INNOVAPATH™
The Premier Journal Bridging Discovery & Innovation

Letter to the Editor
https://doi.org/10.63501/ntga6364

Expanding Treatment Options: Ceftobiprole Against Multidrug-Resistant Infections

Arwa Jabeen[1], Abiha Fatima[1], Abeera Saleem[1,2]

[1]Jinnah Sindh Medical University, Karachi, Pakistan

[2]Corresponding Author Email: abeeras326@gmail.com

Antimicrobial resistance (AMR), which occurs when bacteria adapt to resist antibiotics, has emerged as one of the most serious global health problems of the 21st century. In accordance with the UK government-approved Review on Antibacterial Resistance, AMR might kill ten million people annually by 2050 [1]. In 2019, the worldwide burden of bacterial AMR was expected to be 4.95 million fatalities and 1.27 million deaths, respectively [2].

Zevtera (ceftobiprole medocaril for injection) was approved by the US FDA on April 3, 2024, for the treatment of Staphylococcus aureus-related bloodstream infections (SAB), including right-sided infective endocarditis, in adults, as well as acute bacterial skin and skin structure infections (ABSSSI) in adults and community-acquired bacterial pneumonia (CABP) in adults and children aged 3 months to <18 years [3]. Ceftobiprole is a parenteral, fifth-generation cephalosporin that acts rapidly and efficiently against methicillin-resistant Staphylococcus aureus (MRSA), Enterococcus faecalis, and Enterobacteriaceae [4].

Evidence from several large randomized controlled trials underpins approval of ceftobiprole. In the ERADICATE trial (NCT03138733) [5], 390 adults with complex SAB (including right-sided endocarditis) were randomly assigned to ceftobiprole or daptomycin (± aztreonam). The primary outcome was overall clinical success at 70 days, which included survival, symptom improvement, clearance of bacteremia, absence of new sequelae, and no need for alternative therapy. Clinical success was achieved in 69.8% of ceftobiprole patients compared to 68.7% of comparators (adjusted difference 2.0%; 95% CI −7.1 to +11.1), satisfying the non-inferiority margin (−15%).

Similarly, in complicated skin infections, the TARGET trial (NCT03137173) [6] randomly assigned 679 patients with ABSSSI to either ceftobiprole (n=335) or vancomycin plus aztreonam (n=344). The FDA-defined primary objective of early clinical response at 48-72 hours was achieved in 91.3% vs. 88.1% (adjusted difference 3.3%; 95% CI -1.2 to +7.8), indicating non-inferiority. The investigator-assessed clinical effectiveness at test-of-cure (days 15-22) was 90.1% versus 89.0%.

Beyond bloodstream and skin infections, Ceftobiprole was also evaluated in the CABP trial (NCT00326287) [7] involving 638 people. Clinical cure at the test-of-cure (days 7-14) occurred in 76.4% of ceftobiprole recipients versus 79.3% in comparators (difference −2.9%; 95% CI −9.3 to +3.6). In the clinically evaluable sample (n=469), cure rates were 86.6% vs. 87.4% (difference -0.8%; 95% CI -6.9 to +5.3).

Recognizing the need for pediatric data, the CABP trial BPR-PIP-002 (NCT03439124) [8] was conducted, in which 138 children (aged≥3 months to <18 years) were randomized to either ceftobiprole (n = 94) or a

conventional IV cephalosporin plus vancomycin (n = 44). On day 4, the clinical response was 95.7% compared to 93.2% (difference 2.5%; 95% CI -5.5 to +14.7). The clinical cure rate at test-of-cure was 90.4% versus 97.7% (difference -7.3%; 95% CI -15.7 to +3.6).

In addition to its efficacy, the safety profile of Ceftobiprole has been investigated. Across adult trials, common adverse events (occurring in≥5% of participants) included nausea, vomiting, diarrhea, headache, rash, and transient elevations in hepatic enzymes. Grade ≥3 events, mainly enzyme elevations, leukopenia, or phlebitis, and treatment discontinuations, each occurred in <5% of patients. Pediatric CABP patients exhibited similar profiles, primarily characterized by vomiting, headache, diarrhea, and transient enzyme elevations. Label warnings include increased mortality in ventilator-associated pneumonia (unapproved use), hypersensitivity reactions, seizures/CNS effects, and C. difficile–associated diarrhea [3].

In conclusion, ceftobiprole is a valuable addition to current MRSA-active options, providing an intravenous alternative when vancomycin or daptomycin may be ineffective or poorly tolerated. It is particularly beneficial for adults with Staphylococcus aureus bacteremia, including right-sided infective endocarditis, as well as for pediatric and adult cases of community-acquired bacterial pneumonia. These label-supported indications broaden clinicians' options at a time when antimicrobial resistance continues to limit therapy choices.

Keywords: Ceftobiprole, Antimicrobial resistance, Multidrug-resistant pathogens

Financial Support: None

Conflict of interest: None

REFERENCES

1. Antimicrobial Resistance Collaborators (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet (London, England)*, *399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0

2. Meštrović, T., Haller, S., Robles Aguilar, G., Meinen, A., Gershberg Hayoon, A., Geffers, C., Dörre, A., Abu Sin, M., Gray, A. P., Swetschinski, L. R., Ikuta, K. S., Chung, E., Wool, E. E., Han, C., Araki, D. T., Hsu, R., Dolecek, C., Eckmanns, T., & Naghavi, M. (2025). Antimicrobial Resistance Burden Landscape in Germany in 2019: A Comparative Country-Level Estimation. *JAC-antimicrobial resistance*, *7*(4), dlaf142. https://doi.org/10.1093/jacamr/dlaf142 .

3. US Food and Drug Administration. (2024). The *FDA approves a new antibiotic for three different uses*. https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-three-different-uses
4. El Solh A. (2009). Ceftobiprole: a new broad-spectrum cephalosporin. *Expert opinion on pharmacotherapy*, *10*(10), 1675–1686. https://doi.org/10.1517/14656560903048967 .
5. Hamed, K., Engelhardt, M., Jones, M. E., Saulay, M., Holland, T. L., Seifert, H., & Fowler, V. G., Jr (2020). Ceftobiprole versus daptomycin in *Staphylococcus aureus* bacteremia: a novel protocol for a double-blind, Phase III trial. *Future Microbiology*, *15*(1), 35–48. https://doi.org/10.2217/fmb-2019-0332 .
6. Overcash, J. S., Kim, C., Keech, R., Gumenchuk, I., Ninov, B., Gonzalez-Rojas, Y., Waters, M., Simeonov, S., Engelhardt, M., Saulay, M., Ionescu, D., Smart, J. I., Jones, M. E., & Hamed, K. A. (2021). Ceftobiprole

Compared With Vancomycin Plus Aztreonam in the Treatment of Acute Bacterial Skin and Skin Structure Infections: Results of a Phase 3, Randomized, Double-blind Trial (TARGET). *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *73*(7), e1507–e1517. https://doi.org/10.1093/cid/ciaa974

7. Nicholson, S. C., Welte, T., File, T. M., Jr, Strauss, R. S., Michiels, B., Kaul, P., Balis, D., Arbit, D., Amsler, K., & Noel, G. J. (2012). A randomized, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalization. *International Journal of Antimicrobial Agents*, *39*(3), 240–246. https://doi.org/10.1016/j.ijantimicag.2011.11.005
8. Bosheva, M., Gujabidze, R., Károly, É., Nemeth, A., Saulay, M., Smart, J. I., & Hamed, K. A. (2021). A Phase 3, Randomized, Investigator-blinded Trial Comparing Ceftobiprole With a Standard-of-care Cephalosporin, With or Without Vancomycin, for the Treatment of Pneumonia in Pediatric Patients. *The Pediatric Infectious Disease Journal*, *40*(6), e222–e229. https://doi.org/10.1097/INF.0000000000003077