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ORIGINAL ARTICLE

In vitro activity of omadacycline against pathogens isolated from Mainland China during 2017–2018

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Abstract

Antibiotic resistance of bacterial pathogens isolated in China is a major concern. Omadacycline is a novel tetracycline derivative that has been approved for use in skin infections and community-acquired pneumonia. This study was conducted to determine the in vitro activity of omadacycline against a large collection of patient isolate medical centers across Mainland China. A total of 1041 recent clinical isolates are obtained from patients hospitalized in 29 provinces and municipalities across China. The in vitro activity of omadacycline and comparator agents was assessed using the microbroth dilution methodology. Omadacycline was active against methicillin-susceptible and -resistant *Staphylococcus aureus* with MIC_{90} values of 0.25 and 1 mg/L, respectively. All isolates of *Enterococcus faecalis* and *Enterococcus faecium*, including vancomycin-resistant isolates, were inhibited by ≤ 0.25 mg/L of omadacycline. It was active against *Streptococcus pneumoniae* irrespective of susceptibility to penicillin or macrolides (MIC_{90} =0.12 mg/L). The minimum inhibitory concentration (MIC) distribution of omadacycline was nearly identical against (extended-spectrum beta-lactamases) ESBL-positive, ESBL-negative, and carbapenemase-producing *Escherichia coli* (MIC_{90} = 4 mg/L). Omadacycline also showed good activity against *Acinetobacter baumannii*, inhibiting all isolates at ≤ 8 mg/L. Against *Hemophilus influenzae* and *Moraxella catarrhalis*, the MICs of omadacycline were low and not influenced by the presence of β-lactamase. Overall, the activity of omadacycline was very good against isolates commonly associated with skin infections and pneumonia, and the susceptibility of Chinese isolates was similar to that reported for these pathogens from large surveillance studies outside China. This suggests that omadacycline could be an option for treatment of these infections in Chinese patients.

Keywords Omadacycline · In vitro activity · MRSA · ESBL

Introduction

Omadacycline is a novel semisynthetic derivative of minocycline known as an aminomethylcycline [1]. Like tetracyclines, omadacycline inhibits bacterial protein synthesis by binding to the aminoacyl-transfer ribonucleic acid (A-site) 30S subunit of the bacterial ribosome [2]. Omadacycline was modified by the C-7 and C-9 positions of the D-ring of minocycline, which resulted for it to overcome common tetracycline-specific resistance mechanisms such as efflux pumps and ribosomal protection, which results in activity against many tetracycline-resistant pathogens [1]. Omadacycline has a broad spectrum of activity that includes Gram-positive and many Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, β-hemolytic streptococci, vancomycin-resistant *Enterococcus* spp., and Enterobacteriaceae as well as anaerobes [3, 4].

The safety and efficacy of omadacycline have been well studied in a series of well-controlled clinical trials. In a study that included an IV to oral switch, omadacycline was non-inferior to linezolid for the treatment of acute bacterial skin and skin

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structure infections (ABSSSI) and had similar response rates for patients infected with methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) [5]. In another study of ABSSSI that utilized oral treatment only, omadacycline given once daily was found to be non-inferior to linezolid given twice daily [6]. Omadacycline was also studied in the treatment of community-acquired bacterial pneumonia (CABP) in a trial that included an option for oral stepdown after 3 days of IV therapy, where it was found to be non-inferior to moxifloxacin [7].

The in vitro activity of omadacycline has been well studied in isolates collected in the USA and in Europe; however, data against recent isolates from Asia including China are sparse [3, 8, 9]. Therefore, this study was conducted to determine the in vitro activity of omadacycline against a large collection of patient isolates from a geographically diverse group of medical centers in Mainland China.

Materials and methods

Antimicrobial susceptibility tests

Susceptibility testing was performed by using broth microdilution following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [10]. Drug powders were obtained from the following sources: omadacycline, Zai Laboratory; imipenem, Merck, China; linezolid, Fresenius Kabi Norge AS, Norway; moxifloxacin, Bayer China; tigecycline, Pfizer; amikacin, amoxicillin, ampicillin, azithromycin, cefepime, ceftriaxone, ceftazidime, clavulanic acid, doxycycline, levofloxacin, oxacillin, penicillin, piperacillin, sulfamethoxazole, tazobactam, trimethoprim, and vancomycin, National Institutes of Food and Drug control (Beijing, China). Quality control was conducted with *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, *Escherichia coli* ATCC 25922, and *Haemophilus influenzae* ATCC 49247 as recommended by the CLSI [11]. Interpretive criteria (breakpoints) assigned by the US Food and Drug Administration (FDA) were applied to both omadacycline and tigecycline (www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria). Omadacycline has different breakpoints for *S. aureus* isolated from patients with ABSSSI and CABP. Therefore, for the purpose of this study, the breakpoints for ABSSSI were used to calculate percent susceptibility. CLSI interpretive criteria were applied to all comparator antibiotics with the exception of tigecycline [11]. β-lactamase production in *H. influenzae* was determined using nitrocefin disk (Becton, Dickinson and Company, USA). The designation of extended-spectrum beta-lactamases (ESBL) was determined by using CLSI methods confirmatory testing with clavulanate [11]. Identification of carbapenemase genes KPC and NDM was performed by PCR and DNA sequencing as described previously [12].

Bacterial isolates

A total of 1041 bacterial isolates (1 per patient) were collected from patients in 52 hospitals in 29 provinces and municipalities in China from October 2017 to September 2018 (Fig. 1). Overall, 81.7% of the isolates were collected from hospitalized patients and 18.3% were from out-patients or emergency room patients. The isolates were obtained from various infection source: 44.1% of isolates were cultured from sputum or respiratory tract; 11.7% from secretions including wound, ulcer, and vaginal; 8.3% from blood; 7.9% from urine; 7.1% from pus; 1.2% from cerebrospinal fluid; and 19.8% of isolates were cultured from another body site. The genus and species of the isolates were identified in Huashan Hospital by using automated microbial identification systems VITEK 2 Compact (BioMerieux, Marcy-l'Étoile, France) or MALDI-TOF (Biomerieux). In total, 600 Gram-positive and 441 Gram-negative organisms were collected that included *S. aureus* ($N = 200$), coagulase-negative *Staphylococcus* spp. ($N = 65$), *Enterococcus faecalis* ($N = 22$), *Enterococcus faecium* ($N = 40$), *Streptococcus pyogenes* ($N = 80$), *Streptococcus agalactiae* ($N = 21$), *Streptococcus dysgalactiae* ($N = 29$), *S. pneumoniae* ($N = 103$), viridans group *Streptococcus* spp. ($N = 40$, including *Streptococcus anginosus*, *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus salivarius*), *E. coli* ($N = 98$), *Klebsiella pneumoniae* ($N = 100$), *Enterobacter cloacae* ($N = 15$), *Citrobacter freundii* ($N = 15$), *Proteus mirabilis* (N = 15), *Serratia marcescens* ($N = 14$), *Acinetobacter baumannii* ($N = 39$), *Haemophilus* spp. ($N = 113$), and *Moraxella catarrhalis* ($N = 32$). Analysis of susceptibility data was conducted using the WHONET 5.6 software (http://www.whonet.org/).

Results

Omadacycline demonstrated excellent activity against Gram-positive pathogens (Table 1). Omadacycline was highly potent against MSSA and methicillin-susceptible coagulase-negative *Staphylococcus* spp. (MSCNS) with MIC_{90} values of 0.25 mg/L and 0.5 mg/L for MSSA and MSCNS, respectively. This activity was similar to that of tigecycline and doxycycline; 100% of isolates were susceptible to all 3 antibiotics. Omadacycline was slightly less active against MRSA and methicillin-resistant coagulase-negative *Staphylococcus* spp. compared with methicillin-susceptible strains with an MIC_{90} value of 1 mg/L for both groups. A comparison of the frequency distribution of omadacycline minimum inhibitory

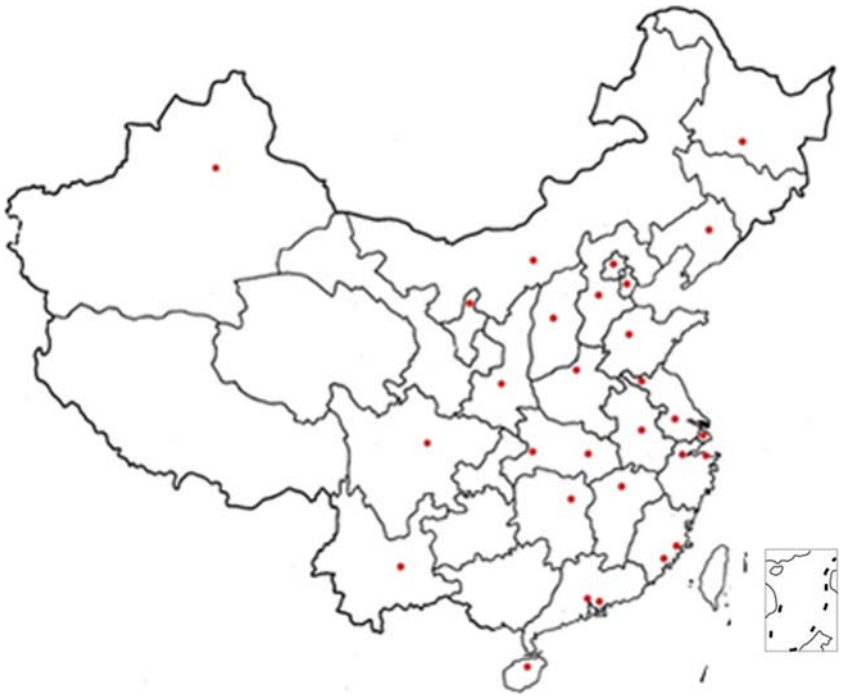

Fig. 1 Distribution of isolate collection sites across China. Clinical isolates of bacterial pathogens obtained from patients hospitalized in 29 provinces and municipalities across China. The location of each contributing hospital is depicted with a red dot

concentrations (MICs) against MRSA and MSSA is shown in Fig. 2a. For MRSA, 81.6% were susceptible to omadacycline, whereas 100% were susceptible to tigecycline (MIC_{90} of 0.25 mg/L). For all groups of staphylococci, omadacycline was more active than the fluoroquinolones that were tested, which showed < 50% susceptibility against methicillin-resistant isolates.

All of the enterococci tested were inhibited by 0.25 mg/L or less of omadacycline. All isolates of *E. faecium* were inhibited by 0.12 mg/L of omadacycline, including isolates that were both susceptible (MIC_{90} 0.12 mg/L) and those that were resistant ($MIC_{90} \leq 0.06$ mg/L) to vancomycin. Omadacycline was as active as tigecycline (100% susceptible, $MIC_{90} =$ 0.25 mg/L), and more active than doxycycline (63.6% susceptible, $MIC_{90} = 4$ mg/L) when tested against *E. faecalis*. For *E. faecium*, the MICs of omadacycline were similar to those of tigecycline (MIC_{90} of 0.12 and ≤ 0.06 mg/L for vancomycin-sensitive *Enterococcus* (VSE) and vancomycin-resistant *Enterococcus* (VRE), respectively, with both compounds) and more active than doxycycline (MIC_{90} of 8 and 4 mg/L for VSE and VRE, respectively). The isolates of *E. faecium* were highly susceptible to omadacycline, to other tetracyclines, and to linezolid, but the majority of the isolates of both vancomycin-susceptible and -resistant *E. faecium* were resistant to fluoroquinolones.

Omadacycline showed good activity against *S. pneumoniae*, with an MIC_{90} of 0.12 mg/L for all groups including penicillin-susceptible (PSSP), -intermediate (PISP), and -resistant *S. pneumoniae* (PRSP) and those resistant to erythromycin. The overall percent susceptibility for all resistance groups of *S. pneumoniae* was 100% for both omadacycline and tigecycline; however, these groups were only 0–35.7% susceptible to doxycycline. The susceptibility of fluoroquinolones remained high; however, the susceptibility of β-lactams (0 and 41.2% for penicillin and ceftriaxone, respectively) and azithromycin (1.5%) was reduced for PRSP. The MIC_{90} values of omadacycline against the β-hemolytic streptococcal isolates *S. pyogenes* and *S. agalactiae* were 0.25 mg/L and 0.12 mg/L, respectively. For *S. pyogenes*, 77.5% of the isolates were susceptible to omadacycline, which was lower than that of tigecycline (100% susceptible). The β-hemolytic streptococci remained highly susceptible to β-lactams; however, *S. pyogenes* had reduced susceptibility to azithromycin and *S. agalactiae* had reduced susceptibility to fluoroquinolones. For viridans group streptococci, the MIC_{90} values for omadacycline, tigecycline, and doxycycline were 0.12 mg/L, ≤ 0.03 mg/L, and 8 mg/L, respectively. For *Streptococcus dysgalactiae*, the MIC_{90} values for omadacycline, tigecycline, and doxycycline were 0.25 mg/L, 0.25 mg/L, and 8 mg/L, respectively.

Omadacycline exhibited good activity against *E. coli* irrespective of ESBL production, exhibiting MIC_{90} values of 4 and 2 mg/L for ESBL-positive and ESBL-negative isolates,

Table 1 In vitro activity of omadacycline and comparators against Gram-positive pathogens isolates in China

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
S. aureus (200)	Omadacycline	≤0.06–2	0.12	0.5	0	91.0
	Tigecycline	≤0.06–0.5	≤0.06	0.12	0 [a]	100
	Doxycycline	0.06–8	0.12	4	0	95.5
	Ampicillin	0.12–> 128	16	64	-[b]	-
	Levofloxacin	0.12–> 128	0.25	32	26.5	73.0
	Moxifloxacin	≤0.06–32	≤0.06	4	22.0	74.0
	Linezolid	0.5–8	1	2	0.5	99.5
	Vancomycin	0.25–1	0.5	0.5	0	100
S. aureus MRSA (98)	Omadacycline	0.12–2	0.25	1	2.0	81.6
	Tigecycline	≤0.06–0.5	0.12	0.25	0[a]	100
	Doxycycline	0.06 - 8	1	4	0	90.8
	Ampicillin	2–> 128	16	64	-[b]	-
	Levofloxacin	0.12–> 128	8	64	52	46.9
	Moxifloxacin	≤0.06–32	1	4	44.9	49.0
	Linezolid	0.5–8	1	2	1.0	99.0
	Vancomycin	0.25–1	0.5	0.5	0	100
S. aureus MSSA (102)	Omadacycline	≤0.06–0.5	0.12	0.25	0	100
	Tigecycline	≤0.06–0.5	≤0.06	0.12	0[a]	100
	Doxycycline	≤0.06–2	0.12	1	0	100
	Ampicillin	0.12–128	2	32	-	-
	Levofloxacin	0.12–8	0.25	0.5	2	98
	Moxifloxacin	≤0.06–1	≤0.06	0.12	0	98
	Linezolid	0.5–4	1	2	0	100
	Vancomycin	0.25–1	0.5	0.5	0	100
Coagulase-negative staphylococci (65)	Omadacycline	0.12–1	0.25	1	-	-
	Tigecycline	≤0.06–0.25	0.12	0.25	-	-
	Doxycycline	0.03–8	0.25	4	0	92.3
	Ampicillin	≤0.06–32	1	8	-	-
	Levofloxacin	0.12–> 128	2	128	30.8	43.1
	Moxifloxacin	≤0.06–64	0.5	8	21.5	66.2
	Linezolid	0.25–> 32	1	1	3.1	95.4
	Vancomycin	0.25–1	0.5	1	0	100
Coagulase-negative staphylococci MRCNS (33)	Omadacycline	0.12–1	0.5	1	-	-
	Tigecycline	≤0.06–0.25	0.12	0.25	-	-
	Doxycycline	0.03–8	0.25	8	0	84.8
	Ampicillin	1–32	4	16	-	-
	Levofloxacin	0.25–> 128	8	> 128	78.8	15.2
	Moxifloxacin	0.06–64	1	16	42.4	39.4
	Linezolid	0.25–> 32	1	1	6.1	93.9
	Vancomycin	0.5–1	0.5	1	0	100
Coagulase-negative staphylococci MSCNS (32)	Omadacycline	0.12–1	0.25	0.5	-	-
	Tigecycline	≤0.06–0.25	0.12	0.12	-	-
	Doxycycline	0.06–4	0.06	0.5	0	100
	Ampicillin	0.06–16	0.25	0.5	-	-
	Levofloxacin	0.12–8	0.25	4	18.8	71.9
	Moxifloxacin	0.06–1	0.06	0.5	0	93.8
	Linezolid	0.5–1	1	1	0	100
	Vancomycin	0.25–1	0.5	1	0	100
Enterococcus faecalis (22)	Omadacycline	0.12–0.25	0.12	0.25	0	100
	Tigecycline	≤0.06–0.25	≤0.06	0.12	0[a]	100
	Doxycycline	0.12–16	4	8	9.1	63.6
	Ampicillin	0.5–1	1	1	0	100
	Levofloxacin	0.5–64	1	2	4.5	95.5
	Moxifloxacin	0.12–16	0.25	0.25	-	-
	Linezolid	0.5–2	1	2	0	100
	Vancomycin	0.25–1	0.5	1	0	100
Enterococcus faecium (40)	Omadacycline	≤0.06–0.12	≤0.06	0.12	-	-
	Tigecycline	≤0.06–0.12	≤0.06	0.12	-	-
	Doxycycline	0.06–8	0.25	8	0	87.5
	Ampicillin	1–> 128	128	> 128	97.5	2.5
	Levofloxacin	1–> 128	64	128	97.5	2.5
	Moxifloxacin	0.25–64	8	16	-	-

Table 1 (continued)

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
	Linezolid	0.5–2	1	1	0	100
	Vancomycin	0.25–> 32	0.5	> 32	45.0	55.0
Enterococcus faecium (vancomycin-susceptible) (22)	Omadacycline	≤ 0.06–0.12	≤ 0.06	0.12	-	-
	Tigecycline	≤ 0.06–0.12	≤ 0.06	0.12	-	-
	Doxycycline	0.06–8	2	8	0	81.8
	Ampicillin	1–> 128	128	> 128	95.5	4.5
	Levofloxacin	1–> 128	64	128	95.5	4.5
	Moxifloxacin	0.25–64	8	16	-	-
	Linezolid	0.5–2	1	1	0	100
	Vancomycin	0.25–0.5	0.5	0.5	0	100
Enterococcus faecium (vancomycin-resistant) (18)	Omadacycline	≤ 0.06–0.12	≤ 0.06	≤ 0.06	-	-
	Tigecycline	≤ 0.06–≤ 0.06	≤ 0.06	≤ 0.06	-	-
	Doxycycline	0.06–8	≤ 0.06	4	0	94.4
	Ampicillin	32–> 128	> 128	> 128	100	0
	Levofloxacin	16–128	64	128	100	0
	Moxifloxacin	4–32	16	16	-	-
	Linezolid	0.5–1	1	1	0	100
	Vancomycin	32–> 32	> 32	> 32	100	0
Streptococcus pneumoniae (103)	Omadacycline	≤ 0.06–0.12	0.12	0.12	0	100
	Tigecycline	≤ 0.015–0.06	≤ 0.015	0.06	0[a]	100
	Doxycycline	0.03–8	2	4	87.4	6.8
	Ceftriaxone	≤ 0.015–16	1	4	35.0	61.2
	Penicillin	≤ 0.015–16	2	4	65.0	14.6
	Levofloxacin	0.25–16	1	1	1.9	98.1
	Moxifloxacin	0.06–8	0.25	0.25	1.0	98.1
	Azithromycin	0.06–> 32	> 32	> 32	94.2	4.9
	Linezolid	≤ 0.25–1	0.5	0.5	0[a]	100
	Vancomycin	≤ 0.12–0.25	≤ 0.12	≤ 0.12	0[a]	100
Streptococcus pneumoniae PSSP (14)	Omadacycline	≤ 0.06–0.12	0.12	0.12	0	100
	Tigecycline	≤ 0.015–0.06	≤ 0.015	0.06	0[a]	100
	Doxycycline	0.03–4	0.5	4	50	35.7
	Ceftriaxone	≤ 0.015–0.06	≤ 0.015	0.03	0	100
	Penicillin	≤ 0.015–0.06	0.06	0.06	0	100
	Levofloxacin	0.5–16	1	1	7.1	92.9
	Moxifloxacin	0.12–2	0.12	0.25	0	92.9
	Azithromycin	0.06–> 32	> 32	> 32	85.7	14.3
	Linezolid	≤ 0.25–1	0.5	0.5	0[a]	100
	Vancomycin	≤ 0.12–0.25	≤ 0.12	≤ 0.12	0[a]	100
Streptococcus pneumoniae PISP (21)	Omadacycline	≤ 0.06–0.12	0.12	0.12	0	100
	Tigecycline	≤ 0.015–0.12	≤ 0.015	0.06	0[a]	100
	Doxycycline	0.5–8	4	8	85.7	0
	Ceftriaxone	≤ 0.015–1	0.12	0.5	0	100
	Penicillin	0.12–1	0.12	1	0	0
	Levofloxacin	0.25–1	1	1	0	100
	Moxifloxacin	0.06–0.25	0.12	0.25	0	100
	Azithromycin	0.25–> 32	> 32	> 32	81	14.3
	Linezolid	≤ 0.25–1	≤ 0.25	0.5	0[a]	100
	Vancomycin	≤ 0.12–0.25	≤ 0.12	≤ 0.12	0[a]	100
Streptococcus pneumoniae PRSP (68)	Omadacycline	≤ 0.06–0.12	0.12	0.12	0	100
	Tigecycline	≤ 0.015–0.06	≤ 0.015	≤ 0.015	0[a]	100
	Doxycycline	0.06–8	2	2	95.6	2.9
	Ceftriaxone	0.5–16	4	4	52.9	41.2
	Penicillin	2–16	2	4	100	0
	Levofloxacin	0.5–32	1	1	1.5	98.5
	Moxifloxacin	0.06–8	0.25	0.25	1.5	98.5
	Azithromycin	1–> 32	> 32	> 32	98.5	1.5
	Linezolid	≤ 0.25–0.5	0.5	0.5	0[a]	100
	Vancomycin	≤ 0.12–0.25	≤ 0.12	≤ 0.12	0[a]	100
Streptococcus pneumoniae (erythromycin-resistant) (96)	Omadacycline	≤ 0.06–0.12	0.12	0.12	0	100
	Tigecycline	≤ 0.015–0.12	≤ 0.015	0.06	0[a]	100
	Doxycycline	0.03–8	2	4	90.6	5.2
	Ceftriaxone	≤ 0.015–16	1	4	37.5	59.4

Table 1 (continued)

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
	Penicillin	≤0.015–16	2	4	3.1	65.6
	Levofloxacin	0.25–32	1	1	2.1	97.9
	Moxifloxacin	0.06–8	0.25	0.25	1	97.9
	Azithromycin	2–> 32	> 32	> 32	100	0
	Linezolid	≤0.25–1	0.5	0.5	0[a]	100
	Vancomycin	≤0.12–0.25	≤0.12	≤0.12	0[a]	100
Streptococcus pyogenes (80)	Omadacycline	≤0.06–0.5	0.12	0.25	1.2	77.5
	Tigecycline	≤0.015–0.06	0.06	0.06	0[a]	100
	Doxycycline	0.06–8	4	4	-	-
	Ceftriaxone	≤0.015–0.25	0.03	0.03	0[a]	100
	Penicillin	≤0.015–0.12	0.06	0.06	0[a]	100
	Levofloxacin	0.25–2	0.5	0.5	0	100
	Moxifloxacin	0.06–0.25	0.12	0.12	-	-
	Azithromycin	0.06–> 32	> 32	> 32	91.1	8.9
	Linezolid	≤0.25–1	0.5	1	0[a]	100
	Vancomycin	≤0.12–0.5	0.25	0.25	0[a]	100
Streptococcus agalactiae (21)	Omadacycline	≤0.06–0.25	0.12	0.12	-	-
	Tigecycline	0.03–0.06	0.06	0.06	0[a]	100
	Doxycycline	0.06–32	4	8	-	-
	Ceftriaxone	0.06–0.06	0.06	0.06	0[a]	100
	Penicillin	0.03–0.12	0.12	0.12	0[a]	100
	Levofloxacin	0.5–> 32	16	32	57.1	42.9
	Moxifloxacin	0.12–4	2	4	-	-
	Azithromycin	0.06–> 32	> 32	> 32	76.2	19
	Linezolid	1–1	1	1	0[a]	100
	Vancomycin	0.25–0.25	0.25	0.25	0[a]	100
Viridans group streptococci (40)	Omadacycline	≤0.06–0.5	0.12	0.12	-	-
	Tigecycline	≤0.015–0.25	≤0.015	0.03	0[a]	100
	Doxycycline	≤0.015–16	1	8	-	-
	Ceftriaxone	0.03–8	0.25	4	17.5	80
	Penicillin	0.06–8	0.25	4	15	45
	Levofloxacin	0.12–32	1	2	10	90
	Moxifloxacin	0.03–4	0.12	0.5	-	-
	Azithromycin	≤0.015–> 32	> 32	> 32	67.5	30
	Linezolid	≤0.25–2	0.5	1	0[a]	100
	Vancomycin	≤0.12–0.5	0.25	0.5	0[a]	100
Streptococcus dysgalactiae (29)	Omadacycline	≤0.06–0.5	0.12	0.25	-	-
	Tigecycline	0.03–0.25	0.06	0.25	0[a]	100
	Doxycycline	0.06–8	0.25	8	-	-
	Ceftriaxone	0.03–0.06	0.03	0.06	0[a]	100
	Penicillin	≤0.015–0.12	0.06	0.06	0[a]	100
	Levofloxacin	0.25–16	0.5	16	24.1	75.9
	Moxifloxacin	0.06–2	0.25	2	-	-
	Azithromycin	0.06–> 32	> 32	> 32	79.3	20.7
	Linezolid	0.5–1	1	1	0[a]	100
	Vancomycin	0.12–0.25	0.25	0.25	0[a]	100

[a] Non-susceptible (susceptible only breakpoint)

[b] No breakpoint assigned

respectively. The MIC frequency distribution for omadacycline is nearly identical when tested against ESBL-positive and -negative strains (Fig. 2b). Omadacycline was highly active against carbapenem-resistant *E. coli* (KPC or NDM producers); 95% of isolates were susceptible to omadacycline (MIC_{90} = 4 mg/L). Overall, for *E. coli*, omadacycline was more active than doxycycline, which had an MIC_{90} value of 32 mg/L and ≤ 56.7% susceptibility for all subsets. Similar to what was seen with *E. coli*, omadacycline showed the same activity against the *Klebsiella pneumoniae* irrespective of ESBL production, with MIC_{90} values of 8 mg/L for both groups, which correlated to 87.5% and 89.3% susceptibility for ESBL-negative and -positive isolates, respectively, which was slightly lower than that for tigecycline (> 90% susceptible). In addition, omadacycline had reduced activity against carbapenem-resistant *K. pneumoniae* (MIC_{90} =

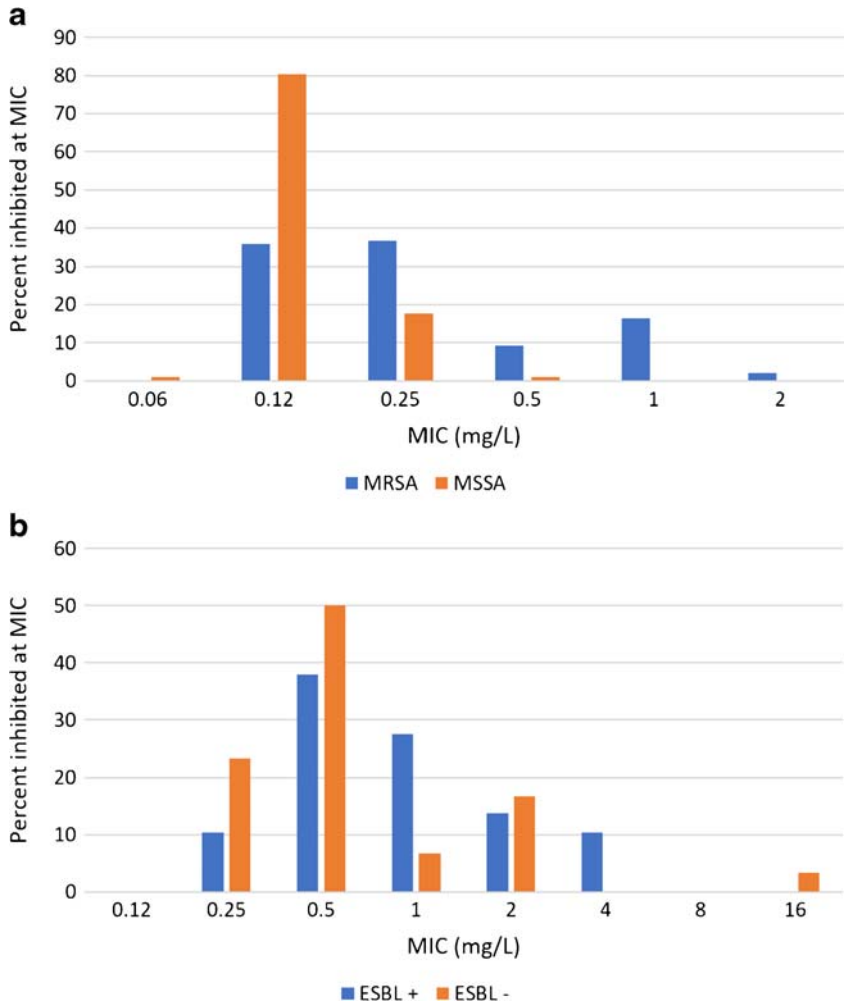

Fig. 2 MIC frequency distribution of omadacycline against key pathogens. The histogram of MIC frequency distribution of omadacycline is shown. **a** *S. aureus*; MRSA ($N = 98$) and MSSA ($N = 102$). **b** *E. coli*; ESBL-positive ($N = 29$) and EBSL-negative ($N = 30$)

32 mg/L, 75% susceptible). Omadacycline was active against *E. cloacae*, *C. freundii*, and *S. marcescens* with MIC_{90} values of 16 mg/L (89.7% susceptible), 4 mg/L (93.3% susceptible), and 4 mg/L (100% susceptible), respectively. All of the isolates of *E. cloacae*, *C. freundii*, and *S. marcescens* were susceptible to tigecycline; however, susceptibility to doxycycline ranged from 66.7 to 86.7%. As expected, omadacycline had limited activity against *P. mirabilis* ($MIC_{90} = 32$ mg/L).

Omadacycline also showed good activity against *A. baumannii*, inhibiting all the carbapenem-susceptible isolates at 1 mg/L. The MIC_{90} increased to 4 mg/L for carbapenem-resistant *A. baumannii*. For comparison, the MIC_{90} values of tigecycline for carbapenem-susceptible and -resistant *A. baumannii* were 0.25 and 2 mg/L, respectively and for doxycycline was 0.25 and 32 mg/L, respectively. Against carbapenem-resistant *A. baumannii*, omadacycline showed similar activity to tigecycline with MIC_{90} values of 4 mg/L and 2 mg/L for omadacycline and tigecycline, respectively. In contrast, none of the comparators had more than 33.3% susceptibility for carbapenem-resistant *A. baumannii*. *H. influenzae* (with or without β-lactamase production) and *Hemophilus parainfluenzae* were very susceptible to omadacycline with MIC_{90} values of 2 mg/L, 1 mg/L, 1 mg/L, respectively (100% susceptible). Omadacycline was highly active against *M. catarrhalis* with all the isolates inhibited at 0.5 mg/L.

Discussion

The overuse and misuse of antibiotics have led to the rapid emergence of antibiotic-resistant bacterial pathogens, thereby reducing their therapeutic potential to treat infections. Multidrug-resistant bacterial pathogens have been widely reported in China, the prevalence of which has been linked to zealous prescribing in the healthcare setting, as well as the availability of these agents in the community pharmacy [13]. In addition, there is still widespread use of antibiotics in veterinary medicine and agriculture, which has led to a high prevalence of antibiotic resistance in livestock [14]. One example is the transmissible colistin-resistance gene *mcr-1* that was first isolated in a porcine *E. coli* strain in China but has

Table 2 In vitro activity of omadacycline and comparators against Gram-negative pathogens isolates in China

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
Escherichia coli (98)	Omadacycline	0.25–16	1	4	-[a]	-
	Tigecycline	≤ 0.06–2	0.12	0.25	0	100
	Doxycycline	≤ 0.25–> 32	8	32	44.9	39.8
	Imipenem	0.12–16	0.25	4	12.2	80.6
	Cefepime	≤ 0.06–> 64	8	> 64	45.9	45.9
	Ceftriaxone	≤ 0.06–> 64	> 64	> 64	60.2	39.8
	Piperacillin/tazobactam	0.5–> 128	2	>128	23.4	75.5
	Amikacin	0.5–> 128	1	16	9.2	92.9
	Levofloxacin	≤ 0.06–> 64	8	32	65.3	30.6
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	72.4	27.6
Escherichia coli (ESBL-positive) (29)	Omadacycline	0.25–4	1	4	-	-
	Tigecycline	0.12–0.5	0.12	0.25	0	100
	Doxycycline	0.5–32	8	32	34.5	44.8
	Imipenem	0.12–0.25	0.25	0.25	0	100
	Cefepime	2–> 64	> 64	> 64	79.3	10.3
	Ceftriaxone	> 64–> 64	> 64	> 64	100	0
	Piperacillin/tazobactam	1–> 128	4	> 128	13.8	86.2
	Amikacin	0.5–> 128	1	> 128	10.3	89.7
	Levofloxacin	≤ 0.06–64	8	32	72.4	24.1
	Trimethoprim-sulfamethoxazole	≤ 0.06/–> 64	> 64	> 64	72.4	27.6
Escherichia coli (ESBL-negative) (30)	Omadacycline	0.25–16	0.5	2	-	-
	Tigecycline	≤ 0.06–0.5	0.12	0.25	0	100
	Doxycycline	0.25–32	4	32	33.3	56.7
	Imipenem	0.12–0.5	0.25	0.25	0	100
	Cefepime	≤ 0.06–0.25	≤ 0.06	0.25	0	100
	Ceftriaxone	≤ 0.06–0.12	≤ 0.06	0.12	0	100
	Piperacillin/tazobactam	0.5–8	1	4	0	100
	Amikacin	0.5–> 128	1	2	3.3	96.7
	Levofloxacin	≤ 0.06–64	0.5	8	36.7	53.3
	Trimethoprim-sulfamethoxazole	≤ 0.06–>64	> 64	> 64	66.7	33.3
Escherichia coli (carbapenemase-positive) (20)	Omadacycline	0.5–8	1	4	-	-
	Tigecycline	0.12–1	0.25	0.25	0	100
	Doxycycline	0.5–> 32	8	32	45	40
	Imipenem	0.25–16	4	8	60	5
	Cefepime	0.25–> 64	64	> 64	80	5
	Ceftriaxone	≤ 0.06–> 64	> 64	> 64	95	5
	Piperacillin/tazobactam	4/–> 128	> 128	> 128	95	5
	Amikacin	0.5–> 128	1	64	15	85
	Levofloxacin	0.25–> 64	16	32	90	10
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	75	25
Escherichia coli tetracycline-R (19)	Omadacycline	0.5–16	1	8	-	-
	Tigecycline	0.12–2	0.12	1	0	100
	Doxycycline	0.5–32	16	32	52.6	31.6
	Imipenem	0.12–0.5	0.25	0.25	0	100
	Cefepime	≤ 0.06–> 64	2	> 64	31.6	57.9
	Ceftriaxone	≤ 0.06–> 64	> 64	> 64	57.9	42.1
	Piperacillin/tazobactam	1–32	2	16	0	94.7

Table 2 (continued)

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
	Amikacin	0.5–128	1	16	5.3	94.7
	Levofloxacin	0.5–> 64	8	> 64	73.7	26.3
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	78.9	21.1
Klebsiella pneumoniae (100)	Omadacycline	0.25–64	2	16	13.0	77.0
	Tigecycline	≤ 0.06–8	0.5	2	2.0	94.0
	Doxycycline	≤ 0.25–32	8	32	33.0	44.0
	Imipenem	≤ 0.06–64	0.25	16	23.0	76.0
	Cefepime	≤ 0.06–> 64	32	> 64	58.0	40.0
	Ceftriaxone	≤ 0.06–> 64	> 64	> 64	63.0	36.0
	Piperacillin/tazobactam	≤ 0.12–> 128	8	> 128	26.0	68.0
	Amikacin	0.25–> 128	0.5	> 128	17.0	83.0
	Levofloxacin	≤ 0.06–> 64	0.5	64	38.0	56.0
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	55.0	45.0
Klebsiella pneumoniae (ESBL-positive) (28)	Omadacycline	1–32	4	8	7.1	89.3
	Tigecycline	0.25–4	0.5	1	0	96.4
	Doxycycline	1–32	8	32	42.9	17.9
	Imipenem	≤ 0.06–1	0.25	0.5	0	100
	Cefepime	0.5–> 64	64	> 64	89.3	10.7
	Ceftriaxone	4–> 64	> 64	> 64	100	0
	Piperacillin/tazobactam	1–> 128	8	> 128	17.9	82.1
	Amikacin	0.5–> 128	0.5	4	3.6	96.4
	Levofloxacin	≤ 0.06–> 64	0.5	32	35.7	60.7
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	78.6	21.4
Klebsiella pneumoniae (ESBL-negative) (32)	Omadacycline	0.25–16	1	8	3.1	87.5
	Tigecycline	≤ 0.06–2	0.25	1	0	100
	Doxycycline	025–16	1	8	6.2	78.1
	Imipenem	0.12–0.5	0.25	0.25	0	100
	Cefepime	≤ 0.06–1	≤ 0.06	0.25	0	100
	Ceftriaxone	≤ 0.06–0.25	≤ 0.06	0.12	0	100
	Piperacillin/tazobactam	≤ 0.12–16	2	8	0	100
	Amikacin	0.25–> 128	0.5	1	3.1	96.9
	Levofloxacin	≤ 0.06–1	≤ 0.06	0.5	0	93.8
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	≤ 0.06	> 64	15.6	84.4
Klebsiella pneumoniae (carbapenemase-positive) (20)	Omadacycline	1–64	4	32	25	75
	Tigecycline	0.25–8	0.5	2	5	90
	Doxycycline	1–32	2	32	35	55
	Imipenem	0.5–32	16	32	95	5
	Cefepime	64–> 64	> 64	> 64	100	0
	Ceftriaxone	> 64–> 64	> 64	> 64	100	0
	Piperacillin/tazobactam	2–> 128	> 128	> 128	90	5
	Amikacin	0.25–> 128	> 128	> 128	55	45
	Levofloxacin	≤ 0.06–> 64	16	> 64	65	25
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	60	40
Klebsiella pneumoniae tetracycline-R (20)	Omadacycline	1–64	8	16	25	45
	Tigecycline	0.25–8	1	4	5	85
	Doxycycline	0.25–32	16	32	60	15
	Imipenem	0.12–64	0.25	16	20	75

Table 2 (continued)

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
	Cefepime	0.25–> 64	64	> 64	65	25
	Ceftriaxone	≤ 0.06–> 64	> 64	> 64	80	20
	Piperacillin/tazobactam	1–> 128	16	> 128	35	55
	Amikacin	0.25–> 128	0.5	> 128	20	80
	Levofloxacin	≤ 0.06–> 64	8	> 64	75	20
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	80	20
Enterobacter cloacae (15)	Omadacycline	1–32	2	16	13.3	86.7
	Tigecycline	0.25–2	0.5	2	0	100
	Doxycycline	0.5–> 32	2	32	13.3	86.7
	Imipenem	0.25–16	0.5	8	20	80
	Cefepime	≤ 0.06–> 64	0.12	> 64	20	73.3
	Ceftriaxone	≤ 0.06–> 64	0.25	> 64	33.3	66.7
	Piperacillin/tazobactam	1–> 128	2	> 128	20	66.7
	Amikacin	0.5–> 128	0.5	> 128	13.3	86.7
	Levofloxacin	≤ 0.06–16	≤ 0.06	8	13.3	80
	Trimethoprim-sulfamethoxazole	≤ 0.0–> 64	≤ 0.06	> 64	26.7	73.3
Citrobacter freundii (15)	Omadacycline	0.5–16	1	4	-	-
	Tigecycline	0.12–1	0.25	0.5	0	100
	Doxycycline	1–32	1	32	20	66.7
	Imipenem	0.25–64	0.5	8	20	80
	Cefepime	≤ 0.06–> 64	0.25	64	20	73.3
	Ceftriaxone	≤ 0.06–> 64	0.5	> 64	46.7	53.3
	Piperacillin/tazobactam	1–> 128	2	> 128	20	73.3
	Amikacin	0.5–> 128	0.5	1	6.7	93.3
	Levofloxacin	≤ 0.06–8	0.5	8	26.7	53.3
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	≤ 0.06	> 64	33.3	66.7
Serratia marcescens (14)	Omadacycline	1–4	2	4	-	-
	Tigecycline	0.5–4	1	1	0	92.9
	Doxycycline	1–8	4	8	0	78.6
	Imipenem	0.5–> 64	0.5	> 64	14.3	85.7
	Cefepime	≤ 0.06– >64	0.25	64	14.3	85.7
	Ceftriaxone	0.12–> 64	0.25	> 64	14.3	85.7
	Piperacillin/tazobactam	1–> 128	2	128	14.3	85.7
	Amikacin	0.5–> 128	1	2	7.1	92.9
	Levofloxacin	≤ 0.06–32	0.25	4	14.3	85.7
	Trimethoprim-sulfamethoxazole	≤ 0.06–0.25	0.12	0.25	0	100
Proteus mirabilis (15)	Omadacycline	8–64	32	64	-	-
	Tigecycline	2–8	4	8	26.7	20
	Doxycycline	16–> 32	32	64	100	0
	Imipenem	0.5–2	1	2	0	60
	Cefepime	≤ 0.06–16	0.25	4	6.7	86.7
	Ceftriaxone	≤ 0.06–> 64	≤ 0.06	> 64	26.7	66.7
	Piperacillin/tazobactam	0.25–2	0.5	1	0	100
	Amikacin	1–8	2	4	0	100
	Levofloxacin	≤ 0.06–32	1	32	46.7	33.3
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	> 64	> 64	66.7	33.3

Table 2 (continued)

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
Acinetobacter baumannii (39)	Omadacycline	≤ 0.06–8	1	4	-	-
	Tigecycline	≤ 0.06–4	0.5	2	-	-
	Doxycycline	≤ 0.25–32	32	32	53.8	46.2
	Imipenem	≤ 0.06–32	8	16	53.8	46.2
	Cefepime	1–> 64	64	> 64	53.8	46.2
	Ceftazidime	2–> 64	64	> 64	51.3	46.2
	Piperacillin/tazobactam	≤ 0.12–> 128	> 128	> 128	53.8	41.0
	Amikacin	0.25–> 128	1	> 128	43.6	56.4
	Levofloxacin	≤ 0.06–32	8	16	53.8	46.2
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	0.5	> 64	38.5	61.5
Acinetobacter baumannii (carbapenem-susceptible) (18)	Omadacycline	≤ 0.06–1	0.12	1	-	-
	Tigecycline	≤ 0.06–0.25	0.12	0.25	-	-
	Doxycycline	0.25–2	0.25	0.25	0	100
	Imipenem	≤ 0.06–0.5	0.25	0.5	0	100
	Cefepime	1–8	2	4	0	100
	Ceftazidime	2–8	4	8	0	100
	Piperacillin/tazobactam	≤ 0.12–32	0.25	32	0	88.9
	Amikacin	0.25–1	0.5	1	0	100
	Levofloxacin	≤ 0.06–0.25	0.12	0.25	0	100
	Trimethoprim-sulfamethoxazole	≤ 0.06–> 64	≤ 0.06	0.12	5.6	94.4
Acinetobacter baumannii (carbapenem-resistant) (21)	Omadacycline	1–8	2	4	-	-
	Tigecycline	0.5–4	2	2	-	-
	Doxycycline	16–32	32	32	100	0
	Imipenem	8–32	16	16	100	0
	Cefepime	32–> 64	> 64	> 64	100	0
	Ceftazidime	16–> 64	> 64	> 64	95.2	0
	Piperacillin/tazobactam	> 128–> 128	> 128	> 128	100	0
	Amikacin	0.5–> 128	> 128	> 128	81	19
	Levofloxacin	8–32	16	16	100	0
	Trimethoprim-sulfamethoxazole	0.12–> 64	32	> 64	66.7	33.3
Haemophilus influenzae (101)	Omadacycline	≤ 0.06–2	1	2	0	100
	Tigecycline	≤ 0.06–2	1	2	0	100
	Doxycycline	≤ 0.015–2	0.12	0.25	-	-
	Ceftriaxone	≤ 0.015–0.25	≤ 0.015	0.12	0	100
	Ampicillin	≤ 0.06–> 128	4	128	48.5	48.5
	Amoxicillin/clavulanic acid	0.12–> 16	2	8	11.9	88.1
	Levofloxacin	≤ 0.015–0.5	≤ 0.015	0.5	0[b]	100
	Moxifloxacin	≤ 0.015–1	0.03	0.5	0 [b]	100
	Azithromycin	≤ 0.06–> 32	2	> 32	34.6[b]	65.3
Haemophilus influenzae (β-lactamase positive) (50)	Omadacycline	≤ 0.06–2	1	2	0	100
	Tigecycline	1–2	2	2	0	100
	Doxycycline	0.06–0.5	0.12	0.25	-	-
	Ceftriaxone	≤ 0.015–0.25	0.06	0.12	0	100
	Ampicillin	0.5–> 128	64	> 128	96	4
	Amoxicillin/clavulanic acid	1–32	4	8	24	76
	Levofloxacin	≤ 0.015–0.5	≤ 0.015	0.5	0[b]	100
	Moxifloxacin	≤ 0.015–1	0.03	0.5	0[b]	100

Table 2 (continued)

Organism (*N*)	Antimicrobial	MIC (mg/L)			R%	S%
		Range	MIC_{50}	MIC_{90}		
	Azithromycin	≤ 0.06–> 32	> 32	> 32	64[b]	36
Haemophilus influenzae (β-lactamase negative) (51)	Omadacycline	0.5–2	1	1	0	100
	Tigecycline	0.06–1	1	1	0	100
	Doxycycline	≤ 0.015–0.25	0.12	0.25	-	-
	Ceftriaxone	≤ 0.015–0.25	≤ 0.015	0.12	-	100
	Ampicillin	≤ 0.06–32	0.5	1	5.9	92.2
	Amoxicillin/clavulanic acid	0.12–4	1	2	7.8	92.2
	Levofloxacin	≤ 0.015–0.5	≤ 0.015	0.12	0[b]	100
	Moxifloxacin	≤ 0.015–0.5	0.03	0.12	0[b]	100
	Azithromycin	≤ 0.06–> 32	2	2	5.9[b]	94.1
Hemophilus parainfluenzae (12)	Omadacycline	0.5–1	1	1	0	100
	Tigecycline	1–2	2	2	0	100
	Doxycycline	0.12–0.5	0.25	0.25	-	-
	Ceftriaxone	≤ 0.015–0.25	0.06	0.25	-	100
	Ampicillin	0.25–> 128	0.5	1	8.3	91.7
	Amoxicillin/clavulanic acid	0.5–4	0.5	2	0	100
	Levofloxacin	0.03–1	0.12	1	-	100
	Moxifloxacin	0.06–1	0.25	1	-	100
	Azithromycin	0.12–2	1	2	-	100
Moraxella catarrhalis (32)	Omadacycline	0.12–0.5	0.25	0.5	-	-
	Tigecycline	0.06–0.5	0.5	0.5	-	-
	Doxycycline	0.06–1	0..12	0.12	-	-
	Ceftriaxone	≤ 0.015–1	0.25	1	-	100
	Ampicillin	≤ 0.06–4	1	4	-	-
	Amoxicillin/clavulanic acid	0.12–0.5	0.25	0.5	0	100
	Levofloxacin	0.03–1	0.06	0.5	-	100
	Moxifloxacin	0.03–0.5	0.06	0.12	-	-
	Azithromycin	≤ 0.06–> 32	≤ 0.06	> 32	-	78.1

[a] No breakpoint assigned

[b] Non-susceptible (susceptible-only breakpoint)

now been found in human infections worldwide [15]. Many of these antibiotics wind up in sewage and wastewater, leading to significant quantities of antibiotics in the rivers of China, compounding the problem of increased exposure to antibiotics [16].

In the clinical setting, the prevalence of antibiotic resistance in China increased to more than three times that of the USA between the years 1999 and 2003 [17]. A recent meta-analysis showed that Chinese patients infected with antibiotic-resistant pathogens were at a greater risk of mortality compared with those with susceptibility or those without infection, with a significant increase in overall costs of the hospital stay [18]. New antimicrobial agents are needed to address the resistant pathogens found in China.

Omadacycline was developed to circumvent resistance mechanisms that affect the older generation of tetracyclines including minocycline and doxycycline. Omadacycline retains activity against bacterial strains that carry resistance genes for ribosomal protection (e.g., *tet*M) and tetracycline efflux (e.g., *tetA*, *tet*K, and *tet*L) [19]. In addition, there is no cross-resistance of omadacycline with other classes of antibiotics [20]. The safety and efficacy of omadacycline have been well studied in a series of well-controlled clinical trials. The clinical efficacy of omadacycline has been demonstrated, and it has been approved for use in adult patients in the treatment of CABP and ABSSSI in the USA [5–7, 21]. The proven efficacy of the oral formulation of omadacycline is an attribute that is not found in the other

new-generation tetracyclines, tigecycline, and eravacycline that are only available through IV therapy.

In this study, the in vitro activity of omadacycline was assessed for a broad range of Gram-positive and Gram-negative pathogens (Table 1 and Table 2). Of note, omadacycline showed good activity against the pathogens that are most commonly associated with ABSSSI and CABP including *S. aureus*, *S. pyogenes*, *E. faecalis*, *S. pneumoniae*, and *H. influenzae*. These results were similar to those of the SENTRY surveillance study that included isolates from China in that the MIC_{50} and MIC_{90} values were nearly identical for the key pathogens causing ABSSSI and CABP [22]. The fact that the isolates for the SENTRY study were collected in 2013 and the isolates examined in the present study were collected in 2017–2018 suggests that there has been no decrease in the overall susceptibility to omadacycline in the intervening time period. The results of this study also mirror studies performed with isolates from the USA and Europe, demonstrating that activity of omadacycline against pathogens causing ABSSSI and CABP is universal across the globe [3].

Of particular importance, omadacycline demonstrated good activity against *S. aureus*, including MRSA. Surveys have shown that almost 50% of hospital-associated infections caused by *S. aureus* in China were attributed to MRSA [23]. Furthermore, the incidence of nasal carriage of MRSA and community-associated (CA) infections caused by MRSA appears to be on the rise in China [24, 25]. Many of these CA-MRSA were found in skin and soft-tissue infections, an indication in which omadacycline has demonstrated clinical efficacy. Therefore, the option of an oral formulation of omadacycline could be beneficial in this setting. The high prevalence of MRSA in hospitals and communities has inevitably led to the increased use of glycopeptides and other anti-MRSA agents and have promoted the development of glycopeptide non-susceptible strains [23]. In this regard, omadacycline could be viewed as a glycopeptide-sparing agent.

In summary, this study confirmed the excellent in vitro activity of omadacycline against Chinese pathogens associated with ABBSSSI and CABP. This, coupled with the oral dosing option, makes omadacycline an attractive option for treatment of these infections in Chinese patients.

Code availability Not applicable.

Authors' contributions All authors made substantial contributions to the conception or design of the work.

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Data availability Data can be provided upon request.

Compliance with ethical standards

Conflict of interest Antimicrobial development specialists, LLC, was contracted to during 2019 to perform services for Boston Pharma, Carb-X, Colgate Palmolive, ContraFect Corp., Emergent Biosciences, Entasis Therapeutics, EXDA, Nabriva, NacuGen, Novartis, RecreoPharma, Sihuan Pharmaceutical, SuperTrans Medical, Tetraphase, Theravance, University of Waterloo, Wellcome Trust, X-Biotix, and Zai Labs.

Ethical approval This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University (Number: 2018-349).

Consent to participate Not applicable.

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