Infectious Diseases Diagnosis & Treatment
Dubey Y, et al. Infect Dis Diag Treat 9: 273.
www.doi.org/ 10.29011/2577- 1515.100273
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Review Article

Management of CRE Infection with a Focus on New Antimicrobial Agents

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Citation: Dubey Y, Ansari A, Gupta N, Kola VR, Petare A, et al. (2025) Management of CRE Infection with a Focus on New Antimicrobial Agents. Infect Dis Diag Treat 9: 273. DOI: 10.29011/2577-1515.100273.

Received Date: 4 April 2025; **Accepted Date:** 10 April 2025; **Published Date:** 14 April 2025

Abstract

Background: Carbapenem-resistant Enterobacterales (CRE) infections represent a critical global health challenge, driven by diverse resistance mechanisms including carbapenemase production. This review synthesizes current knowledge on CRE management, encompassing epidemiology, diagnostics, resistance patterns, and novel antimicrobial therapies. **Methods:** A systematic literature search of PubMed/MEDLINE, Scopus, and Web of Science from 2020-2025 identified high-quality evidence, with a focus on clinical trials pivotal to new pharmacological treatments. **Results:** CRE epidemiology reveals a concerning rise in resistance, particularly in regions like India, with significant mortality implications. Diagnostic strategies have evolved, incorporating culture-based, phenotypic, genotypic, and emerging techniques for rapid and accurate CRE detection. Novel antimicrobial agents, including Cefiderocol and beta-lactam/beta-lactamase inhibitor combinations like Meropenem-Vaborbactam, ceftazidime-Avibactam, and aztreonam-Avibactam, offer promising treatment options. However, metallo-β-lactamase (MBL)-producing CRE strains remain a therapeutic challenge. Combination therapies, antimicrobial stewardship, and infection control are crucial for effective management. Emerging strategies like phage therapy, immunotherapy, and vaccine development hold potential for future interventions. Recent guidelines, including IDSA 2024, ESCMID 2022 & ICMR 2022 provide updated recommendations for CRE treatment, emphasizing the importance of tailored therapy based on resistance mechanisms. **Conclusions:** This review highlights the need for continued research, development, and global collaboration to combat the escalating threat of CRE infections.

Keywords: Carbapenem-resistant Enterobacterales (CRE); Multi-drug resistant organisms (MDR); Ceftazidime-avibactam; Antimicrobial stewardship

Introduction

The 2024 Infectious Diseases Society of America (IDSA) guidelines classify carbapenem-resistant Enterobacterales (CRE) as organisms within the Enterobacterales order demonstrating resistance to at least one carbapenem antibiotic—such as ertapenem, Meropenem, Imipenem, or doripenem [1]. CRE encompass a diverse group of pathogens, exhibiting various resistance mechanisms. They can be categorized as either carbapenemase-producing or non-carbapenemase-producing. Common carbapenemases include *Klebsiella pneumoniae* carbapenemases (KPCs), New Delhi metallo-β-lactamases (NDMs), Verona integron-encoded metallo-β-lactamases (VIMs), Imipenem-hydrolyzing metallo-β-lactamases (IMPs), and OXA-48-like oxacillinases. NDM, VIM, and IMP carbapenemases are collectively known as metallo-β-lactamases (MBLs) [1]. The genes responsible for these enzymes include *blaKPC*, *blaNDM*, *blaVIM*, *blaIMP*, and *blaOXA-48-like*. Identifying the specific carbapenemase produced by a CRE isolate is crucial for determining appropriate treatment, as the efficacy of newer β-lactam antibiotics varies depending on the carbapenemase present [1].

CRE Infection Epidemiology:

Antimicrobial resistance (AMR) contributed to over one million deaths globally in 2021, with projections suggesting a potential rise to 1.91 million annual deaths by 2050 [2]. Since their initial detection in 1980, the prevalence of CRE has significantly increased, leading the World Health Organization to designate them as a critical-priority pathogen, emphasizing the urgent need for effective treatment strategies [3]. CRE infections pose a substantial global public health threat, with India experiencing a notably high incidence. This is often linked to the widespread dissemination of the NDM-1 carbapenemase gene, making it endemic within the Indian subcontinent. In India, the predominant factor contributing to Carbapenem-Resistant Enterobacteriaceae (CRE) is frequently linked to the synthesis of New Delhi Metallo-beta-lactamase (NDM) enzymes, especially the NDM-1 variant. Conversely, in Western countries, the Klebsiella pneumoniae carbapenemase (KPC) is more typically connected with CRE. Additionally, various geographical areas may display distinct patterns of carbapenemase production, such as OXA-48 observed in certain regions of Europe and North Africa. In India, the situation is quite similar, as indicated by the recent ICMR-AMRSN 2022 report, which reveals that CRKP (56%) and CREco (30%) rank among the three most prevalent isolates from all samples, excluding feces and urine, obtained from ICUs in Indian hospitals. [4] CRE infections are associated with high mortality rates, ranging from 26% to 50% [5]. Notably, carbapenem resistance has doubled between 2017 and 2022, according to the ICMR-AMR report [4].

CRE Infection Risk Factors:

Analysis of recent research indicates several factors that elevate the risk of developing carbapenem-resistant Enterobacterales (CRE) infections. These include pre-existing medical conditions, the use of urinary catheters, the presence of indwelling vascular devices, extended periods of hospitalization, prolonged courses of antibiotic therapy, the need for mechanical respiratory support, and a history of exposure to fluoroquinolone, carbapenem, or cephalosporin antibiotics [6].

CRE Detection Techniques:

Diverse methodologies employed for detecting carbapenem-resistant Enterobacterales (CRE), highlighting their respective sensitivities, specificities, and limitations summarised in Table 1 [7]. Culture-based techniques, such as the modified Hodge test (MHT) enhanced with boronic acid, E-test strips that utilize EDTA (ethylenediaminetetraacetic acid), and targeted combination disk diffusion assays, have enhanced antimicrobial susceptibility testing (AST). These methods demonstrate commendable sensitivity and specificity in identifying KPC and MBL, although their effectiveness is diminished when it comes to detecting OXA-48 [8]. Phenotypic methods include the Modified Hodge Test (MHT), which is effective for KPC but not MBL, and carbapenem-inactivation methods (CIM), which can detect all carbapenemases [9]. Selective media offer varying sensitivity and specificity. Rapid phenotypic methods like colorimetric assays and MALDI-TOF MS are useful but may miss OXA-48 [10]. Genotypic methods, such as PCR-based techniques (including qPCR, RT-PCR, and mPCR), are considered the gold standard for rapid and accurate detection and typing of all carbapenemases [7]. Loop-mediated isothermal amplification (LAMP) offers a simpler and more cost-effective alternative [11]. Whole genome sequencing (WGS) provides comprehensive information but has a longer turnaround time [12]. Immunological methods, such as ELISA, have demonstrated poor performance [13]. Biosensors, including electrochemical and optical assays, are emerging technologies but require further development for reliable carbapenemase detection [14]. Emerging Techniques such as microfluidic and Raman spectroscopic techniques, show promise, but more research is required [15].

In India, the identification of Non-Carbapenemase Producing Carbapenem-Resistant Enterobacteriaceae (Non-CP CRE) is primarily conducted through conventional microbiological laboratory methods. This process involves the culture-based identification of Enterobacteriaceae, followed by phenotypic susceptibility testing utilizing disk diffusion or E-test to ascertain carbapenem resistance. Further confirmation is achieved through phenotypic tests such as the modified Hodge test (MHT) or the

Carba NP test, which help distinguish between Carbapenemase Producing CRE (CP-CRE) and non-CP CRE. If necessary, molecular techniques may be employed to detect the specific resistance genes associated with non-CP CRE mechanisms [16].

Rapid commercial tests offer significant benefits within the Indian healthcare landscape. A variety of these tests, which are either cleared by the Food and Drug Administration (FDA) or bear the Conformité Européenne (CE) mark, are accessible for the identification of carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CP CRE). These tests can be divided into two primary categories: phenotypic and molecular tests. The phenotypic detection of carbapenemase-producing organisms can be performed using biochemical assays such as Carba NP®, Blue Carba®, and Carba® tests. Although these assays confirm the presence of carbapenemases in bacterial cultures or isolates, they have limitations in recognizing other antimicrobial resistance (AMR) mechanisms, such as efflux pumps and porin losses, and they do not identify the specific type of carbapenemase enzyme present. Additionally, these methods require the availability of bacterial isolates. In contrast, nucleic acid-based molecular tests, including Xpert Carba-R®, BioFire film Array®, and Nanosphere Verigene BC-GN®, offer several advantages over traditional culture-based phenotypic tests. These benefits include a rapid turnaround time of less than six hours, precise identification of specific carbapenemase genes, and, in certain instances, the ability to directly analyze clinical specimens without prior culture. Nevertheless, molecular tests also encounter challenges, such as the inability to differentiate between mutant and wild-type enzymes, the distinction between silenced and expressed genes, and the detection of increased carbapenemase gene dosage as well as off-panel carbapenemase genes.The potential for misinterpretation regarding susceptibility and resistance to carbapenems and novel beta-lactam/beta-lactamase inhibitors is significant. It is advisable to interpret FDA/CE-validated molecular tests for resistance mechanisms alongside phenotypic tests to effectively manage suspected carbapenem-resistant Enterobacteriaceae (CRE) infections in critically ill patients in India. However, the financial burden associated with molecular testing methods limits their broader implementation in clinical laboratories. Conversely, innovative phenotypic lateral flow immunoassays have emerged as cost-effective alternatives within clinical environments. Previous research has shown that the NG-Test® CARBA 5 lateral flow assay possesses outstanding specificity (100%), sensitivity (98%), and positive predictive value (100%), demonstrating excellent concordance with molecular tests in identifying Enterobacterales that produce carbapenemases, with a rapid turnaround time of approximately 15 minutes. FDA/CE-approved lateral flow tests for detecting phenotypic carbapenemase production offer a swift turnaround time, strong agreement with molecular tests, and user-friendly application for suspected CRE infections in critically ill patients in India [17].

Techniques		Sensitivity	Specificity	Comments
Culture-based methods	Improved AST tests: E-test or disk diffusion test	>82%	>95%	• Detects KPC and MBLs • Insufficient for OXA-48
	Modified Hodge Test (MHT)	>69%	>90%	• Detects KPC • Insufficient for MBLs
	Carbapenem-inactivation methods (CIM)	>90%	>95%	• Detect all carbapenamesase
	Selective media: SUPERCARBA, Colorex KPC, ID Carba, CHROM agar KPC, etc	40–96.5%	>50%	-
Rapid phenotypic methods	Colorimetric assay: CarbaNP test and its automated kits	>70%	>80%	• Insufficient for OXA-48
	MALDI-TOF MS	>72.5%	>95%	• Detects KPC and MBLs • Insufficient for OXA-48
	Emerging techniques: BCDA, FC, microfluidic techniques, and Raman spectroscopic techniques	>80%	>90%	• Insufficient work on carbapenemases

Genotypic methods	PCR-based methods: qPCR, RT-PCR, mPCR, automated PCR (Xpert system, Check-Direct, and Carba-R-assay)	>90	>90	• Gold standard & Rapid • Detect and type all carbapenemases
	Loop-mediated isothermal amplification (LAMP)	>90	>90	• Simple & Moderate cost
	Whole genome sequencing (WGS)	>90	>90	• Discovers new resistance • Longer turn around
	Emerging techniques: FISH, microarray techniques, PCR-ESI-MS, and NucliSENS EasyQKPC	>90	>90	• Insufficient work on carbapenemases
Immunological Methods	Enzyme-linked immunosorbent assay (ELISA), an Immunochromatographic assay	Poor	Poor	• Complex
Biosensors: Emerging Technology	Electrochemical assays: Impedimetric, potentiometric, and voltammetric	-	-	• Insufficient work on carbapenemases
	Optical assays: Raman scattering, SPR, and SERS -Plasmonic biosensors	78%	97%	• Insufficient work on carbapenemases

Table 1: CRE Detection techniques for most common carbapenemases.

Carbapenemases with representing gene [18]**:**

The concise overview of the major carbapenemase families, their associated genes, and the bacterial species in which they originate, highlighting the diverse mechanisms of carbapenem resistance are mentioned in Table 2. This table categorizes the most common carbapenemase enzymes based on the Ambler classification system (A, B, and D) and identifies the corresponding genes and bacterial origins.

Ambler Class	Gene:bacterial origins
A	KPC (Klebsiella pneumoniae carbapenemase)
	GES (Guiana extended spectrum): P. aeruginosa
	IMI (Imipenem-hydrolysing beta-lactamase): *E. cloacae*
	SME (*Serratia marcescencens* enzyme)
	SFC (*Serratia fonticola* carbapenemase-1): *E. cloacae*
	NMC-A (not metalloenzyme carbapenemase A)
	KPC (Klebsiella pneumoniae carbapenemase)
B	NDM (New Delhi metallo-lactamase): Klebsiella pneumoniae
	VIM (Verona integron-encoded metallo-lactamase): P. aeruginosa
	IMP (Imipenemase): *S. marcescencens*
	GIM (German Imipenemase): P. aeruginosa
	SIM (Seoul Imipenemase): P. aeruginosa
D	OXA (Oxacillin-hydrolyzing carbapenemase): Klebsiella pneumoniae

Table 2: The Most common Carbapenemases with representing gene in bacteria.

Newer Agents for Management of CRE Infections

Research into novel antimicrobial therapies against carbapenem-resistant Enterobacterales (CRE) is a priority, with several new agents either recently approved or currently undergoing development, providing potential advancements in combating these resistant infections.

BETA-LACTAM/BETA-LACTAMASE INHIBITOR COMBINATIONS (Serine Carbapenemase Focus):

Ceftazidime-Avibactam:

Ceftazidime-Avibactam is frequently employed as an initial treatment choice for numerous carbapenem-resistant Enterobacterales (CRE) infections, owing to its extensive activity against a range of carbapenemases. Avibactam, a unique non-beta-lactam beta-lactamase inhibitor, effectively recovers the antimicrobial efficacy of ceftazidime against many CRE isolates, including those producing KPC and certain OXA-type carbapenemases. However, it lacks activity against metallo-β-lactamases (MBLs). A systematic review and meta-analysis published in 2025 highlighted the global trends of CAZ-AVI resistance in Gram-negative bacteria, revealing an increase in resistance proportions from 5.6% in 2015-2020 to 13.2% in 2021-2024 [19]. CAZ-AVI frequently exhibits synergistic bactericidal activity when combined with other antimicrobials against carbapenem-resistant Gram-negative bacteria. These findings underscore the importance of considering CAZ-AVI in treatment guidelines and emphasize the need for ongoing monitoring to maintain its effectiveness against resistant infections.

Meropenem-Vaborbactam

Vaborbactam, a novel beta-lactamase inhibitor, specifically targets Klebsiella pneumoniae carbapenemase (KPC) enzymes. It effectively restores the activity of Meropenem against KPC-producing carbapenem-resistant Enterobacterales (CRE). Similar to Avibactam, Vaborbactam does not exhibit activity against metallo-β-lactamases (MBLs). Real-world studies have demonstrated both the efficacy and safety of Meropenem-Vaborbactam in treating CRE infections, with clinical efficacy and survival rates, including 30-day and 90-day survival, as primary endpoints [20]. Pooled data revealed a clinical success rate of 75% (95% CI, 66%-82%), with 30-day and 90-day survival rates of 75% (95% CI, 71%-78%) and 69% (95% CI, 61%-76%), respectively [21]. A retrospective, multicenter cohort study comparing Meropenem-Vaborbactam (MEV) to ceftazidime-Avibactam (CZA) in hospitalized adults with serious infections, including sepsis, urinary tract infections (UTIs), complicated intra-abdominal infections (cIAIs), and pneumonia, was conducted [22]. The analysis showed that less than a third of patients received either drug within two days of infection onset (30.6% MEV vs. 33.0% CZA, p = 0.313). MEV-treated patients required mechanical ventilation less frequently than those receiving CZA (35.0% vs. 41.4%, p = 0.010) [22]. Furthermore, MEV treatment was associated with a lower adjusted mortality rate (17.0% [95% CI 13.6%, 20.3%] vs. 20.6% [95% CI 19.0%, 22.2%], p = 0.048) compared to CZA [22].

Aztreonam-Avibactam [23]:

Recently a study examining bacterial isolates from 69 medical centers between 2020 and 2022 evaluated the activity of aztreonam-Avibactam, using a fixed Avibactam concentration of 4 mg/L and a susceptibility breakpoint of ≤ 8 mg/L. The findings revealed that aztreonam-Avibactam inhibited 100% of Enterobacterales isolates at ≤ 8 mg/L and 99.9% at ≤ 4 mg/L, demonstrating potent activity against carbapenem-resistant Enterobacterales (CRE) with MIC50/90 values of 0.25/1 mg/L. In comparison, ceftazidime-Avibactam and Meropenem-Vaborbactam exhibited activity against 89.4% and 88.5% of CRE isolates, respectively. The most prevalent carbapenemases identified were KPC (69.2%), NDM (9.6%), and SME (4.8%), with 16.3% of CRE isolates lacking identifiable carbapenemase genes. Ceftazidime-Avibactam and Meropenem-Vaborbactam showed strong activity against KPC and SME producers but limited efficacy against metallo-β-lactamase (MBL) producers. Tigecycline (95.2% susceptible), amikacin (73.1% susceptible), and gentamicin (60.6% susceptible) were the most active comparators against CRE. Aztreonam-Avibactam inhibited 79.1% of *Pseudomonas aeruginosa* isolates at ≤ 8 mg/L, while 77.2% were susceptible to both Meropenem and Piperacillin-Tazobactum. Furthermore, aztreonam-Avibactam demonstrated significant activity against *Stenotrophomonas maltophilia*, inhibiting 99.5% of isolates at ≤ 8 mg/L."

Imipenem-Cilastatin/Relebactam:

Relebactam, a new beta-lactamase inhibitor, expands the antimicrobial spectrum of Imipenem-Cilastatin, providing activity against certain serine carbapenemases. While this combination presents a valuable treatment alternative for carbapenem-resistant Enterobacterales (CRE) infections, its efficacy against metallo-β-lactamases (MBLs) is restricted. A meta-analysis of four randomized controlled trials involving 948 patients found that IMI/REL therapy had similar clinical responses to comparator therapies across various treatment visits, with relative risks (RR) of 1.00 (0.88, 1.12) at discontinuation of intravenously administered therapy (DCIV), 1.00 (0.89, 1.14) at early follow-up (EFU), and 1.00 (0.88, 1.13) at late follow-up (LFU) [24]. Another study on patients with complicated urinary tract infections (cUTI) or acute pyelonephritis showed microbiological response rates of 95.5%, 98.6%, and 98.7% for IMI/REL 250 mg, IMI/REL 125 mg, and IMI/Cilastatin alone, respectively [25]. Additionally, a study on hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) found that clinical response rates were comparable

between IMI/REL and piperacillin/Tazobactum across different renal function categories, with a higher response rate (91.7% vs. 44.4%) in patients with augmented renal clearance [26].

BETA-LACTAMASE INHIBITORS (DEVELOPMENTAL):

Zidebactam (with Cefepime) [27]**:**

Study reported over 97% clinical efficacy in infections caused by carbapenem-resistant Gram-negative pathogens Clinical and Laboratory Standards Institute (CLSI) awarded high susceptibility breakpoints to Zidebactam/Cefepime, indicating its effectiveness against Enterobacterales, Pseudomonas, and Acinetobacter combination is currently undergoing a multinational Phase 3 study, expected to be completed by FY 2025, which will further facilitate its global registration and marketing authorization.

Taniborbactam (with Cefepime) [28]**:**

The CERTAIN-1 Phase 3 study, which included 661 adult patients with complicated urinary tract infections (cUTI) and acute pyelonephritis, found that CEF/TAN achieved a composite microbiologic and clinical success rate of 70% compared to 58% for meropenem, with a treatment difference of 11.9 percentage points (95% CI, 2.4, 21.6). Another study reported that CEF/TAN was superior to meropenem in terms of composite success at the Test-of-Cure visit, with a difference of 12.6 percentage points (95% CI, 3.1, 22.2). The safety profile of CEF/TAN was comparable to meropenem, with treatment-emergent adverse events occurring in 35.5% of CEF/TAN-treated patients and 29.0% of meropenem-treated patients.

Nacubactam (with meropenem) [29,30]**:**

The ROSCO Global Surveillance study, which included 4,695 clinical isolates from 50 sites in the United States and Europe, found that MEM/NAC inhibited 99.5%, 99.7%, and 99.9% of Enterobacteriaceae isolates at concentrations of ≤2, ≤4, and ≤8 mg/L, respectively. Another study reported that MEM/NAC displayed MIC ≤8 mg/L for 33 out of 37 CAZ/AVI-resistant multidrug-resistant Enterobacteriaceae isolates.

LYS228 [31]**:**

It is a Monobactam antibiotic, sharing structural similarities with aztreonam. It maintains activity against metallo-β-lactamases (MBLs) and, through specific structural modifications, also gains activity against serine β-lactamases by targeting penicillin-binding protein 3. Laboratory studies have indicated strong activity against both Class A (KPC) and Class B (NDM) carbapenemases. Pharmacokinetic evaluations have demonstrated a favourable safety and tolerability profile. Although two phase 2 clinical trials were initiated for LYS228, they were subsequently discontinued. Currently, there are no registered clinical trials for LYS228 or its related compound, BOS228.

CEPHALOSPORIN (SIDEROPHORE):

Cefiderocol [32-35]**:**

Cefiderocol leverages the bacterial iron uptake mechanism to enhance its cellular entry and bypass bacterial resistance. The United States Food and Drug Administration (FDA) granted approval to Cefiderocol in 2019 for the treatment of complicated urinary tract infections (cUTI) and hospital-acquired/ventilator-associated pneumonia (HAP/VAP). This approval followed successful phase 2 and 3 non-inferiority trials, which compared Cefiderocol to Imipenem-Cilastatin for cUTI and to meropenem for nosocomial pneumonia, respectively, both caused by gram-negative pathogens. Cefiderocol exhibits a strong binding affinity for multiple penicillin-binding proteins, disrupting peptidoglycan synthesis and leading to bacterial cell death. Its safety profile is generally comparable to that of other cephalosporin antibiotics. The CREDIBLE-CR study assessed Cefiderocol's efficacy in severe carbapenem-resistant infections. However, the FDA label now includes a boxed warning concerning an observed increase in all-cause mortality associated with *Acinetobacter* infections, specifically in cases of bloodstream infections (BSI), nosocomial pneumonia, and sepsis. The largest European real-world evidence study (PERSEUS) included 261 critically ill adult patients and found an overall clinical success rate of 84.3% and a 28-day all-cause mortality of 21.5%. Another study, the PROVE study, included 244 patients and reported a clinical cure rate of 64.8%, a clinical response rate of 74.2%, and a 30-day in-hospital all-cause mortality (IH-ACM) of 18.4%. Resistance to Cefiderocol in Enterobacterales has been observed when both serine and metallo-beta-lactamases are co-produced; this resistance mechanism can be potentially circumvented by the addition of Avibactam.

AMINOGLYCOSIDE:

Plazomicin [36-38]:

Plazomicin, a newly developed aminoglycoside, demonstrates antimicrobial activity against certain carbapenem-resistant Enterobacterales (CRE) isolates, including those exhibiting resistance to other aminoglycosides. This agent is less susceptible to specific enzymes that modify aminoglycosides. It displays a broad spectrum of activity against Enterobacterales, encompassing strains with extended-spectrum beta-lactamase (ESBL) enzymes and various CRE classes, such as Class A (KPC), Class B (VIM, IMP), and Class D (OXA-48). However, its clinical effectiveness may be reduced in regions with a high prevalence of NDM-1-producing CRE, due to its variable activity against these strains. The CARE trial, a multicenter, randomized, open-label trial, evaluated Plazomicin compared to colistin for serious CRE infections. The study included 39 patients, with 18 receiving Plazomicin and 21 receiving colistin. The primary endpoint event occurred in 24% of patients receiving Plazomicin compared to 50% of those receiving

colistin, with a difference of -26 percentage points (95% CI, -55 to 6). Among patients with bloodstream infections, the primary endpoint event occurred in 14% of patients receiving Plazomicin compared to 53% of those receiving colistin, with a difference of -39 percentage points (95% CI, -69 to -4). Another meta-analysis of three randomized controlled trials involving 761 patients found that Plazomicin had a clinical remission rate similar to comparators (OR, 1.02; 95% CI, 0.60–1.73) and a lower microbiologic recurrence rate (OR, 0.38; 95% CI, 0.17–0.86) Resistance to Plazomicin can occur through modifications mediated by 16S ribosomal methyltransferases, and bacteria harboring these resistance genes can facilitate their horizontal transfer.

Therapeutic Class	
Antimicrobial	**Remarks**
B-LACTAM/B-LACTAMASE INHIBITOR COMBINATION	
Ceftazidime-Avibactam	cUTI, cIAI (with metronidazole), HAP/VAP. Can be used with Aztreonam for NDM-producing infections.
Meropenem-Vaborbactam	Activity against class A or cUTI, cIAI, HAP/VAP. Effect wide range of carbapenemases.
Imipenem-Relebactam	FDA: cUTI, cIAI EMA: HAP/VAP, BSI, resistant GN infections
Imipenem-Cilastatin/Relebactam	
B-Lactamase Inhibitor	
Zidebactam	Phase 3 trial ongoing with Cefepime. High susceptibility breakpoint
Taniborbactam*	In Phase 3 study in combination with Cefepime for cUTI
Nacubactam*	Fast Track and Qualified Infectious Disease Product (QIDP) designations. Completed phase 3 trial in 2024 for cUTI in combination with Meropenem
AMINOGLYCOSIDES	
Plazomicin	FDA: NDM-carrying CRE in UTI
CEPHALOSPORIN	
Cefiderocol	FDA: cUTI and HAP/VAP EMA: Resistant GN infections
PHAGE THERAPY	
Data is awaited. Currently phase I & II ongoing with case series	
Faecal Microbiota Transplant (FMT)	
Effective for recurrent Clostridioides difficile infection (CDI)	
PENTAGLOBIN	
Used in Sepsis & immunoglobulin substitution in immunocompromised patients	
cUTI=complicated urinary tract infection; cIAI=complicated intraabdominal infection; HAP/VAP=hospital acquired pneumonia/ventilator-associated pneumonia; GN=gram negative; ABSSSI=acute bacterial skin and skin structure infection; CABP=community acquired bacterial pneumonia; FDA= United States Food and Drug Administration; EMA= European Medicines Agency; * antibiotic currently in development.	

Table 3: Summary of Newer Antimicrobial to Manage CRE Infections.

Antibiotic (Combination)	Class	Covers KPC (Class A)	Covers OXA-48 (Class D)	Covers NDM/ VIM/IMP (Class B MBL)	Comments
Ceftazidime-Avibactam	β-lactam/ β-lactamase inhibitor	☑ Yes	☑ Yes	✗ No	Often first-line; increasing resistance observed
Meropenem-Vaborbactam	β-lactam/ β-lactamase inhibitor	☑ Yes	✗ Limited	✗ No	KPC-specific; better mortality outcomes vs CAZ-AVI in some studies
Imipenem-Cilastatin/ Relebactam	β-lactam/ β-lactamase inhibitor	☑ Yes	✗ Limited	✗ No	Useful in select serine carbapenemase cases
Meropenem-Nacubactam	β-lactam/ β-lactamase inhibitor	☑ Yes	☑ Yes	✗ Partial	Activity against some CAZ-AVI-resistant isolates
Aztreonam-Avibactam	Monobactam/ β-lactamase inhibitor	☑ Yes	☑ Yes	☑ Yes	Best option for MBLs; active against most CRE including dual carbapenemases
Cefepime-Zidebactam	β-lactam/ β-lactamase inhibitor	☑ Yes	☑ Yes	☑ Yes	Under phase 3 trials; broad GNB activity including CRE, pseudomonas & Acinetobacter
Cefepime-Taniborbactam	β-lactam/ β-lactamase inhibitor	☑ Yes	☑ Yes	☑ Yes	Promising Phase 3 results; broad-spectrum agent
LYS228	Monobactam derivative	☑ Yes	☑ Yes	☑ Yes	Development halted; retains MBL & serine β-lactamase activity
Cefiderocol	Siderophore cephalosporin	☑ Yes	☑ Yes	⚠ Variable	Caution in Acinetobacter BSI; boxed FDA warning. Resistance when both serine and metallo-beta-lactamases are co-produced
Plazomicin	Aminoglycoside	☑ Yes	☑ Yes	⚠ Variable	Poorer activity in NDM-1 prevalent regions; alternative to colistin

Table 4: Summary of Antibiotic (Combination) Positioning For Different Types Of Carbapenemase Enzymes

Antimicrobial Stewardship:

Novel CRE treatments such as β-lactam-β-lactamase-inhibitor (BLBLI), Cefiderocol, and Plazomicin, have limited availability & accessibility. Recent susceptibilities of ESBL-positive CRE to Ceftolozane/Tazobactam, Ceftazidime/Avibactam and other studied antimicrobials were consistently lesser emphasizing for new innovative treatment strategies. Judicious use of all antimicrobials is crucial to prevent further resistance. Local resistance patterns, patient-specific factors, and the severity of infection must be considered. In severe CRE infections, combination therapy with two or more active agents is often recommended. Always follow your local and national guidelines to support the antimicrobial stewardship.

Recent Recommendations:

IDSA 2024 guidelines for CRE current recommendations [1]**:**

Following Table outlines the recommended and alternative antimicrobial agents for various types of CRE infections, emphasizing the choice of treatment based on the specific type of CRE involved and the infection location. In the guidelines by IDSA, carbapenem-resistant Enterobacteriaceae (CRE) represent a diverse array of pathogens characterized by various resistance mechanisms. These pathogens can be categorized into two main groups: those that do not produce carbapenamesase and those that do. Non-carbapenemase-producing CRE may arise from the amplification of non-carbapenemase β-lactamase genes, such as extended-spectrum β-lactamase (ESBL) genes, alongside the disruption of outer membrane porins. In the United States, carbapenemase-producing strains constitute between 35% and 83% of CRE cases, with the higher percentages noted when the definition of CRE is limited to those exhibiting resistance to meropenem or Imipenem. The Centers for Disease Control and Prevention (CDC) analyzed over 42,000 carbapenem-resistant Enterobacteriaceae (CRE) isolates collected from 2017 to 2019, revealing that approximately 35% of clinical or surveillance isolates in the United States possess one of the five primary carbapenemase genes. The distribution of these carbapenemase-producing isolates by gene family was as follows: blaKPC (86%), blaNDM (9%), blaVIM (<1%), blaIMP (1%), and blaOXA-48-like (4%). A subsequent study involving 261 consecutive clinical CRE isolates, defined by resistance to meropenem or Imipenem, collected from 2019 to 2021 across the United States, indicated that 83% of these isolates were carbapenemase producers. The breakdown of these isolates was as follows: blaKPC (80%), blaNDM (15%), blaIMP (5%), and blaOXA-48-like (7%). Notably, from 2019 to 2021, the proportion of blaKPC decreased from 74% to 57%, while the prevalence of metallo-beta-lactamase (MBL) genes (such as blaNDM, blaVIM, blaIMP) rose from 4% to 20%, and the presence of blaOXA-48-like increased from 1% to 8%.

Infection	Antimicrobial agents
Uncomplicated cystitis CRE	**Preferred:** Nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin **Alternative:** An aminoglycoside (as a single dose), oral fosfomycin (for *E. coli* only), colistin, ceftazidime-Avibactam, Meropenem-Vaborbactam, Imipenem-cilastatin-Relebactam, or Cefiderocol
Pyelonephritis or cUTI due to CRE	**Preferred:** TMP-SMX, ciprofloxacin, or levofloxacin, Ceftazidime-Avibactam, Meropenem-Vaborbactam, Imipenem-cilastatin-Relebactam, and Cefiderocol **Alternative:** Aminoglycosides
CRE outside of the urinary tract that are not carbapenemase producing exhibit susceptibility to Meropenem and Imipenem (i.e., MICs ≤1 μg/mL), but are not susceptible to Ertapenem (i.e., MICs ≥1 μg/mL)	**Preferred:** Use of extended-infusion meropenem (or Imipenem-cilastatin)
CRE outside of the urinary tract that are not carbapenemase producing That do not exhibit susceptibility to any carbapenem	**Preferred:** ceftazidime-Avibactam, Meropenem-Vaborbactam, and Imipenem-cilastatin-Relebactam
CRE infections outside of the urinary tract caused by CRE if KPC production is present	**Preferred:** Meropenem-Vaborbactam, ceftazidime-Avibactam, and Imipenem-cilastatin- Relebactam **Alternative:** Cefiderocol

CRE infections outside of the urinary tract caused by CRE if NDM or other MBL production is present	**Preferred:** Ceftazidime-Avibactam in combination with aztreonam, or Cefiderocol as monotherapy,
CRE infections outside of the urinary tract caused by CRE if OXA-48-like production is present	**Preferred:** Ceftazidime-Avibactam **Alternative:** Cefiderocol

Table 5: Summary of IDSA 2024 Guidelines for CRE Infection.

ESCMID guidelines for CRE [39]**:**

ESCMID & IDSA both guidelines recommend similar agents for treating CRE infections, with slight variations in the preferred agents for specific infection types. The ESCMID guidelines provide more detailed recommendations for uncomplicated cystitis and pyelonephritis or complicated UTI due to CRE, while the IDSA guidelines focus on broader categories of CRE infections.

Indian recommendations:

ICMR 2022 Diagnosis & Management of Carbapenem Resistant Gram-negative Infections Guidance [40]**:**

The ICMR 2022 guidelines provide treatment recommendations tailored to specific carbapenemase types, including Metallo-β-lactamases (MBLs) like NDM, OXA-48-like, and KPC. For Metallo-β-lactamase (MBL) producers, such as NDM, the first-line treatment is prolonged infusion of ceftazidime-Avibactam and aztreonam over three hours; alternative options include Polymyxins plus a susceptible agent, Tigecycline for limited use, or aminoglycosides for uncomplicated infections, with high-dose carbapenems as an option when MICs are borderline. For MBL plus OXA-48 producers, the first-line and alternative options are the same as for NDM alone. For OXA-48-like producers, the first-line treatment is prolonged infusion of ceftazidime-Avibactam, with alternatives being Polymyxins plus a susceptible agent, Tigecycline for limited use, or aminoglycosides for uncomplicated infections, and high-dose carbapenems when MICs are borderline. For KPC producers, the first-line treatment is prolonged infusion of ceftazidime-Avibactam, with the same alternative treatment options as OXA-48-like producers. General considerations across all carbapenemase types include avoiding Polymyxins B for UTIs, not using Tigecycline alone for bloodstream infections or pneumonia, reserving aminoglycosides for uncomplicated infections, and adjusting treatment based on susceptibility testing (MIC) when available.

ICONIC 2.0 consensus statement [41]

A group of Indian experts had consensus over rise in Carbapenem resistance in ICU settings over the past decade, with CRKP and CREco being the most common, making up over 90% of all CRE strains. In India, the prevalent resistance mechanisms include NDM and OXA-48, while PBP-3 inserts notably affect antibiotic efficacy, especially against carbapenems. Diagnosing CRE infections remains challenging due to the complexity of detecting carbapenemase, although rapid tests and molecular assays assist in timely diagnosis, necessitating a combined approach for accuracy. Empirical therapy for CRE infections typically involves the CAZ-AVI + ATM combination, particularly in critically ill patients, with Polymyxins being vital for CNS infections. CAZ-AVI monotherapy is advised for OXA-48–like CP CRE infections, with dosage adjustments being essential, especially for patients with renal impairment. Continuous surveillance, optimized dosing strategies, and further research into new therapies are crucial to addressing the evolving CRE infection landscape in critical care environments.

Conclusion

Carbapenem-Resistant Enterobacteriaceae (CRE) infections represent a critical public health challenge in India, primarily due to the widespread presence of OXA-48-like and NDM-type carbapenemases—often co-produced in the same isolate. This dual mechanism of resistance significantly limits therapeutic options and underscores the need for region-specific strategies, as a one-size-fits-all approach is inadequate.

Traditional combinations like Ceftazidime-Avibactam, though effective against OXA-48, lack activity against NDM, and resistance is increasingly reported. Similarly, agents like Meropenem-Vaborbactam and Imipenem-Cilastatin/Relebactam target KPC and some OXA-48 producers but have no significant activity against NDM. In this setting, combinations like Aztreonam-Avibactam are particularly promising, given their activity against all major classes of carbapenemases—including metallo-β-lactamases (MBLs) like NDM, VIM, and IMP—making them potentially the best choice for dual-carbapenemase producers.

Emerging agents such as Cefepime-Zidebactam and Cefepime-Taniborbactam demonstrate broad-spectrum activity, including against NDM and OXA-48, and are currently in late-stage clinical trials, offering hope for the near future. Cefiderocol, though active against many CRE strains, shows variable activity in MBL producers and carries safety concerns in Acinetobacter bloodstream infections.

Given the adaptability of these pathogens and the complexity of resistance mechanisms, especially in high-burden settings like India, ongoing surveillance and judicious antimicrobial stewardship are imperative. Therapeutic choices must be individualized based on local resistance patterns and molecular diagnostics, to effectively combat CRE infections and preserve future treatment options

Conflict of Interest: Dr Anup Petare, Dr Sagar Bhagat, Dr Amullya Pednekar, Dr Saiprasad Patil, Dr Hanmant Barkate are employees of glenmark pharmaceuticals.

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