Surveillance Trends in the *In Vitro* Activity of Tigecycline, TEST 2004 to 2010: A Global Perspective

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Revised Abstract

Background: Tigecycline, the first member of the glycylcyclines, was marketed in 2005 and has demonstrated activity against multi-resistant species and phenotypes. Due to its chemical structure, resistance to tigecycline is reportedly difficult to produce even in the laboratory. The TEST study is an ongoing surveillance program monitoring the *in vitro* activity of tigecycline and comparator agents globally. **Methods:** 209,704 clinical isolates were collected from 1,770 cumulative investigative sites in 62 countries. MICs were determined by broth microdilution and interpreted according to CLSI/FDA guidelines. **Results:** % susceptible (%S) and MIC_{90} (mcg/ml) for tigecycline and key species are as follows:

	2004		2005		2006		2007		2008		2009		2010	
Organism (n per year)	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}
Acinetobacter spp. 1494/1438/2014/2674/2601/2914/1767	NA	1	NA	1	NA	1	NA	2	NA	2	NA	2	NA	2
Enterobacteriaceae 8570/9267/12939/16763/15576/17457/10470	96.5	1	96.7	1	96.9	1	97.7	1	97.1	2	96.8	2	96.7	2
ESBL producers 468/576/1067/1224/1775/2017/1077	93.0	2	95.7	2	95.6	2	96.5	2	96.2	2	96.6	2	95.5**	2
Enterococcus spp. 1530/1729/2348/3035/2712/3132/1850	99.9	0.12	99.9	0.12	99.8	0.12	99.8	0.25	99.5	0.25	99.5	0.25	100	0.25
VRE 223/287/334/342/253/313/171	100	0.12	99.6	0.12	100	0.12	99.4	0.12	98.0	0.25	97.9	0.25	100*	0.25
S. aureus MSSA 1420/1578/2097/2920/2935/3166/1895	100	0.12	100	0.12	100	0.25	100	0.25	100	0.25	100	0.25	100	0.25
S. aureus MRSA 1162/1412/1537/2097/1660/1770/588	100	0.25	100	0.25	99.9	0.25	100	0.25	100	0.5	99.8	0.5	100	0.5

NA=no breakpoint defined; *significant decrease in %S (p<0.05, Cochran-Armitage test for trend); **significant increase in %S

Conclusions: Tigecycline's MIC_{90} values only changed by one doubling dilution over 6 years from its pre-marketing (2005) baseline values. There was a very slight but statistically significant decreasing linear trend in % susceptible for VRE, while ESBL-producers showed a slight increase in susceptibility over time (p<0.05). Tigecycline activity was retained even against strains resistant to other agents, including ESBL-producers, multi-resistant *Acinetobacter* spp., MRSA and VRE. For all reported organisms with existing breakpoints susceptibility was >95% in 2010.

Introduction

Antimicrobial resistance in bacteria is a global healthcare problem. Particularly troubling has been the spread of extended spectrum beta-lactamase producing (ESBL+) gram-negative pathogens, vancomycin resistant *Enterococci*, methicillin-resistant *S. aureus* and multi-drug resistant *Acinetobacter* spp. that have rendered many antimicrobials ineffective, and which are associated with increased length of hospital stay, costs, and mortality [1-3]. Several collaborative studies have been established to monitor resistance [4-6]. The Tigecycline Evaluation and Surveillance Trial (TEST) was begun in 2004 and examines the susceptibility of tigecycline and comparative antimicrobials against a wide spectrum of gram-positive and gram-negative pathogens worldwide. This report focuses on trends in susceptibility of selected significant pathogens over 7 years from countries worldwide.

Materials & Methods

- Between 2004 and 2010, 1,770 cumulative sites participated in the TEST program in 62 countries. For this report, isolates of *Acinetobacter* spp., *Enterobacteriaceae, Enterococcus* spp. and *S. aureus* were identified to the species level and MICs determined at each participating laboratory using sponsor supplied broth microdilution panels. All isolates were derived from blood, urine, wound, skin, fluids and other defined sources. Only one isolate per patient was accepted into the study.
- 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 using MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA) or TREK (TREK Diagnostic Systems, Cleveland, OH) panels [7]. All antimicrobials were supplied by the panel manufacturers.
- MIC interpretive criteria followed published guidelines of the CLSI and the most recent United States Food and Drug Administration package insert for tigecycline where applicable [7-9].
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [7].
- *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca* were screened for extended spectrum beta-lactamase (ESBL) production by broth microdilution and confirmed using the disc diffusion confirmatory test [7].
- The Cochran-Armitage test was used to assess linear trends in percent susceptible over time.

References

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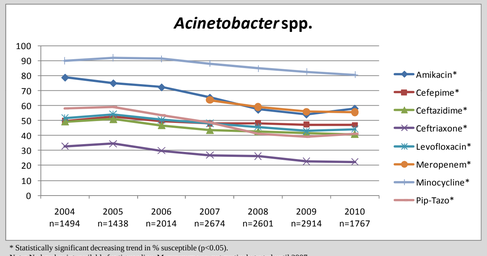
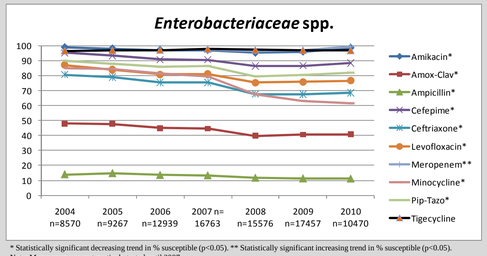
Results

Figure 1. Percent susceptible for *Acinetobacter* spp., 2004-2010.



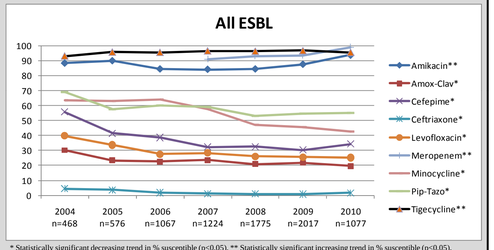
* Statistically significant decreasing trend in % susceptible (p<0.05).
Note: No breakpoint available for tigecycline. Meropenem was not routinely tested until 2007.

Figure 2. Percent susceptible for *Enterobacteriaceae* spp., 2004-2010.



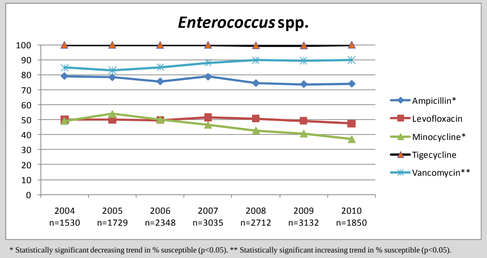
* Statistically significant decreasing trend in % susceptible (p<0.05). ** Statistically significant increasing trend in % susceptible (p<0.05).
Note: Meropenem was not routinely tested until 2007.

Figure 3. Percent susceptible for ESBL-positive *Enterobacteriaceae.*



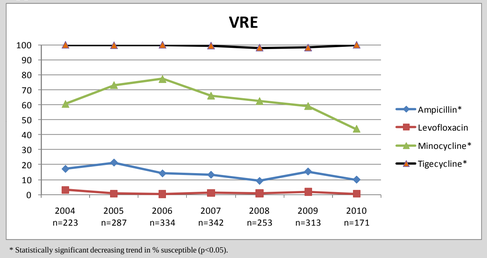
* Statistically significant decreasing trend in % susceptible (p<0.05). ** Statistically significant increasing trend in % susceptible (p<0.05).
Note: Meropenem was not routinely tested until 2007.

Figure 4. Percent susceptible for *Enterococcus* spp., 2004-2010.



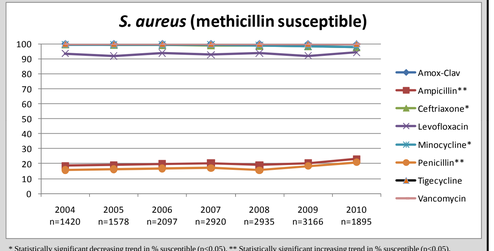
* Statistically significant decreasing trend in % susceptible (p<0.05). ** Statistically significant increasing trend in % susceptible (p<0.05).

Figure 5. Percent susceptible for vancomycin resistant *Enterococcus* spp., 2004-2010.



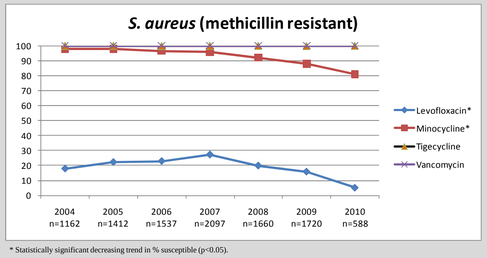
* Statistically significant decreasing trend in % susceptible (p<0.05).

Figure 6. Percent susceptible for *S. aureus* (methicillin susceptible), 2004-2010.



* Statistically significant decreasing trend in % susceptible (p<0.05). ** Statistically significant increasing trend in % susceptible (p<0.05).

Figure 7. Percent susceptible for *S. aureus* (methicillin resistant) 2004-2010.



* Statistically significant decreasing trend in % susceptible (p<0.05).

Conclusions

- Decreasing trends in percent susceptible for all drugs except tigecycline and meropenem was observed for *Enterobacteriaceae*. Meropenem demonstrated a slight but statistically significant increase in percent susceptible.
- ESBL-positive *Enterobacteriaceae* also showed a decreasing trend in percent susceptible for all reported drugs except amikacin, meropenem and tigecycline, for which % susceptible actually increased slightly over time (p<0.05).
- *Enterococcus* spp. including VRE demonstrated a decreasing trend in percent susceptible except for levofloxacin (with tigecycline showing a marginally significant decrease only for VRE), while vancomycin demonstrated an increasing trend for percent susceptible for enterococci overall.
- Several antimicrobials displayed decreasing trends in percent susceptible against *S. aureus* (MSSA and MRSA), while tigecycline demonstrated no significant decrease in activity of the past 7 years.
- All antimicrobials showed a significant decreasing trend in percent susceptible against *Acinetobacter* spp. over the 7 year study period. Only amikacin demonstrated percent susceptible >80%.
- Due to the large organism numbers, some very slight trends are statistically significant, but their clinical significance is to date unknown. However, the trends should continue to be monitored.
- Tigecycline continues to demonstrate excellent *in vitro* activity against a variety of significant pathogens isolated from countries worldwide over the past 7 years.