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Surveillance of The *In Vitro* activity of Eravacycline and Comparators Against Clinical Isolates from Europe During 2017

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Introduction

Eravacycline is a fully-synthetic fluorocycline antibacterial of the tetracycline class that has recently received US and EU approval for the treatment of complicated intra-abdominal infections in patients ≥18 years of age. It retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection).

Eravacycline has shown activity against a broad range of Gram-negative, Gram-positive and anaerobic organisms.

In the present study, we report the *in vitro* activity of eravacycline and comparators against European Gram-negative clinical isolates collected in 2017.

Methods & Materials

Clinical isolates (1171 Enterobacterales & 222 *Acinetobacter baumannii*) from an on-going multi-infection surveillance study in Europe collected during 2017 were evaluated (Fig. 1).

Isolates came from intra-abdominal infections, respiratory-tract infections and urinary-tract infections (Table 1). The Enterobacterales tested are shown in Fig. 2.

MIC values were determined for eravacycline and comparators by CLSI broth microdilution methodology (1) and susceptibility was determined using EUCAST breakpoints, where available (2).

Table 1. Source of the isolates tested

Infection	Number (%)	
	Enterobacterales	*A. baumannii*
Intra-abdominal	471 (40%)	45 (20%)
Respiratory-tract	336 (31%)	131 (59%)
Urinary-tract	334 (29%)	46 (21%)
	1171 (100%)	222 (100%)

Results

Table 2. Susceptibility of Enterobacterales to Eravacycline & Comparators

Organism	Antimicrobial	Breakpoints (S|I|R)	All Enterobacterales [n=1171]							'Target' Enterobacterales with approval in Europe and USA [n=864][1]							C. freundii [n=121]							E. coli [n=189]							E. cloacae [n=216]						
			%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX
All Enterobacterales (see Fig. 3 for species breakdown) [n=1171]	Amikacin	≤8 | 16 | ≥32	95.8	1.5	2.7	1	4	≤ 0.25	> 64	96.8	1.7	1.5	1	4	≤ 0.25	> 64	97.5	1.7	0.8	1	2	0.5	32	96.3	3.2	0.5	2	4	≤ 0.25	> 64	95.8	1.9	2.3	1	2	≤ 0.25	> 64
	Aztreonam	≤1 | 2-4 | ≥8	74.8	2.6	22.6	0.12	> 16	≤ 0.03	> 16	72.0	2.6	25.5	0.12	> 16	≤ 0.03	> 16	70.3	3.3	26.5	0.25	> 16	≤ 0.03	> 16	76.7	3.2	20.1	0.12	> 16	≤ 0.03	> 16	59.7	2.3	38.0	0.25	> 16	≤ 0.03	> 16
	Cefepime	≤1 | 2-4 | ≥8	81.2	3.8	14.9	0.06	> 16	≤ 0.008	> 16	78.1	4.8	17.1	0.06	> 16	≤ 0.008	> 16	82.6	10.7	6.6	0.06	4	≤ 0.008	> 16	80.4	2.1	17.5	0.03	> 16	≤ 0.008	> 16	69.4	10.2	20.4	0.12	> 16	0.015	> 16
	Cefotaxime	≤1 | 2 | ≥4	73.6	1.0	25.4	0.12	> 64	≤ 0.015	> 64	71.9	0.8	27.3	0.12	> 64	≤ 0.015	> 64	68.6	0.8	30.6	0.12	64	≤ 0.015	> 64	76.7	0.0	23.3	0.06	> 64	≤ 0.015	> 64	55.6	2.8	41.7	0.5	> 64	≤ 0.015	> 64
	Ceftazidime	≤1 | 2-4 | ≥8	74.0	3.2	22.8	0.25	128	≤ 0.03	> 128	72.2	3.0	24.8	0.25	128	≤ 0.03	> 128	68.9	3.3	29.8	0.5	128	0.06	> 128	78.8	5.8	15.3	0.12	16	≤ 0.03	64	57.9	2.3	39.8	0.5	> 128	0.06	> 128
	Ceftriaxone	≤1 | 2 | ≥4	73.8	0.9	25.4	0.12	> 4	≤ 0.015	> 4	71.8	0.9	27.3	0.12	> 4	≤ 0.015	> 4	66.9	1.7	31.4	0.25	> 4	0.03	> 4	77.3	0.5	22.2	0.06	> 4	≤ 0.015	> 4	58.3	0.9	40.7	0.5	> 4	≤ 0.015	> 4
	Colistin	≤2 | – | ≥4	100.0	-	0.0	0.5	> 1	0.25	> 1	100.0	-	0.0	0.5	1	0.25	> 1	100.0	-	0.0	0.5	1	0.25	> 1	100.0	-	0.0	0.5	0.5	0.25	> 1	100.0	-	0.0	0.5	1	0.25	> 1
	Eravacycline	**≤0.5 | – | ≥1[2]**	**87.2**	**-**	**12.8**	**0.25**	**1**	**0.06**	**16**	**91.8**	**-**	**8.2**	**0.25**	**0.5**	**0.06**	**16**	**92.6**	**-**	**7.4**	**0.25**	**0.5**	**0.12**	**2**	**98.9**	**-**	**1.1**	**0.12**	**0.25**	**0.06**	**1**	**90.3**	**-**	**9.7**	**0.5**	**0.5**	**0.12**	**4**
	Ertapenem	≤0.5 | – | ≥1	92.1	-	7.9	0.015	0.5	≤ 0.002	> 2	91.8	-	8.2	0.015	0.5	≤ 0.002	> 2	96.7	-	3.3	0.015	0.25	0.004	> 2	100.0	-	0.0	0.008	0.03	≤ 0.002	0.25	83.3	-	16.7	0.06	1	0.008	> 2
	Gentamicin	≤2 | 4 | ≥8	89.0	0.9	10.1	0.25	8	≤ 0.12	> 16	88.0	0.5	11.6	0.25	16	≤ 0.12	> 16	93.4	0.0	6.6	0.25	0.5	≤ 0.12	> 16	91.5	0.0	8.5	0.5	1	≤ 0.12	> 16	81.9	1.4	16.7	0.25	> 16	≤ 0.12	> 16
	Levofloxacin	≤0.5 | 1 | ≥2	79.4	3.1	17.5	0.06	> 8	≤ 0.004	> 8	78.1	3.4	18.5	0.06	> 8	0.008	> 8	86.0	1.7	12.4	0.06	2	0.015	> 8	66.1	3.7	30.2	0.03	> 8	0.015	> 8	82.4	4.2	13.4	0.03	4	0.008	> 8
	Meropenem	≤2 | 4-8 | ≥16	95.6	4.4	0.0	0.03	0.12	0.008	> 4	96.0	4.1	0.0	0.03	0.12	0.008	> 4	97.5	2.5	0.0	0.03	0.06	0.008	> 4	100.0	0.0	0.0	0.015	0.03	0.008	0.06	96.3	3.7	0.0	0.03	0.12	0.008	> 4
	Minocycline	NB**	-	-	-	2	16	≤ 0.12	> 16	-	-	-	2	8	≤ 0.12	> 16	-	-	-	2	8	0.5	> 16	-	-	-	1	16	≤ 0.12	> 16	-	-	-	4	8	1	> 16
	Piperacillin-tazobactam	≤8 | 16 | ≥32	79.1	3.4	17.5	2	128	≤ 0.25	> 128	77.4	3.1	19.4	2	128	≤ 0.25	> 128	71.1	1.7	27.3	2	128	1	> 128	92.1	3.7	4.2	1	4	≤ 0.25	> 128	66.2	5.1	28.7	2	> 128	≤ 0.25	> 128
	Tetracycline	NB	-	-	-	1	> 64	≤ 0.25	> 64	-	-	-	1	> 64	≤ 0.25	> 64	-	-	-	1	> 64	≤ 0.25	> 64	-	-	-	2	> 64	≤ 0.25	> 64	-	-	-	2	64	0.5	> 64
	Tigecycline	≤0.5 | – | ≥1	67.7	-	32.3	0.5	2	0.12	32	71.0	-	29.1	0.5	2	0.12	32	69.4	-	30.6	0.5	2	0.25	4	92.6	-	7.4	0.25	0.5	0.12	4	55.1	-	44.9	0.5	2	0.25	8
	Trimethoprim Sulfa	≤2 | 4 | ≥8	80.8	0.6	18.6	≤ 0.06	> 4	≤ 0.06	> 4	78.8	0.4	20.8	≤ 0.06	> 4	≤ 0.06	> 4	85.1	0.0	14.9	≤ 0.06	> 4	≤ 0.06	> 4	72.0	1.1	27.0	≤ 0.06	> 4	≤ 0.06	> 4	80.6	0.0	19.4	0.12	> 4	≤ 0.06	> 4

Organism	Antimicrobial	Breakpoints (S|I|R)	K. oxytoca [n=171]							K. pneumoniae [n=167]							All ESBL [N=84]							E. coli, ESBL [N=39]							K. pneumoniae, ESBL [N=42]						
			%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX
	Amikacin	≤8 | 16 | ≥32	100.0	0.0	0.0	1	2	≤ 0.25	8	94.6	1.8	3.6	1	4	≤ 0.25	> 64	90.5	7.1	2.4	2	8	≤ 0.25	> 64	84.6	15.4	0.0	2	16	0.5	16	95.2	0.0	4.8	2	4	≤ 0.25	> 64
	Aztreonam	≤1 | 2-4 | ≥8	90.6	2.9	6.4	0.25	1	≤ 0.03	> 16	64.7	1.2	34.1	0.12	> 16	≤ 0.03	> 16	2.4	4.8	92.9	> 16	> 16	≤ 0.03	> 16	0.0	7.7	92.3	> 16	> 16	2	> 16	4.8	2.4	92.9	> 16	> 16	≤ 0.03	> 16
	Cefepime	≤1 | 2-4 | ≥8	96.5	0.6	2.9	0.03	0.12	≤ 0.008	> 16	64.7	0.6	34.7	0.06	> 16	≤ 0.008	> 16	4.8	6.0	89.3	> 16	> 16	0.12	> 16	5.1	10.3	84.6	> 16	> 16	0.5	> 16	4.8	0.0	95.2	> 16	> 16	0.12	> 16
	Cefotaxime	≤1 | 2 | ≥4	95.9	0.0	4.1	0.03	0.25	≤ 0.015	> 64	65.3	0.0	34.7	0.06	> 64	≤ 0.015	> 64	2.4	0.0	97.6	> 64	> 64	0.06	> 64	0.0	0.0	100.0	> 64	> 64	16	> 64	4.8	0.0	95.2	> 64	> 64	0.06	> 64
	Ceftazidime	≤1 | 2-4 | ≥8	95.9	1.2	2.9	0.12	0.5	≤ 0.03	> 128	62.9	2.4	34.7	0.25	> 128	≤ 0.03	> 128	7.1	15.5	77.4	32	> 128	0.5	> 128	12.8	25.6	61.5	8	64	0.5	64	2.4	4.8	92.9	64	> 128	1	> 128
	Ceftriaxone	≤1 | 2 | ≥4	93.6	1.2	5.3	0.06	0.5	≤ 0.015	> 4	64.1	0.6	35.3	0.12	> 4	≤ 0.015	> 4	2.4	0.0	97.6	> 4	> 4	0.12	> 4	0.0	0.0	100.0	> 4	> 4	> 4	> 4	4.8	0.0	95.2	> 4	> 4	0.12	> 4
	Colistin	≤2 | – | ≥4	100.0	-	0.0	0.5	1	0.25	> 1	100.0	-	0.0	0.5	> 1	0.25	> 1	100.0	-	0.0	0.5	0.5	0.25	> 1	100.0	-	0.0	0.5	0.5	0.25	1	100.0	-	0.0	0.5	1	0.25	> 1
	Eravacycline	**≤0.5 | – | ≥1[2]**	**97.1**	**-**	**2.9**	**0.12**	**0.25**	**0.06**	**16**	**79.6**	**-**	**20.4**	**0.25**	**1**	**0.12**	**8**	**86.9**	**-**	**13.1**	**0.25**	**1**	**0.06**	**4**	**100.0**	**-**	**0.0**	**0.12**	**0.5**	**0.06**	**0.5**	**73.8**	**-**	**26.2**	**0.5**	**1**	**0.25**	**4**
	Ertapenem	≤0.5 | – | ≥1	97.7	-	2.3	0.008	0.015	0.004	> 2	83.8	-	16.2	0.015	> 2	0.004	> 2	89.3	-	10.7	0.06	1	≤ 0.002	> 2	100.0	-	0.0	0.03	0.12	≤ 0.002	0.12	78.6	-	21.4	0.12	> 2	0.008	> 2
	Gentamicin	≤2 | 4 | ≥8	97.7	0.0	2.3	0.25	0.5	≤ 0.12	> 16	77.8	0.6	21.6	0.25	> 16	≤ 0.12	> 16	58.3	0.0	41.7	1	> 16	≤ 0.12	> 16	69.2	0.0	30.8	0.5	> 16	0.25	> 16	50.0	0.0	50.0	1	> 16	≤ 0.12	> 16
	Levofloxacin	≤0.5 | 1 | ≥2	95.3	0.6	4.1	0.03	0.12	0.015	> 8	62.9	6.0	31.1	0.25	> 8	0.015	> 8	20.2	6.0	73.8	8	> 8	0.015	> 8	20.5	2.6	76.9	> 8	> 8	0.015	> 8	19.1	9.5	71.4	8	> 8	0.03	> 8
	Meropenem	≤2 | 4-8 | ≥16	98.8	1.2	0.0	0.03	0.06	0.015	> 4	86.8	13.2	0.0	0.03	> 4	0.015	> 4	94.1	6.0	0.0	0.03	0.12	0.015	> 4	100.0	0.0	0.0	0.03	0.03	0.015	0.06	88.1	11.9	0.0	0.03	4	0.03	> 4
	Minocycline	NB	-	-	-	1	2	0.5	> 16	-	-	-	2	> 16	0.5	> 16	-	-	-	2	16	0.5	> 16	-	-	-	2	16	0.5	> 16	0.0	0.0	0.0	4	> 16	1	> 16
	Piperacillin-tazobactam	≤8 | 16 | ≥32	88.9	0.0	11.1	1	64	≤ 0.25	> 128	68.3	4.2	27.5	2	> 128	≤ 0.25	> 128	60.7	7.1	32.1	4	> 128	≤ 0.25	> 128	79.5	7.7	12.8	2	64	≤ 0.25	> 128	45.2	7.1	47.6	16	> 128	1	> 128
	Tetracycline	NB	-	-	-	0.5	2	≤ 0.25	> 64	-	-	-	2	> 64	0.5	> 64	-	-	-	64	> 64	0.5	> 64	-	-	-	> 64	> 64	1	> 64	-	-	-	8	> 64	0.5	> 64
	Tigecycline	≤0.5 | – | ≥1	90.6	-	9.4	0.5	0.5	0.25	32	47.9	-	52.1	1	2	0.25	16	65.5	-	34.5	0.5	2	0.12	8	94.9	-	5.1	0.25	0.5	0.12	1	35.7	-	64.3	1	4	0.25	8
	Trimethoprim Sulfa	≤2 | 4 | ≥8	94.7	0.0	5.3	≤ 0.06	0.12	≤ 0.06	> 4	63.5	0.6	35.9	0.25	> 4	≤ 0.06	> 4	29.8	2.4	67.9	> 4	> 4	≤ 0.06	> 4	48.7	2.6	48.7	4	> 4	≤ 0.06	> 4	9.5	2.4	88.1	> 4	> 4	≤ 0.06	> 4

* %S, percent susceptible, **NB, no defined breakpoint

1. Approved species for eravacycline are *C. freundii, E. cloacae, E. coli, K. oxytoca & K. pneumoniae*. 2. Eravacycline EUCAST breakpoints are for *E. coli* only but for comparative purposes have been applied to all Enterobacterales

Figure 1. Country distribution of (a) Enterobacterales & (b) *A. baumannii* isolates

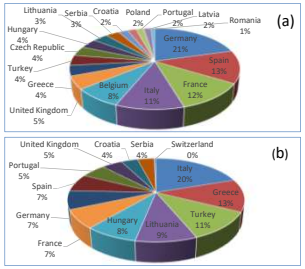

Figure 2. Breakdown of species of Enterobacterales tested

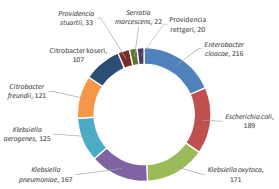

Figure 3. Comparison of Eravacycline susceptibility with Tigecycline susceptibility against Enterobacterales

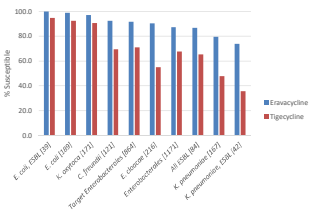

Table 3. Susceptibility of *A. baumannii* to Eravacycline and Comparators

Organism	Antimicrobial	Breakpoints (S|I|R)	A. baumannii [N=222]						
			%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX
	Amikacin	≤8 | 16 | ≥32	27.5	1.8	70.7	> 64	> 64	0.12	> 64
	Ampicillin-sulbactam	NB**	-	-	-	64	> 64	0.5	> 64
	Aztreonam	NB	-	-	-	> 64	> 64	2	> 64
	Cefepime	NB	-	-	-	64	> 64	0.12	> 64
	Ceftazidime	NB	-	-	-	> 64	> 64	0.5	> 64
	Ceftriaxone	NB	-	-	-	> 64	> 64	1	> 64
	Colistin	≤2 | – | ≥4	91.4	-	8.6	0.5	2	0.25	> 32
	Eravacycline	**NB**	**-**	**-**	**-**	**0.25**	**0.5**	**≤ 0.015**	**2**
	Gentamicin	≤4 | – | ≥8	27.5	-	72.5	> 64	> 64	0.06	> 64
	Levofloxacin	≤0.5 | 1 | ≥2	16.7	0.0	83.3	16	> 64	≤ 0.03	> 64
	Meropenem	≤2 | 4-8 | ≥16	20.7	2.7	76.6	64	> 64	0.06	> 64
	Minocycline	NB	-	-	-	4	16	≤ 0.03	> 64
	Piperacillin-tazobactam	NB	-	-	-	> 128	> 128	≤ 0.06	> 128
	Tetracycline	NB	-	-	-	> 64	> 64	0.5	> 64
	Tigecycline	NB	-	-	-	2	4	0.06	16
	Trimethoprim Sulfa	≤2 | 4 | ≥8	34.2	2.3	63.5	64	> 64	0.06	> 64

* %S, percent susceptible, **NB, no defined breakpoint

Results Summary

- Eravacycline showed good activity against Enterobacterales, including ESBL strains (Table 2).
- Isolates of Enterobacterales were more susceptible to eravacycline than tigecycline (Table 2 & Figure 3).
- Enterobacterales were also more susceptible to eravacycline than most other comparators, except colistin, amikacin and carbapenems (Table 2).
- Resistance was high for antibacterial agents against *A. baumannii*, except for colistin (Table 3). Based on MIC_{50} and MIC_{90} values, eravacycline was the most active agent against *A. baumannii* (Table 3).

Conclusions

Eravacycline demonstrated potent *in vitro* activity against a variety of clinically important Enterobacterales and *A. baumannii*.

References

1. CLSI, 2018. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; 11TH Ed. CLSI standard M07. CLSI, Wayne, PA 19087-1898 USA
2. The European Committee on Antimicrobial Susceptibility Testing, 2019. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0 http://www.eucast.org

Acknowledgments

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