

# Trends in Antimicrobial Resistance in *Acinetobacter* spp. from the Asia TEST Program 2004-2010



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## Revised Abstract

**Objectives:** Treatment of *Acinetobacter* infections, especially multi-drug resistant (MDR) phenotypes, is challenging. This report focuses on *in vitro* susceptibility trends of Asian *Acinetobacter* isolates using data from the global Tigecycline Evaluation and Surveillance Trial (TEST). **Methods:** From 2004-2010, 915 *Acinetobacter* spp., including 565 MDR isolates (resistant to  $\geq 3$  drug classes), were collected in 9 Asian countries. MICs were performed at each site per CLSI guidelines using commercially-prepared microbroth panels. Results were interpreted using CLSI breakpoints, where available. MIC trends over time were assessed by Spearman's correlation. **Results:** In 2010, tigecycline inhibited 92.3% of *Acinetobacter* spp. *in vitro* at 2 mcg/ml. The % susceptible, MIC<sub>50</sub>, and p values for MIC trends are shown below.

	% Susceptible / MIC <sub>50</sub>							MIC trend
	2004	2005	2006	2007	2008	2009	2010	
Amikacin	52/16	55/8	45/32	42/64	39/>64	38/>64	46/32	<0.0001
Cefepime	38/16	40/32	40/32	32/32	23/>32	28/32	23/>32	<0.0001
Levofloxacin	53/2	53/2	46/4	32/8	29/8	30/8	29/8	<0.0001
Meropenem	nt	nt	51/2.4	44/6/8	38.0/>16	38.4/>16	29.1/>16	0.006
Minocycline	95/ $\leq 0.5$	98/ $\leq 0.5$	88/1	84/1	67/2	71/1	69/2	<0.0001
Pip-Tazo	47/64	48/64	42/64	31/128	20/>128	28/>128	22/>128	<0.0001
Tigecycline	na/0.25	na/0.5	na/0.5	na/0.5	na/1	na/1	na/1	<0.0001
n	58	40	152	278	150	172	65	

nt=not tested that year; na=not available (no breakpoints defined)

**Conclusions:** All agents studied showed a statistically significant trend toward increasing MICs over the 7-year period. Minocycline demonstrated the highest % susceptible of the agents for which breakpoints were available. Tigecycline's MIC<sub>50</sub> values were either the same as or one doubling dilution lower than minocycline's in each year of the study.

## Introduction

Infections resulting from *Acinetobacter* present a challenge to clinicians with increasing multi-drug resistance worldwide. Resistance of *Acinetobacter* to cephalosporins, aminoglycosides, and fluoroquinolones is now widespread. The emergence of carbapenem resistance in this species is of considerable concern, leaving relatively limited treatment options for infections. This has led to a search for new compounds with activity against these problematic pathogens. Tigecycline has been shown to be highly active against multi-drug resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections [1-3]. This study was undertaken to assess *in vitro* activity trends of tigecycline and comparators against *Acinetobacter* in a diverse population from multiple investigative sites in Asia. The study is part of the larger global Tigecycline Evaluation and Surveillance Trial (TEST) program that has been ongoing since 2004.

## Materials & Methods

- Isolates were derived from blood, respiratory tract, wounds, and various other infection sources. Only one isolate per patient was accepted into the study. From 2004-2010, 915 clinical *Acinetobacter* spp. isolates (867 of which were *A. baumannii*) were collected from 40 medical centers in nine Asian countries. This sample included 565 (62%) multi-drug resistant isolates (resistant to 3 or more drug classes). 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 [4]. Tigecycline was supplied by Pfizer, Inc. (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers MicroScan (Siemens Medical Solutions Diagnostics, 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); amoxicillin-clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); cefepime (0.5-32); ceftazidime (8-32); ceftriaxone (0.06-64); meropenem (0.12-16); levofloxacin (0.008-8); minocycline (0.5-16); piperacillin-tazobactam (0.06/4-128/4); tigecycline (0.008-16).
- Quality control (QC) of broth microdilution panels followed manufacturers and CLSI guidelines using *E. coli* ATCC 25922 and ATCC 35218 as well as *P. aeruginosa* ATCC 27853. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines [5].
- MIC interpretive criteria followed published breakpoints defined by CLSI [5].
- MIC trends over time were assessed by Spearman's correlation, while the Cochran-Armitage test for trend was used to assess linear trends in percent susceptible over time. Any  $p < 0.05$  was considered statistically significant.

## References

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## Results

Figure 1: Number of Asian *Acinetobacter* spp. isolates by country, 2004-2010.

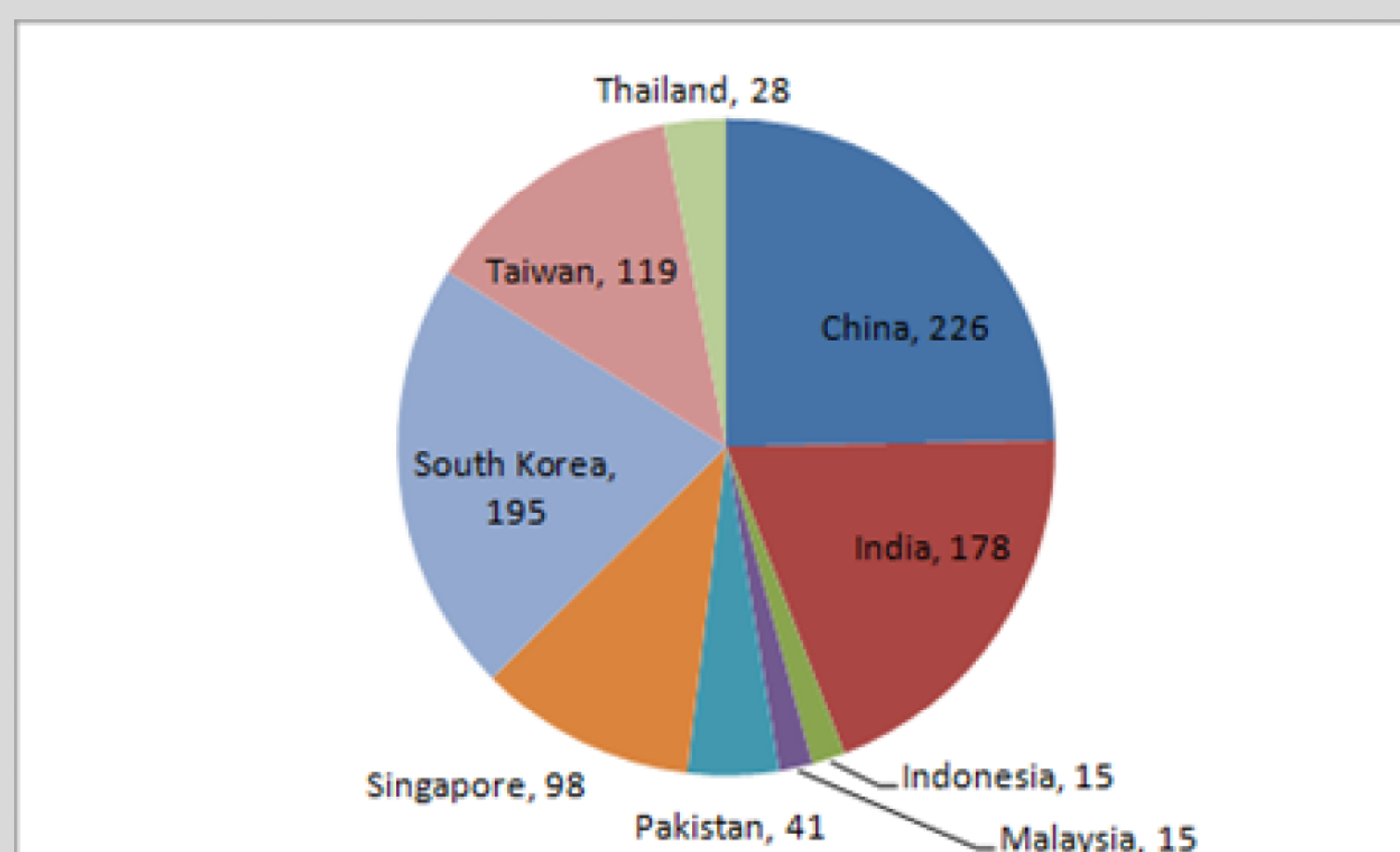


Figure 2: Number of Asian *Acinetobacter* spp. isolates by specimen source, 2004-2010.

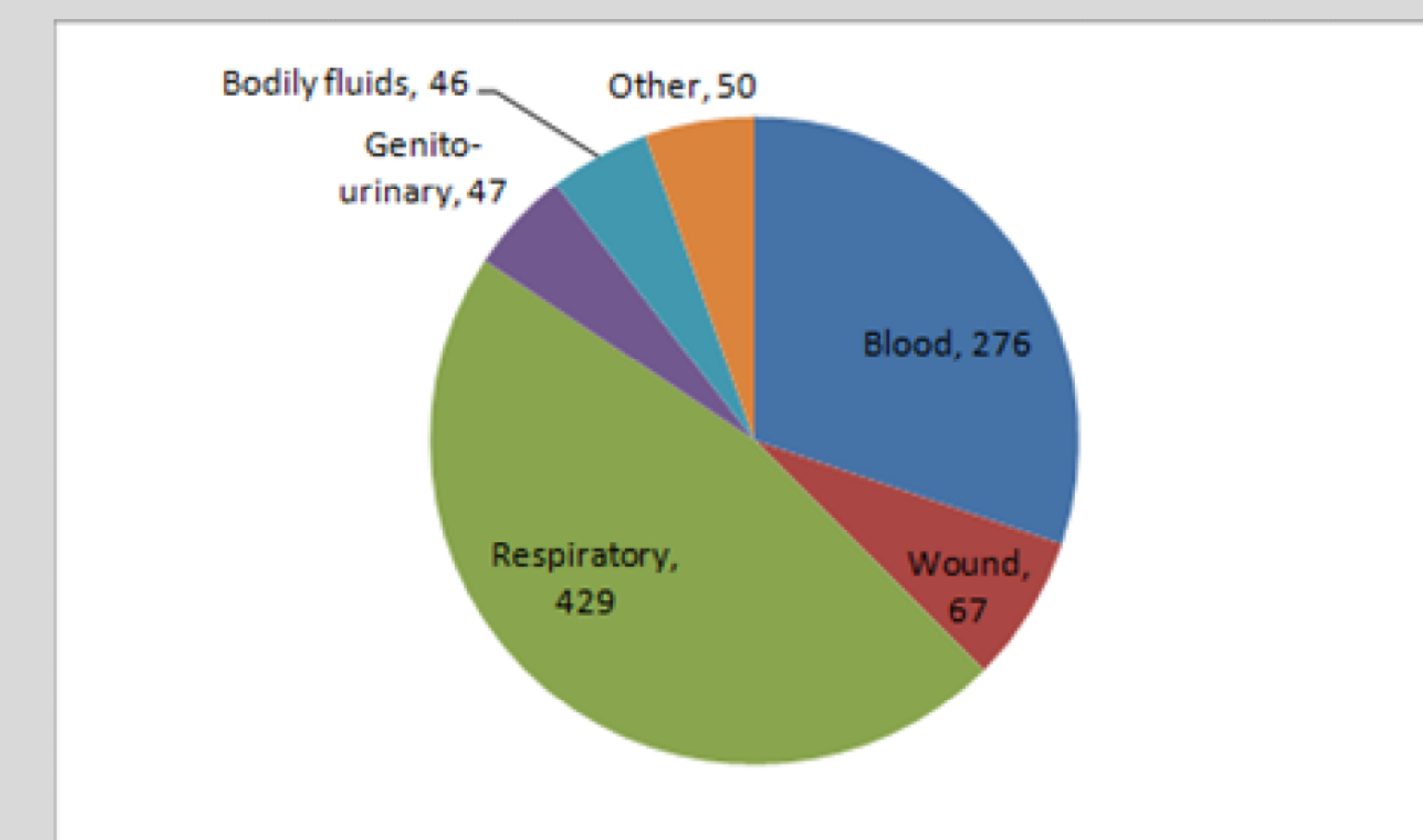


Table 1. *In vitro* activity of tigecycline and comparators against 915 Asian *Acinetobacter* spp. isolates, 2004-2010.

	MIC <sub>50</sub>							Geometric Mean MIC							MIC trend
	2004	2005	2006	2007	2008	2009	2010	2004	2005	2006	2007	2008	2009	2010	
Amikacin	16	8	32	64	>64	>64	32	17	14.7	18.7	24	33.1	35.7	24.3	<0.0001
Cefepime	16	32	32	32	>32	32	>32	12.2	13.7	14.2	19	25.5	19.5	25.9	<0.0001
Levofloxacin	2	2	4	8	8	8	8	0.9	0.9	1.5	2.3	3.2	2.9	2.7	<0.0001
Meropenem	nt	nt	4	8	>16	>16	>16	nt	nt	4.6	5.2	6.4	6.5	8.3	0.006
Minocycline	$\leq 0.5$	$\leq 0.5$	1	1	2	1	2	1	1.1	1.2	1.6	2.1	2	1.9	<0.0001
Pip-Tazo	64	64	64	128	>128	>128	>128	8.9	8.4	14	32.5	76.3	52.1	77.5	<0.0001
Tigecycline	0.25	0.5	0.5	0.5	1	1	1	0.23	0.39	0.39	0.49	0.68	0.71	0.71	<0.0001

MIC=minimum inhibitory concentration (mcg/ml); nt=not tested that year. Any  $p < 0.05$  is significant (Spearman's correlation)

Figure 3. Trends in susceptibility of 915 Asian *Acinetobacter* spp. to agents for which breakpoints are available, 2004-2010.

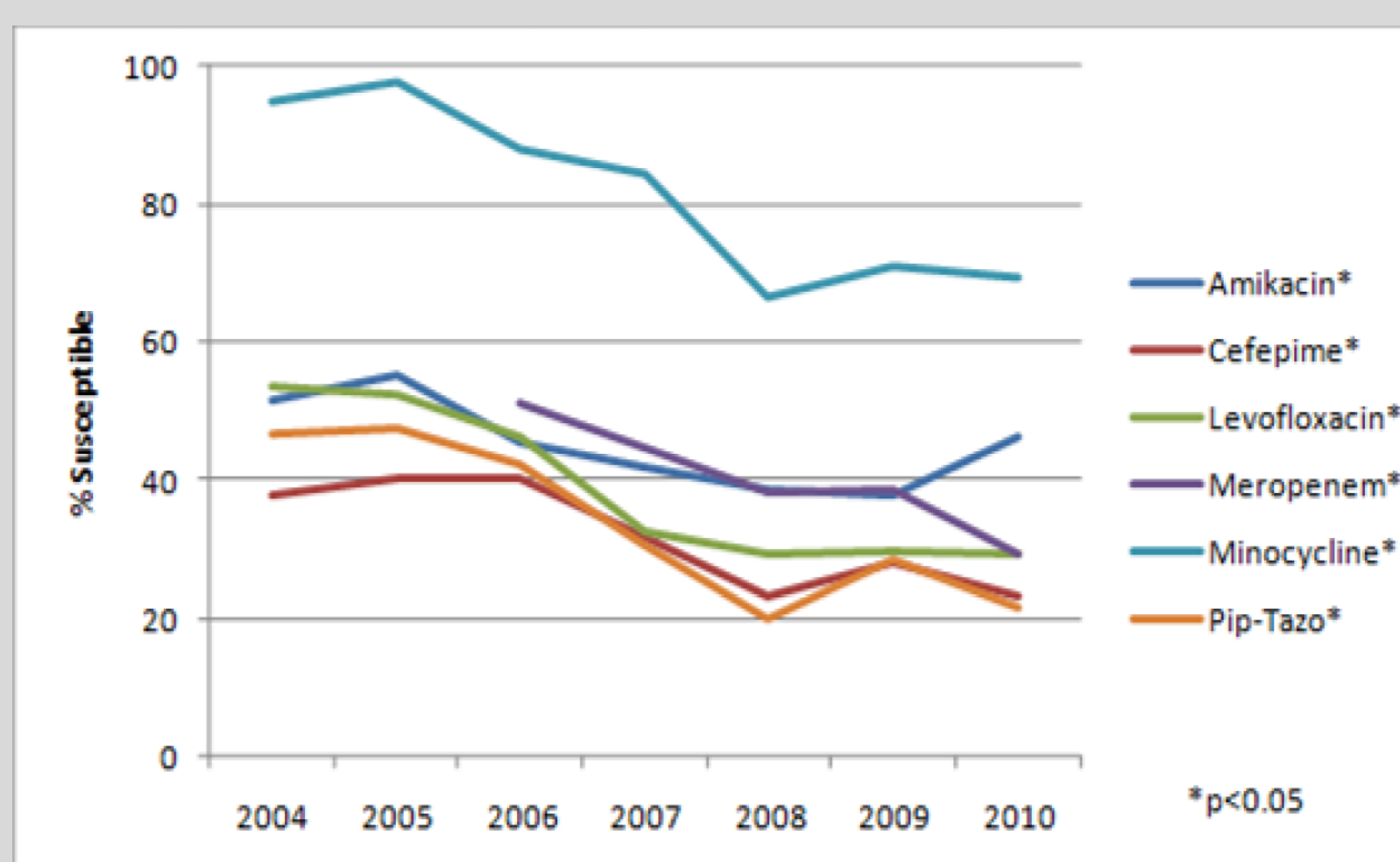
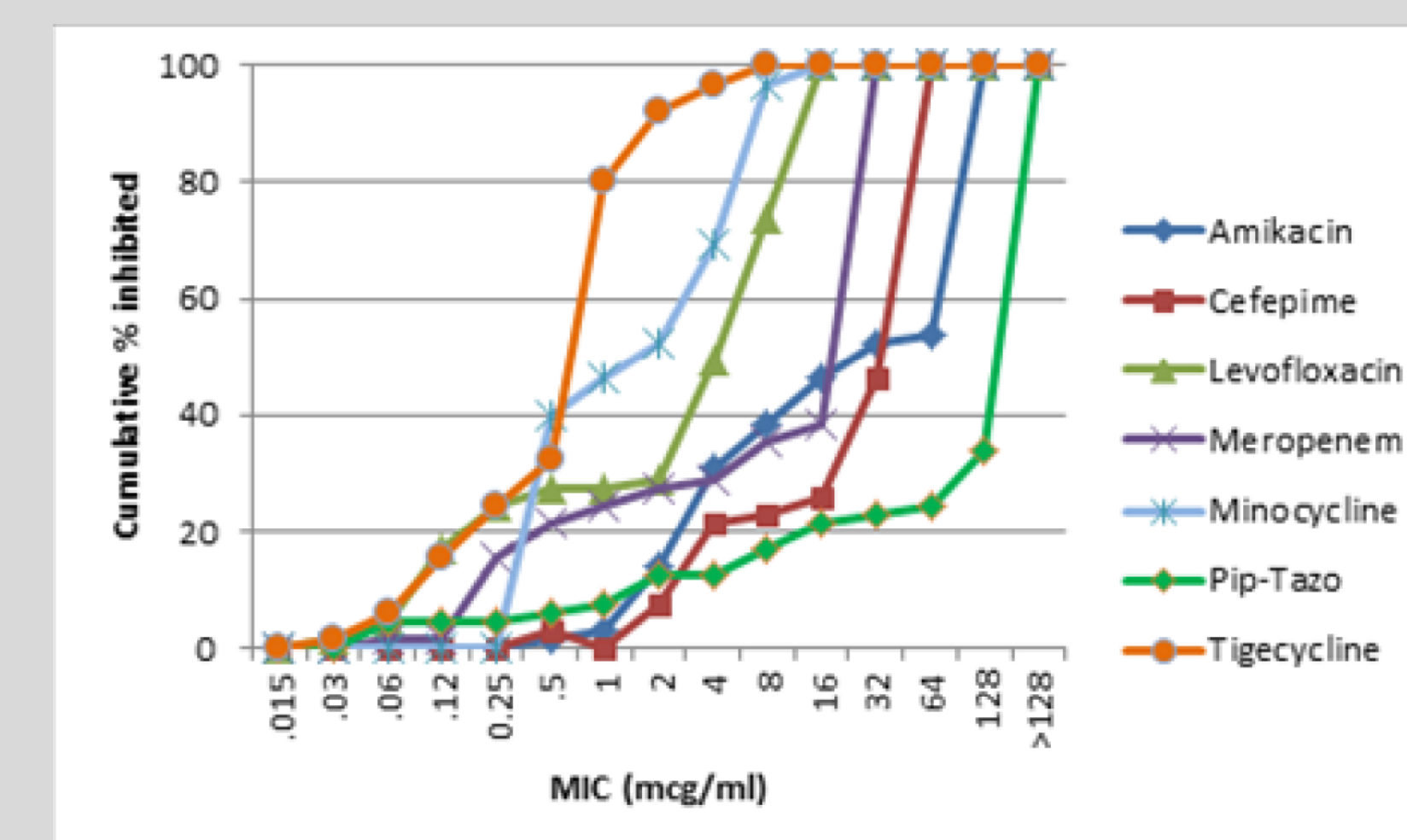


Figure 4. Cumulative percent *Acinetobacter* spp. inhibited by tigecycline and comparators, 2010 (n=65).



## Conclusions

- All agents studied showed a statistically significant trend of increasing MICs over the 7-year period of this study. Similar results were found for percent susceptibility with a significant downward trend for all drugs for which breakpoints were available ( $p < 0.05$ ).
- Minocycline exhibited the highest percent susceptible of the study agents for which breakpoints were available. Tigecycline's MIC<sub>50</sub> values were either the same as or one doubling dilution lower than minocycline's in each year of the study.
- As demonstrated by the 2010 data on cumulative percent inhibited, tigecycline showed the most favorable *in vitro* MIC distribution of all antimicrobials tested, with 92.3% of *Acinetobacter* isolates inhibited at 2 mcg/ml. Although *in vitro* tests do not always correlate with clinical outcome, this study suggests that tigecycline may be an option for the treatment of this serious nosocomial pathogen.