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In vitro Activity of Tigecycline and Comparators vs. ESBL-producing Enterobacteriaceae Globally 2004-2008 - Tigecycline Evaluation and Surveillance Trial (T.E.S.T.)

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Revised Abstract

Objectives: The Tigecycline Evaluation Surveillance Trial (T.E.S.T.), a global longitudinal surveillance study, investigated the *in vitro* activity of tigecycline, a glycylcycline antimicrobial. Tigecycline has demonstrated potent broad spectrum activity against both gram-negative and gram-positive organisms. This analysis of T.E.S.T data compares the *in vitro* activity of tigecycline and comparators against ESBL (extended-spectrum beta-lactamase)-producing *Enterobacteriaceae*. **Methods**: A total of 4,432 ESBL-producing *Enterobacteriaceae* isolates from Europe, US/Canada, Asia/Pacific Rim, Latin America, Africa, Middle East and South Pacific was evaluated. MIC$_{90}$ for tigecycline (TIG), meropenem (MEP), ceftriaxone (CFX), amikacin (AMK) and levofloxacin (LEVO) were determined using common broth microdilution panels and interpreted according to CLSI and FDA guidelines. **Results**: MIC$_{90}$ (mcg/ml) results are in the table as follows:

Region	N=	TIG	MEP	CFX	AMK	LEVO
Europe	1467	2	0.25	> 64	16	>8
US/Canada	992	2	16	> 64	32	>8
Asia/Pacific Rim	471	1	0.5	> 64	>64	>8
Latin America	1203	2	0.5	> 64	>64	>8
Africa	151	2	16	>64	16	>8
Middle East	91	2	4	>64	16	>8
South Pacific	57	2	0.25	>64	16	>8

Conclusion: Meropenem is 2-8 fold more active than tigecycline in the seven regions except US/Canada and Africa. Tigecycline is 8 fold more active than meropenem in the US/Canada and Africa and 8-64 fold more active than ceftriaxone, amikacin and levofloxacin. The unusually high meropenem MIC$_{90}$ value seen in US/Canada and Africa is currently the subject of further investigation.

Introduction

Clinical laboratories have been aware of extended spectrum beta-lactamases (ESBLs) since their discovery in 1983 (1). These enzymes possess a distinctive substrate profile and are increasingly wide-spread among many *Enterobacteriaceae*. The majority of ESBLs are plasmid mediated and hydrolyze penicillins, cephalosporins and aztreonam but are inhibited by beta-lactamase inhibitors such as clavulanate, tazobactam and sulbactam (2).

Although ESBLs occur worldwide with varying but increasing prevalence, they are most commonly found in *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca*. The carbapenems including imipenem, ertapenem, meropenem and doripenem have often been described as the most effective therapeutic agents for infections caused by ESBL-producing isolates and are used clinically in many countries.

Tigecycline, a glycylcycline, has previously been shown to be active against ESBL-producing isolates (3).

The purpose of this study was to examine the in vitro activity of tigecycline and comparator antibiotics against ESBL-producing *Enterobacteriaceae* collected as part of the multi-year global Tigecycline Evaluation and Surveillance Trial (T.E.S.T.).

Materials & Methods

- Isolates were collected from clinical specimens (one isolate per patient only) according to site criteria and deemed clinically significant.
- Isolates were derived from blood, urine, wound, skin, fluids and other defined sources.
- Isolates were collected between 2004-2008 from 697 cumulative sites in 55 countries.
- Isolates were identified to the species level at each site using local laboratory criteria.
- Isolate collection, transport, confirmatory identification and database management were coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (Schaumburg, IL, USA)
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended microbroth dilution testing method (4). Tigecycline was supplied by Wyeth Pharmaceuticals (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, USA).
- The following agents were included on the gram-negative panel with expressed dilution ranges (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 (0.06-16), levofloxacin (0.008-8), minocycline (0.5-16), tigecycline (0.008-16) and piperacillin-tazobactam (0.06/4-128/4).
- QC of broth microdilution panels followed manufacturers' and CLSI guidelines using the following ATCC strains as needed and applicable: *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), *Escherichia coli* (ATCC 35218), *Klebsiella pneumoniae* (ATCC 700603 – ESBL positive control), *Haemophilus influenzae* (ATCC 49247), *Haemophilus influenzae* (ATCC 49766), *Staphylococcus aureus* (ATCC 29213), *Streptococcus pneumoniae* (ATCC 49619) and *Pseudomonas aeruginosa* (ATCC 27853).
- ESBLs were initially screened using ceftazidime and/or ceftriaxone (microbroth panels) and confirmed using ceftazidime +/- clavulanic acid and cefotaxime +/- clavulanic acid as described by the CLSI (4).

References

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Results

Table 1. *In vitro* activity of tigecycline and comparators vs. ESBL positive *Enterobacteriaceae* (2004-2008) by region.

Region	Drug	MIC$_{90}$ (mcg/ml)	%S[a]	%I[a]	%R[a]
Europe (n=1467)	Amikacin	16	91.3	3.4	5.3
	Ceftriaxone	>64	11	13.2	75.9
	Levofloxacin	>8	33.7	6.3	60
	Meropenem	0.25	99	0.5	0.4
	Tigecycline	2	96.6	2.8	0.6
North America (n=992)	Amikacin	32	84.9	12.7	2.4
	Ceftriaxone	>64	21.5	21.4	57.2
	Levofloxacin	>8	22.6	5.4	72
	Meropenem	16	83.1	2.5	14.4
	Tigecycline	2	94.5	4.8	0.7
Asia/Pacific (n=471)	Amikacin	>64	81.5	1.5	17
	Ceftriaxone	>64	8.7	9.3	81.8
	Levofloxacin	>8	29.3	7.2	63.5
	Meropenem	0.5	98.4	0.8	0.8
	Tigecycline	1	98.1	1.7	0.2
Latin America (n=1203)	Amikacin	>64	77.7	6.8	15.5
	Ceftriaxone	>64	9	9.8	81.2
	Levofloxacin	>8	27.7	5	67.3
	Meropenem	0.5	96.3	1.2	2.5
	Tigecycline	2	96.2	3	0.7
Africa (n=151)	Amikacin	16	93.4	5.3	1.3
	Ceftriaxone	>64	13.2	16.6	70.2
	Levofloxacin	>8	47	9.3	43.7
	Meropenem	16	87.9	2	10.1
	Tigecycline	2	92.7	5.3	2
Middle East (n=91)	Amikacin	16	94.5	2.2	3.3
	Ceftriaxone	>64	9.9	15.4	74.7
	Levofloxacin	>8	31.9	3.3	64.8
	Meropenem	4	90.1	2.2	7.7
	Tigecycline	2	92.3	7.7	0
South Pacific (n=57)	Amikacin	16	91.2	1.7	7
	Ceftriaxone	>64	26.3	10.5	63.2
	Levofloxacin	>8	31.6	12.3	56.1
	Meropenem	0.25	97.8	0	2.2
	Tigecycline	2	96.5	3.5	0

[a] % S, I, R defined by CLSI M100-S19 (2009);
Tigecycline % S, I, R defined by FDA breakpoints, Tygacil® package insert, 2009.

Table 2. *In vitro* activity of tigecycline and comparators vs. ESBL positive *Enterobacteriaceae* globally by year.

Year	Drug	MIC$_{90}$ (mcg/ml)	%S[a]	%I[a]	%R[a]
2004 (n=469)	Amikacin	32	88.7	6.4	4.9
	Ceftriaxone	>64	22	20.7	57.4
	Levofloxacin	>8	40.1	9.2	50.8
	Meropenem	0.12	100	0	0
	Tigecycline	2	93	6.4	0.6
2005 (n=578)	Amikacin	32	90	3.8	6.2
	Ceftriaxone	>64	17.3	14.7	68
	Levofloxacin	>8	33.7	5.7	60.6
	Meropenem	>16	77.8	0	22.2
	Tigecycline	2	95.7	3.6	0.7
2006 (n=1022)	Amikacin	32	84.7	7.7	7.5
	Ceftriaxone	>64	13	15.8	71.2
	Levofloxacin	>8	28.1	7.2	64.7
	Meropenem	2	92.2	2.1	5.7
	Tigecycline	2	95.6	3.5	0.9
2007 (n=1209)	Amikacin	32	83.8	6.7	9.5
	Ceftriaxone	>64	10.2	10.8	79
	Levofloxacin	>8	28.4	5.2	66.4
	Meropenem	1	94.2	1.1	4.7
	Tigecycline	2	96.6	2.9	0.5
2008 (n=1140)	Amikacin	64	83.4	5.6	11
	Ceftriaxone	>64	9.4	12	78.6
	Levofloxacin	>8	25.5	4.5	70
	Meropenem	0.5	96.2	1.1	2.7
	Tigecycline	1	96.9	2.5	0.6

[a] % S, I, R defined by CLSI M100-S19 (2009).
Tigecycline % S, I, R defined by FDA breakpoints, Tygacil® package insert, 2009.

Conclusions

- Tigecycline and meropenem, followed by amikacin, were the most active (%S) agents against ESBL positive *Enterobacteriaceae*.
- The activity of tigecycline has remained constant globally between 2004 and 2008 with % susceptible ranging from 93-96.9%.
- Increasing resistance in gram-negative bacilli will dictate continued global surveillance of antimicrobial activity.