

Revised Abstract

Background: Nosocomial pneumonia is a major hospital infection control problem due to its frequency, high mortality rate, and prolongation of hospital stay with attendant additional costs. Monitoring of antimicrobial resistance is necessary for effective therapy. The Tigecycline Evaluation and Surveillance Trial (TEST) program has monitored the activity of tigecycline and comparative antimicrobial agents in ICU patients since 2004.

Methods: 580 ICUs in North America (United States 546; Canada 34) collected 5,196 nosocomial pneumonia isolates from 2004-2009. MICs were determined by broth microdilution, and interpreted using current CLSI and FDA guidelines. Susceptibility rates for isolates were determined for species with ≥10 isolates in every year of evaluation. Differences were evaluated for significance using the Cochran-Armitage Trend Test.

Results: Tigecycline *in vitro* activity against N.A. ICU pneumonia isolates:

Nosocomial Organism (n)	Tigecycline - %Sus/MIC ₅₀ (mcg/ml)					
	2004	2005	2006	2007	2008	2009
<i>A. baumannii</i> (608)	na/1	na/2	na/1	na/2	na/2	na/1
<i>E. aerogenes</i> (278)	95.4/1	91.8/2	90/2	97.1/1	97/2	100/1
<i>E. cloacae</i> (552)	93/2	94.9/1	98.2/1	92.5/2	93.4/2	93.6/2
<i>E. coli</i> (329)	100/0.25	100/0.25	100/0.5	100/0.25	100/1	100/0.5
ESBL+ (14)	100/0.25	100/2	100/0.25	100/0.5	100/0.25	100/0.25
<i>K. oxytoca</i> (184)	100/1	92.3/1	100/0.5	98.2/1	94.7/2	100/0.5
ESBL+ (7)	100/1	66.7/4	--	100/0.5	--	--
<i>K. pneumoniae</i> (620)	94.7/1	92.9/2	88.3/4	93/2	100/1	98.6/1
ESBL+ (80)	100/1	92.9/2	84.6/4	100/2	100/1	100/1
<i>P. aeruginosa</i> (962)	na/>16	na/>16	na/>16	na/>16	na/16	na/16
<i>S. marcescens</i> (433)	96.3/2	96.3/2	97/1	96.6/2	91.8/2	91.4/2
<i>S. aureus</i> , MSSA (309)	100/0.25	100/0.25	100/0.25	100/0.25	100/0.25	100/0.5
<i>S. aureus</i> , MRSA (284)	100/0.12	100/0.12	100/0.12	100/0.12	100/0.25	100/0.25
<i>S. pneumoniae</i> (481)	75.3/0.25	88.7/0.12	94.2/0.06	92.2/0.06	93.4/0.06	100/0.03

na = breakpoints not defined; species with n's <10 are not shown.

Conclusions:

- P. aeruginosa* was the most frequently isolated nosocomial pneumonia isolate in this North American study.
- Tigecycline retains markedly consistent *in vitro* activity over the 6 years of this study against gram-negative *Enterobacteriaceae*, including ESBL producers, and gram-positive nosocomial pneumonia isolates from ICUs. No increasing resistance patterns were noted since 2004 (p-value >0.05).
- Tigecycline demonstrated significant *in vitro* activity against *A. baumannii*, including multi-drug resistant strains, with MIC₉₀ values of 1 to 2 mcg/ml. Tigecycline has little activity against *P. aeruginosa*.

Introduction

Nosocomial, or hospital acquired pneumonia (HAP), refers to any pneumonia contracted by a patient in a hospital at least 48–72 after being admitted. It is usually caused by a bacterial infection, rather than a virus. Nosocomial pneumonia is the second most common nosocomial infection (urinary tract infection is the most common) and accounts for 15–20% of the total [1,2]. HAP is also the most common cause of death among nosocomial infections and is the primary cause of death in intensive care units as well as the leading cause of prolonged hospital stay and costs [2].

This study examined the *in vitro* activity of tigecycline and comparators against the most frequently isolated bacterial pathogens from nosocomial infections in ICU settings from the United States and Canada. This study is part of the larger, ongoing global Tigecycline Evaluation and Surveillance Trial.

Materials & Methods

- A total of 5,196 clinical isolates were collected and tested between January 2004 and December 2009 from 580 cumulative sites in the United States (546) and Canada (34). Isolates were identified to the species level and MICs determined at each site by the participating laboratory.
- All Isolates were chosen from ICU patients with specimens taken from bronchial and tracheal washings, lung biopsy, purulent sputum, or thoracentesis.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [3]. MIC interpretive criteria followed published guidelines established by the CLSI [4], where available, and the FDA (tigecycline) [5]. Statistical comparisons were performed using Cochran-Armitage Trend Test (two-tailed).
- Quality controls (QC) were performed by each testing site on each day of testing using the following ATCC control strains: *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, and *E. coli* ATCC 35218. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2011) guidelines [4].

References

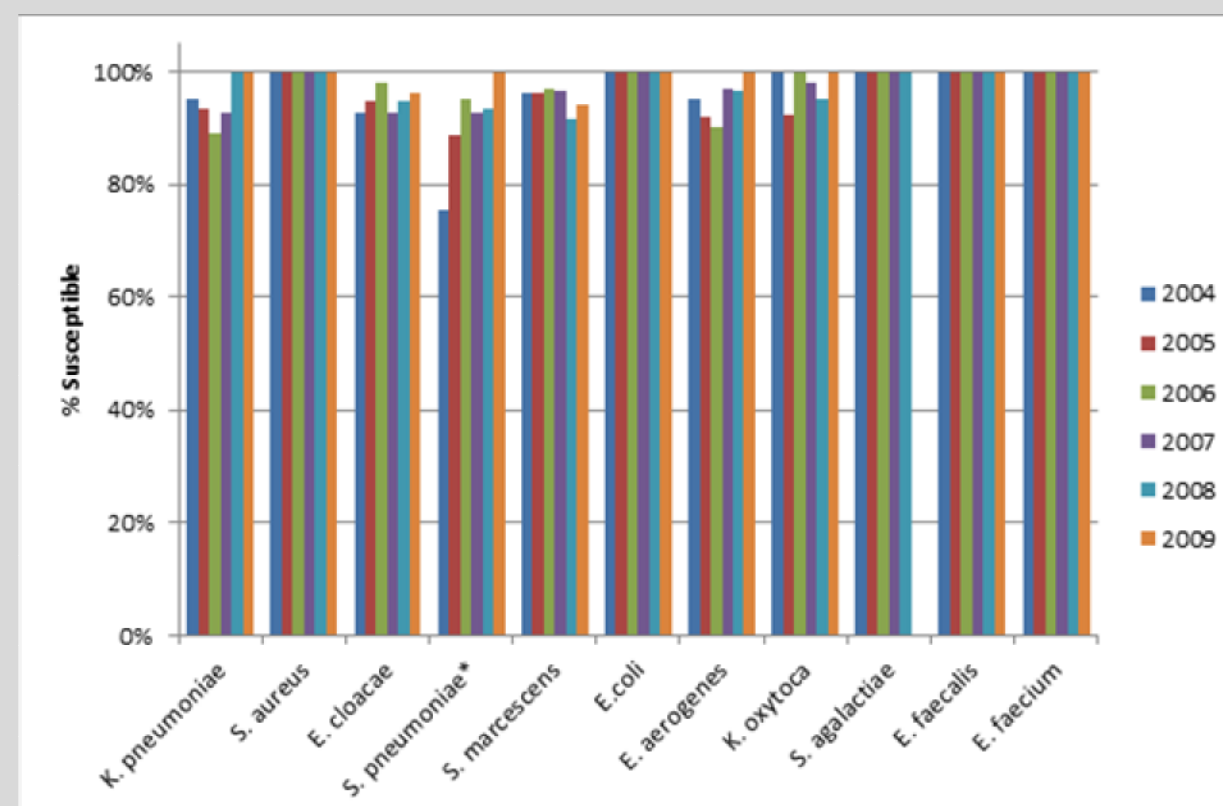
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Results

Table 1. Number of nosocomial species collected and percent of total for each species.

Organism	N	% of Total N	Organism	N	% of Total N
<i>Pseudomonas aeruginosa</i>	962	18.5	<i>Serratia liquefaciens</i>	7	0.13
<i>Klebsiella pneumoniae</i>	620	11.9	<i>Acinetobacter calcoaceticus</i>	4	0.08
<i>Acinetobacter baumannii</i>	608	11.7	<i>Enterobacter asburiae</i>	4	0.08
<i>Staphylococcus aureus</i>	593	11.4	<i>Acinetobacter anitratus</i>	3	0.06
<i>Enterobacter cloacae</i>	552	10.6	<i>Acinetobacter, non-speciated</i>	3	0.06
<i>Streptococcus pneumoniae</i>	481	9.3	<i>Enterobacter sakazakii</i>	3	0.06
<i>Serratia marcescens</i>	433	8.3	<i>Acinetobacter junii</i>	2	0.04
<i>Escherichia coli</i>	329	6.3	<i>Klebsiella ornithinolytica</i>	2	0.04
<i>Enterobacter aerogenes</i>	278	5.4	<i>Klebsiella ozaenae</i>	2	0.04
<i>Klebsiella oxytoca</i>	184	3.5	<i>Serratia, non-speciated</i>	2	0.04
<i>Streptococcus agalactiae</i>	47	0.9	<i>Acinetobacter johnsonii</i>	1	0.02
<i>Enterococcus faecalis</i>	42	0.8	<i>Enterobacter intermedium</i>	1	0.02
<i>Enterococcus faecium</i>	14	0.3	<i>Serratia fonticola</i>	1	0.02
<i>Enterobacter agglomerans</i>	9	0.17	<i>Serratia odorifera</i>	1	0.02
<i>Acinetobacter lwoffii</i>	7	0.13	<i>Serratia rubidaea</i>	1	0.02
			Total N	5196	100

Figure 2. Trend in susceptibility for tigecycline against nosocomial, non-pseudomonal isolates in North America, 2004-2009.



* Represents a significant change in % susceptible from 2004-2009 (p<0.001; Cochran-Armitage Trend Test/Two-tailed).

Figure 1. Distribution of 5,196 nosocomial isolates characterized by ICU.

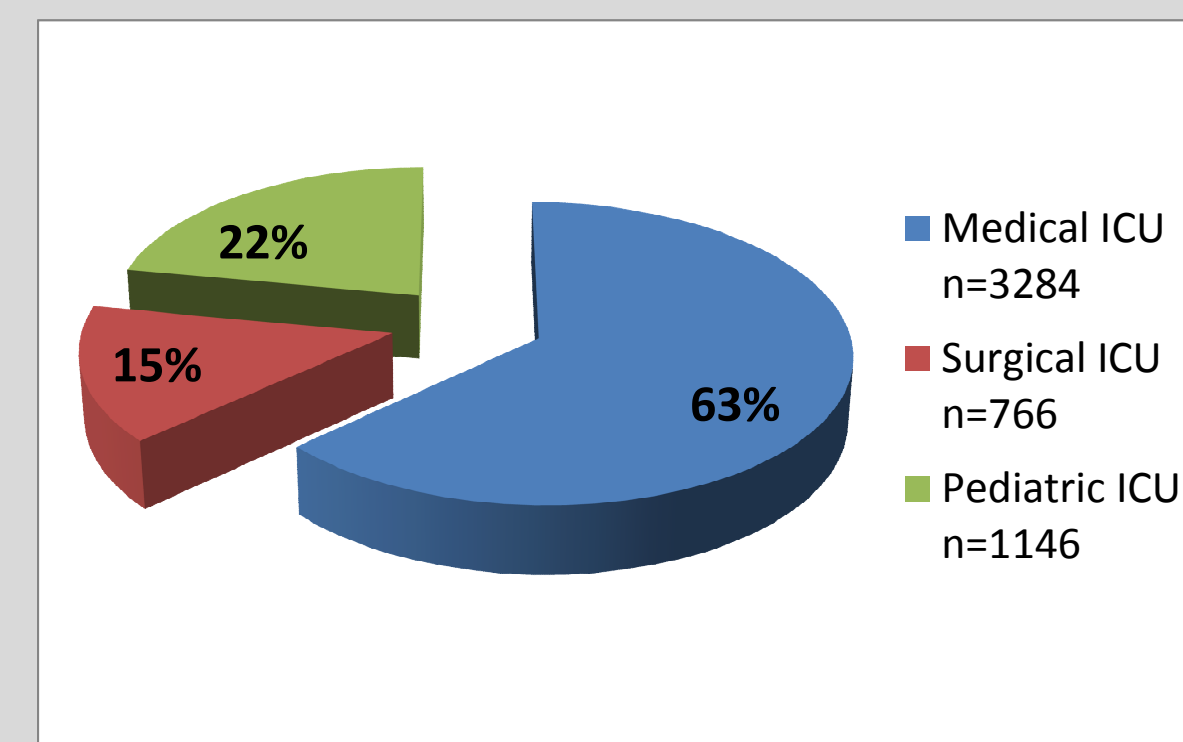


Table 2. In vitro activity (mcg/ml) of tigecycline against 5,196 nosocomial infection isolates from North American ICUs, 2004-2009.

Organism/Phenotype	N†	mcg/ml				
		MIC ₅₀	MIC ₉₀	%Sus‡	%Int	%Res
<i>Acinetobacter baumannii</i>	608	0.5	2	na	na	na
MDR	228	1	2	na	na	na
<i>Enterobacter aerogenes</i>	278	0.5	1	94.6	4.7	0.7
<i>Enterobacter cloacae</i>	552	0.5	2	94.6	4.4	1.1
<i>Enterococcus faecalis</i>	42	0.12	0.12	100	--	0
<i>Enterococcus faecium</i>	14	0.06	0.12	100	--	0
VRE	12	0.06	0.12	100	0	0
<i>Escherichia coli</i>	329	0.12	0.5	100	0	0
ESBL+	14	0.25	0.5	100	0	0
<i>Klebsiella oxytoca</i>	184	0.25	1	97.3	2.7	0
ESBL+	7	†MIC range: 0.03 – 0.25				
<i>Klebsiella pneumoniae</i>	620	0.5	2	94.0	5.3	0.7
ESBL+	80	1	2	96.3	3.8	0
<i>Pseudomonas aeruginosa</i>	962	8	≥16	na	na	na
<i>Serratia marcescens</i>	433	1	2	95.8	3.7	0.5
<i>Staphylococcus aureus</i> , MRSA	309	0.12	0.25	100	--	0
<i>Staphylococcus aureus</i> , MSSA	284	0.12	0.25	100	--	0
<i>Streptococcus agalactiae</i>	47	0.03	0.12	100	--	--
<i>Streptococcus pneumoniae</i>	481	0.03	0.12	90.0	--	--

‡Species with n's <10 are not shown (17 species totaling 53 isolates).

†Breakpoints for tigecycline defined by FDA (Tygacil®, 2010). -- = breakpoints are not available; na = no breakpoints defined.

‡Statistics not calculated for n's <10.

Phenotypes: MDR = multi-drug resistant (resistant to 3 or more drug classes); VRE = vancomycin-resistant enterococci; ESBL+ = extended-spectrum beta-lactamase producer; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*.

Conclusions

- At 18.5% of the total collected isolates, *P. aeruginosa* was the most frequently isolated nosocomial pneumonia pathogen in this North American study followed closely by *K. pneumoniae* (11.9%), *A. baumannii* (11.7%), and *S. aureus* (11.4%).
- Tigecycline retains markedly consistent *in vitro* activity over the 6 years of this study with percents susceptible >90% against all gram-negative *Enterobacteriaceae*, including ESBL producers, and gram-positive nosocomial pneumonia isolates from ICUs including VREs and MRSA. No increasing resistance patterns are noted for any species since 2004 (p-value >0.05).
- Tigecycline demonstrated significant *in vitro* activity against *A. baumannii*, including multi-drug resistant strains, with MIC₅₀ and MIC₉₀ values ranging from 0.5 to 2 mcg/ml. As expected, tigecycline demonstrated limited activity against *P. aeruginosa*.

Acknowledgements

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