority of the carbapenem resistance was detected in *Escherichia coli* (15.23%) followed by *Klebsiella pneumoniae* (13.71%) (Table 1). No resistance was detected in other genera of the Enterobacteriaceae family like *Proteus spp & Enterobacter spp*.

CRE carriage was higher in admitted adult patients (67.8%) in comparison to the admitted paediatric patients (32.14%). Co-morbid conditions observed in the admitted patients were chronic lung disease (n = 12), chronic renal disease (n = 6), cardiovascular illness (n = 4), immunosuppression (n = 10), use of surgical procedure (n = 15) and neoplasia (n = 9).

The screened positive isolates were subjected to a modified carbapenem inactivation method test. It was found that 89.2% (50/56) of the screened positive isolates were positive by mCIM which means that the carbapenem resistance was due to Carbapenemases. When these were further tested for eCIM, it was found that 83.9% (47/56) isolates had resistance due to Metallo-Beta-Lactamases type of Carbapenemases. Other disc synergy tests were also performed (Table 2).

Utilizing an IPM as a substrate, 46 (82.1%) isolates have been MBL-positive by CDST, and 40 (71.4%) isolates were MBL-positive by DDST. Imipenem- EDTA Combined disk synergy test was able to pick up maximum CRE (82.1%) isolates. Using Ceftazidime as substrate,

42 (75%) isolates were MBL positive by CDST as well as 24 (42.8%) isolates were MBL positive by DDST. Thus, the Imipenem- EDTA Combined disk synergy test was able to pick up the maximum number of MBL-producing CRE.

All CRE isolates were sensitive to Colistin but showed resistance to other antibiotics tested such as Cefotaxime, Ciprofloxacin, and Gentamicin (Table 3).

4. DISCUSSION

The appearance and proliferation of CRE have resulted in a crisis in the health of the public on a global scale [16]. Screening contacts of Carbapenemase Producing-CRE (CP-CRE) infected patients is essential to curb CRE transmission and control outbreaks.

Colonization of the gut with CRE is linked to an increased occurrence of clinical infections in the host, which might potentially lead to the spread of infection to other patients. Once they have been brought into a hospital, they do not leave the environment for an indeterminate amount of time and are extremely challenging to remove [17]. Therefore, recognizing potential carriers at an early stage and isolating them are two of the most important components of an efficient infection management approach [18]. In addition, the detection of the incidence of CRE in the intestine will help in the establishment of an antibiotic policy for sepsis management as a consequence of major surgery of the gut or in patients who are dealing with haematological malignancy receiving chemotherapy or with transplantation of bone marrow [19]. There is not a lot of research done in India that concentrates on the amount of CRE that can be found in stool samples.

This information was taken into consideration when planning the current study, which aimed to investigate the prevalence of faecal CRE isolates among the patients, admitted to a tertiary care hospital in the city of New Delhi.

Table 1. Prevalence of CRE in stool samples

	E.coli	***Klebsiella pneumoniae***	***Proteus mirabilis***	***Enterobacter spp***	**Total**
Isolates	210	175	7	6	398
CRE screening positive	32	24	0	0	56
%	15.23	13.71	0	0	14.08

Table 2. Comparison of various MBL detection methods

Screening positive	**mCIM**	**eCIM**	**CDST-IPM**	**DDST-IPM**	**CDST-CAZ**	**DDST-CAZ**
56	50	47	46	40	42	24
%	89.2	83.9	82.1	71.4	75	42.8

Table 3. Antibiotic susceptibility pattern of CRE strains

Antibiotic	**Number of resistant *E coli* (n =32)**	**Percentage (%)**	**Number of resistant *Klebsiella pneumoniae* (n = 24)**	**Percentage (%)**
Amikacin (30 µg)	30	93.7	22	91.6
Cefotaxime (30 µg)	32	100	24	100
Cefotaxime (30 µg)	32	100	24	100
Ciprofloxacin (5 µg)	32	100	24	100
Colistin (Broth Micro-dilution)	0	0	0	0
Gentamicin (10 µg)	32	100	24	100
Meropenem (10 µg)	32	100	24	100

******* *All CRE strains were sensitive to colistin.*

Our study showed that the prevalence of CRE in stools was 14.08 % (56/398), and the most common isolate was *Escherichia coli.* Similar results were observed by Ravikant et al*.,* 2019 (10.8%) [20], and Datta P et al*.,* 2015 [21] who reported a CRE gut colonization of 11%.

This study showed a slightly higher prevalence of CRE in stool samples in comparison to the other studies [22,23]. The reason for this might be due to the bigger sample size in the current study.

According to our findings, *Escherichia coli* had the highest number of carbapenem-resistant isolates (57.14 %, 32/56), followed by the species *K. pneumoniae* (42.8 %, 24/56). Mohan B et al*.,* 2017 [7] and Dandachi I et al*.,* 2016 [24] in Lebanon both came to findings that were very similar to ours. Both of these groups of researchers are from India.

The present study showed that 89.2% (50/56) of the isolates were Carbapenemases producers, all being positive by mCIM. In those isolates that are mCIM negative, carbapenem resistance might be the reason for the existence of porin channels or efflux pumps [25]. Screened positive isolates when tested for eCIM showed that 83.9% (47/56) isolates were resistant due to the production of Metallo-Beta-Lactamases type of Carbapenemases. Thus, in the remaining (3/50) screened positive isolates, carbapenem resistance may have been due to the serine group of Carbapenemases [14].

Utilizing an IPM as a substrate, 46 (82.1%) isolates were MBL positive by CDST and 40 (71.4%) isolates were MBL positive by DDST. Imipenem- EDTA Combined disk synergy test was able to pick up maximum CRE (82.1%) isolates. Using Ceftazidime as substrate, 42 (75%) isolates were MBL positive by CDST and 24 (42.8%) isolates were MBL positive by DDST. Thus, Imipenem- EDTA CDST has been able to pick up maximum MBL-producing CRE. Similar results were seen in studies by Nirav Pandya et al*.* 2011 [15] and Hemant et al*.* 2018 [26]. Therefore, the CDST-IMP synergy test is a useful screening tool that can be used to diagnose CRE carriage in the stool of hospitalized patients who are going to undergo elective or emergency gastrointestinal surgical techniques, patients who are dealing with the haematological malignancies who are receiving chemotherapy, or patients who are going to have bone marrow transplantation. This study could be of great help in planning an appropriate prophylactic antibiotic to be started as and when required, so as to prevent the increasing drug-resistance in the gastrointestinal isolates which are possible sources for endogenous infection.

5. CONCLUSION

The current research conducted in India found a prevalence of CRE faecal carriage among hospitalized patients to be 14.08 %, which is considered to be a moderately high incidence. Active surveillance of CRE carriage is something that must always be done in individuals who are undergoing elective or emergency gastrointestinal surgical techniques and who are already known to have immunocompromised conditions. It is important to keep in mind important factors like proper practice hygiene of hand, contact precautions, and appropriate antibiotic use when taking infection control measures, as this is an effective strategy for reducing the occurrence of infections caused by life-threatening microorganisms. Infection control measures should be implemented.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The institutional human ethics committee of the hospital gave approval to the study's proposed direction.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://prh.ikprress.org/review-history/12152