RESEARCH PAPER

Diagnostic Utility Of The Modified Carbapenem Inactivation Method (Mcim) And Edta-Cim (Ecim) For Phenotypic Identification Of Metallo-Beta-Lactamase Co-Producers

Rajarajeswari B[1], Mathavi Sureshkumar[2*], Reena Rajan[3]

[1]Department Of Microbiology, Vinayaka Mission'S Kirupananda Variyar Medical College & Hospitals, Salem, Vinayaka Mission'S Research Foundation (Deemed To Be University), Salem, Tamilnadu, India. Email: rajarajeswarichandru1997@gmail.com

[2*]Department Of Microbiology, Vinayaka Mission'S Kirupananda Variyar Medical College & Hospitals, Salem, Vinayaka Mission'S Research Foundation (Deemed To Be University), Salem, Tamilnadu, India. Email: drmathavimicro@gmail.com

[3]Department Of Microbiology, Vinayaka Mission'S Kirupananda Variyar Medical College & Hospitals, Salem, Vinayaka Mission'S Research Foundation (Deemed To Be University), Salem, Tamilnadu, India. Email: ReenaRajan83@gmail.com

***Corresponding Author:**

Mathavi Sureshkumar, Professor And Head, Department Of Microbiology, Vinayaka Mission'S Kirupananda Variyar Medical College & Hospitals, Salem, Vinayaka Mission'S Research Foundation (Deemed To Be University), Salem, Tamilnadu, India. Email: drmathavimicro@gmail.com

Abstract

Introduction: The EDTA modified carbapenem inactivation method (eCIM), is a phenotypic assay easy to perform in clinical laboratories, recommended by Clinical Laboratory Standard Institute for distinguishing carbapenemase-producing Enterobacterales and Pseudomonas expressing serine carbapenemases from those producing metallobetalactamases. **Aims & Objectives:** The study aimed to evaluate two phenotypic assays (modified carbapenem inactivation method and EDTA modified carbapenem inactivation method). **Materials & Methods:** A cross- sectional study was done on 35 Carbapenem resistant clinical isolates collected during December 2023 to May 2024**. Results:** Among 35 carbapenem-resistant isolates, 32 (91.4%) were positive by mCIM. Among these, eCIM identified metallo-β-lactamase production in 18 (56.3%) isolates. **Conclusion:** The mCIM and eCIM can be adapted in Clinical laboratories for the rapid and accurate identification of Carbapenem resistant isolates. The eCIM aids in the accurate detection of metallobetalactamases producers, hence can be adapted in settings where the prevalence of MBL is high.

Keywords: Metallo-beta- lactamase, Serine carbapenemases, Phenotypic assay, New Delhi Metallobetalactamases

How To Cite This Article: Rajarajeswari B, Sureshkumar M, Rajan R. Diagnostic utility of the modified carbapenem inactivation method (mcim) and edta-cim (ecim) for phenotypic identification of metallo-beta-lactamase co-producers. Int J Drug Deliv Technol. 2026;16(9s): 333-339; Doi: 10.25258/Ijddt.16.9s.33

Introduction:

Carbapenem resistant organisms are characterized by multiple antimicrobial resistance, resulting in very limited therapeutic options available in clinical practice. Carbapenemase producing Enterobacterales have received much attention since they have the greatest potential to contribute to problem of overall antimicrobial resistance. Moreover, the presence of carbapenemase genes on conjugative plasmids promotes the survival of organisms under antibiotic treatments which is associated with the rapid emergence of carbapenem resistance.[1] Carbapenemases are beta-lactamases that belong to Amber classes (A, B, and D). Class A carbapenemases are serine b-lactamases, with Klebsiella pneumoniae carbapenemases (KPCs) being the most common. Class B carbapenemases are metallo-carbapenemases (also known as metallo-b-lactamases, MBL), with NDM, IMP, and VIM as common types. Class D is predominantly OXA-48-like serine beta-lactamases.[2]

The phenotypic detection of Carbapenem resistant Enterobacteriaceae is complicated by the fact that Enterobacteriaceae may be non susceptible (intermediate

or resistant) to carbapenems via a variety of mechanisms. Proteus, Providencia, and Morganella species demonstrate intrinsically elevated MICs to imipenem.[3] Once carbapenem resistance is detected through standard sus- ceptibility testing, additional phenotypic tests can help to identify Carbapenemase producing organisms. Various phenotypic carbapenemase detection tests have been developed over the last decade which include the modified Hodge test (MHT), the Carba NP test and its variants, and the carbapenem inactivation method (CIM). These tests target carbapenemase production but provide no guidance regarding the specific carbapenemase type.[4] The advantages of phenotypic assays over genotypic tests are that they are substantially less expensive than genotypic tests

The modified carbapenem inactivation method (mCIM) is highly sensitive and specific however, it does not differentiate carbapenemase-producing Enterobacterales expressing serine carbapenemases (i.e., class A and D enzymes) from metallobetalactamases (MBLs)[5]. The EDTA modified carbapenem inactivation method (eCIM) had an overall sensitivity and specificity of 100% and was adopted by the Clinical and Laboratory Standards Institute as a method to use in combination with the mCIM to identify MBL-producing Enterobacteriaceae.[6]

Based on previous literature, two phenotypic assays (modified carbapenem inactivation method and EDTA modified carbapenem inactivation method) that are easy to perform in clinical laboratories were selected for evaluation.

Materials &Methods:

A cross- sectional study was done on 35 Carbapenem resistant clinical isolates collected during December 2023 to May 2024. Non repetitive carbapenem resistant gram negative bacilli obtained from various clinical samples during the study period was included. Gram negative isolates other than Enterobacterales and Pseudomonas aeruginosa were excluded.

Under strict aseptic conditions samples such as blood, urine, sputum, pus, body fluids etc. were inoculated onto blood agar and Mac Conkey agar and incubated at 37°C overnight. Gram negative isolates were identified by staining, colony morphology and subjected to biochemical reactions such as Oxidase test, Triple sugar iron agar, Indole test, Citrate utilization test, Urea hydrolysis test and Phenyl pyruvic acid test. Antimicrobial susceptibility testing was performed by Kirby Bauer disk diffusion method. The following antibiotics were used; Amoxycillin Clavulanate(20/10µg), Piperacillin tazobactam(100/10µg), Cefoperazone sulbactam (75/30µg), Ampicillin (10µg), Levofloxacin (5µg),Ciprofloxacin (5µg), Gentamicin (10µg), Amikacin(30µg), Cefepime(30µg), Cefotaxime(30µg), Ceftazidime(30µg), Cotrimazole(25µg), Imipenem(10µg), Meropenem(10µg), Nitrofurantoin(300µg), Norfloxacin (10µg),Nalidixic acid(30µg) and Doxycycline(30µg). Isolates with a zone diameter of ≤19 mm for meropenem and imipenem were subjected to modified carbapenem inactivation method and EDTA-carbapenem inactivation method. Minimum Inhibitory Concentration of Carbapenems, aminoglycosides, fluoroquinolones, cotrimoxazole and tigecycline was determined by Vitek 2 automated method.

Modified carbapenem Inactivation method (mCIM) test :

The modified carbapenem inactivation method (mCIM) was performed in accordance with CLSI guidelines. Fresh bacterial colonies obtained after 18–24 hours of incubation on blood agar plates were used for testing. One to three well-isolated colonies were emulsified in 2 mL of brain heart infusion (BHI) broth and vortexed for 10–15 seconds. A 10-µg meropenem disk was added to each tube using sterile forceps, and the suspension was incubated at 37 °C for 4 hours.

Following incubation, the meropenem disk was removed from the suspension using a sterile 10-µL loop and placed onto a Mueller–Hinton agar (MHA) plate previously inoculated with a 0.5 McFarland suspension of Escherichia coli ATCC 25922 as the indicator strain. MHA plates were incubated at 37°C for 18-24 hours.[6]

Interpretation mCIM:

A zone diameter of 6-15mm or presence of pinpoint colonies within 16-18mm zone is considered as positive for carbapenemase production

A zone diameter of ≥ 19mm is considered as negative for carbapenemase production

A zone diameter of 16-18mm or zone diameter of ≥19mm and the presence of pinpoint colonies within the zone is considered as indeterminate for carbapenemase production

EDTA-modified carbapenem inactivation method(eCIM) test :

20 µL of the 0.5 M EDTA was added to 2ml Brain Heart Infusion broth to obtain a final concentration of 5mM EDTA. Fresh bacterial colonies obtained after 18–24 hours of incubation on blood agar plates were used for testing. One to three well-isolated colonies were emulsified in 2 mL of brain heart infusion (BHI) broth and vortexed for 10–15 seconds. A 10-µg meropenem disk was added to each tube using sterile forceps, and the suspension was incubated at 37 °C for 4 hours.

Following incubation, the meropenem disk was removed from the suspension using a sterile 10-µL loop and placed onto a Mueller–Hinton agar (MHA) plate previously inoculated with a 0.5 McFarland suspension of Escherichia coli ATCC 25922 as the indicator strain. MHA plates were incubated at 37°C for 18-24 hours. The zone of diameter was interpreted only when mCIM test was positive.

Metallo-beta-lactamase positive: A ≥ 5mm increase in zone diameter for eCIM Vs zone diameter for mCIM is considered as positive for metallo-beta-lactamase production.

Metallo-beta-lactamase negative: A ≤ 4mm increase in zone diameter for the eCIM Vs zone diameter for mCIM is considered as negative for metallobetalactamases production.

Results:

In the present study, 35 carbapenem resistant isolates were evaluated. The minimum inhibitory concentration of carbapenems against these isolates were in the range of 4-16 µg/ml. **[Table:1]**

Table 1: Minimum Inhibitory Concentration (MIC) of Carbapenems against clinical isolates

Organisms	**MIC**					
	Imipenem		**Meropenem**		**Ertapenem**	
N=35	4-8µg/ml (R)	≥16 µg/ml (R)	≥8 µg/ml (R)	≥16 µg/ml (R)	4-8µg/ml (R)	≥16 µg/ml (R)
E. coli (13)	4 (30.77%)	9 (69.23%)	6 (46.15%)	7 (53.85%)	12 (92.31%)	1 (7.69%)
Klebsiella pneumoniae (18)	3 (16.67%)	15 (83.33%)	3 (16.67%)	15 (83.33%)	18 (100%)	0 (0%)
Klebsiella oxytoca (1)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	1 (100%)	0 (0%)
Citrobacter koseri (1)	0 (0%)	1 (100%)	0 (0%)	1 (100%)	1 (100%)	0 (0%)
Pseudomonas aeruginosa (2)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	-	-

Among 35 carbapenem resistant isolates, modified carbapenem inactivation method (mCIM) detected carbapenemase production in 32 (91.4%) isolates, while two (5.7%) were mCIM negative and one (2.9%) yielded an indeterminate result. The EDTA-modified carbapenem inactivation method (eCIM) was performed on mCIM-positive isolates only and identified metallo-β-lactamase production in 18 of 32 (56.3%) isolates, whereas 14 (43.7%) were eCIM negative, suggesting non–metallo-β-lactamase carbapenemase production. **[Table:2]**

Table 2: Results of mCIM and eCIM testing for Carbapenem resistant isolates [N=35]

Organisms	**mCIM**			**eCIM**	
	Positive	**Negative**	**Indeterminate**	**Positive**	**Negative**
E. coli (13)	13 (100%)	0 (0%)	0 (0%)	8 (61.5%)	5 (38.5%)
Klebsiella Pneumoniae (18)	15 (83.3%)	2 (11.1%)	1 (5.6%)	8 (53.3%)	7 (46.7%)

Klebsiella oxytoca (1)	1 (100 %)	0 (0%)	0 (0%)	0 (0%)	1 (100 %)
Citrobacter koseri (1)	1 (100 %)	0 (0%)	0 (0%)	1 (100 %)	0 (0%)
Pseudomonas aeruginosa (2)	2 (100 %)	0 (0%)	0 (0%)	1 (50 %)	1 (50%)

13 (72.22%) isolates of Klebsiella pneumoniae showed intermediate resistance to Amikacin.69.23% E.coli isolates showed susceptibility to Amikacin. **[Table:3]**

Table 3: Minimum Inhibitory Concentration (MIC) of aminoglycosides against clinical isolates

Organisms	**MIC of aminoglycosides**					
	Amikacin				**Gentamicin**	
N=35	2-8µg/ml (S)	≥16 µg/ml (S)	32 µg/ml (I)	≥64 µg/ml (R)	≤ 1µg/ml (S)	≥16 µg/ml (R)
E. coli (13)	9 (69.23%)	1 (7.69%)	1 (7.69%)	2 (15.38%)	3 (23.08%)	10 (76.92%)
Klebsiella pneumoniae (18)	4 (22.22%)	1 (5.56%)	13 (72.22%)	0 (0%)	5 (27.78%)	13 (72.22%)
Klebsiella oxytoca (1)	0 (0%)	0 (0%)	1 (100 %)	0 (0%)	0 (0%)	1 (100 %)
Citrobacter koseri (1)	1 (100 %)	0 (0%)	0 (0%)	0 (0%)	1 (100 %)	0 (0%)
Pseudomonas aeruginosa (2)	2 (100 %)	0 (0%)	0 (0%)	0 (0%)	2 (100 %)	0 (0%)

13 (100%) E coli isolates showed susceptibility to Tigecycline and 6(33.33%) Klebsiella pneumoniae isolates showed resistance to tigecycline. **[Table:4]**

Table 4: Minimum Inhibitory Concentration (MIC) of tigecycline against clinical isolates

Organisms	**MIC of tigecycline**		
(N=33)	≤0.5 µg/ml (S)	1 µg/ml (S)	2-4 µg/ml (R)
E. coli (13)	12 (92.31%)	1 (7.69%)	0 (0%)
Klebsiella pneumoniae (18)	5 (27.78%)	7 (38.89%)	6 (33.33%)
Klebsiella oxytoca (1)	1 (100%)	0 (0%)	0 (0%)
Citrobacter koseri (1)	1 (100%)	0 (0%)	0 (0%)

35(100%) isolates showed resistance to Ciprofloxacin. (≥4 µg/ml). Among the Enterobacterales,23(65.71%) out of 35 isolates showed resistance to Cotrimoxazole (≥320µg/ml).

Discussion:

Carbapenem-resistant Gram-negative organisms, particularly members of the Enterobacterales, represent a significant global public health concern due to limited therapeutic options and high mortality rates. The increasing prevalence of carbapenemase-producing isolates has necessitated the use of reliable, cost-effective phenotypic methods for routine detection, especially in resource-limited settings. In the present study, we evaluated the performance of modified carbapenem inactivation method (mCIM) and EDTA-modified carbapenem inactivation method (eCIM) for the detection and differentiation of carbapenemase-producing isolates and compared our findings with previously published literature.

In our study, mCIM detected carbapenemase production in 32 out of 35 (91.4%) carbapenem-resistant isolates. This detection rate is consistent with earlier studies

reporting high sensitivity and specificity of mCIM, ranging from 90% to 100% for carbapenemase detection among Enterobacterales [4,5,7]. Pierce et al., who originally described the mCIM assay, reported excellent performance of the test with high concordance to molecular methods, supporting its reliability for routine laboratory use [5]. Similarly, Lutgring and Limbago highlighted mCIM as a robust phenotypic method capable of detecting a broad range of carbapenemases [4].

The high mCIM positivity observed in the present study aligns with findings from other Indian studies. Archana et al. reported successful detection of carbapenemase production in nearly all carbapenem-resistant isolates using mCIM and its simplified versions [13]. Cheemala et al. also demonstrated high detection rates of carbapenemase-producing Gram-negative bacilli using phenotypic methods, reinforcing the applicability of mCIM in tertiary care settings in India [16]. These similarities may reflect the widespread circulation of carbapenemase-producing strains in the Indian subcontinent, particularly those harboring NDM and OXA-48-like enzymes.

Among the mCIM-positive isolates in our study, eCIM identified metallo-β-lactamase (MBL) production in 18 (56.3%) isolates. This finding indicates that MBLs constitute a substantial proportion of carbapenem resistance mechanisms in our setting. Comparable proportions of MBL producers have been reported in previous studies from India and other regions [7,8]. Tsai et al. demonstrated that the combined use of mCIM and eCIM provides high sensitivity and specificity for differentiating MBL producers from serine carbapenemases, with strong correlation to molecular detection methods [8].

The predominance of MBL-producing isolates observed in our study is in agreement with global epidemiological trends showing widespread dissemination of NDM-type enzymes, particularly in Enterobacterales [1]. Studies have consistently reported NDM as the most prevalent MBL in Indian clinical isolates, often co-existing with other carbapenemases such as OXA-48-like enzymes [2,10]. Such co-production complicates phenotypic detection and therapeutic decision-making.

In our study, a small proportion of isolates were mCIM negative or yielded indeterminate results. Similar observations have been reported in earlier studies, where low-level expression of carbapenemases or the presence of certain OXA-type enzymes resulted in reduced sensitivity of phenotypic assays [10]. Zhang et al. reported limitations of mCIM in detecting certain OXA-type carbapenemases, particularly OXA-23-like enzymes, emphasizing the need for cautious interpretation of results [10]. These findings suggest that while mCIM is highly reliable, no single phenotypic method is entirely infallible.

The performance of eCIM in detecting MBL-producing isolates in our study was satisfactory and consistent with published data. Sfeir et al. demonstrated that eCIM is an effective phenotypic method for identifying MBL producers among Enterobacterales, although limitations exist in isolates co-harboring both MBL and serine carbapenemase genes [12]. Gill et al. reported reduced performance of eCIM in detecting IMP-type MBLs among Pseudomonas aeruginosa isolates, highlighting organism-specific variability in test performance [11]. Despite these limitations, eCIM remains a valuable adjunct to mCIM for routine laboratory use.

Antimicrobial susceptibility patterns observed in our study further underscore the clinical relevance of carbapenemase detection. High minimum inhibitory concentrations (MICs) to imipenem and meropenem among a significant proportion of isolates are consistent with previous reports documenting extensive resistance among carbapenemase-producing organisms [9]. The observed variability in susceptibility to aminoglycosides and tigecycline aligns with studies demonstrating limited but important therapeutic options for carbapenem-resistant infections [14,15].

Studies by Terbtothakun et al. and Nulsopapon et al. have demonstrated synergistic effects of carbapenems combined with aminoglycosides or tigecycline against carbapenem-resistant Enterobacterales, particularly those harboring NDM enzymes [14,15]. These findings highlight the importance of accurate carbapenemase detection not only for infection control but also for guiding optimized antimicrobial therapy.

Overall, the findings of the present study corroborate previous reports supporting the combined use of mCIM and eCIM as reliable, cost-effective phenotypic tools for detecting and differentiating carbapenemase-producing isolates. Given the high burden of carbapenem resistance in India and other resource-limited settings, these assays offer practical alternatives to molecular methods, which may not be readily available in all laboratories. The incorporation of mCIM and eCIM into routine diagnostic workflows can facilitate early detection, appropriate

antimicrobial stewardship, and effective infection control interventions.

Limitation of the study:

The relatively small sample size and molecular characterization of carbapenemase genes was not performed for all isolates; therefore, complete correlation between phenotypic and genotypic methods could not be established. Although the modified carbapenem inactivation method (mCIM) and EDTA-modified carbapenem inactivation method (eCIM) are recommended and widely used phenotypic assays, they may not detect all carbapenemase variants, particularly isolates with low-level enzyme expression or co-production of multiple carbapenemases. In addition, clinical outcome data were not assessed, limiting the ability to evaluate the impact of laboratory findings on patient management and treatment outcomes.

Conclusion:

Majority of the isolates in this study showed a MIC of more than 16 micrograms/ml for Imipenem and Meropenem. Low susceptibility to aminoglycosides and tigecycline were shown by Klebsiella pneumoniae isolates. This study highlights a high rate of carbapenemase production among carbapenem-resistant isolates, with metallo-β-lactamases accounting for a substantial proportion. The combined use of mCIM and eCIM offers a simple, reliable, and cost-effective phenotypic approach for detection and differentiation of carbapenemase mechanisms in routine clinical microbiology laboratories, supporting timely infection control and antimicrobial stewardship efforts.

References;

1.Guh AY, Limbago BM, Kallen AJ. Epidemiology and prevention of carbapenem-resistant Enterobacteriaceae in the United States. Expert Rev Anti Infect Ther 2014; 12:565–580. http://dx.doi.org/10.1586/14787210.2014.902306

2.Stojanoski, V., Hu, L., Sankaran, B., Wang, F., Tao, P., Prasad, B. V. V., et al. Mechanistic Basis of OXA-48-Like b-Lactamases' Hydrolysis of Carbapenems. ACS Infect. Dis.2021; 7: 445–460. doi: 10.1021/acsinfecdis.0c00798

3.Clinical and Laboratory Standards Institute. 2012. Performance standards for antimicrobial susceptibility testing; 22nd informational supplement. CLSI document M100-S22. Clinical and Laboratory Standards Institute, Wayne, PA.

4. Lutgring JD, Limbago BM. The problem of carbapenemase producing-carbapenem-resistant-Enterobacteriaceae detection. J Clin Microbiol 2016; 54:529–534. doi:10.1128/JCM.02771-15.

5.Pierce VM, Simner PJ, Lonsway DR, Roe-Carpenter DE, Johnson JK, Brasso WB, Bobenchik AM, Lockett ZC, Charnot-Katsikas A, Ferraro MJ, Thomson RB, Jr, Jenkins SG, Limbago BM, Das S. Modified carbapenem inactivation method for phenotypic detection of carbapenemase pro duction among Enterobacteriaceae. J Clin Microbiol 2017; 55:2321–2333. https://doi.org/10.1128/JCM.00193-17.

6. CLSI. 2018 Performance standards for antimicrobial susceptibility testing, 28th ed. CLSI supplement M100. Clinical and Laboratories Standards Institute, Wayne, PA.

7.Zhong, H., Wu, M.L., Feng, W. J., Huang, S. F., and Yang, P. Accuracy and Applicability of Different Phenotypic Methods for Carbapenemase Detection in Enterobacteriaceae: A Systematic Review and Meta-Analysis. J. Glob Antimicrob. Resist.2020; 21, 138–147. doi: 10.1016/j.jgar.2019.10.010

8. Tsai, Y. M., Wang, S., Chiu, H. C., Kao, C. Y., and Wen, L. L. Combination of Modified Carbapenem Inactivation Method (mCIM) and EDTA-CIM (eCIM) for Phenotypic Detection of Carbapenemase-Producing Enterobacteriaceae. BMC Microbiol.2020; 20, 315. doi: 10.1186/s12866-020-02010-3

9. Kumudunie, W. G. M., Wijesooriya, L. I., and Wijayasinghe, Y. S. Comparison of Four Low-Cost Carbapenemase Detection Tests and a Proposal of an Algorithm for Early Detection of Carbapenemase-Producing Enterobacteriaceae in Resource-Limited Settings.2021; PloS One 16, e0245290. doi: 10.1371/journal.pone.0245290.

10. Zhang Z, Wang D, Li Y, Liu Y and Qin X. Comparison of the Performance of Phenotypic Methods for the Detection of Carbapenem Resistant Enterobacteriaceae (CRE) in Clinical Practice. Front. Cell. Infect. Microbiol.2022; 12:849564

11. Gill, C. M., Lasko, M. J., Asempa, T. E., and Nicolau, D. P. Evaluation of the EDTA-Modified Carbapenem Inactivation Method for Detecting Metallo-b Lactamase-Producing Pseudomonas Aeruginosa. J. Clin. Microbiol. 2020;58, e02015-19. doi: 10.1128/JCM.02015-19

12. Sfeir MM, Hayden JA, Fauntleroy KA, Mazur C, Johnson JK, Simner PJ, Das S, Satlin MJ, Jenkins SG, Westblade LF. 2019. EDTA modified carbapenem inactivation method: a phenotypic method for detecting metallo-β lactamase-producing Enterobacteriaceae.2019; J Clin Microbiol 57:e01757-18. https://doi.org/10 .1128/JCM.01757-18.

13. Archana A, Kokkayil P, DebBarma P, Priyadarshi K, Thakuria B. Evaluation of simplified carbapenem inactivation method (sCIM) as a phenotypic method for rapid detection of carbapenemase-producing Enterobacterales: Study from a tertiary care hospital in North India. J Lab Physicians. 2024;16:536-42. doi: 10.25259/JLP_102_2024

14. Terbtothakun, P.; Nwabor, O.F.; Siriyong, T.; Voravuthikunchai, S.P.; Chusri, S. Synergistic Antibacterial Effects of Meropenem in Combination with Aminoglycosides against Carbapenem-Resistant Escherichia coli Harboring blaNDM-1 and blaNDM-5. Antibiotics 2021, 10, 1023. https://doi.org/10.3390/ antibiotics10081023.

15.Nulsopapon, P.; Nasomsong, W.; Pongchaidecha, M.; Changpradub, D.; Juntanawiwat, P.; Santimaleeworagun, W. The Synergistic Activity and Optimizing Doses of Tigecycline in Combination with Aminoglycosides against Clinical Carbapenem-Resistant Klebsiella pneumoniae Isolates. Antibiotics 2021, 10, 736. https:// doi.org/10.3390/antibiotics10060736.

16. Cheemala SS, Vara A, Lakshmi MS, Pradhan S, Kalyani K. Phenotypic Detection of Carbapenemase Production in Gram Negative Bacilli from Clinical Isolates in a Tertiary Care Hospital in Telangana. *J Pure Appl Microbiol.* 2023;17(4):2111-2118. doi: 10.22207/JPAM.17.4.07