

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 (MIC₉₀) in each panel at concentrations ranging from ≤ 0.008 to 2 $\mu\text{g/ml}$ for all species panels except those of *Pseudomonas aeruginosa* and *Burkholderia cenocepacia* (MIC₉₀ values of 32 $\mu\text{g/ml}$ 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 uri-

nary 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 MIC₉₀ values of ≤ 2 $\mu\text{g/ml}$ 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

Received 29 June 2013 Returned for modification 21 July 2013

Accepted 20 August 2013

Published ahead of print 26 August 2013

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doi:10.1128/AAC.01288-13

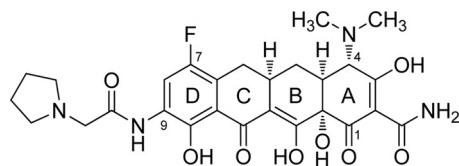


FIG 1 Chemical structure of eravacycline (TP-434).

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 Tetrphase Pharmaceuticals, using previously reported consensus primers for family or multiple-related families of genes, including *bla*_{OXA-1-like}, *bla*_{SHV}, *bla*_{CTX-M-1-3-15}, *bla*_{CTX-M-2}, *bla*_{CTX-M-9-14}, *bla*_{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*_{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 MIC₉₀ value for eravacycline was equivalent to or lower than that of comparators for each organism/phenotypic grouping.

Eravacycline exhibited MIC₉₀ values of ≤ 0.5 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ against the subset of *E. coli* isolates with I/R phenotypes for third-generation cephalosporins, this antibiotic was also equally potent against the fluoroquinolone-resis-

tant ($n = 143$), aminoglycoside-resistant ($n = 79$), and multi-drug-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 $\mu\text{g/ml}$, consistent with previous work showing that eravacycline was minimally affected by major Gram-negative tetracycline-specific resistance mechanisms (16).

Eravacycline MIC₉₀ values were 1 to 2 $\mu\text{g/ml}$ 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 MIC₉₀ values were unchanged (MIC_{50/90} = 0.5/2 $\mu\text{g/ml}$) 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 $\mu\text{g/ml}$) 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 $\mu\text{g/ml}$, 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 $\mu\text{g/ml}$). Activity of eravacycline against *P. mirabilis* isolates expressing fluoroquinolone-resistant ($n = 43$; MIC_{50/90} = 2/4 $\mu\text{g/ml}$), aminoglycoside-resistant ($n = 24$; MIC_{50/90} = 2/4 $\mu\text{g/ml}$), third-generation cephalosporin-I/R ($n = 21$; MIC_{50/90} = 1/4 $\mu\text{g/ml}$), carbapenem I/R ($n = 136$; MIC_{50/90} = 1/4 $\mu\text{g/ml}$), and tetracycline-resistant ($n = 109$; MIC_{50/90} = 1/2 $\mu\text{g/ml}$) phenotypes was within 2-fold the MIC_{50/90} values for all *P. mirabilis* isolates combined (MIC_{50/90} = 1/2 $\mu\text{g/ml}$). 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 $\mu\text{g/ml}$, 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 $\mu\text{g/ml}$ for both organisms.

Activity of eravacycline against Gram-positive pathogens. Eravacycline showed excellent *in vitro* potency, with MIC₉₀ values ranging from 0.016 to 0.5 $\mu\text{g/ml}$ 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
<i>Acinetobacter baumannii</i>	0.25/1 0.016–8 188	8/>32 ≤0.25->32 159	0.5/4 0.13->32 188	2/32 0.13->32 188	8/>32 ≤0.25->32 188	0.13->64 0.13->64 128	>2/>2 0.016->32 188	0.5/2 0.13->4 155	>64/>128 ≤0.5->128 128
<i>Acinetobacter baumannii</i> 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
<i>Acinetobacter baumannii</i> 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
<i>Acinetobacter lwoffii</i>	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
<i>Burkholderia cenocepacia</i>	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
<i>Citrobacter freundii</i>	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
<i>Citrobacter freundii</i> 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
<i>Enterobacter cloacae</i>	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
<i>Enterobacter cloacae</i> 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
<i>Enterobacter cloacae</i> 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
<i>Enterobacter cloacae</i> 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
<i>Enterobacter cloacae</i> 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
<i>Enterobacter cloacae</i> 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
<i>Enterobacter aerogenes</i>	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
<i>Enterobacter aerogenes</i> 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
<i>Escherichia coli</i>	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
<i>Escherichia coli</i> 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
<i>Escherichia coli</i> 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
<i>Escherichia coli</i> 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
<i>Escherichia coli</i> 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)

<i>Escherichia coli</i> 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
<i>Haemophilus influenzae</i>	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
<i>Klebsiella pneumoniae</i>	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
<i>Klebsiella pneumoniae</i> 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
<i>Klebsiella pneumoniae</i> 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
<i>Klebsiella pneumoniae</i> 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
<i>Klebsiella pneumoniae</i> 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
<i>Klebsiella pneumoniae</i> 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
<i>Klebsiella pneumoniae</i> 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 0.5->32 21	>32/>32 >16->64 37	>4/>32 >2->64 37	0.5/>4 0.13->16 21	>128/>128 >64->128 37
<i>Klebsiella oxytoca</i>	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
<i>Klebsiella oxytoca</i> 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
<i>Legionella pneumophila</i>	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
<i>Moraxella catarrhalis</i>	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
<i>Morganella morganii</i>	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
<i>Proteus mirabilis</i>	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
<i>Proteus mirabilis</i> 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
<i>Proteus mirabilis</i> 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
<i>Proteus mirabilis</i> 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
<i>Proteus mirabilis</i> 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
<i>Proteus mirabilis</i> 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
<i>Proteus vulgaris</i>	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
<i>Providencia stuartii</i>	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
<i>Pseudomonas aeruginosa</i>	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
<i>Salmonella</i> 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
<i>Serratia marcescens</i>	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
<i>Shigella</i> 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
<i>Stenotrophomonas maltophilia</i>	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 (MIC₉₀ = 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 MIC₉₀ 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 MIC₉₀ values ranged from 0.06 to 1 µg/ml.

Eravacycline showed MIC₉₀ 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., *Fingoldia magna*, *Lactobacillus* spp., *Peptoniphilus asaccharolyticus*, and *Propionibacterium acnes*. The MIC₉₀ 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*-butylglycylamide 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
<i>Enterococcus faecalis</i>	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
<i>Enterococcus faecalis</i> 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
<i>Enterococcus faecalis</i> 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
<i>Enterococcus faecalis</i> 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
<i>Enterococcus faecium</i>	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
<i>Enterococcus faecium</i> 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
<i>Enterococcus faecium</i> 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
<i>Enterococcus faecium</i> 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
<i>Enterococcus faecium</i> 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
<i>Enterococcus</i> 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
<i>Staphylococcus aureus</i>	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
<i>Staphylococcus aureus</i> 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
<i>Staphylococcus aureus</i> 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
<i>Staphylococcus aureus</i> 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
<i>Streptococcus pneumoniae</i>	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
<i>Streptococcus pneumoniae</i> 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
<i>Streptococcus pneumoniae</i> 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 ≤0.03–>2 53
<i>Streptococcus pneumoniae</i> 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
<i>Streptococcus pneumoniae</i> 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
<i>Streptococcus pyogenes</i>	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
<i>Streptococcus agalactiae</i>	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
<i>Streptococcus anginosus</i>	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
<i>Streptococcus intermedius</i>	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
<i>Streptococcus mitis</i>	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
<i>Streptococcus</i> 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 a 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 MIC₉₀ 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. morgani*, *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. morgani* ($n = 43$), 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 MIC₉₀ 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 MIC₉₀ 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 MIC₉₀ 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
<i>Actinomyces</i> spp.	ND 0.25–0.25 5	ND 0.25–0.5 5	ND ND ND	ND 4–>16 5	ND ND ND
<i>Anaerococcus</i> 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
<i>Bacteroides fragilis</i>	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
<i>B. fragilis</i> 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
<i>Bacteroides ovatus</i>	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
<i>Bacteroides thetaiotaomicron</i>	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
<i>Bacteroides vulgatus</i>	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
<i>Bifidobacterium</i> spp.	ND 0.13–0.5 7	ND 0.25–0.5 7	ND ND ND	ND 2–>16 6	ND ND ND
<i>Clostridium difficile</i>	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
<i>Clostridium perfringens</i>	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
<i>Eggerthella lenta</i>	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
<i>Finegoldia magna</i>	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
<i>Fusobacterium</i> 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
<i>Lactobacillus</i> 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
<i>Parabacteroides distasonis</i>	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
<i>Peptoniphilus asaccharolyticus</i>	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
<i>Peptostreptococcus anaerobius</i>	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
<i>Peptostreptococcus micros</i>	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
<i>Porphyromonas asaccharolytica</i>	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
<i>Prevotella bivia</i>	1/1 0.13–1 13	1/2 0.03–2 13	ND ND ND	1/4 0.5–4 13	ND ND ND
<i>Prevotella buccae</i>	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
<i>Prevotella disiens</i>	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
<i>Prevotella intermedia</i>	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
<i>Prevotella melaninogenica</i>	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
<i>Prevotella</i> spp.	ND 0.03–1 7	ND 0.06–0.5 7	ND ND ND	ND 0.25–>16 7	ND ND ND
<i>Propionibacterium acnes</i>	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 MIC₉₀ values for common cUTI pathogens (MIC₉₀ 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					
	<i>A. baumannii</i>	<i>E. coli</i>	<i>E. cloacae</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>B. fragilis</i>
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 (<i>norA</i>)	SA983 (parent)	SA984 (<i>mepA</i>)
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).

ACKNOWLEDGMENT

This work was funded in part by the Biomedical Advanced Research and Development Authority (BARDA) through contract no. HHSO10020120002C.

REFERENCES

- Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld H, Spellberg B, Bartlett J. 2009. Bad bugs, no drugs: no ESCAPE! An update from the Infectious Diseases Society of America. *Clin. Infect. Dis.* 48:1–12.
- Correa L, Martino MD, Siqueira I, Pasternak J, Gales AC, Silva CV, Camargo TZ, Scherer PF, Marra AR. 2013. A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant *Klebsiella pneumoniae* infection. *BMC Infect. Dis.* 13:80. doi:10.1186/1471-2334-13-80.
- Bratu S, Landman D, Haag R, Recco R, Eramo A, Alam M, Quale J. 2005. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. *Arch. Intern. Med.* 165:1430–1435.
- van Duin D, Kaye KS, Neuner EA, Bonomo RA. 2013. Carbapenem-resistant *Enterobacteriaceae*: a review of treatment and outcomes. *Diagn. Microbiol. Infect. Dis.* 75:115–120.
- Snitkin ES, Zelazny AM, Thomas PJ, Stock F, Henderson DK, Palmore TN, Segre JA. 2012. Tracking a hospital outbreak of carbapenem-resistant *Klebsiella pneumoniae* with whole-genome sequencing. *Sci. Transl. Med.* 4:148ra116. doi:10.1126/scitranslmed.3004129.
- Centers for Disease Control and Prevention. 14 February 2013, posting date. New carbapenem-resistant *Enterobacteriaceae* warrant additional action by healthcare providers. Centers for Disease Control and Prevention, Atlanta, GA. <http://emergency.cdc.gov/HAN/han00341.asp>.
- Liszewskik K. 2010. Resistant bugs necessitate tougher tactics. *Genet. Eng. Biotechnol. News* 30:1, 56–58.
- Roberts RR, Hota B, Ahmad I, Scott RD, II, Foster SD, Abbasi F, Schabowski S, Kampe LM, Ciavarella GG, Supino M, Naples J, Cordell R, Levy SB, Weinstein RA. 2009. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin. Infect. Dis.* 49:1175–1184.
- IDS. 2011. Combating antimicrobial resistance: policy recommendations to save lives. *Clin. Infect. Dis.* 52:S397–S428. doi:10.1093/cid/cir153.
- World Health Organization. 2011. World Health Day 2011: policy briefs. World Health Organization, Geneva, Switzerland. <http://www.who.int/world-health-day/2011/policybriefs/en/index.html>.
- Centers for Disease Control and Prevention. 2013. Vital signs: carbapenem-resistant *Enterobacteriaceae*. *MMWR Morb. Mortal. Wkly. Rep.* 62: 165–170.
- Patel G, Bonomo RA. 2013. “Stormy waters ahead”: global emergence of carbapenemases. *Front. Microbiol.* 4:48.
- Kitchel B, Rasheed JK, Patel JB, Srinivasan A, Navon-Venezia S, Carmeli Y, Brolund A, Giske CG. 2009. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multilocus sequence type 258. *Antimicrob. Agents Chemother.* 53:3365–3370.
- Fyfe C, Grossman T, O’Brien W, Achorn C, Sutcliffe J. 2011. The novel broad-spectrum fluorocycline TP-434 is active against MDR gram-negative pathogens, abstr P-1149. *Abstr. 21st Eur. Congr. Clin. Microbiol. Infect. Dis./27th Int. Congr. Chemother., Milan, Italy, 7 to 10 May 2011.*
- Xiao XY, Hunt DK, Zhou J, Clark RB, Dunwoody N, Fyfe C, Grossman TH, O’Brien WJ, Plamondon L, Ronn M, Sun C, Zhang WY, Sutcliffe JA. 2012. Fluorocyclines. 1. 7-Fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetracycline: a potent, broad spectrum antibacterial agent. *J. Med. Chem.* 55:597–605.
- Grossman TH, Starosta AL, Fyfe C, O’Brien W, Rothstein DM, Mikolajka A, Wilson DN, Sutcliffe JA. 2012. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. *Antimicrob. Agents Chemother.* 56:2559–2564.
- Sutcliffe J, O’Brien W, Achorn C, Appelbaum P, Pillar C, Zurenko G. 2010. *In vitro* activity of fluorocycline TP-434 against panels of recent bacterial clinical isolates, abstr F1-2158. *Abstr. 50th Intersci. Conf. Antimicrob. Agents Chemother., 12 to 15 September 2010.*
- Clark RB, Hunt DK, He M, Achorn C, Chen CL, Deng Y, Fyfe C, Grossman TH, Hogan PC, O’Brien WJ, Plamondon L, Ronn M, Sutcliffe JA, Zhu Z, Xiao XY. 2012. Fluorocyclines. 2. Optimization of the C-9 side-chain for antibacterial activity and oral efficacy. *J. Med. Chem.* 55:606–622.
- Charest MG, Lerner CD, Brubaker JD, Siegel DR, Myers AG. 2005. A convergent enantioselective route to structurally diverse 6-deoxytetracycline antibiotics. *Science* 308:395–398.

20. Solomkin JS, Cesnauskas G, Ramesh M, Walpole S, Sutcliffe J, Horn P. 2012. Efficacy and safety of TP-434 (eravacycline) versus ertapenem in complicated intra-abdominal infection (cIAI), abstr L1-1647a. Abstr. 52nd Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, CA, 9 to 12 September 2012.
21. CLSI. 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 9th ed. CLSI document M07-A9. CLSI, Wayne, PA.
22. CLSI. 2012. Performance standards for antimicrobial susceptibility testing: twenty-second informational supplement. CLSI document M100-S22. CLSI, Wayne, PA.
23. CLSI. 2012. Methods for antimicrobial susceptibility testing of anaerobic bacteria; approved standard, 8th ed. CLSI document M11-A8. CLSI, Wayne, PA.
24. Kaatz GW, Seo SM. 1995. Inducible NorA-mediated multidrug resistance in *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 39:2650–2655.
25. Kaatz GW, McAleese F, Seo SM. 2005. Multidrug resistance in *Staphylococcus aureus* due to overexpression of a novel multidrug and toxin extrusion (MATE) transport protein. *Antimicrob. Agents Chemother.* 49:1857–1864.
26. Dalenne C, Da Costa A, Decre D, Favier C, Arlet G. 2010. Development of a set of multiplex PCR assays for the detection of genes encoding important beta-lactamases in *Enterobacteriaceae*. *J. Antimicrob. Chemother.* 65:490–495.
27. Perez-Perez FJ, Hanson ND. 2002. Detection of plasmid-mediated AmpC beta-lactamase genes in clinical isolates by using multiplex PCR. *J. Clin. Microbiol.* 40:2153–2162.
28. Otto M. 2010. Basis of virulence in community-associated methicillin-resistant *Staphylococcus aureus*. *Annu. Rev. Microbiol.* 64:143–162.
29. Wyeth Pharmaceuticals, Inc. November 2012. Tygacil (tigecycline) for injection for intravenous use, package insert, revised. Wyeth Pharmaceuticals, Inc, Philadelphia, PA.
30. Yoshida H, Bogaki M, Nakamura S, Ubukata K, Konno M. 1990. Nucleotide sequence and characterization of the *Staphylococcus aureus* *norA* gene, which confers resistance to quinolones. *J. Bacteriol.* 172:6942–6949.
31. McAleese F, Petersen P, Ruzin A, Dunman PM, Murphy E, Projan SJ, Bradford PA. 2005. A novel MATE family efflux pump contributes to the reduced susceptibility of laboratory-derived *Staphylococcus aureus* mutants to tigecycline. *Antimicrob. Agents Chemother.* 49:1865–1871.
32. Hersh AL, Newland JG, Beekmann SE, Polgreen PM, Gilbert DN. 2012. Unmet medical need in infectious diseases. *Clin. Infect. Dis.* 54:1677–1678.
33. Sanchez GV, Master RN, Clark RB, Fyyaz M, Duvvuri P, Ekta G, Bordon J. 2013. *Klebsiella pneumoniae* antimicrobial drug resistance, United States, 1998–2010. *Emerg. Infect. Dis.* 19:133–136.
34. Sunenshine RH, Wright M-O, Maragakis LL, Hariss AD, Song X, Hebden J, Cosgrove SE, Anderson A, Carnell J, Jernigan DB, Kleinbaum DG, Perl TM, Standiford HC, Srinivasan A. 2007. Multidrug-resistant *Acinetobacter* infection mortality rate and length of hospitalization. *Emerg. Infect. Dis.* 13:97–103.
35. Evans HL, Lefrak SN, Lyman J, Smith RL, Chong TW, McElearney ST, Schulman AR, Hughes MG, Raymond DP, Pruett TL, Sawyer RG. 2007. Cost of Gram-negative resistance. *Crit. Care Med.* 35:89–95.
36. Maragakis LL, Perencevich EN, Cosgrove SE. 2008. Clinical and economic burden of antimicrobial resistance. *Expert Rev. Anti Infect. Ther.* 6:751–763.
37. Qureshi ZA, Paterson DL, Peleg AY, Adams-Haduch JM, Shutt KA, Pakstis DL, Sordillo E, Polsky B, Sandkovsky G, Bhussar MK, Doi Y. 2012. Clinical characteristics of bacteraemia caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in the era of CTX-M-type and KPC-type beta-lactamases. *Clin. Microbiol. Infect.* 18:887–893.
38. Hirsch EB, Tam VH. 2010. Impact of multidrug-resistant *Pseudomonas aeruginosa* infection on patient outcomes. *Expert Rev. Pharmacoecon. Outcomes Res.* 10:441–451.
39. Peleg AY, Hooper DC. 2010. Hospital-acquired infections due to gram-negative bacteria. *N. Engl. J. Med.* 362:1804–1813.
40. Marchaim D, Chopra T, Perez F, Hayakawa K, Lephart PR, Bheemreddy S, Blunden C, Hujer AM, Rudin S, Shango M, Campbell M, Varkey J, Slim J, Ahmad F, Patel D, Chen TY, Pogue JM, Salimnia H, Dhar S, Bonomo RA, Kaye KS. 2011. Outcomes and genetic relatedness of carbapenem-resistant *Enterobacteriaceae* at Detroit medical center. *Infect. Control Hosp. Epidemiol.* 32:861–871.
41. Perez F, Endimiani A, Ray AJ, Decker BK, Wallace CJ, Hujer KM, Ecker DJ, Adams MD, Toltzis P, Dul MJ, Windau A, Bajaksouzian S, Jacobs MR, Salata RA, Bonomo RA. 2010. Carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* across a hospital system: impact of post-acute care facilities on dissemination. *J. Antimicrob. Chemother.* 65:1807–1818.
42. Sutcliffe J, Grossman T, Ronn M, Xiao X, Leighton A. 2011. TP-434 has potential to treat complicated urinary tract infections (cUTI), abstr F1-1858. Abstr. 51st Intersci. Conf. Antimicrob. Agents Chemother., Chicago, IL, 17 to 20 September 2011.
43. Cunha BA. 2009. Pharmacokinetic considerations regarding tigecycline for multidrug-resistant (MDR) *Klebsiella pneumoniae* or MDR *Acinetobacter baumannii* urosepsis. *J. Clin. Microbiol.* 47:1613. doi:10.1128/JCM.00404-09.
44. Rice LB. 2006. Antimicrobial resistance in gram-positive bacteria. *Am. J. Med.* 119:S11–S19; discussion S62–S70. doi:10.1016/j.amjmed.2006.03.012.
45. Avery TR, Kleinman KP, Klompas M, Aschengrau A, Huang SS. 2012. Inclusion of 30-day postdischarge detection triples the incidence of hospital-onset methicillin-resistant *Staphylococcus aureus*. *Infect. Control Hosp. Epidemiol.* 33:114–121.
46. Van Bambeke F, Reinert RR, Appelbaum PC, Tulkens PM, Peetermans WE. 2007. Multidrug-resistant *Streptococcus pneumoniae* infections: current and future therapeutic options. *Drugs* 67:2355–2382.
47. Calfee DP. 2012. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, and other Gram-positives in healthcare. *Curr. Opin. Infect. Dis.* 25:385–394.
48. Horn PT, Sutcliffe J, Walpole SM, Leighton A. 2011. Pharmacokinetics, safety and tolerability of a novel fluorocycline, TP-434, following multiple dose oral administration with and without food, abstr 603. Abstr. Infect. Dis. Soc. Am. 49th Annu. Meet., Boston, MA, 20 to 23 October 2011.
49. Seng Yue C, Sutcliffe JA, Colucci P, Sprenger CR, Ducharme MP. 2010. Population pharmacokinetic modeling of TP-434, a novel fluorocycline, following single and multiple dose administration, abstr A1-028. Abstr. 50th Intersci. Conf. Antimicrob. Agents Chemother., 12 to 15 September 2010.
50. Leighton A, Zupanets I, Bezugla N, Plamondon L, Macdonald G, Sutcliffe J. 2011. Broad-spectrum fluorocycline TP-434 has oral bioavailability in humans, abstr P-1509. Abstr. 21st Eur. Congr. Clin. Microbiol. Infect. Dis./27th Int. Congr. Chemother., Milan, Italy, 7 to 10 May 2011.
51. Sutcliffe J, Ronn M, Leighton A, Sprenger C. 2010. Phase 1 single and multiple ascending dose studies of a broad-spectrum fluorocycline, TP-434, abstr A1-027. Abstr. 50th Intersci. Conf. Antimicrob. Agents Chemother., 12 to 15 September 2010.
52. Fyfe C, Deane J, Grossman T, Horn P, Moore G, Sahn D, Studeny J, Walpole S, Sutcliffe J. 2013. Characterization of baseline pathogens and microbiological eradication in a phase 2 trial for treatment of complicated intra-abdominal infections comparing eravacycline (TP-434) to ertapenem, abstr O277. Abstr. 23rd Eur. Congr. Clin. Microbiol. Infect. Dis., Berlin, Germany, 27 to 30 April 2013.