Variation in Potency and Spectrum of Tigecycline Activity against Bacterial Strains from U.S. Medical Centers since Its Approval for Clinical Use (2006 to 2012)

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Tigecycline was initially approved by the U.S. Food and Drug Administration (FDA) in June 2005. We assessed the evolution of tigecycline *in vitro* activities since the initial approval of tigecycline for clinical use by analyzing the results of 7 years (2006 to 2012) of data from the SENTRY Antimicrobial Surveillance Program in the United States. We also analyzed trends over time for key resistance phenotypes. The analyses included 68,608 unique clinical isolates collected from 29 medical centers and tested for susceptibility using reference broth microdilution methods. Tigecycline was highly active against Gram-positive organisms, with MIC₅₀ and MIC₉₀ values of 0.12 and 0.25 µg/ml for *Staphylococcus aureus* (28,278 strains; >99.9% susceptible), 0.06 to 0.12 and 0.12 to 0.25 µg/ml for enterococci (99.3 to 99.6% susceptible), and ≤0.03 and ≤0.03 to 0.06 µg/ml for streptococci (99.9 to 100.0% susceptible), respectively. When tested against 20,457 *Enterobacteriaceae* strains, tigecycline MIC₅₀ and MIC₉₀ values were 0.25 and 1 µg/ml, respectively (98.3% susceptible using U.S. FDA breakpoints). No trend toward increasing tigecycline resistance (nonsusceptibility) was observed for any species or group during the study period. The prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacteriaceae* increased from 4.4 and 0.5%, in 2006 to 8.5 and 1.5% in 2012, respectively. During the same period, the prevalence of *Escherichia coli* and *Klebsiella* spp. with an extended-spectrum β-lactamase (ESBL) phenotype increased from 5.8 and 9.1% to 11.1 and 20.4%, respectively, whereas rates of meropenem-nonsusceptible *Klebsiella pneumoniae* escalated from 2.2% in 2006 to 10.8% in 2012. The results of this investigation show that tigecycline generally retained potent activities against clinically important organisms isolated in U.S. institutions, including MDR organism subsets of Gram-positive and Gram-negative pathogens.

Tigecycline is the prototype compound of the new class of broad-spectrum antimicrobial agents known as glycylcyclines (1, 2). Tigecycline was initially approved by the U.S. Food and Drug Administration (FDA) in 2005 for the treatment of adults with complicated skin and skin structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs) (3). In 2009, tigecycline also received FDA approval for treatment of community-acquired bacterial pneumonia (1, 3). This minocycline derivative has provided clinicians with an alternative option for infections caused by difficult-to-treat pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), *Enterobacteriaceae* strains that produce extended-spectrum β-lactamases (ESBLs) and carbapenemases, such as *Klebsiella pneumoniae* carbapenemases (KPCs) and metallo-β-lactamases, and multidrug-resistant (MDR) *Acinetobacter* spp. (4–9).

Data from surveillance monitoring programs such as the SENTRY Antimicrobial Surveillance Program have provided information on the continuing activity of tigecycline against a wide spectrum of clinically important Gram-positive and Gram-negative bacteria over time (8, 10). To understand the evolution of the *in vitro* activity of tigecycline since the initial approval of tigecycline for clinical use, we analyzed the results for 7 years (2006 to 2012) of the U.S. SENTRY Program. We also assessed changes in the prevalence of clinically important resistance phenotypes with time.

MATERIALS AND METHODS

Bacterial isolates. A total of 68,608 unique clinical isolates were consecutively collected from 29 medical centers distributed in 21 states through-

out all nine U.S. Census regions. The vast majority of medical centers participated in the 7 years of the study. The isolates were collected between January 2006 and December 2012, except for *Streptococcus pneumoniae* and *Haemophilus influenzae*, which were collected between January 2010 and December 2012. Species identification was performed by the participating centers and confirmed at JMI Laboratories (North Liberty, IA), when necessary, by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) using a Bruker Daltonics MALDI Biotyper (Billerica, MA), following the manufacturer's instructions. Isolates were from clinically significant infections from patients with bloodstream infections (46%), wound or skin and skin structure infections (22%), pneumonia (in hospitalized patients) (16%), community-acquired respiratory tract infections (7%), urinary tract infections (5%), or other infection types (4%).

Susceptibility testing. Isolates were tested for susceptibility to multiple antimicrobial agents at a central reference laboratory (JMI Laboratories, North Liberty, IA) by reference broth microdilution methods, as described by the Clinical and Laboratory Standards Institute (CLSI) (11), using validated broth microdilution panels produced by Thermo Fisher Scientific, Inc. (formerly TREK Diagnostics, Cleveland, OH). MIC results were interpreted according to CLSI criteria (12) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 3.0, January 2013) (http://www.eucast.org/clinical_breakpoints). Tigecycline

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TABLE 1 Frequency of occurrence of tigecycline MICs for frequently isolated pathogens from U.S. hospitals (2006 to 2012)

Organism and susceptibility	No. of isolates tested	No. of isolates (cumulative %) inhibited at the following MIC (μg/ml):										MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8			
<i>Staphylococcus aureus</i>	28,278	274 (1.0)	12,376 (44.7)	10,104 (80.5)	5,241 (99.0)	281 (>99.9)	2 (100.0)	0	0	0	0	0.12	0.25
MSSA ^a	13,522	183 (1.4)	6,312 (48.0)	4,703 (82.8)	2,266 (99.6)	58 (100.0)	0	0	0	0	0	0.12	0.25
MRSA	14,756	91 (0.6)	6,064 (41.7)	5,401 (78.3)	2,975 (98.5)	223 (>99.9)	2 (100.0)	0	0	0	0	0.12	0.25
<i>Enterococcus faecalis</i>	4,529	598 (13.2)	1,428 (44.7)	1,415 (76.0)	1,071 (99.6)	12 (99.9)	4 (>99.9)	1 (100.0)	0	0	0	0.12	0.25
Vancomycin susceptible	4,322	563 (13.0)	1,373 (44.8)	1,348 (76.0)	1,025 (99.7)	9 (99.9)	1 (100.0)	0	0	0	0	0.12	0.25
Vancomycin nonsusceptible	207	35 (16.9)	55 (43.5)	67 (75.9)	46 (98.1)	3 (99.5)	0 (99.5)	1 (100.0)	0	0	0	0.12	0.25
<i>Enterococcus faecium</i>	2,655	757 (28.5)	916 (63.0)	734 (90.6)	231 (99.3)	12 (99.8)	3 (99.9)	2 (100.0)	0	0	0	0.06	0.12
Vancomycin susceptible	625	175 (28.0)	201 (60.2)	186 (89.9)	63 (100.0)	0	0	0	0	0	0	0.06	0.25
Vancomycin nonsusceptible	2,030	581 (28.7)	715 (63.9)	548 (90.8)	168 (99.1)	12 (99.7)	3 (99.9)	2 (100.0)	0	0	0	0.06	0.12
β-Hemolytic streptococci	3,805	3,290 (86.5)	439 (98.0)	74 (>99.9)	2 (100.0)	0	0	0	0	0	0	≤0.03	0.06
Viridans group streptococci	1,505	1,205 (80.1)	188 (92.6)	89 (98.5)	23 (100.0)	0	0	0	0	0	0	≤0.03	0.06
Group A streptococci	1,759	1,523 (86.6)	226 (99.4)	10 (100.0)	0	0	0	0	0	0	0	≤0.03	0.06
Group B streptococci	1,525	1,446 (94.8)	72 (99.5)	6 (99.9)	1 (100.0)	0	0	0	0	0	0	≤0.03	≤0.03
<i>Streptococcus pneumoniae</i>	3,470	3,100 (89.3)	369 (99.9)	1 (100.0)	0	0	0	0	0	0	0	≤0.03	0.06
<i>Enterobacteriaceae</i>													
All strains	20,457	24 (0.1)	2,598 (12.8)	5,106 (37.8)	6,581 (70.0)	3,215 (85.7)	1,656 (93.8)	933 (98.3)	316 (99.9)	28 (100.0)	0.25	1	
MDR strains	1,359	1 (0.1)	46 (3.5)	138 (13.6)	266 (33.2)	328 (57.3)	289 (78.6)	156 (90.1)	126 (99.3)	9 (100.0)	0.5	2	
XDR strains	224	0	0	6 (2.7)	25 (13.8)	79 (49.1)	57 (74.6)	24 (85.3)	31 (99.1)	2 (100.0)	1	4	
<i>Escherichia coli</i>	8,048	22 (0.3)	2,511 (31.5)	3,782 (78.5)	1,566 (97.9)	148 (99.8)	14 (99.9)	5 (100.0)	0	0	0.12	0.25	
<i>Klebsiella</i> spp.	5,213	0	17 (0.3)	681 (13.4)	2,686 (64.9)	1,183 (87.6)	368 (94.7)	212 (98.7)	61 (99.9)	5 (100.0)	0.25	1	
<i>Enterobacter</i> spp.	2,996	0	11 (0.4)	218 (7.6)	1,685 (63.9)	722 (88.0)	179 (94.0)	140 (98.6)	39 (99.9)	2 (100.0)	0.25	1	
<i>Citrobacter</i> spp.	721	0	11 (1.5)	286 (41.2)	295 (82.1)	78 (92.9)	36 (97.9)	14 (99.9)	1 (100.0)	0	0.12	0.5	
<i>Proteus mirabilis</i>	1,020	0	0	2 (0.2)	32 (3.3)	91 (12.3)	316 (43.2)	394 (81.9)	174 (98.9)	11 (100.0)	2	4	
Indole-positive <i>Proteae</i>	607	0	0	9 (1.5)	61 (11.5)	239 (50.9)	189 (82.0)	81 (95.4)	23 (99.2)	5 (100.0)	0.5	2	
<i>Serratia marcescens</i>	1,398	0	0	1 (0.1)	69 (5.0)	692 (54.5)	533 (92.6)	80 (98.4)	18 (99.6)	5 (100.0)	0.5	1	
<i>Pseudomonas aeruginosa</i>	4,689	0	1 (<0.1)	3 (0.1)	20 (0.5)	74 (2.1)	141 (5.1)	658 (19.1)	1,933 (60.4)	1,898 (100.0)	4	>4	
<i>Acinetobacter</i> spp.	1,257	10 (0.8)	83 (7.4)	224 (25.2)	228 (43.4)	143 (54.7)	290 (77.8)	210 (94.5)	63 (99.5)	6 (100.0)	0.5	2	
<i>S. maltophilia</i>	781	0	1 (0.1)	27 (3.6)	127 (19.9)	262 (53.4)	220 (81.6)	101 (94.5)	40 (99.6)	3 (100.0)	0.5	2	
<i>H. influenzae</i>	1,891	7 (0.4)	32 (2.1)	581 (32.8)	898 (80.3)	311 (96.7)	61 (>99.9)	1 (100.0)	0	0	0.25	0.5	

^a MSSA, methicillin-sensitive *S. aureus*.

MIC breakpoints were those found in the U.S. FDA-approved package insert (3). Vancomycin-resistant enterococci (VRE) were defined on the basis of a vancomycin MIC of ≥ 8 $\mu\text{g/ml}$, i.e., nonsusceptible by CLSI criteria (12) and resistant by EUCAST criteria (http://www.eucast.org/clinical_breakpoints). *Escherichia coli* and *Klebsiella* isolates were grouped as the extended-spectrum β -lactamase (ESBL) phenotype based on the CLSI screening criteria for potential ESBL production, i.e., MIC of ≥ 2 $\mu\text{g/ml}$ for ceftazidime, ceftriaxone, or aztreonam (12). Although an ESBL confirmation test was not performed and other β -lactamases, such as AmpC and *K. pneumoniae* carbapenemases (KPCs), may also produce an ESBL phenotype, these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β -lactam compounds. Meropenem-nonsusceptible *Klebsiella* spp. indicates a meropenem MIC of ≥ 2 $\mu\text{g/ml}$. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) bacteria were classified as such according to recently recommended guidelines (13), using the following antimicrobial class-representative agents and CLSI interpretive criteria (12): ceftriaxone, ≥ 2 $\mu\text{g/ml}$; meropenem, ≥ 2 $\mu\text{g/ml}$; piperacillin-tazobactam, $\geq 32/4$ $\mu\text{g/ml}$; levofloxacin, ≥ 4 $\mu\text{g/ml}$; gentamicin, ≥ 8 $\mu\text{g/ml}$; tigecycline, ≥ 4 $\mu\text{g/ml}$; colistin, ≥ 4 $\mu\text{g/ml}$. Classifications were based on the following recommended parameters: MDR, nonsusceptible to ≥ 1 agent in ≥ 3 antimicrobial classes; XDR, nonsusceptible to ≥ 1 agent in all but ≤ 2 antimicrobial classes; PDR, nonsusceptible to all antimicrobial classes (13). Quality control (QC) was performed according to CLSI methods (12) using (i) *Escherichia coli* ATCC 25922 and 35218, (ii) *Staphylococcus aureus* ATCC 29213, (iii) *Pseudomonas aeruginosa* ATCC 27853, and (iv) *Enterococcus faecalis* ATCC 29212. All QC results were within the published range (12).

Statistical analysis. The chi-square test for trend was applied to assess the yearly trends of resistance phenotypes. Statistical analyses were performed with the Epi Info 7 statistical package. *P* values of <0.05 were considered significant.

RESULTS

The *in vitro* activities of tigecycline tested against clinical bacteria collected during the 7-year period (2006 to 2012) of the study are summarized in the form of MIC distributions (Table 1). Tigecycline was highly active against Gram-positive organisms, with MIC₅₀ and MIC₉₀ values of 0.12 and 0.25 $\mu\text{g/ml}$, respectively, for *S. aureus* (28,278 strains), 0.06 to 0.12 and 0.12 to 0.25 $\mu\text{g/ml}$ for enterococci (*E. faecalis* [4,529 strains] and *Enterococcus faecium* [2,655 strains]), and ≤ 0.03 and ≤ 0.03 to 0.06 $\mu\text{g/ml}$ for streptococci (*S. pneumoniae* [3,470 strains], β -hemolytic *Streptococcus* [3,805 strains], and viridans group *Streptococcus* [1,505 strains]). Among Gram-positive species, tigecycline susceptibility rates ranged from 99.3% for *E. faecium* to $\geq 99.9\%$ for *S. aureus*, *S. pneumoniae*, β -hemolytic *Streptococcus*, and viridans group *Streptococcus*. Furthermore, tigecycline MIC distributions for methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci were very similar to those of their wild-type susceptible counterparts (Table 1).

Among the 20,457 *Enterobacteriaceae* strains evaluated, tigecycline MIC₅₀ and MIC₉₀ values were 0.25 and 1 $\mu\text{g/ml}$, respectively, and 98.3% of the strains were considered susceptible according to the U.S. FDA breakpoint criterion of ≤ 2 $\mu\text{g/ml}$ (12). The most tigecycline-susceptible *Enterobacteriaceae* species was *E. coli* (MIC₅₀, 0.12 $\mu\text{g/ml}$; MIC₉₀, 0.25 $\mu\text{g/ml}$; 100.0% susceptible), followed by *Klebsiella* spp., *Enterobacter* spp., and *Citrobacter* spp. (MIC₅₀ and MIC₉₀ values of 0.25 and 1 $\mu\text{g/ml}$, respectively, for all three genera; 98.6 to 99.9% susceptible) (Table 1). Tigecycline was particularly active against MDR (MIC₅₀, 0.12 $\mu\text{g/ml}$; MIC₉₀, 0.25 $\mu\text{g/ml}$; 90.1% susceptible) and XDR (MIC₅₀, 2 $\mu\text{g/ml}$; MIC₉₀, 4 $\mu\text{g/ml}$; 85.3% susceptible) *Enterobacteriaceae* strains. No PDR *Enterobacteriaceae* strains were observed. The least tigecycline-sus-

TABLE 2 Tigecycline activity, stratified by year, against selected organisms and resistance subsets

Organism	2006	2007	2008	2009	2010	2011	2012	All years
<i>S. aureus</i>	0.12/0.25 (<0.1 [4,357])	0.12/0.25 (0.0 [4,197])	0.12/0.25 (0.0 [4,366])	0.12/0.25 (0.0 [4,197])	0.12/0.25 (0.0 [3,522])	0.06/0.12 (0.0 [3,881])	0.06/0.12 (0.0 [3,781])	0.12/0.25 (<0.1 [28,278])
<i>E. faecalis</i>	0.12/0.25 (0.0 [798])	0.12/0.25 (0.4 [738])	0.12/0.25 (0.8 [763])	0.12/0.25 (0.4 [738])	0.06/0.25 (0.0 [696])	0.06/0.06 (0.5 [438])	0.06/0.06 (0.0 [330])	0.12/0.25 (0.4 [4,529])
<i>E. faecium</i>	0.06/0.12 (0.0 [454])	0.06/0.12 (0.7 [427])	0.06/0.12 (0.4 [450])	0.12/0.25 (1.3 [373])	0.06/0.25 (0.8 [532])	$\leq 0.03/0.06$ (0.4 [253])	0.06/0.12 (0.6 [166])	0.06/0.12 (0.7 [2,655])
β -Hemolytic streptococci	$\leq 0.03/\leq 0.03$ (0.0 [427])	$\leq 0.03/\leq 0.03$ (0.0 [334])	$\leq 0.03/\leq 0.03$ (0.0 [417])	$\leq 0.03/0.06$ (0.0 [617])	$\leq 0.03/\leq 0.03$ (0.0 [857])	$\leq 0.03/0.06$ (0.0 [604])	$\leq 0.03/\leq 0.03$ (0.0 [549])	$\leq 0.03/0.06$ (0.0 [3,805])
Viridans group streptococci	$\leq 0.03/0.06$ (0.0 [159])	$\leq 0.03/0.12$ (0.0 [115])	$\leq 0.03/0.12$ (0.0 [168])	$\leq 0.03/0.12$ (0.0 [224])	$\leq 0.03/0.06$ (0.0 [320])	$\leq 0.03/0.06$ (0.0 [240])	$\leq 0.03/0.06$ (0.0 [279])	$\leq 0.03/0.06$ (0.0 [1,505])
<i>S. pneumoniae</i> ^b					$\leq 0.03/\leq 0.03$ (0.1 [1,185])	$\leq 0.03/0.06$ (0.0 [1,408])	$\leq 0.03/0.06$ (0.0 [877])	$\leq 0.03/0.06$ (<0.1 [3,470])
<i>Enterobacteriaceae</i>								
All	0.25/1 (1.0 [2,204])	0.25/1 (1.5 [2,690])	0.25/1 (1.6 [2,642])	0.25/1 (2.7 [2,537])	0.25/1 (1.2 [3,246])	0.25/1 (2.0 [3,360])	0.25/1 (1.7 [3,778])	0.25/1 (1.7 [20,457])
MDR	0.5/2 (7.3 [96])	1/4 (10.3 [155])	0.5/2 (9.3 [161])	0.5/4 (13.9 [166])	0.5/4 (10.6 [208])	0.5/4 (10.8 [250])	0.5/2 (8.1 [323])	0.5/2 (9.9 [1,359])
XDR	0.5/4 (25.0 [12])	1/4 (15.8 [19])	0.5/2 (6.7 [30])	1/4 (20.5 [39])	0.5/4 (13.8 [29])	1/4 (20.0 [40])	0.5/2 (9.1 [55])	1/4 (14.7 [224])

^a U.S. FDA breakpoints were applied (3).

^b Data were available for 2010 to 2012 only.

TABLE 3 Activity of tigecycline and comparator antimicrobial agents against key organisms and resistance subsets from U.S. hospitals in the SENTRY program (2006 to 2012)

Organism and antimicrobial agent(s)	MIC ($\mu\text{g/ml}$) data			CLSI category (%) ^a			EUCAST category (%) ^a		
	MIC ₅₀	MIC ₉₀	Range	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
<i>Staphylococcus aureus</i> (n = 28,278)									
Tigecycline ^b	0.12	0.25	≤0.03 to 1	>99.9			>99.9	0.0	<0.1
Oxacillin	>2	>2	≤0.25 to >2	47.8	0.0	52.2	47.8	0.0	52.2
Clindamycin	≤0.25	>2	≤0.25 to >2	79.3	0.2	20.5	78.9	0.3	20.7
Daptomycin	0.25	0.5	≤0.06 to 4	99.9			99.9	0.0	0.1
Erythromycin	>2	>2	≤0.25 to >2	36.2	1.3	62.5	36.4	0.5	63.1
Gentamicin	≤2	≤2	≤2 to >8	97.7	0.3	2.0	97.4	0.0	2.6
Levofloxacin	≤0.5	>4	≤0.5 to >4	58.0	1.2	40.8	58.0	1.2	40.8
Linezolid	1	2	≤0.12 to >8	>99.9	0.0	<0.1	>99.9	0.0	<0.1
Tetracycline	≤2	≤2	≤2 to >8	95.3	0.7	4.1	94.0	0.7	5.3
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >2	98.4	0.0	1.6	98.4	0.1	1.5
Vancomycin	1	1	≤0.12 to 4	>99.9	<0.1	0.0	>99.9	0.0	<0.1
<i>Enterococcus faecalis</i> (n = 4,529)									
Tigecycline ^b	0.12	0.25	≤0.03 to 2	99.6			99.6	0.4	0.1
Ampicillin	≤1	2	≤1 to >8	99.9	0.0	0.1	99.7	0.2	0.1
Daptomycin	1	1	≤0.06 to 8	>99.9					
Doxycycline	8	8	≤0.12 to >8	37.6	53.6	8.7	37.6	53.6	8.7
Levofloxacin	1	>4	≤0.5 to >4	67.4	0.3	32.2			
Linezolid	1	2	0.12 to >8	99.9	0.0	0.1	99.9	0.0	0.1
Teicoplanin	≤2	≤2	≤2 to >8	96.5	<0.1	3.4	96.3	0.0	3.7
Vancomycin	1	2	≤0.12 to >16	95.4	0.1	4.4	95.4	0.0	4.6
<i>Enterococcus faecium</i> (n = 2,656)									
Tigecycline ^b	0.06	0.12	≤0.03 to >4	99.3			99.3	0.5	0.2
Ampicillin	>8	>8	≤1 to >8	7.5	0.0	92.5	7.2	0.3	92.5
Daptomycin	2	2	≤0.06 to >4	99.6					
Levofloxacin	>4	>4	≤0.5 to >4	6.4	2.1	91.5			
Linezolid	1	2	0.25 to >8	98.4	0.1	1.4	98.6	0.0	1.4
Teicoplanin	>8	>8	≤2 to >8	25.6	4.6	69.8	25.0	0.0	75.0
Vancomycin	>16	>16	0.25 to >16	23.5	0.6	75.9	23.5	0.0	76.5
<i>Enterobacteriaceae</i> (n = 20,457)									
Tigecycline ^b	0.25	1	≤0.03 to >4	98.3	1.6	0.1	93.8	4.5	1.7
Amikacin	≤4	≤4	≤4 to >32	98.6	1.2	0.3	97.6	1.0	1.4
Cefepime	≤0.5	1	≤0.5 to >16	95.7	0.8	3.4	91.8	3.0	5.2
Ceftazidime	≤1	8	≤1 to >16	89.8	1.0	9.2	87.5	2.3	10.2
Ceftriaxone	≤0.25	8	≤0.25 to >8	87.2	0.8	11.9	87.2	0.8	11.9
Colistin	≤0.5	>4	≤0.5 to >4				81.9	0.0	18.1
Gentamicin	≤2	≤2	≤2 to >8	91.3	1.2	7.6	90.1	1.2	8.7
Levofloxacin	≤0.5	>4	≤0.5 to >4	83.3	1.7	15.1	81.9	1.3	16.7
Meropenem	≤0.12	≤0.12	≤0.12 to >8	98.3	0.2	1.5	98.5	0.5	1.0
Piperacillin-tazobactam	2	16	≤0.5 to >64	91.6	3.3	5.1	88.5	3.1	8.4
MDR <i>Enterobacteriaceae</i> ^c (n = 1,359)									
Tigecycline ^b	0.5	2	≤0.03 to >4	90.1	9.2	0.7	78.6	11.5	9.9
Amikacin	≤4	32	≤4 to >32	82.7	13.5	3.8	73.2	9.5	17.3
Cefepime	8	>16	≤0.5 to >16	52.5	9.7	37.8	29.2	15.7	55.1
Ceftazidime	>16	>16	≤1 to >16	23.1	5.0	71.9	14.8	8.3	76.9
Ceftriaxone	>8	>8	≤0.25 to >8	12.6	2.5	84.9	12.6	2.5	84.9
Colistin	≤0.5	>4	≤0.5 to >4				67.6	0.0	32.4
Gentamicin	>8	>8	≤2 to >8	36.4	10.5	53.1	31.9	4.5	63.6
Levofloxacin	>4	>4	≤0.5 to >4	17.1	9.4	73.5	14.4	2.7	82.9
Meropenem	≤0.12	>8	≤0.12 to >8	75.0	2.1	22.9	77.1	8.0	14.9
Piperacillin-tazobactam	64	>64	≤0.5 to >64	35.2	15.3	49.5	29.4	5.8	64.8
XDR <i>Enterobacteriaceae</i> ^d (n = 224)									
Tigecycline ^b	1	4	0.12 to >4	85.3	13.8	0.9	74.6	10.7	14.7
Amikacin	16	32	≤4 to >32	59.8	31.7	8.5	44.2	15.6	40.2

(Continued on following page)

TABLE 3 (Continued)

Organism and antimicrobial agent(s)	MIC ($\mu\text{g/ml}$) data			CLSI category (%) ^a			EUCAST category (%) ^a		
	MIC ₅₀	MIC ₉₀	Range	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Cefepime	>16	>16	≤0.5 to >16	15.6	18.3	66.1	5.8	2.2	92.0
Ceftazidime	>16	>16	0.12 to >16	3.1	1.4	95.5	1.3	1.8	96.9
Ceftriaxone	>8	>8	2 to >8	0.0	0.4	99.6	0.0	0.4	99.6
Colistin	1	>4	≤0.5 to >4				56.1	0.0	43.9
Gentamicin	>8	>8	≤2 to >8	16.5	19.7	63.8	14.7	1.8	83.5
Levofloxacin	>4	>4	≤0.5 to >4	0.4	5.4	94.2	0.4	0.0	99.6
Meropenem	8	>8	≤0.12 to >8	20.5	5.8	73.7	26.3	26.4	47.3
Piperacillin-tazobactam	>64	>64	1 to >64	4.0	11.6	84.4	4.0	0.0	96.0

^a Criteria were published by the CLSI (12) and EUCAST (http://www.eucast.org/clinical_breakpoints).

^b U.S. FDA breakpoints were applied when available (3).

^c Includes *Citrobacter* spp. (29 strains), *Enterobacter* spp. (246 strains), *E. coli* (259 strains), *Klebsiella oxytoca* (45 strains), *K. pneumoniae* (464 strains), *Morganella morganii* (76 strains), *Proteus mirabilis* (104 strains), *Providencia rettgeri* (7 strains), *Providencia stuartii* (35 strains), *Serratia marcescens* (68 strains), and other species (26 strains).

^d Includes *Citrobacter freundii* (4 strains), *Enterobacter cloacae* complex (36 strains), *E. coli* (7 strains), *K. pneumoniae* (143 strains), *M. morganii* (13 strains), *P. mirabilis* (5 strains), *P. stuartii* (2 strains), *S. marcescens* (11 strains), and other species (3 strains).

ceptible *Enterobacteriaceae* species or groups were *Proteus mirabilis* (MIC₅₀, 2 $\mu\text{g/ml}$; MIC₉₀, 4 $\mu\text{g/ml}$) and indole-positive *Proteae* (MIC₅₀, 0.5 $\mu\text{g/ml}$; MIC₉₀, 2 $\mu\text{g/ml}$), which are not listed as indicated species (3). Tigecycline also showed activity against *Acinetobacter* spp. (MIC₅₀, 0.5 $\mu\text{g/ml}$; MIC₉₀, 2 $\mu\text{g/ml}$), *Stenotrophomonas maltophilia* (MIC₅₀, 0.5 $\mu\text{g/ml}$; MIC₉₀, 2 $\mu\text{g/ml}$), and *H. influenzae* (MIC₅₀, 0.12 $\mu\text{g/ml}$; MIC₉₀, 0.25 $\mu\text{g/ml}$) (Table 1).

The prevalence of tigecycline-nonsusceptible strains was extremely low among Gram-positive species, with the highest rate being observed among *E. faecium* (0.7% nonsusceptible), followed by *E. faecalis* (0.4%), *S. pneumoniae* (<0.1%), and *S. aureus* (<0.1%) (Table 2). Among *Enterobacteriaceae* strains, 1.7% of strains were categorized as nonsusceptible (intermediate, 1.6%; resistant, 0.1%), and nonsusceptibility rates were higher among MDR (9.9%) and XDR (14.7%) strains. Most importantly, no trend toward increased tigecycline resistance was observed for any species or group during the study period (2006 to 2012) (Table 2).

The activities of tigecycline and selected comparator agents for *S. aureus*, *E. faecalis*, *E. faecium*, and *Enterobacteriaceae*, including the MDR and XDR subsets, were analyzed (Table 3). Tigecycline, daptomycin, linezolid, and vancomycin were active against ≥99.9% of *S. aureus* strains, whereas tigecycline (MIC₅₀, 0.12 $\mu\text{g/ml}$; MIC₉₀, 0.25 $\mu\text{g/ml}$) was 2-fold more active than daptomycin (MIC₅₀, 0.25 $\mu\text{g/ml}$; MIC₉₀, 0.5 $\mu\text{g/ml}$) and 8-fold more active than linezolid (MIC₅₀, 1 $\mu\text{g/ml}$; MIC₉₀, 2 $\mu\text{g/ml}$) and vancomycin (MIC₅₀, 1 $\mu\text{g/ml}$; MIC₉₀, 1 $\mu\text{g/ml}$) when tested against this large collection of *S. aureus* strains (Table 3). Tigecycline was also the

most potent (by weight) agent tested against *E. faecalis* (MIC₅₀, 0.12 $\mu\text{g/ml}$; MIC₉₀, 0.25 $\mu\text{g/ml}$; 99.6% susceptible) and *E. faecium* (MIC₅₀, 0.06 $\mu\text{g/ml}$; MIC₉₀, 0.12 $\mu\text{g/ml}$; 99.3% susceptible). Daptomycin was also very active against both *E. faecalis* (MIC₅₀, 1 $\mu\text{g/ml}$; MIC₉₀, 1 $\mu\text{g/ml}$; >99.9% susceptible) and *E. faecium* (MIC₅₀, 2 $\mu\text{g/ml}$; MIC₉₀, 2 $\mu\text{g/ml}$; 99.6% susceptible), whereas ampicillin exhibited good activity against *E. faecalis* (MIC₅₀, ≤1 $\mu\text{g/ml}$; MIC₉₀, 2 $\mu\text{g/ml}$; 99.9% susceptible) but not against *E. faecium* (MIC₅₀, >8 $\mu\text{g/ml}$; MIC₉₀, >8 $\mu\text{g/ml}$; 7.5% susceptible). Vancomycin susceptibility rates were 95.4 and 23.5% for *E. faecalis* and *E. faecium*, respectively (Table 3).

Tigecycline (MIC₅₀, 0.25 $\mu\text{g/ml}$; MIC₉₀, 1 $\mu\text{g/ml}$), amikacin (MIC₅₀, ≤4 $\mu\text{g/ml}$; MIC₉₀, ≤4 $\mu\text{g/ml}$), and meropenem (MIC₅₀, ≤0.12 $\mu\text{g/ml}$; MIC₉₀, ≤0.12 $\mu\text{g/ml}$) were the most active compounds tested against *Enterobacteriaceae* strains overall, with susceptibility rates of 98.3 to 98.6%. The MDR and XDR subsets showed high rates of resistance to most agents, including amikacin (82.7 and 59.8% susceptible, respectively) and meropenem (75.0 and 20.5% susceptible, respectively). Tigecycline was the most active agent against these difficult-to-treat organisms, with susceptibility rates of 90.1 and 85.3% for MDR and XDR strains, respectively (Table 3).

The yearly prevalence of key resistance phenotypes is presented in Table 4, which shows an increase in all resistance phenotypes except for methicillin resistance among *S. aureus* isolates and vancomycin resistance among *E. faecalis* isolates. The prevalence of MDR and XDR *Enterobacteriaceae* escalated from 4.4 and 0.5%,

TABLE 4 Yearly prevalence of key resistance phenotypes in the United States in 2006 to 2012

	Prevalence (% [no. of isolates tested]) for the following yr:							
Resistance phenotype	2006	2007	2008	2009	2010	2011	2012	P ^a
MRSA	54.8 (4,357)	53.9 (4,366)	56.5 (4,197)	51.1 (3,522)	51.7 (4,174)	50.5 (3,881)	53.1 (3,781)	<0.001
Vancomycin-nonsusceptible <i>E. faecalis</i>	4.9 (798)	4.1 (763)	6.2 (738)	2.9 (696)	4.7 (766)	4.6 (438)	4.6 (330)	0.648
Vancomycin-nonsusceptible <i>E. faecium</i>	72.7 (454)	72.4 (450)	77.3 (427)	78.5 (373)	80.9 (533)	77.9 (253)	74.7 (166)	0.008
MDR <i>Enterobacteriaceae</i>	4.4 (2,204)	5.8 (2,690)	6.1 (2,642)	6.5 (2,537)	6.4 (3,246)	7.4 (3,360)	8.5 (3,778)	<0.001
XDR <i>Enterobacteriaceae</i>	0.5 (2,204)	0.7 (2,690)	1.1 (2,642)	1.5 (2,537)	0.9 (3,246)	1.2 (3,360)	1.5 (3,778)	0.001
ESBL-phenotype <i>E. coli</i>	5.8 (905)	5.6 (1,081)	6.8 (1,066)	10.4 (978)	10.0 (1,368)	12.5 (1,187)	11.1 (1,463)	<0.001
ESBL-phenotype <i>K. pneumoniae</i>	9.1 (460)	12.0 (610)	14.6 (584)	13.8 (582)	14.8 (768)	18.3 (656)	20.4 (643)	<0.001
Meropenem-nonsusceptible <i>K. pneumoniae</i>	2.2 (460)	2.9 (610)	5.3 (584)	6.5 (582)	4.6 (762)	6.5 (656)	10.8 (643)	<0.001

^a The chi-square test for trend was applied by using the Epi Info 7 statistical package. P values of <0.05 were considered significant.

respectively, in 2006 to 8.5 and 1.5% in 2012 ($P < 0.001$). In the same period of time, the prevalence of *E. coli* and *Klebsiella* spp. with an ESBL phenotype increased from 5.8 and 9.1%, respectively, to 11.1 and 20.4% ($P < 0.001$ for both). The most marked increase was documented for meropenem-nonsusceptible *K. pneumoniae*, with rates increasing continuously from 2.2% in 2006 to 10.8% in 2012 ($P < 0.001$). In contrast, MRSA rates declined during the study period (Table 4).

DISCUSSION

Tigecycline was initially approved for clinical use in the United States in mid-2005 and has maintained *in vitro* activity against a wide spectrum of aerobic and anaerobic bacteria (9). The results of this investigation corroborate those reported by other investigators, showing that the occurrence of tigecycline-nonsusceptible strains remains low among key, clinically relevant, bacterial organisms (14, 15). Tigecycline was regularly active against the indicated Gram-positive species (3). When 28,278 strains of *S. aureus* were tested, only two strains with tigecycline MIC values of >0.5 $\mu\text{g/ml}$ were observed, both with MIC values of 1 $\mu\text{g/ml}$ (Table 1). Furthermore, the MIC₅₀ and MIC₉₀ values remained very stable and the percentages of strains with tigecycline MIC values of 0.5 $\mu\text{g/ml}$ ranged from 0.1 to 1.9% during the period of the investigation, with no trend toward an increase (MIC creep). Of note, tigecycline activity against *S. aureus* was not affected by resistance to oxacillin.

S. aureus is an extraordinarily adaptable pathogen, with a proven ability to develop antimicrobial resistance (16). Historically, it has taken only a few years following clinical introduction of an antimicrobial agent for resistance to emerge and to increase rapidly. However, the results of this investigation indicate that tigecycline nonsusceptibility remains rare after several years of clinical use, providing potent empirical coverage against MRSA in U.S. medical centers (17).

Tigecycline was also remarkably active against *E. faecalis* and *E. faecium*, including vancomycin-resistant strains, for which very few therapeutic options are available (18). The optimal treatment of systemic VRE infections has not been well established due to the lack of prospective outcome studies comparing available treatment options (19). Due to its potent *in vitro* activity, tigecycline represents an attractive therapeutic option; however, further clinical data are necessary to establish the role of tigecycline in the treatment of VRE infections (20). It is also important to note that tigecycline is not approved by the U.S. FDA for treatment of VRE infections; it is approved only for treatment of cSSSIs and cIAIs caused by vancomycin-susceptible *E. faecalis* (3).

Some of the most noteworthy findings of this investigation were the significant increases in the prevalence of important resistance phenotypes among *Enterobacteriaceae*. ESBL phenotype rates doubled among *E. coli* and *Klebsiella* spp., whereas the prevalence of meropenem-nonsusceptible *K. pneumoniae* increased 5-fold (from 2.2 to 10.8%) between 2006 and 2012. Furthermore, the prevalence of MDR and XDR *Enterobacteriaceae* increased 2- to 3-fold during the same period (Table 4). MDR *Enterobacteriaceae* strains were observed in 26 of 29 medical centers evaluated, which were distributed across 21 states, whereas XDR strains were detected in 15 medical centers in 9 states. Although carbapenem-resistant, MDR, and XDR *Enterobacteriaceae* strains remain relatively uncommon in most U.S. hospitals, these organisms have

become increasingly recognized as causes of infections in the past decade (21, 22).

There are very few options available for the treatment of infections caused by MDR and XDR *Enterobacteriaceae*, especially those caused by carbapenem-resistant strains, and severe infections are frequently treated with combination therapy (23–25). Kelesidis et al. (7) performed a literature review to assess the *in vitro* activity of tigecycline against MDR *Enterobacteriaceae*, as well as the clinical evidence regarding the use of tigecycline for the treatment of infections caused by these organisms. Those authors concluded that tigecycline was microbiologically active (based on U.S. FDA breakpoint criteria) against the great majority of MDR *Enterobacteriaceae* (3). They also observed that clinical reports were limited and further evaluation of the clinical utility of tigecycline is warranted, particularly regarding off-label indications (7).

The results of the present study are in agreement with those of other reports in showing that tigecycline is among the agents that retain *in vitro* activity against MDR and XDR *Enterobacteriaceae*, *Acinetobacter* spp., and *S. maltophilia* (4, 6, 7, 10, 24, 26). Due to its *in vitro* activity, tigecycline has been used for the treatment of infections caused by these organisms, especially when alternative treatments are not suitable; however, the role of tigecycline in the treatment of infections caused by MDR Gram-negative organisms is not well established, and further clinical studies are suggested (3, 25, 27).

In summary, we assessed the progression of the *in vitro* activity of tigecycline since its initial approval by the U.S. FDA, using a total of 68,608 unique clinical isolates, and tigecycline showed sustained potent activity against clinically important organisms, including MDR subsets of Gram-positive and Gram-negative pathogens. Furthermore, the results of this investigation clearly demonstrated marked increases in the prevalence MDR and XDR *Enterobacteriaceae* in U.S. hospitals between 2006 and 2012. A large longitudinal surveillance network, such as the SENTRY Program, is a valuable tool for documenting emerging resistance and longitudinal trends.

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