Research Open

Infectious Diseases and Therapeutics
Volume 7 Issue 1

Commentary Article

Cefiderocol Alongside the Newer B-Lactam/B-Lactamase Inhibitor Combinations

Emir Kobic*

Medical Affairs, Medical Science Liaison, Wockhardt, USA

Corresponding author: Emir Kobic, Medical Affairs, Medical Science Liaison, Wockhardt, USA

Received: July 18, 2026; **Accepted:** July 24, 2026; **Published:** July 28, 2026

Commentary

To date, over 12,000 beta lactamases have been identified among gram-negative bacteria [1]. Due to selective pressures, novel enzymes continue to evolve among clinical isolates while patients are living longer with increasingly complex comorbidities. Selecting the right empiric antibiotic in these vulnerable populations becomes more challenging and delays in effective therapy lead to worse clinical outcomes [2]. To make matters even more challenging, carbapenem resistant bacteria deploy not just beta lactamases with rare escape variants to best the latest agents on the market, but altered penicillin binding proteins (PBP), efflux pump overexpression, and porin channel alterations which modern rapid diagnostic tests are unable to capture without whole genome sequencing.

Cefiderocol represents one of the most innovative attempts to overcome the latter of these obstacles. Instead of focusing on passive diffusion through porin channels, cefiderocol unlocks an alternative pathway of cell entry by mimicking a bacterial siderophore, binding iron, and actively transporting itself across the iron transport system.

This "Trojan horse" strategy becomes a novel approach to bypassing porin channel mutations typically seen among various carbapenem resistant bacteria, including metallo-β-lactamase (MBL) producing organisms [3].

However, the findings from our case series demonstrate that this novelty may not be permanent. Particularly among NDM-5-producing *Klebsiella pneumoniae*, cefiderocol resistance emerged within the siderophore transport pathways, involving CirA. More concerning was the observation that cefiderocol resistance occurred in patients with and without prior cefiderocol exposure. We identified multiple independent CirA disruptions among ST147 isolates suggesting convergent evolution toward a common resistance phenotype rather than simple clonal spread alone. This raises concern that in NDM endemic regions, cefiderocol resistance may become prevalent before drug exposure [4].

The ongoing effort to develop novel therapies for carbapenem-resistant gram-negative infections has increasingly relied on combination approaches. The acquisition of Qpex Biopharma by Shionogi inc and ongoing development of cefiderocol combined with a novel beta lactamase inhibitor xeruborbactam represents a strategy familiar to Infectious Diseases clinicians [5]. The pairing of these two compounds preserves cefiderocol's bactericidal activity and may provide a more potent solution to the resistance observed in our case series. However, relying solely on a β-lactamase inhibitor to stabilize a β-lactam has inherent limitations due to bacterial evolution and production of escape variant β-lactamases, as seen with both avibactam and taniborbactam [6].

The latest frontier among β-lactamase inhibitors, the 2nd generation diazabicyclooctanes (DBO), are designed to pair β-lactamase inhibition with direct antibacterial activity through PBP2 [8]. PBP2 is an especially attractive target in Gram-negative pathogens due to its essential role in cell wall integrity and is present in relatively low copies relative to other PBPs. As a result, even modest disruptions of PBP2 molecules can destabilize the cell wall leading the rod-shaped morphology of gram-negative bacteria to develop fragile, lysis-prone spheroplasts. Therefore, by destabilizing the cell wall, alternative mechanisms of resistance like efflux pumps and impermeable porin channels may become dismantled as well [9].

Second generation DBO's like durlobactam have demonstrated this effect even with modest PBP2 binding affinity against Enterobacterales [10]. Indeed, durlobactam has demonstrated *in vitro* activity among 5 NDM-producing *E. coli* harboring PBP3 alterations with reduced susceptibility to IDSA's preferred MBL treatment options ceftazidime-avibactam plus aztreonam and cefiderocol [11]. The second generation DBO's have unlocked a new frontier in what is unraveling as a multi-pronged approach to the treatment of carbapenem resistant gram-negative infections.

Another second generation DBO, zidebactam, has been combined with cefepime and was recently FDA approved under the brand name Zaynich for complicated urinary tract infections [12]. Zaynich has also shown favorable outcomes in compassionate use cases as rescue therapy for carbapenem resistant therapies without alternative treatment options available [13,14]. Rather than functioning solely as a β-lactamase inhibitor, zidebactam has been described as a β-lactam enhancer with high binding affinity to PBP2, while cefepime, like other cephalosporins, targets PBP1 and PBP3. Together, this multi PBP strategy produces synergistic bactericidal activity against a broad spectrum of gram-negative pathogens, including MBL producing organisms. Early compassionate use data suggests that this approach may retain activity even when IDSA preferred treatment options fail.

Even with these latest novel advances, the field still lacks a true "empiric umbrella" antibiotic capable of reliably covering all carbapenem-resistant Gram-negative pathogens. The emergence of cefiderocol resistance with CirA disruptions among NDM-5-producing ST147 *K. pneumoniae* reinforces that no antibiotic is immune to bacterial adaptation. Clinicians continue to face difficult decisions when treating patients with prior MDR infections, prolonged healthcare exposures, chronic dialysis dependence, or recurrent antibiotic exposure. For these patients, access to rapid diagnostics, thoughtful stewardship, and familiarity with emerging treatment options will remain essential to getting the right antibiotic on board early.

Disclosures

E.K. has received honoraria for participation in speaker bureau and advisory board activities for Shionogi and is currently employed by Wockhardt USA as a Medical Science Liaison.

References

1. Beta-Lactamase DataBase (BLDB). Structure and Function. Updated April 6, 2026. Accessed July 16, 2026. Available at: http://www.bldb.eu/
2. Zasowski EJ, Bassetti M, Blasi F, et al. (2020) A systematic review of the effect of delayed appropriate antibiotic treatment on the outcomes of patients with severe bacterial infections. *Chest* 158: 929-938.
3. Heil EP, Tamma PD (2021) Cefiderocol: the Trojan horse has arrived but will Troy fall? *Lancet Infect Dis* 21: 153-155.
4. Potter MH, Askar W, Gomez-Abundis GF, Carpenter K, Kobic E (2026) NDM-5 and siderophore receptor mutations drive high-level cefiderocol resistance in Klebsiella pneumoniae: a case series. *Infection* 54: 533-538.
5. Shionogi & Co., Ltd. Shionogi Further Extends Infectious Disease Innovation Platform with Planned Acquisition of Qpex Biopharma, Inc. Published June 26, 2023. Accessed July 17, 2026.
6. Compain F, Arthur M (2017) Impaired Inhibition by Avibactam and Resistance to the Ceftazidime-Avibactam Combination Due to the D179Y Substitution in the KPC-2 β-Lactamase. *Antimicrobial Agents and Chemotherapy* 61: e00451-17. [crossref]
7. Lomovskaya O, Tsivkovski R, Totrov M, Dressel D, Castanheira M, et al. (2023) New boronate drugs and evolving NDM-mediated beta-lactam resistance. *Antimicrob Agents Chemother* 67: e00579-23.
8. Morinaka A, Tsutsumi Y, Yamada M, et al. (2015) OP0595, a new diazabicyclooctane: mode of action as a serine β-lactamase inhibitor, antibiotic and β-lactam 'enhancer'. *J Antimicrob Chemother* 70: 2779-2786.
9. Ogura T, Bouloc P, Niki H, D'Ari R (1989) Penicillin-binding protein 2 is essential in Escherichia coli for long-term maintenance of cell shape and envelope integrity. *J Bacteriol* 171: 3025-3030.
10. Durand-Réville TF, Miller AA, O'Donnell JP, et al. (2017) ETX2514 is a broad-spectrum β-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including Acinetobacter baumannii. *ACS Infect Dis* 3: 852-863.
11. Aitken SL, Pierce VM, Pogue JM, Kline EG, Tverdek FP, et al. (2024) The growing threat of NDM-producing Escherichia coli with penicillin-binding protein 3 mutations in the United States: is there a potential role for durlobactam? *Clin Infect Dis* 79: 834-837. [crossref]
12. Wockhardt Ltd. Wockhardt receives U.S. FDA approval for ZAYNICH™ (cefepime and zidebactam), a novel intravenous antibiotic for the treatment of adult patients with complicated urinary tract infection including pyelonephritis [Internet]. Mumbai and Short Hills (NJ): Wockhardt Ltd; 2026 May 30 [cited 2026 Jul 17]. Available from: https://www.wockhardt.com/wp-content/uploads/2026/05/wockhardt-zaynich-fda-approval-press-release.pdf.
13. Tsai S, Nigo M, Kang D, Baptista RP, Tamma PD, et al. (2024) Cefepime-zidebactam therapy for extensively drug-resistant Pseudomonas aeruginosa and Klebsiella pneumoniae infection as a bridge to liver transplantation. *JAC Antimicrob Resist* 6: dlae156.
14. Tirlangi PK, Wanve BS, Dubbudu RR, Yadav BS, Kumar LS, et al. (2023) Successful use of cefepime-zidebactam (WCK 5222) as a salvage therapy for the treatment of disseminated extensively drug-resistant New Delhi metallo-β-lactamase-producing Pseudomonas aeruginosa infection in an adult patient with acute T-cell leukemia. *Antimicrob Agents Chemother* 67: e00500-23.

Citation:

Kobic E (2026) Cefiderocol Alongside the Newer B-Lactam/B-Lactamase Inhibitor Combinations. *Infect Dis Ther* Volume 7(1): 1-2.