

Tigecycline activity tested against 26,474 bloodstream infection isolates: a collection from 6 continents

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Abstract

The activity of tigecycline (formerly GAR936), a novel glycycline, was tested against recent bloodstream infection (BSI) pathogen isolates from 6 continents. Frequency of clinical occurrence of these pathogens was determined and their antibiograms assessed using reference broth microdilution methods. A total of 26474 strains were tested for tigecycline susceptibility according to the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) by the M7-A6 guidelines with interpretations from M100-S15 and the package insert. The rank order of pathogens was *Staphylococcus aureus* (33.1%), *Escherichia coli* (14.0%), coagulase-negative staphylococci (13.5%), *Enterococcus* spp. (12.3%), *Klebsiella* spp. (5.7%), *Pseudomonas aeruginosa* (4.2%), *Enterobacter* spp. (3.0%), β -hemolytic streptococci (2.9%), *Streptococcus pneumoniae* (2.3%), and viridans group streptococci (1.4%). Tigecycline exhibited a broader spectrum of activity against BSI isolates when compared to ciprofloxacin, tetracycline, aminoglycosides, and many β -lactams (imipenem). Tigecycline was highly active against most pathogens tested, including staphylococci (MIC₉₀, 0.5 μ g/mL), enterococci (MIC₉₀, 0.25 μ g/mL), streptococci (MIC₉₀, \leq 0.12 μ g/mL), *Escherichia coli* (MIC₉₀, 0.25 μ g/mL), *Klebsiella* spp. (MIC₉₀, 1 μ g/mL), and *Enterobacter* spp. (MIC₉₀, 2 μ g/mL), but showed limited inhibition of *Pseudomonas aeruginosa* (MIC₉₀, 16 μ g/mL) and indole-positive or indole-negative *Proteae* (MIC₉₀, 4–8 μ g/mL). In summary, tigecycline exhibited a wide spectrum of antimicrobial potency versus BSI isolates collected worldwide. Serious infections in nosocomial environments should benefit from tigecycline use among the investigational phase 3 agents focused toward resistant strains.

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1. Introduction

Clinically significant bloodstream infection (BSI) is a serious consequence of a wide variety of initially localized infections and treatment is routinely emergent. Furthermore, the increased complexity of patients requiring hospitalization and the widespread use of indwelling devices have created higher risks for BSI. Inadequate empiric antimicrobial therapy has been associated with adverse outcomes, including increased mortality, and antimicrobial resistance has become a common reason for inadequate treatment. In this

situation, knowledge of the most likely causative organisms and their expected resistance patterns can maximize the probability of selecting an effective antimicrobial for empiric treatment (Ibrahim et al., 2000; Weinstein et al., 1997).

Tigecycline is the first semisynthetic glycycline to enter phase 3 clinical trials. Tigecycline has documented activity against tetracycline-resistant Gram-positive and Gram-negative pathogens refractory by both efflux and ribosomal protection mechanisms (Bauer et al., 2004; Biedenbach et al., 2001; Fritsche and Jones, 2004; Fritsche et al., 2004; Gales and Jones, 2000; Milatovic et al., 2003). The present study was conducted to evaluate the in vitro activity of tigecycline in comparison to tetracycline and other potential empiric agents when tested against clinical bacterial isolates collected from patients with BSI.

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2. Materials and methods

A total of 26474 Gram-positive and Gram-negative bacterial isolates were recovered from patients hospitalized with clinically significant bacteremia (2000–2004). Consecutively acquired, nonduplicate patient isolates were submitted from >70 participating medical centers representing 29 countries in the 6 continents of Africa, Asia, Australia, Europe, North America, and South America. The rank order of pathogens was *Staphylococcus aureus* (8765 isolates), *Escherichia coli* (3712), coagulase-negative staphylococci (CoNS; 3570), *Enterococcus* spp. (3258), *Klebsiella* spp. (1503), *Pseudomonas aeruginosa* (1121), *Enterobacter* spp. (801), β -hemolytic streptococci (769), *Streptococcus pneumoniae* (605), and viridans group streptococci (378).

All isolates were identified by the participant laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, IA). Each strain was tested by a reference broth microdilution method against more than 30 antimicrobial agents; only selected agents with the widest potential clinical utility and in vitro activity are reported here. Interpretation of quantitative MIC results was in accordance with Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [NCCLS]) methods and criteria (CLSI, 2005; NCCLS, 2003) and the package insert (Tygacil, 2005). Current quality control (QC) testing was performed using the following organisms: *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *E. coli* ATCC 25923, and *P. aeruginosa* ATCC 27853. All QC results were within CLSI (2005) published ranges.

3. Results

The most frequently isolated pathogen from BSI in medical centers worldwide (2000–2004) period was *S. aureus* (33.1%), followed by *E. coli* (14.0%), CoNS (13.5%), and *Enterococcus* spp. (12.3%). These 4 pathogens accounted for 72.9% of the isolates collected during the

study period and >99% of these isolates were inhibited by ≤ 1 $\mu\text{g/mL}$ of tigecycline (Table 1).

Tigecycline was highly active against *S. aureus* isolates (MIC₅₀, 0.12 $\mu\text{g/mL}$ and MIC₉₀, 0.5 $\mu\text{g/mL}$) independent of their susceptibility to oxacillin (Table 2). The highest tigecycline MIC value was only 1 $\mu\text{g/mL}$, and 99.4% of isolates were inhibited at ≤ 0.5 $\mu\text{g/mL}$ of tigecycline. Resistance to oxacillin was observed in 34.8% of *S. aureus* strains. Similar to *S. aureus*, both oxacillin-resistant and oxacillin-susceptible CoNS were highly susceptible to tigecycline (MIC₅₀, 0.25 $\mu\text{g/mL}$ and MIC₉₀, 0.5 $\mu\text{g/mL}$). Resistance to oxacillin was observed in 77.2% of CoNS strains. Vancomycin (MIC₉₀, 2 $\mu\text{g/mL}$) and linezolid (MIC₉₀, 1 $\mu\text{g/mL}$) were active against all CoNS isolates at the applied susceptible break points (CLSI, 2005). The highest tigecycline MIC value was 2 $\mu\text{g/mL}$ (1 strain) and 97.5% of isolates were susceptible at ≤ 0.5 $\mu\text{g/mL}$ of tigecycline (Tables 1 and 2).

Tigecycline was the most active compound against tested *Enterococcus* spp. strains (MIC₅₀, 0.12 $\mu\text{g/mL}$ and MIC₉₀, 0.25 $\mu\text{g/mL}$). Tigecycline was 8-fold more potent than vancomycin (MIC₅₀, 1 $\mu\text{g/mL}$ and MIC₉₀, >16 $\mu\text{g/mL}$) and 16-fold more potent than linezolid (MIC₅₀ and MIC₉₀ at 2 $\mu\text{g/mL}$) against this pathogen (Table 2).

β -Hemolytic streptococcal isolates were highly susceptible to tigecycline. The highest tigecycline MIC value was only 0.5 $\mu\text{g/mL}$ and most strains (>95%) were inhibited at ≤ 0.12 $\mu\text{g/mL}$ of tigecycline. These pathogens were also highly susceptible to penicillin, ceftriaxone, vancomycin, and linezolid. However, resistance to levofloxacin was detected in 1.2% of strains tested (Table 2). Tigecycline was also highly active against *Streptococcus pneumoniae* and viridans group streptococci (MIC₉₀ of ≤ 0.12 $\mu\text{g/mL}$ for both pathogens), including isolates resistant to penicillin and/or tetracycline and/or erythromycin. Resistance to penicillin (MIC, ≥ 2 $\mu\text{g/mL}$) was observed in 10.2% of *S. pneumoniae* and 7.1% of viridans group streptococci (MIC, ≥ 4 $\mu\text{g/mL}$; Table 2).

Table 1

Potency of tigecycline against the principle bacterial pathogens (26474 total isolates) isolated from BSIs worldwide (2000–2004)

Organism (no. tested/% of total)	Cumulative % inhibited at ($\mu\text{g/mL}$)						
	≤ 0.12	0.25	0.5	1	2	4	8
1. <i>Staphylococcus aureus</i> (8765/33.1)	58	89	>99	>99	100	–	–
2. <i>Escherichia coli</i> (3712/14.0)	53	92	>99	>99	100	–	–
3. CoNS (3570/13.5)	48	79	98	100	–	–	–
4. <i>Enterococcus</i> spp. (3258/12.3)	66	93	>99	100	–	–	–
5. <i>Klebsiella</i> spp. (1503/5.7)	1	35	83	94	98	>99	100
6. <i>Pseudomonas aeruginosa</i> (1121/4.2)	<1	<1	1	2	5	23	68
7. <i>Enterobacter</i> spp. (801/3.0)	2	24	78	90	95	>99	100
8. β -Hemolytic streptococci (769/2.9)	95	>99	100	–	–	–	–
9. <i>Streptococcus pneumoniae</i> (605/2.3)	94	97	99	100	–	–	–
10. Viridans group streptococci (378/1.4)	94	98	100	–	–	–	–
11. <i>Acinetobacter</i> spp. (326/1.2)	15	34	52	74	94	>99	100
12. <i>Proteus mirabilis</i> (320/1.2)	0	<1	2	10	47	91	>99
13. <i>Serratia</i> spp. (294/1.1)	<1	1	16	82	95	97	>99
14. <i>Stenotrophomonas maltophilia</i> (203/0.8)	1	8	38	77	93	97	100

Table 2
Antimicrobial activity of tigecycline against Gram-positive bacteria isolated from BSIs

Organism (no. tested)/ antimicrobial agent	MIC ($\mu\text{g/mL}$)			% susceptible/ resistant ^a
	50%	90%	Range	
<i>S. aureus</i> (8765)				
Tigecycline	0.12	0.5	≤ 0.016 –1	99.4/– ^b
Tetracycline	≤ 2	4	≤ 2 –>8	90.3/9.2
Oxacillin	0.5	>8	≤ 0.06 –>8	65.2/34.8
Clindamycin	0.12	>8	≤ 0.06 –>8	74.1/25.7
Levofloxacin	0.25	>4	≤ 0.03 –>4	64.9/34.0
Trimethoprim/ sulfamethoxazole	≤ 0.5	≤ 0.5	≤ 0.5 –>2	95.5/4.5
Quinupristin/ dalbopristin	0.5	0.5	≤ 0.06 –>8	99.9/0.1
Teicoplanin	≤ 2	≤ 2	≤ 2 –>16	99.9/0.0
Vancomycin	1	1	≤ 0.12 –4	100.0/0.0
Linezolid	2	2	0.12–16	100.0/– ^c
Daptomycin	0.25	0.5	≤ 0.06 –2	99.9/–
<i>CoNS</i> ^d (3570)				
Tigecycline	0.25	0.5	≤ 0.016 –2	97.5/– ^b
Tetracycline	≤ 2	>8	≤ 2 –>8	82.5/16.8
Oxacillin	>2	>2	≤ 0.06 –>2	22.8/77.2
Clindamycin	0.12	>8	≤ 0.06 –>8	63.2/36.1
Levofloxacin	2	>4	≤ 0.03 –>4	47.5/45.2
Trimethoprim/ sulfamethoxazole	≤ 0.5	>2	≤ 0.5 –>2	63.6/36.4
Quinupristin/ dalbopristin	≤ 0.25	0.5	≤ 0.25 –>8	99.2/0.3
Teicoplanin	≤ 2	8	≤ 2 –>16	96.1/0.9
Vancomycin	1	2	≤ 0.12 –4	100.0/0.0
Linezolid	1	1	≤ 0.06 –2	100.0/–
Daptomycin	0.25	0.5	≤ 0.016 –2	99.8/–
<i>Enterococcus</i> spp. ^e (3258)				
Tigecycline	0.12	0.25	≤ 0.016 –2	92.7/– ^b
Tetracycline	>8	>8	≤ 2 –>8	38.4/61.2
Ampicillin	2	>16	≤ 0.12 –>16	77.9/22.1
Gentamicin	≤ 500	>1000	≤ 500 –>1000	–/–
Streptomycin	≤ 1000	>2000	≤ 1000 –>2000	62.2/37.8
Levofloxacin	2	>4	0.06–>4	50.8/47.6
Quinupristin/ dalbopristin	>2	>2	≤ 0.25 –>2	22.2/70.2
Teicoplanin	0.5	8	≤ 0.12 –>16	90.0/8.4
Vancomycin	1	>16	≤ 0.12 –>16	87.3/11.7
Linezolid	2	2	≤ 0.06 –>16	99.6/0.2
Daptomycin	1	2	≤ 0.016 –8	99.9/–
β -Hemolytic streptococci ^f (769)				
Tigecycline	≤ 0.12	≤ 0.12	≤ 0.12 –0.5	99.7/– ^b
Tetracycline	>8	>8	≤ 2 –>8	31.0/54.0
Penicillin	≤ 0.016	0.06	≤ 0.016 –0.12	100.0/–
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 –0.5	100.0/–
Erythromycin	≤ 0.06	2	≤ 0.06 –>8	81.1/18.4
Clindamycin	≤ 0.06	≤ 0.06	≤ 0.06 –>8	93.2/6.4
Levofloxacin	0.5	1	≤ 0.03 –>4	98.6/1.2
Vancomycin	0.5	0.5	≤ 0.12 –1	100.0/–
Linezolid	1	1	≤ 0.06 –2	100.0/–
Daptomycin	≤ 0.12	0.25	≤ 0.12 –0.5	100.0/–
<i>Streptococcus pneumoniae</i> (605)				
Tigecycline	≤ 0.12	≤ 0.12	≤ 0.12 –1	97.2/– ^b
Tetracycline	≤ 4	8	≤ 4 –>8	47.8/10.3
Penicillin	≤ 0.016	2	≤ 0.016 –8	78.0/10.2

Table 2 (continued)

Organism (no. tested)/ antimicrobial agent	MIC ($\mu\text{g/mL}$)			% susceptible/ resistant ^a
	50%	90%	Range	
Ceftriaxone	≤ 0.25	1	≤ 0.25 –8	98.2/0.3
Erythromycin	≤ 0.06	8	≤ 0.06 –>32	82.3/17.5
Clindamycin	≤ 0.06	≤ 0.06	≤ 0.06 –>8	92.9/6.6
Levofloxacin	1	1	0.06–>4	99.3/0.7
Vancomycin	0.25	0.5	≤ 0.12 –1	100.0/–
Linezolid	1	1	0.12–2	100.0/–
Daptomycin	≤ 0.12	0.25	≤ 0.12 –0.5	100.0/–
<i>Viridans group streptococci</i> ^g (378)				
Tigecycline	≤ 0.12	≤ 0.12	≤ 0.12 –0.5	98.1/– ^b
Tetracycline	≤ 4	>8	≤ 4 –>8	38.8/28.5
Penicillin	0.06	2	≤ 0.016 –32	66.7/7.1
Ceftriaxone	≤ 0.25	1	≤ 0.25 –16	90.7/5.8
Erythromycin	≤ 0.06	4	≤ 0.06 –>8	57.7/38.1
Clindamycin	≤ 0.06	0.5	≤ 0.06 –>8	88.9/9.3
Levofloxacin	1	2	≤ 0.03 –>4	96.8/2.9
Vancomycin	0.5	1	≤ 0.12 –1	100.0/–
Linezolid	1	1	≤ 0.06 –2	100.0/–
Daptomycin	0.25	1	≤ 0.12 –2	99.7/–

^a Criteria as published by the CLSI/NCCLS (CLSI, 2005; NCCLS, 2003).

^b Tigecycline susceptible break points were defined as in the package insert (Tygacil, 2005).

^c – = no break points have been established by the CLSI/NCCLS (CLSI, 2005; NCCLS, 2003).

^d Includes *Staphylococcus auricularis* (15 strains), *S. capitis* (49 strains), *S. caprae* (1 strain), coagulase-negative staphylococci (1655 strains), *S. cohnii* (1 strain), *S. epidermidis* (1348 strains), *S. haemolyticus* (171 strains), *S. hominis* (144 strains), *S. hyicus* (1 strain), *S. intermedius* (7 strains), *S. lentus* (1 strain), *S. lugdunensis* (16 strains), *S. saprophyticus* (28 strains), *S. schleiferi* (2 strains), *S. sciuri* (3 strains), *S. simulans* (33 strains), *S. spp.* (19 strains), *S. warnerii* (48 strains), and *S. xylois* (28 strains).

^e Includes *Enterococcus* spp. (61 strains), *E. faecalis* (2318 strains), *E. casseliflavus* (19 strains), *E. avium* (20 strains), *E. durans* (13 strains), *E. raffinosus* (2 strains), *Streptococcus* group D (5 strains), *E. gallinarum* (37 strains), *E. faecium* (776 strains), *Enterococcus* group D (1 strain), and *E. hirae* (6 strains).

^f Includes β -hemolytic streptococci (7 strains), *Streptococcus dysgalactiae* (4 strains), *S. equi* (1 strain), *S. equisimilis* (1 strain), *Streptococcus* group A (240 strains), group B (372 strains), group C (29 strains) group F (7 strains), and group G (108 strains).

^g Includes *Streptococcus* α -hemolytic (14 strains), *S. anginosus* (28 strains), *S. constellatus* (25 strains), *S. gordonii* (4 strains), *S. intermedius* (14 strains), *S. milleri* (27 strains), *S. mitis* (85 strains), *S. mutans* (4 strains), *S. oralis* (31 strains), *S. parasanguis* (2 strains), *S. salivarius* (21 strains), *Streptococcus sanguis* (31 strains), *Streptococcus* spp. (18 strains), *S. uberis* (1 strain), and viridans group *Streptococcus* (73 strains).

Among the most frequent Enterobacteriaceae species isolated from BSI, for example, *E. coli*, *Klebsiella* spp., and *Enterobacter* spp., tigecycline MIC₅₀ values ranged from 0.12 to 0.5 $\mu\text{g/mL}$, whereas MIC₉₀ values ranged from 0.25 to 2 $\mu\text{g/mL}$ (Table 3). An extended-spectrum β -lactamase (ESBL) phenotype was detected in 6.2% of *E. coli* and 18.5% of *Klebsiella* spp., whereas 23.3% of *Enterobacter* spp. strains were resistant to ceftazidime (AmpC-mediated resistance). In addition, resistance to ciprofloxacin was detected in 16.8% of *E. coli*, 11.8% of *Klebsiella* spp., and 13.5% of *Enterobacter* spp. strains

Table 3
Antimicrobial activity of tigecycline against Enterobacteriaceae isolated from BSI

Organism (no. tested)/ antimicrobial agent	MIC ($\mu\text{g/mL}$)			% susceptible/ resistant ^a
	50%	90%	Range	
<i>Escherichia coli</i> (3217)				
Tigecycline	0.12	0.25	0.03–4	>99.9/0.0
Tetracycline	≤ 2	>8	$\leq 2 \rightarrow 8$	64.9/34.5
Ceftriaxone	≤ 0.25	≤ 0.25	$\leq 0.25 \rightarrow 32$	96.0/3.2
Ceftazidime	≤ 1	≤ 1	$\leq 1 \rightarrow 16$	96.6/2.0
Cefepime	≤ 0.12	≤ 0.12	$\leq 0.12 \rightarrow 16$	97.4/2.0
Piperacillin/ tazobactam	2	4	$\leq 0.12 \rightarrow 256$	96.1/2.0
Imipenem	≤ 0.5	≤ 0.5	$\leq 0.5 \rightarrow 8$	99.9/0.0
Ciprofloxacin	≤ 0.03	>4	$\leq 0.03 \rightarrow 4$	83.2/16.8
Gentamicin	≤ 2	≤ 2	$\leq 2 \rightarrow 8$	92.1/7.4
Amikacin	2	4	$\leq 0.25 \rightarrow 32$	99.4/0.1
<i>Enterobacter spp.</i> ^b (801)				
Tigecycline	0.5	2	0.06–8	95.5/0.2
Tetracycline	≤ 2	>8	$\leq 2 \rightarrow 8$	82.6/12.9
Ceftriaxone	≤ 0.25	>32	$\leq 0.25 \rightarrow 32$	78.5/14.0
Ceftazidime	≤ 1	>16	$\leq 1 \rightarrow 16$	76.7/20.1
Cefepime	≤ 0.12	4	$\leq 0.12 \rightarrow 16$	95.3/3.5
Piperacillin/ tazobactam	2	64	0.25–256	80.8/9.6
Imipenem	≤ 0.5	1	$\leq 0.5 \rightarrow 8$	99.5/0.1
Ciprofloxacin	≤ 0.03	4	$\leq 0.03 \rightarrow 4$	86.5/11.1
Gentamicin	≤ 2	>8	$\leq 2 \rightarrow 8$	88.6/10.1
Amikacin	2	4	0.5–32	95.9/1.6
<i>Klebsiella spp.</i> ^c (1503)				
Tigecycline	0.5	1	0.06–8	98.1/0.1
Tetracycline	≤ 2	>8	$\leq 2 \rightarrow 8$	81.6/14.8
Ceftriaxone	≤ 0.25	>32	$\leq 0.25 \rightarrow 32$	85.4/10.2
Ceftazidime	≤ 1	>16	$\leq 1 \rightarrow 16$	87.0/10.8
Cefepime	≤ 0.12	8	$\leq 0.12 \rightarrow 16$	91.7/6.9
Piperacillin/ tazobactam	2	>64	0.25–64	87.8/10.1
Imipenem	≤ 0.5	≤ 0.5	$\leq 0.5 \rightarrow 8$	99.5/0.4
Ciprofloxacin	≤ 0.03	4	$\leq 0.03 \rightarrow 4$	88.2/10.3
Gentamicin	≤ 2	>8	$\leq 2 \rightarrow 8$	86.7/11.9
Amikacin	1	8	$\leq 0.25 \rightarrow 32$	95.0/2.6
<i>Proteus mirabilis</i> (320)				
Tigecycline	4	4	0.25–16	46.9/9.4
Tetracycline	>8	>8	$\leq 2 \rightarrow 8$	1.3/98.8
Ceftriaxone	≤ 0.25	≤ 0.25	$\leq 0.25 \rightarrow 32$	96.3/2.8
Ceftazidime	≤ 1	≤ 1	$\leq 1 \rightarrow 16$	98.8/0.3
Cefepime	≤ 0.12	≤ 0.12	$\leq 0.12 \rightarrow 16$	96.9/2.8
Piperacillin/ tazobactam	≤ 0.5	1	$\leq 0.5 \rightarrow 16$	100.0/0.0
Imipenem	1	2	$\leq 0.12 \rightarrow 4$	100.0/0.0
Ciprofloxacin	≤ 0.03	>4	$\leq 0.03 \rightarrow 4$	79.4/15.0
Gentamicin	≤ 2	8	$\leq 2 \rightarrow 8$	89.4/9.7
Amikacin	2	8	0.5–32	98.4/1.3
<i>Serratia spp.</i> (294)				
Tigecycline	1	2	0.12–16	94.6/2.7
Tetracycline	>8	>8	$\leq 2 \rightarrow 8$	6.8/69.2
Ceftriaxone	≤ 0.25	16	$\leq 0.25 \rightarrow 32$	89.1/4.1
Ceftazidime	≤ 1	2	$\leq 1 \rightarrow 16$	93.5/3.4
Cefepime	≤ 0.12	1	$\leq 0.12 \rightarrow 16$	96.9/3.1
Piperacillin/ tazobactam	2	32	$\leq 0.5 \rightarrow 256$	89.5/3.1

Table 3 (continued)

Organism (no. tested)/ antimicrobial agent	MIC ($\mu\text{g/mL}$)			% susceptible/ resistant ^a
	50%	90%	Range	
Imipenem	0.5	1	$\leq 0.12 \rightarrow 8$	98.6/1.4
Ciprofloxacin	0.06	1	$\leq 0.03 \rightarrow 4$	93.9/4.4
Gentamicin	≤ 2	4	$\leq 2 \rightarrow 8$	91.2/7.1
Amikacin	2	4	0.5–32	95.9/1.7

^a Criteria as published by the CLSI/NCCLS or package insert (CLSI, 2005; NCCLS, 2003; Tygacil, 2005).

^b Includes *E. aerogenes* (138 strains), *E. amnigenus* (1 strain), *E. asburiae* (3 strains), *E. cancerogenus* (1 strain), *E. cloacae* (592 strains), *E. gergoviae* (3 strains), *E. sakazakii* (3 strains), *E. spp.* (59 strains), and *E. tylosae* (1 strain).

^c Includes *K. ornithinolytica* (1 strain), *K. oxytoca* (259 strains), *K. ozaenae* (4 strains), *K. pneumoniae* (1217 strains), *K. spp.* (21 strains), and *K. terrigena* (1 strain).

tested. *Serratia spp.* and *P. mirabilis* showed higher tigecycline MIC values (MIC₉₀, 2 and 4 $\mu\text{g/mL}$, respectively) when compared to other Enterobacteriaceae (Tables 1 and 3).

Nonfermentative Gram-negative bacilli exhibited high rates of resistance to most antimicrobial agents tested. However, tigecycline was highly active against *Acinetobacter spp.* (MIC₅₀, 0.5 $\mu\text{g/mL}$ and MIC₉₀, 2 $\mu\text{g/mL}$) and *Stenotrophomonas maltophilia* strains (MIC₅₀, 1 $\mu\text{g/mL}$ and MIC₉₀, 2 $\mu\text{g/mL}$), but showed very limited activity against *P. aeruginosa* strains (MIC₅₀, 8 $\mu\text{g/mL}$ and MIC₉₀, 16 $\mu\text{g/mL}$). Polymyxin B was the most active compound tested against *Acinetobacter spp.* (MIC₉₀, ≤ 1 $\mu\text{g/mL}$; 99.4% susceptible) and *P. aeruginosa* (MIC₉₀, ≤ 1 $\mu\text{g/mL}$; 100.0% susceptible), whereas trimethoprim/sulfamethoxazole was the most active antimicrobial agent against *S. maltophilia* (MIC₉₀, ≤ 0.5 $\mu\text{g/mL}$; 98.0% susceptible; Table 4).

Resistance to tetracycline did not adversely affect tigecycline activity (Table 5). In addition, tigecycline showed excellent activity against oxacillin-resistant *S. aureus* (MIC₉₀, 0.5 $\mu\text{g/mL}$), vancomycin-resistant enterococci (MIC₉₀, 0.25 $\mu\text{g/mL}$), penicillin-resistant *S. pneumoniae* (MIC₉₀, ≤ 0.12 $\mu\text{g/mL}$), and ESBL-producing *E. coli* (MIC₉₀, 0.5 $\mu\text{g/mL}$).

4. Discussion

The treatment of patients with BSI is becoming more complicated in an era of increasing antimicrobial resistance among frequently occurring pathogens (Biedenbach et al., 2004). The mortality rate of BSI has been assessed in several studies and may vary significantly according to patient age, predisposing factors, site of infection, and microorganisms, among other factors. A large study conducted in the United States revealed a mortality rate of 17.5% among adults with BSI. However, patients receiving appropriate antimicrobial therapy had a lower mortality rate

Table 4
Antimicrobial activity of tigecycline against nonfermentative Gram-negative bacilli isolated from BSIs

Organism (no. tested)/ antimicrobial agent	MIC ($\mu\text{g/mL}$)			% susceptible/ resistant ^a
	50%	90%	Range	
<i>Acinetobacter</i> spp. (326)				
Tigecycline	0.5	2	0.06–8	94.5/0.9 ^b
Tetracycline	4	>8	≤ 2 –>8	56.3/31.4
Ceftazidime	>16	>16	≤ 1 –>16	39.9/53.4
Cefepime	16	>16	0.25–>16	46.6/39.6
Piperacillin/ tazobactam	64	128	≤ 0.12 –>256	39.0/48.5
Imipenem	0.5	>8	≤ 0.12 –>8	82.2/15.6
Meropenem	1	>8	0.03–>8	77.6/13.5
Ciprofloxacin	>4	>4	≤ 0.03 –>4	43.6/55.8
Amikacin	4	>32	≤ 0.25 –>32	57.7/38.3
Polymyxin B	≤ 1	≤ 1	≤ 1 –4	99.4/0.6
<i>Pseudomonas aeruginosa</i> (1121)				
Tigecycline	8	16	0.12–>32	5.1/77.2 ^b
Tetracycline	>8	>8	≤ 2 –>8	2.4/85.5
Ceftazidime	4	>16	≤ 1 –>16	74.8/20.2
Cefepime	4	>16	≤ 0.12 –>16	75.0/12.9
Piperacillin/ tazobactam	8	>64	≤ 0.5 –>64	80.6/19.4
Imipenem	1	>8	≤ 0.12 –>8	79.9/12.1
Meropenem	0.5	>8	≤ 0.06 –>8	82.8/12.7
Ciprofloxacin	0.25	>4	≤ 0.03 –>4	69.3/27.6
Amikacin	4	32	≤ 0.25 –>32	87.9/9.4
Polymyxin B	≤ 1	≤ 1	≤ 1 –2	100.0/0.0
<i>Stenotrophomonas maltophilia</i> (203)				
Tigecycline	1	2	0.12–8	93.1/3.0 ^b
Tetracycline	>8	>8	≤ 2 –>8	3.5/68.8
Ceftazidime	8	>16	≤ 1 –>16	56.9/31.7
Cefepime	16	>16	0.5–>16	22.2/44.8
Piperacillin/ tazobactam	>64	>64	2–>64	11.3/64.5
Imipenem	>8	>8	2–>8	2.0/97.5
Meropenem	>8	>8	0.25–>8	5.5/92.5
Ciprofloxacin	2	>4	0.12–>4	29.6/34.0
Amikacin	>32	>32	0.5–>32	9.4/85.7
Polymyxin B	≤ 1	4	≤ 1 –>8	84.6/15.4
Trimethoprim/ sulfamethoxazole	≤ 0.5	1	≤ 0.5 –>2	98.0/2.0

^a Criteria as published by the CLSI/NCCLS (CLSI, 2005; NCCLS, 2003).

^b Tigecycline susceptible break point was defined as ≤ 2 $\mu\text{g/mL}$ and resistance break point as ≥ 8 $\mu\text{g/mL}$ for comparison purposes only (Jones, 1999).

of 13.3% (Weinstein et al., 1997). It has also been documented that one of the most important approaches for reducing mortality rate and infection-related complications is the selection of the initial, often empiric, adequate therapeutic regimen (Ibrahim et al., 2000).

Tigecycline is the 9-*t*-butylglycylamino derivative of minocycline, a new generation of the tetracyclines, called glycylcyclines. Glycylcyclines are a unique chemical class of antimicrobial agents that inhibit protein synthesis at the bacterial ribosome (Bauer et al., 2004;

Bradford, 2004). Based on the results of preclinical (in vitro, in vivo, safety) and clinical (efficacy and safety) studies, tigecycline is being evaluated as an intravenous treatment of serious infections in hospitalized patients (Muralidharan et al., 2005; Nathwani, 2005; Zhanel et al., 2004).

In the present study, tigecycline demonstrated excellent activity against the most frequently isolated pathogens collected from BSI worldwide, except for *P. aeruginosa*. As it has been demonstrated in other studies, tigecycline was also highly active against many resistant organisms, such as oxacillin-resistant *S. aureus*, vancomycin-resistant enterococci, ESBL-producing Enterobacteriaceae, *Acinetobacter* spp., and *S. maltophilia* (Biedenbach et al., 2001; Kitzis et al., 2004; Patel et al., 2000). Thus, this compound may play an important role in the empiric treatment of BSI in some hospitalized patients. Continued surveillance through longitudinal programs remains necessary to monitor the in vitro activity of this important novel compound such as tigecycline after its introduction in the clinical practice.

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Since acceptance of this publication, the US FDA has granted approval of tigecycline (June 15, 2005) for treatment of complicated skin and skin structure infections and for complicated intra-abdominal infections produced by designated organisms. Susceptibility breakpoint interpretations as defined by the FDA indicate that ≤ 2 $\mu\text{g/mL}$ is susceptible for Enterobacteriaceae, ≤ 0.5 $\mu\text{g/mL}$ for *S. aureus* (including methicillin resistant isolates), and ≤ 0.25 $\mu\text{g/mL}$ for *E. faecalis* (vancomycin-susceptible isolates only) and *Streptococcus* spp. other than *S. pneumoniae*.

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Table 5

Antimicrobial activity of tigecycline against commonly occurring susceptible and resistant organism subsets

Organism (no. tested)	Percentage of isolates inhibited at tigecycline MIC of ($\mu\text{g/mL}$)					
	≤ 0.12	0.25	0.5	1	2	4
<i>S. aureus</i>						
Oxacillin-susceptible (5718)	60	90	>99	100	–	–
Oxacillin-resistant (3047)	53	87	99	100	–	–
<i>S. aureus</i>						
Tetracycline-susceptible and intermediate (7944)	59	89	>99	100	–	–
Tetracycline-resistant (806)	44	84	99	100	–	–
<i>Enterococcus</i> spp.						
Vancomycin-susceptible (2843)	65	92	>99	100	–	–
Vancomycin-resistant (381)	74	98	100	–	–	–
<i>Enterococcus</i> spp.						
Tetracycline-susceptible and intermediate (1262)	70	94	>99	>99	100	–
Tetracycline-resistant (1989)	63	92	>99	100	–	–
<i>S. pneumoniae</i>						
Penicillin-susceptible (472)	94	98	99	100	–	–
Penicillin-intermediate and resistant (133)	95	95	98	100	–	–
<i>S. pneumoniae</i>						
Tetracycline-susceptible and intermediate (292)	90	95	98	100	–	–
Tetracycline-resistant (62)	93	95	98	100	–	–
<i>E. coli</i>						
ESBL-screen negative (1108)	43	88	98	>99	>99	100
ESBL-screen positive (179)	30	74	>99	100	–	–
<i>E. coli</i>						
Tetracycline-susceptible and intermediate (2425)	60	95	>99	100	–	–
Tetracycline-resistant (1280)	41	86	98	>99	>99	100

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