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CEFTAZIDIME-AVIBACTAM ACTIVITY IN CARBAPENEM RESISTANT ENTEROBACTERALES (CRE) ISOLATES IN A TERTIARY CARE HOSPITAL IN WESTERN MAHARASHTRA: A RETROSPECTIVE OBSERVATIONAL STUDY

Microbiology

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ABSTRACT

Introduction: Increasing Carbapenem resistance is a global threat. Carbapenem resistance in Indian settings are predominantly mediated via the β lactamases, NDM and OXA 48. The newly approved drug Ceftazidime-avibactam has potent activity against Carbapenem Resistant Enterobacterales (CRE). However a limited literature on Ceftazidime-avibactam activity on CRE. Hence, the aim of this study is to highlight the Ceftazidime-avibactam activity in CRE isolates. **Material and Methods:** We performed a retrospective observational study among 50 CRE and conducted disc diffusion with Ceftazidime- avibactam to determine the susceptibility to the same. **Results:** There were 46 Enterobacteriaceae that were detected to have carbapenemase producing genes. Out of 46, 14 (30.4%) isolates showed susceptibility to Ceftazidime-Avibactam by Disc diffusion method; of which two were pure NDM producers and 7 were NDM co-producers and 5 were non NDM producers. Among 14 isolates which were sensitive to Ceftazidime-Avibactam, the distribution of the isolates were *E. coli* (n=6, 43%) followed by *K. pneumoniae* (n=5, 36%) and *Proteus sps* (n=3, 21%) **Conclusion:** In our study, Ceftazidime-avibactam demonstrated excellent in vitro activity against OXA-48 like producing CRE (*E. coli, K. pneumoniae)* and a little activity was noted against pure NDM producers. Hence the use of the Ceftazidime-avibactam based on antimicrobial susceptibility will be helpful in managing infections with multi drug resistant Gram negative organisms

KEYWORDS

Ceftazidime, Avibactam, CRE, Carbapenem, Resistant, Enterobacterales

INTRODUCTION:

Globally, continuous emergence of multidrug-resistant organisms (MDROs) is a major public health concern, and is associated with significant morbidity and mortality (1). MDROs have historically affected patients in healthcare facilities, where risks for acquisition include exposure to antibiotics, frequent and/or prolonged hospitalization, use of in-dwelling devices, and host factors. With an explosion of antibiotic resistance genes found on mobile genetic elements (MGEs) capable of efficient transmission between bacteria and hosts in and out of hospitals, the line between multidrug-resistant bacterial infections acquired in healthcare settings and community acquired infections has become increasingly blurred over the last two decades (2).

Gram-negative bacteria have recently developed multidrug resistance, rendering earlier therapies useless. The β lactam drug class, which were once the cornerstone of treatment plans for many hospital and community acquired infections, are quickly going out of use because of the widespread production of beta lactamases by bacteria. Even the effectiveness of carbapenems is being undermined by spread of carbapenemases producing genes (3).

Carbapenemases like KPC, IMP, VIM, NDM, and OXA-48 are the primary mediators of carbapenem resistance in Enterobacterales (4). In India, NDM predominates in *E. coli*, whereas in *K. pneumoniae* OXA-48 alone predominates alone or in combination with NDM. Extended spectrum beta-lactamases (ESBLs), AmpC, and/or other mechanisms, such as the expression of efflux pumps or the loss of outer membrane porin function, are frequently produced alongside carbapenemases in CRE (5).

Ceftazidime, a well-known, third-generation broad-spectrum cephalosporin, that kills bacteria by inhibiting the formation of their cell walls by binding to penicillin-binding proteins (PBPs), similar to other β-lactam antibiotics. This results in bacterial cell lysis and death (6).

Avibactam is a novel, non-β-lactam, β-lactamase inhibitor. Compared to traditional β-lactamase inhibitors, it has a wider range of activity and is active against Ambler class A, class C, and some class D enzymes (7). According to in vitro research, many isolates of ESBL, AmpC, Klebsiella pneumoniae carbapenemase (KPC), OXA-48-producing Enterobacteriaceae, and drug-resistant P. aeruginosa can be treated with avibactam to restore the antimicrobial activity of the third-generation, extended-spectrum cephalosporin Ceftazidime (8).

Ceftazidime-avibactam is a 4:1 fixed ratio intravenously administered. It is a combination of Ceftazidime and the β-lactamase inhibitor avibactam. Adults with complicated urinary tract infections (cUTI), including pyelonephritis, complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), as well as other infections caused by aerobic Gram-negative organisms in patients with limited treatment options, may benefit from the use of Ceftazidime-avibactam (9).

The rising prevalence of infectious diseases caused by Carbapenem Resistant Enterobacterales also complicates the selection of empiric antimicrobial therapy for critically ill hospitalised patients. Infections caused by Carbapenem Resistant Enterobacterales result in prolonged hospital stay, increased morbidity and mortality and increased management costs. To address these issues, newer antimicrobials such as Ceftazidime-avibactam were investigated. However, there are limited literature on Ceftazidime-avibactam activity on Carbapenem Resistant Enterobacterales. Hence, the aim of this study is to highlight the Ceftazidime-avibactam activity in Carbapenem Resistant Enterobacterales isolates in the Indian setting.

MATERIAL AND METHODS:

A retrospective observational study conducted on 50 Carbapenem Resistant Enterobacteriaceae (CRE) samples in a tertiary care center laboratory for a period of 6 months (July-December, 2021). The Enterobacteriaceae strains resistant to at least one of the carbapenem antibiotics (Ertapenem, Meropenem, Doripenem, or Imipenem) or producing a carbapenemase (an enzyme that can make them resistant to carbapenem antibiotics) were defined as CRE by Centers for Disease Control and Prevention of USA (10).

Initially, 50 isolates were identified by using VITEK-2 (Bio-merieux) automated bacterial identification system. Antibiotic sensitivity testing was performed by conventional Kirby-Bauer disk diffusion

method and subjected to mCIM (Modified Carbapenem Inactivation Method) test for confirmation of CRE and the results were interpreted as per CLSI guidelines M100 (2021). For genotypic study the isolates were further subjected to conventional PCR and gel electrophoresis to detect panel of resistance associated genes (NDM, IMP, VIM and OXA-48) (11). The isolates on which the carpenemase gene detection had been performed were revived using BHI broth. 05 Mc Farland standard, lawn culture were made and Ceftazidime-avibactam disc were applied. The same was incubated at 37^{0}C for 18 hours. The zone diameters were noted. The data were tabulated in Microsoft excel sheet for analysis.

RESULTS:

Out of the 50 archived isolates, 46 could be revived. Out of 46, 14 (30.4%) isolates showed susceptibility to Ceftazidime-avibactam by Disc diffusion method of which 2 were pure NDM producers, 7 were NDM co-producers (had another mechanism of carbapenemase production, i.e., 5 had OXA 48 gene and 2 had VIM gene) and 5 were non NDM producers, which were sensitive to Ceftazidime-avibactam. Out of remaining sensitive isolates, 3 strains having sole OXA 48 gene, 1 strain having sole VIM and 1 strain having three genes were shown sensitive to Ceftazidime-avibactam. However 32 NDM, OXA 48 and VIM co producers were resistant to Ceftazidime-avibactam as shown in table 1.

Table 1. Distribution of Ceftazidime-Avibactam activity and CRE genes

Gene for Carbapenem Resistance	Total	Ceftazidime-Avibactam activity	
		Sensitive	Resistant
NDM	15	2	13
NDM + OXA 48	26	5	21
NDM + VIM	4	2	2
OXA 48	3	3	0
VIM	1	1	0
NDM+OXA 48+VIM	1	1	0

Among 14 isolates which were sensitive to Ceftazidime-avibactam, most of the isolates were *E. coli* (n=6, 43%) followed by *K. pneumoniae* (n=5, 36%) and *Proteus sps* (n=3, 21%) as shown in figure 1 and following genes for CRE isolates were shown in table 2.

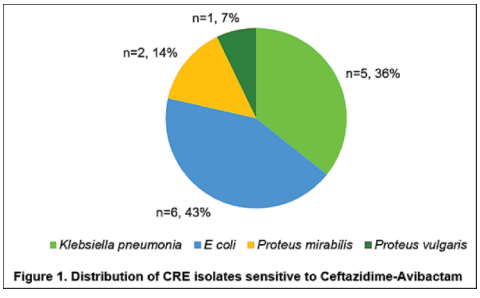

Figure 1. Distribution of CRE isolates sensitive to Ceftazidime-Avibactam

Table 2. CRE Isolates showing sensitivity to Ceftazidime-Avibactam

CRE genes	E.coli	K. pneumonia	P. mirabilis/ P. vulgaris
NDM	1	0	1
NDM + OXA 48	1	4	0
NDM + VIM	1	0	1
OXA 48	2	1	0
VIM	0	0	1
NDM+OXA 48+VIM	1	0	0
Total	6	5	3

DISCUSSION:

Due to the dearth of efficient and secure treatment options, the rising prevalence of CRE infections that are difficult to treat in India is of grave clinical concern. The currently approved b-lactam-based antibiotic Ceftazidime-avibactam, which has potent activity against Enterobacterales that express OXA-48 and NDM, is one option for treating these infections. In the present study, we assessed the in vitro activity of Ceftazidime-avibactam against CRE isolates.

Globally, most of the studies from 2014 to 2020 have reported higher susceptibility rates of ≥90% to Ceftazidime-avibactam against CRE (12–15). Whereas, in India the ATLAS surveillance was shown overall susceptibility of 79% to Ceftazidime-avibactam and similar study in China also shown 61.4% susceptibility to Ceftazidime-avibactam (4,8). However, in our study we found 30.4% isolates were susceptible to Ceftazidime-avibactam which can be evident by increasing pattern of antimicrobial resistance to Ceftazidime-avibactam.

Our study shown most of the Ceftazidime-avibactam sensitive isolates showed pure NDM gene (2/14), NDM co-producers (5/14), OXA 48 gene (7/14). Out of these OXA 48 was most common in *K. pneumoniae* (4, 25%), NDM and OXA 48 in *E. coli* (25%, 25%). Whereas, other studies also showed that in K. pneumoniae, OXA-48 like variants were the most commonly reported genetic elements, which is similar to our study (8).

The molecular characterization of carbapenemase enzymes is critical for tailoring CRE therapy. Ceftazidime-avibactam has emerged as a promising treatment option, even as monotherapy, for severe infections caused by Enterobacterales. The clinical efficacy of Ceftazidime-avibactam in treating CRE bacteraemia has been well established.

CONCLUSION:

In Indian settings, Carbapenem resistance is primarily mediated by the blaNDM, with only a few isolates showing OXA 48. Ceftazidime-avibactam, a recently approved drug, has potent anti-OXA 48 activity. Ceftazidime-avibactam demonstrated excellent in vitro activity against OXA-48 producing CRE (*E. coli, K. pneumoniae)*, but a little activity against NDMs was observed in our study. As a result, using Ceftazidime-avibactam based on antimicrobial susceptibility will be beneficial in treating infections caused by multidrug resistant Gram negative organisms.

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