

# Tigecycline In Vitro Antibacterial Activity Against 1,499 Isolates of *Enterobacteriaceae*

# 57.008

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## REVISED ABSTRACT

**Background:** Tigecycline (GAR-936), a member of a new class of antimicrobials (glycylcyclines), which has been shown to have potent activity against most species of *Enterobacteriaceae*. The in vitro activity of tigecycline was compared with those of other agents against *Escherichia coli*, *Enterobacter cloacae*, *Enterobacter aerogenes* and *Klebsiella pneumoniae* from hospitals throughout Europe, the Middle East and South Africa.

**Methods:** A total of 1,499 clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Isolates were collected between January 2001 - September 2002. MIC's were determined by the central laboratory using broth microdilution panels from Dade Microscan according to NCCLS guidelines and manufacturer's instructions.

**Results:** The susceptibility results of the 1,499 isolates of *Enterobacteriaceae* are listed in Table 1.

Antibiotic	MIC ( $\mu$ g/ml)		
	Range	MIC 50	MIC 90
Tigecycline (GAR-936)	0.12-8	0.5	1
Amoxicillin/clavulanic acid	0.5->64	16	64
Ampicillin/sulbactam	0.5->32	32	>32
Imipenem	0.5->64	0.5	1
Cefepime	0.5->64	0.5	8
Ceftazidime	0.5->64	0.5	>64
Ceftriaxone	0.5->64	0.5	64
Levofloxacin	0.25->64	0.25	8

**Conclusion:** Tigecycline exhibited excellent activity against all isolates tested. These results strongly suggest that tigecycline, a member of a new class of antimicrobials (glycylcyclines), is a promising new antimicrobial agent with excellent activity against *Enterobacteriaceae*.

## BACKGROUND

Tigecycline is a novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although its antibacterial activity is significant, it is perceived to be bacteriostatic [1].

Tigecycline provides activity against tetracycline- and multi-drug-resistant gram-positive pathogens as well as significant broad-spectrum activity against many aerobic and anaerobic gram-positive and gram-negative microorganisms [1-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6]. Most tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [1-3, 7-11]. Since tigecycline possesses no structural beta-lactam ring, it is particularly unaffected by beta-lactamase and extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL) [8].

This study compared the activity of tigecycline with other agents against enterobacteriaceae including *Escherichia coli*, *Enterobacter cloacae*, *Enterobacter aerogenes* and *Klebsiella pneumoniae* from hospitals throughout Europe, the Middle East and South Africa.

## METHODS

All isolates were derived from blood, respiratory tract, urine (no more than 30% of all isolates), skin, wound, fluids and other defined sources. Only one isolate per patient was accepted.

Clinical isolates were collected between January 2001 - September 2002 from 38 study centers in 17 countries.

Antimicrobial agents tested with concentrations (expressed in mcg/ml) were: amoxicillin/clavulanic acid (0.5 - 64); ampicillin/sulbactam (0.5 - 32); cefepime (0.5 - 64); ceftazidime (0.5 - 64); ceftriaxone (0.5 - 64); imipenem (0.5 - 64); levofloxacin (0.25 - 64); tigecycline (0.008 - 16). MIC interpretive criteria followed published guidelines established by the NCCLS where applicable [12]. Tigecycline tentative

breakpoints (in units of mcg/mL) are defined as susceptible  $\leq 2$ ; intermediate = 4; and resistant  $\geq 8$ .

Isolates were identified to genus and species at each site and confirmed by the central laboratory (Laboratories International for Microbiology Studies, Schaumburg, IL, USA).

Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as, construction and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS).

### Antimicrobial Susceptibility Testing

MIC's were determined by the central laboratory using microdilution panels by Dade Microscan (Dade Behring Inc., Sacramento, CA, USA) according to NCCLS.

Quality Control was performed using the following ATCC strains: *E. coli* ATCC.

Extended-spectrum beta-lactamases were confirmed using the NCCLS recommended procedures for Screening and Confirmatory Tests for ESBLs in *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli* [13].

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## RESULTS

The results of this study are presented in the following tables.

Table 2. In Vitro MIC Values and Susceptibility Results of Tigecycline and Comparators Against 1,499 *Enterobacteriaceae*

Organism	Drug	%Sus*	%Int	%Res	MIC <sub>90</sub> (mcg/mL)	
All Enterobacteriaceae (n=1499)	Tigecycline	97.3	2.3	0.4	1	
	Amox/Clav	40.4	14.1	45.5	64	
	Amp/Sulb	28.0	14.0	58.0	>32	
	Cefepime	90.2	3.6	6.2	8	
	Ceftazidime	60.6	4.5	34.9	>64	
	Ceftriaxone	76.2	11.3	12.5	64	
	Imipenem	99.2	0.5	0.3	1	
	Levofloxacin	80.8	3.4	15.8	8	
	<i>Enterobacter aerogenes</i> (n=283)	Tigecycline	96.1	3.9	--	2
		Amox/Clav	3.9	2.1	94.0	64
Amp/Sulb		14.8	13.4	71.7	>32	
Cefepime		94.3	1.4	4.2	4	
Ceftazidime		49.5	6.7	43.8	>64	
Ceftriaxone		86.6	6.4	7.1	16	
Imipenem		96.1	2.1	1.8	1	
Levofloxacin		73.1	2.5	24.4	16	
<i>Enterobacter cloacae</i> (n=280)	Tigecycline	97.1	2.1	0.7	1	
	Amox/Clav	3.2	0.7	96.1	>64	
	Amp/Sulb	12.5	13.6	73.9	>32	
	Cefepime	98.2	1.1	0.7	4	
	Ceftazidime	66.8	2.9	30.4	>64	
	Ceftriaxone	76.8	13.9	9.3	32	
	Imipenem	99.6	0.4	0.0	1	
	Levofloxacin	94.6	0.4	5.0	0.5	
<i>Escherichia coli</i> (n=400)	Tigecycline	100	--	--	0.5	
	Amox/Clav	64.0	20.8	15.3	32	
	Amp/Sulb	34.3	18.0	47.8	>32	
	Cefepime	84.5	5.5	10.0	32	
	Ceftazidime	73.0	3.8	23.3	>64	
	Ceftriaxone	76.3	6.5	17.3	>64	
	Imipenem	100	--	--	0.5	
	Levofloxacin	70.3	3.3	26.5	16	
<i>Klebsiella pneumoniae</i> (n=536)	Tigecycline	95.9	3.4	0.7	2	
	Amox/Clav	61.4	22.6	16.0	32	
	Amp/Sulb	38.4	11.6	50.0	>32	
	Cefepime	88.1	4.7	7.3	16	
	Ceftazidime	54.1	4.7	41.2	>64	
	Ceftriaxone	70.3	16.2	13.4	64	
	Imipenem	100	--	--	0.5	
	Levofloxacin	85.4	5.6	9.0	4	

\* Interpretive criteria based upon approved NCCLS breakpoints where available, from NCCLS document M100-S13; Tigecycline tentative breakpoints (in mcg/mL) defined as susceptible < 2; intermediate = 4; resistant > 8.

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Table 3. In Vitro MIC Values and Susceptibility Results of Tigecycline and Comparators Against 420 ESBL Producers and 516 Non-ESBL Producing *E. coli* and *K. pneumoniae*

Organism	Drug	%Sus*	%Int	%Res	MIC <sub>90</sub> (mcg/mL)	
<i>Escherichia coli</i> , ESBL (n=142)	Tigecycline	100	--	--	1	
	Amox/Clav	49.3	32.4	18.3	32	
	Amp/Sulb	15.5	23.2	61.3	>32	
	Cefepime	57.0	14.8	28.2	64	
	Ceftazidime	26.1	9.9	64.1	>64	
	Ceftriaxone	33.8	18.3	47.9	>64	
	Imipenem	100.0	0.0	0.0	0.5	
	Levofloxacin	50.0	3.5	46.5	32	
	<i>Escherichia coli</i> , Non ESBL (n=258)	Tigecycline	100	--	--	0.5
		Amox/Clav	72.1	14.3	13.6	32
Amp/Sulb		44.6	15.1	40.3	>32	
Cefepime		99.6	0.4	0.0	0.5	
Ceftazidime		98.8	0.4	0.8	0.5	
Ceftriaxone		99.6	0.0	0.4	0.5	
Imipenem		100.0	0.0	0.0	0.5	
Levofloxacin		81.4	3.1	15.5	8	
<i>Klebsiella pneumoniae</i> , ESBL (n=278)	Tigecycline	97.1	2.5	0.4	2	
	Amox/Clav	38.8	35.3	25.9	32	
	Amp/Sulb	9.7	14.0	76.3	>32	
	Cefepime	78.1	8.6	13.3	32	
	Ceftazidime	15.8	8.6	75.5	>64	
	Ceftriaxone	45.7	30.2	24.1	>64	
	Imipenem	100.0	0.0	0.0	0.5	
	Levofloxacin	78.1	9.0	12.9	8	
<i>Klebsiella pneumoniae</i> , non ESBL (n=258)	Tigecycline	94.6	4.3	1.2	1	
	Amox/Clav	85.7	8.9	5.4	16	
	Amp/Sulb	69.4	8.9	21.7	>32	
	Cefepime	98.8	0.4	0.8	0.5	
	Ceftazidime	95.3	0.4	4.3	1	
	Ceftriaxone	96.9	1.2	1.9	0.5	
	Imipenem	100.0	0.0	0.0	0.5	
	Levofloxacin	93.4	1.9	4.7	0.5	

\* Interpretive criteria based upon approved NCCLS breakpoints where available, from NCCLS document M100-S13; Tigecycline tentative breakpoints (in units of mcg/mL) defined as susceptible < 2; intermediate = 4; resistant > 8.

## CONCLUSIONS

- Tigecycline inhibited 97.1% of all tested *Enterobacteriaceae* in vitro at an MIC of 2 mcg/mL.
- Tigecycline's MIC<sub>90</sub> of 1 mcg/mL was equivalent to imipenem and 8 to 64 fold better than the beta-lactams, beta-lactam/beta-lactamase inhibitor.
- Tigecycline demonstrated potent in vitro activity against both ESBL and non-ESBL producing *E. coli* and *K. pneumoniae*.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a promising compound in the treatment of Gram-negative infections caused by selected *Enterobacteriaceae*.