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In Vitro Activity of Cefiderocol and Comparator Agents Against Molecularly Characterized Clinical Isolates of Enterobacterales Causing Infections in United States Hospitals (2020–2021)

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Introduction

- Cefiderocol is approved by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections, including pyelonephritis, as well as hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
- Cefiderocol is a siderophore cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant (MDR) organisms like carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *P e domona ae g no a*, and *A cine obac e ba mannii*.
- The activity of this molecule is due to its ability to achieve high periplasmic concentrations by hijacking the bacterial iron transport machinery, which in turn potentiates cell entry.
  - In addition, cefiderocol remains stable to hydrolysis by serine β-lactamases (ESBLs, KPCs, and OXA-type carbapenemases) and metallo-β-lactamases.
- In this study, the activities of cefiderocol and comparator agents were analyzed against Enterobacterales, including molecularly characterized isolates, as part of the SENTRY Antimicrobial Surveillance Program for USA.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 8,328 Enterobacterales collected from various clinical specimens from patients hospitalized in 32 medical centers in all 9 US Census Divisions during 2020–2021. Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted media per CLSI guidelines.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI-recommended quality control reference strains.
- MIC interpretations were performed using CLSI breakpoints for comparators and FDA/CLSI breakpoints for cefiderocol (≤4/8/≥16 mg/L for susceptible, intermediate, and resistant).
- Imipenem-relebactam MIC interpretations used FDA breakpoints.

E che ichia coli, *Kleb iella ne moniae*, and *P o e mi abili* with ceftriaxone, ceftazidime, or aztreonam MIC values of ≥2 mg/L and any Enterobacterales displaying MIC values ≥2 mg/L for imipenem (excluded for *P. mi abili* , *P. enne i*, and indole-positive Proteeae) or meropenem were subjected to genome sequencing and screening of β-lactamase genes.

Screening of β-lactamase genes

- Selected isolates had total genomic DNA extracted by the fully automated Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processor (Cleveland, OH, USA), which was used as input material for library construction.
- DNA libraries were prepared using the Nextera™ library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on MiSeq Sequencer platforms at JMI Laboratories.
- FASTQ format sequencing files for each sample set were assembled independently using *de no o* assembler SPAdes 3.15.3. An in-house software was applied to align the assembled sequences against a comprehensive in-house database containing known β-lactamase genes.

Conclusions

- Cefiderocol *in i o* activity (98.4% susceptible) was consistent against various subsets, including against Enterobacterales carrying carbapenemase genes other than bla_{KPC}, against which approved β-lactam/β-lactamase inhibitor combinations showed limited activity.
- These data reinforce cefiderocol as an important option for the treatment of serious infections caused by Enterobacterales and resistant subsets in patients hospitalized in US medical centers.

Acknowledgments

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