Trends in Tigecycline Activity against Global Respiratory Pathogens from the T.E.S.T. study, 2004 - 2008

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Revised Abstract

Background: Tigecycline, a glycylcycline has been approved for use in United States for complicated intra-abdominal, skin and soft tissue infections and community acquired pneumonia and has demonstrated success against a broad spectrum of species from these sources including respiratory pathogens. The Tigecycline Evaluation Surveillance Trial (T.E.S.T.) program is an ongoing global surveillance program. This report continues to evaluate trends in susceptibility of tigecycline against multiple pathogens obtained from respiratory sources in a global population between 2004-2008. **Methods:** 30,240 clinical isolates from respiratory sources were collected from 697 cumulative investigative sites in 55 countries. Clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum inhibitory concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI/FDA guidelines. **Results:** Summary data for tigecycline and key respiratory species by year are as follows:

	Tigecycline MIC_{90}/ %Susceptible				
	2004 (n=5176)	2005 (n=4788)	2006 (n=6381)	2007 (n=8227)	2008 (n=5668)
A. baumannii	1/na	2/na	2/na	2/na	2/na
E. cloacae	2/93.3	2/93.5	2/95.1	1/95.7	2/97.4
E. faecalis	0.25/100	0.25/100	0.25/100	0.12/100	0.25/100
E. coli	0.25/100	0.5/100	0.5/100	0.5/100	1/99.4
H. influenzae	0.25/95.1	0.5/85	0.5/73.9	0.5/60.8	0.5/50.6
K. pneumoniae	2/93.7	2/93.5	2/93.8	2/95.6	2/96.0
P. aeruginosa	>16/na	>16/na	>16/na	>16/na	16/na
S. marcescens	2/96.7	2/97.0	2/96.7	2/98.0	2/95.1
S. aureus	0.25/100	0.25/100	0.25/100	0.25/100	0.25/100
S. agalactiae	0.12/100	0.25/100	0.12/100	0.12/100	0.06/100
S. pneumoniae	0.25/70.2	0.12/89.9	0.06/91.7	0.12/89.8	0.12/87.8

%Susceptible as defined by FDA (Tygacil®, 2009) where available;
na = Breakpoints not defined.

Conclusions: Tigecycline demonstrated MIC_{90} values of $\leq$2 mcg/ml against the majority of key gram-negative respiratory pathogens and $\leq$0.25 mcg/ml against key gram-positive pathogens including several resistant phenotypes. These five years of data suggest that tigecycline may be an alternative agent against pathogens from respiratory sources.

Introduction

Respiratory tract infections (RTI) are one of the most common infection processes worldwide. In the United States alone, community acquired pneumonia (CAP) and chronic obstructive pulmonary disease (COPD) account for over 25 million cases annually and are leading causes of death. It is estimated that over 600 million people worldwide are afflicted with COPD (1). *Streptococcus pneumoniae* accounts for 15-40% of CAP cases and is a predominant pathogen in COPD. However, hospitalized patients may acquire a RTI while in hospital and a variety of gram-positive and gram-negative pathogens other than *S. pneumoniae* may be causative.

While outpatient management of RTIs using empirically selected oral antibiotics is common, nosocomial pathogens are managed more effectively with targeted therapy following culture (2).

Tigecycline possesses a broad spectrum of coverage to many pathogens causing RTI including many gram-positive and gram-negatives (3).

This report describes the *in vitro* activity of tigecycline against RTI pathogens isolated globally between 2004 and 2008.

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 sputum, tracheal secretions, bronchial lavage and other defined respiratory sources.
- Isolates were collected between 2004 and 2008 from a total of 697 cumulative sites in 55 countries from Europe, Asia, South Pacific, North America, Latin America and Africa.
- Isolates were identified to the species level at each site using local laboratory criteria.
- Isolate collection, transport, confirmatory identification and data base 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 broth microdilution 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 (9.06-64), meropenem (0.12-16), levofloxacin (0.008-8), minocycline (0.5-16), tigecycline (0.008-16) and piperacillin-tazobactam (0.06/4-128/4).
- The following agents were included in the gram-positive panel with expressed dilution ranges (mcg/ml): amoxicillin-clavulanic acid (0.12/0.06-32/16), ampicillin (0.06-16), ceftriaxone (0.06-64), linezolid (0.5-8), meropenem (0.12-16), levofloxacin (0.008-8), minocycline (0.5-16), tigecycline (0.008-16), penicillin (0.06-8), piperacillin-tazobactam (0.06/4-128/4) and vancomycin (0.12-32).
- 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), *S. pneumoniae* (ATCC 49619) and *Pseudomonas aeruginosa* (ATCC 27853).

References

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Results

The *in vitro* activity of tigecycline against 30,240 respiratory tract pathogens between 2004 and 2008 is shown in Table 1 below.

Table 1. *In vitro* activity of tigecycline[a] against respiratory pathogens globally 2004-2008.

Year Collected	Organism	N	MIC_{90} (mcg/ml)	%S	%I	%R
2004	*Acinetobacter baumannii*	494	1	na	na	na
(Total N=5176)	*Enterobacter cloacae*	415	2	93.3	4.8	1.9
	Enterococcus faecalis	39	0.25	100	na	na
	Escherichia coli	266	0.25	100	0	0
	Haemophilus influenzae	1013	0.25	95.1	na	na
	Klebsiella pneumoniae	474	2	93.7	5.7	0.6
	Pseudomonas aeruginosa	831	>16	na	na	na
	Serratia marcescens	367	2	96.7	3	0.3
	Staphylococcus aureus	551	0.25	100	na	na
	Streptococcus agalactiae	44	0.12	100	na	na
	Streptococcus pneumoniae	682	0.25	70.2	na	na
2005	*Acinetobacter baumannii*	469	2	na	na	na
(Total N=4788)	*Enterobacter cloacae*	370	2	93.5	4.3	2.2
	Enterococcus faecalis	33	0.25	100	na	na
	Escherichia coli	200	0.5	100	0	0
	Haemophilus influenzae	852	0.5	85	na	na
	Klebsiella pneumoniae	416	2	93.5	6	0.5
	Pseudomonas aeruginosa	782	>16	na	na	na
	Serratia marcescens	369	2	97	2.2	0.8
	Staphylococcus aureus	533	0.25	100	na	na
	Streptococcus agalactiae	44	0.25	100	na	na
	Streptococcus pneumoniae	720	0.12	89.9	na	na
2006	*Acinetobacter baumannii*	583	2	na	na	na
(Total N=6381)	*Enterobacter cloacae*	489	2	95.1	4.3	0.6
	Enterococcus faecalis	51	0.25	100	na	na
	Escherichia coli	335	0.5	100	0	0
	Haemophilus influenzae	1193	0.5	73.9	na	na
	Klebsiella pneumoniae	617	2	93.9	5.7	0.5
	Pseudomonas aeruginosa	1096	>16	na	na	na
	Serratia marcescens	460	2	96.8	2.6	0.7
	Staphylococcus aureus	571	0.25	100	na	na
	Streptococcus agalactiae	62	0.12	100	na	na
	Streptococcus pneumoniae	924	0.06	91.7	na	na
2007	*Acinetobacter baumannii*	830	2	na	na	na
(Total N=8277)	*Enterobacter cloacae*	639	1	95.5	3.9	0.6
	Enterococcus faecalis	46	0.12	100	na	na
	Escherichia coli	416	0.5	100	0	0
	Haemophilus influenzae	1611	0.5	60.8	na	na
	Klebsiella pneumoniae	821	2	95.6	4.1	0.2
	Pseudomonas aeruginosa	1376	>16	na	na	na
	Serratia marcescens	581	2	97.9	1.6	0.5
	Staphylococcus aureus	812	0.25	100	na	na
	Streptococcus agalactiae	73	0.12	100	na	na
	Streptococcus pneumoniae	1072	0.12	89.8	na	na
2008	*Acinetobacter baumannii*	631	2	na	na	na
(Total N=5668)	*Enterobacter cloacae*	488	2	96.9	2.3	0.8
	Enterococcus faecalis	34	0.25	100	na	na
	Escherichia coli	325	1	99.4	0.3	0.3
	Haemophilus influenzae	1024	0.5	50.6	na	na
	Klebsiella pneumoniae	607	2	95.9	3.5	0.7
	Pseudomonas aeruginosa	978	16	na	na	na
	Serratia marcescens	410	2	95.4	3.9	0.7
	Staphylococcus aureus	521	0.25	100	na	na
	Streptococcus agalactiae	42	0.06	100	na	na
	Streptococcus pneumoniae	608	0.12	87.8	na	na

[a] Tigecycline % S, I, R defined by FDA breakpoints, Tygacil® package insert, 2009. na = not applicable; breakpoints not defined.

Conclusions

- Tigecycline demonstrated an MIC_{90} of $\leq$2 mcg/ml against all key RTI gram-negative bacilli (excluding *P. aeruginosa*) including *A. baumannii*.
- Tigecycline demonstrated an MIC_{90} of $\leq$0.25 mcg/ml against all key gram-positive RTI cocci including *E. faecalis* and *S. aureus*.
- During 2004-2008 tigecycline maintained its activity against a broad range of pathogens from respiratory sources.