Tigecycline Activity in Europe: A Comparative Analysis by Country 2007

S. Bouchillon[1], M. Hackel[1], R. Badal[1], D. Hoban[1], B. Johnson[1], J. Johnson[1], M. Dowzicky[2]

[1]International Health Management Associates, Schaumburg, IL, USA
[2]Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

REVISED ABSTRACT

Objective: Development of bacterial resistance continues to cause concern world wide, but the availability of newer agents offers clinicians options for therapy. Tigecycline has a very broad spectrum of activity, including strains resistant to other drugs. As part of the global Tigecycline Evaluation Surveillance Trial (TEST), strains collected in 22 European countries in 2007 were evaluated for susceptibility to several commonly used antimicrobials. **Methods:** 15,304 strains were collected and identified at 94 sites in 22 countries. MICs were determined at each site using EUCAST guidelines on microdilution panels. **Results:** The following table summarizes tigecycline results:

Country	*Enterobacteriaceae*			*Acinetobacter* spp.			*S. aureus*			*Enterococcus* spp.		
MIC	50%	90%	n	50%	90%	n	50%	90%	n	50%	90%	n
Austria	0.5	2	175	0.12	1	6	0.12	0.25	50	0.06	0.12	18
Belgium	0.5	2	734	0.25	1	118	0.12	0.25	208	0.12	0.25	131
Czech Rep.	0.5	1	86	0.12	0.5	13	0.12	0.12	19	0.12	0.12	16
Denmark	0.25	1	314	0.12	0.25	49	0.12	0.12	76	0.06	0.12	57
Finland	0.25	0.5	86	0.25	4	9	0.12	0.12	31	0.12	0.25	17
France	0.5	1	1600	0.25	1	279	0.12	0.25	454	0.12	0.25	279
Germany	0.5	2	1324	0.12	0.5	214	0.12	0.25	345	0.12	0.25	219
Greece	0.5	2	421	0.5	2	70	0.12	0.25	127	0.06	0.12	77
Hungary	0.5	2	168	1	2	44	0.12	0.25	50	0.06	0.25	30
Ireland	0.5	2	250	0.12	0.5	45	0.12	0.12	74	0.06	0.25	42
Italy	0.5	1	1848	0.5	1	287	0.12	0.25	489	0.12	0.25	309
Latvia	0.25	1	164	0.5	1	29	0.12	0.25	49	0.06	0.12	30
Lithuania	0.5	1	75	0.25	1	15	0.12	0.12	35	0.12	0.25	15
Norway	0.5	1	79	0.06	0.25	15	0.12	0.12	24	0.06	0.12	15
Poland	0.5	2	84	0.25	0.5	14	0.12	0.12	24	0.12	0.12	15
Portugal	0.25	1	83	0.5	2	15	0.12	0.12	25	0.06	0.12	15
Slovenia	0.5	1	83	0.25	1	15	0.12	0.12	25	0.12	0.12	15
Spain	0.25	1	911	0.5	1	140	0.12	0.25	271	0.12	0.25	159
Sweden	0.25	1	238	0.12	0.12	44	0.12	0.12	57	0.06	0.12	45
Switzerland	0.25	1	176	0.12	0.25	20	0.12	0.12	51	0.12	0.12	33
Netherlands	0.5	1	169	0.12	0.5	30	0.12	0.25	49	0.12	0.12	30
U. Kingdom	0.5	1	405	0.12	1	72	0.12	0.25	120	0.12	0.12	68
Totals	0.5	1	9473	0.25	1	1543	0.12	0.25	2653	0.12	0.25	16354

Conclusion: Bacteria isolated from than 22 different European countries had generally similar antibiograms, with no isolates from any site showing significantly different sensitivity patterns. The greatest variability was seen in *Acinetobacter*, with TIG MIC_{50} values ranging from 0.06 to 1 mcg/mL. TIG's consistent broad spectrum of activity may make it an excellent therapeutic option against European pathogens.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, its anti-bacterial activity is significant and has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10^{-9} [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC_{90} values of ≤0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4,5] with diverse genotypes of vanA, vanB and vanC [6].

The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against common gram-negative and gram-positive pathogens collected from 94 hospitals in 22 European countries over a period of four years from 2004 to 2007.

MATERIALS & METHODS

- For the T.E.S.T program all isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids, and other defined sources. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. Only one isolate per patient was accepted.
- For this study 15,304 fresh clinical isolates were collected prospectively from 2004 to 2007 in 94 hospitals in 22 European countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, The Netherlands, and the United Kingdom).
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [6]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64, gram-negative only); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); cefepime (0.5-32, gram-negative only); ceftazidime (8-32, gram-negative); ceftriaxone (0.06-64); imipenem (0.06-16, MicroScan only); linezolid (0.5-8, gram-positive only); meropenem (0.12-16, TREK only); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8, gram-positive only); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32, gram-positive only).
- MIC interpretive criteria, when needed, followed published breakpoints established by EUCAST where applicable [13]; if no EUCAST guidelines were available for a given antimicrobial, CLSI breakpoints [14] were used.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control); *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.

REFERENCES

1. Sum, P.E. and P. Petersen, *Synthesis and structure-activity relationship of novel glycylcycline derivatives leading to the discovery of GAR-936*. Bioorg Med Chem Lett, 1999. 9(10): p. 1459-62.
2. Abbanat, D., M. Macielag, and K. Bush, *Novel antibacterial agents for the treatment of serious Gram-positive infections*. Expert Opin Investig Drugs, 2003. 12(3): p. 379-99.
3. Betriu, C., et al., *In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain*. Antimicrob Agents Chemother, 2002. 46(3): p. 892-5.
4. Gales, A.C. and R.N. Jones, *Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis, 2000. 36(1): p. 19-36.
5. Henwood, C.J., et al., *Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936)*. J Antimicrob Chemother, 2002. 49(3): p. 479-87.
6. Chopra, I., *New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors*. Drug Resist Updat, 2002. 5(3-4): p. 119-25.
7. Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent*. Pharmacotherapy, 2000. 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
8. Biedenbach, D.J., M.L. Beach, and R.N. Jones, *In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases*. Diagn Microbiol Infect Dis, 2001. 40(4): p. 173-7.
9. Patel, R., et al., *In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and penicillin-resistant Streptococcus pneumoniae*. Diagn Microbiol Infect Dis, 2000. 38(3): p. 177-9.
10. Petersen, P.J., et al., *In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936)*. Antimicrob Agents Chemother, 1999. 43(4): p. 738-44.
11. Petersen, P.J., et al., *In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate Staphylococcus aureus and other resistant gram-positive pathogens*. Antimicrob Agents Chemother, 2002. 46(8): p. 2595-601.
12. CLSI, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Sixth Edition, in Document M7-A6. 2005: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
13. European Committee on Antimicrobial Susceptibility Testing (EUCAST) website, http://www.eucast.org, 03 March 2008
14. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Informational Supplement. CLSI document M100-S17. Wayne, PA, 2007.

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions from the participants in the T.E.S.T. program who have helped make this program a success.

RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against 9,473 *Enterobacteriaceae* according to country of origin.

Country	N	MIC_{50}/MIC_{90} (mcg/mL) TIG	Amox/C	Ceftriax	Imip	Levo
Austria	175	0.5/2	32/>32	0.25/>64	0.25/1	0.06/>8
Belgium	734	0.5/2	16/>32	0.12/64	0.5/1	0.06/>8
Czech Republic	86	0.5/1	32/>32	0.12/32	≤0.06/0.12	0.06/8
Denmark	314	0.25/1	8/>32	≤0.06/2	≤0.06/0.25	0.03/1
Finland	86	0.25/0.5	8/>32	≤0.06/0.25	0.25/0.5	0.03/0.25
France	1600	0.5/1	16/>32	0.12/32	0.25/1	0.06/8
Germany	1324	0.5/2	16/>32	0.12/32	0.25/1	0.06/4
Greece	421	0.5/2	32/>32	0.25/>64	0.25/1	0.06/>8
Hungary	168	0.5/2	8/>32	≤0.06/32	0.25/0.5	0.03/8
Ireland	250	0.5/2	16/>32	<0.06/32	0.25/1	0.06/4
Italy	1848	0.5/1	16/>32	0.12/>64	0.25/1	0.06/>8
Latvia	164	0.25/1	16/>32	0.12/>64	0.5/1	0.03/2
Lithuania	75	0.5/1	8/>32	<0.06/64	<0.06/0.25	0.06/8
Norway	79	0.5/1	16/>32	0.12/2	≤0.06/0.12	0.03/0.12
Poland	84	0.5/2	16/>32	0.12/>64	0.5/1	0.06/8
Portugal	83	0.25/1	16/>32	0.12/>64	0.5/0.5	0.06/4
Slovenia	83	0.5/1	8/>32	≤0.06/0.5	0.5/1	0.06/0.5
Spain	911	0.25/1	16/>32	≤0.06/16	0.5/1	0.06/4
Sweden	238	0.25/1	4/>32	<0.06/1	<0.06/0.25	0.03/0.25
Switzerland	176	0.25/1	16/>32	≤0.06/0.5	0.12/0.5	0.03/0.25
Netherlands	169	0.5/1	8/>32	≤0.06/0.6	0.5/0.5	0.06/0.5
United Kingdom	405	0.5/1	16/>32	0.12/>64	0.5/0.5	0.06/>8
Totals	9473*	0.5/1	16/>32	0.12/64	0.25/1	0.06/8

TIG, tigecycline; Amox/C, amoxicillin/clavulanic acid (2:1 ratio); Ceftriax, ceftriaxone; Imip, imipenem; Levo, levofloxacin.

* Includes 509 (9.1%) ESBL-producing from 5624 *E. coli, K. pneumoniae* and *K. oxytoca*.

Table 2. In vitro activity of tigecycline and comparative agents against 1,543 *Acinetobacter* spp. according to country of origin.

Country	N	MIC_{50}/MIC_{90} (mcg/mL) TIG	Amox/C	Ceftriax	Imip	Levo
Austria	6	0.12/1	16/>32	8/>64	0.25/16	0.06/8
Belgium	118	0.25/1	32/>32	16/>64	0.5/2	0.25/>8
Czech Republic	13	0.12/0.5	16/>32	16/>64	1/8	0.12/4
Denmark	49	0.12/0.25	4/32	4/16	0.25/1	0.06/0.12
Finland	9	0.25/4	16/>32	8/32	0.25/1	0.06/0.12
France	279	0.25/1	16/>32	16/>64	0.5/1	0.25/8
Germany	214	0.12/0.5	16/>32	16/>64	0.5/2	0.12/8
Greece	70	0.5/2	>32/>32	>64/>64	8/>16	4/>8
Hungary	44	1/2	>32/>32	>64/>64	1/4	4/>8
Ireland	45	0.12/0.5	8/>32	8/>64	0.25/4	0.12/4
Italy	287	0.5/1	32/>32	>64/>64	0.5/16	4/>8
Latvia	29	0.5/1	32/>32	32/>64	0.5/1	2/4
Lithuania	15	0.25/1	32/>32	16/>64	1/4	0.12/4
Norway	15	0.06/0.25	16/16	16/16	1/1	0.06/0.25
Poland	14	0.25/0.5	>32/>32	64/>64	4/>16	4/8
Portugal	15	0.5/2	>32/>32	>64/>64	>16/>16	8/>8
Slovenia	15	0.25/1	16/>32	16/>64	4/>16	0.25/8
Spain	140	0.5/1	>32/>32	>64/>64	2/>16	8/>8
Sweden	44	0.12/0.12	16/32	8/32	0.5/2	0.06/0.25
Switzerland	20	0.12/0.25	16/>32	8/32	0.5/16	0.06/0.12
Netherlands	30	0.12/0.5	16/32	8/16	0.5/0.5	0.12/0.5
United Kingdom	72	0.12/1	8/>32	8/>64	0.25/16	0.12/>8
Totals	1543*	0.25/1	32/>32	16/>64	0.5/16	0.25/>8

TIG, tigecycline; Amox/C, amoxicillin/clavulanic acid (2:1 ratio); Ceftriax, ceftriaxone; Imip, imipenem; Levo, levofloxacin.

* 1307 (85%) were *A. baumannii*.

Table 3. In vitro activity of tigecycline and comparative agents against 2,653 *S. aureus* according to country of origin.

Demographics	N	MIC_{50}/MIC_{90} (mcg/mL) TIG	Amox/C	Levo	Linez	Vanco
Austria	50	0.12/0.25	1/>8	0.12/4	2/2	1/1
Belgium	208	0.12/0.25	1/8	0.25/16	2/4	1/1
Czech Republic	19	0.12/0.12	1/>8	0.25/>32	2/2	1/1
Denmark	76	0.12/0.12	1/2	0.12/0.5	2/2	0.5/1
Finland	31	0.12/0.12	1/1	0.12/0.25	2/2	0.5/1
France	454	0.12/0.25	1/8	0.25/16	2/4	1/1
Germany	345	0.12/0.25	1/8	0.25/16	2/4	1/1
Greece	127	0.12/0.25	2/>8	0.25/8	2/2	0.5/1
Hungary	50	0.12/0.25	0.5/4	0.12/32	1/2	0.5/1
Ireland	74	0.12/0.12	1/>8	0.12/8	2/4	0.5/1
Italy	489	0.12/0.25	1/>8	0.25/16	2/4	1/1
Latvia	49	0.12/0.25	1/1	0.12/0.25	2/2	0.5/1
Lithuania	35	0.12/0.12	1/2	0.25/0.5	2/4	0.5/1
Norway	24	0.12/0.12	1/2	0.12/0.5	2/4	1/1
Poland	24	0.12/0.12	1/>8	0.25/4	2/2	0.5/1
Portugal	25	0.12/0.12	1/>8	0.25/16	2/2	0.5/1
Slovenia	25	0.12/0.12	1/>8	0.12/4	2/4	1/1
Spain	271	0.12/0.25	1/>8	0.12/8	2/4	1/1
Sweden	57	0.12/0.12	0.5/1	0.12/0.25	2/4	0.5/1
Switzerland	51	0.12/0.12	1/>8	0.12/4	2/2	1/1
Netherlands	49	0.12/0.25	1/1	0.25/0.5	2/2	1/1
United Kingdom	120	0.12/0.25	1/>8	0.12/8	2/4	1/1
Totals	2653*	0.12/0.25	1/>8	0.25/16	2/4	1/1

TIG, tigecycline; Amox/C, amoxicillin/clavulanic acid (2:1 ratio); Levo, levofloxacin; Linez, linezolid; Vanco, vancomycin.

* Includes 705 (26.6%) methicillin-resistant *S. aureus*.

Table 4. In vitro activity of tigecycline and comparative agents against 1,635 *Enterococcus* spp. by country of origin.

Demographics	N	MIC_{50}/MIC_{90} (mcg/mL) TIG	Pen	Levo	Linez	Vanco
Austria	18	0.06/0.12	4/>8	16/>32	2/2	1/2
Belgium	131	0.12/0.25	2/8	1/>32	2/2	1/2
Czech Republic	16	0.12/0.12	2/>8	1/>32	2/2	1/2
Denmark	57	0.06/0.12	4/>8	32/>32	1/2	0.5/2
Finland	17	0.12/0.25	2/4	1/8	2/2	2/4
France	279	0.12/0.25	2/>8	1/32	2/2	1/2
Germany	219	0.12/0.25	4/>8	16/>32	2/2	1/2
Greece	77	0.06/0.12	4/>8	16/>32	2/2	1/16
Hungary	30	0.06/0.25	2/>8	1/>32	1/2	1/2
Ireland	42	0.06/0.25	4/>8	4/>32	2/2	1/2
Italy	309	0.12/0.25	4/>8	2/>32	2/2	1/>32
Latvia	30	0.06/0.12	2/>8	1/32	1/2	1/2
Lithuania	15	0.12/0.25	2/>8	1/>32	2/2	1/>32
Norway	15	0.06/0.12	2/4	0.5/1	2/2	1/2
Poland	15	0.12/0.12	2/>8	1/32	2/2	1/2
Portugal	15	0.06/0.12	2/>8	1/32	2/2	2/4
Slovenia	15	0.12/0.12	8/>8	>32/>32	2/2	1/2
Spain	159	0.12/0.25	2/>8	2/>32	2/2	1/2
Sweden	45	0.06/0.12	2/>8	1/>32	2/2	1/2
Switzerland	33	0.12/0.12	4/>8	1/>32	2/2	1/2
Netherlands	30	0.12/0.12	4/>8	2/>32	2/2	1/2
United Kingdom	68	0.12/0.12	4/>8	32/>32	2/2	1/4
Totals	1635*	0.12/0.25	2/>8	2/>32	2/2	1/2

TIG, tigecycline; Pen, penicillin; Levo, levofloxacin; Linez, linezolid; Vanco, vancomycin.

* Includes 76 (4.6%) vancomycin-resistant strains from 1199 *E. faecalis* and 401 *E. faecium*.

CONCLUSIONS

- Tigecycline MIC_{50} and MIC_{90} values demonstrated excellent consistency and low variability among the various countries within the organism groups studied. MIC values were generally +/- 1 $\log_2$ dilution which is within the testing error of the broth microdilution system used. MIC_{90} values with the *Acinetobacter* group demonstrated more country to country variability with a range of MICs from 0.06 to 4 mcg/mL.
- The total or overall tigecycline MIC_{90} values were 1 mcg/mL for the gram-negative species (EUCAST and FDA approved for *Enterobacteriaceae* in complicated intra-abdominal and skin and soft tissue), including *Acinetobacter* spp (no current EUCAST or FDA approval for this species), and 0.25 mcg/mL for the gram-positive species studied (EUCAST approved for staphylococcus and enterococci; FDA approved for staphylococcus and VSE *E. faecalis*).
- Tigecycline in vitro activity was demonstrated in this study to be equal to (against *Enterobacteriaceae*) or better than (against *Acinetobacter*) imipenem.
- Tigecycline demonstrated very consistent and potent in vitro activity against *S. aureus* and the enterococci and compared favorably to either linezolid or vancomycin.
- Tigecycline demonstrated broad spectrum in vitro activity against many common European pathogens and should prove to be a useful addition to hospital formularies.