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# Cefiderocol Activity against Carbapenem-Resistant *Acinetobacter baumannii-calcoaceticus* Complex, Including Molecularly Characterized Clinical Isolates, Causing Infections in United States Hospitals (2020–2023)


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## Introduction

- Multidrug-resistant (MDR) *Acinetobacter baumannii-calcoaceticus* complex has gained attention as an important clinical challenge in the last decades, due to its ability to develop resistance to front-line antibiotics.
- Cefiderocol is approved by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections (UTI), 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 *Pseudomonas aeruginosa*, and *A. baumannii-calcoaceticus* complex.
- In this study, the activities of cefiderocol and comparator agents were evaluated against *A. baumannii-calcoaceticus* complex causing infections in US hospitals, including molecularly characterized resistant subsets, as part of the SENTRY Antimicrobial Surveillance Program during 2020–2023.

## Materials and Methods

**Bacterial organisms**

- This study comprised a collection of 1,786 *Acinetobacter* spp. cultured from various clinical specimens in patients hospitalized in 72 medical centers in all 9 US Census Divisions during 2020–2023.
- 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 Element Iowa City (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.
- 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, EUCAST susceptible breakpoint for colistin, and CLSI criteria for all other agents.
- Carbapenem-nonsusceptible *A. baumannii-calcoaceticus* complex isolates were those nonsusceptible to imipenem and/or meropenem based on CLSI criteria (MIC, ≥4 mg/L). These isolates were subjected to genome sequencing for screening of β-lactamase genes.

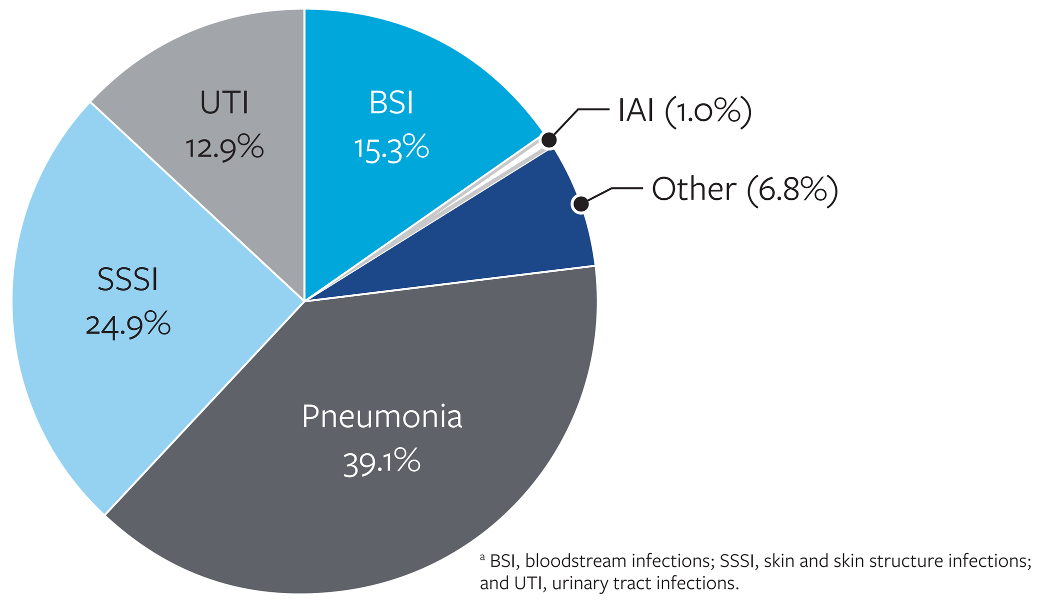
**Screening of β-lactamase genes**

- 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™ or Illumina DNA Prep™ library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on MiSeq or NextSeq Sequencer platforms at JMI Laboratories.
- FASTQ format sequencing files for each sample set were assembled independently using *de novo* 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.

## Results

- Among *Acinetobacter* spp. clinical isolates included here, the majority were responsible for pneumonia (39%) and skin and skin-structure infections (25%), followed by bloodstream (15%) and urinary tract infections (13%) (Figure 1).
- *A. baumannii-calcoaceticus* complex comprised 80.5% (1,438/1,786) of *Acinetobacter* spp. isolates included, followed by *A. ursingii* (5.1%; 91/1,786), *A. radioresistens* (3.8%; 68/1,786), *A. bereziniae* (2.2%; 40/1,786), and *A. lwoffii* (2.2%; 39/1,786) (Table 1).
  - Other *Acinetobacter* spp. isolates were represented by 20 isolates or less.
- A total of 20.0% (411/1,786) of *Acinetobacter* spp. were carbapenem-nonsusceptible. All but 6 (98.5%; 405/411) were identified as *A. baumannii-calcoaceticus* complex.
- Carbapenemase genes were detected in 86.9% (352/405) of carbapenem-nonsusceptible *A. baumannii-calcoaceticus* complex (Figure 2 and Table 1).
  - $bla_{OXA-23}$ (60.0%; 211/352) prevailed, followed by $bla_{OXA-24}$ (34.9%; 123/352).
- Cefiderocol (93.6–98.8% susceptible) had $MIC_{50}$ of 0.12 mg/L and $MIC_{90}$ of 1 mg/L against all *Acinetobacter* spp. and the *A. baumannii-calcoaceticus* complex subset (Table 1).
  - Comparators had limited activity against these isolates (66.5–77.1% susceptible), except for colistin (95.7–96.2% susceptible).
- Cefiderocol (97.0–97.7% susceptible by CLSI) had $MIC_{50}$ of 0.25 mg/L and $MIC_{90}$ of 2 mg/L against carbapenem-nonsusceptible *A. baumannii-calcoaceticus* complex and those carrying carbapenemases (Table 1).
  - Only colistin was also *in vitro* active against these two resistant subsets.
- Cefiderocol (97.2–99.2% susceptible by CLSI) $MIC_{90}$ of 2 mg/L and 1 mg/L were obtained against *A. baumannii-calcoaceticus* complex carrying $bla_{OXA-23}$ and $bla_{OXA-24}$, respectively (Table 1).
- Isolates carrying other carbapenemases were inhibited by cefiderocol MIC of ≤2 mg/L, except for 1 strain with $bla_{OXA-23}$ and $bla_{NDM-1}$ (MIC, 8 mg/L) (Table 1).

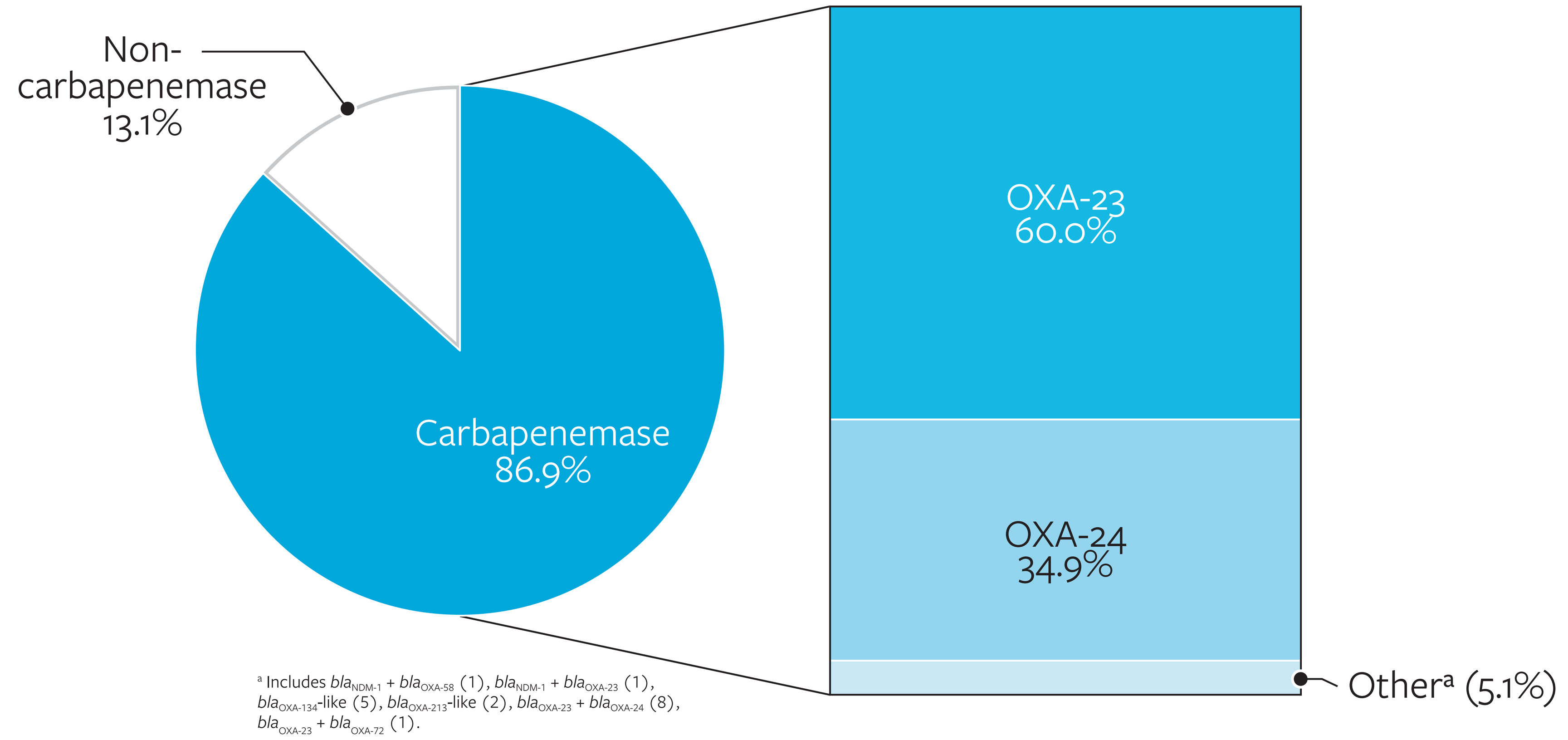
**Figure 1. Distribution of infection types[a] caused by *Acinetobacter* spp.**



UTI
12.9%
BSI
15.3%
IAI (1.0%)
Other (6.8%)
SSSI
24.9%
Pneumonia
39.1%


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

**Figure 2. Distribution of carbapenemase genes detected in carbapenem-nonsusceptible *A. baumannii-calcoaceticus* group**



Non-carbapenemase
13.1%
Carbapenemase
86.9%
OXA-23
60.0%
OXA-24
34.9%
Other[a] (5.1%)


[a] Includes $bla_{NDM-1}$ + $bla_{OXA-58}$ (1), $bla_{NDM-1}$ + $bla_{OXA-23}$ (1), $bla_{OXA-134}$-like (5), $bla_{OXA-213}$-like (2), $bla_{OXA-23}$ + $bla_{OXA-24}$ (8), $bla_{OXA-23}$ + $bla_{OXA-72}$ (1).

**Table 1. Activity of cefiderocol and comparator agents against *Acinetobacter* spp. and resistant subsets from the USA**

| Phenotype[a]/genotype (No.) | $MIC_{50}/MIC_{90}$ in mg/L (% susceptible by CLSI/FDA criteria)[b] | | | | | |
|---|---|---|---|---|---|---|
| | FDC | IMR | MER | A/S | CAZ | COL |
| All[c] (1,786) | 0.12/1 (98.8/94.2) | 0.25/>8 (77.1) | 0.5/>32 (75.9) | 4/64 (72.9) | 8/>32 (68.3) | 0.5/1 (95.7) |
| ACB (1,438) | 0.12/1 (98.5/93.6) | 0.25/>8 (71.8) | 0.5/>32 (70.4) | 4/64 (67.5) | 8/>32 (66.5) | 0.5/1 (96.2) |
| Carbapenem-nonsusceptible[d] (405) | 0.25/2 (97.0/86.9) | >8/>8 (4.2) | >32/>32 (0.2) | 32/>64 (13.3) | >32/>32 (17.3) | 0.5/1 (96.0) |
| Carbapenemase-positive (352) | 0.25/2 (97.7/87.8) | >8/>8 (0.6) | >32/>32 (0.0) | 32/>64 (5.7) | >32/>32 (19.3) | 0.5/1 (96.0) |
| OXA-23 (211) | 0.5/2 (97.2/85.3) | >8/>8 (0.0) | >32/>32 (0.0) | 32/>64 (0.9) | >32/>32 (14.7) | 0.5/1 (94.8) |
| OXA-24 (123) | 0.25/1 (99.2/93.5) | >8/>8 (0.0) | >32/>32 (0.0) | 32/>64 (11.4) | 32/>32 (25.2) | 0.5/0.5 (98.4) |
| Other[e] (18) | 0.25/2 (94.4/77.8) | >8/>8 (11.1) | >32/>32 (0.0) | 32/>64 (22.2) | 32/>32 (33.3) | 0.5/1 (94.4) |
| Carbapenemase-negative[f] (53) | 0.25/4 (92.5/81.1) | 8/>8 (28.3) | 16/32 (1.9) | 8/64 (64.2) | >32/>32 (3.8) | 0.5/2 (96.2) |

Abbreviations: ACB, *A. baumannii-calcoaceticus* species complex; 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 criteria, whereas comparator agent MIC values were interpreted based on the FDA susceptible breakpoint for IMR, EUCAST susceptible breakpoint for colistin, and CLSI criteria for other agents.
[c] Includes *A. baumannii-calcoaceticus* species complex (1,438), *A. beijerinckii* (3), *A. bereziniae* (40), *A. courvalinii* (13), *A. dispersus* (2), *A. guillouiae* (5), *A. gyllenbergii* (1), *A. haemolyticus* (4), *A. indicus* (1), *A. johnsonii* (9), *A. junii* (20), *A. lwoffii* (39), *A. nosocomialis* (1), *A. proteolyticus* (7), *A. radioresistens* (68), *A. schindleri* (5), *A. soli* (2), *A. ursingii* (91), *A. variabilis* (15), *A. venetianus* (1), *A. vivianii* (7), and *Acinetobacter* spp. (14).
[d] All *A. baumannii-calcoaceticus* species complex.
[e] Includes $bla_{NDM-1}$ + $bla_{OXA-58}$ (1), $bla_{NDM-1}$ + $bla_{OXA-23}$ (1), $bla_{OXA-134}$-like (5), $bla_{OXA-213}$-like (2), $bla_{OXA-23}$ + $bla_{OXA-24}$ (8), $bla_{OXA-23}$ + $bla_{OXA-72}$ (1).
[f] Acquired carbapenemase genes not detected.

## Conclusions

- This study demonstrates the MDR nature of *A. baumannii-calcoaceticus* complex causing infections in US hospitals.
- Cefiderocol remained as an active agent against these isolates, regardless of resistance genotype, whereas comparator agents, with the exception of colistin, showed limited *in vitro* activity.
- These *in vitro* data suggest cefiderocol as an important option for the treatment of infections caused by MDR *A. baumannii-calcoaceticus* complex, for which antibiotic treatment options are limited.

## Acknowledgements


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