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Antibacterial Activity of Eravacycline (TP-434), a Novel Fluorocycline, against Hospital and Community Pathogens

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Eravacycline (TP-434 or 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetracycline) is a novel fluorocycline that was evaluated for antimicrobial activity against panels of recently isolated aerobic and anaerobic Gram-negative and Gram-positive bacteria. Eravacycline showed potent broad-spectrum activity against 90% of the isolates (MIC_{90}) in each panel at concentrations ranging from ≤0.008 to 2 μg/ml for all species panels except those of *Pseudomonas aeruginosa* and *Burkholderia cenocepacia* (MIC_{90} values of 32 μg/ml for both organisms). The antibacterial activity of eravacycline was minimally affected by expression of tetracycline-specific efflux and ribosomal protection mechanisms in clinical isolates. Furthermore, eravacycline was active against multidrug-resistant bacteria, including those expressing extended-spectrum β-lactamases and mechanisms conferring resistance to other classes of antibiotics, including carbapenem resistance. Eravacycline has the potential to be a promising new intravenous (i.v.)/oral antibiotic for the empirical treatment of complicated hospital/health care infections and moderate-to-severe community-acquired infections.

Multidrug-resistant bacteria pose a significant threat to public health. Antimicrobial resistance and its global spread threaten the continued effectiveness of many medicines used today, while at the same time, they jeopardize important medical procedures that require antimicrobial therapy to be successful (1). For example, the crude mortality rate was higher for adult patients with carbapenem-resistant *Klebsiella pneumoniae* infections than for those with carbapenem-susceptible *K. pneumoniae* infections (50.0% versus 25.7%) (2). Because carbapenem-resistant *Enterobacteriaceae* (CRE) are also resistant to most antibiotics, including cephalosporins, fluoroquinolones, and most aminoglycosides, few therapeutic options exist for the treatment of invasive infections caused by these pathogens (3–5). Of the 37 CRE that have been reported in the United States, the last 15 have been reported since July 2012 (6). In the United States, methicillin-resistant *Staphylococcus aureus* (MRSA) alone annually infects more than 94,000 people and kills nearly 19,000—more deaths than from homicides, HIV/AIDS, Parkinson's disease, or emphysema (5, 7). Additionally, resistant bacteria create an immense economic burden. The medical costs attributable to antimicrobial resistance ranged from $18,588 to $29,069 per patient in one sensitivity analysis of high-risk patients, with an excess duration of hospital stay of 6.4 to 12.7 days and with higher attributable mortality rates (8). Several studies have suggested that annual costs of antibiotic-resistant infections are a staggering $21 billion to $34 billion in the United States alone (9).

The need for new antibiotics to treat the increasing number of multidrug-resistant bacteria was recognized most recently in April 2011 by the World Health Organization's call for a six-point global policy package that includes joint planning, surveillance, drug regulation, rational use of medicines, infection prevention and control, and innovation and research (10). In some countries, there is little difference in the incidences of multidrug-resistant pathogens in the community and in the hospital; most notably, extended-spectrum β-lactamase (ESBL)-producing and/or carbapenem-resistant *Enterobacteriaceae* are being isolated in patients with no prior contact with the health care system, resulting in increased hospital stays for otherwise healthy adults with urinary tract infection or pyelonephritis (3, 11). In the United States, carbapenem-resistant health care-associated *K. pneumoniae* urinary tract infections are endemic in certain New York hospitals and carbapenem-resistant *K. pneumoniae* have spread to at least 33 U.S. states and have been described in many other countries (12, 13).

Eravacycline is a novel fluorocycline antibiotic designed to overcome resistance to common tetracycline-specific efflux and ribosomal protection mechanisms and is impervious to other antibiotic-specific resistance mechanisms (14–17). Similar to other members of the tetracycline antibiotic class, eravacycline has been shown to be a potent, mechanism-based inhibitor of the bacterial ribosome (16). It has modifications at both the C-7 (fluorine) and C-9 [2-(pyrrolidin-1-yl)ethanamido] positions on the tetracyclic core that were made possible by using a totally synthetic route (Fig. 1) (15, 18, 19). In this work, we show that eravacycline has broad-spectrum antimicrobial activity, with MIC_{90} values of ≤2 μg/ml against panels of all major bacterial species except for *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*.

MATERIALS AND METHODS

Bacterial strains. Recently isolated, demographically diverse clinical isolates were obtained from or evaluated at Micromyx, LLC (Kalamazoo, MI); Eurofins Medinet (Chantilly, VA); International Health Management Associates, Inc. (IHMA; Schaumburg, IL); and Hershey Medical Center (Hershey, PA) and included over 200 baseline isolates from a phase 2 trial for treatment of complicated intra-abdominal infections conducted by Tetraphase Pharmaceuticals (20). Species-appropriate quality control (QC) strains were used to ensure laboratory standards, as guided by Clinical and Laboratory Standards Institute (CLSI) guidelines (21–23). The

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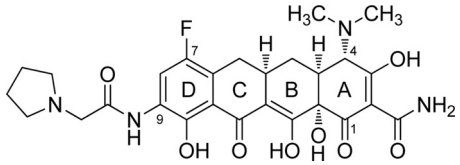

FIG 1 Chemical structure of eravacycline (TP-434).

QC strains were obtained from the American Type Culture Collection (Manassas, VA). *Staphylococcus aureus* strains SA981 (original strain name, K28) and SA982 (original strain name, K40) are an isogenic pair, with SA982 overexpressing the NorA pump (24). *S. aureus* strain SA983 (original strain name, K181) is the parent of SA984 (original strain name, K2068), a strain that overexpresses *mepA* (25).

Genotypic detection of β-lactamases. Detection of ESBL genes by PCR was done at the IHMA or by standard singleplex PCR methodology at Tetraphase Pharmaceuticals, using previously reported consensus primers for family or multiple-related families of genes, including $bla_{\text{OXA-1-like}}$, bla_{SHV}, $bla_{\text{CTX-M-1-3-15}}$, $bla_{\text{CTX-M-2}}$, $bla_{\text{CTX-M-9-14}}$, $bla_{\text{CTX-M-8-25-26-39-41}}$, and bla_{KPC} (26). Plasmid-mediated *ampC* family-specific genes were distinguished by using primers described previously by Perez-Perez and Hanson (27) that targeted MOX-1, MOX-2, CMY-1, CMY-8 to CMY-11, LAT-1 to LAT-4, CMY-2 to CMY-7, BIL-1, DHA-1, DHA-2, ACC, MIR-1T, ACT-1, and FOX-1 to FOX-5b. Primers designed in-house were derived from reported GenBank sequences for bla_{NDM}, bla_{TEM}, bla_{SPM}, bla_{GIM}, bla_{IMP}, bla_{VIM}, bla_{SIM}, bla_{KHM}, $bla_{\text{AIM-1}}$, bla_{PER}, bla_{VEB}, and bla_{ADC}. All in-house samples providing a PCR product were sequenced (Genewiz, South Plainfield, NJ) to confirm ESBL gene identity compared to reported GenBank sequences.

Source of antibiotics. Commercial-grade antibiotics were obtained from the USP (Rockville, MD), ChemPacific Corp. (Baltimore, MD), or Sigma-Aldrich, (St. Louis, MO). Eravacycline was synthesized as described previously by Xiao et al. (15).

Antibiotic susceptibility. MIC values were determined by using microtiter microdilution broth or agar dilution for aerobic and anaerobic organisms, respectively, according to CLSI standardized methodology (21–23). Antibiotic resistance or insensitivity was determined according to current CLSI guidelines (22).

RESULTS

Activity of eravacycline and comparators against Gram-negative pathogens. The *in vitro* activity of eravacycline was evaluated against 2,644 Gram-negative aerobic isolates (Table 1). The collection of organisms contained clinically important species, and many of the isolates were resistant to one or more of the comparator compounds examined. In the vast majority of instances, the MIC_{90} value for eravacycline was equivalent to or lower than that of comparators for each organism/phenotypic grouping.

Eravacycline exhibited MIC_{90} values of ≤0.5 μg/ml against *Escherichia coli* (including ESBL-producing isolates), *Salmonella* spp., *Shigella* spp., *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Acinetobacter lwoffii*. Of the 445 *E. coli* isolates tested, 29% (n = 127) were intermediately resistant (I) or resistant (R) to third-generation cephalosporins, including isolates confirmed by PCR to contain one or more of the following ESBLs or carbapenemases: CTX-M (n = 53), TEM (n = 35), OXA (n = 16), SHV (n = 22), CMY (n = 13), NDM (n = 2), ACT-5 (n = 1), and DHA-1 (n = 1). In addition to eravacycline maintaining an $MIC_{50/90}$ of 0.25/0.5 μg/ml against the subset of *E. coli* isolates with I/R phenotypes for third-generation cephalosporins, this antibiotic was also equally potent against the fluoroquinolone-resistant (n = 143), aminoglycoside-resistant (n = 79), and multidrug-resistant (resistant to all three antibiotic classes) (n = 40) subsets of isolates. The $MIC_{50/90}$ value for eravacycline for a subset of 157 tetracycline-resistant *E. coli* isolates was also 0.25/0.5 μg/ml, consistent with previous work showing that eravacycline was minimally affected by major Gram-negative tetracycline-specific resistance mechanisms (16).

Eravacycline MIC_{90} values were 1 to 2 μg/ml against panels of clinical isolates of *Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *K. pneumoniae*, *Klebsiella oxytoca*, *Legionella pneumophila*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Serratia marcescens*, and *Stenotrophomonas maltophilia* (Table 1). Notably, eravacycline MIC_{90} values were unchanged ($MIC_{50/90}$ = 0.5/2 μg/ml) for subsets of *C. freundii*, *E. cloacae*, *E. aerogenes*, *K. pneumoniae*, and *K. oxytoca* isolates displaying third-generation cephalosporin I or R phenotypes. Among the 210 and 90 *K. pneumoniae* isolates displaying I/R phenotypes for third-generation cephalosporins and carbapenems, respectively, were isolates confirmed by PCR to contain genes encoding one or more of the following: CTX-M (n = 29), TEM (n = 17), OXA (n = 6), SHV (n = 57), KPC (n = 20), NDM (n = 3), DHA (n = 1), and FOX (n = 1). Susceptibility to eravacycline was also unchanged ($MIC_{50/90}$ = 0.5/2 μg/ml) against subsets of *K. pneumoniae* isolates displaying fluoroquinolone-resistant (n = 156), aminoglycoside-resistant (n = 119), and multidrug-resistant (aminoglycoside, fluoroquinolone, and either carbapenem I/R [n = 37] or third-generation cephalosporin I/R [n = 74]) phenotypes. For *A. baumannii* isolates (n = 52) displaying resistance to carbapenems, fluoroquinolones, and aminoglycosides, $MIC_{50/90}$ values for eravacycline were 0.5/2 μg/ml, or 2-fold higher than those of the combined set of strains; eravacycline $MIC_{50/90}$ values were also minimally affected by tetracycline resistance in a subset of *A. baumannii* isolates (n = 69; $MIC_{50/90}$ = 0.5/2 μg/ml). Activity of eravacycline against *P. mirabilis* isolates expressing fluoroquinolone-resistant (n = 43; $MIC_{50/90}$ = 2/4 μg/ml), aminoglycoside-resistant (n = 24; $MIC_{50/90}$ = 2/4 μg/ml), third-generation cephalosporin-I/R (n = 21; $MIC_{50/90}$ = 1/4 μg/ml), carbapenem I/R (n = 136; $MIC_{50/90}$ = 1/4 μg/ml), and tetracycline-resistant (n = 109; $MIC_{50/90}$ = 1/2 μg/ml) phenotypes was within 2-fold the $MIC_{50/90}$ values for all *P. mirabilis* isolates combined ($MIC_{50/90}$ = 1/2 μg/ml). Against carbapenem-I/R (n = 34), fluoroquinolone-resistant (n = 36), aminoglycoside-resistant (n = 26), and tetracycline-resistant (n = 25) *E. cloacae* isolates, eravacycline showed $MIC_{50/90}$ values of 0.5/2, 2/4, 0.5/2, and 2/4 μg/ml, respectively. *P. aeruginosa* isolates (n = 145) and *Burkholderia cenocepacia* isolates (n = 10) were relatively less susceptible to eravacycline, with $MIC_{50/90}$ values of 8/32 μg/ml for both organisms.

Activity of eravacycline against Gram-positive pathogens. Eravacycline showed excellent *in vitro* potency, with MIC_{90} values ranging from 0.016 to 0.5 μg/ml against methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), coagulase-negative staphylococci, vancomycin-susceptible *Enterococcus faecium* and *Enterococcus faecalis* (VSE), vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE), penicillin-susceptible and -resistant *Streptococcus pneumoniae*, and macrolide-resistant *S. pneumoniae*, *Streptococcus pyogenes*, and other important streptococcal species (Table 2). For *S. aureus*, the activity of eravacycline was independent of methi-

TABLE 1 Susceptibilities of Gram-negative aerobic bacteria to eravacycline and comparators[a]

Organism	$MIC_{50/90}$ (μg/ml), MIC range (μg/ml), and no. of isolates								
	ERV	TET	TGC	CARB	AG	3rd GC	FQ	CST	PTZ
Acinetobacter baumannii	0.25/1 0.016–8 188	8/>32 ≤0.25–>32 159	0.5/4 ≤0.016–8 188	2/32 0.13–>32 188	8/>32 ≤0.25–>32 188	>16/>32 0.13–>64 128	>2/>2 0.016–>32 188	0.5/2 0.13–>4 155	>64/>128 ≤0.5–>128 128
Acinetobacter baumannii CARB-I/R,[b] FQ-R,[d] AG-R	0.5/2 ≤0.016–4 52	>8/>32 2–>32 43	2/8 0.13–8 52	>8/>32 >8–>32 52	>8/>32 >8–>32 52	>32/>32 >16–>32 37	>4/16 >2–>32 52	0.5/1 0.13–>4 43	>64/>128 64–>128 44
Acinetobacter baumannii TET-R	0.5/2 0.06–2 69	>8/>32 >8–>32 69	2/4 0.25–8 69	>8/>32 ≤0.25–>32 69	>8/>32 ≤0.25–>32 69	>32/>32 4–>64 39	>4/32 ≤0.25–>32 69	0.5/1 0.13–>4 68	>64/>128 4–>128 56
Acinetobacter lwoffii	0.13/0.25 0.03–0.25 34	1/2 ≤0.25–>8 34	0.13/0.5 0.06–0.5 34	≤1/4 ≤0.25–>8 34	≤0.25/1 ≤0.25–>8 34	1/16 ≤0.5–>64 34	≤0.25/≤0.25 ≤0.25–2 34	0.25/>2 ≤0.13–4 34	≤0.5/8 ≤0.5–16 34
Burkholderia cenocepacia	8/32 0.13–32 10	>32/>32 16–>32 10	8/32 0.25–>32 10	32/>32 1–>32 10	>32/>32 >32–>32 10	16/32 2–>32 10	4/8 0.5–>32 10	>32/>32 >32–>32 10	16/>128 0.5–>128 10
Citrobacter freundii	0.25/1 0.06–2 115	1/>8 0.5–>8 65	0.5/2 0.13–8 115	0.5/2 0.004–>32 103	0.5/>8 ≤0.25–>32 115	1/32 0.06–>64 115	<0.25/>2 0.008–>4 115	0.5/1 0.25–>2 64	4/>128 0.25–>128 115
Citrobacter freundii 3rd-GC-I/R[c]	0.5/1 0.13–2 42	2/8 1–>8 16	1/2 0.25–8 42	1/16 0.25–>32 39	0.5/>32 ≤0.25–>32 42	>16/>64 4–>64 42	1/>4 0.016–>4 42	0.25/1 0.25–>2 16	>64/>128 2–>128 42
Enterobacter cloacae	0.5/2 0.03–4 270	2/>8 0.5–>32 218	0.5/2 0.06–8 270	0.5/2 0.03–>32 270	0.5/8 ≤0.25–>32 270	2/>64 0.03–>64 246	≤0.25/>4 0.008–>32 270	0.5/>4 ≤0.13–>32 178	4/>64 0.5–>128 220
Enterobacter cloacae 3rd-GC-I/R	0.5/2 0.03–4 122	4/>8 1–>32 93	1/4 0.06–8 122	0.5/4 0.03–>32 122	0.5/16 ≤0.25–>32 122	>32/>64 2–>64 122	0.25/>4 0.008–>32 122	0.25/>2 ≤0.13–>32 81	>64/>128 2–>128 107
Enterobacter cloacae CARB-I/R	0.5/2 0.25–4 34	4/>32 2–>32 31	0.5/4 0.13–4 34	2/16 ≤0.016–>32 34	1/>32 ≤0.25–>32 34	>32/>64 0.13–>64 26	≤0.25/>4 0.03–>32 34	0.25/>4 ≤0.13–>32 21	>64/>128 1–>128 21
Enterobacter cloacae FQ-R	2/4 0.25–4 36	8/>32 2–>32 29	2/4 0.25–8 36	0.5/8 ≤0.016–>32 36	1/>32 ≤0.25–>32 36	>32/>64 0.5–>64 35	>4/32 >2–>32 36	0.25/1 ≤0.13–>4 21	>64/>128 2–>128 27
Enterobacter cloacae AG-R	0.5/2 0.25–4 26	8/>32 1–>32 20	1/4 0.25–8 26	0.5/16 0.13–>32 26	16/>32 >8–>32 26	>32/>64 0.25–>64 26	>2/>4 ≤0.016–>32 26	0.25/1 ≤0.13–1 15	>64/>128 2–>128 22
Enterobacter cloacae TET-R	2/4 0.25–4 25	>8/>32 >8–>32 25	1/4 0.25–8 25	0.25/2 0.03–>32 25	1/>32 ≤0.25–>32 25	32/>64 0.13–>64 25	4/16 0.03–>32 25	0.25/>4 ≤0.13–>32 21	16/>64 2–>128 16
Enterobacter aerogenes	0.25/1 0.13–2 77	2/8 0.5–>8 77	0.5/2 0.25–4 77	≤1/1 ≤0.25–8 77	≤0.25/0.5 ≤0.25–8 77	≤0.5/>32 ≤0.5–>64 77	≤0.25/≤0.25 ≤0.25–>4 77	0.25/0.5 ≤0.13–>4 77	4/>64 ≤0.5–>64 77
Enterobacter aerogenes 3rd-GC-I/R	0.25/1 0.13–2 27	2/8 1–>8 27	0.5/2 0.25–4 27	0.5/1 ≤0.25–8 27	≤0.25/1 ≤0.25–2 27	32/>32 4–>64 27	≤0.25/>4 ≤0.25–>4 27	0.25/1 ≤0.13–1 27	64/>64 8–>64 27
Escherichia coli	0.25/0.5 ≤0.016–4 445	4/>32 0.25–>64 390	0.25/0.5 0.06–>8 445	0.25/0.5 ≤0.002–>32 445	1/>8 ≤0.25–>32 445	≤0.5/>32 ≤0.016–>64 445	≤0.25/>4 ≤0.25–>32 445	0.5/0.5 ≤0.13–4 216	2/>64 ≤0.5–>128 359
Escherichia coli 3rd-GC-I/R	0.25/0.5 ≤0.016–1 127	>8/>32 0.5–>32 113	0.25/1 0.03–>8 127	0.06/0.5 ≤1–>32 127	2/>32 ≤0.25–>32 127	>32/>64 2–>64 127	>4/32 ≤0.25–>32 127	0.25/0.5 ≤0.13–4 69	8/128 ≤0.5–>128 93
Escherichia coli FQ-R	0.25/0.5 ≤0.016–4 143	>8/>32 0.25–>32 118	0.25/0.5 0.06–>8 143	0.13/≤0.5 ≤1–>32 143	4/>32 0.25–>32 143	>16/>64 0.06–>64 143	>4/32 >2–>32 143	0.25/0.5 ≤0.13–4 72	8/>64 1–>128 142
Escherichia coli AG-R	0.25/0.5 ≤0.016–1 79	>8/>32 0.25–>32 69	0.25/0.5 0.063–>8 79	0.063/≤0.5 ≤1–>32 79	>8/>32 >8–>32 79	32/>64 0.06–>64 79	>4/32 ≤0.25–>32 79	0.25/0.5 ≤0.13–0.5 44	8/>64 ≤0.5–>128 78
Escherichia coli AG-R, FQ-R, 3rd-GC-I/R	0.25/0.5 ≤0.016–1 40	>8/>32 0.5–>32 35	0.25/0.5 0.063–>8 40	0.063/0.5 ≤1–>32 40	>32/>32 >8–>32 40	>32/>64 4–>64 40	>4/32 >2–>32 40	0.25/0.5 ≤0.12–0.5 21	8/>128 1–>128 40

(Continued on following page)

TABLE 1 (Continued)

Escherichia coli TET-R	0.25/0.5 ≤0.016–2 157	16/>32 >8–>64 157	0.25/0.5 0.06–4 157	0.063/≤0.5 ≤1–>32 157	2/>8 ≤0.25–>32 157	4/>32 0.06–>64 157	1/32 ≤0.25–>32 157	0.25/0.5 ≤0.13–4 94	4/>64 ≤0.5–>128 148
Haemophilus influenzae	0.13/0.25 ≤0.016–0.5 114	0.5/1 ≤0.06–16 114	0.13/0.25 ≤0.016–1 114	1/2 0.06–8 101	ND ND ND	<0.03/0.13 ≤0.016–0.5 114	0.016/0.03 0.004–0.13 114	ND ND ND	ND ND ND
Klebsiella pneumoniae	0.5/2 0.03–16 394	4/>32 ≤0.25–>64 339	0.5/2 0.13–16 394	0.25/>8 ≤0.002–>32 394	0.5/>8 ≤0.25–>32 223	8/>32 ≤0.016–>64 394	0.5/>32 ≤0.25–>64 394	0.5/1 ≤0.13–>16 209	8/>128 ≤0.5–>128 394
Klebsiella pneumoniae 3rd-GC-I/R	0.5/2 0.03–16 210	8/>32 1–>64 187	1/4 0.13–16 210	1/16 ≤1–>32 210	4/16 0.25–>32 82	>32/64 4–>64 210	>4/>32 ≤0.25–>64 210	0.5/4 ≤0.13–>16 110	>64/>128 0.5–>128 209
Klebsiella pneumoniae CARB-I/R	0.5/2 0.13–16 90	8/>32 1–>32 81	1/2 0.25–16 90	>8/>32 2–>32 90	4/>8 0.25–>32 50	>32/>32 1–>64 90	>4/>32 0.06–>64 90	0.5/>4 0.13–>16 57	>64/>128 4–>128 90
Klebsiella pneumoniae FQ-R	0.5/2 0.13–16 156	8/>32 1–>32 134	1/2 0.13–16 156	1/32 ≤1–>32 156	4/32 ≤0.25–>32 82	>32/>32 0.25–>64 156	>4/>32 >2–>64 156	0.5/>4 0.13–>16 78	>64/>128 4–>128 156
Klebsiella pneumoniae AG-R	0.5/2 0.06–16 119	8/>32 1–>32 106	1/4 0.13–16 119	0.5/32 ≤1–>32 119	>8/>32 >8–>32 59	>32/>64 0.25–>64 119	>4/>32 ≤0.25–>64 119	0.5/1 ≤0.13–>16 61	>64/>128 2–>128 118
Klebsiella pneumoniae AG-R, FQ-R, 3rd-GC-I/R	0.5/2 0.13–16 74	8/>32 2–>32 66	1/4 0.13–16 74	1/32 ≤1–>32 74	>8/>32 >8–>32 35	>32/>32 8–>64 74	8/>32 >2–>64 74	0.5/1 0.13- >16 36	>64/>128 4–>128 74
Klebsiella pneumoniae AG-R, FQ-R, CARB-I/R	0.5/2 0.13–16 37	8/>32 4–>32 33	1/2 0.25–16 37	>8/>32 2–>32 37	>8/>32 >8–>32 21	>32/>32 >16–>64 37	>4/>32 >2–>64 37	0.5/>4 0.13–>16 21	>128/>128 >64–>128 37
Klebsiella oxytoca	0.5/1 0.03–2 48	1/>32 0.5–>32 48	0.5/2 0.06–4 48	≤1/≤1 0.004–1 48	0.5/>32 ≤0.13–>32 48	≤0.5/>32 ≤0.016–>32 48	≤0.25/4 0.03–>32 48	≤0.13/0.13 0.03–>2 41	2/16 ≤0.5–>64 48
Klebsiella oxytoca 3rd-GC-I/R	0.5/1 0.03–1 11	>32/>32 0.5–>32 11	0.25/0.5 0.06–1 11	0.06/0.25 0.03–1 11	>32/>32 0.5–>32 11	>32/>32 4–>32 11	0.5/>32 0.03–>32 11	0.13/0.13 0.03–0.13 11	8/>32 0.5–>32 11
Legionella pneumophila	1/2 0.016–2 70	4/8 0.5–8 70	ND ND ND	ND ND ND	ND ND ND	ND ND ND	ND ND ND	ND ND ND	ND ND ND
Moraxella catarrhalis	0.03/0.06 ≤0.016–0.06 92	≤0.25/0.5 ≤0.06–>32 92	0.06/0.13 ≤0.016–0.13 92	≤0.25/≤0.25 ≤0.25–≤0.25 78	≤0.25/≤0.25 ≤0.06–0.25 78	≤0.5/≤0.5 ≤0.5–2 78	≤0.25/≤0.25 ≤0.25–≤0.25 92	1/1 0.5–2 28	≤0.5/≤0.5 ≤0.5–2 28
Morganella morganii	1/2 0.5–4 43	2/>8 0.5–>8 43	2/4 0.25–8 43	≤1/2 0.008–4 43	1/>8 ≤0.25–>8 43	≤0.5/8 ≤0.016–>16 43	≤0.25/4 0.03–>4 43	>2/>4 >2–>4 39	≤0.5/2 ≤0.5–>64 43
Proteus mirabilis	1/2 0.25–16 166	>8/32 2–>64 111	4/8 0.5–16 166	2/4 0.008–>32 166	1/>8 ≤0.25–>64 166	≤0.5/1 ≤0.016–>64 166	≤0.25/>4 0.016–>64 166	>2/>4 >2–>4 95	≤0.5/2 ≤0.016–64 157
Proteus mirabilis 3rd-GC-I/R	1/4 0.5–8 21	>8/64 >8–64 15	4/8 1–16 21	4/8 0.25–32 21	8/16 0.5–>64 21	8/>32 4–>64 21	>2/8 ≤0.25–16 21	ND >2–>4 9	2/4 ≤0.5–64 19
Proteus mirabilis CARB-R	1/4 0.25–16 136	>8/32 2–>64 81	4/8 1–16 136	2/8 0.06–>32 136	1/>8 ≤0.25–>64 136	≤0.5/2 ≤0.016–>64 136	≤0.25/>4 0.016–>64 136	>2/>4 >2–>4 67	≤0.5/2 ≤0.06–>64 127
Proteus mirabilis FQ-R	2/4 0.5–16 43	>8/64 >8–>64 26	4/8 1–16 43	4/8 0.25–32 43	2/16 ≤0.25–>64 43	≤0.5/16 ≤0.016–>64 43	>4/16 >2–>64 43	>2/>4 >2–>4 19	1/2 ≤0.13–64 38
Proteus mirabilis AG-R	2/4 0.5–8 24	>8/>32 >8–64 16	4/8 2–8 24	2/8 0.25–32 24	>8/>64 >8–>64 24	≤0.5/32 ≤0.016–>64 24	>2/>4 0.016–32 24	>2/>4 >2–>4 12	0.5/4 ≤0.13–8 23
Proteus mirabilis TET-R	1/2 0.25–16 109	>8/32 >8–>64 109	4/8 0.5–16 109	2/8 0.008–>32 109	1/>8 ≤0.25–>64 109	≤0.5/1 ≤0.015–>64 109	≤0.25/>4 0.03–>64 109	>2/>4 >2–>4 93	≤0.5/2 ≤0.5–>64 100
Proteus vulgaris	0.5/1 0.25–2 55	8/>8 1–>8 55	2/4 0.5–8 55	≤1/2 ≤0.5–4 55	1/4 ≤0.25–>8 55	≤0.5/32 ≤0.03–>64 55	≤0.25/0.5 ≤0.25–4 55	>2/>2 >2–>4 55	≤0.5/1 ≤0.5–4 55

(Continued on following page)

TABLE 1 (Continued)

Organism	$MIC_{50/90}$ (μg/ml), MIC range (μg/ml), and no. of isolates								
	ERV	TET	TGC	CARB	AG	3rd GC	FQ	CST	PTZ
Providencia stuartii	1/2 0.13–8 101	>8/>8 <0.25–>8 51	2/4 0.06–16 101	2/4 0.25–16 101	4/32 ≤0.25–>32 101	<0.5/16 ≤0.016–>64 101	>2/>4 0.016–>4 101	>2/>2 >2–>4 51	4/64 ≤0.13–>128 101
Pseudomonas aeruginosa	8/32 1–>32 145	>8/64 8–64 93	16/32 1–>32 145	2/>8 0.13–>32 145	2/>8 0.13–>32 145	>16/>32 1–>64 145	1/>4 0.06–>32 145	1/2 0.25–4 85	8/>128 >64–>128 145
Salmonella spp.	0.25/0.25 0.13–0.5 30	1/>8 0.5–>8 30	0.25/0.5 0.13–1 30	≤1/≤1 ≤1–8 30	0.5/1 ≤0.25–>8 30	≤0.5/≤0.5 ≤0.5–≤0.5 30	≤0.25/≤0.25 ≤0.25–>4 30	≤0.13/0.5 ≤0.13–2 30	2/4 1–64 30
Serratia marcescens	1/1 0.25–8 112	>8/>8 2–>8 112	1/2 0.5–4 112	0.5/1 ≤0.25–2 112	0.5/1 ≤0.25–8 112	≤0.5/1 ≤0.5–>64 112	≤0.25/1 ≤0.25–>4 112	>2/>4 0.25–>4 112	2/4 ≤0.5–>64 112
Shigella spp.	0.13/0.5 0.06–1 30	>8/>8 ≤0.25–>8 30	0.25/0.5 0.13–1 30	≤1/≤1 ≤1–≤1 30	1/1 ≤0.25–>8 30	≤0.5/≤0.5 ≤0.5–2 30	≤0.25/0.5 ≤0.25–1 30	≤0.13/≤0.13 ≤0.13–≤0.13 30	2/2 ≤0.5–4 30
Stenotrophomonas maltophilia	0.5/2 ≤0.016–8 105	>8/32 0.5–>32 105	0.5/4 0.03–8 105	>8/>32 2–>32 105	>8/>32 ≤0.25–>32 105	>32/>32 1–>64 105	1/>4 0.13–32 105	>2/>32 ≤0.13–>32 104	>64/>128 8–>128 105

[a] CARB, carbapenem (imipenem, meropenem, or ertapenem); AG, aminoglycoside (gentamicin or tobramycin); 3rd-GC, third-generation cephalosporin (ceftazidime, cefotaxime, or ceftriaxone); FQ, fluoroquinolone (levofloxacin or ciprofloxacin); ERV, eravacycline; TET, tetracycline; TGC, tigecycline; CST, colistin; PTZ, piperacillin-tazobactam; ND, not determined.

[b] For *Enterobacteriaceae*, carbapenem-I/R isolates were defined as having an imipenem/meropenem MIC of ≥2 μg/ml or an ertapenem MIC of ≥1 μg/ml, and for *Acinetobacter*, carbapenem-I/R isolates were defined as having an imipenem/meropenem MIC of ≥16 μg/ml.

[c] Third-generation cephalosporin-I/R isolates were defined as having a ceftazidime MIC of ≥8 μg/ml and a cefotaxime/ceftriaxone MIC of ≥2 μg/ml.

[d] Fluoroquinolone-resistant (FQ-R) isolates were defined as having a levofloxacin MIC of ≥8 μg/ml or a ciprofloxacin MIC of ≥4 μg/ml.

cillin susceptibility or the expression of Panton-Valentine leukocidin, a pore-forming toxin contributing to the virulence of community-acquired MRSA (CA-MRSA) (Table 2) (28). Eravacycline also showed good potency against subsets of MRSA isolates expressing macrolide resistance (n = 132; $MIC_{50/90}$ = 0.06/0.25 μg/ml), fluoroquinolone resistance (n = 178; $MIC_{50/90}$ = 0.06/0.13 μg/ml), and resistance to both antibiotic classes (n = 83; $MIC_{50/90}$ = 0.06/0.25 μg/ml). Eravacycline showed MIC values of ≤0.03 (n = 3) and 0.5 μg/ml (n = 2) against daptomycin-nonsusceptible MRSA isolates, while the daptomycin MIC values for these isolates ranged from 2 to 4 μg/ml. The MIC range of eravacycline against linezolid-resistant MRSA isolates (n = 9) was ≤0.03 to 0.25 μg/ml, while linezolid MIC values ranged from 8 to 64 μg/ml. Eravacycline was similarly highly active against both *E. faecium* and *E. faecalis*, independent of vancomycin resistance (MIC_{90} = 0.06 to 0.13 μg/ml) (Table 2). Eravacycline was also highly active against a subset of levofloxacin-resistant *E. faecalis* (n = 111; $MIC_{50/90}$ = 0.06/0.13 μg/ml) and *E. faecium* (n = 127; $MIC_{50/90}$ = 0.06/0.06 μg/ml) isolates. The activity of eravacycline was not impacted by linezolid-resistant isolates of *E. faecalis* (n = 2; MIC, ≤0.016 and 0.06 μg/ml) and *E. faecium* (n = 1; MIC, ≤0.016 μg/ml). Eravacycline also showed good potency against daptomycin-nonsusceptible isolates, with $MIC_{50/90}$ values against *E. faecium* (n = 44) of 0.06/0.06 μg/ml and an MIC range against *E. faecalis* (n = 7) of ≤0.016 to 0.03 μg/ml.

Eravacycline was highly active against all streptococci, showing MIC_{90} values no higher than 0.13 μg/ml against all species, including *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. intermedius*, and *S. mitis* (Table 2). For *S. pneumoniae*, activity was unaffected by isolates expressing penicillin resistance, macrolide resistance (Table 2), or both phenotypes together (n = 29; $MIC_{50/90}$, ≤0.008/0.016 μg/ml). Against tetracycline-resistant *S. pneumoniae* (n = 34), eravacycline displayed $MIC_{50/90}$ values of ≤0.008/0.016 μg/ml.

Activity of eravacycline against anaerobic pathogens. Eravacycline was tested against 292 clinical Gram-negative and Gram-positive anaerobic strains (Table 3). For Gram-negative species, eravacycline showed $MIC_{50/90}$ values of 0.5/1 μg/ml against *Bacteroides fragilis* (n = 36), with similar potency against a subset of Cefinase-positive isolates (n = 20). Eravacycline was less active against *Bacteroides ovatus* and *Bacteroides thetaiotaomicron* (n = 11 for each species), with $MIC_{50/90}$ values of 1/4 μg/ml, but showed $MIC_{50/90}$ values of 0.25/0.25 μg/ml against *Bacteroides vulgatus*, 0.5/1 μg/ml against *Parabacteroides distasonis* (formerly of the *Bacteroides* genus), and 0.13/0.25 μg/ml against *Fusobacterium* spp., a group similar to *Bacteroides*. For other Gram-negative anaerobes (*Porphyromonas asaccharolytica* and *Prevotella* spp.), eravacycline MIC_{90} values ranged from 0.06 to 1 μg/ml.

Eravacycline showed MIC_{90} values of 0.13 to 0.5 μg/ml for Gram-positive anaerobes, including *Clostridium difficile*, *Peptostreptococcus* spp., *Actinomyces* spp., *Anaerococcus* spp., *Bifidobacterium* spp., *Eggerthella* spp., *Finegoldia magna*, *Lactobacillus* spp., *Peptoniphilus asaccharolyticus*, and *Propionibacterium acnes*. The MIC_{90} value was 2 μg/ml for 11 isolates of *Clostridium perfringens*. The anaerobic panels were biased to contain strains with therapeutically important antibiotic resistance phenotypes, and many of the *Bacteroides* species, *Prevotella* species, *Peptostreptococcus* species, *Propionibacterium acnes*, and *Clostridium perfringens* isolates were vancomycin resistant and/or metronidazole resistant; however, there was no impact on eravacycline activity in strains having the resistance phenotype(s). Eravacycline had the most consistent broad-spectrum activity against the anaerobic species compared to all comparators.

Eravacycline potency compared to that of tigecycline. Tigecycline, a 9-*t*-butylglycylamido derivative of minocycline, is the most recent tetracycline to be approved for intravenous (i.v.) use

TABLE 2 Susceptibilities of Gram-positive aerobic bacteria to eravacycline and comparators[a]

Organism	$MIC_{50/90}$ (μg/ml), MIC range (μg/ml), and no. of isolates							
	ERV	TET	TGC	DAP	LZD	VAN	LEV	MACRO
Enterococcus faecalis	0.06/0.13 ≤0.016–0.13 194	32/>32 0.13–>32 98	0.13/0.25 ≤0.016–0.5 194	2/4 0.13–8 194	2/2 ≤0.5–32 194	2/>64 0.5–>64 150	>8/>32 0.25–>32 194	>8/>8 ≤0.13–>8 59
Enterococcus faecalis VSE	0.06/0.13 ≤0.016–0.13 121	32/>32 0.13–>32 70	0.13/0.25 ≤0.016–0.5 121	2/4 0.13–8 121	2/2 ≤0.5–32 121	1/2 0.5–4 92	2/>32 0.25–>32 121	>4/>8 ≤0.13–>8 38
Enterococcus faecalis VRE	0.06/0.13 ≤0.016–0.13 73	32/>32 1–>32 28	0.13/0.25 0.03–0.25 73	2/4 0.13–8 73	2/2 1–8 73	>64/>64 >16–>64 58	>32/>32 0.25–>32 73	>8/>8 2–>8 21
Enterococcus faecalis FQ-R	0.06/0.13 ≤0.016–0.13 111	32/>32 0.13–>32 48	0.13/0.25 ≤0.016–0.5 111	2/4 ≤0.5–8 111	2/2 1–32 111	>64/>64 1–>64 87	>32/>32 >4–>32 111	>8/>8 ≤0.13–32 34
Enterococcus faecium	0.06/0.06 ≤0.016–0.5 153	≤2/>32 0.25–>32 59	0.06/0.13 ≤0.016–0.5 153	4/8 1–16 153	2/4 ≤0.5–32 153	2/>64 ≤0.5–>64 108	>32/>32 0.25–>32 153	>8/>8 0.25–>8 56
Enterococcus faecium VSE	0.06/0.13 0.03–0.5 84	1/>32 0.25–>32 33	0.06/0.13 0.03–0.25 84	4/8 1–8 84	2/2 1–4 84	1/1 ≤0.5–4 58	>8/>32 0.25–>32 84	>8/>8 0.25–>8 33
Enterococcus faecium VRE	0.06/0.06 ≤0.016–0.25 69	32/>32 0.25–>32 26	0.06/0.13 0.03–0.5 69	4/8 1–16 69	2/4 ≤0.5–32 69	>64/>64 >16–>64 49	>32/>32 1–>32 69	>8/>8 8–>8 24
Enterococcus faecium FQ-R	0.06/0.06 ≤0.016–0.5 127	2/>32 0.25–>32 48	0.06/0.12 ≤0.016–0.5 127	4/8 1–16 127	2/4 ≤0.5–32 127	32/>64 ≤0.5–>64 88	>32/>32 >4–>32 127	>8/>8 >4–>8 45
Enterococcus faecium DAP-NS	0.06/0.06 ≤0.016–0.5 44	ND ND ND	0.06/0.13 0.03–0.25 44	8/16 8–16 44	4/4 1–32 44	>64/>64 0.5–>64 44	>32/>32 2–>32 44	ND ND ND
Enterococcus spp.	0.03/0.06 ≤0.016–0.13 29	0.5/32 ≤0.06–>32 29	0.13/0.13 ≤0.016–0.25 29	0.5/2 0.25–4 29	2/2 1–2 29	ND ND ND	1/>8 ≤0.13–>8 29	0.5/>8 ≤0.13–>8 29
Staphylococcus aureus	0.06/0.25 ≤0.016–4 408	0.25/32 0.06–>64 245	0.13/0.25 ≤0.016–16 408	1/1 0.063–4 407	2/4 1–64 407	1/1 0.5–8 258	1/32 0.06–>64 399	>8/>32 0.13–>64 237
MRSA	0.06/0.13 0.016–4 284	0.25/32 0.063–>64 177	0.13/0.25 ≤0.016–1 284	1/1 0.063–4 283	2/4 1–64 283	1/1 0.5–8 202	8/>32 0.06–>64 275	>8/>32 0.13–>64 169
MRSA PVL$^+$	0.03/0.03 ≤0.016–0.03 30	0.25/0.25 0.13–0.25 30	0.13/0.13 0.06–0.13 30	0.5/1 0.5–1 30	1/2 1–2 30	1/1 1–1 30	0.25/>2 0.25–>2 30	>4/>4 1–>4 30
Staphylococcus aureus MACRO-R[b]	0.06/0.25 ≤0.016–4 132	0.25/32 0.06–>64 132	0.13/0.25 ≤0.016–16 132	0.5/1 0.13–4 131	2/4 1–64 131	1/1 0.5–8 70	8/32 0.06–>64 132	>8/>32 >4–>64 132
Staphylococcus aureus FQ-R	0.06/0.13 ≤0.016–2 178	0.25/32 0.06–>64 109	0.12/0.25 ≤0.016–16 178	1/1 0.125–2 178	2/4 1–64 178	1/1 0.5–8 126	>8/>32 >2–>64 174	>8/>32 0.25–>64 105
Staphylococcus aureus MACRO-R, FQ-R	0.06/0.25 ≤0.016–2 83	0.25/>32 0.06–>64 83	0.13/0.25 ≤0.016–16 83	0.5/1 0.13–2 83	2/4 1–64 83	1/2 0.5–8 45	>8/32 >2–>64 83	>8/>32 >4–>64 83
MSSA	0.13/0.25 0.03–0.25 124	0.5/1 0.25–32 68	0.13/0.25 0.06–0.25 124	1/1 0.25–1 124	4/4 2–4 124	1/1 0.5–2 56	0.25/1 0.13–>32 124	1/>8 0.25–>8 68
Coagulase-negative staphylococci	0.06/0.5 ≤0.016–2 165	0.25/32 ≤0.06–>32 59	0.25/1 0.03–2 165	1/1 0.25–2 165	2/2 ≤0.5–4 165	1/2 0.5–2 111	0.5/>32 0.13–>32 165	0.5/>8 ≤0.13–>8 59
Coagulase-negative staphylococci, methicillin sensitive	0.06/0.5 ≤0.016–1 89	0.25/32 ≤0.06–>32 37	0.25/1 0.03–2 89	1/1 0.25–2 89	2/2 ≤0.5–4 89	1/2 0.5–2 54	0.25/>8 0.13–>32 89	0.25/>8 ≤0.13–>8 37
Coagulase-negative staphylococci, methicillin resistant	0.06/0.5 0.03–2 76	0.25/>32 0.25–>32 22	0.13/0.5 0.06–1 76	1/1 0.25–2 76	1/2 ≤0.5–2 76	1/2 0.5–2 57	8/>32 0.13–>32 76	>4/>8 0.25–>8 22

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TABLE 2 (Continued)

Organism	$MIC_{50/90}$ (μg/ml), MIC range (μg/ml), and no. of isolates							
	ERV	TET	TGC	DAP	LZD	VAN	LEV	MACRO
Streptococcus pneumoniae	0.016/0.016 ≤0.008–0.03 182	0.25/>8 ≤0.03–>8 100	0.016/0.03 ≤0.008–0.06 182	≤0.03/0.5 ≤0.03–2 182	0.5/1 ≤0.13–2 182	0.25/0.5 0.13–0.5 82	1/1 ≤0.03–>8 182	2/>2 ≤0.03–>2 100
Streptococcus pneumoniae penicillin resistant[c]	0.016/0.016 ≤0.008–0.03 60	>8/>8 0.13–>8 33	0.016/0.03 ≤0.008–0.03 60	≤0.03/0.5 ≤0.03–0.5 60	0.5/1 0.25–1 60	0.25/0.25 0.13–0.5 27	1/1 0.5–>8 60	>2/>2 ≤0.03–>2 33
Streptococcus pneumoniae MACRO-R[d]	≤0.008/0.016 ≤0.008–0.016 53	>8/>8 ≤0.03–>8 53	0.016/0.03 ≤0.008–0.03 53	≤0.03/≤0.03 ≤0.03–0.13 53	0.5/0.5 0.25–1 53	ND ND ND	1/1 0.5–>8 53	>2/>2 2–>2 53
Streptococcus pneumoniae penicillin resistant, MACRO-R	≤0.008/0.016 ≤0.008–0.016 29	>8/<8 0.13–>8 29	0.016/0.03 ≤0.008–0.03 29	≤0.03/≤0.03 ≤0.03–≤0.03 29	0.5/0.5 0.25–0.5 29	ND ND ND	1/1 0.5–>8 29	>2/>2 2–>2 29
Streptococcus pneumoniae TET-R	≤0.008/0.016 ≤0.008–0.016 34	>8/>8 >8–>8 34	0.016/0.03 ≤0.008–0.03 34	≤0.03/≤0.03 ≤0.03–0.06 34	0.5/0.5 0.25–0.5 34	ND ND ND	1/1 0.5–>2 34	>2/>2 2–>2 34
Streptococcus pyogenes	0.03/0.03 0.015–0.13 74	0.25/0.25 0.13–>8 20	0.03/0.06 ≤0.016–0.13 74	0.13/0.13 ≤0.03–0.25 74	1/2 0.5–2 74	ND ND ND	0.5/1 0.25–2 74	0.06/0.06 ≤0.03–0.13 20
Streptococcus agalactiae	0.03/0.06 0.016–0.06 123	>8/>8 0.25–>8 79	0.03/0.06 0.016–0.13 123	0.06/0.5 ≤0.03–1 123	1/2 0.5–2 123	0.5/0.5 0.25–0.5 48	0.5/1 0.5–2 123	0.06/>4 ≤0.03–>4 79
Streptococcus anginosus	0.016/0.031 ≤0.008–0.13 47	0.5/>16 ≤0.06–>16 47	0.016/0.06 ≤0.008–0.25 47	0.25/0.5 ≤0.03–0.5 25	1/2 ≤0.25–2 47	0.5/1 ≤0.008–1 46	0.5/1 ≤0.25–2 25	0.03/>0.5 ≤0.016–>2 25
Streptococcus intermedius	0.016/0.06 ≤0.008–0.06 31	0.25/>4 ≤0.06–>4 31	0.03/0.13 ≤0.008–0.25 31	0.5/1 ≤0.03–>1 31	1/1 ≤0.25–1 31	0.5/0.5 ≤0.06–0.5 31	1/2 ≤0.25–>4 30	0.06/>0.5 ≤0.016–>0.5 31
Streptococcus mitis	0.016/0.06 ≤0.008–0.06 32	0.5/>4 0.13–>8 32	0.03/0.13 ≤0.008–0.25 32	0.5/1 0.06–>1 32	1/1 0.5–1 32	0.5/0.5 ≤0.06–1 31	1/2 0.5–>4 32	>0.5/>0.5 ≤0.016–>2 32
Streptococcus spp.	0.016/0.13 ≤0.008–0.25 62	1/>8 ≤0.06–>8 62	0.03/0.13 ≤0.008–0.25 62	0.13/1 ≤0.03–1 62	0.5/1 ≤0.25–2 62	0.5/1 ≤0.06–1 21	1/2 ≤0.25–2 62	0.06/>2 ≤0.016–>2 62

[a] MACRO, macrolide (erythromycin, azithromycin, or clarithromycin); ND, not determined; ERV, eravacycline; TET, tetracycline; TGC, tigecycline; DAP, daptomycin; LZD, linezolid; VAN, vancomycin; LEV, levofloxacin; DAP-NS, daptomycin nonsusceptible; PVL^+, Panton-Valentine leukocidin positive.
[b] Macrolide-resistant staphylococci were defined as having an erythromycin/azithromycin/clarithromycin MIC of ≥8 μg/ml.
[c] Penicillin-resistant streptococcal isolates were defined as having an MIC of ≥2 μg/ml for the oral penicillin breakpoint.
[d] Macrolide-resistant streptococcal isolates were defined as having an erythromycin/clarithromycin MIC of ≥1 μg/ml and an azithromycin MIC of ≥2 μg/ml.

in complicated intra-abdominal infections, complicated skin and skin structure infections, and complicated community-acquired bacterial pneumonia (29). For the vast majority of Gram-negative organisms tested in this study, the MIC_{90} values of eravacycline (Table 1) were found to be ≥2-fold lower than those of tigecycline; these organisms included *A. baumannii*, *A. lwoffii*, *C. freundii*, *E. aerogenes*, *K. oxytoca*, *M. catarrhalis*, *M. morganii*, *P. mirabilis*, *P. vulgaris*, *P. stuartii*, *Salmonella* spp., *S. marcescens*, and *S. maltophilia*, plus certain panels with I/R phenotypes for third-generation cephalosporins (*C. freundii*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. pneumoniae*, and *P. mirabilis*). Notably, eravacycline has $MIC_{50/90}$ values of 1/2, 0.5/1, 1/1, and 1/2 μg/ml against *P. mirabilis* ($n = 166$), *P. vulgaris* ($n = 55$), *P. stuartii* ($n = 101$), and *M. morganii* ($n = 43$), respectively, compared to $MIC_{50/90}$ values of 2/8, 2/4, 2/4, and 2/4 μg/ml for tigecycline against each species of the tribe *Proteeae*, respectively. For Gram-positive organisms, a ≥2-fold greater potency for eravacycline than for tigecycline by MIC_{90} value was noted for *E. faecalis* (VRE and VSE), *E. faecium* (VRE), *Enterococcus* spp., *S. aureus* (MRSA), coagulase-negative staphylococci (methicillin sensitive), *S. pneumoniae*, *S. pyogenes*, *S. anginosus*, *S. intermedius*, and *S. mitis* (Table 2), and similarly for anaerobes, eravacycline exhibited a ≥2-fold greater potency by MIC_{90} value than tigecycline for *Anaerococcus* spp., *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*, *C. perfringens*, *Eggerthella lenta*, *Fusobacterium* spp., *P. distasonis*, *P. asaccharolyticus*, *Prevotella bivia*, *Prevotella disiens*, and *Prevotella intermedia* (Table 3).

The relative MIC_{90} values of eravacycline and tigecycline were examined on a strain-by-strain basis for select Gram-negative pathogen panels (Table 4). This comparison revealed that eravacycline was ≥2-fold more active than tigecycline for 87% of *A. baumannii* isolates, 32% of *E. coli* isolates, 59% of *E. cloacae* isolates, 46% of *K. pneumoniae* isolates, 92% of *P. mirabilis* isolates, and 78% of *B. fragilis* isolates. For the majority of the remaining isolates in each panel, the activity of eravacycline was similar to that of tigecycline.

Eravacycline was also evaluated against *S. aureus* isolates with upregulated expression of *norA* (24) or *mepA* (25), genes encoding pumps conferring antibiotic resistance to quinolones (NorA) and tigecycline (MepA), respectively (30, 31) (Table 5). Eravacycline retained activity in strains overexpressing either *norA* or *mepA*

TABLE 3 Susceptibilities of anaerobic bacteria to eravacycline and comparators[a]

Organism	$MIC_{50/90}$ (μg/ml), MIC range (μg/ml), and no. of isolates				
	ERV	TGC	CARB	MTZ	VAN
Actinomyces spp.	ND 0.25–0.25 5	ND 0.25–0.5 5	ND ND ND	ND 4–>16 5	ND ND ND
Anaerococcus spp.	0.13/0.13 0.03–0.25 10	0.13/0.25 0.06–0.25 10	ND ND ND	2/2 0.5–4 10	ND ND ND
Bacteroides fragilis	0.5/1 0.06–2 36	0.5/4 0.13–8 36	0.25/1 0.13–4 16	1/1 0.25–>16 31	>16/>16 16–>16 11
B. fragilis cefinase positive	0.5/1 0.13–2 20	1/4 0.25–8 20	ND ND ND	1/1 0.25–1 20	ND ND ND
Bacteroides ovatus	1/4 0.016–8 11	0.5/16 0.06–32 11	0.25/0.25 0.03–1 11	1/2 0.13–>16 10	>16/>16 8–>16 10
Bacteroides thetaiotaomicron	1/4 0.13–4 11	8/16 0.25–16 11	0.5/2 0.13–4 11	1/2 0.5–>16 10	>16/>16 16–>16 10
Bacteroides vulgatus	0.25/0.25 0.13–1 12	0.5/0.5 0.13–4 12	0.25/1 0.25–1 12	0.5/1 0.5–1 10	>16/>16 16–>16 10
Bifidobacterium spp.	ND 0.13–0.5 7	ND 0.25–0.5 7	ND ND ND	ND 2–>16 6	ND ND ND
Clostridium difficile	0.06/0.13 0.03–0.25 11	0.13/0.13 0.06–0.5 11	4/8 0.25–8 11	1/1 0.5–2 11	1/2 0.5–4 11
Clostridium perfringens	1/2 0.06–4 11	1/4 0.13–8 11	0.13/0.5 0.06–1 11	4/16 2–>16 10	1/>16 0.5–>16 10
Eggerthella lenta	0.25/0.25 0.25–0.25 12	0.5/0.5 0.25–0.5 12	ND ND ND	0.5/0.5 0.25–0.5 12	ND ND ND
Finegoldia magna	0.25/0.5 0.13–0.5 10	0.25/0.25 0.13–0.25 10	ND ND ND	0.5/1 ≤0.13–1 10	ND ND ND
Fusobacterium spp.	0.13/0.25 0.03–0.25 21	0.13/0.5 0.06–0.5 21	ND ND ND	≤0.13/0.25 ≤0.13–0.25 21	ND ND ND
Lactobacillus spp.	0.25/0.5 0.25–1 7	0.5/0.5 0.25–1 7	ND ND ND	>16/>16 >16–>16 7	ND ND ND
Parabacteroides distasonis	0.5/1 0.25–1 10	1/2 0.25–4 10	ND ND ND	1/1 0.5–1 10	ND ND ND
Peptoniphilus asaccharolyticus	0.06/0.13 0.03–0.13 10	0.13/0.25 0.06–0.25 10	ND ND ND	1/2 0.5–2 10	ND ND ND
Peptostreptococcus anaerobius	0.06/0.25 0.016–0.25 10	0.06/0.25 0.016–0.5 10	0.06/1 0.03–1 10	1/2 0.25–2 10	0.5/2 0.5–>16 10
Peptostreptococcus micros	0.016/0.25 0.016–0.5 10	0.03/0.25 0.016–1 10	0.016/0.03 ≤0.008–0.03 10	0.25/>16 ≤0.008–>16 10	1/1 0.5–2 10
Porphyromonas asaccharolytica	0.03/0.06 0.016–0.13 10	0.06/0.06 0.03–0.13 10	0.016/0.03 ≤0.008–0.06 10	1/2 0.5–4 10	0.25/0.5 0.13–1 10

(Continued on following page)

TABLE 3 (Continued)

Organism	$MIC_{50/90}$ (μg/ml), MIC range (μg/ml), and no. of isolates				
	ERV	TGC	CARB	MTZ	VAN
Prevotella bivia	1/1 0.13–1 13	1/2 0.03–2 13	ND ND ND	1/4 0.5–4 13	ND ND ND
Prevotella buccae	0.06/0.13 0.03–0.13 10	0.13/0.13 0.06–0.25 10	ND ND ND	0.5/1 0.25–1 10	ND ND ND
Prevotella disiens	0.13/0.25 0.06–0.25 12	0.25/0.5 0.13–0.5 12	ND ND ND	1/1 0.5–2 12	ND ND ND
Prevotella intermedia	0.06/0.13 0.03–0.13 10	0.25/0.25 0.13–0.25 10	ND ND ND	0.5/0.5 0.25–1 10	ND ND ND
Prevotella melaninogenica	0.13/1 0.06–1 13	0.5/1 0.06–4 13	ND ND ND	0.25/1 ≤0.008–>16 13	ND 1–>16 8
Prevotella spp.	ND 0.03–1 7	ND 0.06–0.5 7	ND ND ND	ND 0.25–>16 7	ND ND ND
Propionibacterium acnes	ND 0.13–0.13 5	ND 0.13–0.13 5	ND ND ND	ND >16–>16 5	ND ND ND

[a] ERV, eravacycline; TGC, tigecycline; MTZ, metronidazole; VAN, vancomycin; CARB, ertapenem or imipenem; ND, not determined.

(MICs of ≤0.016 μg/ml), whereas tigecycline was 64-fold less active when *mepA* was overexpressed, and ciprofloxacin was 32-fold less active when *norA* was overexpressed.

DISCUSSION

A recent survey of infectious disease specialists rated treatment for multidrug-resistant Gram-negative infections as the most important unmet clinical need in current practice, significantly outranking infections with MRSA and multidrug-resistant *Mycobacterium tuberculosis* (32). In the survey, 63% of physicians reported treating a patient in the past year whose infection was resistant to all available antibacterial agents. Multiple Gram-negative species are responsible for causing substantial increases in the rates of antibiotic-resistant infections and subsequent illness and death. For example, the rate of resistance to ceftazidime among *K. pneumoniae* strains isolated in the United States from 1998 to 2010 rose from 5.5 to 17.2% (33). Recent deaths at the Clinical Center of the U.S. National Institutes of Health due to *K. pneumoniae*, and the difficulty of eradication of this bla_{KPC} clone, are illustrative of a Gram-negative problem with few to no treatment options (5). Infections due to antibiotic-resistant Gram-negative strains of *Acinetobacter*, *Enterobacter*, and *Pseudomonas* can be particularly life threatening, having mortality rates of 26%, 27%, and 21 to 54%, respectively, as well as causing increased hospital costs and length of stay (34–38).

Serious infections caused by Gram-negative bacteria such as *A. baumannii* and ESBL-producing *Enterobacteriaceae* are becoming increasingly more difficult to treat due to the evolution and spread of isolates expressing multiple antibiotic resistance mechanisms (39). ESBL-producing and carbapenem-resistant *Enterobacteriaceae* are frequently seen in complicated urinary tract infections (cUTIs) in patients from either the hospital or the community (3, 40, 41). Treatment with 1.5 mg/kg of body weight i.v. eravacycline every 24 h (q24h) provides urine concentrations within 8 h of the first dose that are 4- to 14-fold in excess of eravacycline's MIC_{90} values for common cUTI pathogens (MIC_{90} values of 0.5 to 2

TABLE 4 Distribution of tigecycline/eravacycline MIC ratios[a] for individual isolates

TGC/ERV MIC ratio	No. of isolates with TGC/ERV ratio					
	A. baumannii	*E. coli*	*E. cloacae*	*K. pneumoniae*	*P. mirabilis*	*B. fragilis*
32		2				
16	1	4		3		
8	39	7	4	4	5	1
4	80	27	21	35	82	6
2	44	106	134	140	65	21
1	20	211	95	185	13	8
0.5	4	86	15	27	0	
0.25		2	1		1	
Total	188	445	270	394	166	36

[a] For each isolate within a given organism panel, the ratio of the tigecycline MIC to the eravacycline MIC (TGC/ERV MIC) was calculated.

TABLE 5 Activity of eravacycline against *S. aureus* strains expressing NorA or MepA efflux pumps

Compound	MIC (μg/ml)			
	SA981 (parent)	SA982 (*norA*)	SA983 (parent)	SA984 (*mepA*)
Eravacycline	0.004	0.004	0.004	0.016
Tigecycline	0.063	0.13	0.016	1
Tetracycline	0.5	0.5	0.5	0.5
Ciprofloxacin	0.5	16	2	4
Meropenem	0.25	0.13	0.13	0.13

μg/ml, except for *P. aeruginosa*) (42). This is in contrast to the reported urine levels of tigecycline of ~0.3 μg/ml after a 100-mg i.v. dose (43).

Multidrug-resistant Gram-positive pathogens in hospital and community settings are of particular public health concern (44). Despite gains made in detecting and reducing MRSA infection during hospitalization, the risk of MRSA infection among critically and chronically ill carriers persists after discharge (45). The spread of resistance and the incidence of multidrug-resistant *Streptococcus pneumoniae* leave few alternatives to effectively treat severe respiratory infections empirically (46). The dissemination of multidrug-resistant *Staphylococcus aureus*, especially the now pandemic, highly virulent CA-MRSA, and vancomycin-resistant enterococci also leaves few empirical antibiotic options for treating serious infections caused by these organisms (28, 47). Eravacycline has the requisite potency *in vitro* against all species of Gram-positive bacteria and was found to cure 100% of patients who had a Gram-positive aerobe as one of their baseline pathogens in a phase 2 trial for treatment of complicated intra-abdominal infections (20).

Anaerobes are important pathogens, especially in patients with weakened immune systems, and are commonly recovered in complicated intra-abdominal infections and diabetic foot ulcers. The *Bacteroides fragilis* group constitutes the most important clinical group of these organisms, but infections with other anaerobes are increasingly being encountered.

Eravacycline possesses unique chemical modifications at C-9 and C-7 of the tetracycline core that confer potent, broad-spectrum antibacterial activity, especially against difficult-to-treat, multidrug-resistant pathogens. The activity of eravacycline was previously shown to be minimally affected by tetracycline-specific efflux and ribosome protection and inactivation (16). In the present study, eravacycline showed greater overall potency than other broad- and narrow-spectrum comparator antibiotics against large panels of isolates with significant representations of multidrug-resistant isolates. Eravacycline is differentiated from tigecycline, the most recently approved tetracycline-class antibiotic in clinical use, by its *in vitro* superior activity across multiple organisms, particularly multidrug-resistant *Acinetobacter* spp. and ESBL-producing *Enterobacteriaceae*, as well as by its promising pharmacokinetics, tolerability, and potential for oral dosing (48–51). The clinical efficacies in the microbiologically evaluable population were 92.9 and 100% for eravacycline intravenous doses of 1.5 mg/kg q24h and 1.0 mg/kg q12h, respectively, in a recent phase 2 trial for i.v. treatment of complicated intra-abdominal infections compared to the standard-of-care antibiotic ertapenem (92.3%). In this trial, 25% of the Gram-negative aerobic pathogens in the microbiological modified intent-to-treat population produced at least one ESBL, with 15.8% of the *Enterobacteriaceae* isolates being resistant to at least three antibiotics (20, 52). Eravacycline is a promising new therapy for empirical use for serious infections caused by new and emerging multidrug-resistant Gram-negative, Gram-positive, and anaerobic pathogens, and phase 3 clinical trials for treatment of complicated intra-abdominal infections and complicated urinary tract infections are planned (20, 48, 51).

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