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In vitro Activity of Cefiderocol against Carbapenem-Nonsusceptible *Acinetobacter baumannii-calcoaceticus* Complex, Including Molecularly Characterized Clinical Isolates, Causing Infections in United States Hospitals (2020–2024)

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Introduction

- *Acinetobacter baumannii-calcoaceticus* complex has spread and caused hospital-acquired infections in many hospitals during the last decades. The spread of *A. baumannii* in health care institutions was helped by its ability to withstand dry and humid environments, its resistance to disinfectants and antibiotics, and its capacity to form biofilm, leading to colonization of inert surfaces and medical devices.
- This group of organisms has become a human health threat, in particular due to its common multidrug resistance (MDR) profile, including carbapenems, challenging antimicrobial therapies.
- 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 demonstrates broad activity against Gram-negative bacteria, including MDR organisms like carbapenem-resistant *A. baumannii*.
  - The activity of this molecule is due to its ability to achieve high periplasmic concentrations by hijacking the bacterial iron transport machinery, which increases cell entry.
  - In addition, cefiderocol remains stable to hydrolysis by serine β-lactamases (ESBLs, KPCs, and OXA-type carbapenemases) and metallo-β-lactamases.
- This study evaluated the activity of cefiderocol and comparator agents against *A. baumannii-calcoaceticus* complex causing infections in US hospitals, including resistant subsets, collected as part of the SENTRY Antimicrobial Surveillance Program during 2020–2024.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 1,999 *A. baumannii-calcoaceticus* complex isolates cultured from various clinical specimens in patients hospitalized in 76 medical centers in all 9 US Census Divisions during 2020–2024. 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).

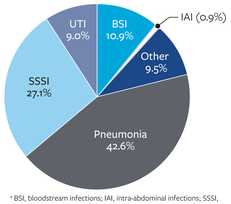
Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) guidelines.
- Frozen-form broth microdilution panels were manufactured by Element Iowa City (JMI Laboratories) (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted CAMHB per CLSI guidelines.
- Cefiderocol MIC results were interpreted according to the CLSI/FDA criteria, whereas comparator agent MIC values were interpreted based on the FDA susceptible breakpoint for imipenem-relebactam, and CLSI criteria for other agents, including intermediate breakpoint used for colistin.
- Carbapenem-nonsusceptible *A. baumannii-calcoaceticus* complex isolates, described here as CRAB, were those isolates nonsusceptible to imipenem and/or meropenem based on CLSI criteria (MIC, ≥4 mg/L), and were subjected to genome sequencing and *in silico* screening of known β-lactamase genes.

Results

- A total of 29.4% (587/1,999) *A. baumannii-calcoaceticus* species complex isolates were classified as CRAB (Table 1).
  - Most CRAB isolates were responsible for pneumonia (42.6%), followed by skin and skin structure infections (27.1%), bloodstream infections (10.9%), and urinary tract infections (9.0%) (Figure 1).
  - The highest prevalence of CRAB was detected among isolates causing infections in West South Central (52.5%), followed by East North Central (40.1%) and Middle Atlantic (34.4%) (Figure 2).
  - Other US Census Regions had CRAB rates of 15.1–21.7%, except for the New England (3.2%) and Pacific (12.4%) regions (Figure 2).
- Among CRAB, a total of 86.4% (507/587) isolates carried carbapenemase genes (Table 1).
  - bla_{OXA-23}-like (59.4%; 301/507) was among the most common carbapenemase genes detected, followed by bla_{OXA-24}-like (35.1%; 178/507) (Table 1).
  - The remainder (5.5%; 28/507) carried mostly bla_{NDM} and/or multiple carbapenemases.
- In general, cefiderocol ($MIC_{50/90}$, 0.12/1 mg/L; 92.9–97.7% susceptible) had the lowest $MIC_{50/90}$ against all *A. baumannii-calcoaceticus* species complex (Table 1).
  - Comparators had limited activity (66.8–72.0% susceptible), and colistin with 96.5% of the isolates tested as intermediate.
- Cefiderocol (81.8–94.4% susceptible) had MIC_{90} values of 2 mg/L against the overall population of CRAB (Table 1).
  - Cefiderocol also had MIC_{90} values of 2 mg/L against those CRAB isolates carrying carbapenemases, as well as the subsets where OXA-23- or OXA-24-like genes were detected.
  - A cefiderocol MIC_{90} of 64 mg/L was obtained against the small subset of CRAB isolates carrying bla_{NDM} or double carbapenemases (Table 1). Only CRAB carrying bla_{NDM} showed cefiderocol MIC ≥2 mg/L (data not shown).
- A small subset of 13.6% (80/587) of CRAB isolates did not carry acquired carbapenemases (Table 1).
  - Cefiderocol inhibited 91.2% and 78.8% of the isolates included in this subset when applying the CLSI and FDA breakpoints for susceptibility, respectively (Table 1).
- Comparator agents were not active against CRAB isolates or any resistant subsets evaluated, and susceptibilities results of ≤61.2% were documented, including colistin with 95.0% of the isolates showing intermediate results (Table 1).

Figure 1. Distribution of infection types[a] caused by carbapenem-nonsusceptible *A. baumannii-calcoaceticus* species complex



[a] BSI, bloodstream infections; IAI, intra-abdominal infections; SSSI, skin and skin structure infections; and UTI, urinary tract infections.

Figure 2. Distribution of carbapenem-nonsusceptible *A. baumannii-calcoaceticus* species complex (CRAB) among US Census Regions

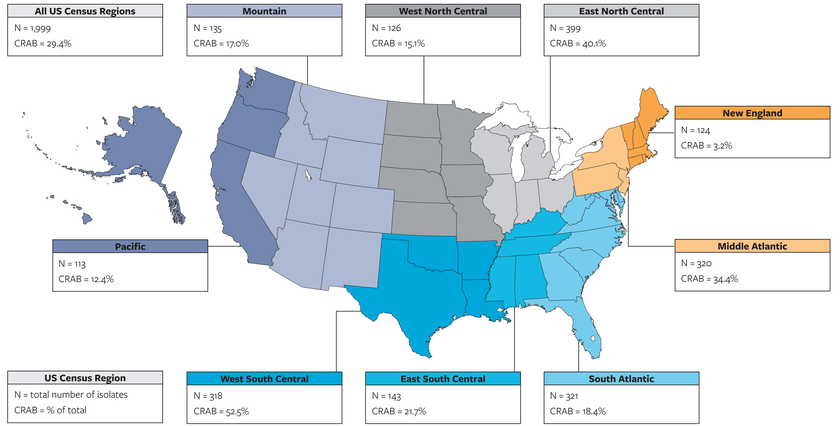


Table 1. Activity of cefiderocol and β-lactam-β-lactamase inhibitor combinations against *A. baumannii-calcoaceticus* species complex and resistant subsets from the USA

Phenotype/genotype[a] (No. tested)	MIC_{50}/MIC_{90} in mg/L (% susceptible by CLSI/FDA criteria)[b]					
	FDC	IMR	MER	A/S	CAZ	COL
All (1,999)	0.12/1 (97.7/92.9)	0.25/>8 (72.0)	0.5/>32 (70.7)	4/64 (67.6)	8/>32 (66.8)	0.5/1 (96.5)
Carbapenem-nonsusceptible (587)	0.25/2 (94.4/81.8)	>8/>8 (4.8)	>32/>32 (0.2)	32/>64 (12.1)	>32/>32 (16.5)	0.5/1 (95.1)
Carbapenemase-positive (507)	0.25/2 (94.9/82.2)	>8/>8 (0.8)	>32/>32 (0.0)	32/>64 (4.3)	>32/>32 (18.3)	0.5/1 (95.1)
OXA-23 (301)	0.5/2 (95.3/81.4)	>8/>8 (0.0)	>32/>32 (0.0)	32/>64 (1.0)	>32/>32 (13.6)	0.5/1 (93.7)
OXA-24 (178)	0.25/2 (97.8/88.2)	>8/>8 (2.2)	>32/>32 (0.0)	32/>64 (9.6)	32/>32 (27.0)	0.5/0.5 (97.7)
Other[c] (28)	0.5/64 (71.4/53.6)	>8/>8 (0.0)	>32/>32 (0.0)	64/>64 (7.1)	>32/>32 (14.3)	0.5/1 (92.9)
Carbapenemase-negative[d] (80)	0.25/4 (91.2/78.8)	8/>8 (30.0)	16/32 (1.2)	8/64 (61.2)	>32/>32 (5.0)	0.5/1 (95.0)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; MER, meropenem; A/S, ampicillin-sulbactam; CAZ, ceftazidime; COL, colistin.
[a] Carbapenem-nonsusceptible, isolates nonsusceptible to imipenem and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L).
[b] Cefiderocol MIC results were interpreted according to the CLSI/FDA breakpoints, whereas comparator agent MIC results were interpreted based on the FDA susceptible breakpoint for imipenem-relebactam, and CLSI criteria for other agents, including intermediate results provided by the respective colistin breakpoint.
[c] Includes bla_{NDM-1} (1), bla_{IMP-1} + bla_{OXA-23} (8), bla_{NDM-1} + bla_{OXA-58} (1), bla_{NDM-5} + bla_{OXA-23} (1), $bla_{OXA-134}$-like (5), bla_{OXA-23} + bla_{OXA-24} (12).
[d] Acquired carbapenemase genes not detected.

Conclusions

- This study demonstrates the resistant nature of *A. baumannii-calcoaceticus* species complex causing infections in US hospitals, and the distribution of CRAB among the US Census Regions.
- Cefiderocol was the most active agent against *A. baumannii-calcoaceticus* species complex and its CRAB subset, regardless of genotype.
  - Other β-lactam agents, including newer and older β-lactam-β-lactamase-inhibitor combinations, showed much lower activity against this collection and respective resistant subsets.
- These *in vitro* data suggest cefiderocol as an important option for the treatment of infections caused by *A. baumannii-calcoaceticus* species complex and resistant subsets, for which antibiotic treatment options are limited.

Acknowledgments

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