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P1854 *In vitro* and *in vivo* activity of cefiderocol against *Burkholderia cepacia* complex clinical isolates

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Background: *Burkholderia* species have been recognized as difficult to treat pathogens causing a range of infections in both immunocompetent and compromised patients. Due to a number of intrinsic mechanisms leading to resistance, susceptibility of these pathogens is variable which can impact treatment options. In this study, we examined the *in vitro* activity and *in vivo* efficacy of cefiderocol (CFDC), a novel parenteral siderophore cephalosporin with potent activity against a diverse collection of *B. cepacia* complex isolates including carbapenem-resistant strains.

Materials/methods: A total of 164 isolates of *B. cepacia* complex (33 *B. cenocepacia*, 94 *B. cepacia*, 1 *B. dolosa*, 34 *B multivorans*, and 2 *B. vietnamensis*) collected in North America and Europe as a part of SIDERO-WT global surveillance in 2014 to 2017 were examined. MICs were determined for CFDC, cefepime (FEP), ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), ciprofloxacin (CIP), colistin (CST), and meropenem (MEM) by broth microdilution and interpreted according to CLSI guidelines. CFDC was tested in iron-depleted cation-adjusted Mueller Hinton broth (ID-CAMHB). *In vivo* efficacy of CFDC, FEP, CZA, MEM/cilastatin, and CST was evaluated using neutropenic murine systemic infection model. CFDC resistant strains were examined by whole genome sequencing to identify potential mechanisms of resistance.

Results: MIC_{90}s of CFDC, MEPM, CZA, and C/T against 164 isolates were 0.25, 16, 8, and 32 mg/L, respectively. MIC_{90} of cefiderocol against *B. cenocepacia*, *B. cepacia*, and *B. multivorans* were 0.03, 0.12, and 32 mg/L, respectively. CFDC was the most active compound among the tested compounds, although 5/34 isolates of *B. multivorans* showed non-susceptibility to CFDC. The ED_{50} of CFDC against *B. cepacia* SR25744 (MIC: 0.016 mg/L) was 2.11 mg/kg/dose. The ED_{50}s against FPM and CZA were >100 mg/kg. Genotypic analysis of CFDC non-susceptible *B. multivorans* illustrated that 3 of 5 isolates exhibited disruptions in homologs of the catecholate siderophore receptor (*fiu*-like) genes.

Conclusion: CFDC demonstrated potent in vitro activity against *B. cepacia* complex, with greater than 95.7 % of tested isolates having MIC values ≤4 mg/L. These findings indicate that CFDC has high potential for treating infections caused by these difficult to treat organisms.