

# Activity of Eravacycline and Comparators Against 15,872 Bacterial Pathogens Isolated from Patients Receiving Care in Canadian Hospitals: CANWARD 2014-18

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## Introduction

Eravacycline is a synthetic, broad-spectrum intravenous fluorocycline antibiotic for the treatment of multidrug-resistant infections [1]. It has completed Phase 3 clinical trials for the treatment of complicated intra-abdominal infections (cIAI) [1,2] and has received FDA approval for this indication. The activity of eravacycline was compared to comparators including meropenem (MER) and piperacillin-tazobactam (PTZ) against Gram-negative and Gram-positive pathogens causing infections in Canadian hospitals.

The purpose of this study was to determine the *in vitro* activity of eravacycline along with comparators versus Gram-negative and Gram-positive pathogens isolated from patients in Canadian hospitals from January 2014 to October 2018.

## Materials and Methods

### Study Background and Bacterial Isolates

The isolates tested in this study were obtained from January 2014 to October 2018, inclusive, from an ongoing cross-Canada surveillance study (CANWARD; www.can-r.ca) organized by the investigators [3]. The goal of the CANWARD study was to assess pathogens and antimicrobial resistance patterns associated with lower respiratory tract, skin/skin structure, urinary, and bacteremic infections in Canadian patients on medical wards, surgical wards, intensive care units, and presenting to emergency rooms and hospital clinics [3]. All isolates of MRSA were typed using staphylococcal protein A (*spa*) typing to assess whether the isolates were community-associated or healthcare-associated [3]. Isolates with a *spa* type associated with CMRSA7 or CMRSA10 were considered CA-MRSA. Isolates with a *spa* type associated with CMRSA1, CMRSA2, CMRSA4, CMRSA5, CMRSA3/6, CMRSA8 or CMRSA9 were considered HA-MRSA [3].

Potential *E. coli* or *Klebsiella* spp. ESBL-producers were identified as isolates with a ceftriaxone and/or ceftazidime MIC of 1 µg/mL or greater and confirmed using the CLSI double disk diffusion method, as previously described [3].

### Antimicrobial Susceptibility Testing Methodology

Isolates were tested for antimicrobial susceptibilities using in-house prepared (Department of Clinical Microbiology, Health Sciences Centre, Winnipeg, Canada) 96-well broth microdilution panels according to CLSI (2018) guidelines [3,4]. The antimicrobial agents tested were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made, as described by the CLSI [4] in cation-adjusted Mueller-Hinton broth (MHB). Following 2 subcultures from frozen stock, the MICs of the antimicrobial agents for the isolates were determined by the CLSI broth microdilution method. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC organisms including: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, and *P. aeruginosa* ATCC 27853. MICs for eravacycline and tigecycline were interpreted using EUCAST breakpoints. MICs for all other comparator were interpreted using CLSI breakpoints [5].

## Acknowledgements

The authors would like to thank the participating CANWARD centres, investigators and laboratory site staff for their support. Financial support for the CANWARD study was provided in part by the University of Manitoba, the National Microbiology Laboratory, and Tetrphase Inc.

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## Results

Table 1. *In vitro* activities of eravacycline and comparators versus Gram-positive cocci

Organism (no. tested)/ antimicrobial agent	MIC (µg/mL)			% S	% I	% R
	50%	90%	Range			
<b>Staphylococcus aureus</b> MSSA (2865)						
Eravacycline <sup>a</sup>	0.06	0.12	≤ 0.015 - 1	99.1		0.9
Ceftazidime	16	> 32	2 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	0.12	0.25	≤ 0.03 - > 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	≤ 1	2	≤ 1 - 64	NA <sup>b</sup>	NA	NA
Ceftriaxone	4	4	≤ 0.25 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	0.5	2	≤ 0.06 - > 16	87.4	3.2	9.4
Tigecycline <sup>a</sup>	0.12	0.25	≤ 0.03 - 2	99.6		0.4
<b>Staphylococcus aureus</b> MRSA (663)						
Eravacycline <sup>a</sup>	0.06	0.25	≤ 0.015 - 1	92.9		7.1
Ceftazidime	> 32	> 32	16 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	4	32	0.12 - > 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	32	128	≤ 1 - 512	NA <sup>b</sup>	NA	NA
Ceftriaxone	> 64	> 64	4 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	16	> 16	≤ 0.06 - > 16	25.3	0.3	74.4
Tigecycline <sup>a</sup>	0.25	0.5	≤ 0.03 - 2	97.4		2.6
<b>CA-MRSA (311)</b>						
Eravacycline <sup>a</sup>	0.06	0.12	≤ 0.015 - 0.5	99.4		0.6
Ceftazidime	> 32	> 32	16 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	4	8	0.12 - > 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	32	64	≤ 1 - 512	NA <sup>b</sup>	NA	NA
Ceftriaxone	64	> 64	8 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	16	> 16	≤ 0.06 - > 16	29.3	0.6	70.1
Tigecycline <sup>a</sup>	0.12	0.25	≤ 0.03 - 1	99.7		0.3
<b>HA-MRSA (318)</b>						
Eravacycline <sup>a</sup>	0.12	0.5	≤ 0.015 - 1	86.2		13.8
Ceftazidime	> 32	> 32	16 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	16	> 32	0.12 - > 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	64	128	≤ 1 - 256	NA <sup>b</sup>	NA	NA
Ceftriaxone	> 64	> 64	4 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	> 16	> 16	0.25 - > 16	15.1		84.9
Tigecycline <sup>a</sup>	0.25	0.5	≤ 0.03 - 2	95.0		5.0
<b>Staphylococcus epidermidis</b> (372)						
Eravacycline	0.12	0.5	≤ 0.015 - 2	NA <sup>b</sup>	NA	NA
Ceftazidime	16	> 32	1 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	1	16	≤ 0.03 - > 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	≤ 1	4	≤ 1 - 128	NA <sup>b</sup>	NA	NA
Ceftriaxone	8	64	≤ 0.25 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	1	> 16	≤ 0.06 - > 16	50.5	1.1	48.4
Tigecycline	0.12	0.25	≤ 0.03 - 1	NA <sup>b</sup>	NA	NA
<b>Enterococcus faecalis</b> (475)						
Eravacycline <sup>a</sup>	0.06	0.12	≤ 0.015 - 0.25	99.6		0.4
Ceftazidime	> 32	> 32	16 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	4	8	0.25 - 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	4	4	≤ 1 - > 512	NA <sup>b</sup>	NA	NA
Ceftriaxone	> 64	> 64	0.5 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	1	> 16	≤ 0.06 - > 16	71.4	11.6	17.1
Tigecycline <sup>a</sup>	0.12	0.25	≤ 0.03 - 1	98.5		1.5

Organism (no. tested)/ antimicrobial agent	MIC (µg/mL)			% S	% I	% R
	50%	90%	Range			
<b>Enterococcus faecium</b> (213)						
Eravacycline <sup>a</sup>	0.06	0.12	≤ 0.015 - 0.5	99.1		0.9
Ceftazidime	> 32	> 32	16 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	> 32	> 32	1 - > 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	> 512	> 512	≤ 1 - > 512	NA <sup>b</sup>	NA	NA
Ceftriaxone	> 64	> 64	0.5 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	> 16	> 16	0.5 - > 16	6.1	0.9	93.0
Tigecycline <sup>a</sup>	0.12	0.12	≤ 0.03 - 0.5	99.1		0.9
<b>VRE (50)</b>						
Eravacycline <sup>a</sup>	0.06	0.12	≤ 0.015 - 0.5	98.0		2.0
Ceftazidime	> 32	> 32	> 32 - > 32	NA <sup>b</sup>	NA	NA
Meropenem	> 32	> 32	> 32 - > 32	NA <sup>b</sup>	NA	NA
Piperacillin-Tazobactam	> 512	> 512	512 - > 512	NA <sup>b</sup>	NA	NA
Ceftriaxone	> 64	> 64	> 64 - > 64	NA <sup>b</sup>	NA	NA
Ciprofloxacin	> 16	> 16	16 - > 16			100
Tigecycline <sup>a</sup>	0.12	0.12	≤ 0.03 - 0.5	98.0		2.0
<b>Streptococcus agalactiae</b> (255)						
Eravacycline	0.03	0.06	≤ 0.004 - 0.06	NA <sup>b</sup>	NA	NA
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - 0.12	100		
Piperacillin-Tazobactam	≤ 1	≤ 1	≤ 1 - ≤ 1	NA <sup>b</sup>	NA	NA
Ceftriaxone	≤ 0.12	≤ 0.12	≤ 0.12 - 0.5	100		
Ciprofloxacin	0.5	1	0.25 - > 16	NA <sup>b</sup>	NA	NA
Tigecycline <sup>a</sup>	0.06	0.12	≤ 0.015 - 0.12	100		0
<b>Streptococcus pneumoniae</b> (634)						
Eravacycline	0.015	0.015	≤ 0.004 - 0.12	NA <sup>b</sup>	NA	NA
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - 1	94.6	3.8	1.6
Piperacillin-Tazobactam	≤ 1	≤ 1	≤ 1 - 4	NA <sup>b</sup>	NA	NA
Ceftriaxone	≤ 0.12	0.25	≤ 0.12 - 1	100		
Ciprofloxacin	1	2	≤ 0.06 - > 16	99.1		0.9
Tigecycline	0.03	0.03	≤ 0.015 - 0.12	NA <sup>b</sup>	NA	NA
<b>Streptococcus pneumoniae</b> PenR (28)						
Eravacycline	0.015	0.03	≤ 0.004 - 0.03	NA <sup>b</sup>	NA	NA
Meropenem	0.5	1	≤ 0.06 - 1	28.6	39.3	32.1
Piperacillin-Tazobactam	4	4	2 - 4	NA <sup>b</sup>	NA	NA
Ceftriaxone	1	1	0.25 - 1	100		
Ciprofloxacin	2	2	0.5 - 8	92.9		7.1
Tigecycline	0.03	0.03	≤ 0.015 - 0.06	NA <sup>b</sup>	NA	NA
<b>Streptococcus pyogenes</b> (212)						
Eravacycline	0.03	0.03	≤ 0.004 - 0.12	NA <sup>b</sup>	NA	NA
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - 0.25	100		
Piperacillin-Tazobactam	≤ 1	≤ 1	≤ 1 - 4	NA <sup>b</sup>	NA	NA
Ceftriaxone	≤ 0.12	≤ 0.12	≤ 0.12 - 0.25	100		
Ciprofloxacin	0.5	1	0.12 - > 16	NA <sup>b</sup>	NA	NA
Tigecycline <sup>a</sup>	0.03	0.06	≤ 0.015 - 0.25	99.5		0.5

CA-MRSA – community associated MRSA; HA-MRSA – healthcare associated MRSA; VRE – vancomycin resistant enterococcus; S, susceptible; I, intermediate; R, resistant

<sup>a</sup> Interpretative breakpoints defined by EUCAST (eravacycline, tigecycline) where applicable.  
<sup>b</sup> NA – not available.

Table 3. Distribution of eravacycline MICs versus Gram-positive organisms

Organism agent	Number of isolates for which the eravacycline MIC (µg/mL) was:											Total		
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16		32	≥64
<i>S. aureus</i> MSSA	25	438	1482	828	66	20	6							2865
<i>S. aureus</i> MRSA	4	61	294	221	36	34		13						663
CA-MRSA	1	32	157	127	12	2								311
HA-MRSA	1	28	127	97	19	31		13						318
<i>S. epidermidis</i>	23	80	82	66	76	38		6	1					372
<i>E. faecalis</i>	19	108	226	120	2									475
<i>E. faecium</i>	15	80	95	21	1	1								213
VRE	3	21	16	9										50
<i>S. agalactiae</i>	28 <sup>a</sup>	161	66											255
<i>S. pneumoniae</i>	584 <sup>a</sup>	48	1	1										634
<i>S. pneumoniae</i> PenR	23 <sup>a</sup>	5												28
<i>S. pyogenes</i>	80 <sup>a</sup>	120	11	1										212

<sup>a</sup> Lowest dilution tested

Table 4. Distribution of eravacycline MICs versus Gram-negative organisms

Organism agent	Number of isolates for which the eravacycline MIC (µg/mL) was:											Total		
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16		32	≥64
<i>E. coli</i> ALL	2	183	905	1361	475	64	3							2993
<i>E. coli</i> ESBL pos	13	47	131	127	25	1								344
<i>E. coli</i> ESBL neg	2	170	858	1230	347	39	2							2648
<i>K. pneumoniae</i> ALL	4	18	322	512	85	40	16	2		2 <sup>b</sup>				1001
<i>K. pneumoniae</i> ESBL pos					14	12	5							77
<i>E. cloacae</i>	1	2	11	104	263	67	16	8	5					477
<i>K. aerogenes</i>			2	29	56	4	3	1						95
<i>S. marcescens</i>				11	116	106	23	3						