DOI: 10.7860/NJLM/2023/61092.2734

Original Article

Microbiology Section

Detection of Carbapenemase Production by Modified Carbapenem Inactivation Method among Carbapenem Resistant Gram-negative Bacilli at a Tertiary Care Centre in Coimbatore, Tamil Nadu, India

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ABSTRACT

Introduction: In the era of increasing antimicrobial resistance, knowing the mechanism of carbapenem resistance can aid in choosing an apt drug for treatment of patients. There are only few studies estimating the burden of carbapenem resistance and determining the mechanism of resistance among the isolates in our locale.

Aim: To determine the prevalence of carbapenemase production by modified Carbapenem Inactivation Method (mCIM) among the Carbapenem Resistant Gram-Negative Bacteria (CRGNB)- *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolated in our hospital.

Materials and Methods: This was a prospective observational study conducted in Department of Microbiology, KMCH, Coimbatore, Tamil Nadu, India during the period of June 2021 to August 2021. A total of 165 isolates of *Enterobacteriaceae* family and *P. aeruginosa* which were resistant to one of the carbapenems (imipenem, meropenem or ertapenem) by Vitek MIC testing were included in the study. All were subjected to mCIM and EDTA-modified CIM (eCIM) test and interpreted as per the CLSI M100 S31 guidelines.

Results: Among the 165 isolates, 130 (78.8%) were *K. pneumoniae*, 27 (16.4%) were other *Enterobacteriaceae* and eight (4.8%) were *P. aeruginosa*. Prevalence of mCIM positivity was 51.5% (85 isolates). Approximately, 98% of the mCIM positives (Carbapenemase Producing Gram-Negative Bacteria [CPGNB]) were eCIM positive indicating Metallo-Beta-Lactamase (MBL) production.

Conclusion: Performing mCIM in CRGNB is important in routine practice to identify CPGNBs. Due to very high prevalence of MBL among carbapenemase producers, it is advisable to choose ceftazidime avibactam plus aztreonam as the treatment option for CPGNB in our locale.

Keywords: Carbapenemase detection, Enterobacteriaceae, Metallo-beta-lactamase

INTRODUCTION

Antimicrobial resistance is one of the most serious threats to humans, in the past decades. Increased prevalence of Multi Drug Resistant GNB (MDR-GNB) is becoming a greatest risk [1-3]. The carbapenems (belonging to the β-lactam group of antibacterial agents) are the common choice of treatment for emerging Extended Spectrum Beta Lactamase (ESBL) and AmpC enzyme producing gram-negative bacilli [4,5]. However, the prevalence of carbapenem resistance is also increasing in the current decade. Carbapenem resistance has been reported widely among *Enterobacteriaceae* particularly in *Klebsiella pneumoniae* and *Escherichia coli* besides *P. aeruginosa* spp. and *Acinetobacter spp.* [3,6,7].

Drugs used to treat CRGNB infections are partly based on the mechanism of resistance to carbapenem. Most common mechanism of carbapenem resistance in GNB is due to the production of carbapenem hydrolysing enzymes called carbapenemase which are either serine beta lactamase or MBL [8-10]. In general, beta lactamases inhibitors like avibactam, relebactam, vaborbactam, and monobactam are found effective in serine beta lactamase producers. Monobactam like aztreonam works against MBLs. However, when both enzymes are present in CRGNB, a combination of ceftazidime avibactam and aztreonam or cefiderocol is found effective and recommended by the Infectious Diseases Society of America guidelines [10,11]. In case of efflux pump-based resistance, alternative group of drugs are chosen as treatment options [10].

Among MBLs, IMP and VIM were discovered first. Later, the New Delhi MBL-1 (NDM-1) *Enterobacteriaceae* has emerged in Asian subcontinent and in European countries (Romania, Hungary, Spain, Denmark) and rapidly spread across the globe [8,12,13].

Hence, it is essential to know the data on the prevalence of carbapenem resistance, carbapenemase prevalence and type of carbapenemase produced by the bacteria to start an effective empirical as well as antibiotic susceptibility guided therapy. There are few data published about the existing prevalence of CPGNB in our locale [14,15]. Current study was performed to estimate the prevalence of carbapenemase production by a screening method- Modified CIM among the Carbapenem Resistant *Enterobacteriaceae* (CRE) and *P. aeruginosa* isolated from clinical samples from our hospital.

MATERIALS AND METHODS

This was a prospective observational study conducted in Department of Microbiology, KMCH, Coimbatore, Tamil Nadu, India on 165 carbapenem resistant gram-negative bacilli collected by convenient sampling method during the period of June 2021 to August 2021, from the clinical isolates after taking approval from the Institutional Ethical Committee. These isolates were identified as resistant or moderately susceptible to one or more of the carbapenems tested (imipenem, meropenem, ertapenem) by Vitek 2 automated AST method according to CLSI M100 S31 guidelines [16,17].

Procedure

Primary growth of all isolates, from blood agar plate, was stored at -20°C, for 4 months, in brain heart infusion-glycerol broth with cryobeads to avoid alteration in resistance property upon repeated subculture. Freshly revived 24-hour growth was subjected to mCIM and eCIM testing as per CLSI guidelines [15]. *E. coli* ATCC 25922 was used as negative control and NDM gene positive *K. pneumoniae* identified by Xpert Carba-R (GeneXpert) was used as positive control [17].

CRE can be defined as *Enterobacteriaceae* that are resistant to one or more of the following carbapenems: ertapenem, meropenem or imipenem using breakpoints in [Table/Fig-1] [17].

Drugs	*Enterobacteriaceae*	*Pseudomonas aeruginosa*
Imipenem or Meropenem	≥2 µg/mL	≥4 µg/mL
Ertapenem	≥2 µg/mL	Not applicable

[Table/Fig-1]: Breakpoint Minimum inhibitory concentration (MIC) for determining the carbapenem resistance in study isolates [15].

mCIM is done for suspected carbapenemase production in Enterobacteriaceae and *P. aeruginosa*; whereas eCIM is used together with mCIM to differentiate metallo b-lactamase from serine carbapenemase in *Enterobacteriaceae*. eCIM was tested for *P. aeruginosa* in the current study though it was not recommended by CLSI, but the data was excluded from statistical analysis. According to CLSI, mCIM screen test has a sensitivity and specificity of >99% for Enterobacterales and >97% and 100% for *P. aeruginosa* respectively. eCIM method demonstrated sensitivity and specificity of >95% and >92% for Enterobacterales, respectively [17].

STATISTICAL ANALYSIS

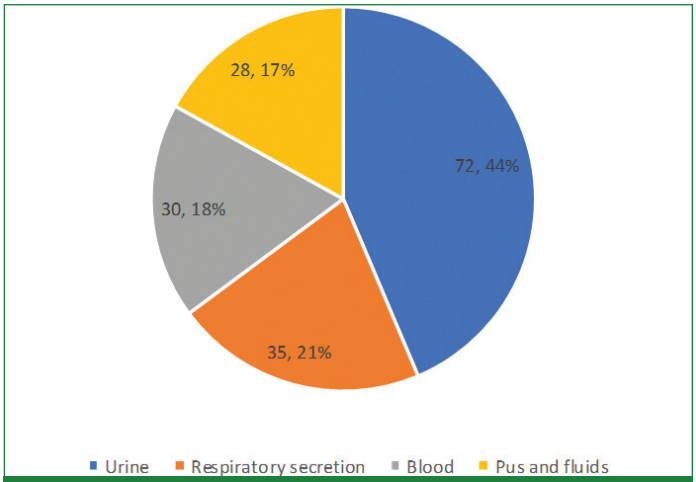
Prevalence of carbapenemase, demographic details and observed association with the types of isolate and type of sample were analysed using excel data sheet. Association between the Vitek MIC based results of carbapenem and results of mCIM was analysed using chi-square test.

RESULTS

Of the 165 isolates, 157 belonged to *Enterobacteriaceae* family and 8 were *P. aeruginosa* isolates. Majority of the CRE isolates were obtained from men (112 [68%]) compared to women (53 [32%]) and 75.32% of the patients were in the age group of 60-90 years.

Distribution of study isolates across the sample is shown in [Table/Fig-2]. Most of isolates were obtained from in-patient wards 101 (61.2%) followed by ICU 43 (26.1%) and a very few percentages were from OPD 21 (12.7%).

[Table/Fig-3] shows the split analysis of samples and different species studied with their mCIM and eCIM results. Among the four different categories of the samples analysed in this study, *K. pneumoniae* (130, 78.8%) was the predominant organism, which was carbapenem resistant. Second common isolate was *E. coli* (20, 12.1%). Fifty percent of *K. pneumoniae* and 80% of *E. coli* tested positive for mCIM indicating one of the carbapenemase enzyme production as their mechanism of resistance.



[Table/Fig-2]: Sample wise distribution of study isolates.

Taking different samples into consideration, *K. pneumoniae* isolated from blood and respiratory samples shows 57.7% carbapenemase production, each, in comparison to other samples, where the prevalence was ranging from 41.7-44.2%. *E. coli* were 50-100% carbapenemase producers across samples. Though mCIM positivity was highest among *E. coli* (16, 80%) in the current study, number of isolates was too small for generalisation of this data.

Prevalence of carbapenemase production by mCIM method was observed to be (85) 51.5% among the CRGNB included in this study. Among the 85 mCIM positive isolates, *Enterobacteriaceae* constituted 83 and the remaining 2 were *P. aeruginosa*. Among the 83 *Enterobacteriaceae*, 81 tested eCIM positive indicating presence of MBL enzyme. Approximately, 81 (97.6%) of CRE were MBL producers. Both the carbapenemase producing *P. aeruginosa* tested MBL positive. As the CIM methodology is not recommended for *P. aeruginosa* under CLSI guidelines, it was excluded from statistical analysis.

Distribution of carbapenemase in CRGNB was ranging from 42.3% to 56.7% in different samples, with higher prevalence being observed in blood samples followed by urine samples as shown in [Table/Fig-4].

Of the 165 isolates, 129 were resistant to all carbapenem tested by Vitek 2, while 36 were either moderately susceptible or susceptible to one or more carbapenem tested. Among these isolates, imipenem was the most common drug which showed moderate susceptibility with MIC of 2 µg/mL for 35 isolates [Table/Fig-5].

[Table/Fig-6] shows the analytics between Vitek AST results and mCIM results. Chi-square test of independence was performed to examine the relation between the susceptibility test result for carbapenems by MIC method (automation) and the mCIM positivity. The relation between the variables was significant, X2 (1, N=165) =18.96, p=0.000013. Isolates which are resistant to all three carbapenems by MIC determination are more likely to be carbapenemase producers compared to isolates which are moderately susceptible or susceptible to one or more of the three carbapenems.

Organism	*Klebsiella pneumoniae*			*Escherichia coli*			*Pseudomonas aeruginosa*			*Enterobacter cloacae*			*Klebsiella aerogenes*		
Sample	No. of isolates	mCIM +ve	eCIM +ve	No. of isolates	mCIM +ve	eCIM +ve	No. of isolates	mCIM +ve	eCIM +ve	No. of isolates	mCIM +ve	eCIM +ve	No. of isolates	mCIM +ve	eCIM +ve
Urine (72)	52	23 (44.2)	23	14	12 (85.7)	12	3	1 (33.3)	1	2	2 (100)	2	1	0 (0)	0
Respiratory sample* (35)	28	16 (57.1)	16	2	1 (50)	1	4	1 (25)	1	0	0 (0)	0	1	0 (0)	0
Blood (30)	26	15 (57.7)	13	2	1 (50)	1	0	0 (0)	0	2	1 (50)	1	0	0 (0)	0
Pus and fluids† (28)	24	10 (41.7)	10	2	2 (100)	2	1	0 (0)	0	0	0 (0)	0	1	0 (0)	0
Total	130	64 (49.2)	62 (97)	20	16 (80)	16 (100)	8	2 (25)	2 (100)	4	3 (75)	3 (100)	3	0 (0)	0

[Table/Fig-3]: The split analysis of samples and different species studied with their mCIM and eCIM results.
* Respiratory samples were Sputum, Endotracheal aspirate and Bronchoalveolar lavage; † Fluids analysed were peritoneal, pleural and pericardial fluids

All isolates which were mCIM positive (85 isolates) were resistant to both ertapenem and meropenem whereas 8.2% (7 isolates) were moderately susceptible to imipenem. Among the 35 isolates, which were moderately susceptible to imipenem, only four were moderately susceptible to either one or two of the other carbapenems tested. All four isolates tested mCIM negative.

Samples	No. of CRGNB	No. of mCIM positive isolates N (%)	No. of eCIM positive isolates N (%)
Urine	72	38 (52.8)	38 (52.8)
Respiratory sample	35	18 (51.4)	18 (51.4)
Blood	30	17 (56.7)	15 (50.0)
Pus and fluids	28	12 (42.3)	12 (42.3)
Total	165	85 (51.5)	83 (50.3)

[Table/Fig-4]: Sample-wise analysis of carbapenemase producers.

Antibiotic	Susceptible N (%)	Moderately susceptible N (%)	Resistant N (%)	Total
Imipenem	1 (0.6)	35 (21.2)	129 (78.2)	165
Meropenem	1 (0.6)	3 (1.8)	161 (97.6)	165
Ertapenem*	0 (0)	3 (2)	151 (98)	154*

[Table/Fig-5]: Vitek 2 carbapenem antibiotic susceptibility testing results of study isolates.
* 11 Isolates comprising of eight *P. aeruginosa*; two *K. pneumoniae* and one *E. coli* were not tested for the Ertapenem susceptibility

Variables	No. of isolates susceptible or moderately susceptible to at least one of the carbapenem	No. of isolates resistant to all carbapenem	Total
mCIM positive	7	78	85
mCIM negative	29	51	80
Total	36	129	165

[Table/Fig-6]: Analysis of carbapenem susceptibility pattern to mCIM positivity.
* The p-value is <0.001

DISCUSSION

Carbapenem hydrolysing beta lactamases are classified into Class A (KPC, IMI) and Class D (OXA-48, OXA-181, OXA-23, OXA-40, OXA-58) serine beta lactamases and Class B (IMP, VIM, NDM) MBLs. KPC followed by OXA is the most common variety found in western countries. Based on the past studies, in Asian subcontinent MBL especially NDM-1 and OXA 48 are the most common ones [9,18].

NDM was first identified in Sweden from an Indian returnee [19]. Later, studies showed that this was the most common gene in India, Pakistan and Bangladesh regions [12]. Study by Walsh TR et al., showed the magnitude of existence of NDM bugs in Indian environment [20]. In 2015, Kazi M et al., demonstrated the co-existence of NDM, OXA 48 and VIM genes in same bacteria [18]. Prevalence of carbapenemase production especially MBLs (51.5% & 97.6%) in current study was similar to other studies in different parts of the country except for Maharashtra study (98% mCIM positivity) [3]. Study in AIIMS, New Delhi 2019 stated carbapenemase prevalence as 65% in Enterobacterales by Modified Hodge test and PCR [21]. A study in Lucknow 2014, recorded 100% prevalence of NDM with or without co-existing AmpC beta lactamase genes in all the carbapenem resistant Enterobacterales [22]. Prevalence of carbapenemase by mCIM was 45.09% in Tumkur study in Karnataka [23]. Studies in Coimbatore region of Tamil Nadu had observed prevalence of 73.33% in 2011-2015 and 82% in 2017. However, these studies have focused on isolates from specific samples in patients with certain comorbidities. Some of these studied were detecting only a specific group of carbapenemase producing genes by PCR [14,15]. Comparative prevalence reports of carbapenemase in various regions of India are collated in [Table/Fig-7] [3,14,15,21-27].

S. no	Region and year of the study	Prevalence of CPGNB	Method of detection of CPGNB	Reference
1	Coimbatore, Tamil Nadu, 2011-2015	73.33 (33/45)	PCR for detection of bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{SPM} genes	[14]
2	Lucknow, Uttar Pradesh, 2014	100 (57/57)	bla_{NDM-1} PCR	[22]
3	Trichy, Tamilnadu, 2014	29.03 (27/93)	PCR for detection of bla_{NDM}, bla_{VIM} bla_{OXA}, bla_{IMP}, bla_{KPC} genes	[26]
		59.3 (16/27)	bla_{NDM} PCR	
4	Kanpur, Uttar Pradesh, 2014-2016	90.3 (282/312)	Multiplex PCR for bla_{IMP}, bla_{VIM}, bla_{KPC}, bla_{OXA48}, bla_{OXA23}, bla_{SPM}, bla_{GIM}, bla_{SIM} and bla_{NDM} genes	[24]
		63 (178/282)	bla_{NDM} PCR	
5	Coimbatore, Tamil Nadu, 2017	82 (82/100)	$bla_{NDM\ 1}$ PCR	[15]
6	Aizawl, Mizoram, 2018-2019	31.25(5/16)	bla_{OXA-48} PCR	[27]
7	Pune, Maharashtra, 2019	98.6 (148/150)	mCIM	[3]
8	AIIMS, New Delhi, 2019	65 (61/94)	Modified Hodge Test	[21]
		100 (94/94)	PCR for detection of bla_{NDM}, bla_{VIM} bla_{OXA}, bla_{IMP}, bla_{KPC} genes	
		61.7 (58/94)	bla_{NDM-1} PCR	
9	Tumkur, Karnataka, 2019	45.09 (23/51)	mCIM	[23]
		86.95 (20/23)	eCIM	
10	Kanchipuram, Tamilnadu, 2021	100 (39/39)	PCR for detection of bla_{NDM}, bla_{VIM} bla_{OXA-48} genes	[25]
		61.54 (24/39)	bla_{NDM} PCR	

[Table/Fig-7]: Prevalence of carbapenemase in various parts of India [3,14,15,21-27].
* PCR: Polymerase chain reaction

AMR surveillance network report states that prevalence of carbapenem resistance was 33% in Enterobacterales and MBL genes were found in 25% of these isolates on an average. A relatively high prevalence of NDM was observed in certain regions of the country. Resistance has increased averagely by 4.9%, 4.4% and 6% in *E. coli*, *K. pneumoniae* and *Enterobacter species* over 5 years (2016-2020) in India, respectively [7].

On analysing the antibiogram pattern of carbapenem, among mCIM positive and negative isolates, it was found that isolates which were moderately susceptible to imipenem were less likely to be carbapenemase producers compared to resistant ones. It was observed that all mCIM positive isolates were resistant to ertapenem and meropenem, by Vitek MIC determination. This observation shows a potential for using antibiogram pattern in helping with empirical choice of drug. However, studies with larger sample size, aimed at confirming this observation is required in future.

Limitation(s)

eCIM gives a positive result irrespective of presence of serine carbapenemase genes along with MBL. Hence, this method can't differentiate presence of co-existence of other carbapenemase genes along with MBL, from presence of only MBL genes. Due to disparity in the distribution of number of isolates, observations made using this variable requires further study to confirm the findings.

CONCLUSION(S)

It is advisable to perform mCIM in carbapenem resistant isolates as a routine, to decide on the best choice of empirical antibiotic for treatment. Very high prevalence of MBLs suggested by eCIM results, show that ceftazidime avibactam plus aztreonam would be the best option for mCIM positive isolates in clinical practice in this study region.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Nov 02, 2022
- Manual Googling: Jan 13, 2023
- iThenticate Software: Jan 17, 2023 (7%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 28, 2022**
Date of Peer Review: **Dec 07, 2022**
Date of Acceptance: **Jan 18, 2023**
Date of Publishing: **Jul 01, 2023**