

# Prediction of Sulopenem Activity Against *Enterobacteriaceae* Using Ertapenem as a Surrogate

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## ABSTRACT

**Background:** Sulopenem is a thiopenem antibiotic with oral and parenteral formulations, which is stable against hydrolytic attack by many  $\beta$ -lactamases, including extended spectrum  $\beta$ -lactamase (ESBL) and AmpC enzymes, that is being developed for the treatment of infections associated with common hospital and community pathogens. There are currently no established susceptibility interpretive criteria for sulopenem. Anticipating the delayed introduction of sulopenem into established antimicrobial susceptibility testing devices, we evaluated the ability of ertapenem to function as a surrogate for predicting in vitro sulopenem susceptibility.

**Materials/methods:** Sulopenem and ertapenem were tested for in vitro activity against 824 recent (2015-2016) *Enterobacteriaceae* urinary tract infection (UTI) isolates collected from patients in Europe and North America through the SENTRY Antimicrobial Surveillance Program. Reference broth microdilution susceptibility testing was conducted per CLSI guidelines using cation-adjusted Mueller-Hinton broth. For analysis purposes, CLSI ertapenem breakpoint interpretive criteria were applied to sulopenem.

**Results:** Sulopenem and ertapenem both achieved inhibition of 95% of *Enterobacteriaceae* at  $\leq 0.5$   $\mu\text{g/mL}$ , with  $\text{MIC}_{50/90}$  values of 0.06/0.25  $\mu\text{g/mL}$  and 0.008/0.12  $\mu\text{g/mL}$  respectively. As shown in the scattergram plot, a total of 800/824 (97.1%) sulopenem MIC values correlated with ertapenem susceptibility categories. Nine isolates (1.1%) that were susceptible to ertapenem had a sulopenem MIC  $>0.5$   $\mu\text{g/mL}$  and 13 isolates (1.6%) with an MIC  $\leq 0.5$   $\mu\text{g/mL}$  to sulopenem were resistant to ertapenem.

Sulopenem MIC ( $\mu\text{g/mL}$ )	Ertapenem MIC ( $\mu\text{g/mL}$ )											# at MIC
	<0.008	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>2	
>2											14	14
2										1	2	6
1					1	4			3	2	2	10
0.5			9	1	2	2	1	1	4	4		24
0.25		20	25	6	4	7	8	4	1			75
0.12		26	17	5	11	7	7	9				82
0.06		151	63	30	20	13	7	3				287
0.03	3	243	50	19	2	2						319
0.015	3	4										7
0.008												
<0.008												
Grand Total	6	444	164	61	36	32	22	25	10	6	18	824

**Conclusions:** While ertapenem activity is generally two tube dilutions lower than sulopenem at the lower end of the MIC values distribution, in vitro activity around the breakpoint for ertapenem is similar. Once clinical breakpoints have been established for sulopenem, ertapenem in vitro testing may serve as a useful surrogate, pending inclusion of sulopenem in antimicrobial susceptibility testing devices.

## INTRODUCTION

- Sulopenem is a thiopenem antibiotic with oral and IV formulations
  - Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins
  - Potent activity against *Enterobacteriaceae*
    - Including ESBLs and AmpC-type  $\beta$ -lactamases
  - Being developed for the treatment of urinary tract and intra-abdominal infections
- Similar to other new antimicrobial agents, diagnostic devices to test susceptibility to sulopenem may not be commercially available at the time of regulatory approval.
- We evaluated the ability of ertapenem to serve as a possible surrogate test to predict sulopenem susceptibility in this analysis

## METHODS

- 824 *Enterobacteriaceae* isolates from a contemporary collection of isolates (2015-2016) from patients in Europe and North America with urinary tract infections tested.
- Reference broth microdilution susceptibility testing was conducted according to Clinical and Laboratory Standards Institute (CLSI M07-A10, 2015) guidelines using cation-adjusted Mueller-Hinton broth (CA-MHB).
- Quality control ranges for bacterial reference strains (Table 1) and interpretive criteria for the comparator compounds tested were as published in CLSI M100-S27 (2017).
- Antimicrobial agents tested included the following compounds and dilution ranges:
  - Sulopenem (12 dilutions; 0.004–8  $\mu\text{g/mL}$ )
  - Ertapenem (12 dilutions; 0.001–2  $\mu\text{g/mL}$ )

## RESULTS

**Table 1:** Summary of sulopenem and ertapenem when tested against quality control reference strains ( $\mu\text{g/mL}$ )

Organism / drug (no. of tests)	No. of occurrences at MIC ( $\mu\text{g/mL}$ ) of:																
	$\leq 0.004$	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>256
<b><i>E. coli</i> ATCC 25922</b>																	
Sulopenem (9)				0	8	1											
Ertapenem (9)	0	9															
<b><i>E. coli</i> ATCC 35218</b>																	
Sulopenem (3)				0	3												
Ertapenem (3)	0	3															
<b><i>E. coli</i> NCTC 13353</b>																	
Sulopenem (3)				0	3												
Ertapenem (3)				0	3												
<b><i>K. pneumoniae</i> ATCC 700603</b>																	
Sulopenem (9)				0	6	2	1										
Ertapenem (9)	0	9															
<b><i>K. pneumoniae</i> ATCC BAA-1705</b>																	
Sulopenem (3)											0						3
Ertapenem (3)										0							3
<b><i>K. pneumoniae</i> ATCC BAA-2814</b>																	
Sulopenem (3)											0						3
Ertapenem (3)										0							3

## RESULTS

**Table 2:** Activity of Sulopenem and Ertapenem Against Key Target Pathogens\*

Organism	Cumulative % inhibited at MIC ( $\mu\text{g/mL}$ ) of:								$\text{MIC}_{50/90}$ ( $\mu\text{g/mL}$ )
	$\leq 0.015$	0.03	0.06	0.12	0.25	0.5	1	2	
<b><i>E. coli</i> (N=207)</b>									
Sulopenem	1.4	82.1	96.6	98.1	100	100	100	100	0.03/0.06
Ertapenem	85.0	93.2	95.7	98.1	98.6	100	100	100	0.008/0.03
<b><i>E. coli</i>, ESBL + (N=32)</b>									
Sulopenem	0	53.1	90.6	96.9	100	100	100	100	0.03/0.06
Ertapenem	28.1	65.6	78.1	87.5	90.6	100	100	100	0.03/0.25
<b><i>Klebsiella pneumoniae</i> (N=191)</b>									
Sulopenem		35.1	90.1	99.5	100	100	100	100	0.06/0.06
Ertapenem	81.2	87.4	92.1	94.8	97.9	100	100	100	0.008/0.06
<b><i>Klebsiella pneumoniae</i>, ESBL + (N=33)</b>									
Sulopenem		18.2	78.8	100	100	100	100	100	0.06/0.12
Ertapenem	15.2	30.3	54.5	69.7	87.9	100	100	100	0.06/0.5
<b><i>P. mirabilis</i> (N=103)</b>									
Sulopenem		3.9	14.6	37.9	80.6	94.2	97.1	100	0.25/0.5
Ertapenem	87.4	90.3	91.3	96.1	97.1	100	100	100	0.015/0.03

\* CRE excluded from this analysis

**Figure 1:** Scattergram of sulopenem versus ertapenem MIC values for *Enterobacteriaceae* employing CLSI ertapenem breakpoint interpretive criteria for both agents

Sulopenem MIC ( $\mu\text{g/mL}$ )	Ertapenem MIC ( $\mu\text{g/mL}$ )											# at MIC
	<0.008	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>2	
>2											14	14
2							3			1	2	6
1					1	4	1		2		2	10
0.5			9	1	2	2	1	1	4	4		24
0.25		20	25	6	4	7	8	4	1			75
0.12		26	17	5	11	7	7	9				82
0.06		151	63	30	20	13	7	3				287
0.03	3	243	50	19	2	2						319
0.015	3	4										7
Grand Total	6	444	164	61	36	32	22	25	10	6	18	824

<sup>a</sup>*Proteus mirabilis* (#882691, 881206, and 876628)  
<sup>b</sup>*Enterobacter cloacae* (#937176)  
<sup>c</sup>*E. Cloacae* (#972888) and *Proteus mirabilis* (#886662, 884983, and 876822)  
<sup>d</sup>*Klebsiella oxytoca* (#930811)

**Figure 2:** Scattergram of sulopenem versus ertapenem MIC values for *E. coli* employing CLSI ertapenem breakpoint interpretive criteria for both agents

Sulopenem MIC ( $\mu\text{g/mL}$ )	Ertapenem MIC ( $\mu\text{g/mL}$ )											# at MIC
	0.004	<0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>2	
>2												
2												
1												
0.5												
0.25			2			1						4
0.12		1					1	1				3
0.06		9	7	6	4	3		1				30
0.03	3	133	18	11	1	1						167
0.015	2	1										3
Grand Total	5	144	27	17	5	5	1	3				207

**Figure 3:** Scattergram of sulopenem versus ertapenem MIC values for *Klebsiella* species employing CLSI ertapenem breakpoint interpretive criteria for both agents

Sulopenem MIC ( $\mu\text{g/mL}$ )	Ertapenem MIC ( $\mu\text{g/mL}$ )											# at MIC
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>2		
>8											6	6
8											4	4
4											1	1
1								1				1
0.5								1	1			2
0.25			1					1	1			3
0.12	7	8	2	1		3	3					24
0.06	103	37	10	9	6	4	2					171
0.03	69	19	7	1	1							97
Grand Total	179	64	20	11	7	7	6	2	2	11		309

**Figure 4:** Scattergram of sulopenem versus ertapenem MIC values for *P. mirabilis* employing CLSI ertapenem breakpoint interpretive criteria for both agents

Sulopenem MIC ( $\mu\text{g/mL}$ )	Ertapenem MIC ( $\mu\text{g/mL}$ )											# at MIC
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	>2		
2								3				3
1						3						3
0.5		9	1	1	2	1						14
0.25	20	22	2									44
0.12	17	7										24
0.06	10	1										11
0.03	4											4
Grand Total	51	39	3	1	5	1	3					103

## CONCLUSIONS

- Sulopenem demonstrated potent activity for *Enterobacteriaceae* with  $\text{MIC}_{90}$  results ranging from 0.06 to 0.25  $\mu\text{g/mL}$  for *E. coli*, *Klebsiella* species and *P. mirabilis*.
- It may be possible to use ertapenem susceptibility test results as a surrogate to predict sulopenem activity
  - E. coli*: 100% correlation
  - Klebsiella* species: at  $\leq 0.5$   $\mu\text{g/mL}$ , 99.7% of isolates correlated and 100% of isolates  $>2$   $\mu\text{g/mL}$
  - P. mirabilis*: 94% correlation
- Establishment of breakpoints for sulopenem will help better understand the potential clinical application of these findings