Does cefiderocol heteroresistance explain the discrepancy between the APEKS-NP and CREDIBLE-CR clinical trial results?

Jacob E Choby, Tugba Ozturk, Sarah W Satola, Jesse T Jacob, David S Weiss

Emory Antibiotic Resistance Center, Atlanta, GA 30329, USA (JEC, TO, SWS, JTJ, DSW); Emory Vaccine Center, Atlanta, GA, USA (JEC, TO, SWS, JTJ, DSW); Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA (SWS, JTJ, DSW); Georgia Emerging Infections Programme, Atlanta, GA, USA (SWS, JTJ)

Cefiderocol is a novel siderophore-cephalosporin conjugate antibiotic approved for treatment of Gram-negative bacterial infections. In-vitro laboratory testing found cefiderocol to be effective against many species, including carbapenem-resistant and multidrug resistant isolates. As part of the APEKS-NP clinical trial, cefiderocol was evaluated in the treatment of health-care-associated pneumonia caused largely by carbapenem-susceptible, cephalosporin-resistant, extended-spectrum β-lactamase (ESBL) producers, or carbapenem-susceptible, non-ESBL strains (referred to from hereon as susceptible). Cefiderocol was non-inferior to meropenem in this trial, suggesting that cefiderocol is a potential option for the treatment of patients with nosocomial pneumonia, including those caused by multidrug-resistant Gram-negative bacteria.

However, concern arose following publication of the CREDIBLE-CR trial, which involved infections caused by carbapenem-resistant Gram-negative bacteria. Cefiderocol had similar efficacy compared with the best available therapy for the treatment of pneumonia, urinary tract infections, and bloodstream infections. But despite 95% of isolates in the trial demonstrating a minimum inhibitory concentration of 4 μg/mL or less, cefiderocol was associated with a higher rate of all-cause mortality, particularly in infections with Acinetobacter.

The incongruity between the performance of cefiderocol in APEKS-NP and CREDIBLE-CR is a major outstanding question in the field. As stated by Heil and Tamma, “how do we reconcile the seemingly conflicting mortality data from these studies?” Cefiderocol is now being used increasingly as a last-line agent against carbapenem-resistant strains (appendix).
despite concerns in treating such strains raised by the CREDIBLE-CR study and uncertainty about when to rely on this new antibiotic. This uncertainty heightens the need to elucidate the basis of the discrepancy of the results between APEKS-NP and CREDIBLE-CR, such that the scope of cefiderocol utility can be defined and best guide patient care.

We previously revealed a correlation between cefiderocol heteroresistance among carbapenem-resistant isolates and the increased all-cause mortality observed in the CREDIBLE-CR trial.9 Heteroresistance is a phenomenon in which only a minor subpopulation of cells are resistant to a given antibiotic.10 In the presence of a given antibiotic, the resistant cells are selected, predominate, and can cause treatment failure during in vivo murine infection.10 On the basis of these previous results, we hypothesised that frequency of cefiderocol heteroresistance could explain the discordant findings of the APEKS-NP and CREDIBLE-CR trials.

Here, we investigated the frequency of cefiderocol heteroresistance among susceptible or cephalosporin-resistant, carbapenem-susceptible bacteria that were predominant in the APEKS-NP trial.

The resistant subpopulation of cells in heteroresistance can be detected using the population analysis profile (PAP) test (appendix).9,10 Using PAP on isolates collected by the Emory Antibiotic Resistance Center’s Investigational Clinical Microbiology Core, we observed that susceptible isolates exhibited no or low rates of cefiderocol heteroresistance (appendix). Cephalosporin-resistant bacteria mostly exhibited increased rates of heteroresistance, but lower than those of carbapenem-resistant strains. These differences in rates of cefiderocol heteroresistance correlated with the mortality data from the APEKS-NP and CREDIBLE-CR trials, across the bacterial species tested (appendix). These data suggest that the lower rates of cefiderocol heteroresistance in susceptible and cephalosporin-resistant isolates that predominated the APEKS-NP trial might explain the enhanced efficacy of the drug in that study compared with the CREDIBLE-CR trial.

Cefiderocol is a welcome and crucial addition to the antibiotic armamentarium. However, our findings raise concern that cefiderocol could often fail in treating infections caused by some species of carbapenem-resistant bacteria, especially Acinetobacter baumannii, because of high rates of heteroresistance. Due to the very low numbers of resistant cells in cefiderocol heteroresistance (often <1 cell in 10 000), this phenotype was largely undetected by recommended antibiotic susceptibility testing among carbapenem-resistant isolates,9 and a similar phenomenon was observed among the susceptible and cephalosporin-resistant isolates in this study. As the use of cefiderocol therapy increases, undetected heteroresistance should be carefully considered and monitored as the utility of this antibiotic is established.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
References

1. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In vitro activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of gram-negative bacilli collected worldwide in 2014 to 2016. Antimicrob Agents Chemother 2018; 62: e01968–17. [PubMed: 29158270]

2. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2021; 21: 213–25. [PubMed: 33058798]

3. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis 2021; 21: 226–40. [PubMed: 33058795]

4. Heil EL, Tamma PD. Cefiderocol: the Trojan horse has arrived but will Troy fall? Lancet Infect Dis 2020; 21: 153–55. [PubMed: 33058794]

5. Shields RK. Case commentary: the need for cefiderocol is clear, but are the supporting clinical data? Antimicrob Agents Chemother 2020;64: e00059–20. [PubMed: 32015037]

6. McCreary EK, Heil EL, Tamma PD. New perspectives on antimicrobial agents: cefiderocol. Antimicrob Agents Chemother 2021; 65: e0217120. [PubMed: 34031052]

7. O’Donnell JN, Putra V, Lodise TP. Treatment of patients with serious infections due to carbapenem-resistant Acinetobacter baumannii: how viable are the current options? Pharmacotherapy 2021; 41: 762–80. [PubMed: 34170571]

8. Naseer S, Weinstein EA, Rubin DB, et al. US Food and Drug Administration (FDA): benefit-risk considerations for cefiderocol. Clin Infect Dis 2021;72: e1103–11. [PubMed: 33393598]

9. Choby JE, Ozturk T, Satola SW, Jacob JT, Weiss DS. Widespread cefiderocol heteroresistance in carbapenem-resistant Gram-negative pathogens. Lancet Infect Dis 2021; 21: 597–98.

10. Band VI, Hufnagel DA, Jaggavarapu S, et al. Antibiotic combinations that exploit heteroresistance to multiple drugs effectively control infection. Nat Microbiol 2019; 4: 1627–35. [PubMed: 31209306]