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# In Vitro Activity of Omadacycline against 7,000 Bacterial Pathogens from the United States Stratified by Infection Type (2019) Michael D. Huband, Michael A. Pfaller, Jennifer M. Streit, Helio S. Sader, Mariana Castanheira JMI Laboratories, North Liberty, Iowa, USA

# 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
- 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 ionizationtime 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.

- strains (Table 1) (Tables 2-3).

#### 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

#### ganism (no. tes

- *Staphylococcus aureus* (736) MRSA (305)
- MSSA (431)
- S. lugdunensis (15)
- Streptococcus agalactiae (28)
- S. pyogenes (68) S. pyogenes macrolide-R (15)
- S. pyogenes tetracycline-R (14) Enterococcus faecalis (60)
- E. faecalis vancomycin-R (2 E. faecium (13)
- E. faecium vancomycin-R (9 Enterobacter cloacae species complex (41
- Klebsiella pneumonia (39)Escherichia coli (87)
- MRSA. methicillin-resistant S. aureus; MSSA, methicillin-susceptible S. aureus; R, resistant madacycline MIC, values are listed in **bol** <sup>a</sup> % inhibited at  $\leq 4$  mg/L.

#### Drganism (no. tes

Streptococcus pneumo S. pneumoniae pe S. pneumoniae ma S. pneumoniae tetr Haemophilus influenza Moraxella catarrhalis ( Omadacycline MIC<sub>an</sub> values are lis Green, susceptible according to C Gray, resistant according to CLSI a – breakpoint interpretive criteria u <sup>b</sup> Oral dosing (penicillin MIC  $\geq 2$  mg/L).

### **RESULTS (CONT.)**

Omadacycline demonstrated potent in vitro activity against S. aureus isolates from SSSI including MRSA and MSSA from PIHP with MIC<sub>50/90</sub> 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<sub>50/90</sub>, 0.06/0.06 mg/L) isolates from SSSI were susceptible to omadacycline (Table 1).

Omadacycline had potent activity against S. pyogenes (MIC<sub>50/90</sub>, 0.06/0.12 mg/L; 98.5%S [FDA]) isolates from SSSI including macrolide- and tetracycline-resistant

Omadacycline was equally active against *S. pneumoniae* isolates from CARTI (MIC<sub>50/90</sub>, 0.06/0.06 mg/L; 99.7%S) and PIHP (MIC<sub>50/90</sub>, 0.06/0.06 mg/L; 100%S)

- Omadacycline was active against penicillin-resistant, macrolide-resistant, and tetracycline-resistant S. pneumoniae isolates from CARTI with MIC<sub>50/90</sub> values of 0.06/0.06-0.12 mg/L and 98.7%-100%S (FDA) (Table 2).

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	Omadacycline			Tetracycline			-	Tigec	ycline	Doxycycline			
ed)	MIC <sub>50 / 90</sub>		%S (FDA)	MIC <sub>50 / 90</sub>		%S (CLSI/ EUCAST)	MIC <sub>50 / 90</sub>		%S (FDA/ EUCAST)		50 / 90	%S (CLSI/ EUCAST	
eus		0.12		≤0.5		94.3 / 92.0			100 / 100		0.25	98.8 / 96.7	
	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	
	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	
	0.06	0.06	100	≤0.5	≤0.5	93.3 / 93.3	0.06	0.06	— <sup>a</sup> / 100	≤0.06	≤0.06	100 / 100	
	0.12	0.25	—	>4	>4	7.1 / 7.1	0.06	0.06	100 / 100	—	—	—	
	0.06	0.12	98.5	0.25	>4	79.4 / 79.4	0.03	0.06	100 / 100	—	—	—	
	0.12	0.12	93.3	>4	>4	40.0 / 40.0	0.06	0.06	100 / 100			—	
)	0.12	0.12	92.9	>4	>4	0.0 / 0.0	0.06	0.06	100 / 100	_	_	_	
is	0.06	0.12	100	>16	>16	21.7 / —	0.12	0.12	100 / 100	—	—	—	
	0.06	—	100	>16	—	0.0 / —	0.06		100 / 100	_	_		
	0.06	0.06	—	>16	>16	23.1 / —	0.06	0.06	— / 100	—	—	—	
	0.06		—	>16	—	11.1 / —	0.06	—	— / 100	_	—	—	
e )	2	4	90.2	2	>16	82.9 / —	0.5	1	95.1 / —	2	8	82.9 / 11	
ae	2	8	89.7	2	>16	66.7 / —	0.5	1	97.4 / —	2	>8	66.7 / —	
	0.5	2	100 <sup>a</sup>	2	>16	78.2 / —	0.25	0.25	100 / 98.9	1	>8	80.5 / —	

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.

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

	On	nadacy	ycline		Tetrac	ycline	Tigecycline			
d)	MIC <sub>50 / 90</sub>		%S (FDA) M		50 / 90	%S (CLSI/ EUCAST)	MIC <sub>50</sub>	0 / 90	%S (FDA/ EUCAST)	
noniae (359)	0.06	0.06	99.7	0.25	>4	78.6 / 78.6	0.03	0.06	98.3 / <u> </u>	
nicillin-R⁵ (40)	0.06	0.06	100	0.25	>4	62.5 / 62.5	0.03	0.06	97.5 / —	
acrolide-R (165)	0.06	0.12	99.4	0.25	>4	60.0 / 60.0	0.03	0.06	97.6 / —	
racycline-R (77)	0.06	0.12	98.7	>4	>4	0.0 / 0.0	0.03	0.06	97.4 / —	
ae (218)	0.5	1	100	0.5	0.5	98.6 / 98.2	0.25	0.5	86.2	
(146)	≤0.12	0.25		0.25	0.25	100 / 100	0.06	0.12	—	
isted in <b>bold</b> ; R, resistant CLSI or FDA breakpoint int or FDA breakpoint interpro unavailable.										

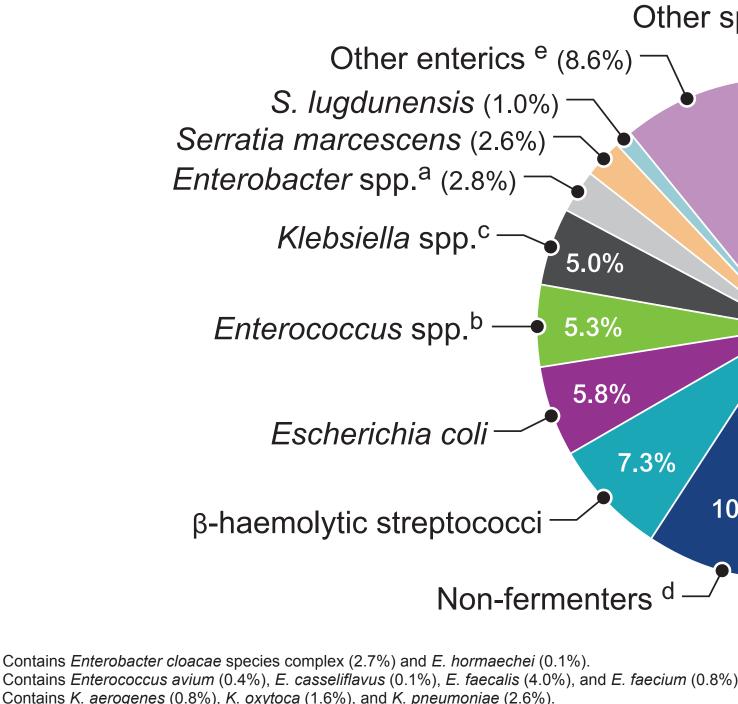
### **RESULTS (CONT.)**

- All vancomycin-susceptible and -resistant *E. faecalis* isolates from SSSI (MIC<sub>50/90</sub>, 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).
- were susceptible to omadacycline (MIC<sub>50/90</sub>, 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
- All *H. influenzae* isolates from CARTI and PIHP (including tigecycline-resistant) 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  $\leq 4 \text{ mg/L}$  of omadacycline (Tables 3-4). - 94.7% of K. pneumoniae isolates from UTI were inhibited by  $\leq 4 \text{ mg/L}$  of
- omadacycline (Table 4).
- 99.8%-100% of *E. coli* isolates from SSSI, CARTI, and UTI (MIC<sub>50/90</sub> values, 0.5/1-2 mg/L) were inhibited by  $\leq 4 \mu g/mL$  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

	C	)madacyclir	ne	Tetracycline				Tigecycli	ne	Doxycycline		
Organism (no. tested)	MIC <sub>50 / 90</sub>		%S (FDA)	MIC <sub>50 / 90</sub>		%S (CLSI/ EUCAST)	MIC <sub>50 / 90</sub>		%S (FDA/ EUCAST)	MIC <sub>50 / 90</sub>		%S (CLSI/ EUCAST)
Staphylococcus aureus (396)		0.25	94.7ª 90.5ª	≤0.5 ≤0.5	≤0.5	94.9 / 93.9	0.12 0.12	0.25 0.25	100 / 100	≤0.06	0.5	97.7 / 96.0
MRSA (168)		0.25			1	94.6 / 94.6			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 / — <sup>ь</sup>	_	_	_
Haemophilus influenzae (73)	0.5	1	100	0.5	0.5	100 / 100	0.25	0.5	87.7	_	_	_
E <i>nterobacter cloacae</i> species complex (65)	2	2	98.5°	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 <sup>d</sup>	2	>16	64.9 / —	0.12	0.25	100 / 100	2	>8	69.1 / —
ARSA, methicillin-resistant <i>S. aureus</i> ; MSSA, methicillin-su Dmadacycline MIC <sub>90</sub> values are listed in <b>bold</b> . Green, susceptible according to CLSI or FDA breakpoint interpr <sup>a</sup> Omadacycline CABP breakpoint for MSSA applied for co <sup>b</sup> breakpoint interpretive criteria unavailable. <sup>c</sup> Omadacycline ABSSSI breakpoint applied for compariso <sup>d</sup> % inhibited at ≤4 mg/L.	terpretive criteria. etive criteria. mparison purpos											

#### Figure 1 Occurrence of Skin and Skin Structure Infection (SSSI) pathogens from **Figure 2 Occurrence of** Figure 3 Occurrence of pathogens from Pneumonia In Hospitalized Patients the omadacycline surveillance program (2019) (PIHP) in the omadacycline surveillance program (2019) **Community Acquired Respiratory Tract Infection (CARTI) pathogens** from the omadacycline Other species (1.3%) Other species (2.2%) surveillance program (2019) Other enterics <sup>e</sup> (8.6%) – S. lugdunensis (1.0%) -Serratia marcescens (2.6%) — Enterococcus spp.<sup>c</sup> (0.6%) -Enterobacter spp.a (2.8%) — Streptococci<sup>a</sup> (2.2%) *Klebsiella* spp.<sup>c</sup> – Haemophilus spp.<sup>b -</sup> /I. catarrha

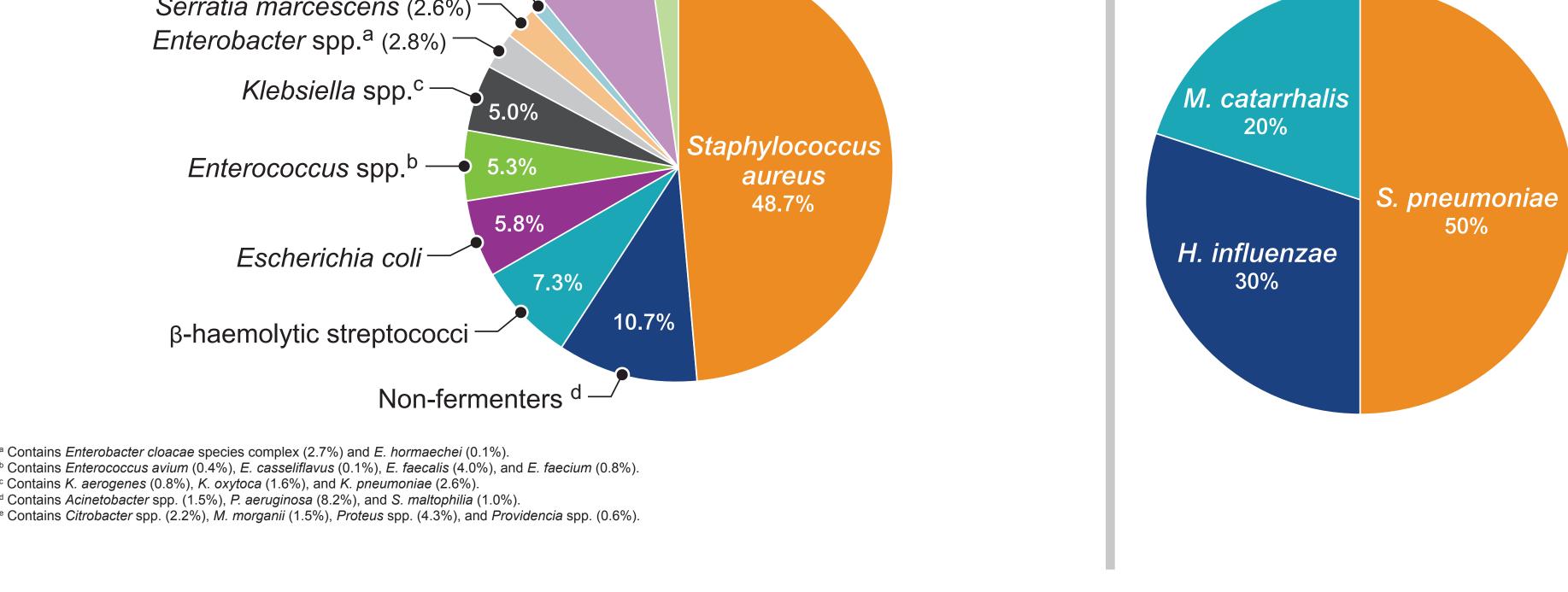


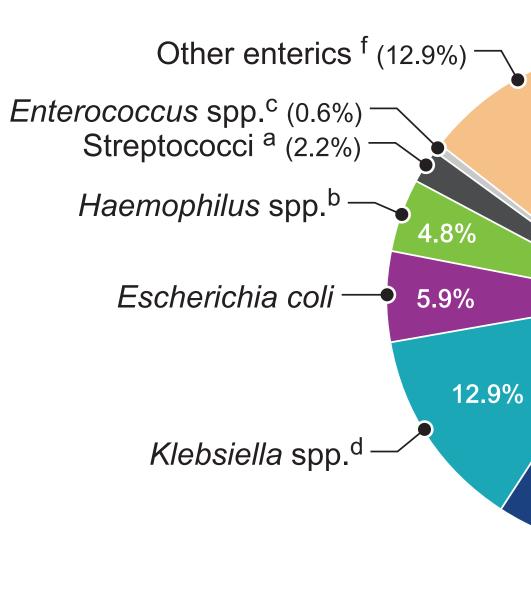
Contains Acinetobacter spp. (1.5%), P. aeruginosa (8.2%), and S. maltophilia (1.0%

### 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.

	Omadacycline			Tetracycline				Tigecyclin	e	Doxycycline			
Organism (no. tested)	MIC <sub>50 / 90</sub>		%S (FDA)	MIC <sub>50 / 90</sub>		%S (CLSI/ EUCAST)	MIC <sub>50 / 90</sub>		%S (FDA/ EUCAST)	МІС	50 / 90	%S (CLSI/ EUCAST)	
<i>Citrobacter freundii</i> 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 / —	
<i>Enterobacter cloacae</i> species complex (32)	2	4	96.9ª	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 <sup>a</sup>	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				
<i>E. faecalis</i> vancomycin-R (2)	0.06	—		>16		0.0 / —	0.12		100 / 100	_	_	_	
<i>E. faecium</i> (18)	0.06	0.25		>16	>16	27.8 / —	0.06	0.12	<u> </u>	_	_	_	
<i>E. faecium</i> vancomycin-R (12)	0.06	0.06		>16	>16	25.0 / —	0.06	0.12	<i>— /</i> 100			_	





<sup>a</sup> Contains β-haemolytic streptococci (0.8%), S. pneumoniae (1.3%), and S. anginosus group (0.1%) <sup>o</sup> Contains *H. influenzae* (4.6%) and *H. parainfluenzae* (0.2%) <sup>2</sup> Contains *E. faecalis* (0.4%) and *E. faecium* (0.2%) <sup>d</sup> Contains K. aerogenes (1.8%), K. oxytoca (2.6%), and K. pneumoniae (8.5%) <sup>e</sup> Contains Acinetobacter spp. (3.1%), P. aeruginosa (25.1%), and S. maltophilia (6.3%). <sup>f</sup> 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 unspeciated *Enterobacteriaceae* (0.3%).

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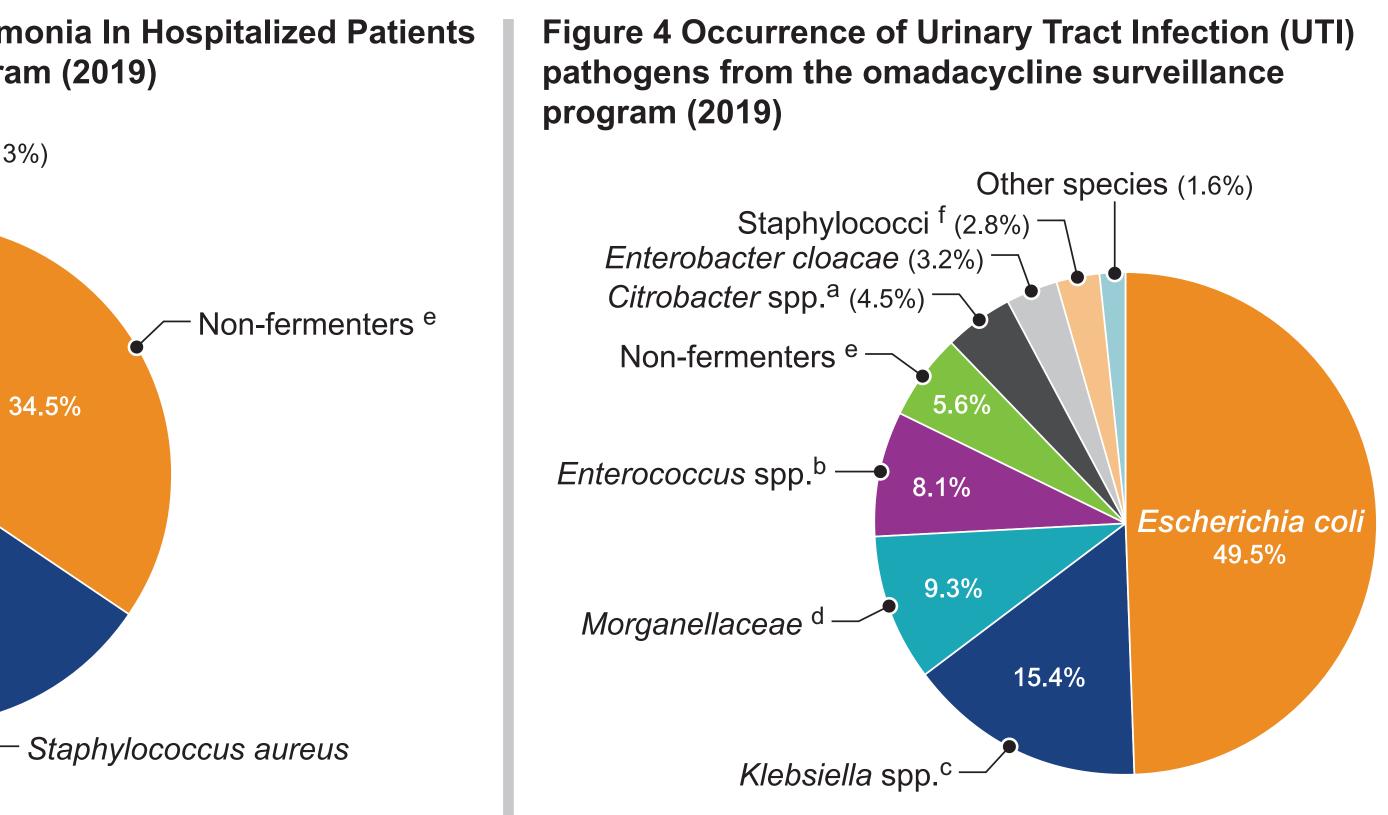
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#### Table 4 Antimicrobial activity of omadacycline and tetracycline comparators against bacterial isolates collected from patients with urinary tract infections (UTI) in United States medical centers during 2019

24.9%



Contains Citrobacter amalonaticus/farmeri (0.1%), C. freundii species complex (3.0%), and C. koseri (1.4%)

Contains Acinetobacter spp. (0.6%), Pseudomonas aeruginosa (4.7%), and Stenotrophomonas maltophilia (0.3%).

Contains K. aerogenes (1.9%), K. oxytoca (2.2%), K. pneumoniae (11.2%), and K. variicola (0.1%).

Contains Enterococcus avium (0.1%), E. faecalis (6.2%), and E. faecium (1.8%)

Contains Morganella morganii (2.6%), Proteus spp. (5%), and Providencia spp. (2%).

<sup>f</sup> Contains Staphylococcus aureus (1.7%) and coagulase-negative staphylococci (1.1%).