819

Potency and Strength of Tigecycline (TIG) Tested Against an International Collection (2000 - 2004) of Bacterial Pathogens Producing Skin and Soft Tissue Infections (SSTI)

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AMENDED ABSTRACT

Objective:

TIG is the sentinel representative of the glycylcycline class to be developed as a parenteral agent targeting bacterial pathogens responsible for pneumonia, intra-abdominal sepsis and SSTI. The aim of this study was to evaluate the activity and potency of TIG when tested against a large collection of bacterial pathogens causing SSTI.

Methods:

Consecutive, non-duplicate bacterial isolates (3,421 strains) were collected from 2000 to 2004 from patients with documented community-acquired or nosocomial SSTI in >70 medical centers participating in the TIG surveillance program in North America (38.6%), Europe (54.0%), South America (3.7%) and the Asia-Pacific region (3.7%). All isolates were tested using NCCLS broth microdilution methods against TIG and representative comparator agents used for empiric and directed therapy of SSTI.

Results:

SSTI pathogen rank order (top ten), potency and cumulative inhibition rates for TIG are in the Table:

Organism (no. tested)	MIC (mg/L) 50%	MIC (mg/L) 90%	% inhibited at MIC (mg/L) ≤1	≤2	≤4
1. *S. aureus* (SA; 1,943)	0.25	0.5	100	-	-
2. *Enterococcus* spp. (328)	0.25	0.5	100	-	-
3. *P. aeruginosa* (PSA; 209)	8	16	6	12	34
4. ß-haemolytic streptococci (184)	≤0.06	0.12	100	-	-
5. *E. coli* (ECL; 171)	0.25	0.5	100	-	-
6. Coag neg staphylococci (CoNS; 168)	0.25	0.5	99	100	-
7. *Enterobacter* spp. (ENT; 95)	0.5	1	95	96	100
8. *Klebsiella* spp. (KSP; 66)	0.5	1	97	100	-
9. *P. mirabilis* (PM; 50)	2	8	12	54	82
10. *Acinetobacter* spp. (ASP; 41)	0.5	1	95	98	98
Overall Total % Inhibited			92	94	98

All SA, streptococci, enterococci, CoNS, KSP and EC were inhibited by ≤ 2 mg/L of TIG, along with 98% of ASP and 96% of ENT. The broad-spectrum of activity exhibited by TIG included tetracycline resistant subsets as well as MRSA, VRE, and ESBL-producing strains. Only PM and PSA isolates were less susceptible (MIC_{90} values at 8 and 16 mg/L, respectively).

Conclusions:

Among the top ten-ranked pathogens producing SSTI, 94% of isolates were inhibited by ≤ 2 mg/L of TIG and 98% were inhibited by ≤ 4 mg/L (the current NCCLS breakpoint for tetracyclines). TIG may represent a welcome choice among newer parenteral agents for the common Gram-positive and negative pathogens producing serious SSTI given in vitro testing results, thus warranting continued investigation for this indication.

INTRODUCTION

Tigecycline (formerly GAR-936) is the first in a new class of antimicrobial agents known as the glycylcyclines and is being developed as a parenteral agent targeting common pathogens responsible for community-acquired pneumonia, intra-abdominal sepsis and skin and soft tissue infections. The compound is a semisynthetic 9-t-butylglycylamido derivative of minocycline, whose action on bacterial ribosomes shows identical and overlapping binding sites when compared to tetracyclines. The position 9 substitution of tigecycline, however, provides additional steric hindrance features that result in a greater spectrum of activity. The agent is currently under expedited review by the US Food and Drug Administration for indications of skin and soft tissue infections and for intra-abdominal sepsis.

Although contemporary tetracycline derivatives such as doxycycline and minocycline display an increased spectrum of activity and favorable pharmacokinetics compared with tetracyclines, cross-resistance within the class persists. The glycylcyclines have 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, and have been major advancements. Recent studies have shown tigecycline to have activity against penicillin-resistant *Streptococcus pneumoniae*, oxacillin-resistant staphylococci, vancomycin-resistant enterococci, extended-spectrum ß-lactamase producing strains of Enterobacteriaceae, anaerobic wound pathogens, *Haemophilus influenzae, Neisseria gonorrhoeae,* chlamydiae, and mycoplasmas.

The present study was conducted to evaluate the in vitro activity of tigecycline and comparator compounds tested against a large worldwide collection of isolates recovered from skin and soft tissue infections (from 2000 - 2004) including those species commonly resistant to tetracyclines.

MATERIALS AND METHODS

To assess the spectrum of activity and potency of tigecycline, recent clinical isolates submitted to a reference laboratory (JMI Laboratories, North Liberty, Iowa) were examined. A total of 3,421 Gram-positive and –negative bacterial isolates recovered from patients with documented skin and soft tissue infections were processed. Consecutively acquired, non-duplicate, patient isolates were submitted from greater than 70 participating medical centers representing 29 countries in the five geographic areas of Asia and Australia (3.7% of strains), Europe (54%), South America (3.7%) and North America (38.6%).

Isolates were identified by the submitting laboratory and confirmed by the monitoring facility (JMI Laboratories, IA) using colonial characteristics on standard media, rapid tests (catalase, oxidase, coagulase, bile solubility, latex agglutination kits), and use of an automated identification system (Vitek bioMerieux, Hazelwood, MO), among others methods, as necessary. Those species and groups comprising the 10 most frequently encountered pathogens are listed in Table 1.

MIC values for tetracycline, tigecycline and other comparators were determined using validated, dry-form broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH). Antimicrobials tested included those classes and examples of drugs most commonly used for the empiric or directed treatment of the indicated infection. When testing *Streptococcus spp.*, supplemental lysed horse blood (2-5%) was added. Testing, incubation and MIC interpretation were performed using the manufacturers recommendations and/or recommendations from the Clinical and Laboratory Standards Institute (formerly NCCLS) [NCCLS, 2003; CLSI 2005]. Quality control was performed using American Type Culture Collection (ATCC) strains including *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619 and *Pseudomonas aeruginosa* ATCC 27853.

SELECTED REFERENCES

1. Bergeron J, Ammirati M, Danley D, James L, Norcia M, Retsema J, Strick CA, Su W-G, Sutliffe J, Wondrack L. (1996). Glycylcyclines bind to the high-affinity tetracycline ribosomal binding site and evade Tet(M)- and Tet(O)-mediated ribosomal protection. *Antimicrobial Agents and Chemotherapy* 40:2226-2228.

2. Betriu C, Rodriguez-Avial I, Sanchez BA, Gomez M, Alvarez J, Picazo JJ, Spanish Group of Tigecycline. (2002). In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain. *Antimicrobial Agents and Chemotherapy* 46:892-895.

3. Boucher HW, Wennersten CB, Eliopoulos GM. (2000). In vitro activities of the glycylcycline GAR-936 against Gram-positive bacteria. *Antimicrobial Agents and Chemotherapy* 44:2225-2229.

4. Cercenado E, Cercenado S, Gomez JA, Bouza E. (2003). In vitro activity of tigecycline (GAR-936), a novel glycylcycline, against vancomycin-resistant enterococci and staphylococci with diminished susceptibility to glycopeptides. *Journal of Antimicrobial Chemotherapy* 52:138-139.

5. Dean CR, Visalli MA, Projan SJ, Sum PE, Bradford PA. (2003). Efflux-mediated resistance to tigecycline (GAR-936) in *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy* 47:972-978.

6. Fritsche TR, Jones RN. (2004). Antimicrobial activity of tigecycline (GAR-936) tested against 3,498 recent isolates of *Staphylococcus aureus* recovered from nosocomial and community-acquired infections. *International Journal of Antimicrobial Agents* 24:567-571.

7. Gales AC, Jones RN. (2000). Antimicrobial activity and spectrum of the new glycylcycline, GAR-936, tested against 1,203 recent clinical bacterial isolates. *Diagnostic Microbiology and Infectious Disease* 36:19-36.

8. Kitzis MD, Ly A, Goldstein FW. (2004). In vitro activities of tigecycline (GAR-936) against multidrug-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*. *Antimicrobial Agents and Chemotherapy* 48:366-367.

9. Low DE, Kreiswirth BN, Weiss K, Willey BM. (2002). Activity of GAR-936 and other antimicrobial agents against North American isolates of *Staphylococcus aureus*. *International Journal of Antimicrobial Agents* 20:220-222.

10. Milatovic D, Schmitz FJ, Verhoef J, Fluit AC. (2003). Activities of the glycylcycline tigecycline (GAR-936) against 1,924 recent European clinical bacterial isolates. *Antimicrobial Agents and Chemotherapy* 47:400-404.

12. National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-sixth edition*. Approved document M7-A6. Wayne, PA:NCCLS.

13. Clinical Laboratory Standards Institute. (2005). *Performance standards for antimicrobial susceptibility testing*, 15th informational supplement, M100-S15. Wayne, PA:CLSI.

14. 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.

15. Petersen PJ, Bradford PA, Weiss WJ, Murphy TM, Sum PE, Projan SJ. (2002). In vitro and in vivo activities of tigecycline (GAR-926), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate *Staphylococcus aureus* and other resistant Gram-positive pathogens. *Antimicrobial Agents and Chemotherapy* 46:2595-2601.

16. Poster RG, Green SL, Klein SR, Ellis-Grosse EJ, Loh E, Tigecycline 200 Study Group. (2004) Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients. *Clinical Therapeutics* 26:704-714.

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RESULTS

- The most frequently isolated pathogens causing infections of skin and soft tissue recovered during 2000-2004 were, in rank order (percent of total): *S. aureus* (56.8%), *Enterococcus* spp. (8.6%), *P. aeruginosa* (6.1%), ß-haemolytic streptococci (5.4%), *E. coli* (5.0%), and coagulase negative staphylococci (4.9%; Table 1). The top ten pathogens accounted for 95.2% of the isolates submitted and displayed high rates of resistance to the commonly used antimicrobial agents (Tables 2-4).

Table 1. Cumulative frequency distributions for the top 10 ranked Gram-positive and -negative pathogens producing skin and soft tissue infections (3,421 strains; 2000 - 2004) tested against tigecycline.

Organism (no. tested/% of total)	MIC (mg/L) 50%	MIC (mg/L) 90%	% inhibited at MIC (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16
1. *S. aureus* (1,943/56.8)	0.25	0.5	40	73	99	100	-	-	-	-
2. *Enterococcus* spp. (328/9.6)	0.25	0.5	49	81	99	100	-	-	-	-
3. *P. aeruginosa* (209/6.1)	8	16	0	0	1	6	12	33	77	93
4. ß-haemolytic streptococci (184/5.4)	≤0.06	0.12	97	99	100	-	-	-	-	-
5. *E. coli* (171/5.0)	0.25	0.5	39	79	99	100	-	-	-	-
6. Coagulase.-negative staphylococci (168/4.9)	0.25	0.5	40	71	95	99	100	-	-	-
7. *Enterobacter* spp. (95/2.8)	0.5	1	1	23	73	95	96	100	-	-
8. *Klebsiella* spp. (66/1.9)	0.5	1	1	35	80	97	100	-	-	-
9. *P. mirabilis* (50/1.5)	2	8	0	0	2	12	54	82	100	-
10. *Acinetobacter* spp. (41/1.2)	0.5	1	22	44	71	95	98	98	100	-

Table 2. Antimicrobial activity of tigecycline compared to other antimicrobial agents tested against Gram-positive pathogens producing infections of skin and soft tissue (2000 - 2004).

Organism (no. tested/antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	MIC (mg/L) Range	% category:[a] Susceptible	% category:[a] Resistant
S. aureus (1,943)					
Tigecycline	0.25	0.5	≤0.12-1	[b]	[b]
Tetracycline	≤4	>8	≤4->8	89.2	10.1
Penicillin	8	>32	≤0.016->32	12.4	87.6
Oxacillin	0.5	>2	≤0.06->8	70.6	29.4
Ciprofloxacin	0.5	>2	0.06->4	70.8	28.3
Levofloxacin	0.25	>4	≤0.03->4	73.2	18.1
Erythromycin	0.5	>8	≤0.06->8	58.8	40.6
Clindamycin	0.12	>8	≤0.06->8	79.9	20.1
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	98.4	1.6
Quinupristin/Dalfopristin	0.25	0.5	≤0.06->2	99.7	0.1
Daptomycin	0.25	0.5	≤0.12-1	100.0	[b]
Linezolid	2	2	≤0.25-4	100.0	[b]
Vancomycin	1	1	≤0.12-2	100.0	0.0
Coagulase-negative staphylococci (168)[c]					
Tigecycline	0.25	0.5	≤0.12-2	[b]	[b]
Tetracycline	≤4	>8	≤4->8	80.2	19.8
Penicillin	2	32	≤0.016->32	25.0	75.0
Oxacillin	2	>8	≤0.06->8	32.1	67.9
Ciprofloxacin	0.25	>4	0.12->4	55.4	42.3
Levofloxacin	0.25	>4	0.12->4	60.7	20.8
Erythromycin	>8	>8	≤0.06->8	47.6	51.8
Clindamycin	≤0.06	>8	≤0.06->8	79.2	20.2
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	88.1	11.9
Quinupristin/Dalfopristin	≤0.25	0.5	≤0.06-2	99.4	0.0
Daptomycin	0.25	0.5	0.12-1	100.0	[b]
Linezolid	1	1	0.25-2	100.0	[b]
Vancomycin	1	2	0.25-4	100.0	0.0
ß-haemolytic streptococci (184)[d]					
Tigecycline	≤0.12	0.12	≤0.12-0.5	[b]	[b]
Tetracycline	≤4	>8	≤4->8	23.4	47.3
Penicilin	≤0.016	0.06	≤0.016-0.12	100.0	[b]
Levofloxacin	0.5	1	0.06-2	100.0	0.0
Erythromycin	≤0.06	2	≤0.06->8	84.8	15.2
Clindamycin	≤0.06	≤0.06	≤0.06->8	93.5	6.0
Quinupristin/Dalfopristin	≤0.25	0.5	0.12-1	[b]	[b]
Daptomycin	0.06	0.25	≤0.016-0.5	100.0	[b]
Linezolid	1	1	0.5-2	100.0	[b]
Vancomycin	0.25	0.5	≤0.12-1	100.0	[b]
Enterococcus spp. (328)[e]					
Tigecycline	0.25	0.5	≤0.12-1	[b]	[b]
Tetracycline	>8	>8	≤4->8	35.1	64.3
Ampicillin	2	>16	≤1->16	84.8	15.2
Erythromycin	>8	>8	≤0.06->8	11.3	58.8
Ciprofloxacin	2	>4	≤0.25->4	49.7	42.7
Levofloxacin	1	>4	0.12->4	60.7	37.5
Daptomycin	1	2	≤0.12-4	100.0	[b]
Linezolid	2	2	≤0.25-2	100.0	0.0
Vancomycin	1	4	0.5->16	93.3	6.1

a. Criteria as published by the CLSI [2005].
b. Breakpoints have not been established by CLSI.
c. Includes: *Staphylococcus auricularis* (one strain), *S. capitis* (four strains), coagulase-negative staphylococci (73 strains), *S. epidermidis* (69 strains), *S. haemolyticus* (six strains), *S. hominis* (two strains), *S. intermedius* (one strain), *S. lugdunensis* (seven strains), *S. sciuri* (one strain), *Staphylococcus* spp. (one strain), *S. warneri* (two strains) and *S. xylosis* (one strain).
d. Includes: ß-haemolytic streptococci (six strains), *Streptococcus* group A (104 strains), group B (41 strains), group C (six strains) and group G (27 strains).
e. Includes: *Enterococcus casseliflavus* (one strain), *E. faecalis* (202 strains), *E. faecium* (60 strains), group D (one strain) and *Enterococcus* spp. (64 strains).

- Tigecycline was among the most potent agents active against *S. aureus* and coagulase negative staphylococci, with MIC_{50} and MIC_{90} values of 0.25 mg/L and 0.5 mg/L, respectively. The highest tigecycline MIC was 2 mg/L (one isolate, coagulase negative staphylococcus); among comparators, only daptomycin and quinupristin/dalfopristin demonstrated similar potencies (Table 2).

- All ß-haemolytic streptococci were inhibited by ≤ 0.5 mg/L of tigecycline and the vast majority (97%) of strains were inhibited by ≤ 0.12 mg/L; among comparators, only penicillin and clindamycin demonstrated greater potency (MIC_{90}, ≤ 0.06 mg/L).

- Tigecycline was the most active compound tested against *Enterococcus* spp., including vancomycin-resistant strains (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L). While 100% of enterococci were susceptible to daptomycin and linezolid, tigecycline was four-fold more active than the former compound and eight-fold more active than the latter.

Table 3. Antimicrobial activity of tigecycline compared to other antimicrobial agents tested against Enterobacteriaceae producing infections of skin and soft tissue (2000 - 2004).

Organism (no. tested/antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	MIC (mg/L) Range	% category:[a] Susceptible	% category:[a] Resistant
E. coli (171)					
Tigecycline	0.25	0.5	0.06-1	[b]	[b]
Tetracycline	4	>8	0.5->8	52.0	47.4
Ampicillin	>16	>16	2->16	39.8	60.2
Amoxicillin/Clavulanate	8	16	2->16	73.1	8.2
Piperacillin/Tazobactam	2	16	≤0.12->64	93.0	2.3
Cefuroxime	4	>16	0.5->16	63.2	15.8
Ceftriaxone	≤0.25	>32	≤0.25->32	88.9	10.5
Ceftazidime	≤1	8	≤1->16	91.2	5.8
Cefepime	≤0.12	4	≤0.12->16	91.8	7.0
Imipenem	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Ciprofloxacin	≤0.03	>4	≤0.03->4	72.5	27.5
Levofloxacin	≤0.03	>4	≤0.03->4	72.5	22.8
Gentamicin	≤2	>8	≤2->8	83.6	14.6
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	68.8	31.2
Klebsiella spp. (66)[c]					
Tigecycline	0.5	1	0.12-2	[b]	[b]
Tetracycline	≤2	>8	≤2->8	75.8	16.7
Ampicillin	>16	>16	8->16	3.0	86.4
Amoxicillin/Clavulanate	4	>16	≤1->16	62.1	10.6
Piperacillin/Tazobactam	4	>64	0.5->64	72.7	16.7
Cefuroxime	2	>16	0.5->16	69.7	21.2
Ceftriaxone	≤0.25	>32	≤0.25->32	80.3	16.7
Ceftazidime	≤1	>16	≤1->16	84.8	10.6
Cefepime	≤0.12	>16	≤0.12->16	83.3	16.7
Imipenem	≤0.5	≤0.5	≤0.5-0.5	100.0	0.0
Ciprofloxacin	≤0.03	>4	≤0.03->4	86.4	13.6
Levofloxacin	0.06	>4	≤0.03->4	86.4	13.6
Gentamicin	≤2	>8	≤2->8	77.3	21.2
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	74.2	25.8
Enterobacter spp. (95)[d]					
Tigecycline	0.5	1	0.12-4	[b]	[b]
Tetracycline	≤2	>8	≤2->8	87.4	11.6
Ampicillin	>16	>16	4->16	2.1	92.6
Amoxicillin/Clavulanate	>16	>16	4->16	2.1	94.7
Piperacillin/Tazobactam	2	64	≤0.12->64	80.0	9.5
Cefuroxime	16	>16	2->16	14.7	37.9
Ceftriaxone	≤0.25	>32	≤0.25->32	77.9	14.7
Ceftazidime	≤1	>16	≤1->16	74.7	21.1
Cefepime	≤0.12	4	≤0.12->16	96.8	2.1
Imipenem	≤0.5	0.5	≤0.5-2	100.0	0.0
Ciprofloxacin	≤0.03	0.5	≤0.03->4	90.5	9.5
Levofloxacin	≤0.03	1	≤0.03->4	90.5	7.4
Gentamicin	≤2	>8	≤2->8	88.4	10.5
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	89.5	10.5
Proteus mirabilis (50)					
Tigecycline	2	8	0.5-8	[b]	[b]
Tetracycline	>8	>8	≤2->8	2.0	98.0
Ampicillin	2	>16	≤1->16	58.0	40.0
Amoxicillin/Clavulanate	≤1	16	≤1->16	80.0	8.0
Piperacillin/Tazobactam	≤0.5	1	≤0.5->64	96.0	2.0
Cefuroxime	2	4	0.25->16	92.0	6.0
Ceftriaxone	≤0.25	≤0.25	≤0.25->16	98.0	0.0
Ceftazidime	≤1	≤1	≤1->16	98.0	2.0
Cefepime	≤0.12	0.25	≤0.12-2	100.0	0.0
Imipenem	1	2	≤0.5-8	98.0	0.0
Ciprofloxacin	≤0.03	2	≤0.03->4	86.0	8.0
Levofloxacin	0.06	2	≤0.03->4	92.0	4.0
Gentamicin	≤2	>8	≤2->8	80.0	20.0
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	64.0	36.0

a. Criteria as published by the CLSI [2005].
b. Breakpoint criteria have not been established by CLSI.
c. Includes: *Klebsiella oxytoca* (15 strains), *K. pneumoniae* (47 strains) and *Klebsiella* spp. (four strains).
d. Includes: *Enterobacter aerogenes* (nine strains), *E. cloacae* (70 strains), *E. sakazakii* (one strain) and *Enterobacter* spp. (15 strains).

- Among Enterobacteriaceae that produce infections of skin and soft tissue, 100% of *E. coli* and *Klebsiella* spp., and 96% of *Enterobacter* spp. were inhibited by tigecycline at 2 mg/L (MIC_{50} and MIC_{90} values, 0.25-0.5 mg/L and 0.5-1 mg/L; Table 3). This includes 14% and 24% of *E. coli* and *Klebsiella* spp., respectively, that display an extended spectrum ß-lactamase phenotype. Only *P. mirabilis* was less susceptible (MIC_{50} and MIC_{90}, 2 mg/L and 8 mg/L).

- *P. aeruginosa* displayed high rates of resistance to most antimicrobial agents tested (including tigecycline) with piperacillin/tazobactam, tobramycin, cefepime and ceftazidime being most active (78.5% to 83.7% susceptible; Table 4). Polymyxin B was the most active agent tested against this pathogen (MIC_{50} and MIC_{90}, ≤ 1 mg/L, 100% susceptible).

- Tigecycline was highly active when tested against *Acinetobacter* spp. (MIC_{50}, 0.5 mg/L and MIC_{90}, 1 mg/L), similar to the potency demonstrated by polymyxin B (MIC_{50} and MIC_{90}, ≤ 1 mg/L; 100% susceptible). All other comparators showed limited activity (17.1% to 58.5% resistance).

Table 4. Antimicrobial activity of tigecycline compared to other antimicrobial agents tested against non-fermentative Gram-negative bacilli producing infections of skin and soft tissue (2000 - 2004).

Organism (no. tested/antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	MIC (mg/L) Range	% category:[a] Susceptible	% category:[a] Resistant
P. aeruginosa (209)					
Tigecycline	8	16	0.5->32	[b]	[b]
Tetracycline	>8	>8	≤2->8	3.3	77.5
Piperacillin/Tazobactam	8	>64	0.5->64	83.7	16.3
Ceftazidime	4	>16	≤1->16	76.6	18.7
Cefepime	4	>16	≤0.12->16	78.5	11.0
Imipenem	1	>8	≤0.5->8	78.5	11.5
Ciprofloxacin	0.25	>4	≤0.03->4	70.8	26.3
Levofloxacin	0.5	>4	0.12->4	69.9	26.8
Tobramycin	0.5	>16	≤0.12->16	80.4	19.6
Polymyxin B	≤1	1	≤1-2	100.0	0.0
Acinetobacter spp. (41)[c]					
Tigecycline	0.5	1	0.06-8	[b]	[b]
Tetracycline	2	>8	1->8	53.7	34.1
Ampicillin/Sulbactam	4	>32	≤0.25->32	58.5	36.6
Piperacillin/Tazobactam	16	>64	≤0.12->64	51.2	46.3
Ceftazidime	8	>16	≤1->16	51.2	43.9
Cefepime	8	>16	≤0.12->16	58.5	26.8
Imipenem	≤0.5	>8	≤0.5->8	80.5	17.1
Ciprofloxacin	4	>4	≤0.03->4	41.5	58.5
Levofloxacin	2	>4	≤0.03->4	56.1	39.0
Tobramycin	1	>16	≤0.12->16	63.4	36.6
Polymyxin B	≤1	≤1	≤1	100.0	0.0

a. Criteria as published by the CLSI [2005].
b. Breakpoint criteria not yet established by CLSI.
c. Includes: *Acinetobacter antratus* (two strains), *A. baumannii* (26 strains), *A. calcoaceticus* (six strains), *A. lwoffii* (three strains) and *Acinetobacter* spp. (four strains).

CONCLUSIONS

- Among the top ranked pathogens that produce skin and soft tissue infections, 100% of staphylococci, enterococci, ß-haemolytic streptococci, *E. coli* and *Klebsiella* spp. were inhibited by ≤ 2 mg/L of tigecycline; in addition 96% of *Enterobacter* spp. and 98% of *Acinetobacter* spp. were inhibited at this level. Only *P. aeruginosa* and *P. mirabilis* display significant resistant to tigecycline.

- Tigecycline is a potent and broad-spectrum agent with demonstrated safety profile that is currently under review by the US FDA with Priority Review status for approval for use in cases of skin and soft tissue infections, and intra-abdominal infections.

- Following approval of this agent, continued local, regional and global surveillance for susceptibility to key pathogens will be necessary to detect emerging resistance patterns, assist with infection control strategies, and serve as a guide for empiric therapy.