Surveillance Of Sulopenem And Comparator Agents Against Recent (2019) Enterobacterales Isolates From The United States

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ABSTRACT

Background: Sulopenem is a thiopenem antibiotic with an oral and parenteral formulation being developed for the treatment of urinary tract infection (UTI) and complicated intra-abdominal infection. We evaluated the *in vitro* antimicrobial activity of sulopenem against 1,647 Enterobacterales isolates from patients in North America with an inpatient or community-acquired infection.

Materials/methods: Enterobacterales isolates from bloodstream infections (BSI: 387 isolates; 23.5% overall), urinary tract infections (UTI: 999 isolates; 60.7% overall), and intra-abdominal infections (IAI: 261 isolates; 15.8% overall) were collected in 2019 from 30 medical centers and tested for susceptibility to sulopenem and comparator agents by Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methods. Cumulative MIC distribution data for sulopenem for each infection type and each pathogen are presented by CLSI, the European Committee on Antimicrobial Susceptibility Testing, and the United States Food and Drug Administration breakpoint interpretive criteria.

Results: Sulopenem demonstrated potent *in vitro* antibacterial activity against Enterobacterales isolates.

Antimicrobial agent	No. of isolates	MIC_{50}	MIC_{90}	MIC Range
Enterobacterales	1,647	0.03	0.25	0.008 to >32
Carbapenem-resistant (CRE)	4	16		8 to >32
Escherichia coli	983	0.03	0.03	0.008 to 1
Klebsiella pneumoniae	273	0.03	0.06	0.015 to >32
Klebsiella oxytoca	41	0.03	0.06	0.03 to 0.06
Klebsiella aerogenes	33	0.12	0.25	0.03 to 1
Proteus mirabilis	91	0.25	0.25	0.015 to 0.5
Enterobacter cloacae species complex	110	0.12	0.5	0.015 to 2
Morganella morganii	20	1	1	0.25 to 1
Citrobacter koseri	9	0.03		0.015 to 0.03
Citrobacter freundii species complex	29	0.06	0.12	0.015 to 0.5
Serratia marcescens	36	0.5	2	0.12 to 4
Providencia spp.	14	0.12	0.5	0.12 to 2

In vitro $MIC_{50/90}$ (µg/mL) was similar across infection types, presence of ESBL and geographic region. A significant number of Enterobacterales were non-susceptible to ciprofloxacin (24.6%), ceftriaxone (17.0%), or trimethoprim-sulfamethoxazole (26.4%).

Conclusions: Sulopenem has potent *in vitro* activity against recent Enterobacterales isolates from BSIs, IAIs, and UTIs, including those resistant to existing classes.

INTRODUCTION

- Sulopenem is a thiopenem antibiotic with an oral and parenteral formulation being developed for the treatment of urinary tract infection (UTI) and complicated intra-abdominal infection.
- We evaluated the *in vitro* antimicrobial activity of sulopenem against 1,647 Enterobacterales isolates from patients in North America with an inpatient or community-acquired infection.

METHODS

- Enterobacterales isolates from bloodstream infections (BSI: 387 isolates; 23.5% overall), urinary tract infections (UTI: 999 isolates; 60.7% overall), and intra-abdominal infections (IAI: 261 isolates; 15.8% overall) were collected in 2019 from 30 medical centers and tested for susceptibility to sulopenem and comparator agents by Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methods.
- Cumulative MIC distribution data for sulopenem for each infection type and each pathogen are presented by CLSI, the European Committee on Antimicrobial Susceptibility Testing, and the United States Food and Drug Administration breakpoint interpretive criteria.

RESULTS

Table 1: *In vitro* Antibacterial Activity of Sulopenem Against Enterobacterales Isolates

Antimicrobial agent	No. of isolates	MIC_{50}	MIC_{90}	MIC Range
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RESULTS

Table 2: Activity of Sulopenem Against Enterobacterales Isolates From Bloodstream, Urinary Tract and Intra-abdominal Infection

Infection type (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:															mg/L	
	≤0.004	0.008	0.15	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
All (1647)	0 0.0	2 0.1	192 11.8	938 68.7	216 81.8	120 89.1	94 94.8	44 97.5	28 99.2	7 99.6	2 99.8	1 99.8	1 99.9	0 99.9	2 100.0	0.03	0.25
CRE (4)											0 0.0	1 25.0	1 50.0	0 50.0	2 100.0	16	
Bloodstream infection (387)	0 0.0	1 0.3	34 9.0	204 61.8	59 77.0	38 86.8	23 92.8	15 96.6	10 99.2	2 99.7	0 99.7	1 100.0				0.03	0.25
CRE (1)											0 0.0	1 100.0					
Urinary tract infection (999)	0 0.0	1 0.1	134 13.5	582 71.8	121 83.9	67 90.6	53 95.9	20 97.9	14 99.3	4 99.7	2 99.9	0 99.9	1 100.0			0.03	0.12
CRE (1)												0 0.0	1 100.0				
Intra-abdominal infection (261)	0 0.0	0 0.0	24 9.2	152 67.4	36 81.2	15 87.0	18 93.9	9 97.3	4 98.9	1 99.2	0 99.2	0 99.2	0 99.2	0 99.2	2 100.0	0.03	0.25
CRE (2)														0 0.0	2 100.0	>32	

Table 3: In vitro Activity of Sulopenem Against Enterobacterales Isolates by U.S. Region

U. S. Census Division (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:															mg/L	
	≤0.004	0.008	0.15	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
New England (181)	0 0.0	0 0.0	25 13.8	121 80.7	22 92.8	7 96.7	3 98.3	3 100.0								0.03	0.06
Middle Atlantic (282)	0 0.0	0 0.0	23 8.2	158 64.2	37 77.3	20 84.4	9 95.4	8 98.2	2 98.9	2 99.7	0 98.9	1 99.3	0 99.3	0 99.3	2 100.0	0.03	0.25
CRE (3)											0 0.0	1 33.3	0 33.3	0 33.3	2 100.0	>32	
East North Central (179)	0 0.0	1 0.6	20 11.7	95 64.8	27 79.9	13 87.2	16 96.1	5 98.9	2 100.0							0.03	0.25
West North Central (197)	0 0.0	0 0.0	32 16.2	114 74.1	22 85.3	12 91.4	9 95.9	5 98.5	1 99.0	0 99.0	2 100.					0.03	0.12
South Atlantic (281)	0 0.0	0 0.0	32 11.4	156 66.9	40 81.1	22 89.0	17 95.0	7 97.5	5 99.3	2 100.						0.03	0.25
East South Central (116)	0 0.0	0 0.0	12 10.3	58 60.3	19 76.7	12 87.1	6 92.2	7 98.3	2 100.							0.03	0.25
West South Central (210)	0 0.0	0 0.0	27 12.9	122 71.0	22 81.4	16 89.0	13 95.2	5 97.6	3 99.0	1 99.5	0 99.5	0 99.5	1 100.0			0.03	0.25
CRE (1)												0 0.0	1 100.0				
Mountain (94)	0 0.0	0 0.0	7 7.4	53 63.8	15 79.8	9 89.4	2 91.5	2 93.6	4 97.9	2 100.						0.03	0.25
Pacific (107)	0 0.0	1 0.9	14 14.0	61 71.0	12 82.2	9 90.7	6 96.3	1 97.2	3 100.							0.03	0.12

Table 4: Antimicrobial Activity of Sulopenem and Comparator Agents Tested Against 1,647 Enterobacterales Isolates

Antimicrobial Agent	No. of Isolates	mg/L			CLSI[a]			EUCAST[a]		
		MIC50	MIC90	MIC Range	%S	%I	%R	%S	%I	%R
Sulopenem	1,647	0.03	0.25	0.008 to >32						
Ertapenem	1,647	≤0.008	0.06	≤0.008 to >2	98.3	0.9	0.9	98.3		1.7
Imipenem	1,647	≤0.12	1	≤0.12 to >8	94.7	4.2	1.1	92.0	7.7	0.2
Meropenem	1,647	≤0.015	0.06	≤0.015 to >32	99.7	0.1	0.2	99.8	0.1	0.1
Amikacin	1,647	2	4	≤0.25 to >32	99.6	0.2	0.1	99.0	0.6	0.4
Amoxicillin-clavulanic Acid	1,647	4	>32	0.5 to >32	71.0	10.9	18.1	71.0[b] 87.4[c]		29.0 12.6
Aztreonam	1,647	0.12	16	≤0.03 to >16	85.2	2.6	12.2	83.6	1.6	14.8
Cefepime	1,647	0.06	8	≤0.008 to >256	87.9[d]	2.8	9.3	86.8	2.4	10.7
Ceftazidime	1,647	0.25	16	0.03 to >32	86.5	1.9	11.6	82.5	3.9	13.5
Ceftriaxone	1,647	≤0.06	>8	≤0.06 to >8	83.1	0.4	16.6	83.1	0.4	16.6
Cefuroxime	1,647	4	>64	≤0.5 to >64	55.9[e] 73.5[f]	22.5 4.9	21.6 21.6			
Ciprofloxacin	1,645	≤0.03	>16	≤0.03 to >16	75.4	3.0	21.6	75.4	3.0	21.6
Gentamicin	1,646	0.5	2	≤0.12 to >16	91.1	0.3	8.6	90.9	0.2	8.9
Nitrofurantoin	1,647	32	>64	≤4 to >64	66.8	14.8	18.5			
Piperacillin-tazobactam	1,645	2	8	≤0.06 to >128	94.2	2.2	3.6	91.7	2.5	5.8
Tetracycline	1,646	2	>16	≤0.5 to >16	68.0	1.9	30.1			
Tigecycline	1,645	0.25	1	≤0.06 to 8	97.0[g]	2.7	0.4			
Trimethoprim-Sulfamethoxazole	1,642	≤0.12	>16	≤0.12 to >16	73.6		26.4	73.6	0.4	26.0

[a] Criteria as published by CLSI 2019 and EUCAST 2019; [b] Using other than uncomplicated urinary tract infection breakpoints; [c] Using uncomplicated urinary tract infection-only breakpoints; [d] Intermediate interpreted as susceptible-dose dependent; [e] Using oral breakpoints; [f] Using parenteral breakpoints; [g] FDA breakpoints published 2017-DEC-13

CONCLUSIONS

- Sulopenem has potent *in vitro* activity against recent Enterobacterales isolates from patients with bloodstream infections (BSI), intra-abdominal infections (IAI) and urinary tract infections (UTI).
- Sulopenem's potent *in vitro* activity against Enterobacterales isolates was similar for all U.S. Census Regions.
- Enterobacterales isolates were non-susceptible to ciprofloxacin (24.6%), ceftriaxone (17%), and trimethoprim-sulfamethoxazole (26.4%).
- Sulopenem has potent *in vitro* activity against Enterobacterales isolates resistant to existing classes, offering both an IV treatment and a potential oral step-down option for inpatients with BSI, IAI and UTI.

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