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**Review Article**

# Tackling carbapenem resistance: ceftazidime - avibactam in contemporary clinical scenarios

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## ABSTRACT

Antimicrobial resistance poses a formidable challenge in treating severe infections, with the prevalence of extended-spectrum beta-lactamase (ESBL) - producing, *Klebsiella pneumoniae* carbapenemase (KPC) - producing, and multidrug-resistant (MDR) organisms on the rise. This necessitates careful consideration of various factors, including local resistance patterns, patient-specific characteristics, and drug properties, in treatment decisions for critically ill patients. Ceftazidime-Avibactam demonstrates efficacy against aerobic Gram-negative bacteria and offers a crucial advancement against carbapenem-resistant organisms (CRO) with its effectiveness against key pathogens, including ESBL, AmpC, KPC, and OXA-48-producing *Enterobacteriaceae* and drug-resistant *P. aeruginosa*. Ceftazidime-Avibactam emerges as a valuable option for critically ill patients with limited treatment choices. The drug's excellent safety profile demonstrated in clinical trials, further positions it as a crucial addition to antimicrobial treatment options. As the global threat of drug-resistant bacteria grows, Ceftazidime-Avibactam plays a pivotal role in addressing this challenge and offers a promising solution for critically ill patients facing infections caused by antimicrobial-resistant pathogens. The article delves into therapeutic efficacy and the prospective role of Ceftazidime-Avibactam in managing MDR Gram-negative organisms, underscoring the critical role of appropriate antibiotic administration in reducing mortality associated with Gram-negative infections.

**Keywords:** Ceftazidime-Avibactam, Antibiotic resistance, Gram-negative bacteria, Carbapenemases, Carbapenem-resistant, Carbapenem-resistant *Enterobacteriaceae*, OXA-48

## INTRODUCTION

In the realm of healthcare and microbiology, the interplay between infections and antibiotics is intricately linked with the profound issue of antibiotic resistance, a subject of paramount importance.[1] Both proper and improper use of antimicrobial medications is on the rise, leading to the emergence and dissemination of antimicrobial resistance (AMR) across various pathogens.[2] AMR is commonly termed the "silent pandemic," underscoring the urgent need for immediate action and more effective management, rather than viewing it solely as a future concern. Global estimates indicate that the direct correlation between deaths and AMR has surged to over 1.2 million in 2019. Projections suggest this figure could escalate to around 10 million annually by 2050 if inadequate measures are implemented to curb AMR.[3]

The six pathogens, namely *E. coli*, *Staphylococcus aureus*, *K. pneumoniae*, *S. pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, individually accounted for over 250,000 deaths related to AMR. Collectively, these pathogens contributed to 929,000 deaths, with their order determined by the respective number of fatalities. All these six predominant pathogens are identified as contributors to the AMR burden in 2019, have been designated as priority pathogens by the World Health Organization (WHO). More than 70% of deaths attributed to AMR across various pathogens were linked to resistance against fluoroquinolones and β-lactam antibiotics, including

carbapenems, cephalosporins, and penicillins. These antibiotics are commonly chosen as the initial treatment for severe infections, emphasizing the concerning impact of resistance on empirical therapy.[4]

## CRITICAL CARE'S SILENT ENEMY: GRAM-NEGATIVE BACTERIA AND ANTIBIOTIC RESISTANCE

The WHO has released a comprehensive inventory of antibiotic-resistant priority pathogens, posing a significant threat to human health. Primarily focusing on Gram-negative bacterial pathogens, the list reflects their inherent resistance compared to Gram-positive counterparts.[5] The rise in resistance among Gram-negative bacteria amplifies the strain on intensive care units (ICUs), evidenced by increases in mortality rates, length of hospital stays, and hospitalization expenses.[6] However, heightened resistance to cephalosporins and the presence of ESBL β-lactamases have restricted the usage of cephalosporins, leading to widespread reliance on carbapenem antibiotics like Meropenem, Imipenem-Cilastatin, and Doripenem. Consequently, this trend has spurred the emergence of carbapenemases.[7]

Gram-negative bacteria commonly employ β-lactamase production as a key resistance mechanism, cleaving the β-lactam ring of antibiotics. Strategies to counteract β-lactamases involve modifying side chains on β-lactams or combining them with β-lactamase inhibitors. The Ambler molecular classification system divides β-lactamases into four categories (A–D). Class A comprises enzymes like TEM and SHV, which are susceptible to existing inhibitors such as Clavulanate. Class B encompasses metallo-β-lactamases, which require a zinc cofactor and lack effective inhibitors. Class C consists of AmpC β-lactamases, present on bacterial chromosomes or plasmids, contributing to resistance in various Gram-negative species. Finally, Class D comprises oxacillinases (OXA enzymes), which confer resistance to penicillins, cephalosporins, extended-spectrum cephalosporins, and carbapenems, and currently lack effective inhibitors among available options like Clavulanate, Tazobactam, and Sulbactam.[7]

Infections caused by carbapenemase-producing bacteria, including bloodstream infections (BSIs), community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), complicated urinary tract infections (cUTIs), and complicated intra-abdominal infections (cIAIs), result in substantial mortality rates. The escalation of the issue is fueled by the emergence and dissemination of plasmid-mediated "big five" carbapenemase genes, namely KPC, NDM, IMP, VIM, and OXA-48-type, among Gram-negative bacteria.[8] The Indian Council of Medical Research (ICMR) has reported significant carbapenem resistance among *Enterobacterales*, with resistance rates reaching up to 30% for *Escherichia coli* and 50% for *Klebsiella pneumoniae*. Among carbapenem-resistant (CR) *K. pneumoniae* isolates, the *Oxacillinase*-48-like (OXA-48-like) gene was identified in 52%, while 20% harbored the NDM gene, and 27% possessed both the NDM and OXA-48-like genes. However, in carbapenem resistant (CR) - *E. coli*, NDM was identified in 68% of isolates followed by OXA-48-like in 24% isolates and 8% isolates carried both NDM with OXA-48-like gene.[9] Carbapenemases is now a common carbapenem resistance mechanism among *Enterobacterales* in many countries including India, Mediterranean and European countries. Carbapenemases have exhibited a wide-ranging substrate profile, encompassing penicillins, cephalosporins, Aztreonam, and carbapenems. They typically display resistance to the majority of conventional beta-lactamase inhibitors such as Clavulanic Acid, Tazobactam, and Sulbactam.[10] Recently, new beta-lactamase inhibitors have been developed with an activity on carbapenemases such as Avibactam, and more recently Vaborbactam and Relebactam.[10] However, considering drug accessibility, the preferred treatment for Carbapenem-resistant *Enterobacteriaceae* (CRE) infection in India continues to be either Ceftazidime–Avibactam (CAZ-AVI) or regimens based on Polymyxins.

## INNOVATIVE DUO: CEFTAZIDIME-AVIBACTAM FOR MULTIDRUG-RESISTANT GRAM-NEGATIVE INFECTIONS

Ceftazidime-Avibactam is a novel antibiotic combination designed to combat challenging infections caused by multidrug-resistant gram-negative bacteria. This antimicrobial agent consists of Ceftazidime, a third-generation cephalosporin with anti-pseudomonal activity, and Avibactam, a non-beta-lactam-beta-lactamase inhibitor.[11] It has *in vitro* activity against a broad range of Gram-negative bacteria, including highly resistant strains, such as ESBL, AmpC, and CRE and *P. aeruginosa*, but not against metallo-β-lactamase (MBL) producers. Ceftazidime-Avibactam has received approval and is accessible in the USA, Europe, India, and numerous other nations. Ceftazidime- Avibactam has demonstrated efficacy generally comparable to carbapenem-based comparator regimens in the primary indications. Ceftazidime-Avibactam (standard dose 2.5 g by 2-h intravenous infusions every 8 h) is approved for cUTI (including pyelonephritis), cIAI (co-administered with metronidazole), and HAP/VAP in adults and children aged >3 months, including for cases of bacteraemia associated with these infections, and for the treatment of infections due to aerobic Gram-negative organisms with limited treatment options.[12]

Ceftazidime-Avibactam is an intravenously administered at a fixed ratio of 4:1. Ceftazidime, a β-lactam antibiotic, induces bacterial cell death by inhibiting cell wall synthesis. The bacterial cell wall, composed of peptidoglycan, undergoes transglycosylation and transpeptidation reactions facilitated by penicillin-binding proteins (PBPs). Ceftazidime, binding mainly to PBP in

gram-negative bacteria decreases cross-linking activity of peptidoglycan.[7]

## COUNTERING BETA-LACTAMASE THREATS WITH AVIBACTAM

Avibactam is a member of a class of β-lactamase inhibitors called diazabicyclooctanes (DBOs). Avibactam is a non–β-lactam, β-lactamase inhibitor that forms a covalent bond with β-lactamase through reversible acylation. This process is different from other β-lactamase inhibitors, as they undergo an irreversible reaction producing intermediates that are hydrolyzed.[7] Despite not being a β-lactam compound, Avibactam exhibits structural features akin to the β-lactam ring present in cephalosporins, such as Ceftazidime. The sulfate moiety at position 6 bears resemblance to the carboxyl group at position 4 in Ceftazidime, while the carboxamide at position 2 parallels the aminoacyl side chain at position 7 in Ceftazidime. Notably, both Ceftazidime and Avibactam demonstrate a lack of interactions that could potentially interfere with their respective activities and kinetic profiles.[13]

Avibactam offers several advantages, including a long half-life, intricate reversibility through deacylation, small molecular size, low molecular weight, polarity, and interaction with crucial catalytic residues near the active sites of β-lactamases. These characteristics enable this innovative β-lactamase inhibitor to exhibit activity against more resistant organisms compared to other similar agents. Additionally, a notable benefit of Avibactam, distinguishing it from other β-lactamase inhibitors, is its propensity for inducing resistance is considerably low.[7,13]

Ceftazidime/Avibactam exhibits extensive Gram-negative activity, targeting *Enterobacteriaceae* and *Pseudomonas aeruginosa*. While maintaining the Ceftazidime spectrum, Avibactam counters specific resistance mechanisms. Nevertheless, its efficacy is limited against Acinetobacter, anaerobic, and Gram-positive organisms. Avibactam, as a broad-spectrum β-lactamase inhibitor, effectively inhibits class A (TEM, SHV, CTX-M), some class C (AmpC), and class D (OXA-48)-lactamases. Notably, Ceftazidime/Avibactam is inactive against MBLs (NDM-1, IMP, VIM). It stands as the first β-lactam/BLI to retain activity against carbapenemase-producing isolates.[14,15]

The addition of Avibactam effectively reverses Ceftazidime resistance, reducing the minimum inhibitory concentration (MIC) of numerous Gram-negative isolates, notably within the susceptible range (<8 mg/L) for *Pseudomonas aeruginosa* and *Enterobacteriaceae*. The addition of Avibactam enhances Ceftazidime's effectiveness, resulting in significant MIC90 reductions (16–1024-fold) in *Enterobacteriaceae*, notably for *E. coli* and *Klebsiella* species, exhibiting over 95% susceptibility to Ceftazidime-Avibactam. In *P. aeruginosa*, Avibactam demonstrates moderate MIC90 reductions (2–8-fold) with an overall susceptibility of 80–90%, presenting an improvement over Ceftazidime alone in numerous studies.[16,17] Moreover, Avibactam markedly enhanced Ceftazidime's efficacy against ESBL-producing *E. coli* and *K. pneumoniae* strains, belonging to Ambler classes A (4-1024-fold MIC reduction) and D (2-512-fold MIC reduction), KPC carbapenemases (32-8192-fold MIC reduction), as well as both chromosomal and mobile Ambler class C β-lactamases (2-512-fold MIC reduction).[18]

## AVIBACTAM'S STANDOUT CHARACTERISTICS IN COMPARISON TO OTHER BETA-LACTAMASE INHIBITORS

At present, six β-lactamase inhibitors have been approved for clinical use. Sulbactam and Tazobactam are penicillanic acid sulfones, and Clavulanic acid is a clavam. All of these inhibitors function as “suicide” inhibitors and take advantage of conserved active-site residues to interact with their targets, resulting in an irreversible inactivity of the targeted β-lactamase. The spectrum of these inhibitors is largely limited to some of the class A serine β-lactamase enzymes, such as temoneira (TEM)-1. The other three recently approved inhibitors are DBOs (Avibactam and Relebactam) and boronic acid (Vaborbactam). Unlike the ‘‘suicide” inhibitors, they function as a competitive inhibitor by binding to targeted β-lactamases in a covalent but slowly reversible manner, followed by the regeneration of the active enzyme and intact inhibitor. Although Vaborbactam was initially designed to inhibit KPC-type carbapenemases, it also exhibits activity against other class A and class C β-lactamases. However, Meropenem-Vaborbactam shows less activity against strains that lack porins or that overexpress efflux pumps. Imipenem-Relebactam is active against carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant *Pseudomonas aeruginosa (P. aeruginosa, CRPA*), which produce KPC and class C β-lactamases. Neither Vaborbactam nor Relebactam is able to inhibit class B and class D β-lactamases.

The addition of Avibactam to Ceftazidime can restore antibacterial activity against *Enterobacterales* and *P. aeruginosa* strains that produce a wide range of class A and class C β-lactamases. Remarkably, Avibactam is the only approved β-lactamase inhibitor that can assist Ceftazidime to inhibit certain class D β-lactamases, such as OXA-48. One of the benefits of Avibactam is that compared to the first-generation β-lactamase inhibitors, this novel inhibitor is extremely effective. To inhibit one molecule of β-lactamase, only 1-5 molecules of Avibactam are needed, while Tazobactam and Sulbactam require 55 and 214, respectively. In comparison with the other approved inhibitors, Avibactam has the advantage of high efficiency in inhibiting β-lactamases, especially in the inhibition of OXA-48-type carbapenemase.[15,19]

In the context of Gram-negative organisms, the co-production of metallo-beta-lactamases, ESBLs, and serine carbapenemase enzymes is prevalent, significantly impacting antibiotic selection and patient outcomes. In

India, NDM-1 rates are consistently high. Aztreonam, a monobactam beta-lactam, inhibits NDM but is hindered by coexisting ESBLs. This situation is very common in patients being referred to tertiary care facilities. Combining Ceftazidime-Avibactam (CAZ-AVI) with Aztreonam (ATM) presents a strategic approach, with CAZ-AVI inhibiting ESBLs and other beta-lactamases, while ATM targets metallo-beta-lactamases.[20]

## CEFTAZIDIME-AVIBACTAM IN CLINICAL SETTINGS

In the RECAPTURE trial focusing on complicated urinary tract infections, including pyelonephritis, involving 1,033 patients, 393 treated with Ceftazidime-Avibactam and 417 with Doripenem were analyzed. Ceftazidime-Avibactam demonstrated non-inferiority for patient-reported resolution at day 5 and combined symptomatic resolution/microbiological eradication at test of cure. Additionally, it showed superior microbiological eradication, suggesting its efficacy and potential as a carbapenem alternative for treating complicated urinary tract infection, including acute pyelonephritis.[21]

RECLAIM study encompassing complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis, patients were treated with Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole (cIAI: n=10; cUTI: n=144) or best available therapy (BAT). Clinical cure rates at the test-of-cure visit were 91% for both CAZ-AVI and BAT in the modified intention-to-treat population. Notably, a numerically higher proportion of patients receiving Ceftazidime-Avibactam achieved a favorable microbiological response, emphasizing its potential in managing these infections.[22]

Similarly, the REPROVE study compared Ceftazidime-Avibactam (CAZ-AVI) to Meropenem for Hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP). CAZ-AVI exhibited a clinical cure rate of 68.8% in the clinically modified intention-to-treat group, compared to 73.0% for Meropenem. In the clinically evaluable population, CAZ-AVI demonstrated a clinical cure rate of 77.4%, while Meropenem had a rate of 78.1%. The addition of Metronidazole to Ceftazidime-Avibactam was determined to be non-inferior to Meropenem.[23]

Real-world studies highlight high susceptibility of tested CRE isolates to Ceftazidime-Avibactam, reinforcing its efficacy in treating CRE infections.[24] Ceftazidime-Avibactam demonstrates effectiveness in patients with various comorbid conditions, including obesity, impaired renal function, diabetes, heart failure, liver diseases, malignancies, asthma, chronic pancreatitis, neurological diseases, and bronchiectasis.[25-27]

Shields et al investigated 109 cases of bacteremia with carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) with secondary bacteremia were treated with different regimens. Clinical success rates were as follows: CAZ-AVI 85%, Carbapenem plus aminoglycoside 48%, Carbapenem plus Colistin 40%, and others 37%. The 30-day survival rates were: CAZ-AVI 92%, Carbapenem plus Aminoglycoside 68%, Carbapenem plus Colistin 70%, and others 68%. The 90-day survival rates were: CAZ-AVI 92%, Carbapenem plus aminoglycoside 56%, Carbapenem plus Colistin 63%, and others 49%.[28]

In a comprehensive meta-analysis by Cheng et al involving 833 patients (CAZ-AVI 325 versus Polymyxin 508), receiving CAZ-AVI exhibited notable clinical advantages. Significantly lower 30-day mortality, heightened clinical cure rates, and enhanced microbial clearance were observed compared to Polymyxin-treated patients. Notably, no substantial difference in acute kidney injury incidence emerged between the two groups. Additionally, among patients with CRE bloodstream infections, those administered CAZ-AVI experienced markedly lower mortality rates than those treated with Polymyxin. These findings underscore CAZ-AVI as a superior therapeutic option for managing CRE infections.[29] An observational study within the consortium on resistance against Carbapenems in *Klebsiella* and other *Enterobacteriaceae* (CRACKLE), the efficacy of Ceftazidime-Avibactam against KPC-producing CRE was compared with Colistin. Analyzing data from 137 patients, the study revealed significantly lower adjusted 30-day mortality (9% versus 32%) for those treated with Ceftazidime-Avibactam. Additionally, patients receiving Ceftazidime-Avibactam had a 64% better outcome at 30 days compared to those treated with Colistin. These findings suggest that Ceftazidime-Avibactam may be a reasonable alternative to Colistin in managing *K. pneumoniae* carbapenemase (KPC)-producing CRE infections.[30] Another study by Almangour et al involving 149 receiving CAZ-AVI and 81 on a Colistin-based regimen revealed a significantly higher clinical cure rate with CAZ-AVI (71% versus 52%) and a lower in-hospital mortality. Notably, CAZ-AVI recipients had a significantly lower incidence of acute kidney injury (15% versus 33%). The study supports the preferential use of CAZ-AVI over Colistin for treating infections caused by carbapenem-resistant *Enterobacteriaceae*.[31]

## CONCLUSION

In addressing challenging infections, decisions encompass various factors, such as pathogen characteristics, local resistance patterns, patient specifics, drug properties, and economic and stewardship considerations. Ceftazidime-Avibactam emerges as an effective and well-tolerated solution for severe infections caused by aerobic Gram-negative bacteria. Clinical trial data align with in vitro studies, indicating its efficacy against significant pathogens, including ESBL-, AmpC-, KPC-, and OXA-48-producing *Enterobacteriaceae* and drug-resistant *P. aeruginosa*. Ceftazidime-Avibactam, proven effective and well-tolerated, offers a valuable treatment option for serious infections caused by carbapenemase resistant gram-negative bacteria.

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