

Revised Abstract

Background: Increasing rates of macrolide resistance in *Streptococcus pneumoniae* (SPN) have been reported worldwide. Macrolide resistance in SPN is mediated by one or both of two main mechanisms: methylation of the ribosomal target site (encoded by the ermB gene) and drug efflux (encoded by the mefA or the mefE gene). Isolates expressing ermB tend to have high-level resistance to macrolides, while those expressing mefA or mefE show lower-level resistance. In addition, SPN isolates containing both mechanisms show high rates of resistance to multiple antibiotic classes. The objective of this study was to evaluate the *in vitro* efficacy of tigecycline and comparators against recent erythromycin-resistant SPN from the Asian Tigecycline Evaluation and Surveillance Trial (TEST), an ongoing global surveillance designed to follow trends in antimicrobial activity. **Methods:** 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 and FDA guidelines. **Results:** Of 110 SPN collected in Asia in 2009-2010, 75 (68.2%) were erythromycin-resistant. MIC results (mcg/ml) and % susceptible (S), intermediate (I) and resistant (R) are shown in the table below.

N=75	MIC ₅₀	MIC ₉₀	%S	%I	%R
Tigecycline	0.015	0.03	100	na	na
AmoxClav	2	> 8	62.7	13.3	24.0
Ceftriaxone	1	8	57.3	28.0	14.7
Erythromycin	64	> 64	0	0	100
Levofloxacin	1	1	97.3	0	2.7
Linezolid	1	2	100	na	na
Meropenem	0.5	2	41.3	21.3	37.3
Penicillin	2	8	28.0	17.3	54.7
Vancomycin	0.5	1	100	na	na

na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*.

Conclusions: Greater than 97% of the macrolide-resistant *S. pneumoniae* from Asia tested were susceptible to tigecycline, vancomycin, linezolid and levofloxacin. Tigecycline demonstrated the lowest *in vitro* MIC₅₀ and MIC₉₀ values of all compounds tested in this study, suggesting that tigecycline may be effective against this important clinical pathogen and resistant phenotype.

Introduction

Infections due to *S. pneumoniae* continue to evolve worldwide and are a major cause of morbidity and mortality. Antimicrobial resistance in *S. pneumoniae* poses a major challenge for the management of pneumococcal infections including pneumonia, otitis media, sinusitis, meningitis, and sepsis. Macrolide resistance among *S. pneumoniae* isolates has increased, with considerable geographical variation among the genotypes and phenotypes involved. New guidelines for the management of in-patient and out-patient community acquired pneumonia have recently been published [1-4]. This study was undertaken to document the current extent of macrolide-resistance and the *in vitro* activity of tigecycline against *S. pneumoniae* with macrolide-resistant determinants from isolates from Asia collected in 2009-2010. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trial (TEST) program.

Materials & Methods

- All isolates were derived from blood, CNS, respiratory, sinuses, sputum, middle ear, and other defined sources. Only one isolate per patient was accepted into the study.
- Clinical isolates were collected and tested between January 2009 and December 2010 from investigative sites in five countries (China, Singapore, South Korea, Malaysia and Taiwan). Isolates were identified to the species level and tested at each site by the participating laboratory.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory site criteria.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [5]. Tigecycline was supplied by Pfizer, Inc. (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer TREK (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12/0.06-32/16); ceftriaxone (0.06-64); erythromycin (0.015-64); linezolid (0.5-8); levofloxacin (0.008-8); meropenem (0.12-16); tigecycline (0.008-16); and penicillin (0.06-8). MIC interpretive criteria followed guidelines published by the CLSI [6], where available. Tigecycline breakpoints are defined in Federal Drug Administration (FDA) product information [7].
- Quality controls (QC) were performed by each testing site on each day of testing using *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2010) guidelines [6].

References

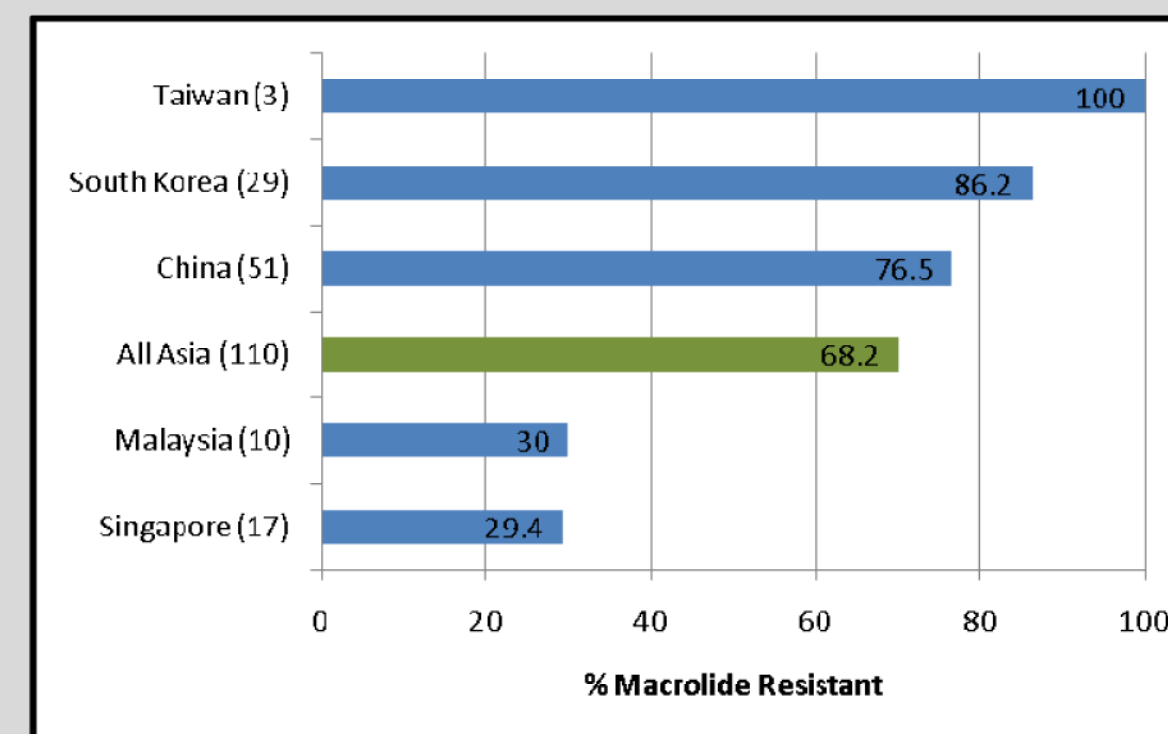
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Results

Figure 1. Macrolide resistant rate (%) for 100 isolates of *S. pneumoniae* from Asia categorized by country.*



*Macrolide resistance based upon the susceptibility to erythromycin (MIC=1 mcg/ml)

Table 2. *In vitro* activity of tigecycline and comparators against 75 macrolide-resistant *S. pneumoniae* from Asia, 2009-2010.

Drug	(mcg/ml)		%S*	%I	%R
	MIC ₅₀	MIC ₉₀			
Tigecycline	0.015	0.03	100	na	na
AmoxClav	2	> 8	62.7	13.3	24.0
Ceftriaxone	1	8	57.3	28.0	14.7
Erythromycin	64	> 64	0	0	100
Levofloxacin	1	1	97.3	0	2.7
Linezolid	1	2	100	na	na
Meropenem	0.5	2	41.3	21.3	37.3
Penicillin	2	8	28.0	17.3	54.7
Vancomycin	0.5	1	100	na	na

*Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®; 2010). na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*.

Table 4. *In vitro* activity of tigecycline and comparators against 5 macrolide-resistant *S. pneumoniae* from Singapore, 2009-2010.

Drug	(mcg/ml)		%S*	%I	%R
	MIC ₅₀	MIC ₉₀			
Tigecycline	--	--	100	na	na
AmoxClav	--	--	100	0	0
Ceftriaxone	--	--	100	0	0
Erythromycin	--	--	0	0	100
Levofloxacin	--	--	100	0	0
Linezolid	--	--	100	na	na
Meropenem	--	--	60.0	20.0	20.0
Penicillin	--	--	40.0	20.0	40.0
Vancomycin	--	--	100	na	na

*Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®; 2010). na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*. (--) MIC_{50/90} not calculated for N<20.

Table 6. *In vitro* activity of tigecycline and comparators against 3 macrolide-resistant *S. pneumoniae* from Taiwan, 2009-2010.

Drug	(mcg/ml)		%S	%I	%R
	MIC ₅₀	MIC ₉₀			
Tigecycline	--	--	100	na	na
AmoxClav	--	--	66.7	33.3	0
Ceftriaxone	--	--	66.7	33.3	0
Erythromycin	--	--	0	0	100
Levofloxacin	--	--	100	0	0
Linezolid	--	--	100	na	na
Meropenem	--	--	33.3	0.0	66.7
Penicillin	--	--	0	33.3	66.7
Vancomycin	--	--	100	na	na

*Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®; 2010). na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*. (--) MIC_{50/90} not calculated for N<20.

Table 1. *In vitro* activity of tigecycline and comparators against 110 *S. pneumoniae* from Asia, 2009-2010.

Drug	(mcg/ml)		%S*	%I	%R
	MIC ₅₀	MIC ₉₀			
Tigecycline	0.015	0.03	100	na	na
AmoxClav	0.06	8	73.6	9.1	17.3
Ceftriaxone	0.06	2	70.9	19.1	10.0
Erythromycin	64	> 64	31.8	0	68.2
Levofloxacin	1	1	98.2	0	1.8
Linezolid	1	1	100	na	na
Meropenem	≤0.12	1	59.1	15.5	25.5
Penicillin	≤0.06	4	50.0	11.8	38.2
Vancomycin	0.5	0.5	100	na	na

*Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®; 2010). na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*.

Table 3. *In vitro* activity of tigecycline and comparators against 39 macrolide-resistant *S. pneumoniae* from China, 2009-2010.

Drug	(mcg/ml)		%S*	%I	%R
	MIC ₅₀	MIC ₉₀			
Tigecycline	0.015	0.03	100	na	na
AmoxClav	0.12	8	66.7	18.0	15.4
Ceftriaxone	0.5	4	71.8	18.0	10.3
Erythromycin	64	> 64	0	0	100
Levofloxacin	1	1	94.9	0	5.1
Linezolid	≤0.5	1	100	na	na
Meropenem	≤0.12	1	61.5	18.0	20.5
Penicillin	0.5	4	43.6	25.6	30.8
Vancomycin	0.25	0.5	100	na	na

*Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®; 2010). na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*.

Table 5. *In vitro* activity of tigecycline and comparators against 25 macrolide-resistant *S. pneumoniae* from South Korea, 2009-2010.

Drug	(mcg/ml)		%S	%I	%R
	MIC ₅₀	MIC ₉₀			
Tigecycline	0.015	0.03	100	na	na
AmoxClav	4	> 8	44.0	8.0	48.0
Ceftriaxone	2	32	24.0	48.0	28.0
Erythromycin	64	> 64	0	0	100
Levofloxacin	1	1	100	0	0
Linezolid	1	2	100	na	na
Meropenem	1	4	8.0	24.0	68.0
Penicillin	4	8	4.0	4.0	92.0
Vancomycin	0.5	1	100	na	na

*Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®; 2010). na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*.

Table 7. *In vitro* activity of tigecycline and comparators against 3 macrolide-resistant *S. pneumoniae* from Malaysia, 2009-2010.

Drug	(mcg/ml)		%S	%I	%R
	MIC ₅₀	MIC ₉₀			
Tigecycline	--	--	100	na	na
AmoxClav	--	--	100	0	0
Ceftriaxone	--	--	66.7	33.3	0
Erythromycin	--	--	0	0	100
Levofloxacin	--	--	100	0	0
Linezolid	--	--	100	na	na
Meropenem	--	--	33.3	66.7	0
Penicillin	--	--	33.3	0	66.7
Vancomycin	--	--	100	na	na

*Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®; 2010). na = Only a susceptible breakpoint is defined for this drug against *S. pneumoniae*. (--) MIC_{50/90} not calculated for N<20.

Conclusions

- The macrolide-resistant rate for the 110 *S. pneumoniae* collected from Asia in 2009-2010 from TEST investigative sites is 68.2%. This compares to 59.3% in 2001 [8]. Rates ranged from 29.4% in Singapore to 86.2% in S. Korea and 100% in Taiwan, although the numbers from the Taiwan was from a single site (n=3).
- Tigecycline, linezolid, and vancomycin demonstrated potent *in vitro* activity against all *S. pneumoniae* including macrolide-resistant isolates with 100% susceptible. Levofloxacin demonstrated >98% susceptible for all isolates including macrolide-resistant isolates.
- The *in vitro* activity of tigecycline in this study suggests that tigecycline is a potent antimicrobial agent that may be beneficial in the treatment of infections due to difficult to treat macrolide-resistant *S. pneumoniae*.