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Antimicrobial Activity of Ceftazidime-Avibactam (CAZ-AVI) among the Carbapenemase-Producing Gram-negative Rods Isolated from Clinical Samples

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ABSTRACT

Introduction: Treating Gram-negative bacteria that produce extended-spectrum beta-lactamases (ESBLs), AmpC Beta lactamases, and carbapenemases is a significant clinical concern worldwide. To address this concern, Ceftazidime-Avibactam has been approved by the United States Food and Drug Administration (USFDA) as a practical option for combating multi-drug resistant (MDR) and extensively drug-resistant (XDR) organisms. Our study focused on determining the extent to which MDR Gram-negative organisms from various clinical samples exhibited resistance to CAZ-AVI. **Methods:** Conducted at a central India tertiary care teaching hospital, our prospective study analyzed 258 Gram-negative bacteria specimens. These bacterial strains were identified using standard biochemical tests. ESBL production was detected using the combination disk method, while the AmpC enzyme was detected using the Epsilometer test (E-test). Furthermore, we assessed carbapenemase production using disk diffusion methods. Our study used the E-test to identify Metallo-beta-lactamases and *Klebsiella pneumonia* carbapenemase (KPC) activity. Additionally, we utilized the E-test to analyze the susceptibility patterns of CAZ-AVI. **Results:** Of the 258 Gram-negative isolates studied, 214 (83%) were ESBL producers. Among these isolates, 90 (35%) showed evidence of AmpC beta-lactamase production, with 17 (19%) being pure AmpC producers and 73 (81%) being ESBL co-producers. 55 (21.50%) were found to be carbapenemase producers. Among these isolates, 34 (62%) were MBL producers, while 11 (20%) were KPC producers. Of the carbapenemase-producing isolates, 14 (25.50%) were resistant to CAZ-AVI. Among the MDR isolates, we found that CI 109 (90%), PB 118 (97.50%), and FO 113 (93.50%) were the most effective antimicrobial agents. **Conclusions:** Gram-negative organisms that produce ESBL, AmpC, Carbapenemase, MBL, and KPC are particularly challenging for clinicians and a significant threat worldwide. However, our study results suggest that CAZ-AVI could be an effective standard therapy for managing MDR Gram-negative organisms.

INTRODUCTION

Over the past few years, the worldwide emergence and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria have posed a significant public health challenge [1]. Beta-lactams and carbapenems were considered effective treatments for Gram-negative bacterial infections for many years. Nevertheless, the effectiveness of beta-lactams as a class of antibiotics has been challenged as bacteria develop various types of beta-lactamases, including ESBL, AmpC, carbapenemases, KPC, New Delhi metallo-beta-lactamases, and oxacillinase-48 [2, 3]. The urgent need for new and effective antimicrobial agents to address this situation has led to the development of new antibiotics. One such antibiotic is ceftazidime-avibactam, which was approved by the FDA in 2015. Ceftazidime-avibactam is a novel, parenterally-administered combination of the third-generation cephalosporin ceftazidime and avibactam, a non-β-lactam β-lactamase inhibitor. This antibiotic has shown promise in treating complicated urinary tract infections and intra-abdominal infections caused by APC, ESBL, and carbapenemase-producing strains, such as *Enterobacteriaceae* and *Pseudomonas* spp. Among the newer beta-lactam and beta-lactamase inhibitors (BL/BLI), ceftazidime-avibactam is the only

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drug showing activity against OXA-48-like producers. However, the combination of avibactam does not increase ceftazidime activity against *Acinetobacter* spp. and most other anaerobic bacteria [4].

Despite its proven effectiveness against MDR or XDR gram-negative organisms, resistance to CAZ-AVI has already been reported in several countries, even though it has been a short time since its approval [5, 6].

More data is needed on CAZ-AVI-resistant isolates in India. Therefore, we conducted the present study to determine the prevalence of CAZ-AVI resistance among the Carbapenemase-producing Gram-negative organisms isolated from different clinical samples in a tertiary care hospital in central India.

MATERIAL AND METHODS

Clinical isolates. We conducted this prospective study from November 2021 to January 2022 in a tertiary care teaching hospital in central India. Before enrolling patients, we obtained permission from the institutional ethical committee (Ref. No. ECR/922/Inst/UP/2017). We calculated the sample size to be 258 using the formula n = Zα2 pq/L2 (power is 80%), assuming that 30% of the Gram-negative isolates were carbapenemase producers. We isolated bacteria from specimens such as urine, wound swab, pus, body fluid, and sputum from the study population. The study population included patients of all age groups whose clinical samples grew *E. coli*, *Klebsiella* spp., *Proteus* spp., and *Pseudomonas* spp. We excluded patients who had received antimicrobial drugs during the past month and samples with polymicrobial infection.

Isolation and identification. We processed samples immediately using standard procedures and identified isolates based on colony morphology on blood agar, MacConkey agar, gram staining, and standard biochemical tests [7].

Preparation of Inoculum for Antibiotic Susceptibility Testing. We used biochemically confirmed pure culture isolates for various antimicrobial susceptibility tests**.** Briefly, we transferred 4-5 similar colonies using a sterile wire to 5 ml Tryptone Soya Broth and incubated them at 35-37 ℃ for 2-8 h until light to moderate turbidity developed. Before testing, we compared the turbidity of the inoculum with 0.5 McFarland standards.

Antibiotic Susceptibility Testing (AST). We performed antimicrobial susceptibility testing (AST) using the modified Kirby-Bauer disk diffusion method by CLSI guidelines [8]. We used antibiotic disks (HiMedia, Mumbai, India) including Ampicillin (10µg) Piperacillin (10µg), Piperacillin-Tazobactam (100/10µg), Ceftriaxone (30 µg), Cefotaxime (30 µg), Ceftazidime (30µg), Cefpodoxime (10µg), Cefoperazone-Sulbactam (75/30 µg), Ampicillin–Sulbactam (10/10µg), Ciprofloxacin (5µg), Norfloxacin (10µg), Amikacin (30 µg.

Screening for ESBL production. We tested isolates for ESBL production using a combination disk method with Cefotaxime (30µg), Cefotaxime/Clavulanic acid (30/10 µg), Ceftazidime (30µg), and Ceftazidime/Clavulanic acid (30/ 10µg). We considered an increase of ≥ 5 mm in the diameter of the inhibition zone of the Cephalosporin + Clavulanate disk compared to the cephalosporin disk alone as evidence of ESBL production [8].

Detection of AmpC production. We used E-test to detect AmpC. Briefly, we inoculated test isolates onto a Mueller Hinton Agar plate. We placed the strip (with Cloxacillin in the lower part and Cloxacillin+ Clavulanic acid in the upper part) at the desired position on an agar plate swabbed with test culture. The plates were then incubated aerobically overnight at 37 °C. We considered bacteria to be AmpC-producing if there was no zone of inhibition in the lower part but a zone of inhibition in the upper part [8].

Detection of carbapenemase production. We inoculated plates of Mueller Hinton Agar with a standardized suspension of the test strains. Then, we applied a set of discs containing IPM, MRP, and ETP (10 µg each) to the agar surface and incubated the plates aerobically overnight at 35 °C. We considered isolates resistant to any carbapenem drugs to be carbapenemase producers [8].

Detection of Metallo-beta-lactamase. We used E-test to detect MBL production. Briefly, we inoculated test isolates onto a Mueller Hinton Agar plate. Then, we placed strips (with Imipenem in the lower part and Imipenem+ EDTA in the upper part) at the desired position on an agar plate swabbed with test culture. We incubated the plates aerobically overnight at 37 °C. We considered bacteria to be MBL-producing if there was no zone of inhibition in the lower part but a zone of inhibition in the upper part [8].

Detection of *k. pneumonia* carbapenemase (KPC). We used E-test strips to detect KPC producers. Briefly, we inoculated test isolates onto a Mueller Hinton Agar plate. Then, we placed a strip (with Ertapenem in the lower part and Ertapenem + Boronic acid in the upper part) at the desired position on an agar plate swabbed with test culture. We incubated the plates aerobically overnight at 37 °C. We considered an organism to be KPC-producing if there was no zone of inhibition in the lower part but a zone of inhibition in the upper part [8].

Susceptibility testing of CAZ-AVI. To determine the MIC of CAZ-AVI, we used E-test. Briefly, we inoculated test isolates onto a Mueller Hinton Agar plate. Then, we placed a strip at the desired position on the agar plate swabbed with test culture. We incubated the plates aerobically overnight at 37 °C.

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MIC values were interpreted as follows: <8 mcg/ml = sensitive and >16 mcg/ml = resistant.

Statistical analysis. We used a chi-square test to determine if there was an association between CAZ-AVI and ESBL, AmpC, and MBL producers. We used the statistical package SPSS 17.0 (IBM, USA) for analysis.

RESULTS

For this study, we included a total of 258 isolates from different clinical samples, with 133 (51.50%) from urine, 53 (20.75%) from pus, 52(20%) from sputum, 9 (3.50%) from the body fluid, 8 (3%) from wound swab and 3 (1.25%) from the intravascular device.

Table 1. Prevalence of ESBL, AmpC, and Carbapenemase producers and resistance pattern of non-beta lactams drugs among the isolates.

Total samples (N=258)	ESBL (N=214)	AmpC (N=90)	Carbapenemase (N=55)
Urine (N=133)	110 (82.50%)	44 (33%)	25 (19%)
Pus (N=53)	51 (96%)	24 (45.50%)	13 (24.50%)
Sputum (N=52)	37 (71%)	18 (34.50%)	09 (17.50%)
Swab (N=8)	07 (87.50%)	02 (25%)	04 (50%)
Body fluid (N=9)	07 (78%)	02 (22%)	02 (22%)
Intravascular device (N=03)	02 (66.50%)	00 (00%)	2 (66.50%)
Organisms			
E. coli (N=115)	94 (81.50%)	35 (30.50%)	21 (18.50%)
Klebsiella spp. (N=70)	51 (73%)	25 (35.50%)	14 (20%)
Pseudomonas (N=71)	68 (96%)	29 (41%)	19 (27%)
Proteus (N=02)	01 (50%)	01 (50%)	01 (50%)
Resistant to Non-β-lactems			
Fluoroquinolones			
Ciprofloxacin	157 (73.50%)	64 (71%)	46 (83.50%)
Norfloxacin	207 (96.50%)	85 (94.50%)	54 (98%)
Sulphonamides			
Co-trimoxazole	207 (96.50%)	83 (92%)	55 (100%)
Aminoglycosides			
Amikacin	34 (16%)	21 (23.50%)	17 (31%)
Gentamicin	30 (14%)	12 (13.50%)	11 (20%)
FO	25 (11.50%)	05 (5.50%)	07 (12.50%)
CL	15 (7%)	06 (6.50%)	03 (5.50%)

Demographic data of patients. Of the 258 samples, 129 (50%) were collected from males and 129 (50%) from females. The age groups were as follows: <1-10= 24 (9.50%), 11-20= 23(9%), 21-40= 89(34.50%), 41-60= 62(24%) and >60=60(23%).

ESBL producers. Out of the 258 *E. coli* isolates, 214 were confirmed as ESBL producers by double disk diffusion assay, resulting in a prevalence of 83% (214/258). Table 1 summarizes the clinical samples of isolation. Analysis of the drug resistance pattern revealed that all ESBL producers showed a higher frequency of co-resistance to non-beta-lactam classes of antibiotics (Table 1).

AmpC Producers. The E-strip test identified AmpC beta-lactamase production in 90 (35%) isolates. Of these, 17 (19%) isolates were pure AmpC producers, whereas 73 (81%) were co-producers of ESBL. Table 1 summarizes the clinical sample and the drug resistance patterns to non-beta-lactam classes of antibiotics observed in the AmpC-producing isolates.

Carbapenemase producers. In this study, 55 (21.50%) of the total isolates (N=258) were carbapenemase producers by disk diffusion test. Of the total isolates (N=258) in the study, the disk diffusion test identified 55 (21.50%) as carbapenemase producers. Among these, the maximum number of isolates was *E. coli* (36.50%), followed by *Pseudomonas* spp. (34.50%) and *Klebsiella* spp. (25.50%; Table.1)

Metallo-beta-lactamase producers. To check for the presence of Metallo-beta-lactamase, carbapenemase-producing isolates were further evaluated using E-strips that contained metal chelating agents such as EDTA. Using the E-strip method, 34 (62%) isolates were identified as MBL producers. Among these, the maximum number of isolates were *E. coli* (15, 44%), followed by *Pseudomonas* spp. (10, 29.50%), *Klebsiella spp.* (8, 23.50%) and *Proteus* spp. (1, 3%).

KPC producers. Carbapenemase-producing isolates were further evaluated phenotypically for the presence of KPC using E-strips containing boronic acid. Using the E-strip method, 11 (20%) isolates were identified as KPC producers. Among these, the maximum number of isolates were *E. coli* (6, 54.50%), followed by *Klebsiella* spp. (4, 36.50%) and *Pseudomonas* spp. (1, 9%).

Out of the 55 Carbapenemase-producing isolates, only one *E. coli* isolate was identified as a co-producer of both MBL and KPC.

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Table 2. Expression of different beta-lactamase enzymes in the CAZ-AVI isolates and the susceptibility pattern of other non-beta-lactamase antibiotics.

CAZ-AVI Resistant isolate	ESBL	AmpC	Carbapenemase	MBL	KPC	CL	FO	PB	TGC	COT	AK	GEN	CIP	NX
Pseudomonas spp.	Yes	Yes	Yes	Yes	No	S	S	S	S	R	R	R	R	R
E. coli	Yes	Yes	Yes	Yes	No	R	S	S	S	R	R	S	R	R
Klebsiella spp.	Yes	Yes	Yes	No	No	S	S	S	S	R	R	R	R	R
E. coli	Yes	Yes	Yes	Yes	No	S	R	S	R	R	R	S	R	R
Pseudomonas spp.	Yes	No	Yes	Yes	No	S	R	S	R	R	R	S	R	R
Klebsiella	Yes	Yes	Yes	Yes	No	S	S	S	S	R	R	S	R	R
E. coli	Yes	No	Yes	Yes	No	S	S	S	S	R	S	R	R	R
Pseudomonas spp.	Yes	Yes	Yes	Yes	No	S	S	S	S	R	R	R	R	R
E. coli	Yes	Yes	Yes	No	No	S	S	S	S	R	R	R	R	R
Pseudomonas spp.	Yes	No	Yes	Yes	No	R	R	S	R	R	R	R	R	R
E. coli	Yes	Yes	Yes	No	Yes	S	S	S	S	R	R	R	R	R
Klebsiella	Yes	Yes	Yes	No	No	S	R	S	S	R	R	R	R	R
Pseudomonas spp.	Yes	Yes	Yes	Yes	No	S	R	S	R	R	R	S	R	R
Proteus	Yes	Yes	Yes	Yes	No	R*	R	R	S	R	R	S	R	R

Ceftazidime-Avibactam resistance. To test the Carbapenemase-producing isolates, the CAZ-AVI MIC E-strip was used. Of the 55 isolates, 14 (25.50%) were resistant to CAZ-AVI. Among the resistance isolates, the maximum number was observed in *Pseudomonas* (36%), followed by *E. coli* (35.5%), *Klebsiella* (21.50%), and *Proteus* (1, 7%). Table 2 summarizes the expression of different beta-lactamase enzymes among the CAZ-AVI isolates and their susceptibility pattern to other non-beta-lactamase antibiotics.

DISCUSSION

Treating Gram-negative pathogens that produce ESBLs, AmpC Beta lactamases, and carbapenemases is a significant clinical concern worldwide, as there is a shortage of effective and safe antimicrobial drugs [7]. Numerous studies conducted in India have revealed a rising occurrence of carbapenem-resistant isolates which produce MBL, OXA NDM, and KPC types of carbapenemase enzymes [3, 9]. Currently, Ceftazidime-avibactam is approved by the US FDA and has demonstrated a strong efficacy against various carbapenemase-producing Gram-negative organisms, making it a practical option for treating MDR and XDR organisms [5, 6].

Our study found that age was a significant risk factor for susceptibility to infection with Gram-negative rods. Specifically, patients over 40 years were more susceptible to infection than younger age groups, supporting findings from several previous studies [10, 11]. We also found a higher proportion of females with UTI than males, which is consistent with the results of Kamat *et al*. [11]. However, in the case of sepsis, wound infection, and pneumonia, the proportion of infected males was significantly higher than females.

ESBL-producing organisms are globally recognized as significant pathogens. They are known to be resistant to many antimicrobial agents, which are commonly recommended for treating infections. In recent years, the incidence of ESBL-producing isolates causing infections has increased considerably. According to our study, the prevalence of Gram-negative bacterial infection caused by ESBL producers in our setting was 83%. Similar studies conducted in India have reported a prevalence ranging from 70-90% among their isolates [12, 13]. Our findings also revealed that most isolates from pyogenic infections were ESBL producers, followed by urine isolates. Several other studies have also observed this trend [12, 13].

Our study found that approximately one-third of isolates were AmpC producers. Other studies conducted in India have reported a prevalence rate of 35-40% for AmpC production among the GNB isolates [15, 16]. Moreover, our findings revealed that 81% of isolates were AmpC and ESBL co-producers, which is consistent with the results of other studies [16]. It is worth noting that *Pseudomonas* spp. is one of the most prevalent AmpC producers when compared to other GNB isolates, and this

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is not the first time this has been observed. A study conducted by Rafiee *et al*. also reported similar findings [17]. It has been established that strains that produce AmpC are frequently resistant to multiple agents, making it challenging to select effective antibiotics. *In vitro* resistance to beta-lactam+ beta-lactamase inhibitor combination, cephalosporins, and penicillin should be avoided because of in vitro resistance. Cefepime is a potential drug of choice as it can penetrate the outer cell membrane and is less susceptible to hydrolysis by the enzyme [18].

Carbapenems are widely regarded as the drug of choice for treating severe infections. These antimicrobial agents exhibit a broad spectrum of activity and are considered effective against many types of bacteria. However, it is worth noting that specific isolates from different infections have been found to produce metallo-β-lactamases, which can hydrolyze carbapenems and lead to carbapenem resistance. Carbapenem resistance is becoming increasingly prevalent on a global scale, which poses a significant public health challenge. In the past, it was mainly observed in *Pseudomonas* spp. and *Acinetobacter* spp. Still, carbapenem resistance has now been detected in medically important pathogens such as *Klebsiella* spp. and *E. coli*. The prevalence of carbapenem-resistant isolates was low in our study, with carbapenemase producers accounting for approximately 20% of the isolates. Similar studies conducted in India have reported a prevalence rate ranging from 15-20% of Gram-negative bacteria isolates being carbapenemase producers [19, 20].

Although the low prevalence rate of carbapenem resistance was observed in our study population, it is worth noting that the resistance can quickly spread in susceptible isolates as it is primarily plasmid-mediated and can transfer rapidly to other organisms through conjugation methods.

Further analysis of the carbapenemase-producing organisms revealed that approximately 60% of our isolates were MBL producers, while around 20% were KPC producers, as determined by phenotypic methods. This finding is consistent with reports from India and other parts of the world, which have documented a high prevalence of MBL and KPC-producing isolates among study populations [19-21]. Studies have suggested that, in addition to MBL and KPC enzymes, other mechanisms such as AmpC, OXA, and NDM production may also contribute to carbapenem resistance [22]. However, we only detected the prevalence of MBL, KPC, and AmpC-producing isolates in the present study. Further evaluation is needed to determine the prevalence of OXA and NDM production. Several reports from India indicated that the OXA-48 enzyme significantly contributes to carbapenem resistance [3, 19].

The primary concern with carbapenemase-producing isolates is their broad-spectrum resistance profile, which is difficult to combat. These strains are typically resistant to beta-lactams, aminoglycosides, and fluoroquinolones but remain susceptible to colistin, tigecycline, polymyxins, and fosfomycin [19, 23]. Although tigecycline, polymyxins, and colistin are commonly used as treatment options for carbapenem-resistant organisms, their efficacy and potential adverse effects remain uncertain and can complicate treatment [24]. Newer agents, such as ceftazidime-avibactam, have shown effectiveness against these organisms and are increasingly used for improved clinical outcomes [25]. The Infectious Diseases Society of America (IDSA) recommends ceftazidime-avibactam as a first-line treatment for pyelonephritis, complicated urinary tract infections (cUTI), and infections outside of the urinary tract caused by OXA-48-like and KPC-producing carbapenem-resistant *Enterobacterales*, in cases where proven in vitro susceptibility to ceftazidime-avibactam has been demonstrated [26].

Several studies worldwide have reported higher susceptibility rates of >85% to CAZ-AVI against Gram-negative organisms [27]. In our research, susceptibility rates were relatively lower at 74.50%. However, a multicentre study from India has reported a sensitivity rate of 79% to CAZ-AVI in the isolates [19].

Upon analyzing the CAZ-AVI-resistant isolates, we found that they all were ESBL and carbapenemase producers, with approximately 80% being ESBL and AmpC co-producers. We also observed that around 75% of the CAZ-AVI-resistant isolates were MBL producers. Only one isolate was identified as a KPC producer, also a co-producer of the MBL enzyme.

Further analysis of the sensitivity pattern of the CAZ-AVI-resistant isolates against non-beta lactam antibiotics revealed that colistin, fosfomycin, and polymyxin B were the most effective. This study found that CAZ-AVI, fosfomycin, colistin, and polymyxin B exhibited acceptable *in vitro* activity against carbapenemase-producing Gram-negative organisms.

In conclusion, Carbapenem resistance remains a persistent global public health challenge, mainly among Gram-negative pathogens. When mediated by transferable carbapenemase-encoding genes, this type of antimicrobial resistance can spread quickly, leading to severe outbreaks and significantly limiting available treatment options. When new effective novel agents are unavailable, CAZ-AVI presents a viable alternative to standard therapy for XDR and MDR Gram-negative organisms. However, timely detection of multidrug-resistant Gram-negative rods by diagnostic microbiology laboratories is crucial for effective antimicrobial selection. Effective communication between the diagnostic laboratory and healthcare workers is essential in improving patient outcomes and controlling the spread of MDR pathogens.

One limitation of our study is that we used only phenotypic methods to detect different drug resistance

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properties of the organism without performing molecular detection. As a result, this study did not evaluate the molecular mechanisms of resistance.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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