ESCMID 2025 | Poster #P1273

Increase in *bla*$_{NDM-1}$ among carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex clinical isolates collected in 2023 from U.S. and European medical centres

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Introduction

- Treatment of infections caused by carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* (CRAB) is challenging due to extensive intrinsic and acquired resistance mechanisms in this species.
- CRAB is designated as a critical priority for new antibiotic development by the World Health Organization.
- Class D OXA-type carbapenemases are common among CRAB, but metallo-β-lactamases, including New Delhi metallo-β-lactamases (NDM), are less frequently identified.
- We screened CRAB isolates collected in U.S. and European medical centres for acquired carbapenemases during the SENTRY Antimicrobial Surveillance program from 2020–2023.

Methods

- *A. baumannii-calcoaceticus* complex isolates (n = 3,506) from documented infections were collected from 112 sites in 20 countries.
- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines, with appropriate quality controls applied throughout.
- Frozen-form broth microdilution panels were manufactured by Element Iowa City (JMI Laboratories; North Liberty, IA, USA) with cation-adjusted Mueller-Hinton broth.
- Susceptibility interpretations (-S%) followed 2024 criteria (CLSI M100ed34, 2024; European Committee on Antimicrobial Susceptibility Testing, EUCAST v14.0, 2024; United States Food and Drug Administration, US FDA 2024) where applicable.
- Isolates with imipenem and/or meropenem MIC values ≥8 mg/L were genome sequenced using a MiSeq or NextSeq instrument (Illumina, San Diego, CA, USA), *de novo* assembled using SPAdes (v3.15.3 or as then current version) and screened for acquired carbapenemase genes. Multi-locus sequence type (ST; Pasteur scheme; pubmlst.org) was determined from genome assemblies.

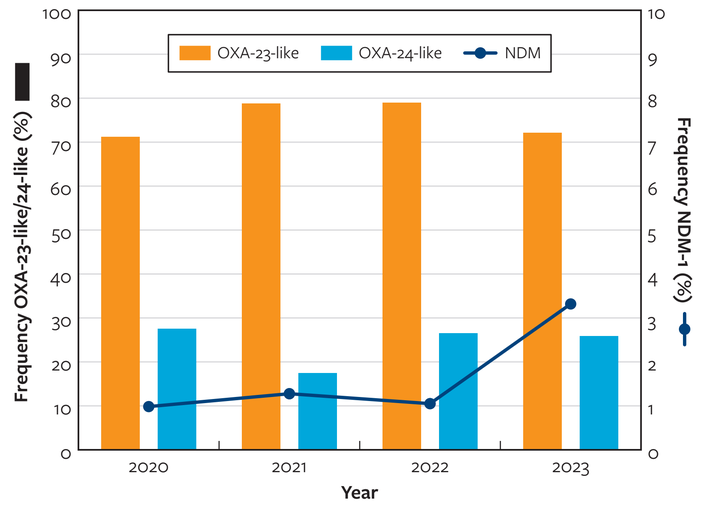
Results

- CRAB accounted for 48.6% (n = 1,703) of tested isolates (Table 1).
- Genes encoding OXA-23-like, OXA-24-like, and NDM-1 carbapenemases were present in 75.7%, 24.0%, and 1.7% of CRAB strains, respectively.
- The frequency of *bla*$_{NDM-1}$ among CRAB increased from 1.0% (n = 3) in 2020 to 3.3% (n = 15) in 2023, while *bla*$_{OXA-23}$-like (71.1–79.0%) and *bla*$_{OXA-24}$-like (17.4–27.5%) frequencies were more stable (Fig. 1).
- Isolates harbouring *bla*$_{NDM-1}$ were collected in 8 countries; Israel (37.9%) and Romania (20.7%) contributed the majority (Fig. 2).
- Isolates from 6 different STs carried *bla*$_{NDM-1}$, and most isolates were ST570 (41.4%) or ST2 (31.0%) (Fig. 3).
- Distinct molecular profiles were apparent between geographically separated *bla*$_{NDM-1}$-carrying clones (Table 2).
- Only colistin (96.6%-S, EUCAST) was effective against the CRAB-NDM-1 subset, while all other agents, including sulbactam-durlobactam (0.0%-S), demonstrated activity against <75% of isolates (Table 1).

Conclusions

- Although still comparatively rare compared to class D OXA-type carbapenemases, genes encoding NDM-type carbapenemases were identified in more CRAB isolates in 2023 than in the three preceding years.
- Furthermore, NDM-1 was identified across a broader geographic range and in increasingly diverse STs over time, with a notable occurrence in isolates from ST570.
- Few antimicrobial agents demonstrated activity against NDM-1-carrying CRAB isolates, underscoring the need for continued development of novel therapies for treatment of these isolates.
- Overall, the results of this study demonstrate the importance of continued surveillance of NDM-harbouring CRAB.

Figure 1. Frequency of genes encoding OXA-23-like (orange bar), OXA-24-like (blue bar), and NDM-1 (blue line) carbapenemases identified in CRAB isolates



Note OXA-type and NDM-1 frequencies are plotted on distinct axes.

Figure 2. Geographic distribution of *bla*$_{NDM-1}$-carrying isolates. Shown are the percentage of all *bla*$_{NDM-1}$-carrying isolates.

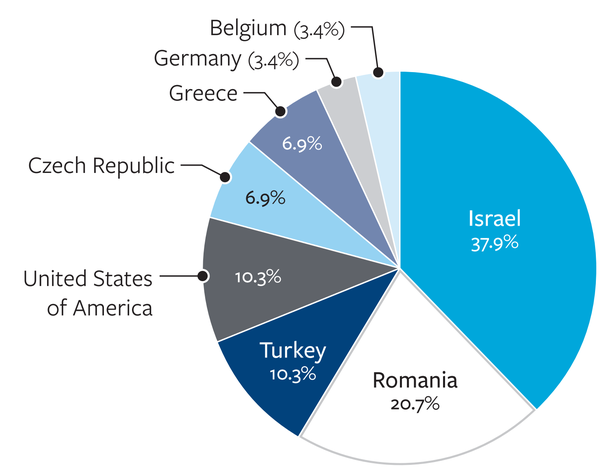


Figure 3. Distribution of sequence types of *bla*$_{NDM-1}$-carrying isolates across study years

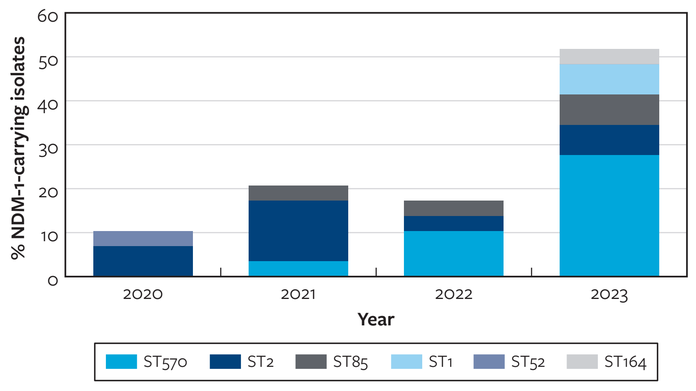


Table 1. Activity of currently available antibiotics against *Acinetobacter baumannii-calcoaceticus* isolates, including phenotypic (CRAB) and genotypic (CRAB-NDM-1) resistance subsets

	All ACB (3,506)				CRAB (1,703)				CRAB-NDM-1 (29)			
	MIC$_{50/90}$	CLSI-S%[a]	EUCAST-S%[a]	FDA-S%[a]	MIC$_{50/90}$	CLSI-S%	EUCAST-S%	FDA-S%	MIC$_{50/90}$	CLSI-S%	EUCAST-S%	FDA-S%
A/S	16/>64	49.1	—	49.1	64/>64	3.8	—	3.8	>64/>64	0.0	—	0.0
SUD[b]	1/4	97.3	—	97.3	2/4	93.8	—	93.8	>32/>32	0.0	—	0.0
AMK	4/>32	60.4	57.7	60.4	>32/>32	21.4	17.7	21.4	>32/>32	17.2	6.9	17.2
LVX	4/>32	49.9	47.5	—	16/>32	0.9	0.5	—	16/>32	0.0	0.0	—
MIN	0.5/16	69.9	—	69.9	8/16	39.6	—	39.6	2/16	72.4	—	72.4
COL	0.5/2	—	91.3	—	0.5/>8	—	84.7	—	0.5/2	—	96.6	—

Abbreviations: ACB, *A. baumannii-calcoaceticus* complex; CRAB, carbapenem-resistant ACB; NDM, New Delhi metallo-β-lactamase; MIC, minimum inhibitory concentration; A/S, ampicillin-sulbactam; SUD, sulbactam-durlobactam; AMK, amikacin; LVX, levofloxacin; MIN, minocycline; COL, colistin
[a] Susceptibility determined using CLSI (2024), EUCAST (2024), and US FDA (2024) breakpoints; [b] SUD MIC values were available for: All ACB n = 1,021; CRAB n = 452; CRAB-NDM-1 n = 29

Table 2. Molecular profile of isolates carrying *bla*$_{NDM-1}$, stratified by sequence type (ST)

ST (n)	Country (n)	Year[a]	ADC	Intrinsic OXA-51	Acquired Carbapenemase
ST570 (12)	Israel (6)[b]	2021/2022/**2023**	ADC-73	OXA-66 (5)/OXA-336[c] (1)	NDM-1, OXA-23
	Romania (6)	2022/**2023**	ADC-73	OXA-336	NDM-1, OXA-23
ST2 (9)	Belgium (1)	2020	ADC-73	OXA-66	NDM-1, OXA-23
	Czech Republic (2)	2022/2023	ADC-73	OXA-66	NDM-1, OXA-23
	Germany (1)	2020	ADC-73	OXA-66	NDM-1, OXA-23
	Israel (2)	2021	ADC-73	OXA-66	NDM-1, OXA-23
	Turkey (2)	2021/2023	ADC-30	OXA-66	NDM-1, OXA-23
	USA (1)	2021	ADC-30	OXA-66	NDM-1, OXA-23
ST85 (4)	Israel (3)	2021/2022/2023	ADC-80 (2)/ADC-176 (2)[d]	OXA-94	NDM-1
	Turkey (1)	2023	ADC-80	OXA-94	NDM-1
ST1 (2)	Greece (2)	2023	ADC-191	OXA-69	NDM-1, OXA-23
ST52 (1)	USA (1)	2020	ADC-158	OXA-98	NDM-1, OXA-58
ST164 (1)	USA (1)	2023	ADC-52	OXA-91	NDM-1

Abbreviations: ADC, *Acinetobacter*-derived cephalosporinase (intrinsic *ampC*); NDM, New Delhi metallo-β-lactamase.
[a] Bold indicates year in which most isolates were collected; [b] Includes 1 ST570-like single locus variant; [c] OXA-336 is a I173N variant of OXA-66; [d] ADC-176 and ADC-80 sequences were identified in a single isolate

Acknowledgments

The authors thank all of the SENTRY Program participants for providing the isolates used in this study.

Funding

JH Kimbrough, MH Karr, TB Doyle, and M Castanheira are employees of Element Materials Technology (JMI Laboratories). No external funding was received for this study.

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