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Antimicrobial Activity of Tigecycline and Other Broad-Spectrum Agents Tested Against Bloodstream Infection Isolates Collected Worldwide

HS SADER, TR FRITSCHE, P STRABALA, RN JONES

JMI Laboratories, North Liberty, IA, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background:

We assessed the activity of the novel glycylcycline tigecycline (TIG) against recent bloodstream infection (BSI) pathogen isolates.

Methods:

Bacterial isolates (non-duplicates) were consecutively collected during 2000-2005 from documented BSI in >80 medical centers worldwide. Frequency of occurrence of BSI pathogens was determined and their antibiograms assessed using reference broth microdilution methods according to the CLSI guidelines. TIG-susceptible (S) breakpoints were defined as ≥2 µg/ml for Gram-negative bacilli, ≤0.5 µg/ml for staphylococci, and ≤0.25 µg/ml for streptococci and enterococci following interpretive criteria established by the US-FDA.

Results:

A total of 39,733 strains were evaluated and the frequency of pathogen occurrence and susceptibility rates to tigecycline are summarized in the table.

Organism (no. / %)	Cumulative % at TIG MIC value of[a]: ≤0.25	0.5	1	2	4	8
1. *S. aureus* (SA; 11,670 / 29.4%)	91.5	99.5	100.0	-	-	-
2. *E. coli* (6,447 / 16.2%)	94.2	99.5	>99.9	>99.9	100.0	-
3. CoNS (4,790 / 12.1%)	83.2	98.1	>99.9	100.0	-	-
4. *Enterococcus* (4,485 / 11.3%)	94.6	99.8	>99.9	100.0	-	-
5. *Klebsiella* spp. (KSP; 2,745 / 6.9%)	45.1	84.2	95.0	98.6	>99.9	100.0
6. *P. aeruginosa* (PSA; 1,948 / 4.9%)	0.6	1.3	2.3	7.5	35.1	61.2
7. *Enterobacter* spp. (1,455 / 3.7%)	37.4	82.2	91.7	96.7	99.9	100.0
8. ß-haemolytic streptococci (1,105 / 2.8%)	99.8	100.0	-	-	-	-
9. *S. pneumoniae* (929 / 2.3%)	98.2	99.2	100.0	-	-	-
10. *Acinetobacter* spp. (ASP; 713 / 1.8%)	41.5	58.5	81.2	96.1	99.3	99.6

a. Underline values indicate % S.

TIG was highly active against the top 10 pathogens isolated from BSI, except for PSA. Among the 5 most common pathogens (30,137 strains; 76% of the total), TIG was active against 98.6% at the S breakpoints. The main resistance phenotypes detected were methicillin-resistant (R) SA (36.2%) and CoNS (77.0%), vancomycin-R enterococci (13.0%), ciprofloxacin-R *E. coli* (17.5%), extend-spectrum beta-lactamase (ESBL)-screen-positive KSP (21.9%), imipenem-R PSA (IRPSA; 20.6%) and ASP (21.6%); TIG showed excellent activity against these R pathogens, except IRPSA.

Conclusions: TIG exhibited a wide-spectrum of activity and potency versus contemporary BSI isolates collected worldwide. R to tetracycline or other antimicrobial classes did not adversely influence TIG activity. Treatment options for serious infections in nosocomial environments should benefit from the availability of TIG.

INTRODUCTION

The increased complexity of patients requiring hospitalization and the widespread use of indwelling devices has created higher risks for nosocomial bloodstream infections (BSI), which is one of the most common nosocomial infections. Nosocomial BSIs account for approximately 3.5 billion dollars in costs and 3.5 million additional hospital-stay days per year in the United States (USA). In addition, the mortality rate directly attributable to BSIs varies from 14% to as high as 38%.

The increasing rates of antimicrobial resistance are creating serious dilemmas for treatment of bacteremic patients, requiring the development of new therapeutic options, advanced diagnostic tests and preventive technologies. Despite such advances, accurate empiric treatment remains critical to minimize inappropriate antimicrobial therapy that may lead to poor clinical outcome.

Tigecycline is a semisynthetic derivative of minocycline which was recently (June, 2005) licensed by the USA Food and Drug Administration (FDA) as a parenteral agent for the treatment of complicated skin and skin structure and intra-abdominal infections. Tigecycline has the distinct advantage of enhanced stability to the major tetracycline resistance mechanisms, specifically an increased binding affinity to Tet M- and Tet O-protected tetracycline-resistant ribosomes and secondarily through the inhibition of tetracycline efflux determinants.

Tigecycline has demonstrated excellent in vitro activity against a variety of clinically important pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), Enterobacteriaceae producing extended-spectrum (ESBL) or Bush group 2f (KPC) ß-lactamases, certain non-fermentative bacilli (*Acinetobacter* spp. and *Stenotrophomonas maltophilia*), anaerobic wound pathogens, *Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae*, chlamydiae and mycoplasmas. Only members of the tribe *Proteae* and *Pseudomonas aeruginosa* display predictably elevated tigecycline MIC values. In this study, we evaluated the in vitro activity of tigecycline tested against a large collection of bacterial pathogens isolated from BSI collected worldwide.

MATERIALS AND METHODS

Bacterial Isolates: A total of 39,733 Gram-positive and -negative bacterial isolates recovered from hospitalized patients with clinically significant bacteremia were processed. Consecutively acquired, non-duplicate patient isolates were submitted from >80 participating medical centers.

Susceptibility Testing: The isolates were tested by a reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines and interpretation criteria. Tigecycline was tested on fresh Mueller-Hinton broth and the breakpoints utilized were those recommended by the US-FDA, which are ≤2 µg/ml (susceptible) and ≥8 µg/ml (resistant) for Enterobacteriaceae; ≤0.5 µg/ml for staphylococci (susceptible only) and ≤0.25 µg/ml for streptococci and enterococci (susceptible only). Concurrent quality control (QC) testing was performed using the following organisms: *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, *E. coli* ATCC 25923, and *P. aeruginosa* ATCC 27853. All QC results were within published ranges.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed. Approved Standard M7-A7*. Wayne, PA: CLSI, 2006.
2. Clinical and Laboratory Standards Institute. (2006). *Performance standards for antimicrobial susceptibility testing, 16th informational supplement M100-S16*. Wayne, PA: CLSI.
3. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y (2005). The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 26: 166-174.
4. Pachon-Ibanez ME, Jimenez-Mejias ME, Pichardo C, Llanos AC, Pachon J (2004). Activity of tigecycline (GAR-936) against *Acinetobacter baumannii* strains, including those resistant to imipenem. *Antimicrob Agents Chemother* 48: 4479-4481.
5. Patel R, Rouse MS, Piper KE, Steckelberg JM. (2000). In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagnostic Microbiology and Infectious Disease* 38:177-179.
6. Tygacil Package Insert (2005). Philadelphia (PA): Wyeth Pharmaceuticals Inc. (June, 2005).

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RESULTS

- *S. aureus* was the most frequently isolated pathogen from BSI (29.4%), followed by *E. coli* (16.2%), coagulase-negative staphylococci (12.1%), *Enterococcus* spp. (11.3%) and *Klebsiella* spp. (6.9%). These five pathogens were responsible for >75% of all BSI isolates (Table 1).

Table 1. Ranked occurrence of bacterial pathogens causing bloodstream infections.

Organism	No. of isolates	Frequency
1. *S. aureus*	11,670	29.4%
2. *E. coli*	6,447	16.2%
3. Coagulase-negative staphylococci	4,790	12.1%
4. *Enterococcus* spp.	4,485	11.3%
5. *Klebsiella* spp.	2,745	6.9%
6. *P. aeruginosa*	1,948	4.9%
7. *Enterobacter* spp.	1,455	3.7%
8. ß-haemolytic streptococci	1,105	2.8%
9. *S. pneumoniae*	929	2.3%
10. *Acinetobacter* spp.	713	1.8%
Total	39,733	100.0%

Table 2. Antimicrobial susceptibility of Gram-positive pathogens commonly isolated from bloodstream infections.

Organism (no. tested) / antimicrobial agent	MIC (µg/ml): 50%	MIC (µg/ml): 90%	% by category:[a] Susceptible	% by category:[a] Resistant
S. aureus (11,670)				
Tigecycline	≤0.12	0.25	99.5	-
Oxacillin	0.5	>2	63.8	36.2
Clindamycin	≤0.25	>8	74.3	25.5
Levofloxacin	≤0.5	>4	63.8	35.0
Linezolid	2	2	>99.9	-
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	94.5	5.5
Vancomycin	0.5	1	>99.9	0.0
Coagulase-negative staphylococci (4,790)				
Tigecycline	≤0.12	0.5	98.1	-
Oxacillin	>2	>2	23.0	77.0
Clindamycin	≤0.25	>8	63.3	36.1
Levofloxacin	2	>4	46.1	46.5
Linezolid	1	1	>99.9	-
Trimethoprim/sulfamethoxazole	≤0.5	>2	59.2	40.8
Vancomycin	1	2	100.0	0.0
Enterococcus spp. (1,455)				
Tigecycline	≤0.12	0.25	94.6	-
Ampicillin	2	>16	75.3	24.7
Levofloxacin	2	>4	50.0	48.4
Quinupristin/dalfopristin	>2	>2	23.9	68.6
Gentamicin-HL[b]	≤500	>1000	68.1	31.9
Linezolid	1	2	99.6	0.3
Vancomycin	1	16	85.9	13.0
ß-haemolytic streptococci (1,105)				
Tigecycline	≤0.12	≤0.12	100.0	-
Penicillin	≤0.016	0.06	100.0	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Erythromycin	≤0.25	>2	80.8	18.7
Clindamycin	≤0.25	≤0.25	93.0	6.6
Levofloxacin	0.5	1	98.9	0.8
Tetracycline	>8	>8	45.1	53.5
Linezolid	1	1	100.0	-
Vancomycin	0.5	0.5	100.0	-
S. pneumoniae (929)				
Tigecycline	≤0.12	≤0.12	98.2	-
Penicillin	≤0.016	2	78.7	10.2
Ceftriaxone	≤0.25	1	98.5	0.3
Erythromycin	≤0.25	>2	80.0	19.6
Clindamycin	≤0.25	≤0.25	91.8	7.8
Tetracycline	≤2	8	88.8	10.6
Levofloxacin	1	1	99.4	0.6
Linezolid	1	1	100.0	-
Vancomycin	0.25	0.5	100.0	-

a. US-FDA susceptibility breakpoints were applied to the tigecycline analysis.
b. HL = high-level resistance.

- Tigecycline was highly active against *S. aureus* (MIC$_{50}$, ≤0.12 µg/ml; MIC$_{90}$, 0.25 µg/ml; 99.5% susceptible) and coagulase-negative staphylococci (MIC$_{50}$, ≤0.12 µg/ml; MIC$_{90}$, 0.5 µg/ml; 98.1% susceptible). Linezolid and vancomycin were also active (>99.9% susceptibility), but less potent (MIC$_{50}$, 0.5 - 2 µg/ml) than tigecycline against these pathogens (Table 2).

Table 3. Antimicrobial susceptibility of Gram-negative pathogens commonly isolated from bloodstream infection.

Organism (no. tested) / antimicrobial agent	MIC (µg/ml): 50%	MIC (µg/ml): 90%	% by category: Susceptible	% by category: Resistant
E. coli (6,447)				
Tigecycline	0.12	0.25	>99.9	0.0
Ampicillin/sulbactam	8	>16	55.9	24.6
Piperacillin/tazobactam	2	4	95.8	2.1
Ceftriaxone	≤0.25	≤0.25	95.4	4.2 (5.2)[a]
Cefepime	≤0.12	0.25	97.2	2.2
Imipenem	≤0.5	≤0.5	>99.9	0.0
Ciprofloxacin	≤0.03	>4	82.5	16.4
Gentamicin	≤2	≤2	92.1	7.2
Klebsiella spp. (2,745)				
Tigecycline	0.5	1	98.6	0.1
Ampicillin/sulbactam	8	>16	65.7	26.4
Piperacillin/tazobactam	2	>64	84.6	12.1
Ceftriaxone	≤0.25	>32	82.8	14.6 (21.1)[a]
Cefepime	≤0.12	16	89.5	7.8
Imipenem	≤0.5	≤0.5	98.7	1.0
Ciprofloxacin	≤0.03	>4	85.6	13.0
Gentamicin	≤2	>8	85.2	13.2
Enterobacter spp. (1,455)				
Tigecycline	0.5	1	96.7	0.1
Ampicillin/sulbactam	>16	>16	25.9	51.9
Piperacillin/tazobactam	2	64	80.1	9.8
Ceftriaxone	≤0.25	>32	76.4	18.6
Cefepime	≤0.12	4	94.4	4.1
Imipenem	≤0.5	1	99.2	0.3
Ciprofloxacin	≤0.03	4	87.4	10.2
Gentamicin	≤2	8	88.4	10.0
P. aeruginosa (1,948)				
Tigecycline	>4	>4	7.5[b]	64.9[b]
Ampicillin/sulbactam	>16	>16	0.8	98.8
Piperacillin/tazobactam	8	>64	82.1	17.9
Ceftazidime	4	>16	75.2	20.0
Cefepime	4	>16	76.4	12.2
Imipenem	1	>8	79.4	11.9
Ciprofloxacin	0.12	>4	70.2	27.1
Amikacin	4	32	88.4	8.9
Polymyxin B	≤1	≤1	>99.9	<0.1
Acinetobacter spp. (713)				
Tigecycline	0.5	2	96.1[b]	0.7[b]
Ampicillin/sulbactam	8	>16	56.5	30.6
Piperacillin/tazobactam	64	>64	39.4	49.5
Ceftazidime	>16	>16	39.6	54.0
Cefepime	16	>16	46.4	29.4
Imipenem	0.5	>8	78.4	18.4
Ciprofloxacin	>4	>4	41.5	57.8
Amikacin	8	>32	55.5	40.7
Polymyxin B	≤1	≤1	99.6	0.4

a. Percentage of strains with ESBL phenotype (MIC, ≥2 µg/ml) in parenthesis.
b. Percentage of susceptible and resistant strains when applying Enterobacteriaceae breakpoints (US-FDA).

- *Enterococcus* spp. showed high rates of resistance to most antimicrobial agents tested. Only tigecycline (MIC$_{50}$, ≤0.12 µg/ml; MIC$_{90}$, 0.25 µg/ml; 94.6% susceptible) and linezolid (MIC$_{50}$, 1 µg/ml; MIC$_{90}$, 2 µg/ml; 99.6% susceptible) showed consistent in vitro activity against this pathogen group (Table 2).

- ß-haemolytic streptococci exhibited high rates of susceptibility to most antimicrobials tested, except for tetracycline (45.1% susceptible) and erythromycin (80.8% susceptible; Table 2).

- Only 78.7% of *S. pneumoniae* strains were susceptible to penicillin (MIC, ≥0.06 µg/ml); and 10.2% of strains showed high-level penicillin resistance (MIC, ≥2 µg/ml). Tigecycline was very potent (MIC$_{90}$, ≤0.12 µg/ml) against the pneumococci and demonstrated a spectrum similar to that of ceftriaxone (98.2 and 98.5% susceptibility, respectively) against this pathogen from BSI (Table 2).

- Tigecycline and imipenem were the most active compounds tested against *E. coli* (>99.9% susceptible), *Klebsiella* spp. (98.6-98.7%) and *Enterobacter* spp. (96.7-99.2%; Table 3).

- Tigecycline was also very active against *Acinetobacter* spp. (MIC$_{50}$, 0.5 µg/ml; MIC$_{90}$, 2 µg/ml) and was the second most active compound tested against this pathogen after polymyxin B (99.6% susceptible). Only 78.4% of *Acinetobacter* spp. strains were susceptible to imipenem (Table 3).

CONCLUSIONS

- Tigecycline exhibited a wide-spectrum of activity and high potency tested against contemporary BSI isolates collected worldwide.

- Resistance to tetracycline or other antimicrobial classes did not adversely influence tigecycline activity.

- Treatment options for serious multidrug-resistant organism infections in nosocomial environments should benefit from the availability of tigecycline.