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CEFTAZIDIME AVIBACTAM: STILL A HOPE FOR CARBAPENEM RESISTANT INFECTION?

Microbiology

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ABSTRACT

An ongoing public health problem of global aspect is carbapenem resistance seen mainly among Gram-negative pathogens. This is leading to rapidly spreading and causing serious outbreaks specially the type of antimicrobial resistance mediated by transferable Carbapenemase-encoding genes. The outcome of the article might give a hope that may be still we can treat multi drug resistant carbapenem resistant infections. The findings will help the clinician to think about the treatment options beyond the available drugs and resistant infections can be treated if timely decision is made.

KEYWORDS

Carbapenam Resistance, Gram Negative Pathogen, Ceftazidime Avibactam, Multidrug Resistance

INTRODUCTION

Antimicrobial resistance is one of the major healthcare priorities in today's time. It leads to increase chances of morbidity and mortality in patients infected with antimicrobial resistant microorganism along with increased costs in healthcare. [1] In India, the burden of antimicrobial resistance is estimated to be very high; however, systematic data is limited.[1] However the importance of such data cannot be emphasized enough as it serves as an empiric guide to antimicrobial therapy, aids in guiding hospital antibiotic policy and thus helps in implementation of antibiotic stewardship programs.

Carbapenems, a class of β-lactam group of antibiotics, are considered as last resort treatment for Gram-negative infections.[2] A wide variation in carbapenem resistance has been reported throughout the world. The problem is especially rampant in developing countries.[3,4] Carbapenemases (Beta lactamases) are a diverse group of enzymes that have the ability to inactivate β-lactam antibiotics. These enzymes have emerged as a significant clinical threat due to their diverse nature and the fact that they can disseminate rapidly.[5]

Enterobacteriaceae members, *Escherichia coli* and *Klebsiella pneumoniae* are among the most common Gram negative bacilli isolated in the Microbiology laboratory.[6] The clinical infections caused by these multidrug resistant organism are wide in nature, also quick to spread the resistance to other microorganism giving rise to public health emergencies.[7]

The Infectious Diseases Society of America, in collaboration with various International health organizations, has launched a global initiative called the "10 x '20".[8] Under this initiative several novel and broad-spectrum β- lactamase inhibitors (βLIs) have been developed. When used in combination with β-lactams, these newer β- lactamase inhibitors have been found to restore former's activity and thus thwart the emergence of resistance. Ceftazidime/avibactam have been found to be effective against Ambler class A,C and D group of β-lactamases.[5,20]This antibiotic combination have been approved by the Food and Drug Administration (FDA) and are available in injectable forms for use in critical care settings.[5,19] This development might be termed as a renaissance of the antibiotic era.

In India, empirical use, easy availability of antibiotics and lack of adherence to antibiotic policy guidelines in healthcare setups has led to development of widespread resistance among the microorganisms.[9] Despite the unflinching efforts of various governmental agencies (Indian Council of Medical Research, National Centre of Disease Control), healthcare institutes and professionals by launching of antibiotic policy, antibiotic stewardship program, accreditation etc antimicrobial resistance continues to grow as a health crisis throughout the country.[1]

Against this backdrop, the present study aims to determine the susceptibility of *Escherichia coli* and *Klebsiella pnuemoniae* towards ceftazidime/avibactam.

MATERIALS AND METHODS:

The present study was conducted in a tertiary care teaching hospital for a period of 2 months. A total of 100 *Escherichia coli* and *Klebsiella pnuemoniae* isolates were collected from various clinical samples like blood, urine, pus , aspirates etc from patients admitted during study period. Isolation of *Escherichia coli* and *Klebsiella pnuemoniae* was done by standard bacteriological culture techniques by inoculating the clinical samples on blood , Mac-conkey and CLED agar for urine samples and incubated aerobically at 37C. *E. coli and K. pneumoniae* isolates were identified by Gram staining, biochemical tests and antimicrobial susceptibility was performed by Kirby-Bauer technique. The identity of laboratory confirmed *Escherichia coli* and *Klebsiella pnuemoniae* was revalidated with the help of VITEK2 system GN ID AST card (Biomerieux) each sample was processed and result interpretated according to the manufacturer guide and literature.

Fifty *E.coli and K. pnuemoniae* isolates which were resistant to 10g Ertapenam disc (disc diffusion zone diameter $\leq$ 18 mm).[10] were assigned as carbapenem resistant isolates. Fifty *E.coli and K. pnuemoniae* isolates which were sensitive to 10g Ertapenam disc (disc diffusion zone diameter $\geq$22 mm).[10] were assigned as carbapenem sensitive isolates. The quality control of the isolates was checked by *Klebsiella pneumonia* ATCC BAA-1705 (carbapenemase positive) and *Klebsiella pneumonia* ATCC BAA-1706 (carbapenemase negative) was used.

The MIC of ceftazidime/avibactam 16/4 µg for all the 100 *E. coli and K. pneumoniae* isolates was determined by E-test method. The test was performed on Mueller Hinton agar plates. Inoculum was prepared and matched with 0.5 Macfarland solution and test performed as per kit literature. Plates were incubated at 36 ^{0}C ± 1^{0}C for 18- 24hours. MIC was read where the ellipse intersects the MIC scale on the strip. The result was interpreted as per CLSI guideline. MIC was compared between the cases and controls and statistical significance was calculated.

Statistical analysis

The prevalence of carbapenem resistance is expressed as percentage of *Escherichia coli and Klebsiella pnuemoniae* isolates showing resistance to ertapenem among total isolates of *Escherichia coli and Klebsiella pnuemoniae*. The comparison of categorical data was done by Chi square test. p value <0.05 was calculated as statistically significant.

RESULT:

Our study included various samples coming to the microbiology laboratory from the duration 15 September 21 to 15 November 21. The isolates were identified as *E.coli and K.pneumoniea* by conventional biochemical methods. These 50 isolates were further confirmed by VITEK2 GN ID & AST card. They were characterised as carbapenem resistant *Enterobacteriacea* (CRE) as all the isolates were resistant to Ertapenem with the zone diameter ≤ 18 mm by Kirby Bauer disk diffusion technique and VITEK 2. They were further tested for the sensitivity with the drug Ceftazidime/avibactam. It was done by E-test gradient strip method and MIC was determined.

Out of the 50 isolates which were tested for Ertapenem and found resistant with the zone diameter ≤ 18 mm, only one isolate was found resistant to the combination drug Ceftazidime/avibactam MIC ≤ 8/4 µg/ml. This isolate was characterised as *Escherichia coli* by conventional methods and revalidated by automated method VITEK 2. All the isolates which were carbapenem sensitive were also sensitive to Ceftazidime/avibactam.

The comparison of categorical data was done by Chi square test. The p value was calculated. It was observed as <0.01 which was statistically significant.

DISCUSSION :

In our study we demonstrated a clinically noteworthy cause of CAZ-AVI for treatment of CRE infections as compared to the failed standard therapy. Even though the sample size of our study was not large, we were still able to find statistically significant. Results. Our study highlights the use of ceftazidime- avibactam treatment for adults with serious multi drug resistant Gram-negative infections which have meagre therapeutic choice. There are lot of studies which have investigated the part of variety of combination therapy available for CRE treatment. Two such large studies have retrospectively showed that combination therapy (with two or more in vitro-active drugs) were associated with lesser number of deaths then single drug therapy in severe disease population. [11,12]

The drug CAZ-AVI has come out hopeful treatment options for CRE infections in lot of clinical research. However mostly studies have taken patients suffering by *K.pneumonaie* infections [13]. In a multicentre cohort study they have described clinical outcomes of the patients having CRE infections prospectively where 38 patients were successfully treated with combination of CAZ-AVI as compared to 99 patients who were given colistin for KPC-producing CRE, it resulted in lesser number of deaths CAZ-AVI group [14,19].

In a surveillance study conducted in Taiwan in 2016 CAZ–AVB showed exceptional in vitro task against *E. coli* (99%) and *K. pneumoniae* (100%) isolates, which is similar in our study. These results observations implicit the use of CAZ–AVB as an empirical and therapeutical choice for infections arising by *Enterobacteriaceae* [15] A research done by Sousa A. et al in 57 patients suffering with infections by OXA-48 produced by Enterobacteriaceae, the drug CAZ -AVI was found as a salvage therapy in 81% of them, as they received CZA-AVI single drug therapy. [14]

Nonetheless, the rise of carbapenem-resistant pathogens is a vital obstacle for successful therapy with this agent. The resistant to this new drug CAZ-AVI is also emerging and has been reported, which could give us the insight of increase in death rates among patients with OXA-48 type CRE infections. [16]. As reported by Shields et al, non-success of treatment with CZA-AVI was seen in 3/10 patients who received therapy for more than 15 days.[21]We suggest integration of the combination drug in routine antibiogram susceptibility testing.

CONCLUSION

The remarkable health benefits accomplished by antibiotics are intimidated by the menace of emerging multi drug resistant bacteria. The overuse of the available drugs and dearth of development of new antibiotic agents by drug companies has led to a global crisis and worldwide challenge to public health.[17] It also possess a considerable threat on economic burden on health care systems.[18] Our study included patients with confirm CRE infections, and it showed that CAZ-AVI is a propitious antibiotic to be used in therapy of patients for whom treatment options are restricted. In our study as the majority of sample were of outpatient department, there is a chance for reduced resistance seen in our isolates. Further studies may be required for in depth knowledge of resistance pattern of CAZ-AVI in our hospital setting.

Due to unavailability of some oral carbapenems (tebipenem and faropenem), ceftolozane, and other new β-lactam combination agents, including diazabicyclooctane-based inhibitors and boronic acid-based inhibitor such as vaborbactam (meropenem–vaborbactam) we could not perform in vitro susceptibility of these drugs. This is a limitation in our study. In spite of small size of the study, we could make it apparent that in patients with documented CRE infections, CAZ-AVI is potent and analogous to routine treatment.

Table 1: Statistical Analysis

	SENSITIVE	RESISTANT
CASES(CEFTAZIDIME/AVIBACTAM)	99	1
CONTROL(CARBAPENAM SENSTIVITY)	50	50
p Value=<0.1		
Chi square=63.19		

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