World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 3.454
Year - 2024
Volume: 3; Issue: 4
Page: 160-165

TREATING CARBAPENEM-RESISTANT ENTEROBACTERALES INFECTIONS: SIGNIFICANCE OF COMBINING CEFTAZIDIME-AVIBACTAM WITH AZTREONAM IN INDIAN SCENARIO

Dr. Sreevalsan T. V.*[1] and Dr. Rohitha S. Chandra[2]

[1]Senior Consultant and Head, Department of Critical Care Medicine, Lisie Hospital, Kochi, Kerala.

[2]Clinical Microbiologist and Infection Control Officer, Lisie Hospital, Kochi, Kerala.

Article Received: 15 June 2024 || ***Article Revised: 06 July 2024*** || ***Article Accepted: 28 July 2024***

Corresponding Author: Dr. Sreevalsan T. V.
Senior Consultant and Head, Department of Critical Care Medicine, Lisie Hospital, Kochi, Kerala.
DOI: https://doi.org/10.5281/zenodo.13151249

ABSTRACT

In Indian ICUs, carbapenem resistance is seen among a significant proportion of Gram-negative infections. In India, NDM and OXA-48 enzymes are the predominant carbapenemases unlike the Western countries where KPC is the commonest. As the MBLs including NDM are not inhibited by Avibactam, Ceftazidme- Avibactam (CAZ-AVI) will be of limited use in India. As Aztreonam (ATM) is not hydrolyzed by the NDM, combining it with CAZ-AVI can be effective in this context. This single centre retrospective study aimed to find out the susceptibility of CRE isolates to CAZ-AVI and the usefulness of combining it with ATM to treat CRE resistant to CAZ-AVI. 294 CRE isolates were tested from 30 May 2022 to 30 July 2023. Susceptibility to CZA-AVI, ATM was studied. Synergy of the combination of the two among the isolates resistant to CAZ-AVI was also studied. It was found that Klebsiella pneumoniae was the most common CRE. 56.12% of the CRE isolates were resistant individually to CAZ-AVI and ATM. However, 83% of these isolates were found to be sensitive on synergy testing. This pattern is suggestive of the presence of NDM along with OXA-48 among CREs as reported by other Indian studies. Since Ceftazidime-Avibactam as a monotherapy for CREs will likely result in clinical failure, susceptibility testing with CAZ-AVI and synergy testing with ATM should be used to guide the treatment of CRE infections.

KEYWORDS: Carbepenem-resistant Enterobacterales (CRE), carbapenemase, Ceftazidme Avibactam NDM, MBLs.

INTRODUCTION

Infection caused by Carbapenem resistant Enterobacteriaceae (CRE) strains has been associated with prolonged hospital stay, increased mortality, and elevated healthcare expenses.[1-4] In Indian ICUs, a significant proportion of Gram-negative organisms are carbapenem-resistant. There are only a few options to treat CRE infections. In the Western world Klebsiella pneumoniae carbapenemase (KPC) is the main enzyme responsible for carbapenem resistance in CREs. In India, the scenario is different with CRE strains often harbouring New Delhi metallo-beta-

lactamase (NDM) and oxacillinase (OXA-48) enzymes.[5-8] A few years back Ceftazidime avibactam (CAZ-AVI) was introduced as a promising molecule for treating CRE infections. As the Metallo betalactamases (MBLs) enzymes are not inhibited by avibactam, it is not useful where NDM or other MBLs are responsible for carbapenem resistance. NDM enzyme does not hydrolyse Aztreonam (ATM) effectively. In India, where NDM is predominantly seen combining CAZ-AVI and ATM is an effective way of treating infections caused by CRE. Another in vitro study found the same combination to be effective for CRE isolates harbouring the NDM and OXA-48 enzymes.[9] CAZ-AVI has been recommended by The Infectious Diseases Society of America (IDSA) as the first-line antibiotic for CREs producing KPC or OXA-48 beta lactamases with proven in vitro susceptibility to CAZ-AVI.[10] The Indian Council of Medical Research (ICMR) also has recommended CAZ-AVI as the first-line therapy for CRE harbouring OXA-48 enzymes.[11] This study aimed to find out the susceptibility pattern of CRE to CAZ-AVI and the effectiveness of CAZ-AVI/ATM combination in overcoming their resistance to CAZ-AVI.

MATERIALS AND METHODS

This single-centre retrospective study was conducted at a tertiary care centre in central Kerala. 294 CRE isolates which were tested from 30 May 2022 to 30 July 2023 were included. Approvals from the Institutional Research Board and the Institutional Ethics Committee were obtained. Being a retrospective study, informed consent was not taken.

Test Methods

Synergy testing for Ceftazidime avibactam and Aztreonam was performed by the modified E test method. For this, a lawn culture of the test organism with turbidity 0.5Mf was performed on a Mueller Hinton Agar (MHA) plate. Ceftazidime avibactam E test strip and Aztreonam 30µg disc were placed on the plate in such a way that the distance between the two was 15mm. After overnight incubation, the MIC for ceftazidime avibactam and the zone diameter for Aztreonam were measured and interpreted as per Central Laboratory Standards Institute (CLSI) guidelines. An inverse D zone with the flattening towards the Aztreonam disc or increase in the zone of inhibition between the Ceftazidime-Avibactam strip and the Aztreonam disc was used to demonstrate synergy as per the guidance document of ICMR (Fig. 1).[12] Using this method, susceptibility to Cefatzidime- Avibactam and Aztreonam individually was obtained apart from synergy testing.

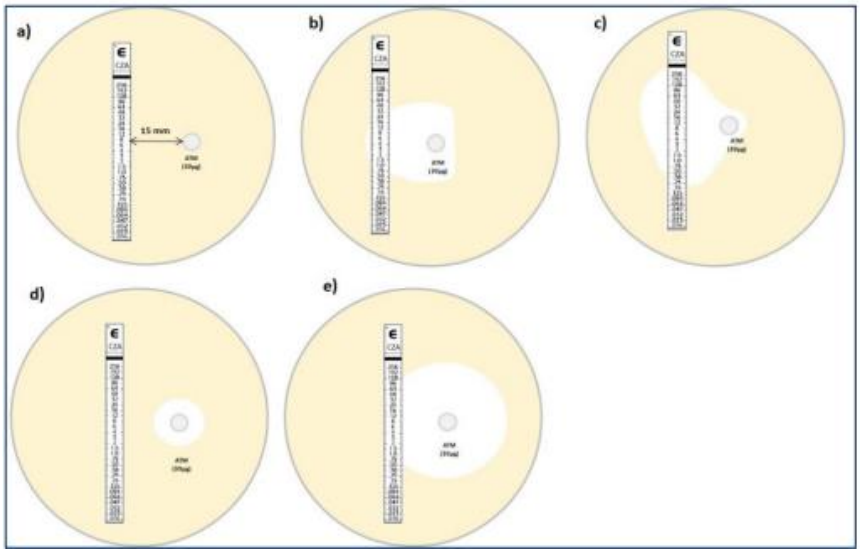

Fig. 1: E test method used to demonstrate synergy between Ceftazidime-Avibactam and Aztreonam.

RESULTS

Among 294 isolates of CRE, 125 (42.517%) were susceptible to CAZ-AVI and 4(1.36%) to ATM. The remaining 165 (56.122%) were resistant to both. These isolates were tested for synergy. Among these 165, 137 (83%) isolates exhibited synergy and 27 (17%) exhibited no synergy (Fig. 2).

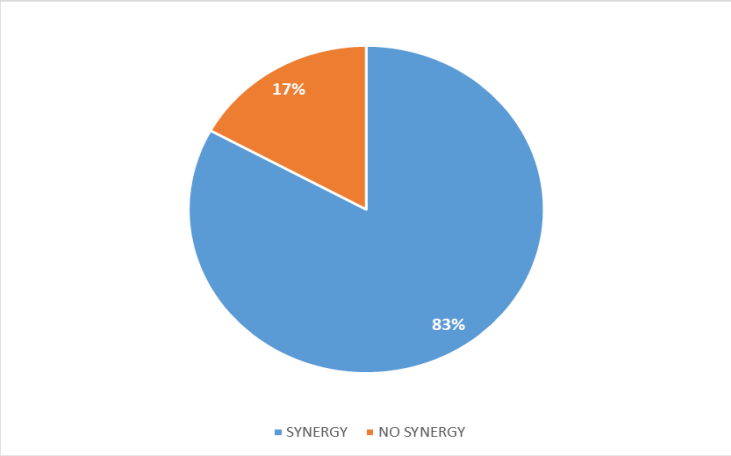

Fig. 2: Synergy between CAZ-AVI and ATM among CRE isolates resistant individually to CAZ-AVI and ATM.

In the 137 isolates which were individually resistant to CAZ-AVI and ATM, but exhibited synergy, presence of MBL along with OXA-48 like or KPC enzymes are likely to be responsible for carbapenem resistance, where as in the 27 isolates which did not exhibit synergy, other enzymatic and non-enzymatic mechanisms or a combination of both are likely. Colistin-resistance was found in 12 isolates. Respiratory secretions accounted for the maximum number of CRE infections (112/294 -38.1%). Urine and blood accounted for 20.1% each (59/294). The remaining samples included tissues and other body fluids. Urinary and respiratory infections with secondary bacteraemia were included under blood to avoid duplication of data. Klebsiella pneumoniae was the most predominant organism (239/294) followed by E coli (42/294) accounting for 81.3% and 14.3% respectively. All other organisms collectively accounted for less than 5% of the CRE isolates (Fig. 3).

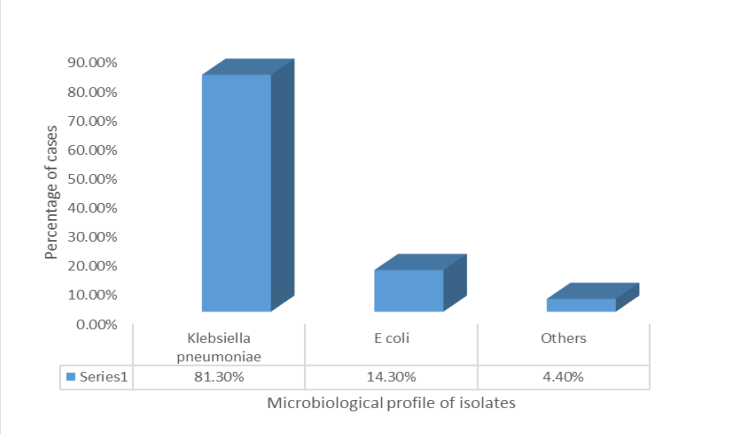

Fig. 3: Microbiological profile of CRE Isolates.

Out of the total 294 isolates included in this study, PCR was done for 14 as per the treating clinician's request. In this, OXA-48 was found in 10 (71.4%) cases and NDM in 9 (64.3%). CTX-M and VIM were detected in 12 and 1 cases respectively.

DISCUSSION

Significant regional differences in enzyme epidemiology have been reported. In the United States, the KPC enzyme is endemic and NDM as well as OXA-48 enzymes are reported as sporadic cases.[13] Significant regional variation in the predominant carbapenemase genes was reported in a multinational study from different centres across 36 countries. 1098 CRE isolates were screened for carbapenemase (CPE) genes after genome sequencing. The most predominant carbapenemase enzyme was KPC in Western European and Latin American countries with its presence detected in 66.5% and 70.0% respectively in CRE isolates. Among CRE isolates from the Asia-Pacific region MBL genes were detected in 61.6% of which 92.7% (101/109) were NDM. KPC, MBL and OXA-48-like enzymes were detected in 25.6%, 29.5% and 31.7% of CRE isolates from Eastern Europe, respectively. In Greece and Romania, KPC predominated while in Russia and Turkey OXA-48-like was the predominant enzyme. MBLs, mainly NDM, were found to be common in Russia, Turkey Poland Belarus, and Greece.[14] In a Japanese study IMP-type MBLs were uniquely dominant in CREs.[15] According to a study from Ghana, carbapenem resistance among Enterobacteriaceae was low 5.7% and among these NDM was the commonest carbapenemase.[16] An Egyptian study reported resistance to both CAZ-AVI and ATM in 90% of 100 carbapenem-resistant Klebsiella pneumoniae and E. coli isolates, but 90% of these showed synergy between the two. These isolates were found to produce both metallo β-lactamases and serine β-lactamases. [17] In another similar study, the combination of CAZ-AVI and ATM was found to be synergistic for all CRE isolates, and hence the same was found to be useful against MBL-producing Klebsiella pneumoniae and particularly against those isolates producing more than one carbapenemases. Therefore, the combination of CAZ-AVI and ATM is considered an effective therapeutic option particularly against Klebsiella pneumoniae and E. coli isolates producing multiple metallo β-lactamases and serine β-lactamases.[18] A recent Indian study from Pune detected NDM in 62.5% of the CRE isolates. OXA-48 enzyme was also predominant its presence detected in 66.3% of the isolates. KPC enzyme was detected only in 3.8% of CRE isolates.[19] Presence of NDM were more in E coli compared to Klebsiella . Another Indian study revealed the same pattern where Klebsiella was the predominant CRE accounting for two-third of the isolates and presence of NDM in a great majority (nearly 80%).[20] In our study as well, among CREs, Klebsiella pneumoniae was the most common (239/294), followed by E coli (42/294). 121/239 Klebsiella pneumoniae isolates were sensitive to CAZ-AVI whereas only 3/42 Escherichia coli were sensitive to CAZ-AVI. This indicates most of the E coli harboured MBLs. In India, empirical therapy with Ceftazidime-Avibactam will be ineffective among 50-75% of CRE. A majority of these will be sensitive to CAZ-AVI-ATM. Empirical therapy with Ceftazidime-Avibactam alone will be ineffective among 50-75% of CRE in Indian scenario and a majority of these will be sensitive to CAZ-AVI-ATM. According to IDSA, if Enterobacterales isolates produce NDMs (or any other MBLs), preferred antibiotic options include Ceftazidime-Avibactam plus Aztreonam, or cefiderocol monotherapy. IDSA also suggests combining ATM with CAZ-AVI to treat CRE resistant to both Ertapenem and Meropenem, when carbapenemase testing results are not available, if the risk of MBL is high.[10] CAZ-AVI is freely available in India these days as it has become a generic drug. Indiscriminate use of CAZ-AVI alone or in combination with ATM to treat CRE infections is a potential challenge in places where the antibiotic stewardship system is fragile.[21]

CONCLUSION

Klebsiella pneumoniae was the commonest organism among CREs. 56% of CRE isolates were resistant to Ceftazidime-avibactam and Aztreonam individually. However majority (83%) of them exhibited synergy when used together. This pattern is suggestive of the presence of NDM along with OXA 48 among CREs as reported by other Indian studies. This indicates that Ceftazidime-Avibactam as a monotherapy will likely result in clinical failure in a majority of CRE

infections. Susceptibility testing with Ceftazidime Avibactam and synergy testing with Aztreonam should be used to guide treatment of CREs to ensure good outcome and to avoid misuse of these drugs.

REFERENCES

1. Stewardson AJ, Marimuthu K, Sengupta S, Allignol A, El-Bouseary M, Carvalho MJ, et al. Effect of carbapenem resistance on outcomes of bloodstream infection caused by Enterobacteriaceae in low income and middle-income countries (PANORAMA): A multinational prospective cohort study. Lancet Infect Dis, 2019; 19(6): 601–610. DOI: 10.1016/S1473-3099(18)30792-8.
2. Snyder BM, Montague BT, Anandan S, Madabhushi AG, Pragasam AK, Verghese VP, et al. Risk factors and epidemiologic predictors of bloodstream infections with New Delhi Metallo-b-lactamase (NDM-1) producing Enterobacteriaceae. Epidemiol Infect, 2019; 147: e137. DOI: 10.1017/S0950268819000256.
3. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant Klebsiella pneumoniaee infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol, 2008; 29(12): 1099–1106. DOI: 10.1086/592412.
4. Martin A, Fahrbach K, Zhao Q, Lodise T. Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to Enterobacteriaceae: Results of a systematic literature review and meta-analysis. Open Forum Infect Dis, 2018; 5(7): ofy150. DOI: 10.1093/ofid/ofy150.
5. Nagvekar V, Shah A, Unadkat VP, Chavan A, Kohli R, Hodgar S, et al. Clinical outcome of patients on ceftazidime–avibactam and combination therapy in carbapenem-resistant Enterobacteriaceae. Indian J Crit Care Med, 2021; 25(7): 780–784. DOI: 10.5005/ jp-journals-10071-23863.
6. Walia K, Ohri VC, Madhumathi J, Ramasubramanian V. Policy document on antimicrobial stewardship practices in India. Indian J Med Res, 2019; 149(2): 180–184. DOI: 10.4103/ijmr.IJMR_147_18.
7. Veeraraghavan B, Shankar C, Karunasree S, Kumari S, Ravi R, Ralph R. Carbapenem resistant Klebsiella pneumoniae isolated from bloodstream infection: Indian experience. Pathog Glob Health, 2017; 111(5): 240–246. DOI: 10.1080/20477724.2017.1340128.
8. Kazi M, Khot R, Shetty A, Rodrigues C. Rapid detection of the commonly encountered carbapenemases (New Delhi metallo-β lactamase, OXA-48/181) directly from various clinical samples using multiplex real-time polymerase chain reaction assay. Indian J Med Microbiol, 2018; 36(3): 369–375. DOI: 10.4103/ijmm.IJMM_18_324
9. Pragasam AK, Veeraraghavan B, Shankar BA, Bakthavatchalam YD, Mathuram A, George B. et al. Will ceftazidime/avibactam plus Aztreonam be effective for NDM and OXA-48-Like producing organisms: Lessons learnt from in vitro study. Indian J Med Microbiol, 2019; 37(1): 34–41. DOI: 10.4103/ijmm.IJMM_19_189.
10. Pranita D Tamma, Samuel L Aitken, Robert A Bonomo, Amy J Mathers, David van Duin, Cornelius J Clancy, Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa), Clinical Infectious Diseases, 15 July 2022; 75(2): 187–212, https://doi.org/10.1093/cid/ciac268.
11. Annual Report: Antimicrobial Resistance Research and Surveillance Network. Accessed June 2022. https://main.icmr.nic.in/sites/default/ f iles/guidelines/AMRSN_annual_report_2020.pdf. 2022. 11. Soman R, Veeraraghavan B, Hegde A, Jiandani P, Mehta Y, Nagavekar V, et al. Indian consensus on the management of

CRE infection in critically ill patients (ICONIC) - India. Expert Rev Anti Infect Ther, 2019; 17(8): 647–660. DOI: 10.1080/14787210.2019.1647103.

12. Indian Council of Medical Research. New Delhi, India: ICMR; 2022. Guidance on Diagnosis & Management of Carbapenem Resistant Gram-negative Infections.
13. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant enterobacteriaceae: The impact and evolution of a global menace. J Infect Dis, 2017; 215(suppl_1): S28–S36. DOI: 10.1093/infdis/jiw282.
14. Aztreonam/avibactam activity against a large collection of carbapenem-resistant Enterobacterales (CRE) collected in hospitals from Europe, Asia and Latin America (2019–21) Helio S. Sader 1*, Mariana Castanheira 1 1, John H. Kimbrough 1, Valerie Kantro 1 and Rodrigo E. Mendes. JAC Antimicrob Resist https://doi.org/10.1093/jacamr/dlad032
15. Oka, Keisuke & Matsumoto, Akane & Tetsuka, Nobuyuki & Morioka, Hiroshi & Iguchi, Mitsutaka & Ishiguro, Nobuhisa & Nagamori, Tsunehisa & Takahashi, Satoshi & Saito, Norihiro & Tokuda, Koichi & Igari, Hidetoshi & Fujikura, Yuji & Kato, Hideaki & Kanai, Shinichiro & Kusama, Fumiko & Iwasaki, Hiromichi & Furuhashi, Kazuki & Baba, Hisashi & Nagao, Miki & Fujita, Jiro. (2022). Clinical characteristics and treatment outcomes of carbapenem-resistant Enterobacterales infections in Japan. Journal of Global Antimicrobial Resistance. 29. 10.1016/j.jgar.2022.04.004.
16. Sampah J, Owusu-Frimpong I, Aboagye FT, Owusu-Ofori A. Prevalence of carbapenem-resistant and extended-spectrum beta-lactamase-producing Enterobacteriaceae in a teaching hospital in Ghana. PLoS One, 2023 Oct 30; 18(10): e0274156. doi: 10.1371/journal.pone.0274156. PMID: 37903118; PMCID: PMC10615269.
17. Taha R, Kader O, Shawky S, Rezk S. Correction: Ceftazidime-Avibactam plus Aztreonam synergistic combination tested against carbapenem-resistant Enterobacterales characterized phenotypically and genotypically: a glimmer of hope. Ann Clin Microbiol Antimicrob, 2023 Apr 18; 22(1): 26. doi: 10.1186/s12941-023-00578-y. Erratum for: Ann Clin Microbiol Antimicrob, 2023 Mar 21; 22(1): 21. doi: 10.1186/s12941-023-00573-3. PMID: 37072825; PMCID: PMC10114405.
18. Jayol A, Nordmann P, Poirel L, Dubois V. Ceftazidime/avibactam alone or in combination with Aztreonam against colistin-resistant and carbap enemase-producing Klebsiella pneumoniae. J Antimicrob Chemother, 2017; 73(2): 542–4.
19. Prayag PS, Patwardhan SA, Panchakshari S, Sambasivam R, Dhupad S, Soman RN, et al. Ceftazidime-avibactam with or without Aztreonam vs Polymyxin-based Combination Therapy for Carbapenem-resistant Enterobacteriaceae: A Retrospective Analysis. Indian J Crit Care Med, 2023; 27(6): 444–450.
20. Vijayakumar M, Selvam V, Renuka MK, Rajagopalan RE. The Comparative Efficacy of Ceftazidime–Avibactam with or without Aztreonam vs Polymyxins for Carbapenem-resistant Enterobacteriaceae Infections: A Prospective Observational Cohort Study. Indian J Crit Care Med, 2023; 27(12): 923–929.
21. Veeraraghavan, Balaji & Bakthavatchalam, Yamuna & Sahni, Rani Diana & Malhotra, Shilpi & Bansal, Nitin & Walia, Kamini. (2023). Loss of exclusivity of ceftazidime/avibactam in low- and middle-income countries: a test for antibiotic stewardship practice. The Lancet Regional Health - Southeast Asia. 15. 100225. 10.1016/j.lansea.2023.100225.