#E-825

Comparison of Tigecycline with most Commonly-Used Antimicrobials Against Isolates Collected in Spain and Portugal including MRSA between 2004-2009

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Revised Abstract

Background: Development of bacterial resistance has become an important concern world-wide, but availability of newer agents offers clinicians options for therapy. Tigecycline (Tig) exhibits potent activity against a broad spectrum of bacteria, including strains resistant to other drugs. As part of the global Tigecycline Evaluation Surveillance Trial, strains collected in Iberia from 2004 to 2009 were evaluated for susceptibility to several antimicrobials. **Methods:** Strains were collected and identified at 49 cumulative sites in Spain and Portugal. MICs were determined at each site using microdilution panels following EUCAST guidelines. **Results:** The following table summarizes MIC_{90} results for all isolates, and for specific key pathogens.

	All gram-positives	*S. aureus* (MR)	*S. aureus* (MS)	Enterococci	*S. pneumoniae*
	n=1683	n=203	n=500	n=459	n=271
Tigecycline	0.25	0.25	0.25	0.25	0.12
Amox/Clav	>8	>8	1	>8	2
Ampicillin	>16	>16	>16	>16	4
Ceftriaxone	>64	>64	4	>64	1
Imipenem	4	>16	0.25	>16	0.5
Levofloxacin	32	32	0.5	>32	1
Linezolid	2	4	2	2	1
Minocycline	8	1	0.5	>8	8
Penicillin	8	>8	>8	>8	2
Pip/Tazo	16	>16	2	>16	2
Vancomycin	1	2	1	2	0.5
	All gram-negatives	*E. coli*	*K. pneumoniae*	*Enterobacter* spp.	*Acinetobacter* spp.
	n=4174	n=815	n=604	n=780	n=451
Tigecycline	4	0.5	1	1	2
Amikacin	8	8	4	4	>64
Amox/Clav	>32	32	32	>32	>32
Ampicillin	>32	>32	>32	>32	>32
Cefepime	16	8	16	4	32
Ceftazidime	32	≤8	16	>32	>32
Ceftriaxone	>64	64	64	64	>64
Imipenem	2	0.5	0.5	1	>16
Levofloxacin	8	>8	>8	4	>8
Minocycline	16	16	>16	8	8
Pip/Tazo	>64	32	128	64	>128

Conclusions: Tig had the lowest MIC_{90} vs. gram-positive isolates (incl. MRSA), and was nearly as active as imipenem vs. gram-negative strains (incl. ESBL+). It was also 4 to 128-fold more active than all comparators vs. *Acinetobacter*.

Introduction

Resistance rates of bacteria to modern-era antimicrobials are increasing worldwide. Portugal and Spain have experienced particularly high resistance rates for a number of key pathogens, which in recent years seems to have stabilized [1-3]. This study examined the changes in resistance among selected gram-positive and gram-negative bacteria in these two countries from the TEST program from its inception in 2004 through the latest compiled data in 2009.

Materials & Methods

- 5851 clinical isolates were collected and tested between January 2004 and March 2009 from 49 cumulative total investigative sites (51% participated in more than one year) from Spain and Portugal. 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]. MIC interpretive criteria followed published guidelines established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), where applicable [5]. Breakpoints used for tigecycline against *S. pneumoniae* are defined by the FDA [6].
- 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; *K. pneumoniae* ATCC 700603 (positive ESBL control); *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *P. aeruginosa* ATCC 27853; *E. 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 (2009) guidelines [7].

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Acknowledgements

This study was sponsored by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge the contributions of all investigators, laboratory personnel and from the members of the Tigecycline Evaluation Surveillance Trial program group worldwide.

Results

Table 1. *In vitro* activity of tigecycline and comparators against all gram-positive pathogens from 2004 to 2009.

		MIC (mcg/ml)				
Organism	Drug	MIC_{50}	MIC_{90}	%SUS*	%INT	%RES
S. aureus MRSA n=203	Tigecycline	0.12	0.25	100	0	0
	Amox/Clav	>8	>8	0	0	100
	Ampicillin	>16	>16	0	0	100
	Ceftriaxone	>64	>64	0	0	100
	Imipenem	4	>16	0	0	100
	Levofloxacin	8	32	8.37	0.99	90.64
	Linezolid	2	4	100	0	0
	Minocycline	≤0.25	1	87.19	3.94	8.87
	Penicillin	>8	>8	0	0	100
	Pip/Taz	>16	>16	0	0	100
	Vancomycin	1	2	100	0	0
S. aureus MSSA n=500	Tigecycline	0.12	0.25	100	0	0
	Amox/Clav	0.5	1	99.2	0	0.8
	Ampicillin	4	>16	13.6	0	86.4
	Ceftriaxone	2	4	99.2	0.6	0.2
	Imipenem	≤0.12	0.25	100	0	0
	Levofloxacin	0.12	0.5	94.2	3	2.8
	Linezolid	2	2	100	0	0
	Minocycline	≤0.25	0.5	98	1	1
	Penicillin	8	>8	10.4	0	89.6
	Pip/Taz	1	2	99.8	0	0.2
	Vancomycin	0.5	1	100	0	0
E. faecalis n= 343	Tigecycline	0.12	0.25	100	0	0
	Amox/Clav	0.5	1	99.71	0.29	0
	Ampicillin	1	2	99.42	0.58	0
	Ceftriaxone	>64	>64	na	na	na
	Imipenem	1	2	99.07	0.93	0
	Levofloxacin	1	>32	62.68	1.17	36.15
	Linezolid	1	2	100	0	0
	Meropenem	4	8	na	na	na
	Minocycline	8	>8	35.57	29.15	35.28
	Penicillin	2	4	100	0	0
	Pip/Tazo	2	8	na	na	na
	Tigecycline	0.06	0.25	100	0	0
E. faecium n= 109	Amox/Clav	>8	>8	21.1	5.5	73.39
	Ampicillin	>16	>16	20.18	0	79.82
	Ceftriaxone	>64	>64	na	na	na
	Imipenem	>16	>16	20.83	4.17	75
	Levofloxacin	>32	>32	22.02	4.59	73.39
	Linezolid	2	2	100	0	0
	Meropenem	>16	>16	na	na	na
	Minocycline	≤0.25	>8	76.15	8.26	15.6
	Penicillin	>8	>8	25.69	0	74.31
	Pip/Tazo	>16	>16	na	na	na
	Vancomycin	1	2	91.74	2.75	5.5
S. agalactiae n= 250	Tigecycline	0.03	0.12	99.6	0	0.4
	Ampicillin	≤0.06	0.12	100	0	0
	Ceftriaxone	0.06	0.12	100	0	0
	Imipenem	0.25	0.5	100	0	0
	Levofloxacin	0.5	1	97.2	2.4	0.4
	Linezolid	1	1	100	0	0
	Minocycline	8	>8	12.8	0.8	86.4
	Penicillin	≤0.06	0.12	100	0	0
	Pip/Taz	≤0.25	≤0.25	na	na	na
	Vancomycin	0.5	0.5	100	0	0

* SUS, INT or RES are defined by EUCAST. http://www.srga.org/eucastwt/MICTAB/index.html (July 2009).
* na = not available; intermediate and resistant breakpoints are undefined.

Table 2. *In vitro* activity of tigecycline and comparators against all *Enterobacteriaceae* pathogens from 2004 to 2009.

		MIC (mcg/ml)				
Organism	Drug	MIC_{50}	MIC_{90}	%SUS*	%INT	%RES
ESBL producers combined *(E. coli, K. pneumoniae, K. oxytoca)* n=173	Tigecycline	0.5	1	93.06	4.62	2.31
	Amikacin	2	16	89.02	8.67	2.31
	Amox/Clav	16	>32	36.42	0	63.58
	Ampicillin	>32	>32	0.58	0	99.42
	Cefepime	8	>32	13.29	39.88	46.82
	Ceftazidime	16	>32	0	49.13	50.87
	Ceftriaxone	>64	>64	1.73	1.16	97.11
	Imipenem	0.5	0.5	100	0	0
	Levofloxacin	8	>8	35.84	1.73	62.43
	Minocycline	4	>16	61.85	13.87	24.28
	Pip/Taz	4	>128	63.58	7.51	28.9
Enterobacter spp. n=780	Tigecycline	0.5	1	95.13	2.44	2.44
	Amikacin	2	4	97.69	1.28	1.03
	Amox/Clav	>32	>32	0.9	0	99.1
	Ampicillin	>32	>32	0	0	100
	Cefepime	≤0.5	4	82.44	13.33	4.23
	Ceftazidime	≤8	>32	0	74.49	25.51
	Ceftriaxone	0.25	64	66.54	3.08	30.38
	Imipenem	0.5	1	99.01	0.99	0
	Levofloxacin	0.06	4	88.97	0.77	10.26
	Minocycline	2	8	83.33	8.97	7.69
	Pip/Taz	2	64	72.31	5.77	21.92
Klebsiella spp n=788	Tigecycline	0.5	1	91.75	5.2	3.05
	Amikacin	1	4	96.19	1.65	2.16
	Amox/Clav	4	32	69.16	0	30.84
	Ampicillin	>32	>32	0.13	0	99.87
	Cefepime	≤0.5	8	80.84	9.64	9.52
	Ceftazidime	≤8	16	0	87.69	12.31
	Ceftriaxone	≤0.06	64	78.17	1.4	20.43
	Imipenem	0.5	0.5	100	0	0
	Levofloxacin	0.06	8	79.95	3.55	16.5
	Meropenem	≤0.06	0.12	97.77	0.86	1.37
	Minocycline	2	>16	75	8.38	16.62
	Pip/Taz	2	>128	76.4	3.68	19.92
E. coli n=815	Tigecycline	0.12	0.5	99.39	0.61	0
	Amikacin	2	8	96.32	2.58	1.1
	Amox/Clav	8	32	62.21	0	37.79
	Ampicillin	>32	>32	24.17	0	75.83
	Cefepime	≤0.5	8	82.33	10.18	7.48
	Ceftazidime	≤8	≤8	0	91.41	8.59
	Ceftriaxone	≤0.06	64	78.41	1.72	19.88
	Imipenem	0.25	0.5	100	0	0
	Levofloxacin	0.12	>8	60.49	2.94	36.56
	Minocycline	2	16	78.16	9.69	12.15
	Pip/Tazo	2	32	87.12	2.7	10.18
Serratia spp. n=305	Tigecycline	1	2	86.56	11.48	1.97
	Amikacin	2	4	98.69	1.31	0
	Amox/Clav	>32	>32	3.93	0	96.07
	Ampicillin	>32	>32	4.26	0	95.74
	Cefepime	≤0.5	≤0.5	95.74	2.3	1.97
	Ceftazidime	≤8	≤8	0	97.05	2.95
	Ceftriaxone	0.25	1	92.13	1.97	5.9
	Imipenem	0.5	2	100	0	0
	Levofloxacin	0.12	0.5	94.75	1.31	3.93
	Minocycline	4	8	77.7	15.74	6.56
	Pip/Tazo	1	4	96.07	0.98	2.95

* SUS, INT or RES are defined by EUCAST. http://www.srga.org/eucastwt/MICTAB/index.html (July 2009), where available.
* na = not available; intermediate and resistant breakpoints are undefined.

Table 3. *In vitro* activity of tigecycline and comparators against all fastidious respiratory pathogens from 2004 to 2009.

		MIC (mcg/ml)				
Organism	Drug	MIC50	MIC90	%SUS*	%INT	%RES
S. pneumoniae n=271	Tigecycline	0.03	0.12	82.22	na	na
	Amox/Clav	≤0.03	2	92.59	4.81	2.59
	Ampicillin	≤0.06	4	76.3	11.85	11.85
	Ceftriaxone	≤0.03	1	85.19	14.44	0.37
	Imipenem	≤0.12	0.5	100	0	0
	Levofloxacin	0.5	1	99.26	0	0.74
	Linezolid	≤0.5	1	100	0	0
	Minocycline	≤0.25	8	60.37	7.78	31.85
	Penicillin	≤0.06	2	60.74	35.56	3.7
	Pip/Taz	≤0.25	2	na	na	na
	Vancomycin	0.25	0.5	100	0	0
Haemophilus influenzae n=377	Tigecycline	0.25	0.5	65.25	na	na
	Amikacin	4	8	Na	na	na
	Amox/Clav	0.5	1	90.98	0	9.02
	Ampicillin	≤0.5	32	79.58	0	20.42
	Cefepime	≤0.5	≤0.5	0	0	100
	Ceftazidime	≤8	≤8	na	na	Na
	Ceftriaxone	≤0.06	≤0.06	97.35	0	2.65
	Imipenem	0.5	1	98.41	0	1.59
	Levofloxacin	0.015	0.03	100	0	0
	Minocycline	≤0.5	2	89.92	6.37	3.71
	Pip/Taz	≤0.06	≤0.06	99.47	0	0.53
Haemophilus influenzae Positive n=65	Tigecycline	0.25	0.5	69.23	na	Na
	Amikacin	4	8	na	na	Na
	Amox/Clav	1	2	89.23	0	10.77
	Ampicillin	32	>32	0	0	100
	Cefepime	≤0.5	≤0.5	0	0	100
	Ceftazidime	≤8	≤8	na	na	Na
	Ceftriaxone	≤0.06	≤0.06	92.31	0	7.69
	Imipenem	0.5	1	100	0	0
	Levofloxacin	0.015	0.12	100	0	0
	Minocycline	≤0.5	2	83.08	7.69	9.23
	Pip/Taz	≤0.06	0.12	96.92	0	3.08

* SUS, INT or RES are defined by EUCAST. http://www.srga.org/eucastwt/MICTAB/index.html (July 2009), where available. Tigecycline susceptibility defined by FDA (Tygacil®, 2009); na = not available; intermediate and resistant breakpoints are undefined.

Table 4. *In vitro* activity of tigecycline and comparators against all Gram-negative non-fermenting pathogens from 2004 to 2009.

		MIC (mcg/ml)				
Organism	Drug	MIC_{50}	MIC_{90}	%SUS*	%INT	%RES
Acinetobacter species n=451	Tigecycline	0.5	2	na	na	na
	Amikacin	8	>64	54.99	7.54	37.47
	Amox/Clav	>32	>32	na	na	na
	Ampicillin	>32	>32	na	na	na
	Cefepime	16	>32	36.59	22.17	41.24
	Ceftazidime	32	>32	29.71	17.29	52.99
	Ceftriaxone	>64	>64	18.4	16.63	64.97
	Imipenem	2	>16	56.9	4.31	38.79
	Levofloxacin	8	>8	26.61	4.88	68.51
	Meropenem	16	>16	35.82	7.46	56.72
	Minocycline	1	8	81.6	14.19	4.21
	Pip/Tazo	>128	>128	29.49	6.65	63.86
Pseudomonas aeruginosa n=653	Tigecycline	8	16	na	na	na
	Amikacin	4	8	91.58	3.52	4.9
	Amox/Clav	>32	>32	na	na	na
	Ampicillin	>32	>32	na	na	na
	Cefepime	4	16	80.24	na	19.76
	Ceftazidime	≤8	32	76.42	na	23.58
	Ceftriaxone	64	>64	15.93	31.85	52.22
	Imipenem	1	8	83.24	11.17	5.59
	Levofloxacin	1	>8	53.6	8.12	38.28
	Meropenem	1	16	72.78	14.56	12.66
	Minocycline	16	>16	na	na	na
	Pip/Tazo	4	128	77.64	na	22.36

* SUS, INT or RES are defined by EUCAST. http://www.srga.org/eucastwt/MICTAB/index.html (July 2009), where available. na = not available; intermediate and resistant breakpoints are undefined.

Conclusions

- Tigecycline demonstrated potent inhibitory activity against the gram-positive study organisms, comparable to that of vancomycin and linezolid during the first five years of monitoring in the TEST program.
- Tigecycline's MIC_{90}'s of 0.5 to 4 mcg/ml against the gram-negative study organisms were equivalent to those of imipenem.
- Tigecycline demonstrated potent inhibitory activity against all fastidious respiratory pathogens in the study with MIC_{90} values of 0.12 for *S. pneumoniae* and 0.5 for *H. influenzae*.