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Activity of cefiderocol and comparator agents against carbapenem-resistant Enterobacterales, including molecularly characterized isolates recovered from United States hospitals in 2020–2024

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Introduction

- Carbapenem-resistant Enterobacterales (CRE) are often multidrug resistant.
- The Infectious Diseases Society of America (IDSA) recommends meropenem-vaborbactam, ceftazidime-avibactam, imipenem-relebactam, and cefiderocol for the treatment of serious infections caused by KPC-producing organisms.
- The treatment of isolates producing metallo-β-lactamases (MBLs) is more challenging and cefiderocol is among the agents recommended by the IDSA for the treatment of these isolates.
- Cefiderocol is a siderophore cephalosporin that has increased stability to hydrolysis by β-lactamases, including serine-carbapenemases and MBLs.
- We evaluated the activity of cefiderocol and comparator agents against CRE isolates collected in US hospitals from 2020 to 2024.

Materials and Methods

- A total of 18,597 Enterobacterales were collected from 35 US hospitals during 2020–2024.
 - Isolates were identified as the cause of infection.
 - Isolates were limited to 1 per patient.
- Susceptibility testing was performed by the CLSI reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2022) and M100 (2025) documents.
 - Cefiderocol was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
- Quality control (QC) was performed according to the CLSI M100 (2025) criteria.
 - All QC MIC results were within acceptable ranges.
- Categorical interpretations for all comparator agents were those criteria found in the CLSI M100 (2025) or the US FDA website.
- CRE isolates resistant to imipenem (excluding *Proteus mirabilis*, *P. penneri*, and indole-positive Proteeae) or meropenem were submitted to whole genome sequencing and data analysis for the detection of β-lactam resistance mechanisms.
- WGS was performed on MiSeq or NextSeq (Illumina, San Diego, California, USA) instruments targeting a 30X coverage.
 - Sequences were *de novo* assembled.
 - Analysis of β-lactam resistance mechanisms was performed *in silico*.

Results

- Among surveillance Enterobacterales isolates, 176 (0.9% overall) were CREs.
 - A total of 76 isolates were *K. pneumoniae* and 100 isolates belonged to 9 other species/complexes.
- CRE isolates were observed in all US Census Divisions, except for the West North Central, with percentages ranging from 0.3% in New England to 2.0% in the Mid-Atlantic (Figure 1).
- Serine-carbapenemase-encoding genes were detected in 106 isolates, with bla_{KPC-2} (n=41) and bla_{KPC-3} (n=52) being the most common.
- MBL-encoding genes were observed in 29 (16.5% of the CRE) isolates and bla_{NDM-1} was noted in 13 isolates alone or with other carbapenemases.
 - MBL-producing isolates were detected in all US Census Divisions but the Pacific and West North Central divisions.
- A total of 41 CRE isolates carried no carbapenemase genes.
- Cefiderocol inhibited 96.0% of the CREs at the CLSI/FDA breakpoint (Figure 2).
 - Ceftazidime-avibactam, impenem-relebactam, and meropenem-vaborbactam were active against 81.2%, 72.2%, and 75.0% of the CRE isolates, respectively.
 - The activity of non-β-lactam agents ranged from 31.2% to 96.6% (tigecycline).
- Cefiderocol was active against 99.1%, 89.7%, and 92.7% of the isolates producing serine carbapenemases, MBLs, and carbapenemase-negative isolates, respectively.
 - β-lactam/β-lactamase inhibitor combinations had limited activity against MBL isolates.
 - Other comparators, with the exception of tigecycline (93.1% susceptible), inhibited <60% of the MBL-producing isolates.
 - 79.3% of the MBL-producing isolates were intermediate to colistin.
- Carbapenemase-negative isolates were more susceptible to comparator agents when compared to isolates producing carbapenemases.
 - The agents with lower susceptibility rates against carbapenemase-negative isolates were levofloxacin and imipenem-relebactam (53.7% and 75.6% susceptible).

Figure 1. Distribution of CRE isolates in the US Census Divisions

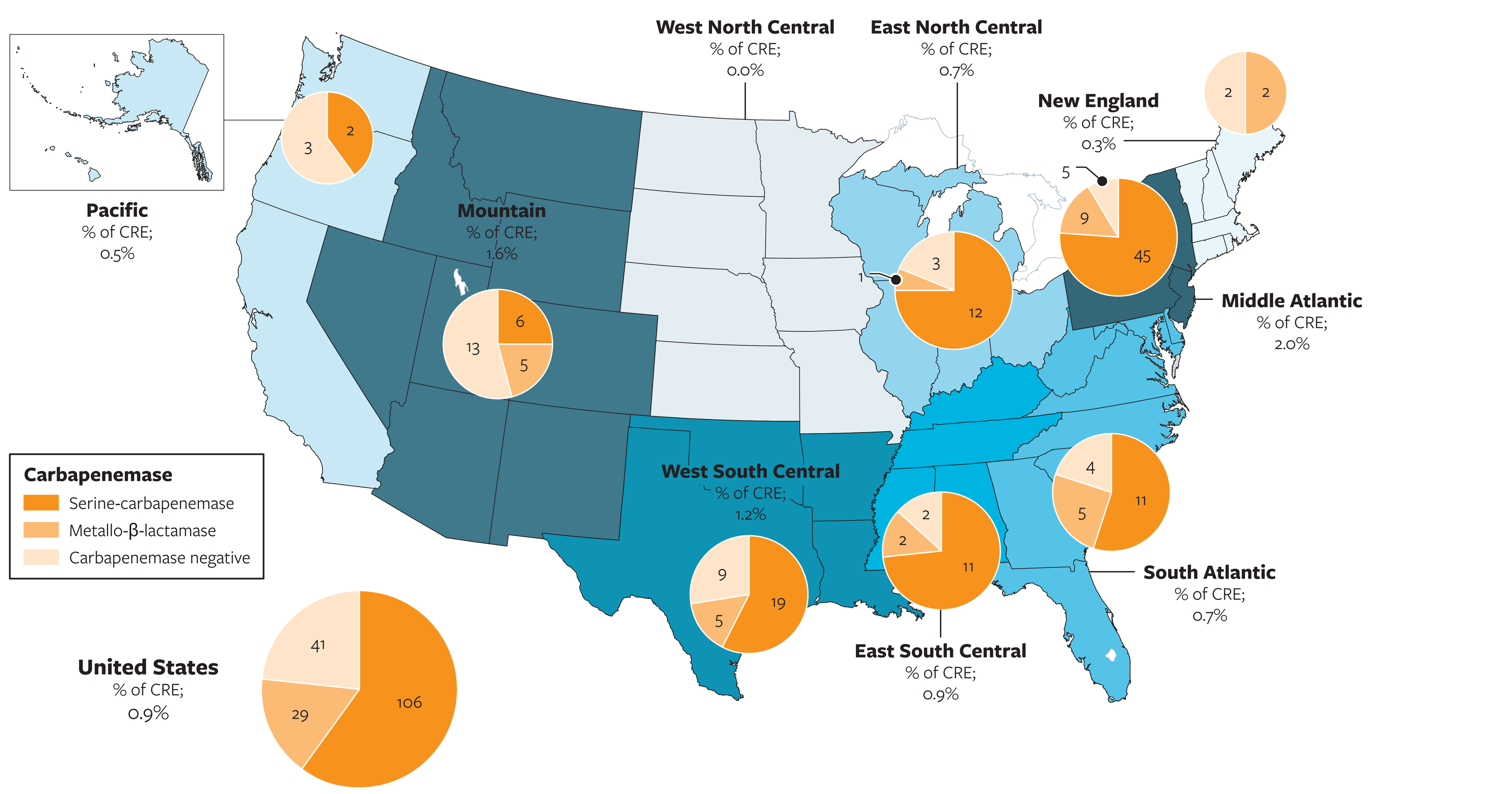
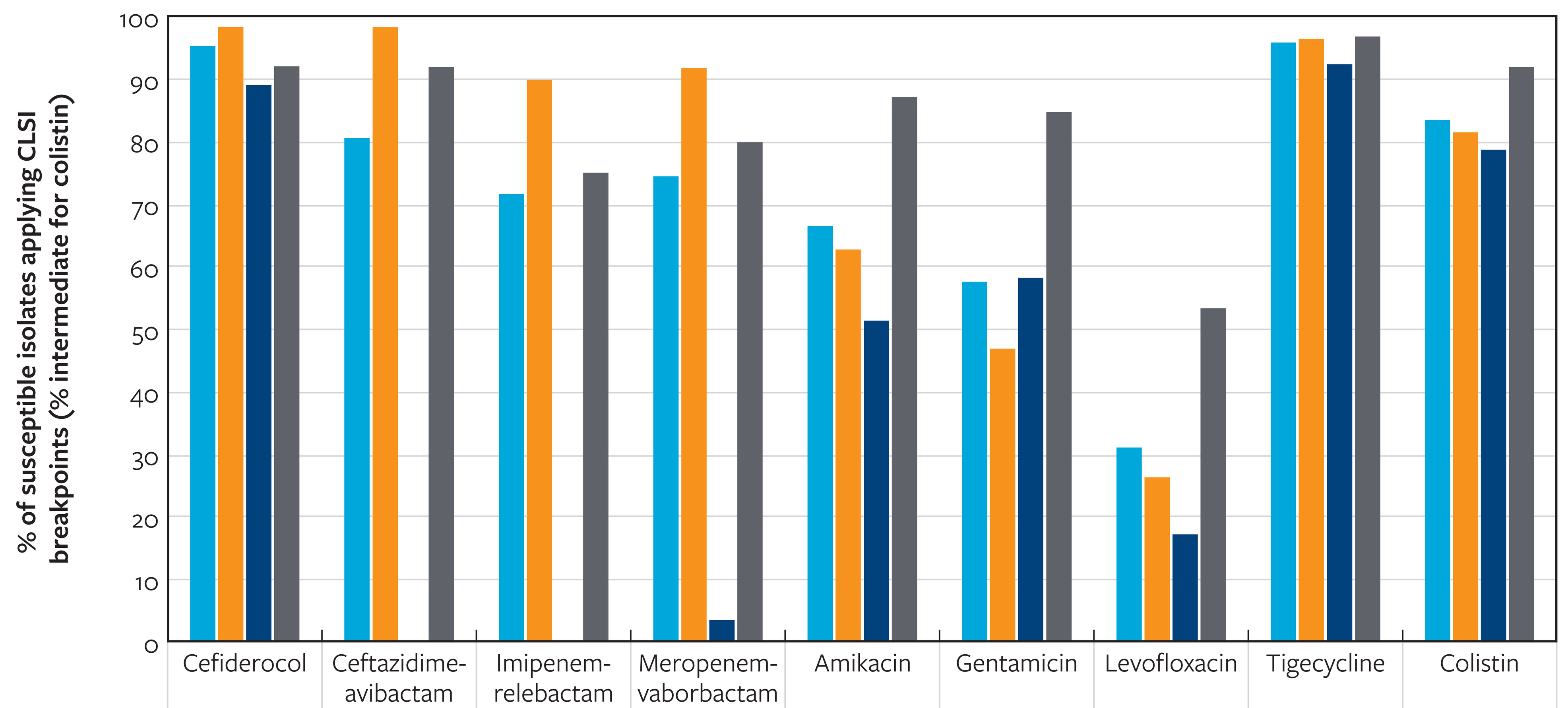

West North Central
% of CRE;
0.0%
East North Central
% of CRE;
0.7%
New England
% of CRE;
0.3%
Pacific
% of CRE;
0.5%
Mountain
% of CRE;
1.6%
Middle Atlantic
% of CRE;
2.0%
Carbapenemase
Serine-carbapenemase
Metallo-β-lactamase
Carbapenemase negative
West South Central
% of CRE;
1.2%
South Atlantic
% of CRE;
0.7%
East South Central
% of CRE;
0.9%
United States
% of CRE;
0.9%
41
29
106

Figure 2. Antimicrobial activity of cefiderocol and comparator agents against CRE isolates from US hospitals


% of susceptible isolates applying CLSI breakpoints (% intermediate for colistin)
100
90
80
70
60
50
40
30
20
10
0

	Cefiderocol	Ceftazidime-avibactam	Imipenem-relebactam	Meropenem-vaborbactam	Amikacin	Gentamicin	Levofloxacin	Tigecycline	Colistin
All CRE (n=176)	96.0	81.2	72.2	75.0	67.0	58.0	31.2	96.6	84.1
Serine-carbapenemase (n=106)	99.1	99.1	90.6	92.5	63.2	47.2	26.4	97.2	82.1
Metallo-β-lactamase (n=29)	89.7	0.0	0.0	3.4	51.7	58.6	17.2	93.1	79.3
Carbapenemase-negative (n=41)	92.7	92.7	75.6	80.5	87.8	85.4	53.7	97.6	92.7

Conclusions

- CRE isolates are observed in all but one US Census Division and MBL-producing Enterobacterales isolates were noted in all but two, highlighting the broad dissemination of these isolates.
- Cefiderocol displayed activity against most CRE isolates, including isolates carrying MBL genes that are resistant to multiple comparator agents and CRE isolates with no carbapenemases.
- Cefiderocol should be considered as an important option for the treatment of infections caused by these resistant organisms.

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