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

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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[1]. As part of the APEKS-NP clinical trial,[2] 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.[2]

However, concern arose following publication of the CREDIBLE-CR trial,[3] 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*.[3]

The incongruity between the performance of cefiderocol in APEKS-NP and CREDIBLE-CR is a major outstanding question in the field.[4–8] As stated by Heil and Tamma,[4] “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),

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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 pheno-type 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.

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