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Phenotypic detection of Carbapenemase production by combination of Modified Carbapenem inactivation method (mCIM) and EDTA- Carbapenem inactivation method (eCIM) among carbapenem resistant Enterobacterales at a tertiary care teaching hospital of Southern Rajasthan, India

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ABSTRACT

Background: Infections caused by Carbapenem resistant organism are well acknowledged for their detrimental effects on both healthcare facilities and patients. These effects include rise in mortality rates, prolonged hospital stays, and increased financial expenses. In addition to this, inappropriate treatment regime worsens the problem of antimicrobial resistance. Carbapenemase production is the most common mechanism of carbapenem resistance, so rapid detection of carbapenemase production is essential to initiate appropriate treatment and to implement appropriate infection control practices to prevent further dissemination. In this study we aimed to identify the carbapenemase producing Enterobacterales by phenotypic methods i.e modified carbapenem inactivation method (mCIM), EDTA- Carbapenem inactivation method (eCIM).

Methodology: It was a cross sectional study and data was collected over a period of 8 months in the Department of Microbiology, in a tertiary care teaching hospital of Southern Rajasthan.100 clinical isolates which were resistant to one of the carbapenems (imipenem, meropenem or ertapenem) by Kirby-Baurer disk diffusion method were included in the study. All these isolates were subjected for carbapenemase detection by phenotypic methods i.e modified carbapenem inactivation method (mCIM) and EDTA- carbapenem inactivation method (eCIM) and the result were analysed to find out carbapenemase production as per CLSI 2023.

Results: Among 100 CRE isolates, 66% were Klebsiella pneumonia followed by Escherichia coli i.e 34%.Out of these 100 CRE isolates, 94% isolates were mCIM test positive, from which 62% isolates were eCIM test positive. 59%of the total isolates tested were Metallo β-lactamase producers and 35% were serine β–lactamase producers.

Conclusion: we would like to conclude that performing mCIM and eCIM methods on carbapenem-resistant isolates as a routine can help clinicians to choose most appropriate treatment regime. Timely identification and the implementation of effective infection prevention and control measures are crucial in reducing the prevalence of carbapenem-resistant Enterobacterales (CRE) among patients.

Keywords: *Carbapenem resistant Enterobacterales,Modifiedcarbapenem inactivation method,EDTA- carbapenem inactivation method, Carbapenemase production, Metallo β-lactamase producers, serine β–lactamase producers.*

1. INTRODUCTION

Carbapenem-resistant Enterobacteriales (CRE) have emerged as a significant cause of antimicrobial resistance in healthcare-associated infections, leading to considerable morbidity and mortality and has become a matter of serious concern worldwide among patients.[1–3]

Carbapenems, including meropenem, imipenem, ertapenem, and doripenem, are effective in treating multi-drug-resistant (MDR) gram negative bacterial infections due to its broad spectrum activity, so considered as antibiotics of choice for

critically ill patients. However, these bacteria quickly develop resistance to carbapenems even after being sensitive to them. This rapid development of resistance and the dissemination of these bacteria in hospital settings as well as in community is a matter of universal concern.[4–7]

Enterobacterales can resist the action of carbapenems through various mechanisms, the most common being the production of carbapenem-hydrolyzing enzymes (carbapenemase). These enzymes are classified as classes A, B and D beta-lactamases that hydrolyze carbapenems and render them inactive against these bacteria. Other mechanisms include the alteration of porin channels and efflux pumps that expel the drug, enabling them to survive under carbapenem treatment.

Carbapenemases are generally divided into two categories: Metallo-β-lactamases (MBLs) and serine carbapenemases. MBLs depend on zinc ion for their action and EDTA being a chelating agent, can prevent their enzymatic activity.[7,8]Furthermore, genes that mediate carbapenemase production are often located on transferable plasmids, giving them the potential to spread rapidly. Hence, infections caused by carbapenemase-producing Enterobacterales are difficult to manage once they emerge and spread in health care settings.[3,7]

Therefore, detection of carbapenemase production is crucial for starting appropriate treatment, and for implementation of infection control practices so as to prevent the further spread of the bacteria. Though, molecular methods are considered as the gold standard for detecting carbapenemase enzyme production. But, these methods are expensive and not available in resource constraint settings.Clinical and Laboratory Standards (CLSI), also recommends detection of carbapenemase production by performing phenotypic tests: i.e mCIM, eCIM.

The newer generation of β-lactamase inhibitors compounds such as ceftazidime avibactam and meropenem vaborbactam are effective against serine carbapenemase producers but not against Metallo-β-lactamase producers as they need combination therapies, such as ceftazidime-avibactam with aztreonam, as well as tigecycline, aminoglycosides, and colistin. So,detection and differentiation between the two classes of carbapenemase is important.[2,9]

The mCIM and eCIM tests are cost-effective, and differentiates between serine beta-lactamases and metallo-beta-lactamases, which in turn proves helpful in selecting appropriate treatment options and implemention of appropiate infection control measures to curtail the spread of carbapenemase producing bacteria in hospital set up's. This will also help especially the resource poor laboratories where molecular methods are not readily available. so, it is advisable to microbiology laboratories to perform mCIM and eCIM phenotypic methods for carbapenemase detection.

Keeping this background in mind our study aimed to detect Carbapenemase production in Carbapenem resistant Enterobacterales using combination of the modified carbapenem inactivation (mCIM) and the EDTA-Carbapenem inactivation (eCIM) phenotypic methods.

These findings will be valuable in selecting appropriate empirical therapy, developing effective antibiotic policies, updating local antibiotic guidelines for healthcare professionals, and identifying cases of clinical treatment failure.

2. MATERIALS AND METHODS

This cross sectional study was carried out in the Department of Microbiology at a tertiary care teaching hospital of Udaipur, Rajasthan for the period of eight months after obtaining ethical clearance from the institutional ethical committee.

A total of 100 clinical isolates of Carbapenem resistant Enterobacterales (CRE) were included in the study,comprising of Klebsiella pneumoniae (66 out of 100) and Escherichia coli(34 out of 100). These isolates were resistant to at least one of the carbapenems (imipenem, meropenem or ertapenem) by Kirby-Baurer disk diffusion method as per CLSI guidelines M100 33rd edition 2023[10].

- These carbapenem resistant isolates were further subjected to (mCIM) and EDTA- carbapenem inactivation method (eCIM) phenotypic testsas per CLSI guidelines M100 33rd edition 2023. When mCIM test yielded a positive result, then only eCIM was conducted to differentiate between metallo-β lactamases(MBL)and serine β - lactamase enzyme.
- Modified carbapenem inactivation method in conjugation with the EDTA-carbapenem inactivation method: mCIM and eCIM were performed on CRE isolates according to the CLSI guidelines to detect the presence of carbapenemase . In brief, a 1-µL loopful of test bacterial inoculum was resuspended in a 2-mL tube of TSB. Another 1-µL loopful of test bacteria was resuspended in a 2-mL tube of TSB supplemented with EDTA at a final concentration of 5 mM (addition of 20 µL of 0.5M EDTA to 2mL of TSB). A meropenem disk was placed in each tube, and the tubes were incubated at 35°C for 4 h. Subsequently, the disks were removed and applied to MH agar plates, which were freshly plated with a 0.5 McFarland suspension of a carbapenem-susceptible Escherichia coli ATCC 25922 strain. Then the plates were incubated at 35°C for 16–20 h, and the mCIM and eCIM results were interpreted as described by CLSI23. The mCIM is considered negative if the zone size is ≥19 mm, positive if the zone size is 6–15 mm, or intermediate (defined as positive) if pinpoint colonies are present within a 16–18-mm zone . An isolate is positive for metallo-β lactamase production when the eCIM zone size increases by ≥5 mm compared

to the zone size observed for the mCIM and is considered negative for a matello-β lactamase if the increase in zone size is<4mm.

3. RESULTS

All the100 isolates (Klebsiellapneumoniae (66%) and Escherichia coli (34%))were found to be resistant to one of the carbapenem antibiotics i.e meropenem, imipenem, ertapenem, and doripenem ,were included in the study and labelled as carbapenem-resistant Enterobacterales (CRE).

Majority of CRE isolates were obtained from males 62(62.0%) as compared to female 38(38.0%) and 49(49.0%) of the patients were in the age group of 60-90 years. Among 100 CRE isolates most of the isolates were obtained from ICU 59(59.0%), followed by in patient wards 32(32.0%)and very few percentage were obtained from OPD 9(9.0%).In our study, out of 100 CRE isolates the maximum isolates were obtained from urine 54(54.0)%, followed by respiratory samples 26(26.0)% followed by blood.(9.0%).

Table 1: Distribution of Carbapenemase-producing Enterobacterales (CRE) in various clinical samples based on mCIM and eCIM positivity. (n=100)

Samples (N=100)	No. of CRGNB	No. of mCIM positive isolates N(%)	No. of eCIM positive isolates N(%)
Urine	54	53(98.1%)	27(50%)
Respiratory samples*	26	24(92.3%)	18(75%)
Blood	9	9(100%)	9(100%)
Pus and fluids*	5	4(80%)	3(75%)
Swab*	5	3(60%)	2(66%)
Tissue	1	1(100%)	0(0%)
Total	100	94(94.0%)	59(62.0%)

**Swabs include wound swab, vaginal swab, conjuctival swab, etc..*Respiratory secretions include sputum, endotracheal secretions, bronchial aspirate, etc. *Body fluids include CSF, pleural fluid, ascitic fluid, etc.*

Out of 100 carbapenem resistant gram negative bacteria(CRGNB) , maximum number isolates were obtained from urine(54%) followed by respiratory sample (26%),blood(9%),pus and fluids(5%), swabs(5%),and tissue(1%). Urine isolates showed 98.1% positivity by modified carbapenem inactivation method (mCIM), whereas EDTA carbapenem inactivation method (eCIM) showed 50% positivity. Blood samples showed 100% positivity for both mCIM and eCIM. Respiratory isolates had 92.3% mCIM positivity, with 69% positivity by eCIM method. Lower positivity rates were observed in pus, fluids, swabs, and tissue samples.

A total of 100 carbapenem-resistant Enterobacterales isolates i.e.66 (66.0%) Klebsiella pneumoniaeand 34 (34.0%) Escherichia colii solates were subjected to themodified Carbapenem Inactivation Method(mCIM) test. Of these 100 isolates , 94 (94.0%) testedpositive by mCIM indicating that they were carbapenemase producers. All 94 mCIM positive isolates were further subjected toEDTA-modified Carbapenem Inactivation Method(eCIM).Of these, 59 (62%) were eCIMpositive, indicating they were metallo-β -lactamase producers (MBL)**.(Table 1)**

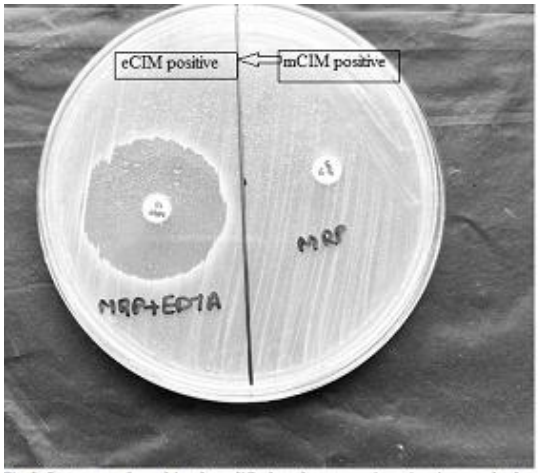

Fig-1 Outcome of combined modified carbapenem inactivation method (mCIM) and EDTA modified carbapenem inactivation method (eCIM). mCIM positive and eCIM positive result implies the isolate is a Metallo β lactamase producer

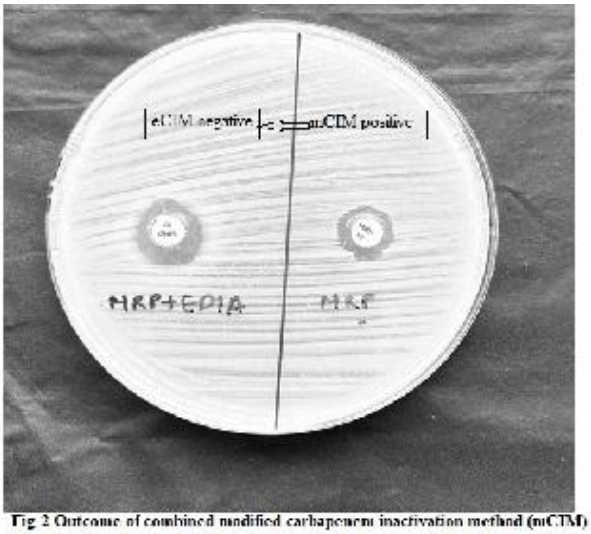

Fig 2 Outcome of combined modified carbapenem inactivation method (mCIM) and EDTA modified carbapenem inactivation method (eCIM). mCIM positive and eCIM negative result implies the isolate is a Serine carbapenemase producer.

Table 2: Split analysis of samples and different Enterobacterales isolated with their mCIM and eCIM results. (n=100)

samples(N=100)	Klebsiella pneumonia			Escherichia coli		
	No. of isolates	mCIM +ive	eCIM +ive	No. of isolates	mCIM +ive	eCIM +ive
Urine	30	30 (100%)	21 (70%)	24	23 (95%)	6(26%)
Respiratory samples	22	20 (90.9%)	16 (80%)	4	4 (100%)	2(50%)
Blood	6	6 (100%)	6 (100%)	3	3 (100%)	3(100%)
Pus and fluids	4	3 (75.0%)	3 (100%)	1	1(100%)	0(0%)
Swab	3	2(66.7%)	2 (100%)	2	1(50%)	0(0%)
Tissue	1	1(100%)	0 (0%)	0	0(0%)	0(0%)
Total	66	62	48	34	32	11

Out of 100 carbapenem-resistant Enterobacterales (CRE),the mCIM test showed consistently high positivity for Klebsiella pneumoniae i.e (66.7–100%) and Escherichia colii.e (50–100%) in different type of samples. eCIM positivity varied, being highest in blood samples i.e (100% for both organisms), followed by respiratory samples - 80%for Klebsiella pneumoniae and 50%for Escherichia coli. The lowest eCIM positivity was observed in tissue samples(0%).

Table : 3 Differentiation of Carbapenemase producing Enterobacterales into different classes based on mCIM conjunction with eCIM test. (n=100)

Organism (N=100)	Metallo-β lactamase(MBL)	Serine-β lactamase	Indeterminate
Klebsiella pneumoniae(66)	48(72.7%)	14(21.2%)	4(6.0%)
Escherichia coli (34)	11(32.3%)	21(61.7%)	2(5.8%)

Klebsiella pneumoniae (66% of the CRE)predominantly produced metallo-β-lactamase (72.7%), with a smaller percentage producing serine-β-lactamase production (21.2%). On the other hand, **Escherichia coli** (34% of the CRE) mainly produced serine-β-lactamase (61.7%), with a lower percentage producing metallo-β-lactamase (32.3%).

Of the 94 mCIMpositive isolates,62 (65.9%) wereKlebsiellapneumoniaeand 32(34.0%)wereEscherichia coli.Of these, 59 (62%) eCIM positive isolates, 48(81.3 %) wereKlebsiellapneumoniaeand 11(18.64%)wereEscherichia coli. **(Table 2).**

Of these 59 (59.0%) mCIM and eCIMpositive isolates, 48(72.7 %) wereKlebsiellapneumoniaeand 11(32 %) were Escherichia coli. indicating that they were metallo-β -lactamase producers (MBL). The remaining 35 (35.0%) mCIMpositive buteCIM negative isolates, 14(21%) were Klebsiellapneumoniaeand 21(61%) wereEscherichia coliindicating that they were serine carbapenemase producers. **(Table3)**

4. DISCUSSION

Multi drug resistant gram negative bacteria especially Enterobacterales are important agents of hospital-acquiredand community-acquired infections. This results in increased use of carbapenems for treatment of these infections leading to emergence of carbapenem resistant Enterobacterales.This is due to the reason that carbapenemases are enzymes that hydrolyze carbapenems, monobactams, cephalosporins and penicillins and thus provide the bacteria with resistance to those drugs.Along with this they also acquire carbapenem resistant genes primarily NDM,KPC,OXA-48,VIM and IMP which are usually located on transferable plasmids making it easier for these genes to spread among bacterial strains.Thus, early identification of CRE isolates is important not only for choosing the appropriate treatment regime but also to interrupt the extension of resistance population of bacteria in hospital settings.[6]

According to CLSI guidelines we performed phenotypic tests such as the modified Carbapenem Inactivation Method (mCIM) and the EDTA- Carbapenem Inactivation Method (eCIM) to identify carbapenemase producing isolates. These methods are simple and cost effective as compared to molecular techniques, it is very useful in resource limited settings and would help in differentiating between the different types of carbapenemases.[9,11]

In our study, out of 100 CRE isolates the maximum isolates were obtained from urine (54%) followed by respiratory samples (26%) and blood (09%).This is similar to the study done by verma et al[1] who also reported the similar distribution pattern among clinical isolates of CRE and reported maximium isolates from urine (47.2%)followed by respiratory samples (30.2%) and blood (3.8%).

In our study, maximum number of CRE isolates were obtained from male patients (62%) whereas female patients accounts for (38%). This is similar to the study done by Baskaranet al[12], vermaet al[1]who also reported maximum number of CRE isolates in males(68%), (61.2%) respectively.

In our study, maximum isolates of CRE were obtained from ICU (59%) followed by in patient wards(32%) and (9%) isolates were obtained from OPD. Similar results were obtained from the study done by sinha et al[13]who also reported maximium CRE isolation from ICU (33.33%) followed by in patient wards (14.45%) and (6.74%)were obtained outdoor patients. The reason for increased isolation of CRE isolates from ICU patients may be due to use of catheters, invasive procedures, antibiotic exposure and prolonged stay.

In our study, out of 100 CRE isolates Klebsiella pneumoniae (66%) and E. coli (34%) are two most common Carbapenem resistant organisms isolated. Similar pattern of isolation was reported byAliaa et al[14], and verma et at[1]who also reported dominance of Klebsiella pneumoniae with (70%), (60.4%)and E. coli with (28%), (13.75%)respectively. Most of the studies reported dominance of Klebsiellapneumoniaethis may be due to the reason that it can produce biofilms, easily survive in hospital environment, and can spread easily from one patient to another[15].

In the present study 94% isolates were mCIM positive which is similar to the study done by cheemala et al.[9],li. Et al[16],sinha et al[13]Who found (93%), (97.5%), (87%) percentage of isolates tested positive by mCIM method.The high positivity of carbapenemase production can be attributed by the fact that carbapenemase enzymes are encoded by genes on mobile genetic elements, such as plasmids, which are highly transmissible between organisms and increase the potential spread of resistance[3].

In this study mCIMtest detected carbapenemase production in 52% of Klebsiellapneumoniae which is similar to the study done by Tsai et al (65%)[8],Koul et al[5].(48.48%). Similarly 32% of the Escherichiea coli were positive by mCIM test which is similar to the study done by Alemaychu et al[17] who reported(20%) positivity by mCIM test.

In the present study,59% of total isolates were metallo-β- lactamase producersand 35% were serine-β- lactamase producers. The prevalence of serine and metallo-β- lactamase production in CRE known varies across various regions. The study done by NupurKoul et al.in uttrakhandreported (58.4%) MBL, (41.6%)serine-β- lactamase production which is similar to our study whereas the study done by RaheelA et al. in Egypt reported 37.2% serine and 30.2% metallo-β- lactamase production. Similarly Segagni et al in Austria also reported 63.8% serine-β- lactamase production and only 27.6% metallo-β- lactamase production among CRE isolates.

5. CONCLUSION

CRE infections are becoming a serious and growing public health threat.These carbapenem resistant Enterobacterales are not only responsible for therapeutic failure but are also a major cause of concern in disseminating multidrug resistance gene.

Thereforeunderstanding the mechanism of carbapenem resistance is very important. Hence, we suggest to perform mCIM and eCIM test which can identifyand differentiate between these two types of carbapenemase i.e MBL and serine which is ultimately aiding in the development of more effective treatment stratergies to reduce therapeutic failures. Newly developed β-lactam-β-lactamase inhibitors, such as ceftazidime-avibactam and meropenem-vaborbactam, are effective against serine carbapenemase producers, while certain combination therapies are effective against metallo-β-lactamase producers(MBLs). Clinicians can utilize these drugs to prevent theraputicfailure.Moreover their judicious use can control the spread of drug resistance within the hospital which is need of the hour.MBL production is found to be more prevalent, strict infection control measures should be implemented. In addition to this, mCIM andeCIM tests are important for proper surveillance and to apply effective infection control measures in this sector.

6. LIMITATIONS

Genotypic study for genes responsible for carbapenem resistance is needed to know more accurate results.

7. ACKNOWLEDMENTS

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8. CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

9. AUTHOR'S CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work,and approved it forpublication.

10. FUNDING STATEMENT

Nil

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