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Global 2018 Surveillance of Eravacycline Against Gram-negative Pathogens, Including Multi-drug Resistant Isolates

Virgil Lijfrock[1], Steven Morgan[1], Sara Hwang[1], Ekaterina Efimova[1], Kenneth Lawrence[1], Stephen Hawser[2], Ian Morrissey[2]

[1]Tetraphase Pharmaceuticals, Watertown, MA; [2]IHMA Europe Sàrl, Monthey, Switzerland

Contact: IHMA Europe, Rte. de l'Ile-au-Bois 1A, 1870 Monthey, Switzerland

Contact: Tetraphase Pharmaceuticals Medical Information medinfo@tphase.com 617-715-3600

Introduction

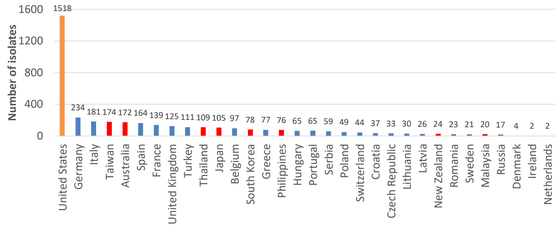
Eravacycline is a novel, fully-synthetic, fluorocycline antibiotic that is approved by the Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infections (cIAI) caused by susceptible microorganisms including *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, *K. oxytoca*, *Enterococcus faecalis*, *E. faecium*, *Staphylococcus aureus*, *Streptococcus anginosus* group, *Clostridium perfringens*, Bacteroides species, and *Parabacteroides distasonis* in patients 18 years or older. The current study evaluated the *in vitro* activity of eravacycline and comparators against Gram-negative pathogens collected worldwide as part of an ongoing global surveillance program.

Methods & Materials

Clinical *Enterobacteriaceae* and *Acinetobacter baumannii* isolates were collected in 2018 from hospitals in 32 countries. In brief, totals of 758, 1,605 and 1,518 were from the Asia/Pacific, Europe and USA regions. Minimum inhibitory concentration (MIC) results for eravacycline and comparators were determined by the Clinical and Laboratory Standards Institute (CLSI) methods (1). Antibiotic susceptibility was determined and interpreted following CLSI guidelines (2) except for eravacycline and tigecycline where FDA breakpoints were used (3). European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are available for eravacycline & tigecycline against *Escherichia coli* and tigecycline against *Citrobacter koseri* (4) and analysis using these was also performed for comparative purposes. Multi-drug-resistance (MDR) was defined as resistance (CLSI/FDA breakpoints) to ≥3 antibiotics from aztreonam, a carbapenem (meropenem or ertapenem), cefepime/cefotaxime/ceftazidime/ceftriaxone (any one), gentamicin, levofloxacin, piperacillin-tazobactam, tetracycline or tigecycline (5).

Results

Figure 1. Distribution of All Isolates by Country*



*Total of 3,881 isolates, Asia/Pacific (n=758), Europe (n=1,605) and the USA (n=1,518); Isolates from USA in orange, Asia-Pacific in red and Europe in blue

Table 1. Susceptibility of combined *Enterobacteriaceae* and MDR *Enterobacteriaceae* to Eravacycline and Comparators

Organism	Drug	%S*	MIC_{50}	MIC_{90}	MIN MIC	MAX MIC
Enterobacteriaceae (n=3,385)	Aztreonam	77.5	0.12	> 16	≤ 0.03	> 16
	Cefepime	88.2	0.06	4	≤ 0.008	> 16
	Cefotaxime	74.9	0.12	> 64	≤ 0.015	> 64
	Ceftazidime	78.3	0.25	128	≤ 0.03	> 128
	Ceftazidime-avibactam	99.0	0.12	0.5	≤ 0.03	> 8
	Ceftriaxone	74.6	0.12	> 4	≤ 0.015	> 4
	Colistin	NSB	0.25	0.5	≤ 0.03	> 8
	Eravacycline (FDA)	92.6	0.25	0.5	≤ 0.015	> 16
	Ertapenem	93.2	0.015	0.5	≤ 0.008	> 8
	Gentamicin	91.8	0.5	2	≤ 0.12	> 16
	Levofloxacin	84.4	0.06	4	≤ 0.004	> 4
	Meropenem	97.7	0.03	0.06	≤ 0.004	> 16
	Minocycline	85.6	2	8	≤ 0.12	> 16
	Piperacillin Tazobactam	81.8	2	128	≤ 0.25	> 128
	Tetracycline	81.1	1	> 16	≤ 0.25	> 16
	Tigecycline (FDA)	95.5	0.5	2	≤ 0.015	> 8
	Trimethoprim Sulfa	83.2	0.12	> 4	≤ 0.06	> 4
MDR *Enterobacteriaceae* (n=681)	Aztreonam	16.6	> 16	> 16	≤ 0.03	> 16
	Cefepime	44.8	4	> 16	0.03	> 16
	Cefotaxime	13.5	> 64	> 64	≤ 0.015	> 64
	Ceftazidime	22.6	64	> 128	0.12	> 128
	Ceftazidime-avibactam	95.0	0.25	1	≤ 0.03	> 8
	Ceftriaxone	12.0	> 4	> 4	0.03	> 4
	Colistin	NSB	0.25	1	0.06	> 8
	Eravacycline (FDA)	80.9	0.25	1	0.06	> 16
	Ertapenem	71.4	0.25	8	≤ 0.008	> 8
	Gentamicin	62.4	1	> 16	≤ 0.12	> 16
	Levofloxacin	40.5	1	> 4	≤ 0.004	> 4
	Meropenem	89.1	0.06	2	0.015	> 16
	Minocycline	62.4	4	> 16	0.25	> 16
	Piperacillin Tazobactam	38.5	64	> 128	1	> 128
	Tetracycline	43.5	16	> 16	≤ 0.25	> 16
	Tigecycline (FDA)	91.5	0.5	2	0.12	> 8
	Trimethoprim Sulfa	42.1	> 4	> 4	≤ 0.06	> 4

Table 2. Susceptibility of individual species of *Enterobacteriaceae* to Eravacycline and Comparators

Organism	Drug	%S*	MIC_{50}	MIC_{90}	MIN MIC	MAX MIC
Klebsiella pneumoniae (n=533)	Aztreonam	74.5	0.12	> 16	≤ 0.03	> 16
	Cefepime	75.2	0.06	> 16	≤ 0.008	> 16
	Cefotaxime	73.9	0.06	> 64	≤ 0.015	> 64
	Ceftazidime	73.9	0.25	128	0.06	> 128
	Ceftazidime-avibactam	97.6	0.12	0.5	≤ 0.03	> 8
	Ceftriaxone	73.6	0.06	> 4	≤ 0.015	> 4
	Colistin	NSB	0.25	0.5	0.12	> 8
	Eravacycline (FDA)	84.1	0.25	1	0.12	> 16
	Ertapenem	90.4	0.015	0.5	≤ 0.008	> 8
	Gentamicin	83.1	0.25	> 16	≤ 0.12	> 16
	Levofloxacin	72.8	0.12	> 4	≤ 0.004	> 4
	Meropenem	93.1	0.03	0.12	0.015	> 16
	Minocycline	73.7	2	> 16	0.5	> 16
	Piperacillin Tazobactam	79.9	4	> 128	≤ 0.25	> 128
	Tetracycline	71.5	2	> 16	0.5	> 16
	Tigecycline (FDA)	91.2	0.5	2	0.25	> 8
	Trimethoprim Sulfa	72.1	0.25	> 4	≤ 0.06	> 4
Escherichia coli (n=515)	Aztreonam	78.8	0.12	> 16	≤ 0.03	> 16
	Cefepime	80.8	0.06	> 16	≤ 0.008	> 16
	Cefotaxime	76.3	0.06	> 64	≤ 0.015	> 64
	Ceftazidime	81.2	0.25	32	0.06	> 128
	Ceftazidime-avibactam	100.0	0.06	0.25	≤ 0.03	8
	Ceftriaxone	76.7	0.06	> 4	≤ 0.015	> 4
	Colistin	NSB	0.25	0.5	0.03	4
	Eravacycline (FDA)	98.8	0.12	0.25	≤ 0.015	2
	Eravacycline (EUCAST)	98.8	0.12	0.25	≤ 0.015	2
	Ertapenem	98.1	0.015	0.06	≤ 0.008	> 8
	Gentamicin	87.6	0.5	> 16	≤ 0.12	> 16
	Levofloxacin	66.0	0.12	> 4	≤ 0.004	> 4
	Meropenem	99.6	0.015	0.03	≤ 0.004	8
	Minocycline	82.1	1	16	≤ 0.12	> 16
	Piperacillin Tazobactam	89.9	2	32	≤ 0.25	> 128
	Tetracycline	57.5	2	> 16	0.5	> 16
	Tigecycline (FDA)	99.2	0.25	1	≤ 0.015	4
	Tigecycline (EUCAST)	85.1				
	Trimethoprim Sulfa	63.7	0.12	> 4	≤ 0.06	> 4
Enterobacter cloacae (n-508)	Aztreonam	68.5	0.25	> 16	≤ 0.03	> 16
	Cefepime	83.7	0.12	4	≤ 0.008	> 16
	Cefotaxime	61.2	0.5	> 64	≤ 0.015	> 64
	Ceftazidime	67.1	0.5	128	≤ 0.03	> 128
	Ceftazidime-avibactam	98.0	0.25	0.5	≤ 0.03	> 8
	Ceftriaxone	64.4	0.5	> 4	≤ 0.015	> 4
	Colistin	NSB	0.25	2	≤ 0.03	> 8
	Eravacycline (FDA)	89.8	0.25	1	0.06	8
	Ertapenem	81.3	0.06	1	≤ 0.008	> 8
	Gentamicin	92.9	0.5	1	≤ 0.12	> 16
	Levofloxacin	86.6	0.06	1	≤ 0.004	> 4
	Meropenem	96.3	0.03	0.12	0.008	> 16
	Minocycline	84.5	2	16	0.5	> 16
	Piperacillin Tazobactam	76.0	4	128	≤ 0.25	> 128
	Tetracycline	84.1	2	> 16	0.5	> 16
	Tigecycline (FDA)	92.7	0.5	2	0.25	> 8
	Trimethoprim Sulfa	85.8	0.12	> 4	≤ 0.06	> 4
Klebsiella oxytoca (n=508)	Aztreonam	84.8	0.25	16	≤ 0.03	> 16
	Cefepime	92.7	0.03	1	≤ 0.008	> 16
	Cefotaxime	89.8	0.06	2	≤ 0.015	> 64
	Ceftazidime	94.9	0.12	1	≤ 0.03	> 128
	Ceftazidime-avibactam	98.8	0.12	0.25	≤ 0.03	> 8
	Ceftriaxone	83.7	0.06	> 4	≤ 0.015	> 4
	Colistin	NSB	0.25	0.5	0.12	> 8
	Eravacycline (FDA)	95.1	0.25	0.25	0.06	4
	Ertapenem	98.6	0.015	0.03	≤ 0.008	> 8
	Gentamicin	95.1	0.5	1	≤ 0.12	> 16
	Levofloxacin	94.3	0.06	0.5	0.015	> 4
	Meropenem	98.8	0.03	0.03	0.015	> 16
	Minocycline	91.1	1	4	≤ 0.12	> 16
	Piperacillin Tazobactam	84.5	2	> 128	≤ 0.25	> 128
	Tetracycline	90.0	1	8	≤ 0.25	> 16
	Tigecycline (FDA)	97.1	0.25	2	0.12	4
	Trimethoprim Sulfa	90.6	0.12	1	≤ 0.06	> 4
Klebsiella aerogenes (n=494)	Aztreonam	73.3	0.25	> 16	≤ 0.03	> 16
	Cefepime	97.6	0.06	0.5	0.015	> 16
	Cefotaxime	66.0	0.25	32	≤ 0.015	> 64
	Ceftazidime	70.0	0.5	64	0.06	> 128
	Ceftazidime-avibactam	100.0	0.12	0.5	≤ 0.03	8
	Ceftriaxone	66.0	0.12	> 4	≤ 0.015	> 4
	Colistin	NSB	0.25	0.5	0.06	8
	Eravacycline (FDA)	91.1	0.25	0.5	0.12	4
	Ertapenem	91.9	0.12	0.5	≤ 0.008	> 8
	Gentamicin	97.8	0.5	1	≤ 0.12	> 16
	Levofloxacin	91.9	0.06	0.5	0.015	> 4
	Meropenem	98.6	0.06	0.12	0.015	16
	Minocycline	88.9	2	8	0.5	> 16
	Piperacillin Tazobactam	73.7	4	64	≤ 0.25	> 128
	Tetracycline	88.5	1	8	0.5	> 16
	Tigecycline (FDA)	93.9	0.5	2	≤ 0.015	8
	Trimethoprim Sulfa	96.2	0.12	0.5	≤ 0.06	> 4
Citrobacter freundii (n=462)	Aztreonam	71.4	0.25	> 16	≤ 0.03	> 16
	Cefepime	93.3	0.06	2	0.015	> 16
	Cefotaxime	66.0	0.25	64	0.06	> 64
	Ceftazidime	69.1	0.5	> 128	0.12	> 128
	Ceftazidime-avibactam	98.9	0.25	0.5	0.06	> 8
	Ceftriaxone	66.2	0.25	> 4	0.03	> 4
	Colistin	NSB	0.5	0.5	0.06	4
	Eravacycline (FDA)	92.9	0.25	0.5	0.06	4
	Ertapenem	95.2	0.015	0.5	≤ 0.008	> 8
	Gentamicin	90.9	0.5	2	≤ 0.12	> 16
	Levofloxacin	84.2	0.12	1	0.008	> 4
	Meropenem	98.7	0.03	0.06	0.015	> 16
	Minocycline	85.9	2	8	0.25	> 16
	Piperacillin Tazobactam	75.8	4	128	0.5	> 128
	Tetracycline	85.7	1	> 16	0.5	> 16
	Tigecycline (FDA)	97.6	0.5	2	0.12	8
	Trimethoprim Sulfa	82.9	0.06	> 4	≤ 0.06	> 4
Citrobacter koseri (n=365)	Aztreonam	95.9	0.06	0.25	≤ 0.03	> 16
	Cefepime	98.4	0.03	0.12	0.015	> 16
	Cefotaxime	95.6	0.06	0.5	≤ 0.015	> 64
	Ceftazidime	96.2	0.12	1	0.06	> 128
	Ceftazidime-avibactam	99.7	0.12	0.25	≤ 0.03	> 8
	Ceftriaxone	96.7	0.06	0.25	≤ 0.015	> 4
	Colistin	NSB	0.25	0.25	0.12	1
	Eravacycline (FDA)	98.6	0.25	0.25	0.12	1
	Ertapenem	98.9	0.008	0.015	≤ 0.008	4
	Gentamicin	97.5	0.25	0.5	≤ 0.12	> 16
	Levofloxacin	97.8	0.03	0.12	0.008	> 4
	Meropenem	100.0	0.015	0.03	0.008	0.5
	Minocycline	96.4	1	4	0.25	> 16
	Piperacillin Tazobactam	95.9	2	16	0.5	> 128
	Tetracycline	96.2	1	4	0.5	> 16
	Tigecycline (FDA)	97.8	0.25	1	0.12	4
	Tigecycline (EUCAST)	82.2				
	Trimethoprim Sulfa	95.9	0.12	0.25	≤ 0.06	> 4

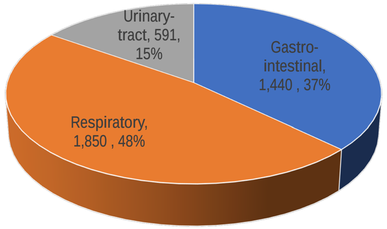
*%S, percent susceptible; MIC_{50} = concentration required to inhibit 50% of the population; MIC_{90} = concentration required to inhibit 90% of the population; NSB, colistin does not have a susceptible breakpoint.

Table 3. Susceptibility of *Acinetobacter baumannii* and carbapenem-resistant *A. baumannii* (CRAB) to Eravacycline and Comparators

Organism	Drug	%S*	MIC_{50}	MIC_{90}	MIN MIC	MAX MIC
Acinetobacter baumannii (n=496)	Amikacin	55.2	8	> 64	≤ 0.5	> 64
	Ampicillin Sulbactam	42.5	32	> 64	≤ 1	> 64
	Aztreonam	NB	64	> 64	2	> 64
	Cefepime	34.1	64	> 64	≤ 0.25	> 64
	Ceftazidime	39.5	64	> 64	1	> 64
	Ceftriaxone	18.2	> 64	> 64	1	> 64
	Colistin	NSB	0.5	1	≤ 0.12	> 8
	Eravacycline	NB	0.5	1	≤ 0.015	4
	Gentamicin	44.2	16	> 16	≤ 0.12	> 16
	Levofloxacin	40.3	8	> 32	≤ 0.12	> 32
	Meropenem	42.5	> 16	> 16	≤ 0.12	> 16
	Minocycline	66.9	1	16	≤ 0.12	> 32
	Piperacillin Tazobactam	35.9	> 128	> 128	≤ 0.12	> 128
	Tetracycline	36.9	16	> 32	≤ 0.12	> 32
	Tigecycline	NB	2	4	0.03	> 4
	Trimethoprim Sulfa	47.4	4	> 32	≤ 0.06	> 32
CRAB (n=280)	Amikacin	23.2	> 64	> 64	1	> 64
	Ampicillin Sulbactam	3.9	64	> 64	4	> 64
	Aztreonam	NB	64	> 64	16	> 64
	Cefepime	1.1	> 64	> 64	4	> 64
	Ceftazidime	3.6	> 64	> 64	4	> 64
	Ceftriaxone	0.4	> 64	> 64	8	> 64
	Colistin	NSB	0.5	2	≤ 0.12	> 8
	Eravacycline	NB	0.5	1	0.03	4
	Gentamicin	12.9	> 16	> 16	0.25	> 16
	Levofloxacin	2.9	16	> 32	≤ 0.12	> 32
	Meropenem	0.0	> 16	> 16	8	> 16
	Minocycline	45.4	8	16	≤ 0.12	> 32
	Piperacillin Tazobactam	1.8	> 128	> 128	≤ 0.12	> 128
	Tetracycline	6.4	> 32	> 32	1	> 32
	Tigecycline	NB	2	4	0.12	> 4
	Trimethoprim Sulfa	18.6	> 32	> 32	≤ 0.06	> 32

*%S, percent susceptible; MIC_{50} = concentration required to inhibit 50% of the population; MIC_{90} = concentration required to inhibit 90% of the population; NSB, colistin does not have a susceptible breakpoint; NB, no defined breakpoints.

Figure 2. Number and Percent of Isolates by Infection Source



Summary

- Eravacycline exhibited excellent *in vitro* activity against the combined *Enterobacteriaceae* with 92.6% susceptibility overall ranging from 84.1% in *K. pneumoniae* to 98.8% in *E. coli* and remained more active against MDR *Enterobacteriaceae* than most other agents.
- FDA breakpoints are significantly lower for eravacycline (set in 2018) compared to tigecycline (set in 2005), which may reflect differences in breakpoint setting over the years. More up to date EUCAST breakpoints are available for both agents against *E. coli* and tigecycline only against *C. koseri*. Although susceptibility of *E. coli* to eravacycline and tigecycline was similar by FDA breakpoints (98.8% vs 99.2%), susceptibility to eravacycline was higher than tigecycline when analyzing the data using EUCAST breakpoints (98.8% vs 85.1%). Similarly, tigecycline susceptibility in *C. koseri* by FDA breakpoints was 98.6% compared to 82.2% using EUCAST breakpoints.
- Interpretative criteria are not available for eravacycline or tigecycline against *A. baumannii* but MIC_{50} and MIC_{90} values for eravacycline were the lowest of the drugs tested (0.5 and 1 µg/ml, respectively) along with colistin. MIC_{50} and MIC_{90} values for tigecycline were 4-times higher than that of eravacycline versus *A. baumannii*. The activity of eravacycline was retained against CRAB.

Conclusion

Eravacycline demonstrated potent *in vitro* activity against *Enterobacteriaceae* and *A. baumannii* collected worldwide, many of which were susceptible to eravacycline.

Further surveillance monitoring is warranted and interpretation using different regulatory criteria should continue to be adopted for comparative purposes.

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Acknowledgments

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