Consistency of Activity of Tigecycline and Comparators vs. Gram-Positive Bacteria in Europe from 2004-2008

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Revised Abstract

Background: Tigecycline is a broad-spectrum antimicrobial that was approved for use in Europe in 2006. The Tigecycline Evaluation and Surveillance Trial (TEST) is an ongoing global surveillance study that monitors the activity of tigecycline (TIG) and comparators against a variety of aerobic and anaerobic pathogens. This report evaluates changes in *in vitro* activity of TIG and comparators from 2004 (pre-marketing baseline) through 2008 in Europe. **Methods:** 40 (2004) to 142 (2008) sites in 16-25 European countries collected >13,000 gram-positive clinical isolates from 2004-2008. MICs were determined by CLSI broth microdilution, but interpreted using EUCAST guidelines. $MIC_{50/90}$ and percent susceptible (%S) in 2004 and 2008 of each species with 100 or more isolates per year were evaluated for changes. **Results:** Of 6 organism groups evaluated in both 2004 and 2008, MRSA and *S. agalactiae* had no significant (p>.05) changes in %S; *E. faecalis* had 2 (minocycline [MIN] and imipenem [IMP]); MSSA had 2 (levofloxacin [LVX] and MIN); *E. faecium* had 5 (amox/clav [AC], ampicillin [AM], IMP, LVX, and penicillin [P]); and *S. pneumoniae* had 5 (AC, AM, ceftriaxone [CAX], MIN, P and piperacillin-tazobactam [PT]). MIC_{50} values often changed without affecting categorical %S values. **Conclusions:** The *in vitro* activity of TIG, vancomycin, and linezolid remained virtually unchanged against gram-positive pathogens in Europe from 2004-2008. CAX, MIN, LVX, AC, AM, PT, and P had significant (p<.05) decreases in %S vs 1, 4, 2, 2, 2, 1, and 1 species, respectively. *E. faecium* and *S. pneumoniae* had significant declines in %S vs. 5 and 6 study drugs, respectively, and continued monitoring is warranted. TIG's retention of activity vs. European gram-positive pathogens, especially those resistant to one or more other agents, makes it a potentially effective therapy option for these isolates.

Introduction

Over the last decade the European Union has placed special emphasis on combating the problem of drug resistant gram-negative and gram-positive bacteria [1] and has noted the persistent increase in rates of resistance. Particular attention is paid to resistance rates of gram-positive bacteria because of the link between resistance, treatment failures, higher mortalities, and higher costs of prolonged hospital stays [2, 3].

This study examined the changes in resistance patterns of several antimicrobials against selected gram-positive bacteria from the TEST program in the intervening years between its inception in 2004 and the latest compiled data in 2008.

Materials & Methods

- Clinical isolates were collected and tested between January 2004 and December 2008 from 425 cumulative total investigative sites (78% participated in more than one year) from 26 European 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 CLSI recommended broth microdilution testing method [4]. MIC interpretive criteria followed published guidelines established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), where applicable [5]. Breakpoints for tigecycline against *S. pneumoniae* are defined by the FDA [6].
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619.

References

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Results

Table 1. *In vitro* activity of tigecycline and comparators against *Enterococcus faecalis* from 2004 to 2008.

	MIC_{90} / %Susceptible					
Drug	2004 (n=361)	2005 (n=224)	2006 (n=412)	2007 (n=639)	2008 (n=745)	P-Value
Tigecycline	0.25/99.7	0.12/100	0.25/100	0.25/100	0.25/100	>0.05
Amox-Clav	1/99.7	1/100	1/100	1/99.7	1/99.6	>0.05
Ampicillin	2/99.7	2/100	2/99.5	2/99.7	2/99.2	>0.05
Imipenem	2/99.1	2/98.6	8/79.7	na	na	**<0.05***
Levofloxacin	32/66.2	32/74.6	>32/67.2	>32/70.7	>32/69.8	>0.05
Linezolid	2/100	2/100	2/100	2/100	2/100	>0.05
Minocycline	>8/37.1	>8/47.8	>8/34.5	>8/38.2	>8/27.4	**<0.05***
Penicillin	8/100	4/99.6	8/100	4/100	4/99.9	>0.05
Pip-Tazo	8/100	8/99.6	8/100	8/100	8/99.9	>0.05
Vancomycin	2/98.3	2/98.7	2/98.8	2/99.1	2/98.9	>0.05

•P-value calculated for %S for years 2004 and 2008 using Fisher's exact test (two tailed); <0.05 is significant; >0.05 is not significant. P-value for imipenem calculated for years 2004 and 2006, the last full year of imipenem implementation.

Table 2. *In vitro* activity of tigecycline and comparators against *Enterococcus faecium* from 2004 to 2008.

	MIC_{90} / %Susceptible					
Drug	2004 (n=111)	2005 (n=86)	2006 (n=160)	2007 (n=224)	2008 (n=332)	P-Value
Tigecycline	0.12/100	0.12/100	0.12/100	0.12/100	0.25/100	>0.05
Amox-Clav	>8/30.6	>8/19.8	>8/12.5	>8/15.2	>8/15.7	**<0.05***
Ampicillin	>16/27	>16/18.6	>16/11.9	>16/13.8	>16/15.4	**<0.05***
Imipenem	>16/23.8	>16/14.5	>16/8.2	na	na	**<0.05***
Levofloxacin	>32/29.7	>32/26.7	>32/13.8	>32/19.2	>32/13.9	**<0.05***
Linezolid	2/100	2/100	4/100	2/100	2/100	>0.05
Minocycline	>8/72.1	>8/79.1	>8/74.4	>8/71.4	>8/74.7	>0.05
Penicillin	>8/25.2	>8/16.3	>8/10.6	>8/13.4	>8/15.1	**<0.05***
Vancomycin	>32/85.6	>32/87.2	>32/80	>32/85.3	32/87.1	>0.05

•P-value calculated for %S for years 2004 and 2008 using Fisher's exact test (two tailed); <0.05 is significant; >0.05 is not significant. na = p-value for imipenem calculated for years 2004 and 2006, the last full year of imipenem implementation.

Table 3. *In vitro* activity of tigecycline and comparators against methicillin-resistant *Staphylococcus aureus* (MRSA) from 2004 to 2008.

	MIC_{90} / %Susceptible					
Drug	2004 (n=211)	2005 (n=138)	2006 (n=241)	2007 (n=331)	2008 (n=414)	P-Value
Tigecycline	0.25/100	0.5/100	0.25/100	0.25/100	0.5/100	>0.05
Levofloxacin	16/11.9	>32/10.9	32/14.9	32/11.2	32/7.3	>0.05
Linezolid	2/100	4/100	2/100	4/100	4/100	>0.05
Minocycline	4/76.8	8/78.3	4/77.6	2/87.6	8/76.1	>0.05
Vancomycin	2/100	1/100	1/100	1/100	2/100	>0.05

* P-value calculated for %S for years 2004 and 2008 using Fisher's exact test (two tailed); <0.05 is significant; >0.05 is not significant.

Table 4. *In vitro* activity of tigecycline and comparators against methicillin-susceptible *Staphylococcus aureus* (MSSA) from 2004 to 2008.

	MIC_{90} / %Susceptible					
Drug	2004 (n=532)	2005 (n=374)	2006 (n=699)	2007 (n=1100)	2008 (n=1210)	P-Value
Tigecycline	0.25/100	0.25/100	0.12/100	0.25/100	0.25/100	>0.05
Amox-Clav	2/100	2/100	2/100	1/99.6	1/99.8	>0.05
Ampicillin	>16/20.5	>16/20.1	>16/24.9	>16/24.2	>16/18.9	>0.05
Ceftriaxone	4/99.4	4/99.7	4/99.7	4/99.5	4/98.6	>0.05
Imipenem	0.25/100	0.5/100	0.25/100	na	na	>0.05
Levofloxacin	0.25/97.9	0.25/98.7	0.5/95.1	0.5/95.5	0.5/95.3	**<0.05***
Linezolid	4/100	4/100	4/100	4/100	4/100	>0.05
Meropenem	0.25/100	0.25/100	0.25/100	0.25/100	0.25/99.4	>0.05
Minocycline	0.5/98.5	≤0.25/98.1	≤0.25/97.7	0.5/96.7	0.5/94	**<0.05***
Penicillin	>8/17.1	>8/15.8	>8/21.6	>8/20.7	>8/15.9	>0.05
Pip-Tazo	1/100	1/100	1/100	2/100	2/99.8	>0.05
Vancomycin	1/100	1/100	1/100	1/100	1/100	>0.05

*P-value calculated for %S for years 2004 and 2008 using Fisher's exact test (two tailed); <0.05 is significant; >0.05 is not significant. na = p-value for imipenem calculated for years 2004 and 2006, the last full year of imipenem implementation.

Table 5. *In vitro* activity of tigecycline and comparators against *Streptococcus agalactiae* from 2004 to 2008.

	MIC_{90} / %Susceptible					
Drug	2004 (n=291)	2005 (n=159)	2006 (n=389)	2007 (n=556)	2008 (n=638)	P-Value
Tigecycline	0.25/100	0.06/100	0.12/100	0.12/99.6	0.12/100	>0.05
Ampicillin	0.12/100	0.12/100	0.12/99.7	0.12/99.8	0.12/100	>0.05
Ceftriaxone	0.12/100	0.12/100	0.12/99.7	0.12/99.8	0.12/100	>0.05
Imipenem	0.25/99.7	0.5/100	≤0.12/100	na	na	>0.05
Levofloxacin	1/97.9	1/97.5	1/98.7	1/98.4	1/98.9	>0.05
Linezolid	1/100	1/100	1/100	1/100	1/100	>0.05
Meropenem	≤0.12/100	≤0.12/100	≤0.12/99.5	≤0.12/99.8	≤0.12/100	>0.05
Minocycline	>8/20.3	>8/17.6	>8/18.5	>8/15.1	>8/16.1	>0.05
Penicillin	0.12/100	0.12/100	0.12/99.7	0.12/99.8	0.12/100	>0.05
Pip-Tazo	≤0.25/100	≤0.25/100	0.5/99.7	0.5/99.8	0.5/100	>0.05
Vancomycin	0.5/100	0.5/100	0.5/100	0.5/100	0.5/100	>0.05

*P-value calculated for %S for years 2004 and 2008 using Fisher's exact test (two tailed); <0.05 is significant; >0.05 is not significant. na = p-value for imipenem calculated for years 2004 and 2006, the last full year of imipenem implementation.

Table 6. *In vitro* activity of tigecycline and comparators against *Streptococcus pneumoniae* from 2004 to 2008.

	MIC_{90} / %Susceptible					
Drug	2004 (n=395)	2005 (n=243)	2006 (n=513)	2007 (n=671)	2008 (n=643)	P-Value
Tigecycline	0.25/69.4	0.06/91.4	0.12/87.5	0.12/88.7	0.12/86.9	**<0.05***
Amox-Clav	1/98.5	1/96.3	0.5/99	1/97.9	2/94.7	**<0.05***
Ampicillin	2/84.8	2/83.1	1/88.9	2/84.5	2/77.8	**<0.05***
Ceftriaxone	1/89.9	0.5/91	0.5/91.4	0.5/91.5	1/83.7	**<0.05***
Imipenem	0.25/98.9	0.5/98.9	≤0.12/100	na	na	>0.05
Levofloxacin	1/100	1/99.6	1/99	1/99.6	1/99.1	>0.05
Linezolid	1/100	1/100	1/100	1/100	1/100	>0.05
Meropenem	0.5/99.1	1/98.6	0.5/100	0.5/99.8	0.5/100	>0.05
Minocycline	8/76.5	4/77.8	4/76	4/74.8	>8/37.3	**<0.05***
Penicillin	1/71.4	2/71.2	1/73.9	2/71.5	2/64.5	**<0.05***
Pip-Tazo	1/84.8	2/83.1	1/88.9	2/84.5	4/77.8	**<0.05***
Vancomycin	0.5/100	0.5/100	0.5/100	0.5/100	0.5/100	>0.05

*P-value calculated for %S for years 2004 and 2008 using Fisher's exact test (two tailed); <0.05 is significant; >0.05 is not significant. na = p-value for imipenem calculated for years 2004 and 2006, the last full year of imipenem implementation.

Conclusions

- There has been no significant reduction in *in vitro* activity for tigecycline, vancomycin, or linezolid against any of the gram-positive study organisms in the first five years of monitoring in the TEST program and no change in susceptibility for any study drug was noted against MSSA and *S. agalactiae* during the course of the study.
- A significant reduction in imipenem activity was seen from 2004 to 2006 against *E. faecalis* with at least a 20% drop in susceptibility (p<0.05). Although several antibiotics experienced statistically significant decreases in susceptibility against *E. faecium*, the decreases are not deemed clinically relevant due to overall low susceptibility rates of these drugs against this species.
- Tigecycline's retention of activity vs. European gram-positive pathogens, especially those resistant to one or more other agents, makes it a potentially effective therapy option for these isolates.