

Promising Future of Novel Beta-Lactam Antibiotics Against Bacterial Resistance

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Background: Antimicrobial resistance is a growing global concern that compromises the efficacy of antibiotics, particularly due to the misuse and overuse of these agents. Beta-lactam antibiotics, widely used for their broad-spectrum activity, are increasingly threatened by bacterial resistance mechanisms. Recent studies showed that resistant Gram-negative bacteria cause many hospital infections, which makes the search for new treatments very urgent.

Objective: This review explores recent advancements in the development of novel beta-lactam antibiotics, including new drug combinations and structural modifications designed to overcome beta-lactamase degradation and effectively target mutated penicillin-binding proteins (PBPs).

Literature Review: One of the main resistance mechanisms in Gram-negative bacteria is the production of beta-lactamases, which break the beta-lactam ring and stop the drug from working. New ideas include adding more than one beta-lactam ring in the drug, combining with strong beta-lactamase inhibitors, and making hybrid structures. These strategies have shown promising results in preclinical evaluations.

Conclusion: Novel beta-lactam antibiotics demonstrate significant potential in combating resistant bacterial strains. Future directions should emphasize large-scale in vivo validation, the incorporation of novel β -lactamase inhibitors, and the development of advanced drug delivery systems. Integration of these strategies may enhance the clinical applicability of β -lactams and provide sustainable solutions to address the global burden of antimicrobial resistance.

Keywords: beta-lactamase, Gram-negative bacteria, Gram-positive bacteria, penicillin-binding proteins, cross-resistance, polymer inclusion nano-complex, beta-lactam antibiotics

Introduction

Antibiotic resistance is a growing global health concern, largely driven by the overuse, misuse, and frequent prescription of antibiotics—particularly beta-lactam agents.^{1–4} Beta-lactam antibiotics are characterised by the presence of a beta-lactam ring in their chemical structure and include several subclasses such as penicillins, cephalosporins, and carbapenems. Each subclass possesses unique properties and exhibits varying antibacterial spectra. These agents are active against a wide range of Gram-positive and Gram-negative bacteria.^{5–7}

The efficacy of beta-lactam antibiotics is primarily determined by their affinity for penicillin-binding proteins (PBPs), which are essential for bacterial cell wall synthesis. In Gram-positive bacteria, resistance to beta-lactams commonly arises from alterations in PBPs, reducing drug binding and efficacy.^{8–10}

One of the major challenges in combating beta-lactam resistance, especially among Gram-negative organisms, is the production of beta-lactamase enzymes. These enzymes hydrolyze the beta-lactam ring, rendering the antibiotic inactive by breaking its structural integrity. This mechanism significantly contributes to resistance development, as bacteria not only inactivate the antibiotic but also evolve additional defenses, compounding the problem.^{9,11,12}

The emergence and spread of beta-lactamase-producing “superbugs” pose a serious threat to public health. These multidrug-resistant organisms are associated with prolonged hospitalizations, treatment failures, increased adverse drug events, greater healthcare costs, and diminished quality of care. Addressing this issue requires multifaceted strategies, including the discovery of novel antibiotics that bypass conventional resistance mechanisms, implementation of antibiotic stewardship programs, and ongoing surveillance of resistance trends.^{13–15}

An important aspect of resistance mitigation involves the use of beta-lactamase inhibitors. Agents such as clavulanic acid, tazobactam, and sulbactam are frequently co-administered with beta-lactam antibiotics to inhibit enzymatic degradation.^{16,17} Combination therapies like piperacillin–tazobactam and ceftazidime–avibactam have demonstrated substantial efficacy against resistant strains, improving clinical outcomes by preserving the activity of the beta-lactam component.^{18,19}

Given the limitations of existing treatment options and the growing threat of beta-lactamase-mediated resistance, ongoing research has focused on the development of novel beta-lactam antibiotics. These new agents aim to overcome common resistance mechanisms and expand the spectrum of activity against multidrug-resistant organisms. The objective of this review is to define and summarise the roles of emerging beta-lactam antibiotics and highlight their potential advantages based on findings from developmental pipelines and in vitro studies. These insights may help inform future clinical use and guide strategies for combatting antimicrobial resistance more effectively.

Mechanisms of Beta-Lactam Resistance and the Need for Novel Therapeutics

Beta-lactamase enzymes are key mediators of bacterial resistance, capable of hydrolysing the beta-lactam ring, thereby diminishing the affinity and efficacy of beta-lactam antibiotics. This enzymatic activity contributes significantly to rising morbidity and mortality rates, particularly when driven by the misuse or overuse of beta-lactam agents.^{19–21} Beta-lactamases are classified into four main groups based on molecular structure and catalytic mechanism (Figure 1). Class A includes Extended-Spectrum Beta-Lactamases (ESBLs) and carbapenemases such as *Klebsiella pneumoniae* carbapenemase (KPC), *Temoniera* β -lactamase (TEM), *Sulphydryl variable* β -lactamase (SHV), *Cefotaximase-Munich* (CTX-

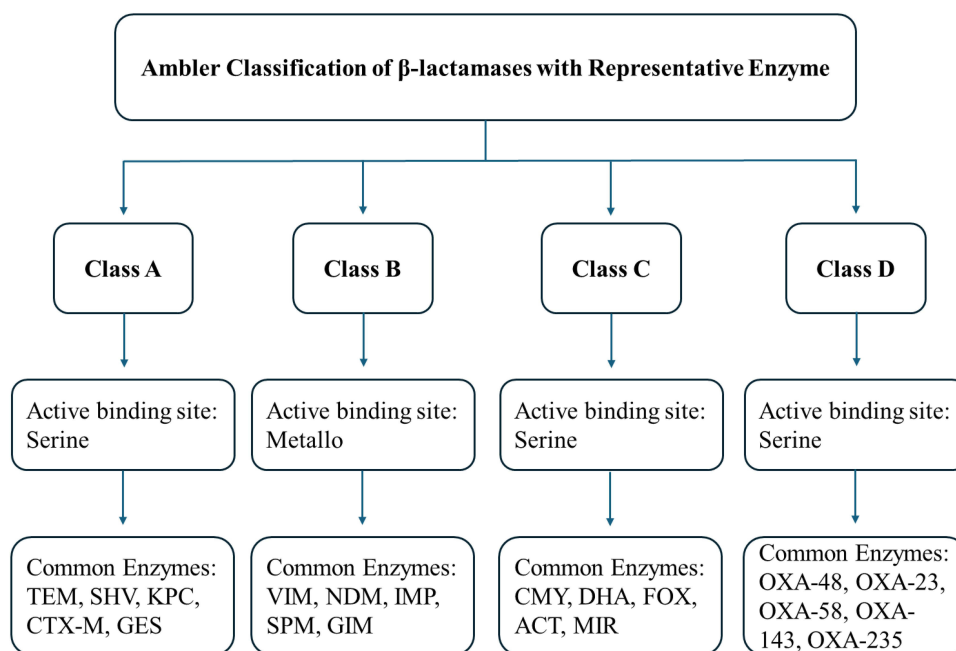


Figure 1 Ambler classification of β -lactamases (Classes A–D) with their active binding sites and representative enzymes. Class A includes serine β -lactamases such as TEM, SHV, KPC, CTX-M, and GES. Class B metallo- β -lactamases comprise VIM, NDM, IMP, SPM, and GIM. Class C serine-based β -lactamases include CMY, DHA, FOX, ACT, and MIR. Class D oxacillinases (OXA-type) are represented by OXA-48, OXA-23, OXA-143, and OXA-235. This schematic highlights the molecular diversity of β -lactamases contributing to antibiotic resistance in clinically significant bacteria, Adapted from.^{22,26,31,32}

M), and *Guiana extended-spectrum β -lactamase* (*GES*), which are predominantly produced by Enterobacteriaceae. These enzymes can hydrolyze penicillins and cephalosporins, complicating treatment outcomes. Clavulanic acid is a known inhibitor of many Class A enzymes.^{12,22–24} Class B, or *Metallo- β -lactamases* (*MBLs*), require divalent metal ions, typically zinc, for enzymatic activity. Important examples include *New Delhi metallo- β -lactamase* (*NDM*), *Verona integron-encoded metallo- β -lactamase* (*VIM*), *Imipenemase* (*IMP*), *São Paulo metallo- β -lactamase* (*SPM*), and *German imipenemase* (*GIM*). These enzymes are resistant to most β -lactamase inhibitors but can be inactivated by chelating agents such as EDTA.^{25–29} Class C, or AmpC beta-lactamases, confer resistance to cephamycins and oxyimino-cephalosporins. Representative examples include *Cephamecinase* (*CMY*), *Dhahran Hospital AmpC* (*DHA*), *Cephamecin-hydrolyzing AmpC* (*FOX*), *AmpC-type cephalosporinase* (*ACT*), and *Klebsiella pneumoniae MIR cephalosporinase* (*MIR*). Unlike clavulanic acid, these enzymes can be inhibited by boronic acid derivatives. They are often encoded on the chromosome and can be inducible, posing additional therapeutic challenges.^{30–33} Class D includes oxacillinases (OXA-type), frequently found in *Acinetobacter* spp. and *Pseudomonas aeruginosa*. Clinically significant examples include *Oxacillinase-48* (*OXA-48*), *Oxacillinase-23* (*OXA-23*), *Oxacillinase-58* (*OXA-58*), *Oxacillinase-143* (*OXA-143*), and *Oxacillinase-235* (*OXA-235*). These enzymes exhibit variable activity, and some variants are capable of hydrolysing carbapenems, which are often considered antibiotics of last resort.^{22,26,34,35}

A recent systematic review focusing on *Acinetobacter baumannii* in intensive care units reported a striking clinical burden.³⁶ Among 317 isolates analyzed, nearly 60% were linked to pneumonia and about one-third to bloodstream infections, making these the most common hospital-acquired complications. The same study also revealed very high rates of β -lactamase genes that ADC2 was detected in almost all isolates (98.4%), OXA-23 was similarly prevalent (95.6%), and the carbapenemase gene NDM-1 was present in more than half of the strains (57.1%).³⁶ These findings emphasize the dominance of β -lactamase-mediated resistance and reinforce the urgent need for innovative β -lactam antibiotics to manage such infections.

In addition, recent in vitro studies have explored combining more than one beta-lactam ring within a single molecular structure to enhance antibacterial efficacy and reduce the likelihood of resistance development.^{18,30}

While traditional beta-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam have been used successfully, the emergence of resistant strains highlights the limitations of current therapies. There is a pressing need to develop new generations of inhibitors with activity against both serine- and metallo-beta-lactamases. For example, Taniborbactam (VNRX-5133), a novel cyclic boronate β -lactamase inhibitor, has shown potent activity against class A, C, and D serine β -lactamases as well as clinically relevant class B metallo- β -lactamases. This compound, currently in late-phase clinical trials, represents one of the first broad-spectrum inhibitors with dual coverage.^{31,37} In addition, other recently approved inhibitors such as Avibactam (a diazabicyclooctane, combined with ceftazidime) and Relebactam (also a diazabicyclooctane, combined with imipenem) have broadened treatment options against carbapenem-resistant Enterobacterales, although they remain largely ineffective against metallo- β -lactamases.^{16,38}

Moreover, the continuous identification of novel beta-lactamase variants underscores the necessity for ongoing research into innovative antibiotic designs that are less susceptible to conventional resistance mechanisms.^{9,11,13,19}

Trimer of Phenoxy-Methyl Penicillin

The trimer of phenoxy-methyl penicillin sulphone, as shown in Figure 2, exhibits enzyme inhibitory activity (IC_{50}) against *Enterobacter cloacae* P99 at a concentration of 20 $\mu\text{g/mL}$ (0.018 $\mu\text{mol/mL}$),^{39,40} which is comparable to sulbactam's IC_{50} of 5 $\mu\text{g/mL}$ (0.02 $\mu\text{mol/mL}$). Against *Proteus vulgaris* 1028/Bc, the trimer demonstrates an IC_{50} of 196 $\mu\text{g/mL}$ (0.22 $\mu\text{mol/mL}$), whereas sulbactam shows significantly greater potency with an IC_{50} of 0.12 $\mu\text{g/mL}$ (0.0048 $\mu\text{mol/mL}$).⁴¹

Bis-Beta-Lactam Antibiotics

Bis-beta-lactams are novel antibiotic agents structurally derived from conventional beta-lactam antibiotics such as ampicillin and amoxicillin. These compounds are nearly symmetrical dimers and exhibit enhanced affinity for the *PBP1a* mutation in *Escherichia coli* (*E. coli*). Their bifunctional nature allows them to simultaneously bind to two

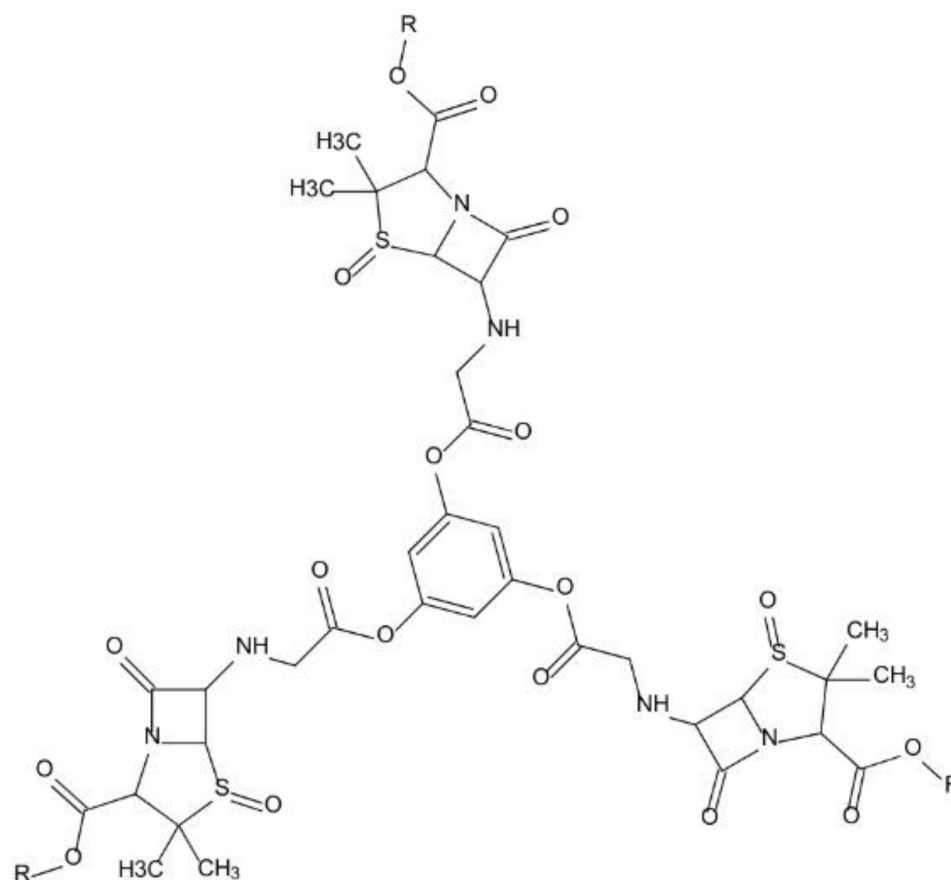


Figure 2 Trimer phenoxy-methyl penicillin sulphone. All rights reserved for *The Journal of Antibiotics*.⁴¹

mutated PBPs, increasing their antibacterial potential. Structurally, compound II* is derived from 6-amino-penicillanic acid (6-APA), while compounds III* and V* originate from Ampicillin (α -aminobenzylpenicillin), and compounds VII* and XI* are derived from Amoxicillin (α -amino-p-hydroxybenzylpenicillin),^{42,43} as shown in Table 1.

Table 1 Affinity of Bis-Beta-Lactam Antibiotics for PBPIa*, PBPIb*, PBPIc* of *E. coli*.⁴³ Values Represent IC₅₀ (μ g/mL) for Inhibition of Penicillin-Binding Proteins (PBPs). PBPIa*, PBPIb*, PBPIc* Indicate Mutated Penicillin-Binding Proteins of *Escherichia coli*. “< 3” Indicates Activity Below Detection Threshold

B-Lactam Antibiotics	IC50 for PBPI Mutation		
	Ia	Ib	Ic
	mcg/mL		
Compound II*	2	20	50
Ampicillin	13	5.6	-
Compound III*	0.5	50	100
Compound V*	< 3	< 3	< 3
Amoxicillin	10	20	5
Compound VII*	< 3	< 3	< 3
Compound XI*	< 3	12	< 3

Macrocycle-Embedded Beta-Lactam

This class represents bicyclic beta-lactam antibiotics that offer high conformational adaptability, allowing acylation of PBP2a* in either head-to-head (HH) or head-to-tail (HT) orientations. These compounds have shown promise against methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP5fm* in *Enterococcus faecium* (E. faecium). Some compounds from the 4-series and 5-series bind PBP2a* near the ceftobiprole binding site.

Notably, compound 5c, which contains 32 atoms and is the largest of its kind investigated in this field, demonstrated potential as a novel antibiotic. Interestingly, compound activity varied with structural orientation: in some instances, pure HH was more potent (eg, 5a and 5b), whereas in others (eg, 5c and 5e), the HH/HT mixture was more effective. Compound 5d showed no activity with pure HH^{42,44} (Figure 3).

The 4-series compounds displayed higher general potency than the 5-series. This is attributed to their structural composition, particularly the presence of two double bonds in the macrocyclic ring, in contrast to the saturated 5-series^{42,44} (Figure 4).

Beta-Lactam Polymer Inclusion Nano-Complex

This strategy aims to protect beta-lactam antibiotics, especially ampicillin trihydrate, from beta-lactamase-mediated degradation and to enhance their stability against resistant pathogens. This is achieved by combining ampicillin with the polymer PAM-18Na (sodium salt of poly(maleic acid-alt-octadecene)). PAM-18Na has the ability to solubilise organic molecules, making it a promising protector of beta-lactams from enzymatic attack.⁴⁵

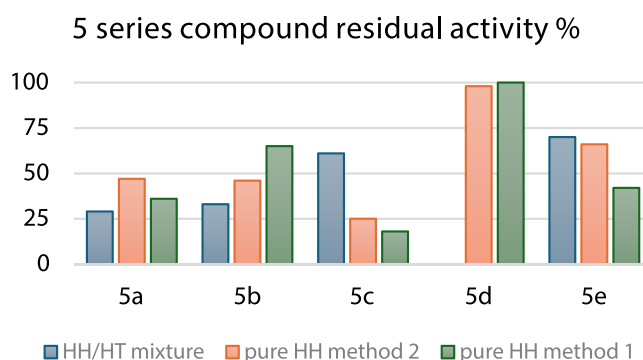


Figure 3 Percentage residual activity of 5-series compounds.⁴⁴ The figure shows the residual activity of macrocycle-embedded β -lactam compounds from the 5-series tested against penicillin-binding protein 2a (PBP2a) of *Staphylococcus aureus*. Differences in activity are associated with conformational orientation (head-to-head vs head-to-tail). **Abbreviations:** MRSA, Methicillin-resistant *Staphylococcus aureus*; PBP2a, penicillin-binding protein 2a of *Staphylococcus aureus*.

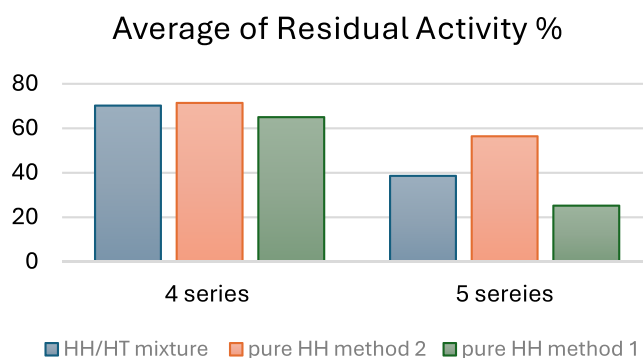


Figure 4 Average percentage residual activity of 4-series and 5-series compounds.⁴⁴ The figure compares the activity of macrocycle-embedded β -lactam antibiotics from two structural series. The 4-series compounds displayed higher potency due to the presence of two double bonds in the macrocyclic ring, whereas the 5-series compounds were fully saturated.

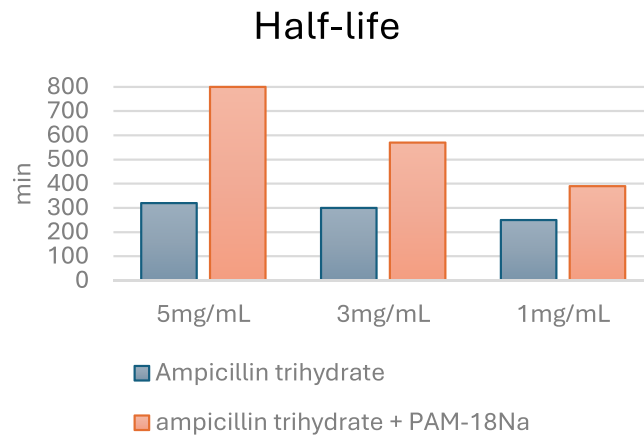


Figure 5 Half-life of ampicillin trihydrate, alone and with PAM-18Na, at different initial concentrations.⁴⁵ This figure illustrates the protective effect of the polymer PAM-18Na (sodium salt of poly(maleic acid-alt-octadecene)) on ampicillin trihydrate. Measurements were performed at concentrations of 1, 3, and 5 mg/mL under acidic conditions. PAM-18Na significantly increased the half-life of ampicillin by reducing β -lactamase-mediated degradation.

The polymer maintains stable hydrophobicity in aqueous solutions regardless of pH (I3/I1 of pyrene $\approx$ 0.95). When combined with ampicillin trihydrate, its protective effect is pH-dependent, being highest at pH 7.0 (approx. 80% activity) and decreasing to 20% at pH 10.0.⁴⁵

Degradation tests evaluated three concentrations of ampicillin trihydrate (1, 3, and 5 mg/mL) both with and without PAM-18Na. After 240 minutes in acidic conditions, the standalone drug retained 65%, 60%, and 55% bioavailability at 5, 3, and 1 mg/mL, respectively. When combined with PAM-18Na, these values rose significantly to around 90%, 75%, and 65% respectively. The half-life also improved in a concentration-dependent manner when co-administered with PAM-18Na (Figure 5).

A beta-lactamase inhibition test using class C beta-lactamase (AmpC) from *Pseudomonas fluorescens* demonstrated that PAM-18Na reduced enzyme activity against ampicillin trihydrate from 0.207 U/mL to 0.029 U/mL. Disk diffusion results against *S. aureus* strains are summarised in Table 2.

Minimum inhibitory concentration (MIC) values were also lowered with polymer inclusion. For *S. aureus* ATCC 29213, MIC decreased from 8 μ g/mL (alone) to 3.5 μ g/mL (with PAM-18Na). For ATCC 43300, it dropped from 34 μ g/mL to 7 μ g/mL.⁴⁵

Novel Beta-Lactam/Beta-Lactamase Inhibitor Combinations

Several new β -lactam/ β -lactamase inhibitor (BL/BLI) combinations have shown promising efficacy against resistant bacterial strains and β -lactamase enzymes. These combinations are particularly valuable in treating multidrug-resistant (MDR) organisms. Below are some of the most clinically significant recent developments:

Table 2 Ampicillin Disk Diffusion Assay.⁴⁵ Values Represent Mean Inhibition Zone Diameters (Mm). ATCC Refers to American Type Culture Collection Reference StrainS. “Sensitive” Indicates Susceptible Control Strain, and “Resistant” Refers to Methicillin-Resistant *S. Aureus* (MRSA)

Strain	Average Diameter (mm)
<i>S. aureus</i> ATCC 25923 (sensitive)	33.99
<i>S. aureus</i> ATCC 29213 (resistant)	20.15
<i>S. aureus</i> ATCC 43300 (resistant)	12.9

Table 3 Ceftazidime-Avibactam Susceptibility Test According to Clinical and Laboratory Standards Institute (CLSI) Against Some MDR Organisms.⁴⁷ Values Represent Percentage of Isolates Susceptible According to Clinical and Laboratory Standards Institute (CLSI) Breakpoints. MDR Indicates Multidrug-Resistant. Organisms Tested Include *Klebsiella pneumoniae*, *Providencia stuartii*, *Escherichia coli*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, and *Morganella morganii*

Organism	Susceptibility Test (CLSI)
<i>K. pneumoniae</i>	97.8%
<i>P. stuartii</i>	92.9%
<i>E. coli</i>	99.5%
<i>K. aerogenes</i>	98.5%
<i>K. oxytoca</i>	96%
<i>M. morganii</i>	100%

Ceftazidime-Avibactam (CZA)

This combination consists of ceftazidime, a third-generation cephalosporin, and avibactam, a non- β -lactam β -lactamase inhibitor⁴⁶ (Table 3).

Since avibactam does not induce chromosomal AmpC or MBLs, it is effective against AmpC-producing organisms.²¹ CZA has broad activity against serine carbapenemases (eg, KPC), class C cephalosporinases, some class D oxacillinases, and class A extended-spectrum β -lactamases (ESBLs), but it is ineffective against metallo- β -lactamases. Notably, CZA is effective against *Pseudomonas aeruginosa*.^{46,48} Clinical studies have shown that CZA is non-inferior to meropenem in cure rates and 28-day mortality.^{46,49}

Ceftolozane-Tazobactam (C/T)

C/T combines ceftolozane, a novel cephalosporin with improved membrane permeability and resistance to β -lactamases, and tazobactam, an irreversible β -lactamase inhibitor of the penicillinase sulfone class.⁴⁸ It is particularly effective against Gram-negative nosocomial pneumonia and has demonstrated efficacy in critically ill, mechanically ventilated patients when administered at 2 g/1 g every 8 hours.^{48,49}

Meropenem-Vaborbactam (MVB)

This combination pairs meropenem, a carbapenem, with vaborbactam, a cyclic boronic acid β -lactamase inhibitor (Table 4).

Vaborbactam does not inhibit MBLs or OXA-type carbapenemases like OXA-48 but enhances meropenem activity against class A and C β -lactamase-producing Gram-negative bacteria. It is also effective against some KPC variants that are resistant to CZA.^{46,48}

Imipenem-Relebactam (IMR)

IMR consists of imipenem, a carbapenem, and relebactam, a non- β -lactam bicyclic diazabicyclooctane β -lactamase inhibitor⁴⁶ (Table 5).

Relebactam inhibits class A and C β -lactamases, including *Pseudomonas*-derived cephalosporinases (PDC), but is ineffective against class B (MBLs) and has limited activity against class D β -lactamases.^{46,48}

Table 4 Meropenem-Vaborbactam Susceptibility According to CLSI Against Some MDR Organisms.⁴⁷ Values Represent Percentage of Isolates Susceptible According to CLSI Criteria. MDR Indicates Multidrug-Resistant. Organisms Tested Include *Klebsiella pneumoniae*, *Providencia stuartii*, *Escherichia coli*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, and *Morganella morganii*

Organism	Susceptibility Test (CLSI)
<i>K. pneumoniae</i>	97.1%
<i>P. stuartii</i>	100%
<i>E. coli</i>	99.6%
<i>K. aerogenes</i>	97%
<i>K. oxytoca</i>	98%
<i>M. morganii</i>	100%

Table 5 Imipenem-Relebactam Susceptibility Test According to CLSI Against Some MDR Organisms.⁴⁷ Values Represent Percentage of Isolates Susceptible According to CLSI Breakpoints. MDR Indicates Multidrug-Resistant. Organisms Tested Include *Klebsiella pneumoniae*, *Providencia stuartii*, *Escherichia coli*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, and *Morganella morganii*

Organism	Susceptibility Test (CLSI)
<i>K. pneumoniae</i>	95%
<i>P. stuartii</i>	50%
<i>E. coli</i>	99.4%
<i>K. aerogenes</i>	92.1%
<i>K. oxytoca</i>	92.7%
<i>M. morganii</i>	65.2%

Novel Beta-Lactam Antibiotic: Cefiderocol

Cefiderocol is a novel cephalosporin β -lactam antibiotic with potent in vitro activity against Gram-negative bacteria, especially MDR strains such as *Enterobacterales*.^{49–51} It features a chlorocatechol side chain that enables ferric iron chelation, facilitating siderophore-mediated uptake into bacteria and evading efflux pumps^{52–54} (Figure 6).

Cefiderocol exhibits strong stability against β -lactamase degradation, attributed to its C-3 and C-7 side chains. The C-7 side chain is structurally similar to ceftazidime, while the C-3 side chain resembles that of cefepime^{52,55} (Figure 7).

In clinical settings, resistance has emerged. For example, in a case of *P. aeruginosa* infection, MIC increased from 2 mg/L to 8 mg/L following treatment with ceftolozane–tazobactam, suggesting possible cross-resistance. Resistance mechanisms are believed to involve mutations in *ampC* and TonB-dependent receptor (TBDR) genes.^{50,56}

Clinical trials with cefiderocol further support its therapeutic role. The APEKS-NP trial demonstrated that cefiderocol was non-inferior to meropenem in treating nosocomial pneumonia, including ventilator-associated cases.⁵⁷ The CREDIBLE-CR trial evaluated cefiderocol for carbapenem-resistant infections and found similar microbiological responses compared with best available therapy, but higher mortality in *A. baumannii* infections, underscoring both the promise and the limitations of this novel agent.⁵⁸

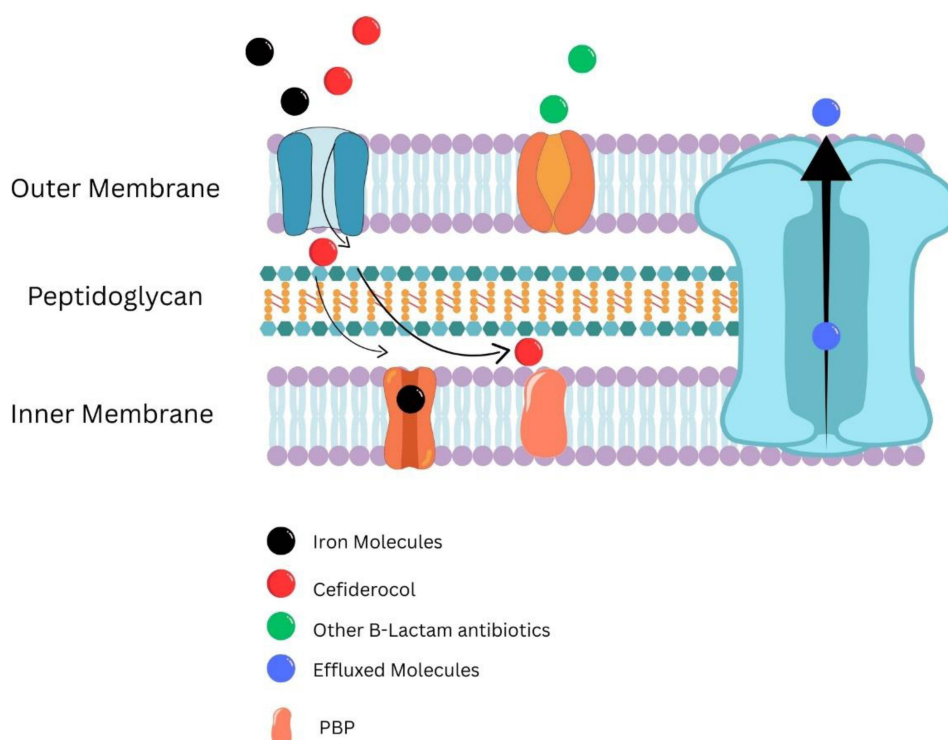


Figure 6 Mechanism of action of cefiderocol against Gram-negative bacteria. (Created with Canva). Cefiderocol functions as a siderophore cephalosporin that binds ferric iron (Fe^{3+}) via its chlorocatechol moiety and is actively transported into Gram-negative bacteria through iron uptake systems. Once inside the periplasmic space, cefiderocol binds to penicillin-binding proteins (PBPs), inhibiting cell wall synthesis and leading to bacterial death. This dual mechanism allows cefiderocol to overcome porin loss and efflux pump resistance.

Abbreviations: Fe^{3+} , ferric iron; PBPs, penicillin-binding proteins.

Real-world studies have also reported variable outcomes with cefiderocol, confirming its effectiveness in some cases but also highlighting resistance development during therapy, particularly in *A. baumannii* infections.^{59,60}

The activity and stability of β -lactam antibiotics are strongly influenced by their chemical structures, particularly the β -lactam ring, fused rings, and side-chain substitutions. Modifications at the acyl side chain of penicillins and cephalosporins alter both spectrum and resistance to β -lactamases. For example, incorporation of bulky oxime groups in third-generation cephalosporins (eg, cefotaxime, ceftazidime) enhances stability against hydrolysis by class A enzymes and expands Gram-negative activity.⁹ The addition of a 7- α -methoxy group in cephamycins (eg, cefoxitin) improves resistance to AmpC β -lactamases.^{33,61} In carbapenems, the trans-1-hydroxyethyl substituent provides resilience against most serine β -lactamases, while the absence of a sulfur atom in the thiazolidine ring enhances penetration through porin channels of Gram-negative bacteria.^{29,30}

More recent structural innovations have generated agents with unique mechanisms. Cefiderocol, for instance, contains a catechol side chain that allows siderophore-mediated uptake, bypassing efflux pumps and porin mutations while maintaining strong stability against a broad range of β -lactamase.^{55,56} Bis- β -lactams, designed by linking two β -lactam nuclei, achieve dual binding to mutated PBPs, thereby restoring antibacterial activity in resistant *Escherichia coli*.^{39,43} Similarly, macrocycle-embedded β -lactams improve conformational flexibility, enhancing acylation of PBP2a in methicillin-resistant *Staphylococcus aureus* (MRSA).^{44,62}

These SAR-guided modifications illustrate how structural tailoring directly impacts antibacterial spectrum, resistance profile, and clinical applicability, forming the basis for the continuous development of novel β -lactams to overcome evolving resistance.

Despite the encouraging progress in the development of novel β -lactam antibiotics and β -lactamase inhibitors, several limitations must be acknowledged. Taniborbactam (VNRX-5133), although demonstrating potent in vitro activity against serine and metallo- β -lactamases, is still under late-phase clinical investigation, and its long-term safety and efficacy

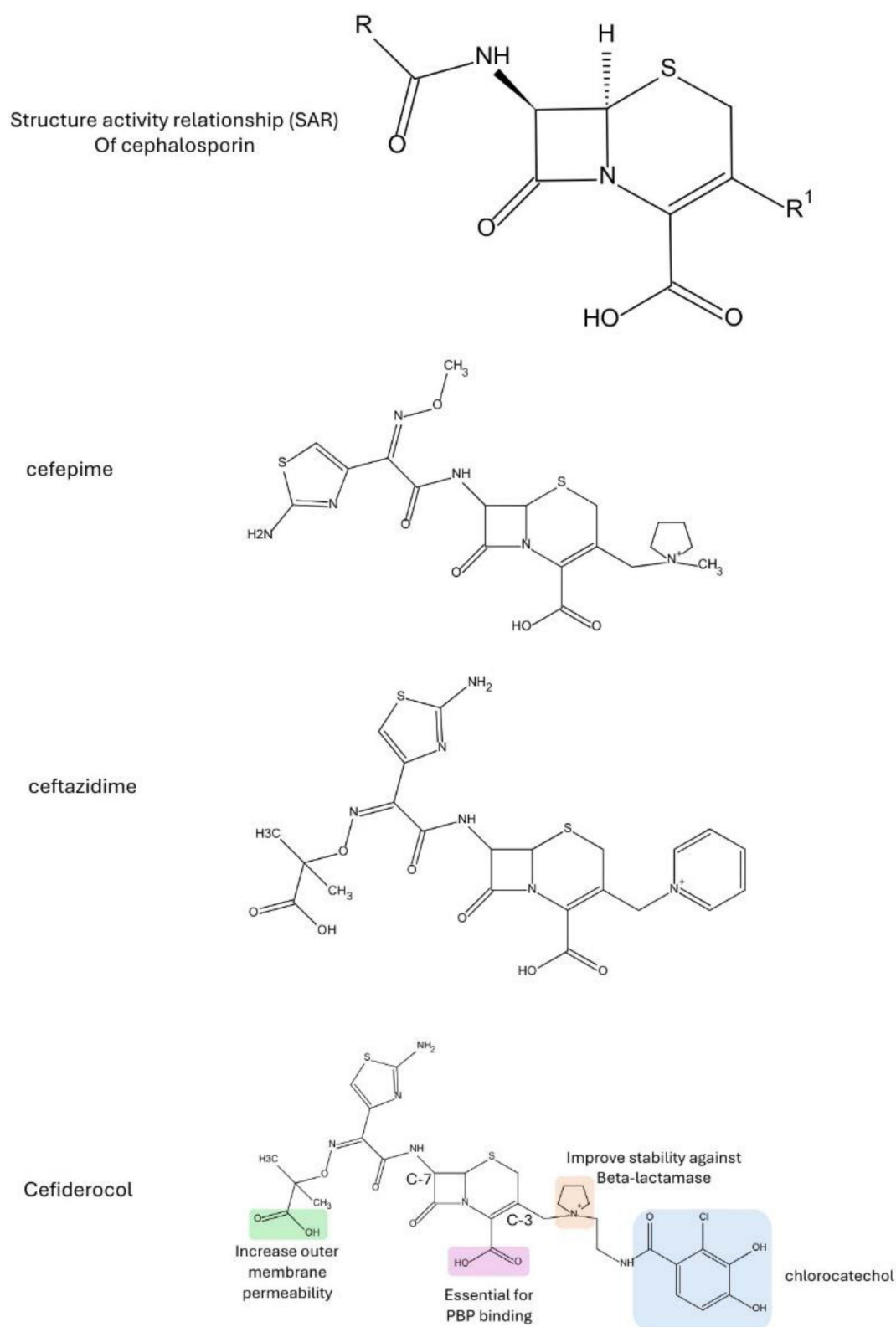


Figure 7 SAR of beta-lactam cephalosporins showing cefiderocol structure relative to ceftazidime and cefepime. The figure illustrates the structural similarities and differences between cefiderocol, ceftazidime, and cefepime. Cefiderocol contains a chlorocatechol side chain that enables ferric iron chelation and siderophore-mediated uptake into Gram-negative bacteria, enhancing penetration and evasion of efflux pumps. The C-7 side chain is structurally similar to ceftazidime, and the C-3 side chain resembles cefepime, both contributing to stability against β -lactamase degradation.

remain to be confirmed.^{41,42} Similarly, Cefiderocol, a siderophore cephalosporin, has shown strong stability against β -lactamases, but resistance has already emerged in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* during therapy, raising concerns about cross-resistance mechanisms.^{28,29} Moreover, many approved β -lactam/ β -lactamase inhibitor (BL/BLI) combinations, such as ceftazidime–avibactam and imipenem–relebactam, remain ineffective against class B metallo- β -lactamases, limiting their utility in infections caused by NDM-, VIM-, or IMP-producing pathogens.^{38,44} These challenges underscore the need for continuous clinical trials, robust antimicrobial stewardship, and ongoing surveillance programs to ensure the sustainable use of these agents in combating multidrug-resistant Gram-negative infections.

Conclusion

Superbugs pose an escalating threat to global healthcare, with the overproduction of β -lactamases and the improper use of antibiotics accelerating resistance among pathogenic bacteria, particularly Gram-negative species. This challenge has intensified the need for innovative antibiotics and novel therapeutic strategies. Novel β -lactam antibiotics represent a promising approach to overcoming these barriers. Although encouraging outcomes have been demonstrated in preclinical and early clinical studies, their long-term effectiveness requires further validation. Future research should focus on large-scale in vivo studies, the development of next-generation β -lactamase inhibitors with broader activity, and advanced drug delivery systems to improve stability and therapeutic outcomes. Efforts to counteract resistance have already included both established β -lactamase inhibitors—such as clavulanic acid, sulbactam, and tazobactam—and newer approaches, including polymer inclusion complexes, macrocycle-embedded β -lactams, bis- β -lactam antibiotics, next-generation β -lactam/ β -lactamase inhibitor combinations, and novel agents like cefiderocol that employ unique resistance-evading mechanisms. Sustained research and development are therefore essential to counter the rapid evolution of antimicrobial resistance and ensure that effective treatment options remain available in clinical practice. Emphasizing these directions will enhance the clinical applicability of novel β -lactams and support their role as viable treatment options against resistant bacterial pathogens.

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Disclosure

The authors report no conflicts of interest in this work.

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