Activity of omadacycline against multidrug-resistant and molecularly characterized *Acinetobacter baumannii-calcoaceticus* complex clinical isolates from United States hospitals (2020–2023)

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Omadacycline demonstrated potent *in vitro* activity against *A. baumannii-calcoaceticus* species complex, including resistant subsets and those carrying carbapenemase genes.

Introduction

- Multidrug-resistant (MDR) and carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRAB) has gained attention as an important clinical challenge in the last decades, due to its resistance to front-line antibiotics.
- Omadacycline is a third-generation tetracycline class antibacterial approved for treatment of adults with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia caused by indicated organisms.
  - Omadacycline is available in both oral and intravenous formulations.
- Minocycline or tigecycline is recommended by guidance documents as part of combination treatment regimens for CRAB. Thus, this study evaluated the *in vitro* activity of omadacycline, minocycline, tigecycline, and other comparator agents against *Acinetobacter* spp. and molecularly characterized subsets of *A. baumannii-calcoaceticus* species complex from United States hospitals (2020–2023).

Materials and Methods

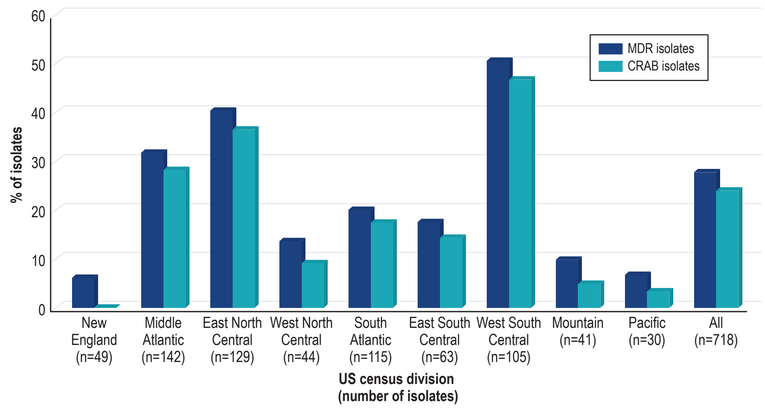
Bacterial organisms

- This study surveyed a collection of 718 *A. baumannii-calcoaceticus* species complex and 192 isolates from 17 other *Acinetobacter* species collected from 35 hospitals in 9 US Census divisions (2020–2023), as part of the omadacycline surveillance program.
- 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 containing fresh cation-adjusted Mueller-Hinton broth were manufactured by Element Iowa City (JMI Laboratories; North Liberty, IA, USA).
- MIC results for comparator agents were interpreted according to CLSI criteria, except for colistin, which utilized EUCAST breakpoints.
- Isolates exhibiting an MDR phenotype (resistant to ≥3 classes) were subjected to screening for β-lactamase genes by genome sequencing and *in silico* analysis.

Figure 1. Distribution of MDR and carbapenem resistance phenotypes among *A. baumannii-calcoaceticus* species complex isolates within the United States



Results

- In general, 21.9% (199/910) of all *Acinetobacter* spp. showed an MDR phenotype, and all MDR isolates were identified as *A. baumannii-calcoaceticus* species complex (Table 1).
  - These MDR isolates were mainly the causative agents of pneumonia (40%) and skin infections (32%), followed by bloodstream infections (12%) and urinary tract infections (8%).
- Among the *A. baumannii-calcoaceticus* species complex subset, 27.7% (199/718) displayed an MDR phenotype, whereas 24.0% (172/718) were classified as CRAB isolates (Figure 1).
  - The highest rates of MDR/CRAB isolates among the *A. baumannii-calcoaceticus* species complex were from the West South Central (50.5/46.7%), East North Central (40.3/36.4%), and Middle Atlantic (31.7/28.2%) regions.
- Among MDR *A. baumannii-calcoaceticus* species complex isolates, 83.4% (166/199) carried acquired carbapenemase genes, and 97.0% (161/166) of isolates were CRAB (Tables 1 and 2).
  - The most frequent carbapenemase genes identified were bla_{OXA-23} (60.8%; 101/166) and bla_{OXA-24} (32.5%; 54/166).
- Omadacycline ($MIC_{50/90}$, 0.25/4 mg/L), minocycline, and tigecycline had similar MIC values against all *Acinetobacter* spp. (Table 2).
  - Ampicillin-sulbactam and imipenem had elevated MIC_{90} values.
- Omadacycline ($MIC_{50/90}$, 4/8 mg/L) and tigecycline had the lowest MIC_{90} values against the MDR subset, followed by minocycline (Table 2).
  - Low susceptibilities were observed for ampicillin-sulbactam and imipenem against the MDR subset.
- Omadacycline ($MIC_{50/90}$, 4/8 mg/L), minocycline ($MIC_{50/90}$, 2–8/16 mg/L), and tigecycline ($MIC_{50/90}$, 2/4 mg/L) MIC_{90} values were unaffected by MDR isolates carrying acquired carbapenemases, including subsets carrying bla_{OXA-23}, bla_{OXA-24}, or other genes (Table 2).

Table 1. MIC distribution for omadacycline against *Acinetobacter* spp. and *A. baumannii-calcoaceticus* species complex and resistant subsets

Phenotype/genotype[a] (No. tested)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:										MIC (mg/L)	
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	MIC_{50}	MIC_{90}
All *Acinetobacter* spp. (910)	16 1.8	225 26.5	304 59.9	111 72.1	58 78.5	73 86.5	88 96.2	29 99.3	5 99.9	1 100	0.25	4
Non-MDR (711)	16 2.3	225 33.9	301 76.2	105 91.0	36 96.1	14 98.0	11 99.6	2 99.9	1 100		0.25	0.5
MDR *A. baumannii-calcoaceticus* (199)			3 1.5	6 4.5	22 15.6	59 45.2	77 83.9	27 97.5	4 99.5	1 100	4	8
Carbapenemase-positive[b] (166)			3 1.8	3 3.6	13 11.4	54 44.0	67 84.3	21 97.0	4 99.4	1 100	4	8
OXA-23 (101)			3 3.0	3 5.9	7 12.9	37 49.5	36 85.1	12 97.0	3 100		4	8
OXA-24 (54)					5 9.3	15 37.0	25 83.3	7 96.3	1 98.1	1 100	4	8
Other[c] (11)					1 9.1	2 27.3	6 81.8	2 100			4	8
Carbapenemase-negative[d] (33)				3 9.1	9 36.4	5 51.5	10 81.8	6 100			2	8

[a] MDR, isolates non-susceptible to 3 or more classes of antimicrobial agents based on CLSI criteria. All MDR isolates were identified as *A. baumannii-calcoaceticus* species complex, and a total of 86.4% (172/199) of MDR isolates were CRAB.
[b] All but 5 (97.0%) MDR and carbapenemase-positive *A. baumannii-calcoaceticus* species complex isolates were CRAB.
[c] Includes bla_{NDM-1} (1), $bla_{OXA-134}$-like (3), bla_{OXA-23} + bla_{OXA-24} (7).
[d] Includes MDR isolates where acquired carbapenemase genes were not detected.

Table 2. Activity of omadacycline and comparator agents against *Acinetobacter* spp., *A. baumannii-calcoaceticus* species complex and resistant subsets

Phenotype[a]/genotype (No.)	MIC_{50}/MIC_{90} in mg/L (% susceptible by CLSI or EUCAST)[b]					
	OMC	MIN	TIG	A/S	IMI	COL
All *Acinetobacter* spp. (910)	0.25/4 (—)	0.12/4 (90.8)	0.25/2 (—)	4/32 (74.5)	0.25/>8 (80.1)	0.5/1 (95.9)
Non-MDR (711)	0.25/0.5 (—)	0.12/0.25 (99.6)	0.25/0.5 (—)	2/8 (91.0)	0.25/0.25 (99.6)	0.25/1 (95.5)
MDR *A. baumannii-calcoaceticus* (199)	4/8 (—)	4/16 (59.3)	2/4 (—)	32/>64 (15.6)	>8/>8 (10.6)	0.25/1 (97.5)
Carbapenemase-positive[c] (166)	4/8 (—)	4/16 (56.6)	2/4 (—)	32/>64 (4.8)	>8/>8 (1.2)	0.25/1 (97.0)
OXA-23 (101)	4/8 (—)	4/16 (57.4)	2/4 (—)	64/>64 (0.0)	>8/>8 (0.0)	0.25/1 (97.0)
OXA-24 (54)	4/8 (—)	2/16 (57.4)	2/4 (—)	32/>64 (11.1)	>8/>8 (1.9)	0.25/0.5 (100)
Other[d] (11)	4/8 (—)	8/16 (45.5)	2/4 (—)	32/>64 (18.2)	>8/>8 (9.1)	0.25/0.5 (90.9)
Carbapenemase-negative[e] (33)	2/8 (—)	2/16 (72.7)	2/4 (—)	8/32 (69.7)	2/>8 (57.6)	0.5/2 (97.0)

Abbreviations: OMC, omadacycline; MIN, minocycline; TIG, tigecycline; A/S, ampicillin-sulbactam; IMI, imipenem; COL, colistin.
[a] MDR, isolates non-susceptible to 3 or more classes of antimicrobial agents based on CLSI criteria. All MDR isolates were identified as *A. baumannii-calcoaceticus* species complex, and a total of 86.4% (172/199) of MDR isolates were CRAB.
[b] MIC results were interpreted according to the CLSI criteria (as available), except for colistin that used EUCAST; "—", no breakpoints available for MIC interpretation.
[c] All but 5 (97.0%) MDR and carbapenemase-positive *A. baumannii-calcoaceticus* species complex isolates were CRAB.
[d] Includes bla_{NDM-1} (1), $bla_{OXA-134}$-like (3), bla_{OXA-23} + bla_{OXA-24} (7).
[e] Includes MDR isolates where acquired carbapenemase genes were not detected.

Conclusions

- More than 20% of *A. baumannii-calcoaceticus* species complex displayed an MDR phenotype and limited susceptibility to standard-of-care beta-lactam agents (e.g. ampicillin-sulbactam and imipenem).
- The data presented here show that omadacycline had MIC values similar to those of other recommended tetracycline class agents against MDR and other resistant subsets.
- These *in vitro* data, combined with the advantageous pharmacokinetic properties and available intravenous and oral formulations, suggest that further investigation of omadacycline as part of a combination option for the treatment of infections caused by *A. baumannii-calcoaceticus* species complex, including isolates resistant to other classes of antibiotics, is warranted.

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