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In Vitro Activity of Omadacycline against 7,000 Bacterial Pathogens from the United States Stratified by Infection Type (2019)

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INTRODUCTION

- Omadacycline is a novel aminomethylcycline approved by the United States Food and Drug Administration (FDA) in 2018 (oral and intravenous formulations) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) caused by indicated organism groups.
- Omadacycline phase 2 clinical trials for the treatment of uncomplicated urinary tract infection (NCT03425396) and acute pyelonephritis (NCT03757234) recently have been completed.
- Omadacycline has potent *in vitro* activity against gram-positive (staphylococci, streptococci, and enterococci) and gram-negative (*Enterobacter cloacae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Escherichia coli*) bacterial pathogens commonly associated with ABSSSI, CABP, and urinary tract infection (UTI).
- Omadacycline is active against organism groups including *Staphylococcus aureus*, coagulase-negative staphylococci (*S. lugdunensis*), *Enterococcus faecalis*, streptococci (*S. pneumoniae*, *S. pyogenes*, *S. anginosus*), *Enterobacteriaceae* (*Enterobacter cloacae* and *Klebsiella pneumoniae*), and *Haemophilus* spp. (*Haemophilus influenzae* and *H. parainfluenzae*), including isolates expressing common tetracycline-, penicillin/oxacillin-, fluoroquinolone-, and macrolide-resistance mechanisms.
- The *in vitro* activity of omadacycline and comparator agents against 7,000 bacterial clinical isolates collected from patients in United States medical centers during 2019 (SENTRY Antimicrobial Surveillance Program) and stratified by infection type is presented.

MATERIALS AND METHODS

- A total of 7,000 bacterial isolates were recovered from patients with documented infections of multiple infection types in the United States (31 medical centers; 9 Census Divisions). These isolates included 1,780 staphylococci, 729 streptococci, 350 enterococci, 328 *Haemophilus* spp., 162 *Moraxella* spp., 911 non-fermenters, and 2,740 *Enterobacterales*.
- Isolates were collected from patients with skin and skin structure infections (SSSI; 1,511 isolates; 21.6%), bloodstream infection (BSI; 1,665 isolates; 23.8%), community-acquired respiratory tract infection (CARTI; 725 isolates; 10.4%), intra-abdominal infection (IAI; 433 isolates; 6.2%), pneumonia in hospitalized patients (PIHP; 1,592 isolates; 22.7%), urinary tract infections (UTI; 1,013 isolates; 14.5%), and other infections (61 isolates; 0.9%).
- Only 1 isolate per patient infection episode was tested.
- Organism identifications were performed at participating medical sites and confirmed at JMI Laboratories using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).
- Broth microdilution susceptibility testing was performed according to Clinical and Laboratory Standards Institute M07 (CLSI; 2018) reference methodology and results were interpreted using CLSI M100 (2020), European Committee on Antimicrobial Susceptibility Testing (EUCAST; v10.0, 2020), and FDA (omadacycline and tigecycline) breakpoint interpretive criteria.
  - CLSI quality control reference strains (M100: 2020) were tested concurrently and included *S. aureus* ATCC 29213; *E. faecalis* ATCC 29212; *E. coli* ATCC 25922 and ATCC 35218; *K. pneumoniae* ATCC 700603, ATCC BAA-1705, and ATCC BAA-2814; *S. pneumoniae* ATCC 49619; *H. influenzae* ATCC 49247 and ATCC 49766; and *Pseudomonas aeruginosa* ATCC 27853.

RESULTS

- Susceptibility data for omadacycline and tetracycline comparators against key gram-positive and gram-negative bacterial pathogens collected from patients with SSSI, CARTI, PIHP, and UTI in the United States during 2019 are presented in Tables 1-4.
- The occurrence of bacterial pathogens by infection type for SSSI, CARTI, PIHP, and UTI are presented in Figures 1-4, respectively.

RESULTS (CONT.)

- Omadacycline demonstrated potent *in vitro* activity against *S. aureus* isolates from SSSI including MRSA and MSSA from PIHP with $MIC_{50/90}$ values of 0.12/0.12-0.25 mg/L and corresponding susceptibility (S) values of 99.0%S, 97.7%S, and 97.8%S, respectively (Tables 1 and 3).
  - Overall susceptibilities for tetracycline, tigecycline, and doxycycline against *S. aureus* from SSSI were 94.3%/92.0%S (CLSI/EUCAST), 100%/100%S (FDA/EUCAST), and 98.8%/96.7%S (CLSI/EUCAST), respectively (Table 1).
  - Tetracycline, tigecycline, and doxycycline susceptibilities against MSSA from PIHP were 95.2%/93.4%S (CLSI/EUCAST), 100%/100%S (FDA/EUCAST), and 98.2%/96.9%S (CLSI/EUCAST), respectively (Table 3).
- All *S. lugdunensis* ($MIC_{50/90}$, 0.06/0.06 mg/L) isolates from SSSI were susceptible to omadacycline (Table 1).
- Omadacycline had potent activity against *S. pyogenes* ($MIC_{50/90}$, 0.06/0.12 mg/L; 98.5%S [FDA]) isolates from SSSI including macrolide- and tetracycline-resistant strains (Table 1).
- Omadacycline was equally active against *S. pneumoniae* isolates from CARTI ($MIC_{50/90}$, 0.06/0.06 mg/L; 99.7%S) and PIHP ($MIC_{50/90}$, 0.06/0.06 mg/L; 100%S) (Tables 2-3).
  - Omadacycline was active against penicillin-resistant, macrolide-resistant, and tetracycline-resistant *S. pneumoniae* isolates from CARTI with $MIC_{50/90}$ values of 0.06/0.06-0.12 mg/L and 98.7%-100%S (FDA) (Table 2).

Table 1 Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from patients with skin and skin structure infections (SSSI) in United States medical centers during 2019

Organism (no. tested)	Omadacycline			Tetracycline			Tigecycline			Doxycycline		
	MIC_{50}	MIC_{90}	%S (FDA)	MIC_{50}	MIC_{90}	%S (CLSI/ EUCAST)	MIC_{50}	MIC_{90}	%S (FDA/ EUCAST)	MIC_{50}	MIC_{90}	%S (CLSI/ EUCAST)
Staphylococcus aureus (736)	0.12	**0.12**	99.0	≤0.5	≤0.5	94.3 / 92.0	0.12	0.12	100 / 100	≤0.06	0.25	98.8 / 96.7
MRSA (305)	0.12	**0.25**	97.7	≤0.5	1	94.8 / 92.5	0.12	0.12	100 / 100	≤0.06	0.5	99.0 / 96.4
MSSA (431)	0.12	**0.12**	100	≤0.5	≤0.5	94.0 / 91.6	0.12	0.12	100 / 100	≤0.06	0.25	98.6 / 97.0
S. lugdunensis (15)	0.06	**0.06**	100	≤0.5	≤0.5	93.3 / 93.3	0.06	0.06	—[a] / 100	≤0.06	≤0.06	100 / 100
Streptococcus agalactiae (28)	0.12	**0.25**	—	>4	>4	7.1 / 7.1	0.06	0.06	100 / 100	—	—	—
S. pyogenes (68)	0.06	**0.12**	98.5	0.25	>4	79.4 / 79.4	0.03	0.06	100 / 100	—	—	—
S. pyogenes macrolide-R (15)	0.12	**0.12**	93.3	>4	>4	40.0 / 40.0	0.06	0.06	100 / 100	—	—	—
S. pyogenes tetracycline-R (14)	0.12	**0.12**	92.9	>4	>4	0.0 / 0.0	0.06	0.06	100 / 100	—	—	—
Enterococcus faecalis (60)	0.06	**0.12**	100	>16	>16	21.7 / —	0.12	0.12	100 / 100	—	—	—
E. faecalis vancomycin-R (2)	0.06	**—**	100	>16	—	0.0 / —	0.06	—	100 / 100	—	—	—
E. faecium (13)	0.06	**0.06**	—	>16	>16	23.1 / —	0.06	0.06	— / 100	—	—	—
E. faecium vancomycin-R (9)	0.06	**—**	—	>16	—	11.1 / —	0.06	—	— / 100	—	—	—
Enterobacter cloacae species complex (41)	2	**4**	90.2	2	>16	82.9 / —	0.5	1	95.1 / —	2	8	82.9 / 11
Klebsiella pneumoniae (39)	2	**8**	89.7	2	>16	66.7 / —	0.5	1	97.4 / —	2	>8	66.7 / —
Escherichia coli (87)	0.5	**2**	100[a]	2	>16	78.2 / —	0.25	0.25	100 / 98.9	1	>8	80.5 / —

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; R, resistant
Omadacycline MIC_{50} values are listed in **bold**.
Green, susceptible according to CLSI or FDA breakpoint interpretive criteria.
Yellow, intermediate according to CLSI or FDA breakpoint interpretive criteria.
Gray, resistant according to CLSI or FDA breakpoint interpretive criteria.
[a] % inhibited at ≤4 mg/L.

Table 2 Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from patients with community-acquired respiratory tract infections (CARTI) in United States medical centers during 2019

Organism (no. tested)	Omadacycline			Tetracycline			Tigecycline		
	MIC_{50}	MIC_{90}	%S (FDA)	MIC_{50}	MIC_{90}	%S (CLSI/ EUCAST)	MIC_{50}	MIC_{90}	%S (FDA/ EUCAST)
Streptococcus pneumoniae (359)	0.06	**0.06**	99.7	0.25	>4	78.6 / 78.6	0.03	0.06	98.3 / —[a]
S. pneumoniae penicillin-R[b] (40)	0.06	**0.06**	100	0.25	>4	62.5 / 62.5	0.03	0.06	97.5 / —
S. pneumoniae macrolide-R (165)	0.06	**0.12**	99.4	0.25	>4	60.0 / 60.0	0.03	0.06	97.6 / —
S. pneumoniae tetracycline-R (77)	0.06	**0.12**	98.7	>4	>4	0.0 / 0.0	0.03	0.06	97.4 / —
Haemophilus influenzae (218)	0.5	**1**	100	0.5	0.5	98.6 / 98.2	0.25	0.5	86.2
Moraxella catarrhalis (146)	≤0.12	**0.25**	—	0.25	0.25	100 / 100	0.06	0.12	—

Omadacycline MIC_{50} values are listed in **bold**; R, resistant
Green, susceptible according to CLSI or FDA breakpoint interpretive criteria.
Gray, resistant according to CLSI or FDA breakpoint interpretive criteria.
[a] — breakpoint interpretive criteria unavailable.
[b] Oral dosing (penicillin MIC ≥2 mg/L).

RESULTS (CONT.)

- All vancomycin-susceptible and -resistant *E. faecalis* isolates from SSSI ($MIC_{50/90}$, 0.06/0.12 mg/L) were susceptible to omadacycline (Table 1).
  - All *E. faecalis* and *E. faecium* isolates from SSSI and UTI (including vancomycin-resistant) were inhibited by ≤0.25 mg/L of omadacycline (Tables 1 and 4).
- All *H. influenzae* isolates from CARTI and PIHP (including tigecycline-resistant) were susceptible to omadacycline ($MIC_{50/90}$, 0.5/1 mg/L; 100%S) (Tables 2-3).
- 90.2% of *E. cloacae* species complex and 89.7% of *K. pneumoniae* isolates from SSSI were susceptible to omadacycline, as were 90.4% of *K. pneumoniae* isolates from PIHP (Tables 1 and 3).
  - 98.5% and 96.9% of *E. cloacae* species complex isolates from PIHP and UTI, respectively, were inhibited by ≤4 mg/L of omadacycline (Tables 3-4).
  - 94.7% of *K. pneumoniae* isolates from UTI were inhibited by ≤4 mg/L of omadacycline (Table 4).
- 99.8%-100% of *E. coli* isolates from SSSI, CARTI, and UTI ($MIC_{50/90}$ values, 0.5/1-2 mg/L) were inhibited by ≤4 µg/mL of omadacycline (Tables 1, 3, and 4).

Table 3 Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from patients hospitalized with pneumonia (PIHP) in United States medical centers during 2019

Organism (no. tested)	Omadacycline			Tetracycline			Tigecycline			Doxycycline		
	MIC_{50}	MIC_{90}	%S (FDA)	MIC_{50}	MIC_{90}	%S (CLSI/ EUCAST)	MIC_{50}	MIC_{90}	%S (FDA/ EUCAST)	MIC_{50}	MIC_{90}	%S (CLSI/ EUCAST)
Staphylococcus aureus (396)	0.12	**0.25**	94.7[a]	≤0.5	≤0.5	94.9 / 93.9	0.12	0.25	100 / 100	≤0.06	0.5	97.7 / 96.0
MRSA (168)	0.12	**0.25**	90.5[a]	≤0.5	1	94.6 / 94.6	0.12	0.25	100 / 100	≤0.06	0.5	97.0 / 94.6
MSSA (228)	0.12	**0.12**	97.8	≤0.5	≤0.5	95.2 / 93.4	0.12	0.25	100 / 100	≤0.06	0.12	98.2 / 96.9
Streptococcus pneumoniae (21)	0.06	**0.06**	100	1	>4	52.4 / 52.4	0.03	0.06	100 / —[b]	—	—	—
Haemophilus influenzae (73)	0.5	**1**	100	0.5	0.5	100 / 100	0.25	0.5	87.7	—	—	—
Enterobacter cloacae species complex (65)	2	**2**	98.5[c]	2	4	90.8 / —	0.5	0.5	98.5 / —	2	4	93.8 / —
Klebsiella pneumoniae (136)	1	**4**	90.4	2	>16	77.2 / —	0.5	1	95.6 / —	2	>8	77.9 / —
Escherichia coli (94)	0.5	**2**	100[d]	2	>16	64.9 / —	0.12	0.25	100 / 100	2	>8	69.1 / —

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*
Omadacycline MIC_{50} values are listed in **bold**.
Green, susceptible according to CLSI or FDA breakpoint interpretive criteria.
Gray, resistant according to CLSI or FDA breakpoint interpretive criteria.
[a] Omadacycline CARP breakpoint for MSSA applied for comparison purposes only.
[b] breakpoint interpretive criteria unavailable.
[c] Omadacycline ABSSSI breakpoint applied for comparison purposes only.
[d] % inhibited at ≤4 mg/L.

Table 4 Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from patients with urinary tract infections (UTI) in United States medical centers during 2019

Organism (no. tested)	Omadacycline			Tetracycline			Tigecycline			Doxycycline		
	MIC_{50}	MIC_{90}	%S (FDA)	MIC_{50}	MIC_{90}	%S (CLSI/ EUCAST)	MIC_{50}	MIC_{90}	%S (FDA/ EUCAST)	MIC_{50}	MIC_{90}	%S (CLSI/ EUCAST)
Citrobacter freundii species complex (31)	1	**8**	—	1	>16	74.2 / —	0.25	1	100 / —	2	>8	74.2 / —
C. koseri (14)	0.5	**1**	—	1	2	100 / —	0.25	0.25	100 / 100	1	2	100 / —
Enterobacter cloacae species complex (32)	2	**4**	96.9[a]	2	16	81.2 / —	0.5	1	100 / —	2	4	90.6 / —
Escherichia coli (501)	0.5	**1**	—	2	>16	72.7 / —	0.12	0.25	99.8 / 99.8	1	>8	76.0 / —
Klebsiella aerogenes (19)	2	**2**	—	1	>16	89.5 / —	0.5	0.5	94.7 / —	1	>8	89.5 / —
K. oxytoca (22)	1	**2**	—	≤0.5	1	95.5 / —	0.25	0.5	100 / —	1	1	95.2 / —
K. pneumoniae (113)	1	**4**	94.7[a]	1	>16	79.6 / —	0.5	1	97.3 / —	1	>8	82.3 / —
Staphylococcus aureus (17)	0.12	**0.12**	—	≤0.5	≤0.5	100 / 100	0.12	0.25	100 / 100	≤0.06	0.12	100 / 100
Enterococcus faecalis (63)	0.06	**0.12**	—	>16	>16	30.2 / —	0.12	0.12	100 / 100	—	—	—
E. faecalis vancomycin-R (2)	0.06	**—**	—	>16	—	0.0 / —	0.12	—	100 / 100	—	—	—
E. faecium (18)	0.06	**0.25**	—	>16	>16	27.8 / —	0.06	0.12	— / 100	—	—	—
E. faecium vancomycin-R (12)	0.06	**0.06**	—	>16	>16	25.0 / —	0.06	0.12	— / 100	—	—	—

Omadacycline MIC_{50} values are listed in **bold**; R, resistant.
Green, susceptible according to CLSI or FDA breakpoint interpretive criteria.
Gray, resistant according to CLSI or FDA breakpoint interpretive criteria.
[a] % inhibited at ≤4 mg/L.

CONCLUSIONS

- Omadacycline demonstrated potent *in vitro* activity against Gram-positive and Gram-negative bacterial isolates from multiple infection sites, including strains with resistance to macrolides, oxacillin/penicillin, vancomycin, and tetracycline drug classes.
  - Omadacycline was active against staphylococci, including *S. aureus* (MRSA and MSSA) from multiple infection sites and *S. lugdunensis* from SSSI.
  - Omadacycline was highly active against *S. pneumoniae* isolates from PIHP and penicillin-resistant, tetracycline-resistant, and macrolide-resistant *Streptococcus pneumoniae* isolates from CARTI.
  - Omadacycline exhibited potent *in vitro* activity against vancomycin-susceptible and -resistant *E. faecalis* and *E. faecium* isolates from SSSI and UTI.
  - Omadacycline was highly active against *H. influenzae* isolates from CARTI and PIHP including tigecycline-resistant strains.
  - Omadacycline demonstrated good activity against *E. cloacae* and *K. pneumoniae* regardless of infection type.
- The results of this surveillance study support the continued use of omadacycline, especially in infections where resistant pathogens are likely to be encountered, including ABSSSI and CABP.

ACKNOWLEDGEMENTS

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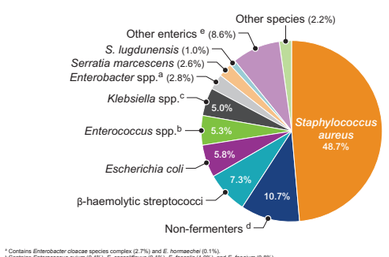
Figure 1 Occurrence of Skin and Skin Structure Infection (SSSI) pathogens from the omadacycline surveillance program (2019)



[a] Contains *Enterobacter cloacae* species complex (2.7%) and *E. hormaechei* (0.1%).
[b] Contains *Enterococcus avium* (0.4%), *E. casseliflavus* (0.1%), *E. faecalis* (4.0%), and *E. faecium* (0.8%).
[c] Contains *K. aerogenes* (0.8%), *K. oxytoca* (1.6%), and *K. pneumoniae* (2.6%).
[d] Contains *Acinetobacter* spp. (1.5%), *P. aeruginosa* (8.2%), and *S. maltophilia* (1.0%).
[e] Contains *Citrobacter* spp. (2.2%), *M. morganii* (1.5%), *Proteus* spp. (4.3%), and *Providencia* spp. (0.6%).

Figure 2 Occurrence of Community Acquired Respiratory Tract Infection (CARTI) pathogens from the omadacycline surveillance program (2019)

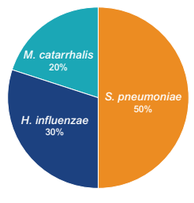
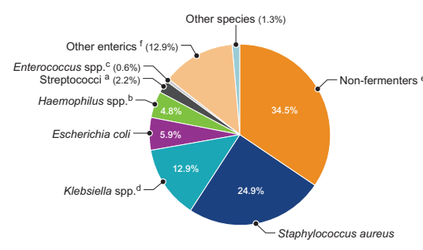
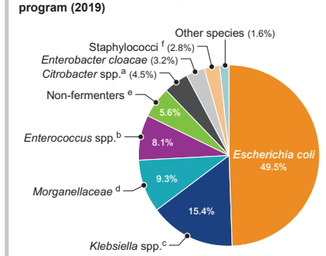


Figure 3 Occurrence of pathogens from Pneumonia In Hospitalized Patients (PIHP) in the omadacycline surveillance program (2019)



[a] Contains β-haemolytic streptococci (0.8%), *S. pneumoniae* (1.3%), and *S. anginosus* group (0.1%).
[b] Contains *H. influenzae* (4.6%) and *H. parainfluenzae* (0.2%).
[c] Contains *E. faecalis* (0.4%) and *E. faecium* (0.2%).
[d] Contains *K. aerogenes* (1.8%), *K. oxytoca* (2.6%), and *K. pneumoniae* (8.5%).
[e] Contains *Acinetobacter* spp. (3.1%), *P. aeruginosa* (25.1%), and *S. maltophilia* (6.3%).
[f] Contains *Citrobacter* spp. (1.4%), *Enterobacter* spp. (4.1%), *M. morganii* (0.3%), *Proteus* spp. (1.9%), *Providencia* spp. (0.6%), *Serratia marcescens* (4.3%), and unspecified *Enterobacteriaceae* (0.3%).

Figure 4 Occurrence of Urinary Tract Infection (UTI) pathogens from the omadacycline surveillance program (2019)



[a] Contains *Citrobacter amalonaticus/farmeri* (0.1%), *C. freundii* species complex (3.0%), and *C. koseri* (1.4%).
[b] Contains *Enterococcus avium* (0.1%), *E. faecalis* (6.2%), and *E. faecium* (1.8%).
[c] Contains *K. aerogenes* (1.9%), *K. oxytoca* (2.2%), *K. pneumoniae* (11.2%), and *K. variicola* (0.1%).
[d] Contains *Morganella morganii* (2.6%), *Proteus* spp. (6%), and *Providencia* spp. (2%).
[e] Contains *Acinetobacter* spp. (0.6%), *Pseudomonas aeruginosa* (4.7%), and *Stenotrophomonas maltophilia* (0.3%).
[f] Contains *Staphylococcus aureus* (1.7%) and coagulase-negative staphylococci (1.1%).