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In Vitro Activity of Omadacycline against 14,000 Bacterial Isolates from the United States by Infection Type (2020–2021)

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INTRODUCTION

- Omadacycline is a novel aminomethylcycline tetracycline antibacterial with oral and intravenous formulations that was approved by the United States Food and Drug Administration (FDA) for treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) caused by indicated organisms.
- Ongoing clinical trials for omadacycline include for the treatment of diabetic foot infection (NCT04714411), community-acquired bacterial pneumonia (NCT04779242), and pulmonary disease caused by *M. abscessus* complex (NCT04922554) as well as for the evaluation of pharmacokinetics in cystic fibrosis (NCT04460586) and pharmacokinetics of intravenous and oral omadacycline in children and adolescents with suspected or confirmed bacterial infections (NCT05217537).
- Omadacycline has previously demonstrated 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, community-acquired respiratory tract infection (CARTI), and pneumonia in hospitalized patients (PIHP), including isolates expressing common tetracycline-, penicillin/oxacillin-, fluoroquinolone-, and macrolide-resistance mechanisms.
- The activity of omadacycline and tetracycline comparators against 14,000 recent (2020–2021) bacterial isolates collected from patients in United States medical centers (SENTRY Antimicrobial Surveillance Program) and stratified by infection type is presented.

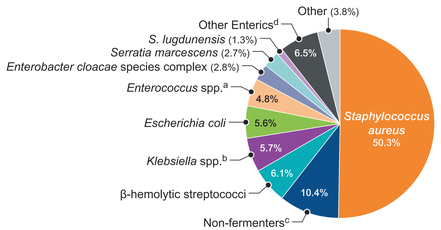
MATERIALS AND METHODS

- 14,000 bacterial isolates were recovered (1 per patient infection episode) from patients with documented infections in 31 United States medical centers in 9 Census Divisions representing multiple infection types.
- The isolates included 3,769 *Staphylococcus* spp., 1,231 *Streptococcus* spp., 720 *Enterococcus* spp., 466 *Haemophilus* spp., 211 *Moraxella* spp., 1,830 non-fermenters, and 5,773 Enterobacterales.
- Isolates were collected from patients with skin and skin structure infections (SSSI; 3,131 isolates; 22.4%), bloodstream infections (BSI; 3,371 isolates; 24.1%), CARTI (1,162 isolates; 8.3%), intra-abdominal infections (IAI; 776 isolates; 5.5%), PIHP (3,167 isolates; 22.6%), urinary tract infections (UTI; 2,224 isolates; 15.9%), and other infections (169 isolates; 1.2%).
- Bacterial identifications were confirmed at JMI Laboratories using standard microbiology methods and 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) methodology.
- Susceptibility results were interpreted using CLSI M100 (2022), European Committee on Antimicrobial Susceptibility Testing (EUCAST; v12.0, 2022), and FDA breakpoint interpretive criteria.

RESULTS

- Omadacycline and comparator agent MIC and susceptibility data against key Gram-positive and Gram-negative bacterial pathogens collected from patients with SSSI, CARTI, and PIHP in United States medical centers during 2020–2021 are presented in Tables 1–3.
- Bacterial pathogen occurrence by infection type for omadacycline is presented in Figures 1–3 for SSSI, CARTI, and PIHP, respectively.
- Omadacycline demonstrated potent *in vitro* activity against methicillin-resistant S. aureus (MRSA) and methicillin-susceptible S. aureus (MSSA) from SSSI ($MIC_{50/90}$ values of 0.12/0.12-0.25 mg/L) with percent susceptibility (%S) of 98.0%S (FDA) and 99.8%S (FDA), respectively (Table 1).
  - Omadacycline ($MIC_{50/90}$, 0.12/0.12 mg/L) was active against 99.6% of MSSA isolates from PIHP (Table 1).
- 97.6% of *S. lugdunensis* isolates from SSSI ($MIC_{50/90}$, 0.06/0.06 mg/L) were susceptible to omadacycline (FDA; Table 1).
- Omadacycline ($MIC_{50/90}$, 0.06/0.06 mg/L; 95.5%S [FDA]) and tigecycline ($MIC_{50/90}$, 0.03/0.06 mg/L; 100.0%S [EUCAST]) demonstrated activity ≥90.0% against *S. anginosus* group isolates from SSSI (Table 1).
- All *S. pyogenes* isolates from SSSI were susceptible to omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L; 100.0%S [FDA]), including macrolide- and tetracycline-resistant strains (Table 1).
- All *E. faecalis* isolates from SSSI were susceptible to omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L; 100%S [FDA]), including vancomycin-resistant strains (Table 1).
- Omadacycline was active against *S. pneumoniae* isolates from CARTI ($MIC_{50/90}$, 0.06/0.06 mg/L; 99.8%S [FDA]) and PIHP ($MIC_{50/90}$, 0.06/0.06 mg/L; 100%S [FDA]) (Tables 2–3).
  - Omadacycline ($MIC_{50/90}$, 0.06/0.06 mg/L) was active against 100% of penicillin-resistant, macrolide-resistant, and tetracycline-resistant *S. pneumoniae* isolates from CARTI (Table 2).
- Omadacycline was active against *H. influenzae* isolates from CARTI ($MIC_{50/90}$, 0.5/1 mg/L; 99.7%S [FDA]) and PIHP ($MIC_{50/90}$, 0.5/1 mg/L; 100%S [FDA]) (Tables 2–3).
- Susceptibility of *E. cloacae* species complex and *K. pneumoniae* isolates from SSSI to omadacycline was 87.5%S and 88.9%S, respectively (Table 1).
  - 88.3% of *K. pneumoniae* isolates from PIHP were susceptible to omadacycline (Table 3).
- 97.1% of *E. coli* from SSSI and 99.1% of *E. coli* from PIHP were inhibited by ≤4 µg/mL of omadacycline (Tables 1 and 3).
- 90.0% of *A. baumannii-calcoaceticus* species complex isolates from PIHP were inhibited by ≤4 µg/mL of omadacycline (Table 3).

Figure 1. Occurrence of skin and skin structure infection pathogens in the omadacycline surveillance program (*n*=3,131; 2020–2021)



[a] Contains *Enterococcus avium* (0.1%), *E. casseliflavus* (0.1%), *E. faecalis* (3.6%), *E. faecium* (1.0%), *E. gallinarum* (0.1%), and *E. mundtii* (0.1%).
[b] Contains *K. aerogenes* (0.8%), *K. oxytoca* (1.7%), *K. pneumoniae* (3.2%), and *K. variicola* (0.1%).
[c] Contains *Acinetobacter* spp. (2.1%), *P. aeruginosa* (7.6%), and *S. maltophilia* (0.7%).
[d] Contains *Citrobacter* spp. (1.3%), *M. morganii* (1.5%), *Proteus* spp. (3.5%), and *Providencia* spp. (0.4%).

Figure 2. Occurrence of community-acquired respiratory tract infection pathogens in the omadacycline surveillance program (*n*=1,162; 2020–2021)

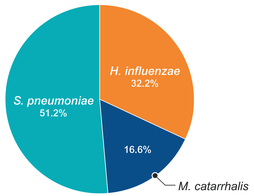
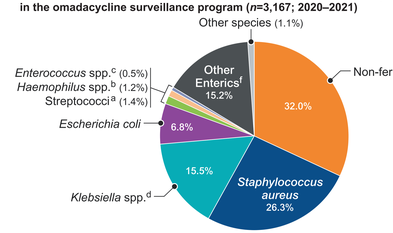


Figure 3. Occurrence of pathogens from pneumonia in hospitalized patients in the omadacycline surveillance program (*n*=3,167; 2020–2021)



[a] Contains *Streptococcus agalactiae* (0.4%), *S. anginosus* group (0.1%), *S. dysgalactiae* (0.2%), *S. mitis* group (0.03%), *S. pneumoniae* (0.4%), and *S. pyogenes* (0.2%).
[b] Contains *H. influenzae* (1.0%) and *H. parainfluenzae* (0.2%).
[c] Contains *E. faecalis* (0.2%) and *E. faecium* (0.3%).
[d] Contains *K. aerogenes* (3.4%), *K. oxytoca* (2.9%), *K. planticola* (0.03%), *K. pneumoniae* (8.9%), and *K. variicola* (0.3%).
[e] Contains *Acinetobacter* spp. (3.8%), *P. aeruginosa* (22.9%), and *S. maltophilia* (5.2%).
[f] Contains *Citrobacter* spp. (1.4%), *Enterobacter* spp. (4.4%), *M. morganii* (0.3%), *Proteus* spp. (1.7%), *Providencia* spp. (0.3%), and *Serratia marcescens* (7.0%).

Table 1. Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from patients with skin and skin structure infections in United States medical centers (2020–2021)

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 (1,575)	0.12	**0.12**	99.0	≤0.5	1	92.1 / 90.2	0.06	0.12	100.0 / 100.0	≤0.06	0.5	97.1 / 95.1
MRSA (659)	0.12	**0.25**	98.0	≤0.5	8	88.0 / 86.5	0.06	0.12	100.0 / 100.0	≤0.06	1	95.1 / 92.4
MSSA (916)	0.12	**0.12**	99.8	≤0.5	≤0.5	95.1 / 92.6	0.06	0.12	100.0 / 100.0	≤0.06	0.12	98.5 / 97.0
S. lugdunensis (41)	0.06	**0.06**	97.6	≤0.5	≤0.5	95.1 / 95.1	0.03	0.06	—[a] / 100.0	≤0.06	≤0.06	100.0 / 95.1
Streptococcus anginosus group (22)[g]	0.06	**0.06**	95.5	4	>4	40.9 / —[b]	0.03	0.06	100.0 / —[a]	0.5	>1	—[a] / —[a]
S. pyogenes (104)	0.06	**0.12**	100.0	0.25	>4	66.3 / 66.3	0.06	0.06	100.0 / 100.0	0.12	>1	—[b] / 66.3
S. pyogenes macrolide-R (28)	0.06	**0.12**	100.0	>4	>4	7.1 / 7.1	0.06	0.06	100.0 / 100.0	>1	>1	—[b] / 7.1
S. pyogenes tetracycline-R (35)	0.06	**0.12**	100.0	>4	>4	0.0 / 0.0	0.06	0.06	100.0 / 100.0	>1	>1	—[b] / 0.0
Enterococcus faecalis (114)	0.06	**0.12**	100.0	>16	>16	26.3 / —[b]	0.06	0.12	100.0 / 100.0	8	8	49.1 / —[b]
E. faecalis vancomycin-R (4)	0.12	—	100.0	>16	—	0.0 / —[b]	0.06	—	100.0 / 100.0	8	8	0.0 / —[b]
E. faecium (30)	0.06	**0.12**	—[b]	>16	>16	6.7 / —[b]	0.06	0.12	—[b] / 100.0	8	8	40.0 / —[b]
E. faecium vancomycin-R (21)	0.06	**0.12**	—[b]	>16	>16	9.5 / —[b]	0.06	0.12	—[b] / 100.0	8	8	38.1 / —[b]
Enterobacter cloacae species complex[d] (88)	2	**8**	87.5	2	16	81.8 / —[b]	0.5	1	96.6 / —[b]	2	>8	80.7 / —[b]
Klebsiella pneumoniae (99)	2	**8**	88.9	2	>16	70.7 / —[b]	0.5	1	99.0 / —[b]	2	>8	71.7 / —[b]
Escherichia coli (174)	0.5	**2**	97.1[c]	2	>16	62.6 / —[b]	0.12	0.25	100.0 / 100.0	1	>8	68.4 / —[b]

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; R, resistant; S, susceptible
Bold, omadacycline MIC_{50} values.
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, EUCAST, or FDA breakpoint interpretive criteria.
[a] Includes *S. anginosus* group (20) and *S. constellatus* (2).
[b] Breakpoint interpretive criteria were unavailable.
[c] % inhibited at ≤2 mg/L.
[d] Includes *E. cloacae* (30) and *E. cloacae* species complex (58).

Table 2. Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from patients with community-acquired respiratory tract infections in United States medical centers (2020–2021)

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)
Streptococcus pneumoniae (594)	0.06	**0.06**	99.8	0.25	>4	79.4 / 79.4	0.03	0.06	98.3 / —[a]	0.12	>1	78.6 / 80.5
S. pneumoniae penicillin-R[b] (64)	0.06	**0.06**	100.0	0.25	>4	51.6 / 51.6	0.06	0.06	98.4 / —[a]	0.25	>1	50.0 / 53.1
S. pneumoniae macrolide-R (270)	0.06	**0.06**	100.0	0.25	>4	58.4 / 58.4	0.06	0.06	98.9 / —[a]	0.12	>1	57.4 / 59.6
S. pneumoniae tetracycline-R (119)	**0.06**	**0.06**	100.0	>4	>4	0.0 / 0.0	0.06	0.06	98.3 / —[a]	>1	>1	0.8 / 2.5
Haemophilus influenzae (371)	0.5	**1**	99.7	0.5	0.5	98.9 / 98.9	0.25	0.25	90.8 / —[a]	—	—	—[a] / —[a]
Moraxella catarrhalis (193)	≤0.12	**0.25**	100.0[c]	0.25	0.5	99.0 / 99.0	0.06	0.06	—[a] / —[a]	—	—	—[a] / —[a]

R, resistant; S, susceptible. **Bold**, omadacycline MIC_{50} values.
Green; susceptible according to CLSI or FDA breakpoint interpretive criteria.
Gray; resistant according to CLSI or FDA breakpoint interpretive criteria.
[a] Breakpoint interpretive criteria were unavailable.
[b] Oral dosing (penicillin MIC, ≥2 mg/L).
[c] % inhibited at ≤0.25 mg/L.

Table 3. Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from pneumonia in hospitalized patients in United States medical centers (2020–2021)

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 (832)	0.12	**0.25**	94.4[a]	≤0.5	≤0.5	94.7 / 92.4	0.06	0.12	100.0 / 100.0	≤0.06	0.5	97.8 / 96.2
MRSA (321)	0.12	**0.5**	86.0[a]	≤0.5	2	90.9 / 87.8	0.06	0.25	100.0 / 100.0	≤0.06	1	95.3 / 92.8
MSSA (511)	0.12	**0.12**	99.6	≤0.5	≤0.5	97.1 / 95.3	0.06	0.12	100.0 / 100.0	≤0.06	0.12	99.4 / 98.2
Streptococcus pneumoniae (12)	0.06	**0.06**	100.0	0.25	>4	83.3 / 83.3	0.06	0.06	100.0 / —[b]	0.12	>1	83.3 / 83.3
Haemophilus influenzae (32)	0.5	**1**	100.0	0.5	0.5	100.0 / 100.0	0.12	0.25	100.0	—	—	—[b] / —[b]
A. baumannii-calcoaceticus species complex (110)	0.5	**4**	90.0[c]	2	>16	67.3 / —[b]	0.25	4	98.2[c] / —[b]	0.12	>8	80.0 / —[b]
Klebsiella pneumoniae (281)	2	**8**	88.3	1	>16	77.2 / —[b]	0.5	1	96.8 / —[b]	2	>8	77.6 / —[b]
Escherichia coli (214)	0.5	**2**	99.1[c]	2	>16	59.8 / —[b]	0.12	0.25	100.0 / 99.5	1	>8	64.0 / —[b]

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; S, susceptible.
Bold, omadacycline MIC_{50} values.
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 EUCAST breakpoint interpretive criteria.
[a] Omadacycline CABP breakpoint for MSSA was applied for comparison purposes only.
[b] Breakpoint interpretive criteria were unavailable.
[c] % inhibited at ≤4 mg/L.

CONCLUSIONS

- Omadacycline demonstrated potent *in vitro* activity against Gram-positive and -negative bacterial isolates from SSSI, CARTI, and PIHP, including strains expressing resistance to macrolides, oxacillin/penicillin, vancomycin, and tetracycline.
  - Omadacycline was active against staphylococci, including 99.0% of *S. aureus* isolates from SSSI, 99.6% of MSSA from PIHP, and 97.6% of *S. lugdunensis* isolates from SSSI.
  - 99.8%–100% of *S. pneumoniae* isolates from CARTI and PIHP, including penicillin-resistant, tetracycline-resistant, and macrolide-resistant strains, were susceptible to omadacycline.
  - All *E. faecalis* isolates from SSSI, including vancomycin-resistant strains, were susceptible to omadacycline.
  - Omadacycline was active against *H. influenzae* isolates, including 99.7% of *H. influenzae* from CARTI and 100% of *H. influenzae* isolates from PIHP.
  - Omadacycline demonstrated good *in vitro* activity against *E. cloacae* from SSSI (87.5%S [FDA]) and *K. pneumoniae* from SSSI and PIHP (88.3%–88.9%S [FDA]).
  - 97.1%–99.1% of *E. coli* from SSSI and PIHP and 90.0% of *A. baumannii-calcoaceticus* species complex from PIHP were inhibited by ≤4 mg/L of omadacycline.
- The results of this surveillance study support the continued use of omadacycline, especially in ABSSSI and CABP infections where resistant pathogens are likely to be encountered.

ACKNOWLEDGMENTS

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