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In vitro Activity of Omadacycline and Comparators against Gram-Negative Bacterial Isolates Collected from Patients in European Medical Centres (2016): Results from the SENTRY Antimicrobial Surveillance Program

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REVISED ABSTRACT

Background: Omadacycline is a broad-spectrum aminomethylcycline of the tetracycline family in late-stage clinical development for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (intravenous and oral formulations). Omadacycline has shown potent in vitro activity against key bacterial pathogens, including gram-negative bacterial isolates expressing resistance to β-lactams, fluoroquinolones, and/or common tetracycline-resistance mechanisms. This study evaluated the in vitro antibacterial activity of omadacycline and comparators against gram-negative bacterial isolates collected from patients in European medical centres that participated in the 2016 SENTRY surveillance program.

Methods: A total of 4,019 clinically significant Enterobacteriaceae, 358 Haemophilus influenzae, 162 Moraxella catarrhalis, and 297 Acinetobacter baumannii calcoaceticus species complex (A. baumannii) isolates representing multiple infection types were collected during 2016. One isolate/patient/infection episode was included. Species identification confirmation and antimicrobial susceptibility testing was performed in a central laboratory according to reference (CLSI) broth microdilution methodology and results interpreted per EUCAST/CLSI breakpoints.

Results: Gram-negative isolates were collected from bloodstream infection (BSI; 30.4%), pneumonia in hospitalized patients (PIHP; 22.1%), urinary tract infection (UTI; 16.5%), skin and skin structure infection (SSSI; 14.1%), intra-abdominal infection (IAI; 7.5%), respiratory tract infection (RTI; 9.1%), and other infection types (0.3%). Against *Enterobacteriaceae*, omadacycline (MIC_{50/90} 1/8 mg/L) was very active, inhibiting 87.1% of isolates at ≤4 mg/L; corresponding susceptibilities (EUCAST/CLSI) to levofloxacin, ceftazidime, piperacillin-tazobactam, and tetracycline were 73.4%/73.4%, 74.5%/79.1%, 80.4%/85.0%, and —/60.1%, respectively. Where treatment options may be limited, omadacycline remained active against resistant organisms/groups, including ESBL phenotype Escherichia coli (MIC_{50/90} 1/2 mg/L) and Klebsiella pneumoniae (MIC_{50/90} 2/8 mg/L; 76.9% inhibited at ≤4 mg/L), ceftazidime-nonsusceptible *Enterobacter cloacae* species complex (*E. cloacae*, MIC_{50/90} 2/8 mg/L; 88.5% inhibited at ≤4 mg/L), and A. baumannii (MIC_{50/90} 4/8 mg/L; 64.6% inhibited at ≤4 mg/L). Haemophilus influenzae and M. catarrhalis isolates were also very susceptible to omadacycline with MIC_{50/90} values of 0.5/1 mg/L and 0.25/0.25 mg/L, respectively.

Conclusions: Omadacycline was very active against contemporary gramnegative isolates from Europe, including resistant strains. Omadacycline inhibited ≥90% of Enterobacteriaceae, A. baumannii, H. influenzae, and M. catarrhalis isolates at ≤8, 8, 1, and 0.25 mg/L, respectively. These data support further clinical investigation, especially where resistant pathogens may occur.

		Omada MIC (cycline mg/L)	Tetracycline MIC (mg/L)				
Organism	# tested	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	%S EUCAST / CLSI		
Enterobacteriaceae	4,019	1	8	2	>16	— a / 60.1		
Escherichia coli	1,849	1	2	2	>16	— / 60.6		
E. coli (ESBL phenotype)	422	1	2	>16	>16	— / 36.0		
Klebsiella pneumoniae	830	2	8	2	>16	— / 63.1		
Enterobacter cloacae	323	2	4	2	>16	— / 81.4		
A. baumannii	297	4	8	>16	>16	— / 17.8		
H. influenzae	358	0.5	1	0.5	1	100.0 / 100.0		
M. catarrhalis	162	0.25	0.25	0.25	0.5	100.0 / 100.0		

INTRODUCTION

- Omadacycline is a broad-spectrum aminomethylcycline antibacterial of the tetracycline family in late-stage clinical development (intravenous and oral formulations) for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI)
- Omadacycline has demonstrated potent in vitro antibacterial activity against gram-negative bacterial pathogens expressing resistance to β-lactams, fluoroquinolones, and common tetracycline-resistance mechanisms

 This study evaluated the in vitro antibacterial activity of omadacycline and comparators against gram-negative bacterial isolates collected from patients with multiple infection types in European medical centres participating in the 2016 SENTRY surveillance program

MATERIALS AND METHODS

- A total of 4,987 gram-negative bacterial isolates composed of 315 Acinetobacter spp., 4,019 Enterobacteriaceae, 358 Haemophilus influenzae, 162 Moraxella catarrhalis, and 133 Stenotrophomonas maltophilia were collected from patients with multiple infection types in 38 medical centres in 18 European countries and Israel during 2016. Only one isolate per patient/ infection episode is represented
- Bacterial isolates were initially identified by the submitting laboratories and confirmed by JMI Laboratories using matrix-assisted laser desorption/ionizationtime of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- Susceptibility testing was performed according to CLSI (M07-A10, 2015) reference broth microdilution methodology, and results were interpreted using EUCAST (2017) breakpoint interpretive criteria. CLSI quality control (QC) reference strains (M100-S27, 2017) were tested concurrently and included Escherichia coli ATCC 25922, ATCC 35218 and NCTC 13353. Klebsiella pneumoniae ATCC 700603, ATCC BAA-1705 and ATCC BAA-2814, Haemophilus influenzae ATCC 49247 and ATCC 49766, and Pseudomonas aeruginosa ATCC 27853

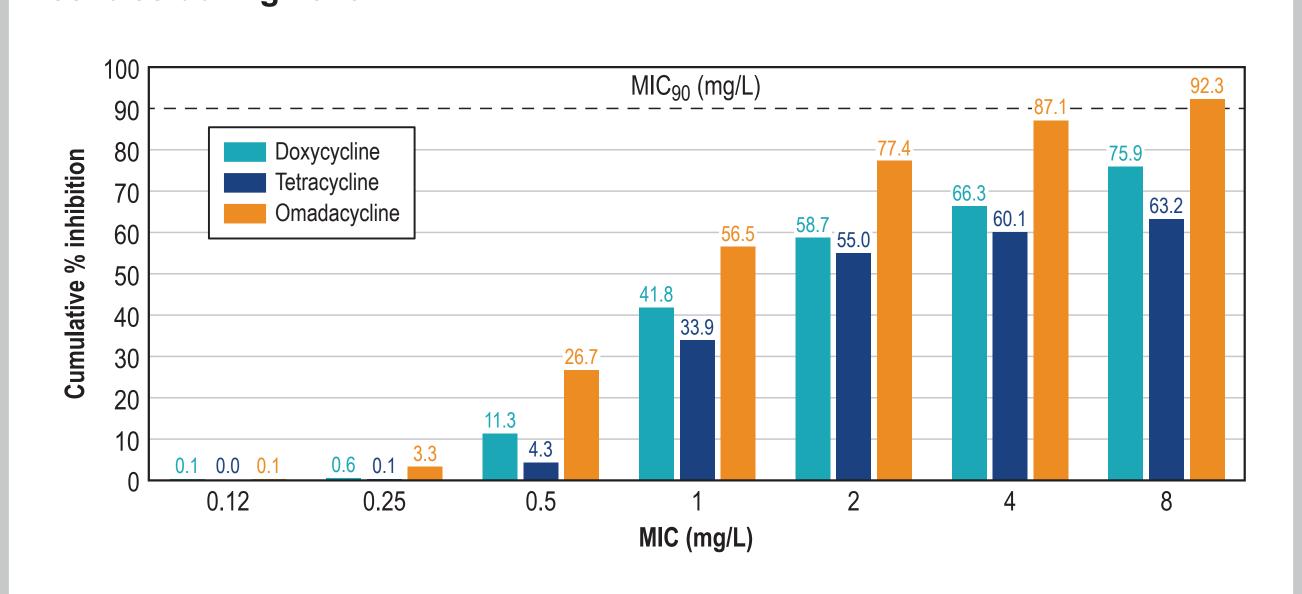
RESULTS

- Overall, 15.7% of the Enterobacteriaceae isolates and 15.2% of the Acinetobacter baumannii calcoaceticus species complex (A. baumannii) isolates obtained in 2016 from European patients were associated with skin and skin structure infections (SSSI; Table 1). The percentages increased to 19.9% and 54.5%, respectively, in patients hospitalized with pneumonia (PIHP; Table 1). Similarly, 12.8% and 63.2% of Stenotrophomonas maltophilia isolates were associated with either SSSI or PIHP infections, respectively (Table 1)
- Cumulative percent inhibition data are presented in Table 2 for omadacycline against Enterobacteriaceae, nonfermenters (Acinetobacter spp. and S. maltophilia), and fastidious gram-negatives (H. influenzae and M. catarrhalis). Figure 1 displays cumulative percent inhibition data for omadacycline and comparator tetracyclines versus Enterobacteriaceae. Omadacycline was significantly more active than either doxycycline or tetracycline at each MIC concentration tested (Figure 1)

Table 1 Gram-negative organism counts collected during the 2016

		Infection type									
Organism / organism group	Total	BSI	RTI	PIHP	SSSI	IAI	UTI	Others			
Enterobacteriaceae	4,019	1,406	0	800	631	361	810	11			
Escherichia coli	1,849	795	0	185	194	194	478	3			
ESBL phenotype	422	170	0	53	54	48	96	1			
Klebsiella pneumoniae	830	277	0	226	98	62	165	2			
ESBL phenotype	386	126	0	101	48	34	76	1			
Klebsiella oxytoca	192	58	0	59	30	15	28	2			
Enterobacter cloacae	323	85	0	94	80	32	32	0			
Ceftazidime-nonsusceptible	87	24	0	21	21	6	15	0			
Other Enterobacter spp.	102	18	0	40	23	8	12	1			
Citrobacter spp.	144	29	0	43	33	18	19	2			
Proteus mirabilis	236	58	0	43	75	12	48	0			
Indole-positive <i>Proteus</i> spp.	130	27	0	24	49	12	18	0			
Serratia marcescens	153	38	0	62	41	5	6	1			
Other Serratia spp.	8	0	0	4	3	0	1	0			
Acinetobacter baumannii	297	77	0	162	45	5	8	0			
Other Acinetobacter spp.	18	3	0	4	9	1	1	0			
Stenotrophomonas maltophilia	133	21	0	84	17	5	6	0			
laemophilus influenzae	358	9	303	44	0	0	0	2			
β-lactamase-positive	60	2	50	8	0	0	0	0			
β-lactamase-negative	298	7	253	36	0	0	0	2			
Moraxella catarrhalis	162	1	149	10	0	0	0	2			
Totals	4,987	1,517	452	1,104	702	372	825	15			

Figure 1 Cumulative % inhibition results for omadacycline and comparators against 4,019 Enterobacteriaceae isolates collected in European medical centres during 2016



- Omadacycline demonstrated good in vitro activity against Enterobacteriaceae isolates (MIC_{50/90} 1/8 mg/L; 87.1% inhibited at ≤4 mg/L) and was most active against *E. coli*, *E. coli* exhibiting an ESBL phenotype, and *Klebsiella* oxytoca isolates (MIC_{50/90} values, 1/2 mg/L; Table 2). Omadacycline inhibited 93.8% of Enterobacter cloacae species complex (E. cloacae), 88.5% of ceftazidime-nonsusceptible E. cloacae, 95.8% of Citrobacter spp., 86.6% of K. pneumoniae, 76.9% of ESBL-phenotype K. pneumoniae, and 83.0% of Serratia marcescens isolates at ≤4 mg/L (Table 2)
- Enterobacteriaceae susceptibilities (EUCAST/CLSI) to comparators composed of levofloxacin, ceftazidime, piperacillin-tazobactam, and tetracycline were 73.4%/73.4%, 74.5%/79.1%, 80.4%/85.0%, and —/60.1%, respectively (Table 3)

Table 2 Antimicrobial activity of omadacycline tested against the main organisms and organism groups of isolates included in this study

	No. of isolates at MIC (mg/L); cumulative % ^a										o	NUC			
Organisms / organism group	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>	MIC ₅₀	MIC ₉₀
Enterobacteriaceae (4,019)			0 0.0	3 0.1	128 3.3	943 26.7	<u>1,198</u> <u>56.5</u>	837 77.4	393 87.1	207 92.3	162 96.3	108 99.0	40 100.0	1	8
Escherichia coli (1,849)			0 0.0	2 0.1	121 6.7	798 49.8	<u>561</u> 80.2	252 93.8	88 98.5	22 99.7	3 99.9	2 100.0		1	2
ESBL phenotype (422)				0 0.0	13 3.1	109 28.9	<u>161</u> 67.1	102 91.2	27 97.6	9 99.8	0 99.8	1 100.0		1	2
Klebsiella pneumoniae (830)				0 0.0	2 0.2	46 5.8	272 38.6	<u>269</u> 71.0	130 86.6	66 94.6	27 97.8	16 99.8	2 100.0	2	8
ESBL phenotype (386)				0 0.0	2 0.5	25 7.0	68 24.6	<u>101</u> 50.8	101 76.9	54 90.9	20 96.1	13 99.5	2 100.0	2	8
Klebsiella oxytoca (192)				0 0.0	1 0.5	24 13.0	<u>127</u> 79.2	21 90.1	12 96.4	6 99.5	1 100.0			1	2
Enterobacter cloacae (323)					0 0.0	7 2.2	108 35.6	<u>148</u> 81.4	40 93.8	8 96.3	8 98.8	4 100.0		2	4
Ceftazidime-nonsusceptible (87)					0	1 1.1	20 24.1	37 66.7	19 88.5	6 95.4	3 98.8	1 100.0		2	8
Other Enterobacter spp. (102)					0	11 10.8	48 57.8	31 88.2	5 93.1	2 95.1	5 100.0			1	4
Citrobacter spp. (144)				0 0.0	1 0.7	44 31.2	<u>56</u> 70.1	26 88.2	11 95.8	4 98.6	2			1	4
Proteus mirabilis (236)						J	0	5 2.1	5 4.2	27 15.7	84 51.3	82 86.0	33 100.0	16	>32
Indole-positive <i>Proteus</i> spp. (130)						0 0.0	1 0.8	15 12.3	30 35.4	47 71.5	28 93.1	4 96.2	5 100.0	8	16
Serratia marcescens (153)						0 0.0	2 1.3	56 37.9	69 83.0	23 98.0	3 100.0			4	8
Other <i>Serratia</i> spp. (8)					0 0.0	2 25.0	<u>3</u> 62.5	2 87.5	1 100.0					1	_
Acinetobacter baumannii (297)			0 0.0	7 2.4	21 9.4	11 13.1	18 19.2	28 28.6	<u>107</u> 64.6	81 91.9	19 98.3	4 99.7	1 100.0	4	8
Other <i>Acinetobacter</i> spp. (18)		0 0.0	1 5.6	4 27.8	<u>8</u> 72.2	3 88.9	2 100.0							0.25	1
Stenotrophomonas maltophilia (133)				0 0.0	1 0.8	3 3.0	15 14.3	43 46.6	<u>47</u> 82.0	<u>18</u> 95.5	3 97.7	2 99.2	1 100.0	4	8
Haemophilus influenzae (358)			0 0.0	1 0.3	10 3.1	169 50.3	144 90.5	31 99.2	2 99.7	0 99.7	1 100.0			0.5	1
β-lactamase-positive (60)				0	1 1.7	27 46.7	31 98.3	1 100.0						1	1
β-lactamase-negative (298)			0 0.0	1 0.3	9	142 51.0	113 88.9	30 99.0	2 99.7	0 99.7	1 100.0			0.5	2
Moraxella catarrhalis (162)			0 0.0	64 39.5	91 95.7	7 100.0	23.0		23	33				0.25	0.25
MIC ₅₀ values are underlined; MIC ₉₀ values are bold					_										

Table 3 In vitro activity of omadacycline and comparators against gramnegative isolates collected from patients in European medical centres during 2016

Develope	2	× 0	66.0	0.6	24.4			
Doxycycline	2	>8	66.3	9.6	24.1	_	_	_
Tetracycline	2	>16	60.1	3.1	36.8	-		_
Tigecycline	0.25	1	97.8	2.1	0.1°	92.5	5.3	2.2
Levofloxacin	0.06	>4	73.4	0.9	25.7	73.4	0.9	25.7
Ceftazidime	0.25	>32	79.1	2.1	18.8	74.5	4.6	20.9
Piperacillin-tazobactam	2	64	85.0	5.8	9.3	80.4	4.6	15.0
Escherichia coli (1,849)								
Omadacycline	1	2	_	_	_	_	_	_
Doxycycline	2	>8	66.3	12.3	21.4	_	_	_
Tetracycline	2	>16	60.6	0.3	39.2			
•						_	_	_
Tigecycline	0.12	0.25	99.9	0.1	0.0°	99.9	0.1	0.1
ESBL phenotype (422)								
Omadacycline	1	2	_	_	_	_	_	_
Doxycycline	8	>8	46.2	23.7	30.1	_	_	_
Tetracycline	>16	>16	36.0	0.2	63.7			
						_	_	_
Tigecycline	0.12	0.25	99.8	0.2	0.0°	99.8	0.0	0.2
Klebsiella pneumoniae (830)								
Omadacycline	2	8	_	_	_	_	_	_
Doxycycline	2	>8	65.0	8.6	26.4	_	_	_
Tetracycline	2	>16	63.1	4.7	32.2	_	_	_
							E 1	1.6
Tigecycline	0.5	1	98.4	1.6	0.0°	93.4	5.1	1.6
ESBL phenotype (386)								
Omadacycline	2	8	_	_	_	_	_	_
Doxycycline	8	>8	44.0	14.8	41.2	_	_	_
Tetracycline	16	>16	40.2	7.8	52.1	_	_	
-						00.4	0.0	-
Tigecycline	0.5	2	97.7	2.3	0.0°	89.4	8.3	2.3
K. oxytoca (192)								
Omadacycline	1	2	_	_	_	_	_	_
Doxycycline	1	4	92.1	3.7	4.2	_	_	_
Tetracycline	1	8	89.6	2.1	8.3	_	_	_
	-	_						_
Tigecycline	0.25	0.5	100.0	0.0	0.0°	98.4	1.6	0.0
Enterobacter cloacae (323) ^d								
Omadacycline	2	4	_	_	_	_	_	_
Doxycycline	2	8	83.9	7.7	8.4	_	_	_
Tetracycline	2	>16	81.4	1.9	16.7	_		
-						_	_	_
Tigecycline	0.5	0.5	99.4	0.6	0.0°	94.4	5.0	0.6
Ceftazidime-nonsusceptible ((87) ^e							
Omadacycline	2	8	_	_	_	_	_	_
Doxycycline	4	>8	57.5	23.0	19.5	_	_	_
	8	>16	46.0	4.6	49.4			
Tetracycline						_	_	_
Tigecycline	0.5	2	100.0	0.0	0.0°	89.7	10.3	0.0
Other <i>Enterobacter</i> spp. (102	2) ^f							
Omadacycline	1	4	_	_	_	_	_	_
Doxycycline	1	4	90.2	2.0	7.8	_	_	_
Tetracycline	1	4	90.2	1.0	8.8	_		
-						_	_	_
Tigecycline	0.25	0.5	100.0	0.0	0.0°	94.1	5.9	0.0
Citrobacter spp. (144) ⁹								
Omadacycline	1	4	_	_	_	_	_	_
Doxycycline	1	4	92.4	2.8	4.9	_	_	_
Tetracycline	1	2	93.1	2.8	4.2	_	_	_
-	-					07.0	0.4	0.0
Tigecycline	0.25	0.5	100.0	0.0	0.0°	97.9	2.1	0.0
Serratia marcescens (153)								
Omadacycline	4	8	_	_	_	_	_	_
Doxycycline	4	8	66.0	25.5	8.5	_	_	_
Tetracycline	>16	>16	7.8	26.8	65.4	_	_	_
-	4	4				00.0	0.0	-
Tigecycline	1	1	100.0	0.0	0.0°	90.8	9.2	0.0
Acinetobacter baumannii (29	7)							
Omadacycline	4	8	_	_	_	_	_	_
Doxycycline	>8	>8	42.8	2.0	55.2	_	_	_
Tetracycline	>16	>16	17.8	5.7	76.4	_	_	_
			17.0	J.1	, 0.7			
Tigecycline	2	4	_	_	_	_	-	_
Acinetobacter spp. (18) ⁱ								
Omadacycline	0.25	1	_	_	_	_	_	_
Doxycycline	0.12	0.5	100.0	0.0	0.0	_	_	_
Tetracycline	1	4	100.0	0.0	0.0	_	_	
			100.0		0.0			
Tigecycline	0.12	0.5	<u> </u>	_	_	_	_	_
Stenotrophomonas maltophil	ıa (133)							
Omadacycline	4	8	_	_	_	_	_	_
Doxycycline	2	4	_	_	_	_	_	_
Tetracycline	>16	>16	_	_	_	_	-	
				_				_
Tigecycline	1	2	_	_	_	_	-	_
Haemophilus influenzae (358	3) ^j							
Omadacycline	0.5	1	_	_	_	_	_	_
Tetracycline	0.5	1	99.7	0.0	0.3	99.2	0.6	0.3
Tigecycline	0.12	0.25	95.5		с			3.0
5 ,	0.12	0.20	90.0	_		_	_	_
Moraxella catarrhalis (162)								
Omadacycline	0.25	0.25	_	_	_	_	_	_
Tetracycline	0.25	0.5	100.0	0.0	0.0	100.0	0.0	0.0
Tigecycline	0.06	0.06	<u>—</u>	_	<u> </u>	_	_	
	0.00	0.00						
Criteria as published by CLS								
			cus / farmeri (2) C	braakii (2) C fal	rmeri (1), C. freun	dii (25), C. freundi	ï species complex	: (37).

- Raoultella (6), unspeciated Serratia (2). Yersinia enterocolitica (1) Breakpoints from FDA Package Insert revised 2016 Organisms include: Enterobacter asburiae (9), E. cloacae (184), E. cloacae species complex (128), E. kobei (2)
- Organisms include: Enterobacter asburiae (2), E. cloacae (46), E. cloacae species complex (39) Organisms include: *Enterobacter aerogenes* (101) and *E. amnigenus* (1) Organisms include: Citrobacter amalonaticus (1), C. amalonaticus / farmeri (2), C. braakii (2), C. farmeri (1), C. freundii (25), C. freundii species complex (37), C. koseri

Organisms include: Morganella morganii (76), Proteus vulgaris group (31), Providencia rettgeri (8), P. stuartii (15) Organisms include: Acinetobacter iohnsonii (2), A. junii (1), A. lwoffii (4), A. radioresistens (3), A. schindleri (1), A. soli (1), A. ursingii (3), A. vivianii (1), unspeciated Acine-Organisms include: 60 β-lactamase-positive and 298 β-lactamase-negative *H. influenzae*

- The in vitro activity of omadacycline and comparator compounds against Enterobacteriaceae, nonfermenters, and fastidious gram-negative isolates are presented in Table 3. Omadacycline (MIC_{50/90} 1/8 mg/L) was ≥2-fold more active than doxycycline (MIC_{50/90} 2/>8 mg/L; 66.3% susceptible [CLSI criteria]) and tetracycline (MIC_{50/90} 2/>16 mg/L; 60.1% susceptible [CLSI criteria]) and four- to eight-fold less active than tigecycline (MIC_{50/90}, 0.25/1 mg/L; 92.5% susceptible [EUCAST]) against Enterobacteriaceae
- Against *A. baumannii* isolates, omadacycline (MIC_{50/90}, 4/8 mg/L; 64.6% inhibited at ≤4 mg/L) was slightly less active than tigecycline (MIC_{50/90}, 2/4 mg/L), whereas susceptibility to doxycycline (MIC_{50/90}, >8/>8 mg/L; 42.8% susceptible [CLSI]) and tetracycline (MIC_{50/90}, >16/>16 mg/L; 17.8% susceptible [CLSI]) was low (Tables 2 and 3)
- Omadacycline was active against S. maltophilia isolates, inhibiting 82.0% at ≤4 mg/L (Table 2)
- Haemophilus influenzae (including β-lactamase-producing strains) were inhibited by omadacycline, tetracycline, and tigecycline (MIC_{on} values 1, 1, and 0.25 mg/L, respectively) (Table 3)
- Moraxella catarrhalis isolates were inhibited by low levels of omadacycline (MIC_{50/90}, 0.25/0.25 mg/L; 100.0% susceptible at ≤0.5 mg/L), tetracycline (MIC_{50/90}, 0.25/0.5 mg/L), and tigecycline (MIC_{50/90}, 0.06/0.06 mg/L; Table 3)

CONCLUSIONS

- Omadacycline was active against Enterobacteriaceae isolates of multiple infection types, inhibiting 87.1% of all isolates tested at ≤4 mg/L
- The in vitro spectrum of omadacycline included ESBL-phenotype isolates of *E. coli* (MIC_{50/90}, 1/2 mg/L) and *K. pneumoniae* (MIC_{50/90}, 2/8 mg/L; 76.9% inhibited by ≤4 mg/L) and ceftazidime-nonsusceptible isolates of *E. cloacae* (MIC_{50/90}, 2/8 mg/L; 88.5% inhibited by ≤4 mg/L)
- Omadacycline was active against nonfermenters, inhibiting 64.6% of A. baumannii and 82.0% of S. maltophilia isolates at ≤4 mg/L
- Haemophilus influenzae (including β-lactamase-positive) and M. catarrhalis isolates were inhibited by low levels of omadacycline (MIC_{oo}, 1 and 0.25 mg/L, respectively)
- The results of this surveillance study support the continued development of omadacycline in infections where susceptible and drug-resistant gram-negative isolates composed of Enterobacteriaceae, A. baumannii, S. maltophilia, H. influenzae, and M. catarrhalis are likely to occur, including CABP and ABSSSI

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