ASM Microbe 2019
SATURDAY - AAR - 775

CARA

www.can-r.ca

In Vitro Activity of Sulopenem and Comparative Agents against Bacterial Pathogens Isolated from Canadian Patients: CANWARD 2016

G.G. ZHANEL[1], H.J. ADAM[1,2], M.R. BAXTER[1], P. LAGACE-WIENS[2], A. WALKTY[2], J.A. KARLOWSKY[2]
[1]University of Manitoba and [2]Shared Health, Winnipeg, Manitoba, Canada

University of Manitoba

Dr. George G. Zhanel
Department of Medical Microbiology
Max Rady College of Medicine
MS673-820 Sherbrook St.
Winnipeg, MB R3A 1R9
Email: ggzhanel@pcs.mb.ca

Introduction

Sulopenem, formerly CP-70,429, is an investigational thiopenem currently under development for the treatment of uncomplicated and complicated urinary tract infections, and intra-abdominal infections, including multidrug-resistant (MDR) infections and infections attributable to quinolone-non-susceptible and/or ESBL-producing Gram-negative bacilli (1). Sulopenem is in development in both parenteral and oral prodrug (sulopenem-etzadroxil) formulations, may be combined with probenecid, and has a safety and efficacy profile similar to other penems and β-lactams (1). Sulopenem is stable to renal dehydropeptidase I, unlike imipenem, and has been reported to be stable against hydrolytic attack by many β-lactamases, including ESBLs and AmpC enzymes which confer resistance to third-generation cephalosporins. The activity of sulopenem addresses several of the most urgent, serious, and concerning drug-resistant antimicrobial threats defined by the CDC, including ESBL-producing *Enterobacteriaceae* (2).

The current study assessed the *in vitro* activities of sulopenem and comparator antibacterial agents against clinical isolates of Gram-negative and Gram-positive pathogens submitted by Canadian hospital laboratories to the CANWARD surveillance study in 2016.

Materials and Methods

Study Background and Bacterial Isolates

The isolates tested in this study were obtained from January 2016 to October 2016, inclusive, from an ongoing cross-Canada surveillance study (CANWARD; www.can-r.ca) organized by the investigators (2). 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 (2). All isolates of MRSA were typed using staphylococcal protein A (*spa*) typing to assess whether the isolates were community-associated or healthcare-associated (2). Potential *E. coli* or *Klebsiella* spp. ESBL-producers were identified as isolates with a ceftriaxone and/or ertapenem MIC of ≥1 µg/ml and confirmed using the CLSI double disk diffusion method, as previously described (2).

Antimicrobial Susceptibility Testing

Isolates were tested for antimicrobial susceptibilities using in-house prepared 96-well broth microdilution panels according to CLSI (2018) guidelines (3). 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 (3) in cation-adjusted Mueller-Hinton broth. 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 were interpreted using CLSI breakpoints (4), unless otherwise noted.

Results

Table 1. *In vitro* activities of sulopenem and comparators versus Gram-negative bacilli.

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL) MIC_{50}	MIC_{90}	Range	%S	%I	%R
***Escherichia coli* ALL (612)**						
Sulopenem	0.03	0.06	≤ 0.008 - 0.5	NA[a]	NA	NA
Ertapenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.5	100.0	0	0
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.12	100.0	0	0
TZP	≤ 1	4	≤ 1 - > 512	97.1	1.8	1.1
Ceftriaxone	≤ 0.25	16	≤ 0.25 - > 64	87.6	0.5	11.9
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06 - > 16	76.5	0.8	22.7
Tigecycline[b]	0.25	0.5	0.06 - 1	100.0	0	0
TMP/SMX	≤ 0.12	> 8	≤ 0.12 - > 8	74.2	-	25.8
***Escherichia coli* ESBL Pos (68)**						
Sulopenem	0.03	0.06	0.015 - 0.12	NA[a]	NA	NA
Ertapenem	≤ 0.03	0.25	≤ 0.03 - 0.5	100.0	0	0
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.06	100.0	0	0
TZP	2	8	≤ 1 - 512	97.1	1.5	1.5
Ceftriaxone	64	> 64	2 - > 64	0	2.9	97.1
Ciprofloxacin	> 16	> 16	≤ 0.06 - > 16	7.4	0	92.6
Tigecycline[b]	0.25	1	0.12 - 1	100.0	0	0
TMP/SMX	> 8	> 8	≤ 0.12 - > 8	25.0	-	75.0
***Escherichia coli* ESBL Neg (544)**						
Sulopenem	0.03	0.03	≤ 0.008 - 0.5	NA[a]	NA	NA
Ertapenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.5	100.0	0	0
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.12	100.0	0	0
TZP	≤ 1	4	≤ 1 - > 512	97.1	1.8	1.1
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 - > 64	98.5	0.2	1.3
Ciprofloxacin	≤ 0.06	16	≤ 0.06 - > 16	85.1	0.9	14.0
Tigecycline[b]	0.25	0.5	0.06 - 1	100.0	0	0
TMP/SMX	≤ 0.12	> 8	≤ 0.12 - > 8	80.3	-	19.7
***Klebsiella pneumoniae* ALL (184)**						
Sulopenem	0.06	0.12	0.015 - 4	NA[a]	NA	NA
Ertapenem	≤ 0.03	0.06	≤ 0.03 - 8	98.4	0.5	1.1
Meropenem	≤ 0.03	0.06	≤ 0.03 - 2	99.5	0.5	0
TZP	4	16	≤ 1 - > 512	92.9	3.3	3.8
Ceftriaxone	≤ 0.25	1	≤ 0.25 - > 64	90.2	0.5	9.2
Ciprofloxacin	≤ 0.06	2	≤ 0.06 - > 16	86.4	1.6	12.0
Tigecycline[b]	0.5	1	0.12 - 4	98.9	1.1	0
TMP/SMX	≤ 0.12	> 8	≤ 0.12 - > 8	87.5	-	12.5
***Klebsiella pneumoniae* ESBL Pos[c] (18)**						
Sulopenem	0.06	4	0.03 - 4	NA[a]	NA	NA
Ertapenem	0.12	8	≤ 0.03 - 8	83.3	5.6	11.1
Meropenem	≤ 0.03	0.5	≤ 0.03 - 2	94.4	5.6	0
TZP	16	> 512	2 - > 512	55.6	22.2	22.2
Ceftriaxone	> 64	> 64	≤ 0.25 - > 64	11.1	0	88.9
Ciprofloxacin	> 16	> 16	≤ 0.06 - > 16	5.6	0	94.4
Tigecycline[b]	1	2	0.5 - 2	100.0	0	0
TMP/SMX	> 8	> 8	≤ 0.12 - > 8	5.6	-	94.4
***Enterobacter cloacae* (92)**						
Sulopenem	0.12	0.5	0.03 - 2	NA[a]	NA	NA
Ertapenem	0.06	0.5	≤ 0.03 - 4	92.4	5.4	2.2
Meropenem	≤ 0.03	0.06	≤ 0.03 - 0.25	100.0	0	0
TZP	2	32	≤ 1 - > 512	85.9	8.7	5.4
Ceftriaxone	≤ 0.25	> 64	≤ 0.25 - > 64	76.1	0	23.9
Ciprofloxacin	≤ 0.06	0.25	≤ 0.06 - > 16	91.3	3.3	5.4
Tigecycline[b]	0.5	1	0.12 - 8	96.7	2.2	1.1
TMP/SMX	≤ 0.12	1	≤ 0.12 - > 8	90.2	-	9.8
***Serratia marcescens* (60)**						
Sulopenem	0.5	4	≤ 0.008 - > 8	NA[a]	NA	NA
Ertapenem	≤ 0.03	0.06	≤ 0.03 - 0.25	100.0	0	0
Meropenem	0.06	0.06	≤ 0.03 - 0.12	100.0	0	0
TZP	≤ 1	4	≤ 1 - 16	100.0	0	0
Ceftriaxone	≤ 0.25	0.5	≤ 0.25 - 4	95.0	1.7	3.3
Ciprofloxacin	≤ 0.06	0.25	≤ 0.06 - 8	90.0	1.7	8.3
Tigecycline[b]	1	2	1 - 16	90.0	6.7	3.3
TMP/SMX	0.5	1	0.25 - 2	100.0	-	0
***Klebsiella oxytoca* (67)**						
Sulopenem	0.06	0.12	0.015 - 0.25	NA[a]	NA	NA
Ertapenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.12	100.0	0	0
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.12	100.0	0	0
TZP	2	4	≤ 1 - > 512	98.5	0	1.5
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 - > 64	95.5	0	4.5
Ciprofloxacin	≤ 0.06	≤ 0.06	≤ 0.06 - 0.12	100.0	0	0
Tigecycline[b]	0.25	0.5	0.25 - 4	98.5	1.5	0
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	98.5	-	1.5
***Stenotrophomonas maltophilia* (62)**						
Sulopenem	> 8	> 8	> 8 - > 8	NA[a]	NA	NA
Ertapenem	> 32	> 32	16 - > 32	NA[a]	NA	NA
Meropenem	> 32	> 32	4 - > 32	NA[a]	NA	NA
TZP	256	> 512	4 - > 512	NA[a]	NA	NA
Ceftriaxone	> 64	> 64	4 - > 64	NA[a]	NA	NA
Ciprofloxacin	4	16	0.5 - > 16	NA[a]	NA	NA
Tigecycline	1	2	0.12 - 8	NA[a]	NA	NA
TMP/SMX	0.25	1	≤ 0.12 - > 8	98.4	-	1.6
***Proteus mirabilis* (40)**						
Sulopenem	0.25	0.5	0.015 - 1	NA[a]	NA	NA
Ertapenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.12	100.0	0	0
Meropenem	0.06	0.06	≤ 0.03 - 0.12	100.0	0	0
TZP	≤ 1	≤ 1	≤ 1 - 64	97.5	2.5	0
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 - 2	97.5	2.5	0
Ciprofloxacin	≤ 0.06	4	≤ 0.06 - > 16	77.5	0	22.5
Tigecycline[b]	4	8	2 - 16	10.0	62.5	27.5
TMP/SMX	≤ 0.12	> 8	≤ 0.12 - > 8	80.0	-	20.0
***Acinetobacter baumannii* (15)**						
Sulopenem	1	4	0.5 - 8	NA[a]	NA	NA
Ertapenem	4	16	2 - 16	NA[a]	NA	NA
Meropenem	0.5	2	0.12 - 2	100.0	0	0
TZP	4	32	≤ 1 - 32	80.0	20.0	0
Ceftriaxone	8	32	4 - 32	60.0	40.0	0
Ciprofloxacin	0.25	1	≤ 0.06 - 8	93.3	0	6.7
Tigecycline	0.5	4	0.12 - 4	NA[a]	NA	NA
TMP/SMX	≤ 0.12	> 8	≤ 0.12 - > 8	86.7	-	13.3
***Klebsiella aerogenes* (15)**						
Sulopenem	0.12	0.5	0.03 - 0.5	NA[a]	NA	NA
Ertapenem	0.12	0.5	0.06 - 0.5	100.0	0	0
Meropenem	0.06	0.06	≤ 0.03 - 0.12	100.0	0	0
TZP	4	32	2 - 64	86.7	13.3	0
Ceftriaxone	≤ 0.25	16	≤ 0.25 - 32	53.3	0	46.7
Ciprofloxacin	≤ 0.06	0.12	≤ 0.06 - 0.12	100.0	0	0
Tigecycline[b]	0.5	1	0.5 - 1	100.0	0	0
TMP/SMX	≤ 0.12	0.25	≤ 0.12 - 0.25	100.0	-	0
***Citrobacter freundii* (10)**						
Sulopenem	0.06	0.06	0.03 - 0.25	NA[a]	NA	NA
Ertapenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.5	100.0	0	0
Meropenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.06	100.0	0	0
TZP	2	2	≤ 1 - > 512	90.0	0	10.0
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 - > 64	90.0	0	10.0
Ciprofloxacin	≤ 0.06	0.12	≤ 0.06 - 2	90.0	0	10.0
Tigecycline[b]	0.5	0.5	0.25 - 0.5	100.0	0	0
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	90.0	-	10.0
***Morganella morganii* (12)**						
Sulopenem	1	1	0.03 - 1	NA[a]	NA	NA
Ertapenem	≤ 0.03	≤ 0.03	≤ 0.03 - 0.06	100.0	0	0
Meropenem	0.06	0.12	0.06 - 0.12	100.0	0	0
TZP	≤ 1	2	≤ 1 - 4	100.0	0	0
Ceftriaxone	≤ 0.25	1	≤ 0.25 - 2	91.7	8.3	0
Ciprofloxacin	≤ 0.06	4	≤ 0.06 - > 16	83.3	0	16.7
Tigecycline[b]	2	4	1 - 16	58.3	33.3	8.3
TMP/SMX	0.25	> 8	≤ 0.12 - > 8	83.3	-	16.7
***Pseudomonas aeruginosa* (324)**						
Sulopenem	> 8	> 8	0.12 - > 8	NA[a]	NA	NA
Ertapenem	8	> 32	0.06 - > 32	NA[a]	NA	NA
Meropenem	0.5	8	≤ 0.03 - > 32	85.2	4.3	10.5
TZP	4	64	≤ 1 - > 512	81.8	9.0	9.3
Ceftriaxone	16	> 64	0.5 - > 64	NA[a]	NA	NA
Ciprofloxacin	0.12	4	≤ 0.06 - > 16	74.4	9.3	16.4
Tigecycline[b]	8	16	0.25 - > 16	NA[a]	NA	NA
TMP/SMX	8	> 8	0.25 - > 8	NA[a]	NA	NA
***Haemophilus influenzae* (133)**						
Sulopenem	0.12	0.5	≤ 0.03 - 2	NA[a]	NA	NA
Ertapenem	0.06	0.25	≤ 0.03 - 1	99.3	-	-
Meropenem	≤ 0.06	0.25	≤ 0.06 - 0.5	100.0	-	0
TZP	≤ 1	≤ 1	≤ 1 - ≤ 1	100.0	-	-
Ceftriaxone	≤ 0.06	≤ 0.06	≤ 0.06 - ≤ 0.06	100.0	-	-
Ciprofloxacin	≤ 0.015	≤ 0.015	≤ 0.015 - 0.06	100.0	-	-
TMP/SMX	≤ 0.12	8	≤ 0.12 - > 8	71.6	8.2	20.1

[a] NA, breakpoints not available; [b] interpretive breakpoints defined by FDA (tigecycline) where applicable. [c] *K. pneumoniae* ESBL positive category may also include CPE isolates. TZP, piperacillin-tazobactam. TMP/SMX, trimethoprim-sulfamethoxazole.

Table 2. *In vitro* activities of sulopenem and comparators versus Gram-positive cocci.

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL) MIC_{50}	MIC_{90}	Range	%S	%I	%R
***Staphylococcus aureus* MSSA (550)**						
Sulopenem	0.06	0.12	0.015 - 0.25	NA[a]	NA	NA
Ertapenem	0.25	0.5	≤ 0.03 - 0.5	NA	NA	NA
Meropenem	0.12	0.25	≤ 0.03 - 0.5	NA	NA	NA
TZP	≤ 1	≤ 1	≤ 1 - 4	NA	NA	NA
Ceftriaxone	4	4	0.5 - 8	NA	NA	NA
Ciprofloxacin	0.25	2	≤ 0.06 - > 16	88.0	2.5	9.4
Tigecycline[b]	0.12	0.25	0.06 - 1	99.8	-	-
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	99.8	-	0.2
***Staphylococcus aureus* MRSA (112)**						
Sulopenem	> 8	> 8	0.06 - > 8	NA[a]	NA	NA
Ertapenem	16	> 32	0.5 - > 32	NA	NA	NA
Meropenem	4	16	0.12 - > 32	NA	NA	NA
TZP	32	128	≤ 1 - 256	NA	NA	NA
Ceftriaxone	> 64	> 64	8 - > 64	NA	NA	NA
Ciprofloxacin	16	> 16	0.25 - > 16	25.0	0	75.0
Tigecycline[b]	0.25	0.25	0.12 - 0.5	100.0	-	-
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - 2	100.0	-	-
CA-MRSA (53)						
Sulopenem	4	> 8	0.12 - > 8	NA[a]	NA	NA
Ertapenem	4	16	0.5 - > 32	NA	NA	NA
Meropenem	2	8	0.12 - 32	NA	NA	NA
TZP	16	64	2 - 128	NA	NA	NA
Ceftriaxone	64	> 64	8 - > 64	NA	NA	NA
Ciprofloxacin	16	16	0.25 - > 16	28.3	0	71.7
Tigecycline[b]	0.12	0.25	0.12 - 0.5	100.0	-	-
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - 0.5	100.0	-	-
HA-MRSA (49)						
Sulopenem	> 8	> 8	0.06 - > 8	NA[a]	NA	NA
Ertapenem	32	> 32	1 - > 32	NA	NA	NA
Meropenem	8	> 32	0.25 - > 32	NA	NA	NA
TZP	64	128	≤ 1 - 256	NA	NA	NA
Ceftriaxone	> 64	> 64	16 - > 64	NA	NA	NA
Ciprofloxacin	> 16	> 16	0.25 - > 16	12.2	0	87.8
Tigecycline[b]	0.25	0.5	0.12 - 0.5	100.0	-	-
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - 0.5	100.0	-	-
***Staphylococcus epidermidis* (90)**						
Sulopenem	0.5	> 8	0.015 - > 8	NA[a]	NA	NA
Ertapenem	2	32	≤ 0.03 - > 32	NA	NA	NA
Meropenem	0.5	8	≤ 0.03 - 16	NA	NA	NA
TZP	≤ 1	≤ 1	≤ 1 - 32	NA	NA	NA
Ceftriaxone	8	32	≤ 0.25 - > 64	NA	NA	NA
Ciprofloxacin	0.25	> 16	≤ 0.06 - > 16	54.4	2.2	43.3
Tigecycline	0.12	0.25	0.06 - 0.5	100.0	-	-
TMP/SMX	≤ 0.12	8	≤ 0.12 - > 8	70.0	-	30.0
***Enterococcus faecalis* (101)**						
Sulopenem	8	8	2 - > 8	NA[a]	NA	NA
Ertapenem	16	16	2 - > 32	NA	NA	NA
Meropenem	4	8	0.25 - 16	NA	NA	NA
TZP	2	4	≤ 1 - 16	NA	NA	NA
Ceftriaxone	> 64	> 64	0.5 - > 64	NA	NA	NA
Ciprofloxacin	1	> 16	0.06 - > 16	73.5	12.7	13.7
Tigecycline[b]	0.12	0.25	0.06 - 0.25	100.0	-	-
TMP/SMX	≤ 0.12	0.25	≤ 0.12 - > 8	NA	NA	NA
***Enterococcus faecium* (38)**						
Sulopenem	> 8	> 8	8 - > 8	NA[a]	NA	NA
Ertapenem	> 32	> 32	4 - > 32	NA	NA	NA
Meropenem	> 32	> 32	1 - > 32	NA	NA	NA
TZP	> 512	> 512	≤ 1 - > 512	NA	NA	NA
Ceftriaxone	> 64	> 64	2 - > 64	NA	NA	NA
Ciprofloxacin	> 16	> 16	0.5 - > 16	2.6	2.6	94.7
Tigecycline	0.12	0.12	≤ 0.03 - 0.25	NA	NA	NA
TMP/SMX	≤ 0.12	2	≤ 0.12 - > 8	NA	NA	NA
VRE (9)						
Sulopenem	> 8	> 8	> 8 - > 8	NA[a]	NA	NA
Ertapenem	> 32	> 32	> 32 - > 32	NA	NA	NA
Meropenem	> 32	> 32	> 32 - > 32	NA	NA	NA
TZP	> 512	> 512	> 512 - > 512	NA	NA	NA
Ceftriaxone	> 64	> 64	> 64 - > 64	NA	NA	NA
Ciprofloxacin	> 16	> 16	16 - > 16	0	0	100
Tigecycline	0.12	0.12	0.06 - 0.12	NA	NA	NA
TMP/SMX	0.5	> 8	≤ 0.12 - > 8	NA	NA	NA
***Streptococcus agalactiae* (38)**						
Sulopenem	0.03	0.06	0.03 - 0.06	NA[a]	NA	NA
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - 0.12	100.0	0	0
TZP	≤ 1	≤ 1	≤ 1 - ≤ 1	NA	NA	NA
Ceftriaxone	≤ 0.12	≤ 0.12	≤ 0.12 - 0.5	100.0	0	0
Ciprofloxacin	1	1	0.5 - 8	NA	NA	NA
Tigecycline[b]	0.06	0.06	≤ 0.015 - 0.12	100.0	-	-
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - 0.25	NA	NA	NA
***Streptococcus pneumoniae* (124)**						
Sulopenem	≤ 0.008	0.06	≤ 0.008 - > 8	NA[a]	NA	NA
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - 1	96.6	2.6	0.9
TZP	≤ 1	≤ 1	≤ 1 - 4	NA	NA	NA
Ceftriaxone	≤ 0.12	≤ 0.12	≤ 0.12 - 1	100.0	0	0
Ciprofloxacin	1	2	0.25 - 2	100.0	0	0
Tigecycline	≤ 0.015	0.03	≤ 0.015 - 0.12	99.1	-	-
TMP/SMX	0.25	1	≤ 0.12 - 8	88.9	4.3	6.8
***Streptococcus pyogenes* (45)**						
Sulopenem	0.015	0.03	≤ 0.008 - 0.03	NA[a]	NA	NA
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - ≤ 0.06	100.0	0	0
TZP	≤ 1	≤ 1	≤ 1 - ≤ 1	NA	NA	NA
Ceftriaxone	≤ 0.12	≤ 0.12	≤ 0.12 - 0.25	100.0	0	0
Ciprofloxacin	0.5	1	0.12 - 2	NA	NA	NA
Tigecycline	0.03	0.06	≤ 0.015 - 0.12	100.0	-	-
TMP/SMX	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	NA	NA	NA

[a] NA, breakpoints not available; [b] interpretive breakpoints defined by FDA (tigecycline) where applicable. TZP, piperacillin-tazobactam. TMP/SMX, trimethoprim-sulfamethoxazole.

Table 3. Distributions of sulopenem MICs versus Gram-negative organisms

Organism	Number of isolates for which the Sulopenem MIC (µg/ml) was: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
E. coli ALL (612)	2	105	437	58	8	1	1					
E. coli ESBL pos (68)		2	51	12	3							
E. coli ESBL neg (544)	2	103	386	46	5	1	1					
K. pneumoniae ALL (184)		4	75	79	20	2	2			2		
K. pneumoniae ESBL pos (18)			2	11	2		1			2		
E. cloacae (92)			12	14	27	24	12	2	1			
K. aerogenes (15)			1	4	4	3	3					
S. marcescens (60)	1		1		2	19	24	3	2	5	2	1
K. oxytoca (67)		1	26	30	8	2						
S. maltophilia (62)												62
P. mirabilis (40)		1	4	4	7	10	13	1				
A. baumannii (15)							1	9	3	1	1	
C. freundii (10)			2	7		1						
M. morganii (12)			1			1	3	7				
P. aeruginosa (324)					2		5	2	2	4	24	285
H. influenzae (133)			25[a]	8	44	29	19	7	1			

[a] lowest dilution tested.

Table 4. Distributions of sulopenem MICs versus Gram-positive organisms

Organism	Number of isolates for which the Sulopenem MIC (µg/ml) was: ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
S. aureus MSSA (550)		1	28	312	202	7						
S. aureus MRSA (112)				2	2		4	9	8	18	11	58
CA-MRSA (53)					1		2	5	7	16	5	17
HA-MRSA (49)				2	1		2	2		2	4	36
S. epidermidis (90)		2	18	19	3	2	9	8	10	2	3	14
E. faecalis (101)									5	40	52	4
E. faecium (38)											1	37
VRE (9)												9
S. agalactiae (38)			21	17								
S. pneumoniae (124)	87	5	18	2	2	5	3	1				1
S. pyogenes (45)	8	30	7									

Conclusions

1. Sulopenem demonstrated *in vitro* activity versus Gram-negative bacilli.
2. Sulopenem demonstrated potent *in vitro* activity against Enterobacteriaceae including ESBL-producing *E. coli* and *K. pneumoniae* and its activity was unaffected by the presence of ESBL phenotype.
3. Sulopenem demonstrated potent *in vitro* activity against Enterobacteriaceae including AmpC producing strains and MDR isolates.
4. Sulopenem was not active versus *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia.*
5. Sulopenem demonstrated potent *in vitro* activity against MSSA but not MRSA.
6. Sulopenem demonstrated potent *in vitro* activity against streptococci.
7. Sulopenem demonstrated limited to poor *in vitro* activity against *E. faecalis* and *E. faecium,* including VRE.

Acknowledgements

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

References

1. Karlowsky JA, et al. *Antimicrob Agents Chemother.* 2018; 63(1): e01832-18.
2. Zhanel GG, et al. *J Antimicrob Chemother*. 2019; In Press.
3. Clinical and Laboratory Standards Institute. *M07 11th Edition*. Wayne, PA. CLSI 2018.
4. Clinical and Laboratory Standards Institute. *M100 28th Edition*. Wayne, PA. CLSI 2018.