

# Comparing Tigecycline and Comparators Against Multi-drug Resistant (MDR) Pathogens in Turkey in 2008

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R. Badal<sup>1</sup>, S. Hawser<sup>1</sup>, M. Hackel<sup>1</sup>, S. Bouchillon<sup>1</sup>, B. Johnson<sup>1</sup>, D. Hoban<sup>1</sup>, M. Renteria<sup>1</sup>, J. Johnson<sup>1</sup>, M. Dowzicky<sup>2</sup>

<sup>1</sup>International Health Management Associates, Inc., Schaumburg, IL, USA  
<sup>2</sup>Wyeth Pharmaceuticals, Collegeville, PA, USA



IHMA, Inc.  
2122 Palmer Dr.  
Schaumburg, IL  
60173  
Tel: 847.303.5003  
Fax: 847.303.5601

## Revised Abstract

**Objectives:** The TEST program determined the in vitro activity of tigecycline compared to broad spectrum antimicrobials against multidrug resistant gram-negative and gram-positive species collected from hospitals within Turkey throughout 2004-2008. **Methods:** Clinical isolates were identified to the species level and confirmed by a reference laboratory. Minimum Inhibitory Concentration (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Out of 641 isolates collected, 201 (31.5%) were determined to be multidrug resistant as defined by resistant to 3 or more antimicrobial drug classes. *A. baumannii* had the highest percentage of MDR strains with 40/48 (83%) followed in order by *E. coli* 47/116 (41%); *P. aeruginosa* 29/78 (37%); *Klebsiella* spp. 29/87 (33%); *S. marcescens* 10/35 (29%) *Enterobacter* spp. 14/60 (23%); and *S. aureus* 20/100 (20%). Tigecycline inhibited 84% of the gram-negative MDR strains at 2 mcg/ml compared to the next most active drug, imipenem (78.6% at 4 µg/ml). All 32 MDR Gram-positive strains (mostly MRSA) were inhibited by linezolid at 4 µg/ml and tigecycline at 0.5 µg/ml. **Conclusions:** Turkey had a high level of MDR strains (> 30%) and was one of only seven countries that had levels superseding 30% in the TEST program. 100 % of Gram-positive MDR isolates and at least 83% of Gram-negative MDR isolates, with the exception of *P. aeruginosa* were susceptible to tigecycline.

## Introduction

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restore activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3].

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90<sup>th</sup> percentile inhibited at or below 2 µg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against a selected geographical group of multidrug resistant isolates from Turkey. This study is part of the ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

## Materials & Methods

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. There were 641 clinical isolates were collected and tested from 2004 to 2008 from 8 investigative sites in Turkey. 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 [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West Sacramento, CA, USA). 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 (0.5-32, gram-negative panel, and 0.06-16, gram-positive panel); cefepime (0.5-32); ceftazidime (0.06-64); ceftazidime (8-32); imipenem (0.06-16); meropenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent United States Food and Drug Administration (FDA) package insert for tigecycline [9], where applicable.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2008) guidelines [8].

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## Results

Results are presented in the following tables and graphs.

Table 1. Comparative in vitro activity of tigecycline against 201 multidrug resistant clinical isolates from Turkey.\*

Organisms: MDR (Total N)	Drug	MIC (mcg/ml)			%Sus <sup>a</sup>	%Res
		MIC <sub>50</sub>	MIC <sub>90</sub>	Range		
<b>Gram-Positives</b>						
<i>Staphylococcus aureus</i> , MRSA n=20 (100)	Tigecycline	0.25	0.5	0.25-0.5	100	0
	AmoxClav	>8	>8	>8-8	0	100
	Ampicillin	>16	>16	>16-16	0	100
	Ceftriaxone	>64	>64	>64-64	0	100
	Imipenem	>16	>16	>16-16	0	100
	Levofloxacin	8	16	4-16	0	100
	Linezolid	2	4	1-4	100	0
	Minocycline	8	8	4-8	7.7	7.7
	Penicillin	>8	>8	>8-8	0	100
	PipTazo	>16	>16	>16-16	0	100
Vancomycin	1	1	0.5-2	100	0	
<i>Enterococcus faecium</i> n=12 (28)	Tigecycline	0.12	0.25	0.12-0.25	100	0
	Ampicillin	>16	>16	>16-16	0	100
	Levofloxacin	>32	>32	>32-32	0	100
	Linezolid	2	2	2-2	100	0
	Minocycline	>8	>8	>0.25-8	33.3	66.7
	Penicillin	>8	>8	>8-8	0	100
Vancomycin	2	>32	0.5-32	66.7	33.3	
<b>Gram-Negatives</b>						
<i>Acinetobacter baumannii</i> n=40 (48)	Tigecycline <sup>b</sup>	1	2	0.5-4	96.2	0
	Amikacin	>64	>64	2-64	38.5	57.7
	Cefepime	32	>32	16-32	0	96.2
	Ceftazidime	>32	>32	>32-32	0	100
	Ceftriaxone	>64	>64	64-64	0	100
	Imipenem	2	>16	0.5-16	53.8	46.2
	Levofloxacin	8	>8	8-8	0	100
	Minocycline	1	8	<0.5-16	88.5	3.8
	PipTazo	>128	>128	64-128	0	96.2
	<i>Enterobacter</i> spp. <sup>c</sup> n=14 (60)	Tigecycline	0.5	4	0.5-8	83.3
Amikacin		2	16	1-32	91.7	0
AmoxClav		>32	>32	>32-32	0	100
Ampicillin		>32	>32	>32-32	0	100
Cefepime		8	8	2-16	91.7	0
Ceftazidime		>32	>32	32-32	0	100
Ceftriaxone		64	>64	2-64	8.3	58.3
Imipenem		0.5	1	0.25-2	100	0
Levofloxacin		0.12	>8	0.03-8	66.7	16.7
Minocycline		2	16	2-16	66.7	16.7
PipTazo	64	>128	2-128	16.7	41.7	
<i>Escherichia coli</i> n=47 (116)	Tigecycline	0.5	1	0.25-2	100	0
	Amikacin	4	16	2-32	92	0
	AmoxClav	32	>32	16-32	0	96
	Ampicillin	>32	>32	32-32	0	100
	Cefepime	>32	>32	<0.5-32	12	84
	Ceftazidime	16	>32	<8-32	28	48
	Ceftriaxone	>64	>64	1-64	4	88
	Imipenem	0.5	0.5	0.25-2	100	0
	Levofloxacin	>8	>8	0.03-8	4	96
	Minocycline	8	>16	2-16	32	44
PipTazo	8	32	1-128	88	8	
<i>Klebsiella</i> spp. <sup>d</sup> n=29 (87)	Tigecycline	1	2	0.5-2	100	0
	Amikacin	4	32	1-64	79.2	4.2
	AmoxClav	32	>32	16-32	0	95.8
	Ampicillin	>32	>32	>32-32	0	100
	Cefepime	>32	>32	<0.5-32	37.5	62.5
	Ceftazidime	32	>32	<8-32	12.5	75
	Ceftriaxone	>64	>64	0.12-64	16.7	70.8
	Imipenem	0.5	1	0.25-1	100	0
	Levofloxacin	0.12	>8	0.03-8	83.3	16.7
	Minocycline	4	>16	2-16	62.5	29.2
PipTazo	128	>128	4-128	31.3	68.8	
<i>Pseudomonas aeruginosa</i> n=29 (78)	Tigecycline <sup>b</sup>	>16	>16	0.5-16	6.3	93.8
	Amikacin	16	32	2-32	62.5	0
	Cefepime	>32	>32	4-32	12.5	75
	Ceftazidime	<8	>32	<8-32	50	43.8
	Ceftriaxone	>64	>64	64-64	0	100
	Imipenem	16	16	0.25-16	25	56.3
	Levofloxacin	>8	>8	1-8	12.5	81.3
	Minocycline	4	8	2-8	77.8	0
	PipTazo	128	>128	4-128	31.3	68.8
	<i>Serratia marcescens</i> n=10 (35)	Tigecycline	1	2	1-2	100
Amikacin		4	8	1-8	100	0
AmoxClav		>32	>32	>32-32	0	100
Ampicillin		>32	>32	>32-32	0	100
Cefepime		>32	>32	4-32	22.2	77.8
Ceftazidime		>32	>32	<8-32	11.1	88.9
Ceftriaxone		>64	>64	16-64	0	88.9
Imipenem		2	4	0.5-4	100	0
Levofloxacin		0.12	8	0.06-8	77.8	11.1
Minocycline		4	8	2-8	77.8	0
PipTazo	128	>128	2-128	11.1	77.8	

\* Multidrug resistance is resistance to 3 or more drug classes.  
<sup>a</sup> Breakpoints as defined by CLSI where available (M100-S18), 2008. Breakpoints for tigecycline against *Acinetobacter* and *Pseudomonas* spp. have not been established.  
<sup>b</sup> A breakpoint of susceptible  $\leq 2$  µg/ml and resistant  $\geq 8$  µg/ml for *Enterobacteriaceae* from the US FDA is applied as a conservative measure of tigecycline activity for these species and is presented here for comparative purposes only.  
<sup>c</sup> *E. aerogenes* (2); *E. agglomerans* (1); *E. cloacae* (10); *E. intermedium* (1).  
<sup>d</sup> *K. oxytoca* (2); *K. pneumoniae* (27).

Figure 1. Cumulative percents inhibited by tigecycline and comparators against 32 multidrug resistant Gram-positive isolates from Turkey.\*

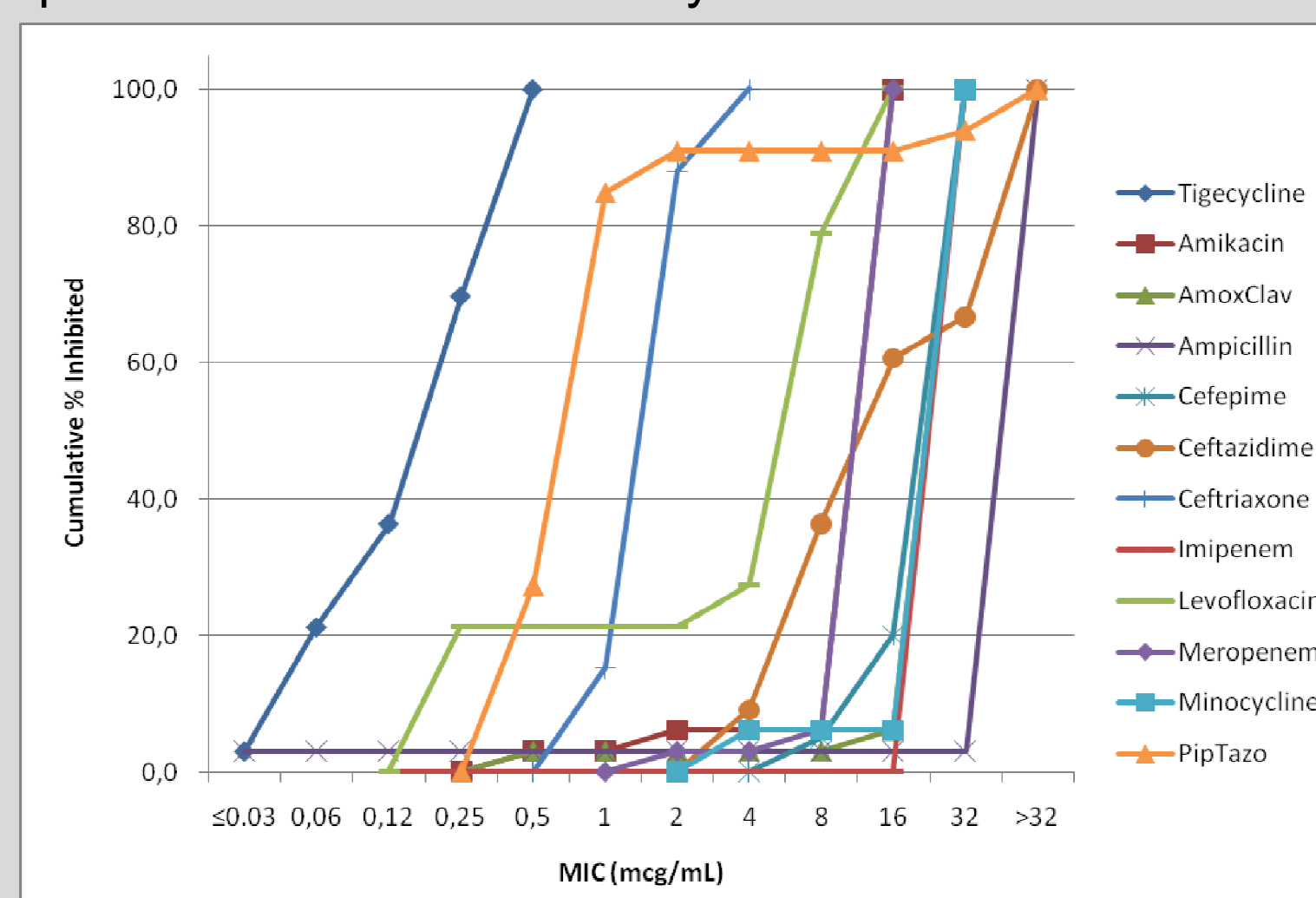
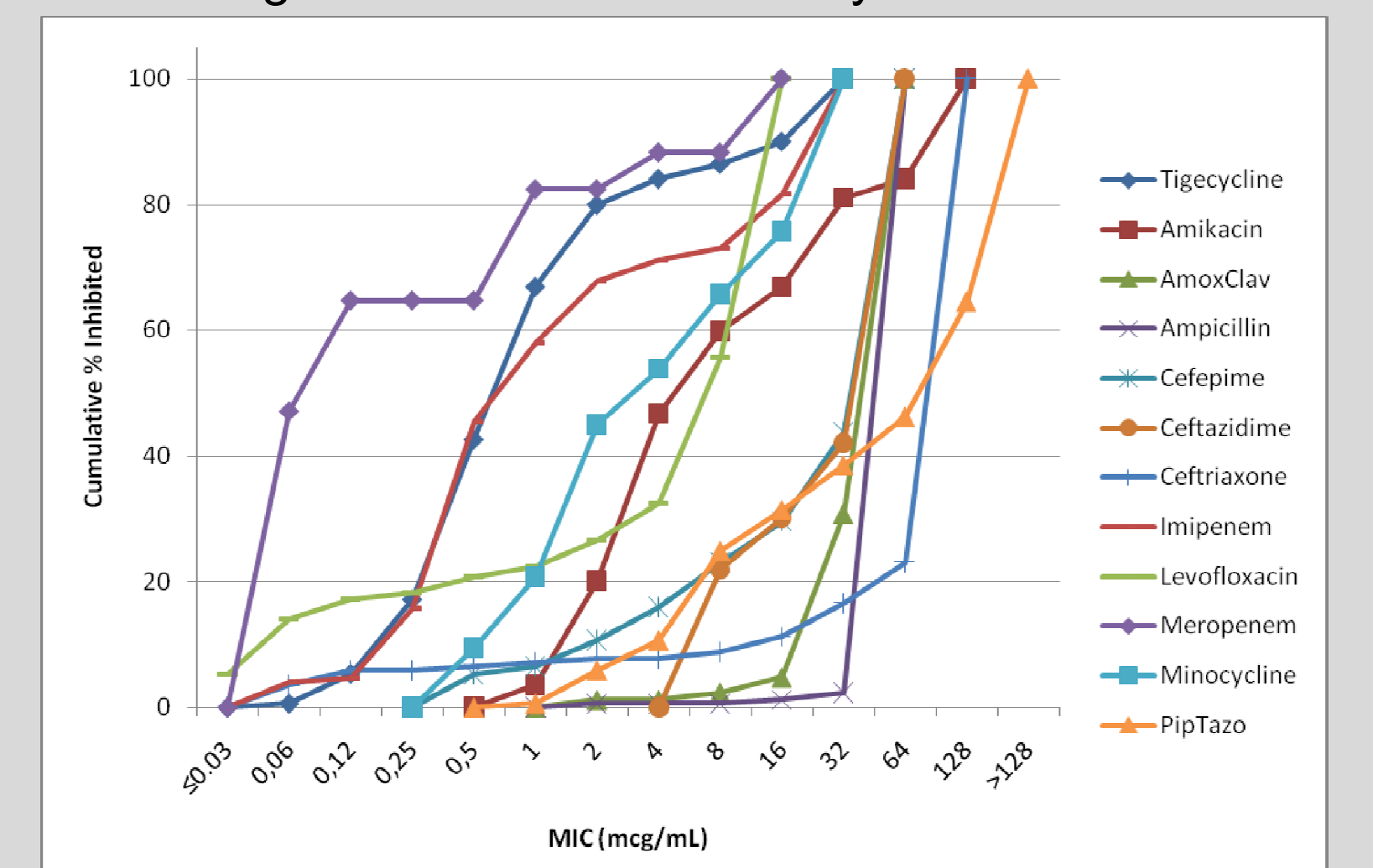


Table 2. Multidrug resistance (MDR) per country in the T.E.S.T. program ranked by % MDR.\*

Country	MDR		Country	MDR	
	(Total N)	% MDR		(Total N)	% MDR
Turkey	202(641)	31.5	Portugal	32(196)	16.3
Guatemala	186(377)	49.3	Austria	84(523)	16.1
India	492(1173)	41.9	Latvia	71(450)	15.8
Chile	396(1044)	37.9	Singapore	179(1139)	15.7
Brazil	280(753)	37.2	Belgium	306(2011)	15.2
Puerto Rico	47(135)	34.8	United Kingdom	145(1015)	14.3
Pakistan	161(509)	31.6	Philippines	106(786)	13.5
Honduras	55(185)	29.7	Ireland	125(966)	12.9
Poland	57(193)	29.5	United States	7143(56770)	12.6
Colombia	349(1194)	29.2	Spain	383(3178)	12.1
Mexico	850(2943)	28.9	Hong Kong	69(584)	11.8
China	161(565)	28.5	France	656(6081)	10.8
Argentina	908(3358)	27	Germany	449(4675)	9.6
Korea	484(1848)	26.2	Slovenia	71(768)	9.2
Jamaica	50(197)	25.4	Australia	188(2242)	8.4
Greece	382(1523)	25.1	The Netherlands	59(741)	8
Panama	92(382)	24.1	Switzerland	30(395)	7.6
Lebanon	35(147)	23.8	Hungary	59(845)	7
Indonesia	41(175)	23.4	Czech Republic	49(746)	6.6
Italy	1356(5933)	22.9	Canada	165(2890)	5.7
Nicaragua	10(44)	22.7	Denmark	63(1133)	5.6
Taiwan	285(1292)	22.1	Slovak Republic	9(167)	5.4
Croatia	112(514)	21.8	Oman	6(196)	3.1
Israel	270(1299)	20.8	Sweden	31(1132)	2.7
Lithuania	72(378)	19	Finland	16(648)	2.5
South Africa	410(2291)	17.9	Norway	3(190)	1.6
Venezuela	96(561)	17.1	Totals	18336(120121)	15.3

\* Data collected from 1,016 investigative sites.

Figure 2. Cumulative percents inhibited by tigecycline and comparators against 169 multidrug resistant Gram-negative isolates from Turkey.\*



## Conclusions

- There were 7 of 53 countries that demonstrated MDR isolate rates equal to or greater than 30% in the TEST program. These included Guatemala, India, Brazil, Puerto Rico, Pakistan and Turkey (31.5%). The highest level of MDR isolates was seen in Guatemala (49.3%) and the lowest seen in Norway (1.6%).
- All 76 Gram-positive MDR isolates from Turkey were inhibited by tigecycline and linezolid at their respective breakpoints. 33% of *E. faecium* were vancomycin-resistant.
- Tigecycline was the most potent drug *in vitro* against MDR *Acinetobacter baumannii* with 96.2% inhibited at  $\leq 2$  mcg/ml, while imipenem was the most potent antimicrobial agent against MDR *Enterobacter* with 100% susceptible at the CLSI breakpoint of  $\leq 2$  mcg/ml. Tigecycline and imipenem inhibited 100% of all MDR *E. coli*, *Klebsiella* spp., and *S. marcescens* at their respective breakpoints.
- None of the study drugs were very active against MDR *P. aeruginosa*, including piperacillin-tazobactam.
- Amikacin was the most active drug against these isolates, inhibiting 62.5% at its susceptible breakpoint of  $\leq 16$  mcg/ml.