Section: Microbiology

Original Research Article

MINIMUM INHIBITORY CONCENTRATION OF CEFTAZIDIME/AVIBACTAM AGAINST MULTIDRUG RESISTANT GRAM NEGATIVE BACILLI ISOLATED FROM CLINICAL ISOLATES: A CROSS SECTIONAL STUDY

Roopashree S[1], Soumya Kaup[1], Swarupa Rani N M[2], G.K. Megha[3]

[1]Professor, Department of Microbiology, Shridevi Institute of Medical Sciences & Research Hospital, Tumkur, Karnataka, India
[2]Tutor, Department of Microbiology, Siddaganga Medical college & Research Institute, Tumkur, Karnataka, India
[3]PhD Scholar, Department of Microbiology, JSS Medical College & Hospital, Mysuru, India

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Corresponding Author:
Dr. Roopashree S,
Professor, Department of Microbiology, Shridevi Institute of Medical Sciences & Research Hospital, Tumkur, Karnataka, India.
Email: rupasrinivas.shree7@gmail.com

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ABSTRACT

Background: Ceftazidime–avibactam (CAZ/AVI) is a novel cephalosporin/β-lactamase inhibitor combination approved for the treatment of complicated intra-abdominal infections, urinary tract infections, hospital-acquired pneumonia, and infections caused by multidrug-resistant (MDR) Gram-negative bacteria. The increasing prevalence of MDR organisms, particularly Enterobacterales and non-fermenting Gram-negative bacilli, poses a serious therapeutic challenge. The objective is to evaluate the Minimum Inhibitory Concentration (MIC) and susceptibility profile of CAZ/AVI against MDR Gram-negative bacilli isolated from clinical samples.

Materials and Methods: A cross-sectional study was conducted from September 2022 to August 2023 in the department of Microbiology. Ninety MDR Gram-negative isolates were included. Identification was performed using standard Microbiological techniques. Antimicrobial susceptibility testing was carried out according to CLSI guidelines. MIC of CAZ/AVI was determined using the Epsilometric (E-strip) method.

Results: Out of 90 MDR isolates, the majority were obtained from urine (41%), followed by pus (35%). Escherichia coli (45.6%) was the predominant isolate, followed by Klebsiella pneumoniae(25.6%). Overall, 54.44% isolates were sensitive and 45.6% were resistant to CAZ/AVI. High-level resistance (MIC ≥256 µg/mL) was observed in 34.4% of isolates. CAZ/AVI demonstrated better activity against Enterobacterales compared to non-fermenters.

Conclusion: CAZ/AVI retains moderate activity against MDR Enterobacterales; however, emerging resistance is concerning. Continuous antimicrobial surveillance and stewardship are essential to preserve its therapeutic utility.

Keywords: Antimicrobialresistance, Ceftazidime/Avibacatam, Multidrug Resistant Gram Negative Bacilli

INTRODUCTION

Multidrug-resistant (MDR) Gram-negative organisms are a major health concern due to lack of effective therapy. Antimicrobial resistance is feared to become the leading cause of death globally by 2050 with a disproportionate impact on low- and middle-income countries. In spite of the increased demand for new antimicrobial agents, the pace of their discovery has considerably slowed down in the recent past. Emergence of resistance to newer agents like Ceftazidime-avibactam (CZA) further magnifies the problem.[1]

According to a work reported by CDC ,Klebsiella spp. accounts for the highest percentage of healthcare-associated Carbapenem Resistant Enterobacteriaceae (11%), and the estimated number

of deaths attributed to these infections was 520 out of 7,900 infected patients in 2013.[2] Multidrug-resistant (MDR) Pseudomonas aeruginosa are considered to be urgent public health threats by the Centres for Disease Control (CDC), requiring urgent and aggressive actions to contain their dissemination and find new therapies for these organisms.[3]

Ceftazidime-Avibactam (CZA) is a relatively new combination of a third-generation cephalosporin and a novel β-lactamase inhibitor. Avibactam (AVI) re-establishes the in vitro activity of Ceftazidime against Ambler class A, class C, and some class D β-lactamase-producing pathogens.[4,5]

CZA has been shown to have clinical efficacy similar to that of Meropenem and Doripenem for the treatment of complicated infections.[1] However, off late CZA is showing increasing trend of resistance especially to Carbapenem Resistant Enterobacterales (CRE) and Pseudomonas aeruginosa ranging between 1.7% to over 20% particularly in high risk settings.[6] In India the scenario is no different with rapidly increasing resistance of >25% to Enterobacterales in many hospitals.[7] With increased isolation of MDR organisms and not many new antibiotics which are effective against these available in the market we conducted this study to see the susceptibility patterns of CZA against MDR organisms in our hospital.

MATERIALS AND METHODS

Study design: Cross sectional study.
Sampling Method: Convenience sampling.
Inclusion criteria
All Multidrug Resistant Gram-negative bacilli belonging to family of Enterobacteriaceae and Non-fermenters (Pseudomonas aeruginosa and Acinetobacter species) isolated in the Microbiology department from various clinical samples were included in the study.
Exclusion criteria
Isolates of salmonella and shigella species were excluded

- Isolates of Gram-Negative Bacilli that were resistant to at least one agent in three or more antimicrobial categories were classified as Multidrug resistant (MDR)
- The Minimum Inhibitory Concentration for CZA of all the Multidrug resistant isolates was assessed using Epsilometric method (E-strip).
- The inoculum was prepared by making a direct broth suspension of isolated colonies selected from an overnight growth on blood agar plate and incubated overnight in aerobic condition at 37°C. The suspension was adjusted to achieve a turbidity equivalent to a 0.5 McFarland. The E-strip test was performed on Mueller-Hinton agar plates. A Lawn culture was prepared from broth suspension using a swab according to standard protocol. The E-strip of Ceftazidime/Avibactum was applied onto inoculated surface of the agar plate after 10 minutes; the plates were incubated at 37°C for 24 hours. A tear drop-shaped zone of inhibition was observed after overnight incubation. Minimum Inhibitory Concentration (MIC) was determined at the point where the ellipse intersected the MIC scale on the strip. MIC value of ≤ 8 was considered Sensitive and MIC value of ≥16 was considered Resistant for Ceftazidime-Avibactam against Enterobacterales and Pseudomonas aeruginosa according to Clinical Laboratory Standards Institute(CLSI) guidelines.
- All antibiotic discs and E strip were procured from Himedia Laboratories Pvt. Ltd. Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853 were used for quality control.

RESULTS

Demographic Distribution: A total of 90 MDR-GNB were isolated from various clinical samples. Majority were isolated from Urine (41%) and Pus (35%), followed by blood (8.8%), sputum (7.7%), Endotracheal secretions (4.4%) and Bronchio-Alveolar Lavage (1.1%). [Figure 1] shows the distribution of MDR-GNB species isolated from various clinical samples.

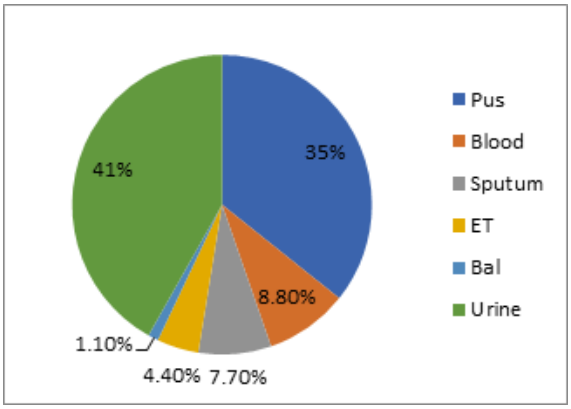

Figure 1: Distribution of MDR-GNB species in various clinical samples

ET: Endotracheal Secretions, BAL: Bronchoalveolar Lavage

Out of 90 Multidrug-resistant Gram negative bacilli isolates included in the study, 46 (51.1%) were isolated from male patients and 44 (48.8%) were isolated from female patients.

Majority of the isolates were obtained from patients in the age group between 48-57 years (23.3%) followed by 58-67 years age group (21.1%).

The highest number of isolates were obtained from the department of General Surgery (41.1%) followed by General Medicine (21.1%). [Table 1] lists the department-wise distribution of the isolates.

Table 1: Department-wise distribution of the isolates.

Departments	Number	Percentage (%)
General Surgery	37	41.11
General Medicine	19	21.11
Emergency Medicine	8	8.89
Respiratory Medicine	7	7.78
Obstetrics & Gynaecology	5	5.56
Intensive Care Unit	5	5.56
Orthopaedics	4	4.44
Otorhinolaryngology	3	3.33
Neurosurgery	2	2.22
Total	90	100

Out of 90 Multi-drug resistant organisms, the predominant organism isolated was Escherichia coli accounting for (45.6%), followed by Klebsiella species which accounted for 37.78% of the isolates. [Table 2] shows the organism-wise distribution of the isolates.

Table 2: Organism-wise frequency of MDR-GNB species

Organism	Number	Percentage (%)
Escherichia coli	41	45.56
Klebsiella species	34	37.78
Acinetobacter species	6	6.67
Citrobacter species	5	5.56
Proteus species	3	3.33
Pseudomonas aeruginosa	1	1.10
Total	90	100

[Table 3 and Figure 2] enumerate the sensitivity pattern of the isolates. Among the urinary isolates, Fosfomycin and Nitrofurantoin were the most effective antibiotics demonstrating 62.16% susceptibility. Amikacin was sensitive in 44.44% of the isolates followed by Carbapenems with Meropenem showing 41.11% and Imipenem 35.56% sensitivity. All the MDR isolates showed 100% resistance to Ampicillin, first, second and third generation Cephalosporins.

Table 3: Sensitivity pattern of the MDR-GNB isolates

Antibiotics	Number tested	Sensitive (%)	Resistant (%)
Ampicillin	90	0 (0)	90 (100)
Cefazolin	90	0 (0)	90 (100)
Cefuroxime	90	0 (0)	90 (100)
Ceftazidime	90	0 (0)	90 (100)
Cefotaxime	90	0 (0)	90 (100)
Piperacillin/Tazobactam	90	10 (11.11)	80 (88.89)
Amikacin	90	40 (44.44)	50 (55.56)
Ciprofloxacin	64	4 (6.25)	60 (93.75)
Imipenem	90	32 (35.56)	58 (64.44)
Meropenem	90	37 (41.11)	53 (58.89)
Nitrofurantoin	37	23 (62.16)	14 (37.84)
Cotrimoxazole	90	8 (8.89)	82 (91.11)
Fosfomycin	37	23 (62.16)	14 (37.84)

Numbers in parenthesis represent percentages.

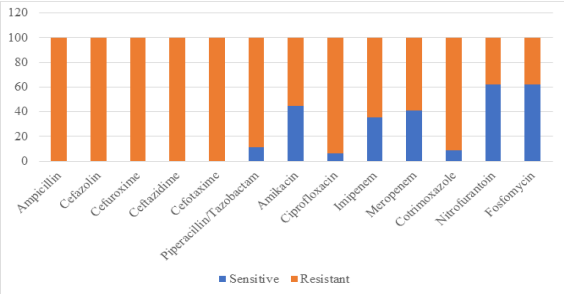

Figure 2: Sensitivity Pattern of MDR-GNB isolates

Cftazidime-Avibactam Susceptibility pattern

Out of the total 90 isolates tested for CAZ/AVI susceptibility, 54.4% of the isolates were found to be sensitive while 45.6% were resistant. The highest susceptibility was observed among isolates of Escherichia coli (65.85%) followed by Proteus species (66.85%) and Klebsiella species (52.94%). Table 4 enumerates the organism-wise susceptibility to CAZ/AVI.

Table 4: Organism-wise Susceptibility to CAZ/AVI

Organism	Interpretation		Total	% Susceptibility
	Susceptible	Resistant		
Escherichia coli	27	14	41	65.85
Proteus species	2	1	3	66.67

Klebsiella species	18	16	34	52.94
Citrobacter species	1	4	5	20
Acinetobacter species	1	5	6	16.67
Pseudomonas aeruginosa	0	1	1	0

DISCUSSION

The rapid emergence and dissemination of Multidrug-Resistant Gram-Negative Bacilli (MDR-GNB) represent a formidable challenge to modern medicine, severely limiting empirical therapeutic options. In 2019 alone, an estimated 1.27 million global deaths were directly attributable to bacterial antimicrobial resistance, underscoring the urgent need for robust surveillance and novel therapeutics.8 The present cross-sectional study evaluated the susceptibility profile of Ceftazidime-Avibactam (CAZ/AVI) against MDR-GNB clinical isolates, alongside an assessment of their broader antimicrobial resistance patterns.

In our study, urinary tract infections (41%) and pyogenic infections (35%) were the predominant sources of MDR isolates. Consistent with global epidemiological trends, Escherichia coli (45.56%) and Klebsiella species (37.78%) were the most frequently isolated pathogens. Klebsiella pneumoniae, in particular, is notorious for its robust defence mechanisms and its propensity to acquire and disseminate antimicrobial resistance genes, making it a primary driver of hospital-acquired MDR infections.[2] Similarly, the high isolation rate of Escherichia coli from urinary sources aligns with the study conducted by Kot B et al., demonstrating expanding phenotypic resistance among uropathogenic strains globally.[9]

The antimicrobial susceptibility profile of these isolates revealed an alarming baseline of resistance. We observed 100% resistance to traditional first-line agents, including Ampicillin and all tested generations of cephalosporins, along with profound resistance to fluoroquinolones (93.75%). Most critically, resistance to carbapenems was exceptionally high (58.89% for Meropenem and 64.44% for Imipenem). The CDC has classified Carbapenem-Resistant Enterobacterales (CRE) and MDR Pseudomonas aeruginosa as urgent public health threats due to their high associated mortality.[3] Interestingly, among urinary isolates, older agents like Fosfomycin and Nitrofurantoin retained efficacy in 62.16% of cases. This corroborates findings by Endimiani et al., who demonstrated the retained in vitro activity of fosfomycin against complex MDR pathogens, including Carbapenemase-producing Klebsiella pneumoniae, highlighting its value as a carbapenem-sparing alternative for lower urinary tract infections.[4]

Ceftazidime-Avibactam was introduced as a targeted therapy to combat the CRE crisis, demonstrating a favourable safety profile and efficacy comparable to carbapenems in complicated intra-abdominal and urinary tract infections.[6] Avibactam, a non-β-lactam β-lactamase inhibitor, restores the activity of ceftazidime against Ambler class A (e.g., KPC, ESBLs), class C (AmpC), and some class D (e.g., OXA-48) β-lactamases.[7] In our study, CAZ/AVI demonstrated moderate overall activity, effectively inhibiting 54.44% of the MDR isolates. It performed best against Enterobacterales, specifically Proteus species (66.67%) and Escherichia coli (65.85%).

However, the high overall resistance rate of 45.6% to CAZ/AVI observed in this study is a matter of profound clinical concern. Resistance was notably high among Klebsiella species (47% resistant). As Gonçalves et al. recently highlighted, CAZ/AVI resistance in Klebsiella pneumoniae is rapidly evolving into a global public health crisis across diverse sublineages.[6] The high failure rate of CAZ/AVI in our study correlates strongly with recent Indian surveillance data. Bakthavatchalam et al. reported that CAZ/AVI resistance among Carbapenem-Resistant Enterobacterales frequently exceeds 25% across Indian hospitals.[7] This pronounced resistance in the Indian subcontinent is primarily driven by the high endemicity of Metallo-β-lactamases (MBLs), such as NDM (New Delhi metallo-β-lactamase), which limits the clinical utility of CAZ/AVI monotherapy in regional Intensive Care Units.10 Because avibactam is fundamentally unable to inhibit Ambler Class B MBLs, empirical use of CAZ/AVI monotherapy in settings with high NDM prevalence often results in high resistance rates. Recent clinical evidence strongly supports that in regions endemic to MBL-producing Enterobacterales, CAZ/AVI should ideally be partnered with Aztreonam to ensure bactericidal activity.[11]

Furthermore, CAZ/AVI demonstrated remarkably poor activity against non-fermenting Gram-negative bacilli in our study, with 83.3% of Acinetobacter species and 100% of Pseudomonas aeruginosa isolates showing resistance. This underscores that CAZ/AVI should not be relied upon as a primary agent for MDR non-fermenters without prior susceptibility testing, reflecting the well-documented intrinsic resistance of Acinetobacter baumannii to this specific combination.[12] To overcome these complex resistance phenotypes, recent data by Karaiskos I et al. suggest that combining CAZ/AVI with other agents—such as Aztreonam (which is stable against MBLs), Colistin, or Amikacin—can yield synergistic effects and restore bactericidal activity against highly refractory Klebsiella pneumoniae and Pseudomonas aeruginosa isolates.[13] This synergistic approach forms the basis of current Infectious Diseases Society of America (IDSA) guidance, which positions the CAZ/AVI plus Aztreonam combination as a preferred therapy for MBL-producing infections.[14]

CONCLUSION

This study shows a high prevalence of Multidrug-resistant Gram-negative bacilli(MDRGNB) among clinical isolates with urine being the most common source of infection and Escherichia coli was determined as the leading organism to exhibit Multidrug resistance.

Ceftazidime–Avibactam showed moderate overall activity, with 54.44% of isolates being sensitive. However, a significant proportion (45.6%) exhibited resistance including high-level MIC values. The drug showed better efficacy against Enterobacterales such as Escherichia coli and Klebsiella species, while limited activity was observed against Acinetobacter species and Pseudomonas aeruginosa.

A higher resistance pattern was observed in commonly used antibiotics such as cephalosporins, fluoroquinolones and carbapenems highlighting the growing antimicrobial resistance crisis. Continuous surveillance, strict antimicrobial stewardship, and routine MIC-based testing are essential to guide appropriate therapy and prevent further emergence of resistance.

Ceftazidime–Avibactam should be used judiciously to preserve its effectiveness as a last-resort treatment option for multidrug-resistant Gram-negative infections.

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