Antimicrobial Activity of Sulopenem Tested against Gram-positive and Gram-negative Organisms from the United States and Europe (2013-2015)

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ABSTRACT

Background: Sulopenem is a broad-spectrum beta-lactam penem antibiotic with oral pro-drug and intravenous formulations being developed for the treatment of urinary tract infections (UTI) and complicated intra-abdominal infections (cIAI). We evaluated the *in vitro* antimicrobial activity of sulopenem against contemporary clinical isolates of gram-positive and gram-negative organisms.

Methods: Isolates from an intraabdominal or urinary tract infection from patients in the US and Europe collected in the period between 2013 and 2015 were chosen randomly from a global repository [IHMA (International Health Management Associates, Inc.) Schaumburg, IL]. Minimal inhibitory concentrations (MICs) of sulopenem and 18 comparators were determined against 838 isolates following CLSI guidelines including 713 aerobes (682 gram-negative, 31 gram-positive) and 125 anaerobes. Aerobes were tested by broth microdilution and anaerobes were tested by agar dilution.

Organism Class		N	MIC_{50}	MIC_{90}	% ≤ 1 µg/mL
Enterobacteriaceae*		682	0.03	0.25	97.9
Gram-negative Anaerobes		125	0.12	0.25	95.2
Staphylococcus saprophyticus		31	0.25	0.25	100
Extended Spectrum Beta-lactamase Activity					
		N	MIC_{50}	MIC_{90}	% ≤ 1 µg/mL
Escherichia coli	**negative**	169	0.015	0.03	100
	positive	20	0.03	0.06	100
Klebsiella spp.	**negative**	108	0.03	0.06	100
	positive	16	0.03	0.25	100

*Includes *E.coli, K.pneumoniae, K.oxytoca, C.freundii, C.koseri, E.cloacae, E.aerogenes, M.morganii, P.mirabilis, P.retgerii, S.marcescens*

Conclusions: Sulopenem demonstrates potent *in-vitro* activity against organisms commonly implicated in urinary tract and complicated intra-abdominal infections. Additional surveillance studies in specific patient populations are warranted to support the further study of sulopenem in clinical trials.

INTRODUCTION

Sulopenem is a penem β-lactam antibiotic which is being developed for the treatment of infections caused by multi-drug resistant bacteria. Sulopenem possesses potent activity against species of the Enterobacteriaceae that encode ESBLs or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. It has also demonstrated good in vitro microbiological activity against a range of bacterial pathogens including penicillin-resistant *Streptococcus pneumoniae,* β-lactamase-producing *Hemophilus influenzae* and *Moraxella catarrhalis*. Sulopenem exerts bactericidal activity through inhibition of bacterial cell wall synthesis by binding to penicillin-binding proteins. The activity of sulopenem aligns with the most urgent drug-resistant antimicrobial threats defined by the CDC including ESBL producing *E.coli*, drug-resistant *Neisseria gonorrheae*, ESBL producing *K.pneumoniae*, Salmonella spp., Shigella spp., *Streptococcus pneumoniae* and Streptococcus Groups A & B. Sulopenem is available as intravenous and oral pro-drug formulations.

METHODS

Isolates from an intraabdominal or urinary tract infection from patients in the US and Europe collected in the period between 2013 and 2015 were chosen randomly from a global repository [IHMA (International Health Management Associates, Inc.) Schaumburg, IL]. Minimal inhibitory concentrations (MICs) of sulopenem and 18 comparators were determined against 838 isolates following CLSI guidelines including 713 aerobes (682 gram-negative, 31 gram-positive) and 125 anaerobes. Aerobes were tested by broth microdilution and anaerobes were tested by agar dilution. QC ranges and interpretive criteria for comparator compounds and QC reference strains were as published in CLSI M100-S26

Carbapenem-resistant Enterobacteriaceae (CRE) were defined as an MIC, ≥4 µg/mL (CLSI) to imipenem or ≥1 µg/mL to ertapenem. MIC distribution and $MIC_{50/90}$ values are presented for carbapenem susceptible isolates.

RESULTS

Table 1. Activity of sulopenem and comparator antimicrobials tested against ESBL-phenotype, and carbapenemase producing Enterobacteriaceae from a worldwide surveillance program from 2013 - 2015.

	MIC (µg/mL)		CLSI Criteria
Organism / Antibiotic	MIC_{50}	MIC_{90}	%S / %I / %R
Escherichia coli, ESBL -			
Sulopenem	0.015	0.03	-
Ceftriaxone	1	1	100.0 / 0.0 / 0.0
Ciprofloxacin	0.12	2	81.7 / 18.3 / 0.0
Ertapenem	0.5	0.5	100.0 / 0.0 / 0.0
Fosfomycin	1	8	99.4 / 0.6 / 0.0
Nitrofurantoin	16	16	98.8 / 1.2 / 0.0
Trimethoprim-Sulfamethoxazole	2	≥ 32	76.9 / 0.0 / 23.1
Escherichia coli, ESBL +			
Sulopenem	0.03	0.06	-
Ceftriaxone	≥ 32	≥ 32	0.0 / 5.0 / 95.0
Ciprofloxacin	2	2	35.0 / 65.0 / 0.0
Ertapenem	0.5	0.5	100.0 / 0.0 / 0.0
Fosfomycin	2	≥ 32	90.0 / 10.0 / 0.0
Nitrofurantoin	16	≥ 32	85.0 / 15.0 / 0.0
Trimethoprim-Sulfamethoxazole	2	≥ 32	50.0 / 0.0 / 50.0
Klebsiella Species, ESBL -			
Sulopenem	0.03	0.06	-
Ceftriaxone	1	1	100.0 / 0.0 / 0.0
Ciprofloxacin	0.12	0.12	99.1 / 0.9 / 0.0
Ertapenem	0.5	0.5	100.0 / 0.0 / 0.0
Fosfomycin	16	≥32	88.9 / 11.1 / 0.0
Nitrofurantoin	≥ 32	≥ 32	56.5 / 43.5 / 0.0
Trimethoprim-Sulfamethoxazole	2	2	97.2 / 0.0 / 2.8
Klebsiella Species, ESBL +			
Sulopenem	0.03	0.25	-
Ceftriaxone	≥ 32	≥ 32	0.0 / 12.5 / 87.5
Ciprofloxacin	0.25	2	56.3 / 43.8 / 0.0
Ertapenem	0.5	0.5	100.0 / 0.0 / 0.0
Fosfomycin	16	≥ 32	87.5 / 12.5 / 0.0
Nitrofurantoin	≥ 32	≥ 32	50.0 / 50.0 / 0.0
Trimethoprim-Sulfamethoxazole	≥ 32	≥32	43.8 / 0.0 / 56.3
Enterobacteriaceae, ESBL -			
Sulopenem	0.03	0.12	-
Ceftriaxone	1	1	100.0 / 0.0 / 0.0
Ciprofloxacin	0.12	0.5	91.1 / 8.9 / 0.0
Ertapenem	0.5	0.5	100.0 / 0.0 / 0.0
Fosfomycin	4	≥ 32	93.0 / 7.0 / 0.0
Nitrofurantoin	≥ 32	≥ 32	61.2 / 38.8 / 0.0
Trimethoprim-Sulfamethoxazole	2	≥ 32	87.8 / 0.0 / 12.2
Enterobacteriaceae, ESBL +			
Sulopenem	0.12	0.25	--
Ceftriaxone	≥ 32	≥ 32	0.0 / 6.7 / 93.3
Ciprofloxacin	0.12	2	67.6 / 32.4 / 0.0
Ertapenem	0.5	0.5	100.0 / 0.0 / 0.0
Fosfomycin	8	≥ 32	89.5 / 10.5 / 0.0
Nitrofurantoin	≥ 32	≥ 32	49.5 / 50.5 / 0.0
Trimethoprim-Sulfamethoxazole	2	≥ 32	68.6 / 0.0 / 31.4

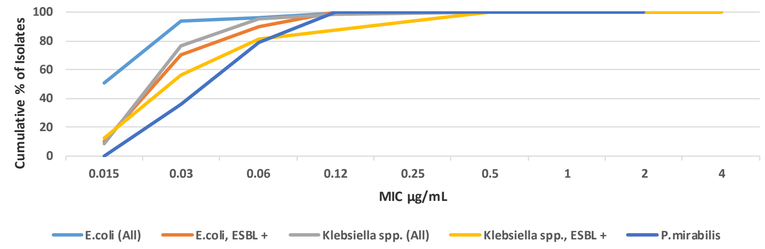
RESULTS

Table 2. Activity and cumulative % distribution for sulopenem against target pathogens in UTI and cIAI,

	Cumulative % inhibited at MIC (µg/mL) of:											
Organism	**≤0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**$MIC_{50/90}$ (µg/mL)**
Enterobacteriaceae (N=636)												
ESBL -	23.0	69.3	82.5	93.8	98.3	99.4	99.6	99.8	100	100	100	0.03/0.12
ESBL +	3.8	25.7	41.9	69.5	91.4	99.0	99.0	99.0	100	100	100	0.12/0.25
E. coli (N=189)												
ESBL -	55.6	96.4	97.0	99.4	100	100	100	100	100	100	100	0.015/0.03
ESBL +	10.0	70.0	90.0	100	100	100	100	100	100	100	100	0.03/0.06
Klebsiella spp (N=124)												
ESBL -	7.4	79.6	97.2	100	100	100	100	100	100	100	100	0.03/0.06
ESBL +	12.5	56.3	81.3	87.5	93.8	100	100	100	100	100	100	0.03/0.25
P. mirabilis (N=14)	0	0	35.7	78.6	100	100	100	100	100	100	100	0.12/0.25
S. saprophyticus (N=31)	0	0	0	9.7	93.5	100	100	100	100	100	100	0.25/0.25
B. fragilis (N=73)	8.2	31.5	64.4	82.2	93.2	93.2	94.5	95.9	95.9	97.3	100	0.06/0.25

*Inclusion of CRE isolates did not change MIC_{90}

Figure 1. Sulopenem cumulative % inhibition of *E.coli, K . pneumoniae and P mirabilis*



CONCLUSIONS

- **Sulopenem demonstrates potent *in-vitro* activity against organisms commonly implicated in urinary tract and complicated intra-abdominal infections.**
- **Sulopenem may represent a valuable treatment option for Gram-negative infections, including those caused by ESBL producing pathogens.**
- **These data support the further clinical development of sulopenem.**

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