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Activity of cefiderocol against carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex, including molecularly characterized clinical isolates, causing infections in hospitals in European and adjacent regions (2020–2023)

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Introduction

- Cefiderocol is approved in Europe for the treatment of infections in adult patients due to aerobic Gram-negative organisms, where limited treatment options are available.
  - Cefiderocol is also 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 *Acinetobacter 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 collected from hospitals in European countries, Israel, and Turkey during 2020–2023.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 2,067 *A. baumannii-calcoaceticus* complex collected from various clinical specimens in patients hospitalized in 42 medical centers in 17 European countries, Israel, and Turkey during 2020–2023.
- Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local institutional 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 (2024) 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.
- Quality assurance was performed by sterility checks, bacterial inoculum (colony counts), and testing CLSI-recommended quality control reference strains.
- MIC results for cefiderocol and comparator agents were interpreted according to the FDA/EUCAST (PK/PD)/CLSI criteria.
- Isolates with imipenem and/or meropenem MIC ≥8 mg/L (resistant based on CLSI criteria) were subjected to genome sequencing and screening of β-lactamase genes.

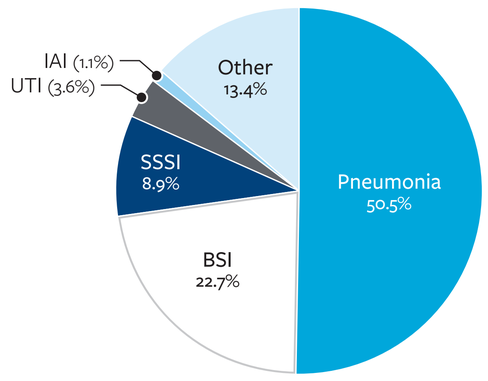
Table 1. Distribution of carbapenem-resistant *A. baumannii-calcoaceticus* complex in European countries, Israel, and Turkey

Region Country (Number included)	Number of carbapenem-resistant (%)
Eastern (1291)	1009 (78.2)
Czech Republic (23)	8 (34.8)
Greece (161)	158 (98.1)
Hungary (61)	44 (72.1)
Israel (441)	304 (69.0)
Poland (135)	125 (92.6)
Romania (70)	63 (90.0)
Slovakia (11)	8 (72.7)
Slovenia (54)	12 (22.2)
Turkey (335)	287 (85.7)
Western (776)	279 (36.0)
Belgium (25)	2 (8.0)
France (75)	5 (6.7)
Germany (202)	20 (9.9)
Ireland (13)	1 (7.7)
Italy (269)	206 (76.6)
Portugal (27)	12 (44.4)
Spain (53)	22 (41.5)
Sweden (17)	2 (11.8)
Switzerland (64)	9 (14.1)
UK (31)	0 (0.0)
Total (2067)	1288 (62.3)

Results

- A total of 62.3% (1288/2067) *A. baumannii-calcoaceticus* species complex isolates were classified as carbapenem-resistant (Table 1).
  - Most carbapenem-resistant isolates originated from pneumonia patients (50%), whereas smaller percentages originated from bloodstream infections (23%), skin and skin structure infections (9%), and urinary tract infections (4%) (Figure 1).
- A carbapenem resistance phenotype amongst *A. baumannii-calcoaceticus* species complex was observed in 78.2% and 36.0% of isolates originating from Eastern (including Israel and Turkey) and Western European countries, respectively (Table 1).
  - Isolates originating from most Eastern European regions showed high carbapenem resistance (≥69%), except for Czech Republic (35%) and Slovenia (22%).
  - Most countries in Western Europe had carbapenem resistance at <15%, except for Italy (77%), Portugal (44%), and Spain (42%).
- Among carbapenem-resistant *A. baumannii-calcoaceticus* species complex, all but 9 (99.3%; 1279/1288) carried carbapenemase genes (Table 2).
  - bla_{OXA-23}-like (73.5%; 940/1279) was among the most common carbapenemase gene detected, followed by bla_{OXA-24}-like (16.3%; 209/1279) (Table 2).
  - A smaller subset (9.8%; 125/1279) carried bla_{NDM-1}, dual carbapenemases or bla_{OXA} carbapenemases in combination with Class A extended-spectrum β-lactamases (bla_{GES-22} or bla_{PER-1} or bla_{PER-7}).
- In general, cefiderocol ($MIC_{50/90}$, 0.25/1 mg/L; 92.7–97.0% susceptible) had the lowest $MIC_{50/90}$ against all *A. baumannii-calcoaceticus* species complex (Table 2).
  - Comparators had limited activity (34.6–37.7% susceptible), except for colistin (87.9% susceptible).
- Cefiderocol (89.4–95.4% susceptible) had $MIC_{50/90}$ values of 0.25/2 mg/L against the carbapenem-resistant and carbapenemase-positive subsets, whereas comparator agents shown in Table 2 were not active (0.0–1.2% susceptible), except for colistin, which was active against 81.1% of these isolates (Table 2).
- Cefiderocol (89.0–98.3% susceptible) showed $MIC_{50/90}$ of 0.25/1-2 mg/L against isolates carrying bla_{OXA-23}-like and bla_{OXA-24}-like
  - All isolates carrying bla_{OXA-58}-like were inhibited by cefiderocol at MIC of ≤0.25 mg/L, as well as those with no acquired carbapenemases and carrying only the intrinsic bla_{OXA-51}-like and $bla_{OXA-213}$-like genes (n=9), except for 1 *A. baumannii-calcoaceticus* species complex isolate with a cefiderocol MIC of 2 mg/L.
- Cefiderocol (62.4–68.8% susceptible) had $MIC_{50/90}$ of 0.5/64 mg/L against a small subset of isolates carrying bla_{NDM-1}, dual carbapenemases or bla_{OXA} carbapenemases in combination with bla_{GES-22} or bla_{PER-1} or bla_{PER-7}.

Figure 1. Distribution of infection types[a] caused by carbapenem-resistant *A. baumannii-calcoaceticus* complex in European countries, Israel, and Turkey



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

Conclusions

- Cefiderocol had the highest *in vitro* activity against all and each resistant subset of *A. baumannii-calcoaceticus* species complex causing infections in hospitals in European countries, Israel, and Turkey.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by these resistant pathogens, as comparator and recommended agents are not active.

Acknowledgments

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Table 2. Activity of cefiderocol, β-lactam-β-lactamase inhibitor combinations and other comparator agents against *A. baumannii-calcoaceticus* complex and carbapenem-resistant subsets

Phenotype[a]/genotype (No.)	MIC_{50}/MIC_{90} in mg/L (% susceptible by FDA/EUCAST/CLSI criteria)[b]					
	FDC	IMR	MER	A/S	CAZ	COL
All (2,067)	0.25/1 (92.7/95.5/97.0)	>8/>8 (37.7)	>32/>32 (37.5)	32/>64 (36.3)	>32/>32 (34.6)	0.5/8 (87.9)
Carbapenem-susceptible (774)	0.06/0.25 (98.4/99.4/99.6)	0.25/0.25 (100)	0.25/1 (100)	2/8 (94.3)	4/8 (91.2)	0.25/1 (99.0)
Carbapenem-resistant (1288)	0.25/2 (89.4/93.2/95.4)	>8/>8 (0.2)	>32/>32 (0.0)	64/>64 (1.3)	>32/>32 (0.7)	0.5/>8 (81.1)
Carbapenemase-positive (1,279)	0.25/2 (89.4/93.1/95.4)	>8/>8 (0.1)	>32/>32 (0.0)	64/>64 (1.2)	>32/>32 (0.7)	0.5/>8 (81.1)
OXA-23-like (940)	0.25/1 (93.0/96.4/98.3)	>8/>8 (0.0)	>32/>32 (0.0)	64/>64 (0.4)	>32/>32 (0.6)	0.5/>8 (77.8)
OXA-24-like (209)	0.25/2 (89.0/95.2/98.1)	>8/>8 (0.0)	>32/>32 (0.0)	64/>64 (4.3)	>32/>32 (1.4)	0.5/8 (87.1)
OXA-58-like (5)	0.12/- (100/100/100)	16/- (2.4)	16/- (0.0)	64/- (0.0)	>32/- (0.0)	0.25/- (100)
Other[c] (125)	0.5/64 (62.4/64.8/68.8)	>8/>8 (0.8)	>32/>32 (0.0)	>64/>64 (0.0)	>32/>32 (0.0)	0.5/1 (95.2)
Carbapenemase-negative[d] (9)	0.25/- (88.9/100/100)	>8/- (11.1)	>32/- (0.0)	16/- (22.2)	>32/- (0.0)	0.25/- (77.8)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; MER, meropenem; A/S, ampicillin-sulbactam; CAZ, ceftazidime; COL, colistin.
[a] Carbapenem-susceptible, isolates susceptible to imipenem and meropenem based on EUCAST/CLSI criteria (MIC values ≤2 mg/L); carbapenem-resistant, isolates resistant to imipenem and/or meropenem based on CLSI criteria (MIC values ≥8 mg/L).
[b] Cefiderocol MIC results were interpreted according to the FDA/EUCAST (PK/PD)/CLSI criteria, whereas comparator agent MIC were interpreted based on EUCAST criteria, except for imipenem-relebactam that used FDA, and ampicillin-sulbactam and ceftazidime that used CLSI criteria.
[c] Includes bla_{NDM-1} (4), bla_{NDM-1} + bla_{OXA-23} (21), bla_{OXA-23} + bla_{OXA-72} (54), bla_{OXA-23} + bla_{OXA-58} (25), bla_{OXA-23} + bla_{OXA-72} + bla_{PER-7} (6), bla_{OXA-23} + bla_{PER-1} (4), bla_{OXA-23} + bla_{PER-7} (8), bla_{OXA-72} + bla_{PER-7} (1), bla_{OXA-72} + bla_{GES-22} (2).
[d] Includes *A. pittii* (5) and *A. baumannii* (4), where $bla_{OXA-213}$- and bla_{OXA-51}-variants are intrinsic, respectively. Acquired carbapenemases were not detected in these isolates.