

Revised Abstract

Background: Tigecycline has been shown to have an expanded spectrum of activity, including activity against drug-resistant gram-positive organisms. This multi-year global study assists in the recognition of differences in susceptibility of bacteria isolated from different countries. In this report, vancomycin resistant enterococci were evaluated from 2004 through 2009, comparing the effectiveness of tigecycline and comparators from different sites around the world.

Methods: 1,341 clinical isolates of vancomycin-resistant enterococci (VRE) were evaluated between 2004 and 2009, from five grouped regions: Asia/Pacific Rim, Europe, Latin America, Middle East, and North America. Minimum inhibitory concentrations (MICs) were determined at each site using common lots of broth microdilution panels and interpreted according to CLSI and FDA guidelines.

Results: Results for tigecycline are shown in the following table:

Region	N	%S	MIC ₅₀	MIC ₉₀
Asia / Pacific Rim	64	100	0.06	0.12
Europe	147	100	0.06	0.12
Latin America	120	100	0.06	0.25
Middle East	11	100	0.12	0.25
North America	999	99.9	0.06	0.12
Global	1341	99.9	0.06	0.12

Conclusion:

In this study, VRE isolates from five geographic areas (Europe, North America, Asia/Pacific Rim, Middle East, and Latin America) exhibit a consistent response to tigecycline, with all MIC₉₀ values at ≤ 0.25 mcg/ml and no significant differences between regions.

Introduction

Vancomycin-resistant enterococci (VRE) first appeared in the United Kingdom in 1986 [1]. Since that time VRE have become persistent and prominent pathogens in nosocomial infections worldwide [2-3]. Tigecycline has been shown to effective *in vitro* against VRE as well as other multidrug resistant gram-negative and -positive organisms [4].

This multi-year global study assists in the recognition of differences in susceptibility of bacteria isolated from different countries. In this report, vancomycin-resistant *Enterococcus* spp. were evaluated from 2004 through 2009, comparing the effectiveness of tigecycline and comparators from different sites around the world.

Materials & Methods

Clinical isolates were collected and tested between January 2004 and March 2009 from 1,258 cumulative sites (44.5% participated in multiple years) in five regions that include 57 countries. Isolates were identified to the species level and tested at each site by the participating laboratory.

Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.

Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [5]. MIC interpretive criteria followed published guidelines established by CLSI, where applicable [6]. Breakpoints for tigecycline are defined by the US Food and Drug Administration (FDA) [7].

Quality controls (QC) were performed by each testing site on each day of testing using *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 according to CLSI guidelines [6].

References

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Acknowledgements

We acknowledge the contribution of the investigators and laboratory personnel. This study was sponsored by a grant from Wyeth Pharmaceuticals.

Results

Figure 1. Percentage of sites per region.

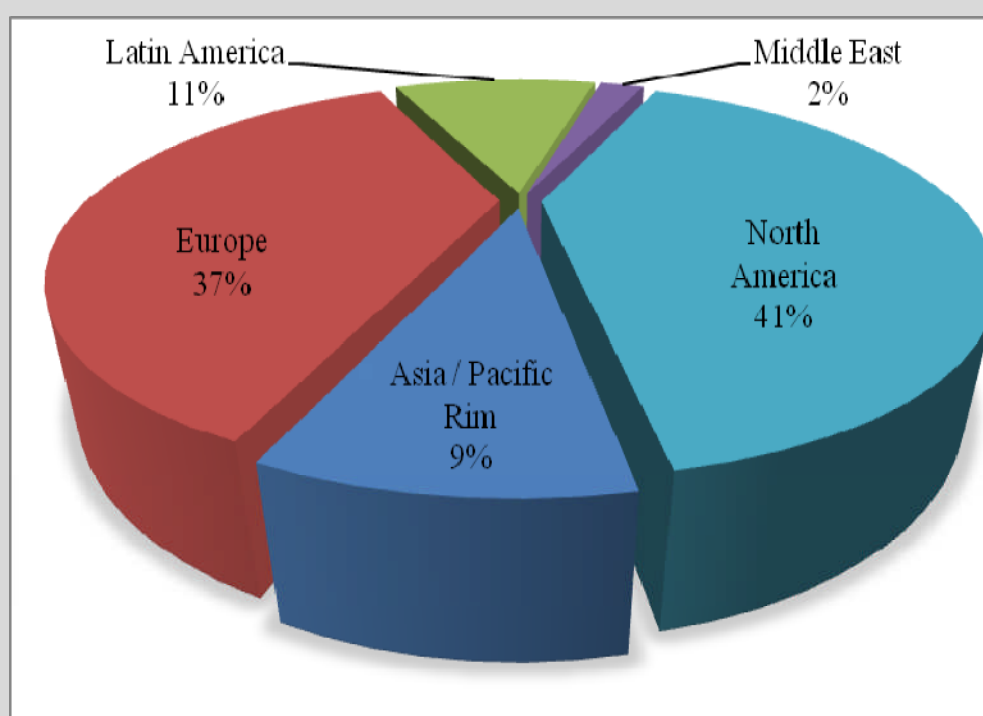


Figure 2. Relative proportions of *E. faecalis* and *E. faecium* exhibiting vancomycin resistance from a global population.

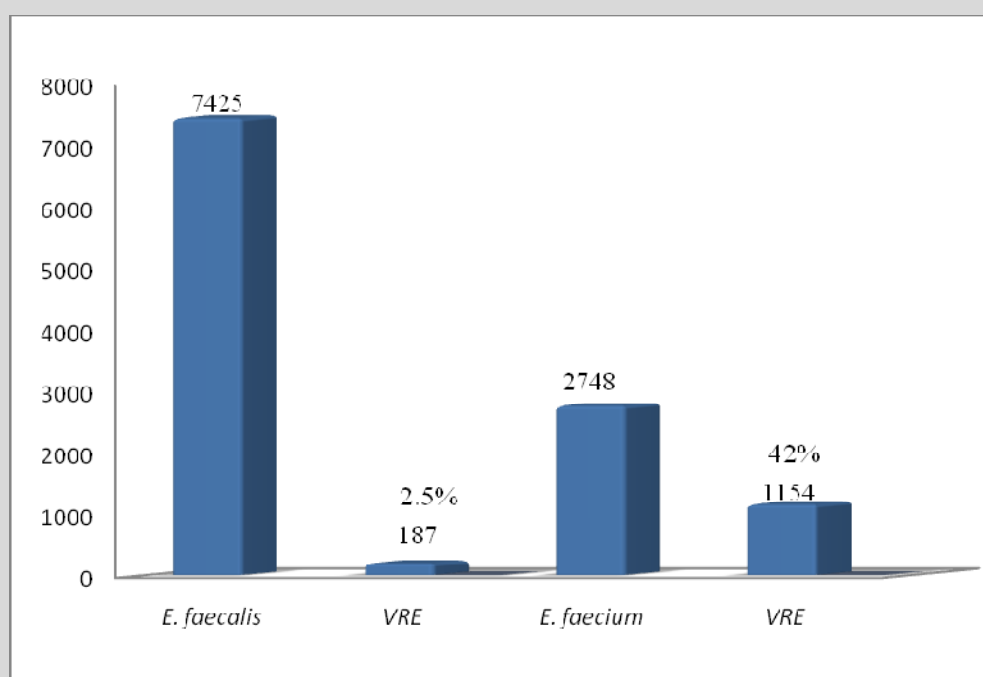


Table 1. *In vitro* activity of tigecycline and comparative agents against VRE globally from 2004-2009.

Region	Drug	MIC ₅₀	MIC ₉₀	% Sus ^a	Range
Global n=1341	Tigecycline	0.06	0.12	99.93 ^b	0.015-0.5
	Levofloxacin	> 32	> 32	1.04	1-> 32
	Linezolid	2	2	95.3	≤ 0.5 -> 8
	Minocycline	≤ 0.25	> 8	69.35	≤ 0.25 -> 8
	Penicillin	> 8	> 8	14.99	≤ 0.06 -> 8
	Vancomycin	> 32	> 32	0	32-> 32

^a Interpretive criteria are defined in CLSI document M100-S19 (2009), where available.
^b Tigecycline breakpoints are defined by the FDA (Tygacil®, 2005) for vancomycin-susceptible *E. faecalis*. The susceptible breakpoint of 0.25 mcg/ml was applied to all enterococci for comparison purposes only.

Table 2. *In vitro* activity of tigecycline and comparative agents against VRE in Europe from 2004-2009

Region	Drug	MIC ₅₀	MIC ₉₀	% Sus ^a	Range
Europe n=147	Tigecycline	0.06	0.12	100 ^b	0.015-0.25
	Levofloxacin	> 32	> 32	2.72	1-> 32
	Linezolid	2	4	97.2	≤ 0.5 -4
	Minocycline	≤ 0.25	> 8	70.07	≤ 0.25 -> 8
	Penicillin	> 8	> 8	18.37	1-> 8
	Vancomycin	> 32	> 32	0	32-> 32

^a Interpretive criteria are defined in CLSI document M100-S19 (2009), where available.
^b Tigecycline breakpoints are defined by the FDA (Tygacil®, 2005) for vancomycin-susceptible *E. faecalis*. The susceptible breakpoint of 0.25 mcg/ml was applied to all enterococci for comparison purposes only.

Table 3. *In vitro* activity of tigecycline and comparative agents against VRE in Asia/Pacific Rim from 2004-2009

Region	Drug	MIC ₅₀	MIC ₉₀	% Sus ^a	Range
Asia/Pacific n=64	Tigecycline	0.06	0.12	100 ^b	0.03-0.25
	Levofloxacin	> 32	> 32	0	8-> 32
	Linezolid	2	2	95.31	1-4
	Minocycline	≤ 0.25	> 8	81.25	≤ 0.25 -> 8
	Penicillin	> 8	> 8	7.81	4-> 8
	Vancomycin	> 32	> 32	0	32-> 32

^a Interpretive criteria are defined in CLSI document M100-S19 (2009), where available.
^b Tigecycline breakpoints are defined by the FDA (Tygacil®, 2005) for vancomycin-susceptible *E. faecalis*. The susceptible breakpoint of 0.25 mcg/ml was applied to all enterococci for comparison purposes only.

Table 4. *In vitro* activity of tigecycline and comparative agents against VRE in Latin America from 2004-2009

Region	Drug	MIC ₅₀	MIC ₉₀	% Sus ^a	Range
Latin America n=120	Tigecycline	0.06	0.25	100 ^b	0.015-0.25
	Levofloxacin	> 32	> 32	1.67	2-> 32
	Linezolid	2	2	98.33	1-4
	Minocycline	≤ 0.25	> 8	67.5	≤ 0.25 -> 8
	Penicillin	> 8	> 8	15	2-> 8
	Vancomycin	> 32	> 32	0	32-> 32

^a Interpretive criteria are defined in CLSI document M100-S19 (2009), where available.
^b Tigecycline breakpoints are defined by the FDA (Tygacil®, 2005) for vancomycin-susceptible *E. faecalis*. The susceptible breakpoint of 0.25 mcg/ml was applied to all enterococci for comparison purposes only.

Table 6. *In vitro* susceptibility of tigecycline and comparative agents against VRE in North America 2004-2009

Region	Drug	MIC ₅₀	MIC ₉₀	% Sus ^a	Range
North America n=999	Tigecycline	0.06	0.12	99.9 ^b	0.015-0.5
	Levofloxacin	> 32	> 32	0.8	1-> 32
	Linezolid	2	2	96.5	≤ 0.5 -> 8
	Minocycline	0.5	8	68.57	≤ 0.25 -> 8
	Penicillin	> 8	> 8	15.12	≤ 0.06 -> 8
	Vancomycin	> 32	> 32	0	32-> 32

^a Interpretive criteria are defined in CLSI document M100-S19 (2009), where available.
^b Tigecycline breakpoints are defined by the FDA (Tygacil®, 2005) for vancomycin-susceptible *E. faecalis*. The susceptible breakpoint of 0.25 mcg/ml was applied to all enterococci for comparison purposes only.

Table 5. *In vitro* susceptibility of tigecycline and comparative agents against VRE in the Middle East from 2004-2009

Region	Drug	MIC ₅₀	MIC ₉₀	% Sus ^a	Range
Middle East n=11	Tigecycline	0.12	0.25	100 ^b	0.03-0.25
	Levofloxacin	> 32	> 32	0	32-> 32
	Linezolid	2	2	92.9	1-4
	Minocycline	≤ 0.25	8	81.82	≤ 0.25 -8
	Penicillin	> 8	> 8	0	> 8-> 8
	Vancomycin	> 32	> 32	0	> 32-> 32

^a Interpretive criteria are defined in CLSI document M100-S19 (2009), where available.
^b Tigecycline breakpoints are defined by the FDA (Tygacil®, 2005) for vancomycin-susceptible *E. faecalis*. The susceptible breakpoint of 0.25 mcg/ml was applied to all enterococci for comparison purposes only.

Conclusions

Tigecycline exhibited very good *in vitro* activity worldwide, with susceptibility rates >99.9% against vancomycin-resistant enterococci from all regions (using the susceptible breakpoint for vancomycin-susceptible *E. faecalis*, as there is no FDA or CLSI susceptible breakpoint for vancomycin-resistant enterococci). The MIC₉₀ values were much lower than for other antimicrobials with similar spectrum.

Tigecycline *in vitro* activity was similar to that of linezolid in all regions. Although tigecycline MIC₅₀ and MIC₉₀ values were 8- to 32-fold lower than linezolid, the FDA susceptible breakpoint of 0.25 mcg/ml for tigecycline against vancomycin-susceptible enterococci is 16-fold lower than the CLSI susceptible breakpoint of 4 mcg/ml for linezolid.