Descriptive Study for Detection of Carbapenem Resistant Enterobacteriaceae by the Modified Carbapenem Inactivation Method in a Tertiary Care Hospital of Western Maharashtra

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ABSTRACT

BACKGROUND

In an infection caused by multidrug-resistant Enterobacteriaceae, carbapenems is one the last antibiotics used, but the carbapenemase producing Enterobacteriaceae pose a clinical challenge. A relatively new test which was described few years back known as modified carbapenem inactivation method (mCIM) is used to detect the presence of carbapenemase activity in Gram-negative bacilli. Various studies show this test be to be very sensitive and specific. We aim to study mCIM positivity on samples which are positive by Kirby-Bauer disk diffusion antibiotic sensitivity test method used for detection of carbapenem resistant Enterobacteriaceae (CRE) from clinical specimens.

METHODS

The study is a cross sectional descriptive study conducted in a tertiary care hospital. Samples received from February 2019 to September 2019 were included in the study. During this period 150 samples were collected which were resistant to meropenem by Kirby-Bauer disk diffusion method. These CREs isolates were further subjected to mCIM and the result was analysed.

RESULTS

Out of the total 150 CRE isolates which were 100 % resistant to meropenem by the conventional disc diffusion method it is found that mCIM was positive for 148 (98.66 %) isolates and negative for only 02 (1.33 %). Two most common CRE were *Klebsiella pneumonia* (58 %) and *Escherichia coli* (32 %). In statistical analysis chi square test revealed statistically significant difference ($P < 0.05$) in percentage of positivity between the two methods (98.66 % vs 100 %).

CONCLUSIONS

mCIM is highly sensitive and specific method; however, in practice it showed no added advantage over Kirby-Bauer disk diffusion method in detecting CRE.

KEYWORDS

Modified Carbapenem Inactivation Method (mCIM), Kirby-Bauer Disk Diffusion Method, Carbapenem Resistant Enterobacteriaceae

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BACKGROUND

The current worldwide emergence of resistance to carbapenems in Enterobacteriaceae constitutes a growing public health threat.[1] Early detection of these drug resistant organisms is important for instituting early end effective treatment to the patient. There is universal presence of resistant bacteria in both hospital and community settings, but more so in a hospital setting.[2] Carbapenems are used as one of the last resort antibiotics in treating infections caused by multidrug-resistant Enterobacteriacea.[3,4] But once susceptible to carbapenems are now rapidly acquiring resistance to carbapenems and their global dissemination is a matter of concern.[5,6]

Many reports shows increase in incidence of nosocomial infections caused by multidrug-resistant (MDR) organisms.[7] Over a period of time, bacteria have developed different mechanism of drug resistance for different class of antibiotics,[8] such as production of enzymes,[8] alteration of target site of action, excessive efflux pump system, modification of diffusion barriers and altered metabolic activity.[9,10] Among all the available β lactam antibiotics, carbapenem have maximum antimicrobial spectrum.[11] It is because of their more affinity for penicillin binding proteins (PBPs), bearing good stability against most serine based β lactamases and having excellent outer membrane permeability.[12] However usage of carbapenems are now threatened by widespread dissemination of CREs. Centres for Disease Control and Prevention (CDC) define CREs as bacteria that test resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem or imipenem) or produce a carbapenemase (an enzyme that makes them resistant to carbapenem antibiotics).[13,14] Multiplication of such organism and their ability to horizontally transfer these plasmid carrying resistant genes to other organisms have resulted in increased expansion of carbapenem resistant organisms.[15] Various important carbapenemase are acquired class A (KPC), class B (IMP, VIM, NDM), and class D (OXA-48, OXA-181).[16]

Outcomes of infections caused by CRE are poor.[17] Very few antibiotics are available for the treatment of these virulent organisms and also these antibiotics have more adverse effects and are costlier.[18] Antibiotics which are currently used to treat CRE infections include polymyxins, tigecycline, fosfomycin, aminoglycosides and temocillin.[19] The role of combination antibiotic treatment, including carbapenem containing regimens, is yet to be defined.[20]

To prevent and contain the spread of these pathogens, rapid and reliable detection of carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) is of upmost important.[21] Modified carbapenem inactivation method is one such test which was recently developed to detect carbapenemase activity in Gram-negative bacteria. Various studies have shown mCIM to be a simple, economical and a very sensitive and specific test which can be used as a screening method for detection of carbapenemase activity.[22] In the validation study the sensitivity of the mCIM was observed to be 99 % (95 % confidence interval 93 - 100) and the specificity was 100 % (95 % CI 82 - 100). In the second stage of the study, the range of sensitivities that was observed across nine laboratories was 93 - 100 %, with a mean of 97 %; the specificity ranged from 97 - 100 %, mean of 99 %.[23] Test mCIM was easy to perform and interpret for Enterobacteriaceae, with results made available in less than 24 hours after a pure growth was obtained with excellent reproducibility across laboratories.[23]

As mCIM method was recently included in the 27 th edition of the Clinical and Laboratory Standards Institute (CLSI) performance standards for antimicrobial susceptibility testing M100 supplement as a highly sensitive and specific method for identifying CP-CRE and since very few studies are available which have evaluated mCIM and the Kirby Bauer method, this descriptive study was undertaken to find the difference in positivity rate between mCIM and Kirby Bauer in detecting carbapenemase producing Enterobacteriaceae isolates from clinical samples. This study is a preliminary phenotypic study which shall be corroborated and correlated with molecular study subsequently.

METHODS

The study was a cross sectional descriptive study which was carried out after institutional ethical clearance was taken. Clinical samples which were received at a tertiary care hospital during a period of eight months from February 2019 to September 2019 were included in the study. All Enterobacteriaceae isolates found resistant to carbapenems (meropenem) as per CLSI M100 2019 standards by the Kirby-Bauer disk diffusion method were included in the study. These isolates were further subjected to mCIM tests to detect CP-CRE and the result was analysed. Samples which showed a mixed growth or were contaminated were excluded. The samples were processed by the conventional microbiological techniques and identified by biochemical reactions. The mCIM test was done as per CLSI M100 2019 29th Edition guidelines[24] as –

Modified Carbapenem Inactivation Method

Enterobacteriaceae isolate found resistant to carbapenem by the Kirby Bauer disc diffusion was sub-culture on blood agar plate and incubated at 35^0 C for 18 to 24 hours. From the sub-cultured plate 1 µl loopful of isolated colony was taken and suspended in a 2 ml of trypticase soy broth (TSB). The mixture was vortexed, 10 µg meropenem (carbapenem) disc was added and was incubated for 4 hours at 35^0 C (Fig 1). Just prior to completion of 4 hours incubation, a 0.5 McFarland suspension of *Escherichia coli* ATCC 25922 was prepared and lawn cultured onto a Mueller Hinton Agar (MHA) plate. After the completion of 4 hours the meropenem disc was removed from the mixture using a 10 µl loop, taking care to remove excess liquid from the disc and then the meropenem disc was immediately placed on *Escherichia coli* ATCC 25922 prepared MHA plate. This plate was then incubated overnight (18 – 24 hrs.) at 35^0 C. Next day the size of the zone of inhibition was measured (Fig 2). Zone size ≥ 19 mm was taken as negative and a zone size of 6 –

15 mm or presence of pinpoint colonies within a 16 - 18 mm zone was taken as positive for carbapenemase producing Enterobacteriaceae as per CLSI M100 2019 29th Edition guidelines.

RESULTS

Patients' age ranged from new born to 88 yrs. old. Mean age of patients in the study was 52 years, standard deviation (SD) 19.01. Median: 57 and mode: 62 yrs. Total number of males were 117 and females were 33. Total Enterobacteriaceae isolated during the study period was 849 of which 150 were found to be meropenem resistant. Prevalence rate of carbapenem resistant Enterobacteriaceae during study period was estimated to be 18 %. Sample distribution was as follows: urine : 44 (29.33 %), blood: 30 (20 %), pus: 17 (11.33 %), tracheal aspirate: 15 (10 %), sputum - 09 (6 %), stool - 06 (4 %), ascitic fluid - 5 (3.33 %), wound swab - 04 (2.67 %), tissue - 04 (2.67 %), drain fluid: 03 (2 %), pancreatic collection: 03 (2 %), pleural fluid: 02 (1.33 %), bronchioalveolar lavage (BAL): 01 (0.66 %), bile aspirate: 01 (0.66 %), central line tip: 01 (0.66 %), dressing foam: 01 (0.66 %), gall bladder aspirate: 01 (0.66 %), high vaginal swab: 01 (0.66 %), peritoneal dialysis fluid: 01 (0.66 %), and placental tissue: 01 (0.66 %).

The various CREs isolates were as follows: *Klebsiella pneumonia*: 87 (58 %), *Escherichia coli: 48 (32 %), Proteus mirabilis: 04 (2*.67 %), *Citrobacter frieundii*: 03 (2 %), *Enterobacter cloacae*: 03 (2 %), *Citrobacter koseri*: 02 (1.33 %), *Pantoea agglomerans*: 01 (0.66 %), *Proteus vulgaris*: 01 (0.66 %), *Providencia rittgeri*: 01 (0.66 %).

All these 150 clinical isolates (100 %) were meropenem resistant as per disk diffusion method using CLSI 2019 criteria. Out of these 150 isolates, 148 (98.66 %) were mCIM positive and only 02 (1.33 %) were mCIM negative. Chi square test was used to check for difference in percentage of positivity by both methods which revealed statistically significant difference ($P < 0.05$) in percentage of positivity between the two methods (98.66 % vs 100 %). An effort to seek any significant correlation between demographic variable and CRE was also made. Three age ranges were created 0 - 18 years, 19 - 50 years and > 50 years and checked for any significant association between age and the presence of CRE by using chi square test. It showed no statistical difference ($P > 0.05$).

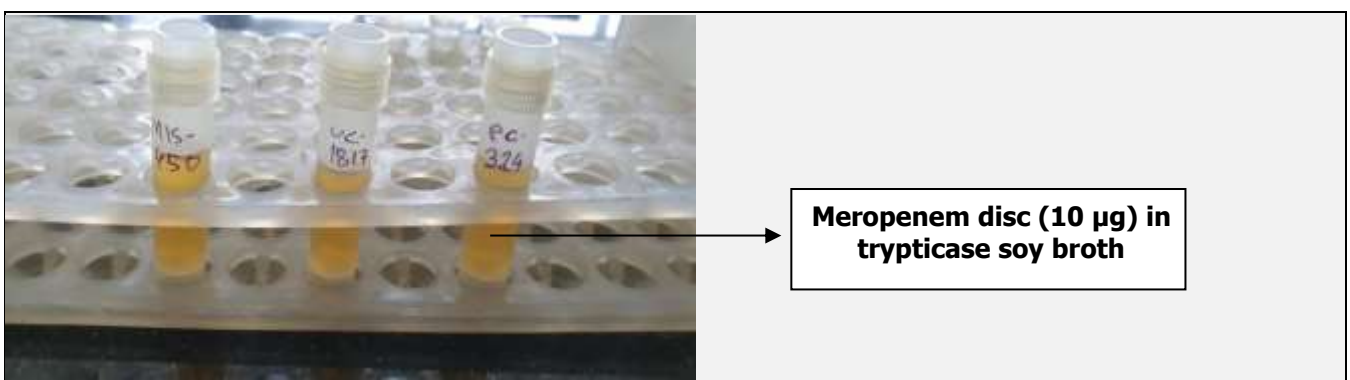

Figure 1. Tubes with 2 mL of Trypticase Soya Broth (TSB) with 1 µL Bacterial Inoculum and 10 µg Meropenem Disc

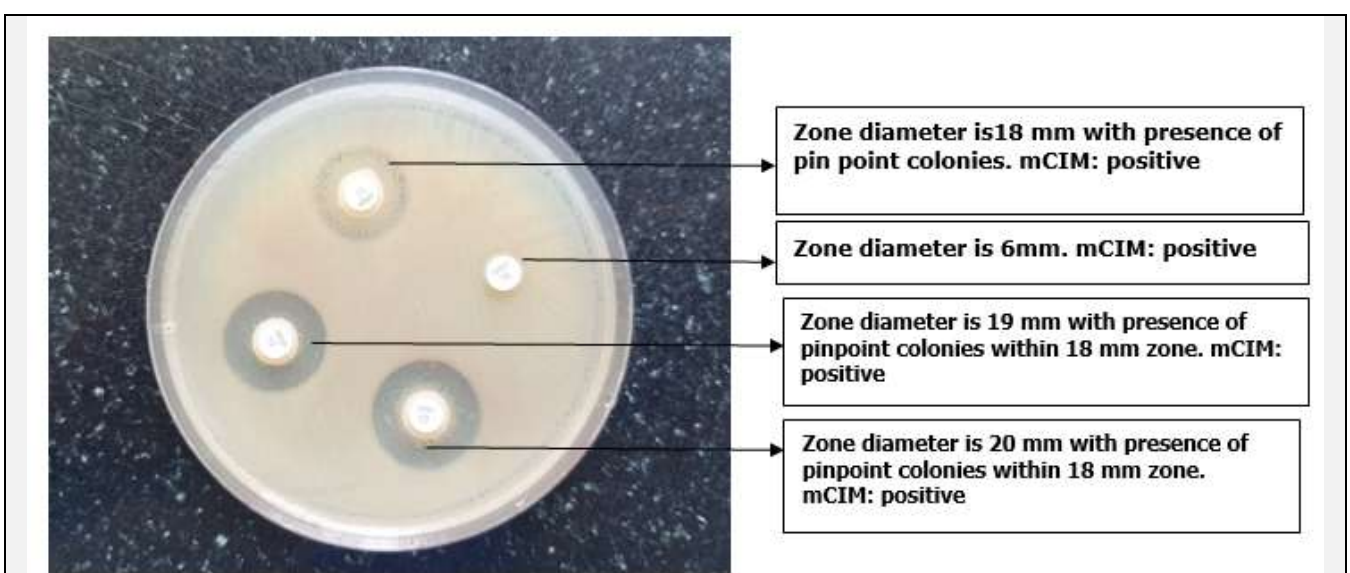

Figure 2. Overnight Lawn Cultured Escherichia coli ATCC 25922, with Meropenem (10 µg) Disc in Place. The Test Isolates Which were Incubated in Trypticase Soy Broth with Meropenem Disc (Fig: 1) Produced Carbapenemase, the Meropenem in the Disc was Hydrolysed and There was No Inhibition or Limited Growth Inhibition of the Meropenem-Susceptible E. Coli ATCC 25922.

DISCUSSION

Carbapenem which was once very effective drug in treating Gram negative infection is found to be ineffective in treating serious infections caused by Gram negative bacteria due to acquisition of resistance gene by such organisms.[25] mCIM method is one such phenotypic test devised for early and accurate detection of CREs. This study was conducted to see if there is any difference in positivity rate of mCIM over Kirby-Bauer disk diffusion method in detecting CRE.

In this study patient's age ranged from new born to 88 yrs. old. This wide range was because the study included all clinical samples which were CRE positive by conventional method, and the place of study was a tertiary care hospital where all age group population reports for the treatment. Mean age was 52, median: 57, and mode: 62 yrs. It was observed that the measures of central tendency for age was of older age group, which may be because older age group are frequently admitted[26] and they have a prolonged hospital stay due to their other associated chronic illness. These older age group also have decrease immune response, which makes them prone for infections, increase use of antibiotics, subjecting to increased risk of harbouring resistant organisms.[27] Vered Schechner et al.,[28] showed mean age 72 + / - 19 years (range, 15 – 97 years). Our age distribution findings corroborate with other studies.

In this study male constituted 78 % and female constituted only 22 %. Sarita Rani Jaiswal et al.,[29] showed male predominance of 61 %. The higher male prevalence in our study is because our study was conducted in a military based tertiary care hospital where predominant population are males.

In this study prevalence of CRE was estimated to be 18 % which corroborates with the various studies conducted in India. Various study conducted in India showed CRE prevalence ranging from 3 % to 60 % depending on the place of study and the study population,[30] being higher in hospitalized ICU patients. Ekadashi Rajni et al., 2018 shows prevalence of CRE to be 27 %.[31] Ruchika Bagga et al., 2015 study conducted in India, was presented on 4th International Conference on Clinical Microbiology and Microbial Genomics October 05 - 07, 2015 Philadelphia, USA showed high prevalence of CRE to be 60.22 % of all samples.[32]

The three most common samples in our study were urine, blood and pus each constituting 29.33 %, 20 %, and 11.33 % respectively. Pravin K. Nair et al., showed three most common samples were urine, pus and wound swab 46 %, 16 %, and 11 % respectively.[33] There is a higher prevalence of CRE found in blood sample in our study which was because the study was conducted in a tertiary care hospital where critically ill patient got referred who have already received some treatment in other hospitals and are not responding to the treatment.

Present CLSI guidelines 2019 with revised zone diameter for resistance and sensitive criteria does not mandate to conduct mCIM on routine basis on patient's sample.[24] As mCIM detects only CP-CRE, however there are other mechanisms of resistance other than carbapenemase production like, excessive efflux pump system, decrease in drug penetration by modification of diffusion barriers and altered metabolic activity.[9,10] In this study there are two isolates (one each of *Klebsiella pneumonia*e and *Escherichia coli*) which were mCIM negative which probably may be due to presence of non CP-CRE which needs to be further validated by genetic study.

The two most common CRE organisms were *Klebsiella pneumonia* (58 %) and *Escherichia coli* (32 %) which corroborates with various studies. Bo Gao et al.,[34] showed *Klebsiella pneumonia*e (44.8 %) the most common, followed by *Escherichia coli* (25.8 %) and *Enterobacter cloacae*. (13.8 %). Ravikant Porwal et al.,[35] showed two most common CRE in ICU setting to be *Klebsiella pneumonia*: 44 % and *Escherichia coli*: 26 %. Another study Satyajeet K Pawar et al.,[36] {Citation} also showed *Klebsiella pneumonia*e (63 %) and *E. coli* (19 %) the two most common CRE species isolated.

mCIM and Kirby Bauer disk diffusion tests are phenotypic tests used to detect carbapenem resistance in CREs which is dependent on many variables like media components and thickness, incubation period and temperature, reading method, subjective variation in interpreting the result depending on the person reading the result etc. Though most of the parameters are standardised but few are difficult to standardise consistently which affects the reproducibility of phenotypic tests like mCIM and Kirby Bauer disk diffusion tests. However, mCIM is shown to have excellent reproducibility. In one of studies, validation study on mCIM was conducted to see its reproducibility, where the mCIM test which was carried out by a lab was repeated by nine other labs. The result showed excellent reproducibility across laboratories.[23]

The limitation of this study is that the findings are not compared with the genetic study to see for the presence of resistant genes. These tests were carried out in a laboratory setting where the environment subjected to the organisms is not similar as in vivo, hence, the induction of certain genes may vary which may affect the results of the phenotypic study. Whether the organisms which were negative for mCIM harbour resistance genes or not needs to be validated by a molecular study. By doing so, it will further add to the clarity that whether Kirby Bauer test following CLSI 2019 revised zone diameter guidelines are over estimating the prevalence of CRE or not, and will also help in finding the accuracy of both the phenotypic tests.

CONCLUSIONS

There is significant difference in the percentage positivity as observed in this study. mCIM is a test which has high sensitivity and high specificity. However, to get accurate and consistent result, mCIM being a phenotypic test, is to be done under standardised conditions as described in CLSI. If any deviation from the standardised method is followed, then the result is often inconsistent and inaccurate. This descriptive study itself is not adequate to comment as to which test is better in detecting CRE unless the findings are compared with molecular study. However, in this study it is found that there is no practical added advantage of mCIM

over Kirby-Bauer method in detecting CRE as both the tests took similar amount of time (overnight incubation) for the result to be made available.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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