

## RISK FACTOR AND PREVALENCE OF CARBAPENEM NON-SUSCEPTIBLE ENTERBACTERIACEAE AT A TERTIARY CARE HOSPITAL, INDORE

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### Abstract

**Background:** Carbapenem resistant enterobacterales is an alarming concern globally, as they are non-susceptible to most available antibiotics. However, various attempts to make a proper regimen of treatment of such infections are needed. Therefore researches are going on to better understand the CRE related infections, mechanisms of resistance and prevalence around the world. Studies have found correlations of underlying conditions, extreme ages, old history of strong antibiotic exposure and severe infections as some common risk factors. The knowledge on risk factors and prevalence should be known to further control it. **Materials and Methods:** In this cross-sectional study, 145 Carbapenem resistant Enterobacterales were isolated from various samples based on inclusion and exclusion criteria at a tertiary care hospital in Indore. The isolates were taken from 81 male and 64 female patients. **Result:** The isolated CRE organisms were studied for risk factors and prevalence. Increased prevalence seen compared to previous studies done from this area. Among different samples CRE isolated from blood stream infections were associated with bad clinical outcomes which recovered from combination therapy. **Conclusion:** CRE infection is related to worsening the condition of disease in patients. We conclude that prevalence of CRE among the patients was 24.8% which was seen slightly more in males as compared to females. Risk factors to CRE were found to be previous use of broad line antimicrobials, prolonged stay in hospitals and patients with compromised immune status.

## INTRODUCTION

An emerging health concern worldwide is the Carbapenem non-susceptible infections with limited treatment options and increasing spread. CDC has put CRE as global threat because of high morbidity and mortality.<sup>[1]</sup> Various studies done in India show prevalence of 15- 31 % and a high socioeconomic burden on patients who are infected with CRE due to high treatment costs.<sup>[1,5,10]</sup> Carbapenems are used in treatment practices due to the broad spectrum activity on life threatening infections and now along the years organisms have become resistance to these lifesaving drugs and still continue.<sup>[6]</sup> There are limited options available for treatment because of resistance to certain antibiotics like fluoroquinolones, aminoglycosides and beta lactams. Compared to susceptible carbapenem strains these carbapenem resistant isolates lead to lengthy hospital stays and mortality.<sup>[8]</sup> Different

levels of resistance makes it difficult to detect these organisms. Prevalence of Carbapenem resistant gram negative organisms varies depending on regions. Infections of *Pseudomonas* and *Acinetobacter baumannii* are more prevalent in middle east and the US while studies done in India show resistance by Enterobacteriaceae.<sup>[6]</sup> All hospitals where CRE is isolated should modify antibiotic policy and focus on timely identification which will further help in suitable treatment.<sup>[3]</sup> CRE in patients should be detected early which can contain further spread and reduce the patient cost burden.<sup>[6]</sup> The present study was done to understand associated risk factors and prevalence of CRE.

## MATERIALS AND METHODS

### Location

In the present study, patient samples received in Department of microbiology, Index medical college

hospital and research centre, Indore were included based on inclusion and exclusion criteria. The samples will be processed for growth and biochemical testing to identify the organism isolated.

#### Study Design

This is a cross sectional study. A detailed history of patients is taken and details of any change in antibiotic course during treatment after carbapenem resistance isolates reported was noted. An informed consent form filled by all study participants was taken.

#### Selection criteria:

##### Inclusion criteria

All Enterobacteriaceae isolated from samples that show resistance to atleast one carbapenem (ETP, MRP and IMP) will be included.

##### Exclusion criteria

Enterobacteriaceae not showing resistance to any carbapenem and duplicate isolates from samples collected from same patients by different sites will be excluded.

Clinical samples were cultured on Blood and MacConkey agar and incubated at 37°C for 24 hours. Isolates were gram stained and gram negative rods were further subjected to biochemicals of IMViC panel. ATCC strains were used as quality control for comparison.

#### Antibiotic sensitivity testing:

AST performed according to CLSI guidelines by Kirby bauer disc diffusion method on Mueller hinton agar using 0.5 Mcfarland to adjust turbidity of inoculums. Resistance shown by isolated to one of the carbapenem with the susceptibility zones, 22mm, 23mm, 23mm and 23 mm respectively are identified as resistant to carbapenem.

All Enterobacteriaceae isolated from samples that show resistance to atleast one carbapenem (Ertapenem, Imipenem and Meropenem).

Carbapenem phenotypic analysis done by different enzymatic methods.

#### Ethical Clearance

The research study received ethical clearance from the Ethics and Research Committee of Index Medical College Hospital & Research Centre in Indore, Madhya Pradesh.

## RESULTS

Out of 583 Enterobacteriaceae isolates, 145 showed carbapenem resistance. The 145 culture positive CRE isolates belonged from 64 urine samples, 42 blood samples, 21 pus samples and 13 from sputum and 5 body fluids. These isolates were identified from ICU wards and OPD patients. Out of them, 81 isolates were from male's patients and 64 from female patients. Most predominant carbapenem non-susceptible Enterobacteriaceae isolated were Klebsiella pneumoniae (47%), Escherichia coli (28%), Citrobacter freundii(15%) followed by Proteus spp(8%). The various areas CRE was isolated from Intensive care units (54.4%), Wards (39.3%) and OPDs (6.2%). The highest number of resistance to colistin (15%) was seen in Klebsiella pneumonia isolated from inpatients. One patient died within 7 days of admission in whom carbapenem resistant Klebsiella pneumoniae was isolated from blood having underlying pneumonia as comorbidity. Our study found colistin was seen resistant in this patient by both BMD and E test.

**Table 1: Distribution of CRE by age gender wise**

Gender	Total	Percentage
Male	81	
0-15 year	3	3.7%
16-30 year	10	12.4%
31- 45 year	14	17.4%
46-60 year	46	56.7%
Above 60 year	8	9.8%
Female	64	
0-15 year	1	1.5%
16-30 year	9	14.1%
31- 45 year	17	26.6%
46-60 year	31	48.4%
Above 60 year	6	9.4%

**Table 2: Carbapenem resistant Enterobacteriaceae isolated from different areas of the hospital**

Location	Total Enterobacteriaceae isolated	CRE isolates	Percentage
ICU	389	117	30.0%
Wards	103	20	19.4%
OPD	91	8	8.7%

**Table 3: Risk factors**

	Factors	Result
1.	Age	
	Pediatric( less than 16 yrs)	10(6.8%)
	Adult(17- 60 yrs)	121(83.4%)
	Old age(above 60yrs)	14(9.6%)
2.	Gender	

	Male	81(55.8%)
	Female	64(44.1%)
3.	Infection	
	Polymicrobial	37(25.5%)
	Monomicrobial	108(74.4%)
5.	Immunocompromised status	
	COPD	14(9.6%)
	Heart disease	6(4.1%)
	Diabetes	28(19.3%)
	Liver disease	8(5.5%)
	CKD	7(4.8%)
	Pneumonia	8(5.5%)
6.	Previous carbapenem exposure	96(66.2%)

## DISCUSSION

Carbapenem resistant Enterobacteriaceae is becoming prevalent globally with high mortality rate. These strains make the clinical management worse having a mortality of 28-70%.<sup>[5,9]</sup> The associated risk factors include previously treated patients with carbapenems, having medical diseases like chronic pneumonia/ lung conditions, frequent hospitalization, long admission in ICU's, extreme age and wide range of antibiotics used for primary treatment and severe neurologic diseases.<sup>[2,4,11]</sup> Our study showed these similar factors as risk factors for CRE apart of the only difference being that CRE was not mostly associated to older age group but depends on various other factors like previous hospitalization etc. and these organisms were isolated from previously treated patients having polymicrobial infection who had been treated with broad spectrum antibiotics. This study showed high carbapenem resistance in patients with underlying conditions.

In a study done for five years by Modi CM et al. in Gujarat, India showed CRE prevalence of 29%. The isolation of these organisms were from different units like critical care 49%, wards 38%, emergency trauma centres 6% and OPD's 1%. There is increase in Carbapenem resistance strains compared to previous years.<sup>[5]</sup> The present study found prevalence of 25% and CRE isolation was higher in ICU's (30%) followed by wards(19%) and OPD's(8.7%).

Studies done by Joshi DN et al. , Modi CM et al. , stated that the commonest organisms among CRE were Klebsiella pneumoniae (93%), (51%) followed by Escherichia coli (6%),(31%),<sup>[1,5]</sup> similarly our study also found that Klebsiella pneumonia (47%) being the predominant organism followed by E. coli (28%). Among all the different genes isolated in indian regions NDM and OXA- 48 gene together was found highest in most strains of K. Pneumoniae and a study done by Thomas N et al. stated Escherichia coli to be the most predominant CRE.<sup>[1,6]</sup>

A study done in Noida, India by Thomas N et al. Showed CRE were commonly isolated from men (54%) compared to women (46%) compared to our study that also concluded concordance that a slight higher isolation of these organism was seen in males

(55.8%) compared to females (44.2%). CRE cases were primarily obtained from urine samples and the probable reason given was that it can be due to patients admitted to hospitals have high chance of contracting urinary tract infection.<sup>[6]</sup>

Our study showed similarity with studies done by Barber KE et al. in which patients that were previously exposed to certain antibiotics like flouroquinolones, beta lactams and CRE isolated in patients having old exposure to levofloxacin. Continuous use of antimicrobials for treatment of these resistant strains and less methods known for early detection of infection by CRE leads to its spread.

We found these CRE isolated from urine sample (49%), Pus (24.1%), Blood (17.2%) Sputum (5.5%) and Endotracheal sample (4%). BSI from these organisms was difficult to treat. In a study done by Thomas N et al. CRE was predominantly isolated from urine samples (52%), Pus (20%), Stool (11%), Sputum (10%) and other samples (6.25%).<sup>[6]</sup>

## CONCLUSION

Our study found previous exposure to third line antibiotics, patients with comorbidities having a strong association in developing these CRE infections in patients. A proper intervention to improve the antimicrobial distribution across immunocompromised patients having underlying disease should be monitored closely. CRE phenotypic isolation in blood stream infections should be included in general antibiotic susceptibility testing protocols.

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