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# The Susceptibility of Eravacycline and Comparators to Global Isolates of *Acinetobacter baumannii*

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## Amended abstract

**Background:** Eravacycline (ERV) is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class being developed for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. The purpose of this study was to evaluate the activity of ERV and comparators against global, non-duplicate isolates of carbapenem-resistant *Acinetobacter baumannii* (CRAB).

**Materials and methods:** Clinical isolates (n=286) were collected from various body sites in patients in nine mainly European countries from 2005-2015. Antimicrobial susceptibility testing was performed by broth microdilution in cation-adjusted Mueller–Hinton broth according to CLSI guidelines. The concentration ranges tested in 2-fold dilutions were: ERV, 0.015–16 mg/L; amikacin, 0.125–128 mg/L; colistin, 0.125-128mg/L; doxycycline, 0.06–32 mg/L; imipenem, 1–128 mg/L; levofloxacin, 0.125–64 mg/L; meropenem, 1–128 mg/L; minocycline, 0.06–64 mg/L; sulbactam, 0.125–128 mg/L; tigecycline, 0.06–32 mg/L; and tobramycin, 0.06–128 mg/L. Susceptibility was determined using CLSI 2015 breakpoints. Based on rep-PCR and MLST, isolates represented 6 international clonal lineages (IC) and included 231 isolates with *bla*$_{\text{OXA-23-like}}$, 17 isolates with *bla*$_{\text{OXA-40-like}}$, 27 isolates with *bla*$_{\text{OXA-58-like}}$ and 9 isolates with overexpression of intrinsic *bla*$_{\text{OXA-51}}$.

**Results**: The ERV MIC$_{50/90}$ values for all isolates were 0.5/1 mg/L. Comparatively, tigecycline, minocycline and doxycycline MIC$_{50/90}$ values were 1/2, 4/8, 32/>32 mg/L, respectively. One versus 19 strains had MICs of ≥4 µg/mL to eravacycline and tigecycline, respectively.

**Conclusion:** ERV was the most potent antibiotic against tested isolates including those that were resistant to sulbactam, imipenem/meropenem, levofloxacin, and amikacin/tobramycin, compared to other compounds. ERV may be a therapeutic option for treatment of multidrug-resistant *A. baumannii*.

## Introduction and Purpose

- Multidrug-resistant *Acinetobacter baumannii* is a growing threat leaving few therapeutic options. Carbapenem-resistance in *A. baumannii* mediated mainly through the action of intrinsic and acquired OXA-type enzymes is an increasing cause of concern. Efflux does not significantly affect carbapenems, however it plays a role in the intrinsic resistance to fluorquinolones, tetracyclines, aminoglycosides and macrolides.
- Eravacycline (ERV) is a novel fully synthetic fluorocycline antibiotic of the tetracycline class with in vitro activity against key Gram-negative pathogens, including multidrug-resistant *Enterobacteriaceae* and *A. baumannii*. The activity of ERV was compared with anti-Acinetobacter reference drugs against well-defined *A. baumannii* isolates.

## Methods

### Bacterial isolates:

- 286 non-duplicate carbapenem-resistant *A. baumannii* (CRAb) isolates were collected from various body sites in patients from eight European countries and Singapore between 2005 and 2015.
- The isolates were molecularly typed with repPCR (DiversiLab) (1) and MLST and characterised for carbapenem-resistance mechanisms. They represented 6 of the 8 previously described international clonal lineages and included 231 isolates with *bla*$_{\text{OXA-23-like}}$, 17 isolates with *bla*$_{\text{OXA-40-like}}$, 27 isolates with *bla*$_{\text{OXA-58-like,}}$ one isolate with *bla*$_{\text{OXA-23-like}}$ and *bla*$_{\text{OXA-58-like,}}$ one isolate with *bla*$_{\text{NDM-1}}$, and 9 isolates with overexpression of intrinsic *bla*$_{\text{OXA-51}}$.

## Methods cont.

### MIC testing:

- Broth microdilution (BMD) testing in cation-adjusted Mueller-Hinton broth was performed in accordance with CLSI guidelines (2).
- The antimicrobial agents and concentration ranges tested were ERV, 0.015–16 mg/L; amikacin, 0.125–128 mg/L; colistin, 0.125-128mg/L; doxycycline, 0.06–32 mg/L; imipenem, 1–128 mg/L; levofloxacin, 0.125–64 mg/L; meropenem, 1–128 mg/L; minocycline, 0.06–64 mg/L; sulbactam, 0.125–128 mg/L; tigecycline, 0.06–32 mg/L; and tobramycin, 0.06–128 mg/L.
- MICs were interpreted according the CLSI guidelines except where indicated.

## Results

**Table 1. MIC distribution, MIC$_{50}$ and MIC$_{90}$ values of the 286 carbapenem-resistant *A. baumannii* isolates**

| Antimicrobial Agent | ≤0.06 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | ≥128 | MIC$_{50}$ | MIC$_{90}$ | MIC Range | | | %S | %I | %R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amikacin | | | | 4 | 11 | 11 | 11 | 3 | **15**[a] | 11 | 32 | 188 | ≥128 | ≥128 | 0.5 | - | ≥128 | 19.2 | 3.9 | 76.9 |
| Colistin | | | 1 | 51 | 149 | **47**[a] | 12 | 11 | 2 | 1 | 2 | 10 | 1 | 4 | 0.125 | - | ≥128 | 86.7 | - | 13.3 |
| Doxycycline | 3 | 7 | 7 | 13 | 33 | 21 | **5**[a] | 4 | 10 | 61 | 122[c] | | 32 | >32 | ≤ 0.06 | - | ≥64 | 67.5 | 1.4 | 31.1 |
| Eravacycline[b] | 11 | 20 | 45 | 147 | 53 | 9 | | 1 | | | | | 0.5 | 1 | ≤ 0.06 | - | 8 | - | - | - |
| Imipenem | | | | | | | 2 | 9 | 66 | 161 | 43 | 5 | 32 | 64 | 4 | - | 128 | 0.0 | 0.7 | 99.3 |
| Levofloxacin | | | 1 | | 1 | **5** | 32 | 87 | 127 | 15 | 13 | 5 | 16 | 32 | 0.25 | - | ≥128 | 2.4 | 11.2 | 86.4 |
| Meropenem | | | | | | **1**[a] | 2 | 18 | 36 | 88 | 106 | 35 | 32 | 128 | 2 | - | ≥128 | 0.3 | 0.7 | 99.0 |
| Minocycline | 10 | 5 | 12 | 37 | 33 | 21 | **66**[a] | 74 | 28 | | | | 4 | 8 | ≤ 0.06 | - | 16 | 64.3 | 25.9 | 9.8 |
| Sulbactam[b] | | | | | | 3 | 12 | 39 | 79 | 114 | 35 | 4 | 32 | 64 | 2 | - | ≥128 | - | - | - |
| Tigecycline[b] | | 3 | 23 | 42 | 140 | 59 | 18 | 1 | | | | | 1 | 2 | 0.125 | - | 8 | - | - | - |
| Tobramycin | | 2 | 23 | 38 | 15 | 5 | **4**[a] | 11 | 18 | 26 | 6 | 138 | 64 | ≥128 | 0.125 | - | ≥128 | 30.4 | 3.8 | 65.8 |

[a] susceptible breakpoint values are indicated in boldface; [b] no CLSI breakpoint available; [c] ≥ 64 mg/L

## Results cont.

- The majority of *A. baumannii* isolates apart from being resistant to carbepenems were also resistant to levofloxacin and aminoglycosides and had high sulbactam MICs. The resistance to colistin was 13%.
- The ERV MIC$_{50/90}$ values for all isolates were 0.5/1 mg/L. Comparatively, tigecycline, minocycline and doxycycline MIC$_{50/90}$ values were 1/2, 4/8, 32/>32 mg/L, respectively. Only one versus 19 strains had MICs of ≥4 µg/mL to eravacycline and tigecycline, respectively.

## References and Acknowledgements

1.Higgins PG et al. J Antimicrob Chemother. 2010; 65: 233-238

2.CLSI. M100-S25 Performance Standards for Antimicrobial Susceptibility Testing_25th Informational Supplement (2015).

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## Conclusions

- ERV was the most potent antimicrobial against *A. baumannii* isolates, including those that were resistant to sulbactam, imipenem/meropenem, levofloxacin, and amikacin/tobramycin, compared to other compounds.
- ERV has the potential to become a useful addition to the limited armamentarium of drugs that can be used to treat this problem pathogen.