ESCMID 2026 | Poster #P1351

Activity of Zosurabalpin Against Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) Isolates Producing NDM and/or Oxacillinase Enzymes

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Introduction

- Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CRABC) is a major cause of hospital-acquired infections and is recognized as a critical threat by the US Centers for Disease Control and Prevention and by the World Health Organization.
- Resistance to carbapenems in CRABC isolates is usually mediated by the presence of acquired oxacillinases and/or New Delhi metallo-β-lactamase (NDM) and the presence of these enzymes can confer resistance to most β-lactam agents, including agents recently developed to target CRABC such as cefiderocol and sulbactam-durlobactam.
- We evaluated the activity of zosurabalpin and comparator agents against a collection of CRABC isolates producing NDM and/or oxacillinases submitted to a global surveillance program.

Materials and Methods

- A total of 502 CRABC isolates producing NDM and/or oxacillinases were collected in 56 hospitals located in 16 European countries (n=362) and the US (n=140) during 2024.
- Bacterial identification was confirmed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany).
- 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 except for cefiderocol that used broth microdilution panels containing iron-depleted media.
- Zosurabalpin was tested in CAMHB supplemented with 20% heat-inactivated horse serum (HoS) as per CLSI guidelines.
- Zosurabalpin MIC endpoints were determined at complete inhibition of growth (100% read).
- Quality assurance was performed by sterility checks, bacterial inoculum (colony counts), and testing CLSI-recommended quality control reference strains.
- Whole genome sequencing was performed on a NextSeq (Illumina, San Diego, California, USA) instrument targeting a 30X coverage.
  - Sequences were *de novo* assembled.
  - Analysis of β-lactamases was performed *in silico.*

Results

- A total of 29 isolates harbored bla_{NDM-1} (n=27) or bla_{NDM-5} (n=2) of which 20 also carried bla_{OXA-23} (n=19) or bla_{OXA-72} (n=1; Figure 1).
- The gene encoding OXA-23 was observed alone among 348 CRABC isolates and these isolates included one variant harboring a P225T alteration.
- A total of 95 isolates carried genes encoding OXA-24 variants alone, including bla_{OXA-24}, bla_{OXA-72} and $bla_{OXA-139}$.
- Four isolates carried the bla_{OXA-58} variants bla_{OXA-58} or $bla_{OXA-420}$.
- Double oxacillinases were noted among 26 isolates and included 11 bla_{OXA-23} plus bla_{OXA-72}, 10 bla_{OXA-23} plus bla_{OXA-58}, 4 bla_{OXA-23} plus bla_{OXA-24} and one isolate carried $bla_{OXA-499}$, a $bla_{OXA-143}$-like gene, plus bla_{OXA-72}.
- Zosurabalpin displayed good activity against CRABC isolates ($MIC_{50/90}$, 0.25/0.5 mg/L; Table 1) inhibiting 99.8% and 100.0% of the isolates at ≤1 mg/L and ≤2 mg/L, respectively.
- Zosurabalpin displayed similar activity against isolates harboring genes encoding NDM (n=29; $MIC_{50/90}$, 0.25/0.25 mg/L) or oxacillinases without bla_{NDM} (n=473; $MIC_{50/90}$, 0.25/0.5 mg/L) inhibiting 99.8% or 100% of the isolates at ≤1 mg/L and ≤2 mg/L (Figure 2).
- Cefiderocol and sulbactam-durlobactam were active against 85.3% and 90.2% of the CRABC isolates when applying CLSI breakpoints (Table 1).
- Against isolates producing NDM alone or with oxacillinases (n=29), the activity of cefiderocol (10.0% susceptible) and sulbactam-durlobactam (0.0%) was markedly decreased.
- Cefiderocol and sulbactam-durlobactam were the only β-lactam agents with appreciable activity against oxacillinase producing isolates without bla_{NDM} (n=473) inhibiting >89% and >95% of the isolates carrying bla_{OXA-23}, bla_{OXA-24} and bla_{OXA-58}-like genes alone.
  - Both agents displayed the lower susceptibility rates against isolates carrying double oxacillinases (80.8% and 88.5%, respectively; Table 1).
- The activity of zosurabalpin ($MIC_{50/90}$, 0.25/0.5 mg/L) was unchanged against isolates harboring double oxacillinases.
- All other agents exhibited susceptibility rates <54.3% against all isolate groups when using the CLSI breakpoint criteria.

Conclusions

- Zosurabalpin displayed potent in vitro activity against CRABC isolates producing NDM and/or oxacillinases.
- CRABC isolates were resistant to most clinically available comparator agents except for cefiderocol and sulbactam-durlobactam that displayed good activity against isolates carrying single acquired oxacillinases, but the activity of these agents was reduced against isolates carrying double oxacillinases and limited against isolates harboring NDM.
- The low susceptibility of CRABC against clinically available agents highlights the need for additional agents active against these organisms, including zosurabalpin.

Acknowledgments

The work study described in this presentation was funded in whole with federal funds from the U.S. Department of Health and Human Services (HHS); Administration for Strategic Preparedness and Response (ASPR); Biomedical Advanced Research and Development Authority (BARDA), under contract number HHSO100201600038C. The contract and federal funding are not an endorsement of the study results, product or company.

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Figure 1. Distribution of acquired carbapenemases among 502 CRABC clinical isolates

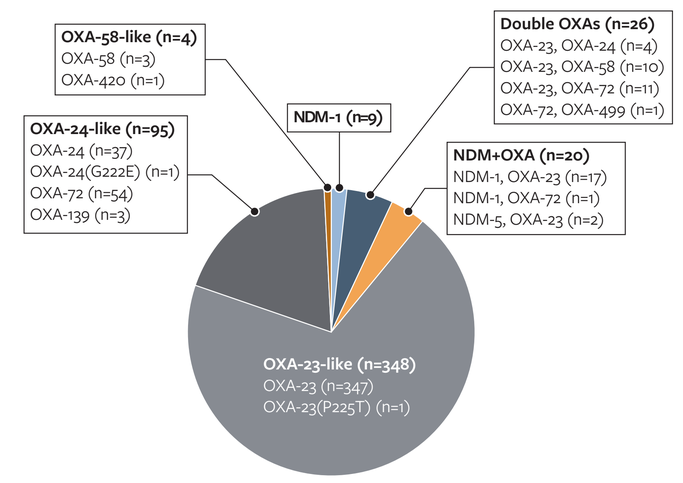

Table 1. Activity of zosurabalpin and comparator agents against CRABC isolates producing NDM and/or oxacillinases

Antimicrobial agents	Isolates producing (no. of isolates)[a]						
	All CRABC (n=502)	All NDM (n=29)	NDM+OXA (n=20)	All OXAs (n=473)	OXA-23-like (n=348)	OXA-24-like (n=95)	Double OXAs (n=26)
	$MIC_{50/90}$ (mg/L)						
Zosurabalpin	0.25/0.5	0.25/0.25	0.25/0.25	0.25/0.5	0.25/0.5	0.25/0.5	0.25/0.5
Tigecycline	2/4	2/4	2/4	2/4	2/4	2/4	2/4
Colistin	0.5/2	0.5/1	0.5/1	0.5/2	0.5/2	0.5/1	0.5/1
	% Susceptible by CLSI criteria						
Ampicillin-sulbactam	1.4	0	0	1.5	0.3	5.3	3.8
Piperacillin-tazobactam	0	0	0	0	0	0	0
Sulbactam-durlobactam	90.2	0	0	95.8	95.4	98.9	88.5
Cefepime	2.2	0	0	2.3	0.6	7.4	3.8
Ceftazidime	6.4	0	0	6.8	4.0	16.8	3.8
Cefiderocol	85.3	10.0	10.0	89.4	89.1	92.6	80.8
Meropenem	0	0	0	0	0	0	0
Imipenem	0.6	0	0	0.6	0.3	2.1	0
Levofloxacin	1.8	0	0	1.7	1.7	1.1	3.8
Amikacin	24.0	10.0	10.0	23.3	15.5	54.3	15.4
Gentamicin	20.7	15.0	15.0	19.7	15.5	37.9	11.5
Minocycline	22.7	15.0	15.0	21.6	20.4	20.0	42.3
Trimethoprim-sulfamethoxazole	21.9	15.0	15.0	22.2	23.3	21.1	15.4

[a]OXAs, OXA-23, OXA-24-like and double OXAs do not include isolates carrying genes encoding NDM

Figure 2. Activity of zosurabalpin and new agents used for treatment of all 502 CRABC, 29 CRABC isolates producing NDM with or without oxacillinases, and 473 CRABC isolates producing oxacillinases only