Antimicrobial Activity of Tigecycline and Cefoperazone/Sulbactam Tested against 14,850 Gram-negative Organisms from Europe and the Asia-Pacific Region (2013-2014)

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AMENDED ABSTRACT

Background: We evaluated the antimicrobial activities of tigecycline (TIG) and cefoperazone/sulbactam (CFP/SUL) tested against contemporary clinical isolates of Gram-negative organisms.

Methods: A total of 14,850 organisms, including 13,224 Enterobacteriaceae, 1,254 *Acinetobacter* spp. (ACB) and 372 *Stenotrophomonas maltophilia* (XM) were collected from Western-Europe (W-EU; n=8,350), Eastern-EU (E-EU; n=3,865) and the Asia-Pacific region (APAC; n=2,635 [including 820 from China and 478 from Australia/New Zealand]) in 2013-2014 as part of the SENTRY Antimicrobial Surveillance Program and tested for susceptibility against TIG, CFP/SUL and comparator agents by a reference broth microdilution method.

Results: Overall, 95.3% of Enterobacteriaceae were susceptible (≤1 mg/L; EUCAST) to TIG ($MIC_{50/90}$, 0.12/1 mg/L), with regional EUCAST susceptibility rates of 95.0-98.2% (98.9-99.5% inhibited at ≤2 mg/L [CLSI]; see Table 1). Among ACB, 66.1 (E-EU) and 79.5% (W-EU) were inhibited at ≤1 mg/L of TIG (overall $MIC_{50/90}$, 1/2 mg/L; 94.9 and 97.3% inhibited at ≤2 mg/L); 65.4 (China) to 88.9% (E-EU) of XM were inhibited at ≤1 mg/L of TIG (overall $MIC_{50/90}$, 0.5/2 mg/L; 80.8-100.0% inhibited at ≤2 mg/L). ESBL-phenotype rates (CLSI criteria) among *E. coli* (EC)/*K. pneumoniae* (KPN) were 15.4/33.3% in W-EU, 31.5/65.7% in E-EU and 40.0/38.6% in APAC (66.9/45.6% in China). Overall, 99.9/94.5% ESBL-phenotype EC/KPN were susceptible (EUCAST) to TIG. Among Enterobacteriaceae, meropenem susceptibility rates were 98.3/94.3/97.8% and CFP/SUL inhibited 94.6/83.5/91.5% at ≤16 mg/L in W-EU/E-EU/APAC, respectively. Among meropenem-non-susceptible Enterobacteriaceae (n=360), TIG ($MIC_{50/90}$, 0.5/1 mg/L) inhibited 91.7/98.9% at ≤1/≤2 mg/L. In China, 84.8% of Enterobacteriaceae were inhibited at ≤16 mg/L of CFP/SUL, and 95.9% were susceptible (≤1 mg/L) to TIG (99.5% inhibited at ≤2 mg/L). CFP/SUL and most comparators exhibited limited activity against ACB and XM. Against ACB, meropenem (MIC_{50}, >8 mg/L) susceptibility rates were 51.3/20.3/21.1 in W-EU/E-EU/Asia (excluding China), respectively, and 22.3% in China.

Conclusions: TIG and CFP/SUL continue to demonstrate good *in vitro* activity against Enterobacteriaceae isolated from Europe and APAC medical centres. Based on the potency and spectrum, TIG continues to have a role for treating of infections caused by indicated Enterobacteriaceae organisms, and remains among the most active compounds *in vitro* against ACB and XM at published or suggested breakpoints.

INTRODUCTION

Tigecycline, the first in the glycylcycline class, received approvals from the United States Food and Drug Administration (US-FDA) and the European Medicines Agency (EMA) for treatment of complicated acute bacterial skin and skin structure infections (ABSSSI) and complicated intraabdominal infections (cIAI) in 2005 (US-FDA) and 2006 (EMA). Tigecycline also received approval from the US-FDA for treatment of community acquired bacterial pneumonia (CABP) in 2008. Tigecycline binds to the 30S ribosomal subunit blocking access of amino-acyl tRNA molecules to the A site, and is not affected by tetracycline resistance mechanisms: efflux pumps and ribosomal protection. The expanded broad spectrum of activity of tigecycline includes a broad range of antimicrobial resistant Gram-positive and -negative aerobes, anaerobes, and “atypical” bacteria.

Cefoperazone is a broad-spectrum third-generation cephalosporin with activity against Gram-positive and Gram-negative organisms, including *Pseudomonas aeruginosa*. Its pharmacologic properties include a long elimination half-life of approximately 2 hours, which allows for twice-daily administration. Cefoperazone was widely used in the 1980’s to treat infections in neutropenic patients as well as in immunocompetent individuals. Due to its lability to β-lactamases, cefoperazone was combined with the β-lactamase inhibitor sulbactam, and this combination has been used in many geographic regions for the treatment of several types of infections, including nosocomial pneumonia, intraabdominal infections, gynaecological infections, sepsis and infections in febrile neutropenic patients.

METHODS

Organism collection: A total of 14,850 organisms, including 13,224 Enterobacteriaceae, 1,254 *Acinetobacter* spp. and 372 *Stenotrophomonas maltophilia*, were collected from Western-Europe (W-EU; n=8,350), Eastern-EU (E-EU; n=3,865) and the Asia-Pacific region (APAC; n=2,635 [including 820 from China and 478 from Australia/New Zealand]) in 2013-2014 as part of the SENTRY Antimicrobial Surveillance Program. The medical centres were guided by a common protocol. Species identification was performed by the participant centre and confirmed at JMI Laboratories (North Liberty, Iowa, USA) when necessary by Vitek 2 or Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions.

Susceptibility testing: Isolates were tested for susceptibility to multiple antimicrobial agents at a central reference laboratory by reference broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document using validated broth microdilution panels produced by ThermoFisher Scientific Inc. (Cleveland, Ohio, USA). Cefoperazone/sulbactam was tested at 1:1 ratio. Minimum inhibitory concentration (MIC) results were interpreted according to CLSI criteria in M100-S26, as well as European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 6.0, January 2016). Tigecycline MIC breakpoints were those found in the US-FDA approved package insert, and cefoperazone/sulbactam MIC breakpoints were those found in the Sulperazone® package insert as well as the Cefobid® package insert (≤16 mg/L for susceptible and ≥64 mg/L for resistance). *Escherichia coli* and *Klebsiella* spp. isolates were grouped as “ESBL-phenotype” based on the CLSI screening criteria for potential ESBL production: i.e., MIC of ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam. Quality control (QC) was performed according to CLSI methods using *E. coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853 and *Enterococcus faecalis* ATCC 29212.

RESULTS

- Overall, 95.3% of Enterobacteriaceae were susceptible (≤1 mg/L; EUCAST) to tigecycline ($MIC_{50/90}$, 0.12/1 mg/L), with susceptibility rates varying from 98.2% in Australia/New Zealand to 95.0% in Asia (excluding China). Furthermore, 98.9 (W-EU) to 99.5% (China) of Enterobacteriaceae isolates were inhibited at ≤2 mg/L of tigecycline (CLSI susceptible breakpoint; Table 1).
- Tigecycline was active against *Acinetobacter* spp., with 62.0 (China) to 94.1% (Australia/New Zealand) of isolates inhibited at ≤1 mg/L (Table 1). The overall MIC_{50} and MIC_{90} values were 1 and 2 mg/L, with 67.2 and 94.7% of all isolates inhibited at ≤1 and ≤2 mg/L, respectively (Table 1).
- When tested against *S. maltophilia*, tigecycline MIC_{50} and MIC_{90} values were 0.5 and 2 mg/L, respectively. Furthermore, 84.9% of isolates were inhibited at ≤1 mg/L, varying from 65.4% in China to 88.9% in E-EU (Table 1).
- ESBL-phenotype rates (CLSI criteria) among *E. coli* and *K. pneumoniae* were 15.4 and 33.3% in W-EU, 31.5 and 65.7% in E-EU, 10.7 and 7.5% in Australia/New Zealand, 35.1 and 40.8% in Asia (excluding China) and 66.9 and 45.6% in China, respectively. Overall, 99.9% of ESBL-phenotype *E. coli* and 94.5% of ESBL-phenotype *K. pneumoniae* were susceptible (EUCAST) to tigecycline (data not shown).
- Among Enterobacteriaceae, meropenem susceptibility rates (EUCAST) were 98.3, 94.3 and 98.7%, respectively; and cefoperazone/sulbactam inhibited 94.6, 83.5 and 93.6% at ≤16 mg/L in W-EU, E-EU and Asia (excluding China), respectively (Tables 2 and 3).
- In China, 84.8% of Enterobacteriaceae were inhibited at ≤16 mg/L of cefoperazone/sulbactam and 95.9% were susceptible (≤1 mg/L) to tigecycline (99.5% inhibited at ≤2 mg/L; Tables 2 and 3). Meropenem susceptibility rate among Enterobacteriaceae in China was 94.9% (Table 3).
- Among meropenem-non-susceptible Enterobacteriaceae (n=360), tigecycline ($MIC_{50/90}$, 0.5/1 mg/L) inhibited 91.7 and 98.9% at ≤1 and ≤2 mg/L, respectively (data not shown).
- Cefoperazone/sulbactam and all other β-lactam compounds exhibited limited activity against *Acinetobacter* spp. and *S. maltophilia*. Against *Acinetobacter* spp., meropenem (MIC_{50}, >8 mg/L) susceptibility rates were 51.3, 20.3 and 21.1% in W-EU, E-EU and Asia (excluding China), respectively, and 22.3% in China (data not shown).

Table 1. Summary of tigecycline *in vitro* activity when tested against Enterobacteriaceae, *Acinetobacter* spp. and *S. maltophilia* from Europe and the Asia-Pacific region.

	Number of isolates (cumulative %) inhibited at tigecycline MIC (mg/L) of:										MIC (mg/L)	
Organism (no.)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	50%	90%
All regions combined												
Enterobacteriaceae (13,224)	69 (0.5)	2754 (21.3)	3918 (51.0)	3436 (77.0)	1558 (88.7)	872 (95.3)	492 (99.1)	117 (99.9)	7 (>99.9)	1 (100.0)	0.12	1
Acinetobacter spp. (1,154)	3 (0.2)	66 (5.5)	106 (14.0)	107 (22.5)	177 (36.6)	424 (70.4)	312 (95.3)	46 (99.0)	12 (99.9)	1 (100.0)	1	2
S. maltophilia (372)	--	3 (0.8)	12 (4.0)	72 (23.4)	123 (56.5)	106 (84.9)	30 (93.0)	21 (98.7)	5 (100.0)	--	0.5	2
Western Europe												
Enterobacteriaceae (7,945)	44 (0.6)	1695 (21.9)	2429 (52.5)	1959 (77.1)	899 (88.4)	537 (95.2)	298 (98.9)	78 (99.9)	6 (100.0)	--	0.12	1
Acinetobacter spp. (224)	1 (0.4)	33 (15.2)	33 (29.9)	36 (46.0)	31 (59.8)	44 (79.5)	40 (97.3)	5 (99.6)	1 (100.0)	--	0.5	2
S. maltophilia (181)	--	1 (0.6)	7 (4.4)	38 (25.4)	54 (55.2)	59 (87.8)	11 (93.9)	10 (99.4)	1 (100.0)	--	0.5	2
Eastern Europe												
Enterobacteriaceae (3,126)	18 (0.6)	624 (20.5)	863 (48.1)	855 (75.5)	402 (88.4)	221 (95.4)	114 (99.1)	28 (>99.9)	0 (>99.9)	1 (100.0)	0.25	1
Acinetobacter spp. (622)	1 (0.2)	21 (3.5)	25 (7.6)	40 (14.0)	111 (31.8)	213 (66.1)	179 (94.9)	27 (99.2)	4 (99.8)	1 (100.0)	1	2
S. maltophilia (117)	--	2 (1.7)	3 (4.3)	22 (23.1)	53 (68.4)	24 (88.9)	8 (95.7)	4 (99.1)	1 (100.0)	--	0.5	2
Australia, New Zealand												
Enterobacteriaceae (332)	--	95 (28.6)	97 (57.8)	90 (84.9)	29 (93.7)	15 (98.2)	4 (99.4)	2 (100.0)	--	--	0.12	0.5
Acinetobacter spp. (17)	--	4 (23.5)	11 (88.2)	1 (94.1)	0 (94.1)	0 (94.1)	1 (100.0)	--	--	--	0.12	0.25
S. maltophilia (12)	--	--	--	4 (33.3)	3 (58.3)	3 (83.3)	2 (100.0)	--	--	--	0.5	2
China												
Enterobacteriaceae (628)	1 (0.2)	62 (10.0)	209 (43.3)	194 (74.2)	100 (90.1)	36 (95.9)	23 (99.5)	3 (100.0)	--	--	0.25	0.5
Acinetobacter spp. (166)	--	6 (3.6)	16 (13.3)	9 (18.7)	9 (24.1)	63 (62.0)	59 (97.6)	3 (99.4)	1 (100.0)	--	1	2
S. maltophilia (26)	--	--	--	1 (3.8)	7 (30.8)	9 (65.4)	4 (80.8)	3 (92.3)	2 (100.0)	--	1	4
Asia (excluding China)												
Enterobacteriaceae (1,193)	6 (0.5)	278 (23.8)	320 (50.6)	338 (79.0)	128 (89.7)	63 (95.0)	53 (99.4)	6 (99.9)	1 (100.0)	--	0.12	1
Acinetobacter spp. (225)	1 (0.4)	2 (1.3)	21 (10.7)	21 (20.0)	26 (31.6)	104 (77.8)	33 (92.4)	11 (97.3)	6 (100.0)	--	1	2
S. maltophilia (36)	--	--	2 (5.6)	7 (25.0)	6 (41.7)	11 (72.2)	5 (86.1)	4 (97.2)	1 (100.0)	--	1	4

Table 2. Summary of cefoperazone/sulbactam *in vitro* activity when tested against Enterobacteriaceae, *Acinetobacter* spp. and *S. maltophilia* from Europe and the Asia-Pacific region.

	Number of isolates (cumulative %) inhibited at cefoperazone/sulbactam MIC (mg/L) of:									MIC (mg/L)	
Organism (no.)	≤0.25	0.5	1	2	4	8	16	32	>32	50%	90%
All regions combined											
Enterobacteriaceae (13,167)	4021 (30.5)	1889 (44.9)	2026 (60.3)	1337 (70.4)	953 (77.7)	1019 (85.4)	795 (91.4)	511 (95.3)	616 (100.0)	1	16
Acinetobacter spp. (1,154)	12 (1.0)	21 (2.6)	76 (8.7)	101 (16.8)	62 (21.7)	68 (27.1)	163 (40.1)	346 (67.8)	404 (100.0)	32	>32
S. maltophilia (370)	--	0 (0.0)	1 (0.3)	5 (1.6)	32 (10.3)	75 (30.5)	72 (50.0)	86 (73.2)	99 (100.0)	16	>32
Western Europe											
Enterobacteriaceae (7,911)	2608 (33.0)	1237 (48.6)	1391 (66.2)	860 (77.1)	558 (84.1)	493 (90.3)	333 (94.6)	182 (96.9)	249 (100.0)	1	8
Acinetobacter spp. (224)	8 (3.6)	17 (11.2)	25 (22.4)	36 (38.6)	16 (45.7)	21 (55.2)	34 (70.4)	34 (85.7)	32 (100.0)	8	>32
S. maltophilia (180)	--	0 (0.0)	1 (0.6)	3 (2.2)	18 (12.2)	35 (31.7)	32 (49.4)	42 (72.8)	49 (100.0)	32	>32
Eastern Europe											
Enterobacteriaceae (3,111)	766 (24.6)	363 (36.3)	392 (48.9)	279 (57.9)	218 (64.9)	299 (74.5)	280 (83.5)	227 (90.8)	287 (100.0)	2	32
Acinetobacter spp. (622)	2 (0.3)	2 (0.6)	30 (5.5)	28 (10.0)	24 (13.8)	38 (19.9)	90 (34.4)	188 (64.6)	220 (100.0)	32	>32
S. maltophilia (116)	--	--	0 (0.0)	1 (0.9)	8 (7.8)	23 (27.6)	27 (50.9)	25 (72.4)	32 (100.0)	16	>32
Australia, New Zealand											
Enterobacteriaceae (332)	142 (42.8)	45 (56.3)	53 (72.3)	38 (83.7)	18 (89.2)	20 (95.2)	5 (96.7)	7 (98.8)	4 (100.0)	0.5	8
Acinetobacter spp. (17)	--	--	2 (11.8)	9 (64.7)	4 (88.2)	0 (88.2)	0 (88.2)	1 (94.1)	1 (100.0)	2	32
S. maltophilia (12)	--	--	--	0 (0.0)	1 (8.3)	3 (33.3)	1 (41.7)	2 (58.3)	5 (100.0)	32	>32
China											
Enterobacteriaceae (624)	128 (20.5)	73 (32.2)	63 (42.3)	52 (50.6)	47 (58.2)	83 (71.5)	83 (84.8)	48 (92.5)	47 (100.0)	2	32
Acinetobacter spp. (166)	1 (0.6)	1 (1.2)	8 (6.0)	19 (17.5)	4 (19.9)	3 (21.7)	9 (27.1)	54 (59.6)	67 (100.0)	32	>32
S. maltophilia (26)	--	--	0 (0.0)	1 (3.8)	1 (7.7)	5 (26.9)	6 (50.0)	8 (80.8)	5 (100.0)	16	>32
Asia (excluding China)											
Enterobacteriaceae (1,189)	377 (31.7)	171 (46.1)	127 (56.8)	108 (65.9)	112 (75.3)	124 (85.7)	94 (93.6)	47 (97.6)	29 (100.0)	1	16
Acinetobacter spp. (225)	1 (0.4)	1 (0.9)	11 (5.8)	9 (9.8)	14 (16.0)	6 (18.7)	30 (32.0)	69 (62.7)	84 (100.0)	32	>32
S. maltophilia (36)	--	--	--	0 (0.0)	4 (11.1)	9 (36.1)	6 (52.8)	9 (77.8)	8 (100.0)	16	>32

Table 3. Activity of tigecycline, cefoperazone/sulbactam and comparator antimicrobial agents when tested against Enterobacteriaceae.

Antimicrobial Agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
All Regions (13,224)						
Tigecycline	0.12	1	99.1[b]	0.1	95.3	0.9
Cefo/sulb	1	16	91.4[c]	4.7	-	-
Pip/taz	2	64	85.8	8.6	81.5	14.2
Ceftriaxone	0.12	>8	73.2	25.6	73.2	25.6
Ceftazidime	0.25	>16	79.9	17.0	75.4	20.1
Meropenem	≤0.06	≤0.06	97.0	2.7	97.3	1.9
Levofloxacin	≤0.12	>4	77.0	20.5	75.1	23.0
Amikacin	2	4	97.5	1.3	95.7	2.5
Western Europe (7,945)						
Tigecycline	0.12	1	98.9[b]	0.1	95.2	1.1
Cefo/sulb	1	8	94.6[c]	3.1	-	-
Amikacin	2	4	98.4	0.5	97.4	1.6
Ceftazidime	0.25	16	86.1	11.6	82.3	13.9
Ceftriaxone	≤0.06	>8	80.4	18.2	80.4	18.2
Levofloxacin	≤0.12	>4	81.9	15.9	80.2	18.1
Meropenem	≤0.06	≤0.06	98.3	1.7	98.3	1.4
Pip/taz	2	32	89.1	6.1	85.2	10.9
Eastern Europe (3,126)						
Tigecycline	0.25	1	99.1[b]	<0.1	95.4	0.9
Cefo/sulb	2	32	83.5[c]	9.2	-	-
Amikacin	2	8	94.9	2.9	90.9	5.1
Ceftazidime	0.25	>32	67.3	28.5	62.3	32.7
Ceftriaxone	0.25	>8	60.1	38.9	60.1	38.9
Levofloxacin	0.25	>4	67.1	29.5	64.6	32.9
Meropenem	≤0.06	0.25	93.5	5.7	94.3	3.3
Pip/taz	4	>64	75.7	16.5	70.4	24.3
Australia and New Zealand (332)						
Tigecycline	0.12	0.5	99.4[b]	0.0	98.2	0.6
Cefo/sulb	0.5	8	96.7[c]	1.2	-	-
Amikacin	2	4	99.7	0.0	99.4	0.3
Ceftazidime	0.25	1	93.1	6.0	91.0	6.9
Ceftriaxone	≤0.06	1	90.1	9.3	90.1	9.3
Levofloxacin	≤0.12	0.5	93.4	6.0	93.1	6.6
Meropenem	≤0.06	≤0.06	99.7	0.0	100.0	0.0
Pip/taz	2	8	93.4	3.3	90.4	6.6
China (628)						
Tigecycline	0.25	0.5	99.5[b]	0.0	95.9	0.5
Cefo/sulb	2	32	84.8[c]	7.5	-	-
Amikacin	2	4	95.0	4.6	94.9	5.0
Ceftazidime	0.5	>32	67.5	24.5	59.2	32.5
Ceftriaxone	4	>8	48.7	50.5	48.7	50.5
Levofloxacin	0.5	>4	64.1	32.1	62.0	35.9
Meropenem	≤0.06	≤0.06	94.9	5.1	94.9	4.1
Pip/taz	2	64	86.1	8.3	81.9	13.9
Asia excluding China (1,193)						
Tigecycline	0.12	1	99.4[b]	0.1	95.0	0.6
Cefo/sulb	1	16	93.6[c]	2.4	-	-
Amikacin	2	4	98.2	1.5	96.4	1.8
Ceftazidime	0.25	>16	73.9	21.7	68.5	26.1
Ceftriaxone	0.12	>8	67.2	31.8	67.2	31.8
Levofloxacin	0.25	>4	72.7	25.1	70.4	27.3
Meropenem	≤0.06	≤0.06	98.6	1.3	98.7	1.0
Pip/taz	2	32	87.6	6.5	82.7	12.4

Abbreviations:Cefo/sulb = Cefoperazone/sulbactam; Pipt/taz = Piperacillin/tazobactam.
a. Criteria as published by CLSI [2016] and EUCAST [2016].
b. Criteria as published in the Tygacil® Package Insert [2016].
c. Criteria as published in the Sulperazone® Package Insert [2009].

CONCLUSIONS

- Tigecycline and cefoperazone/sulbactam continue to demonstrate good *in vitro* activity against Enterobacteriaceae isolated from Europe and APAC medical centres.
- Based on the potency and spectrum, tigecycline continues to have a role for treating of infections caused by indicated Enterobacteriaceae organisms, and remains among the most active compounds *in vitro* against *Acinetobacter* spp. and *S. maltophilia* at published or suggested breakpoints.

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