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

RE Mendes, A Scullin, JH Kimbrough, M Karr, JM Maher, M Castanheira

Element Iowa City (JMI Laboratories), North Liberty, IA, USA

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 irondepleted media per CLSI guidelines.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSIrecommended 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. Iwoffii (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 carbapenemnonsusceptible 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 MIC₅₀ of 0.12 mg/L and MIC₉₀ of 1 mg/L against all *Acinetobacter* spp. and the *A. baumannii-calcoaceticus* complex subset
- 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 MIC₅₀ of 0.25 mg/L and MIC₉₀ 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) MIC₉₀ 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 caused by Acinetobacter spp.

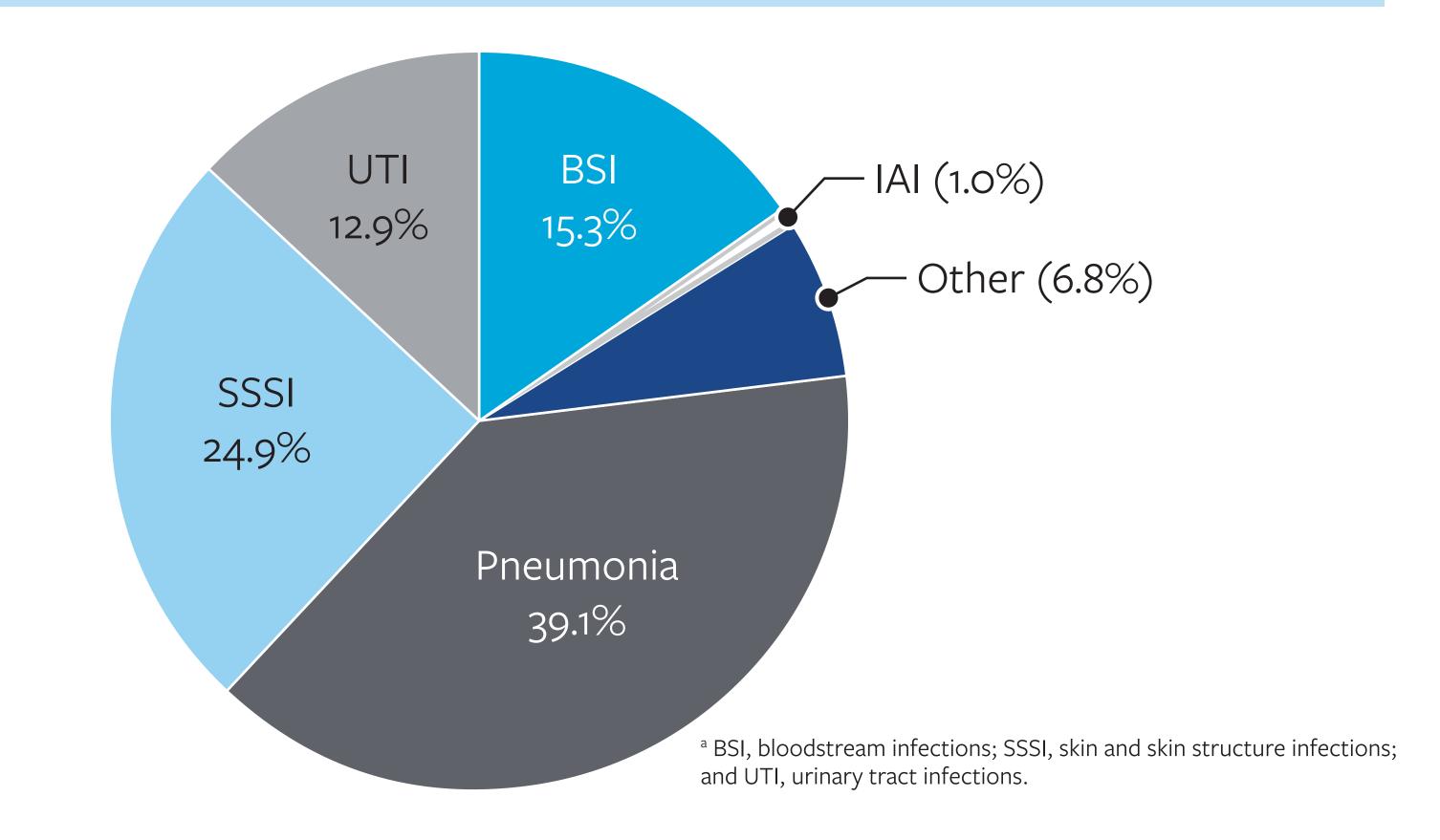


Figure 2. Distribution of carbapenemase genes detected in carbapenem-nonsusceptible A. baumannii-calcoaceticus group

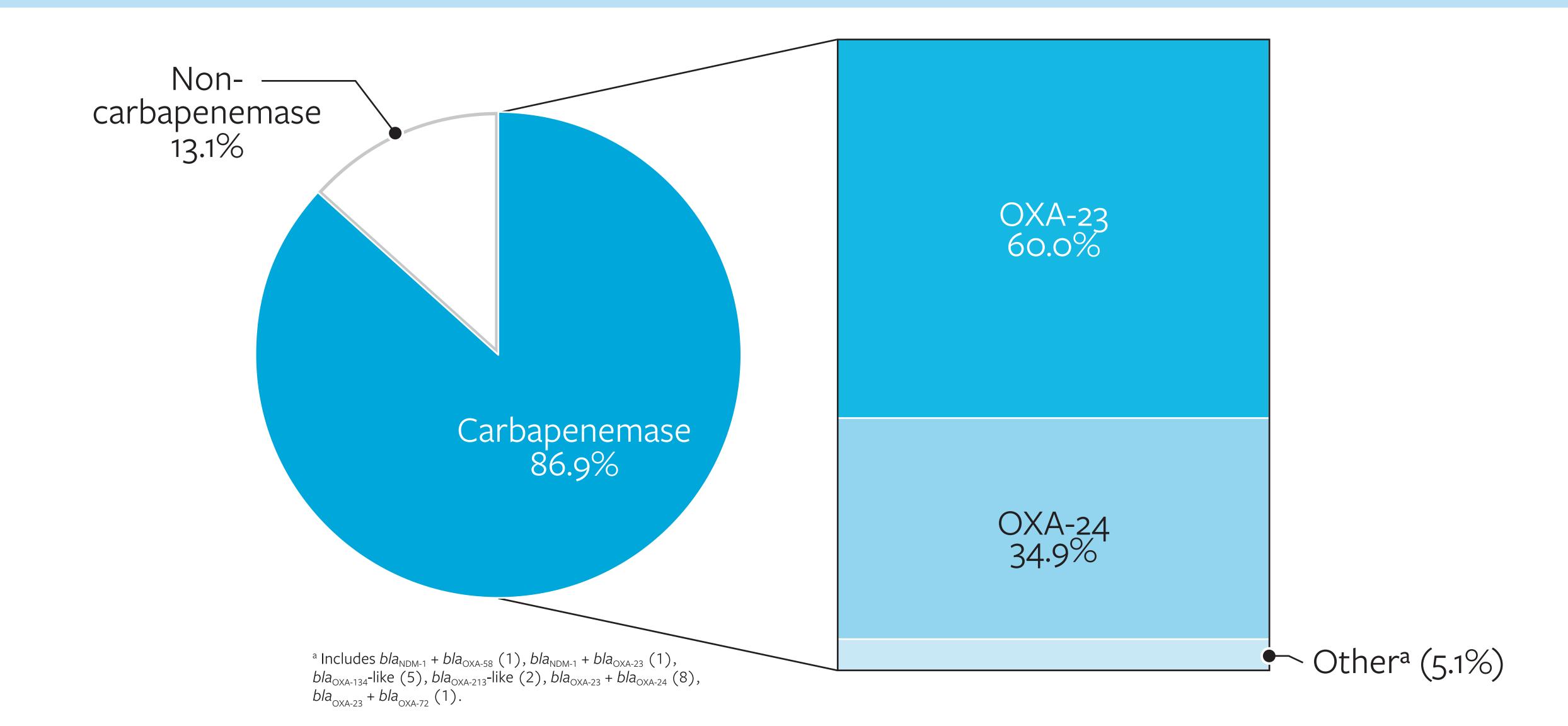


Table 1. Activity of cefiderocol and comparator agents against *Acinetobacter* spp. and resistant subsets from the USA

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-nonsusceptibled (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)

eviations: ACB, *A. baumannii-calcoaceticus* species complex; FDC, cefiderocol; IMR, imipenem-relebactam; MER, meropenem; A/S, ampicillin-sulbactam; CAZ, ceftazidime; COL, colistin. bapenem-nonsusceptible, isolates nonsusceptible to imipenem and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L).

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

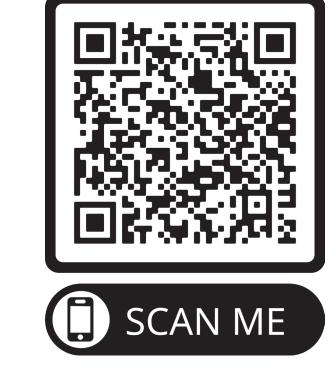
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Contact





Rodrigo E. Mendes, Ph.D.

JMI Laboratories

345 Beaver Kreek Centre, Suite A

North Liberty, Iowa 52317

Phone: (319) 665-3370

Fax: (319) 665-3371

Email: rodrigo.mendes@element.com

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c Includes A. baumannii-calcoaceticus species complex (1,438), A. beijerinckii (3), A. schindleri (5), A. guillouiae (5), A. guillouiae (5), A. guillouiae (5), A. guillouiae (7), A. radioresistens (68), A. schindleri (5), A. soli (2), A. ursingii (91), A. variabilis (15), A. variabilis

A. variabilis (15), A. venetianus (1), A. vivianii (7), and Acinetobacter spp. (14).

^a All A. baumannii-calcoaceticus species complex.

^e Includes $bla_{NDM-1} + bla_{OXA-58}$ (1), $bla_{NDM-1} + bla_{OXA-23}$ (1), bla_{OXA-23} (1), $bla_{OXA-134}$ -like (5), $bla_{OXA-213}$ -like (2), $bla_{OXA-23} + bla_{OXA-24}$ (8), $bla_{OXA-23} + bla_{OXA-23}$ (1).