

Revised Abstract

Background: The increasing incidence of antimicrobial resistance represents a major threat to hospitalized patients, especially those in intensive care units (ICUs). The Tigecycline Evaluation and Surveillance Trial (TEST) program has monitored the *in vitro* activity of tigecycline and comparators since 2004. The current study investigated the activity of tigecycline and comparators against isolates from medical and surgical intensive care units isolated during 2009-2010. **Methods:** All isolates (n=9,015) were identified to species level by participating sites in 48 countries and confirmed by the central laboratory. Isolates came from medical and surgical ICUs. Minimum inhibitory concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI or FDA (tigecycline) guidelines. **Results:** MIC₉₀ (µg/ml) and %S of select groups of isolates are shown below.

Drug	<i>Enterobacteriaceae</i> (n=3,527)		<i>Acinetobacter</i> spp (n=1,172)		<i>P. aeruginosa</i> (n=1,271)	
	MIC ₉₀	%S	MIC ₉₀	%S	MIC ₉₀	%S
Tigecycline	2	94.1	2	na	16	na
Amikacin	8	95.1	>64	42.2	64	84.1
Cefepime	16	87.6	>32	32.7	32	66.9
Meropenem	0.25	96.6	>16	42.2	>16	67.6
Levofloxacin	>8	81.8	>8	29.4	>8	58.3
Minocycline	>16	54.7	8	76.3	>16	na
Pip-tazo	>128	62.8	>128	25.9	>128	76.0

Drug	<i>S. aureus</i> (n=909)		<i>Enterococcus</i> spp (n=809)	
	MIC ₉₀	%S	MIC ₉₀	%S
Tigecycline	0.5	100	0.25	99.5
Levofloxacin	32	57.3	>32	38.7
Linezolid	4	100	2	99.6
Minocycline	4	90.2	>8	40.3
Vancomycin	1	99.7	>32	88.5

Conclusion: Meropenem was the most active compound against *Enterobacteriaceae*, while tigecycline had the lowest MIC₉₀ against gram-positive organisms, with activity comparable to linezolid and vancomycin. Tigecycline's *in vitro* activity was comparable to or greater than most commonly prescribed broad spectrum antimicrobials for all ICU strains tested in this study, including methicillin resistant *S. aureus* and extended spectrum beta-lactamase producers.

Introduction

Bacterial resistance presents a challenge to clinicians with increasing multi-drug resistance worldwide. This is especially true of intensive care units (ICUs) where antibiotic resistance is generally higher than non-ICU settings [1]. Early targeted antibiotic therapy is an important factor in managing patient outcomes. The Tigecycline Evaluation and Surveillance Trial (TEST) program has been monitoring infections for epidemiologic and antimicrobial susceptibility trends globally since 2004. This study was designed to assist clinicians, interventionists, epidemiologists, and pharmacologists in their assessments of current trends and developments in the susceptibilities of commonly utilized antimicrobial agents within hospital settings, particularly as they pertain to variations between ICU and non-ICU settings.

Materials & Methods

- A total of 9,015 clinical isolates from medical and surgical intensive care units were collected and tested between January 2009 and December 2010 from 1,667 cumulative sites in 61 countries. Isolates were identified to the species level and MICs determined at each site by the participating laboratory using supplied dried broth microdilution panels.
- 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 [2]. MIC interpretive criteria followed published guidelines established by the CLSI [3], where available. FDA interpretive guidelines were used for tigecycline [4].
- Quality controls (QC) were performed by each testing site on each day of testing using appropriate ATCC control strains. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines [3].

Table 1. Top twelve species isolated in surgical and medical intensive care units from a global population, 2009-2010.

Organism	N	% of Total N
<i>Pseudomonas aeruginosa</i>	1271	14.1
<i>Acinetobacter baumannii</i>	1139	12.6
<i>Klebsiella pneumoniae</i>	1073	11.9
<i>Enterobacter cloacae</i>	950	10.5
<i>Escherichia coli</i>	929	10.3
<i>Staphylococcus aureus</i>	909	10.1
<i>Serratia marcescens</i>	575	6.4
<i>Enterococcus faecalis</i>	462	5.1
<i>Haemophilus influenzae</i>	371	4.1
<i>Enterococcus faecium</i>	325	3.6
<i>Streptococcus pneumoniae</i>	308	3.4
<i>Streptococcus agalactiae</i>	150	1.7
Others	553	6.2
Total	9015	100

* Others includes the combined totals from 22 different species.

References

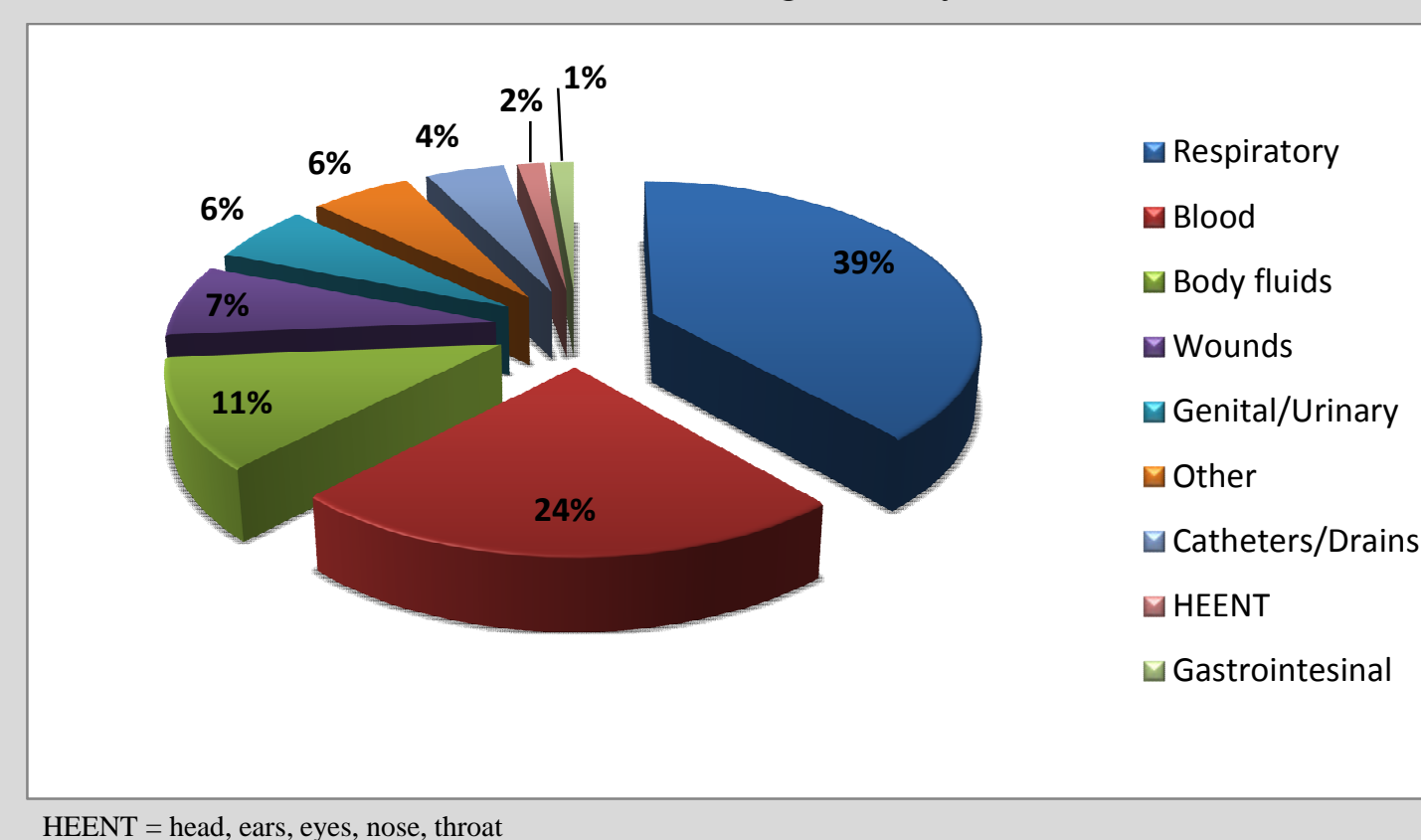
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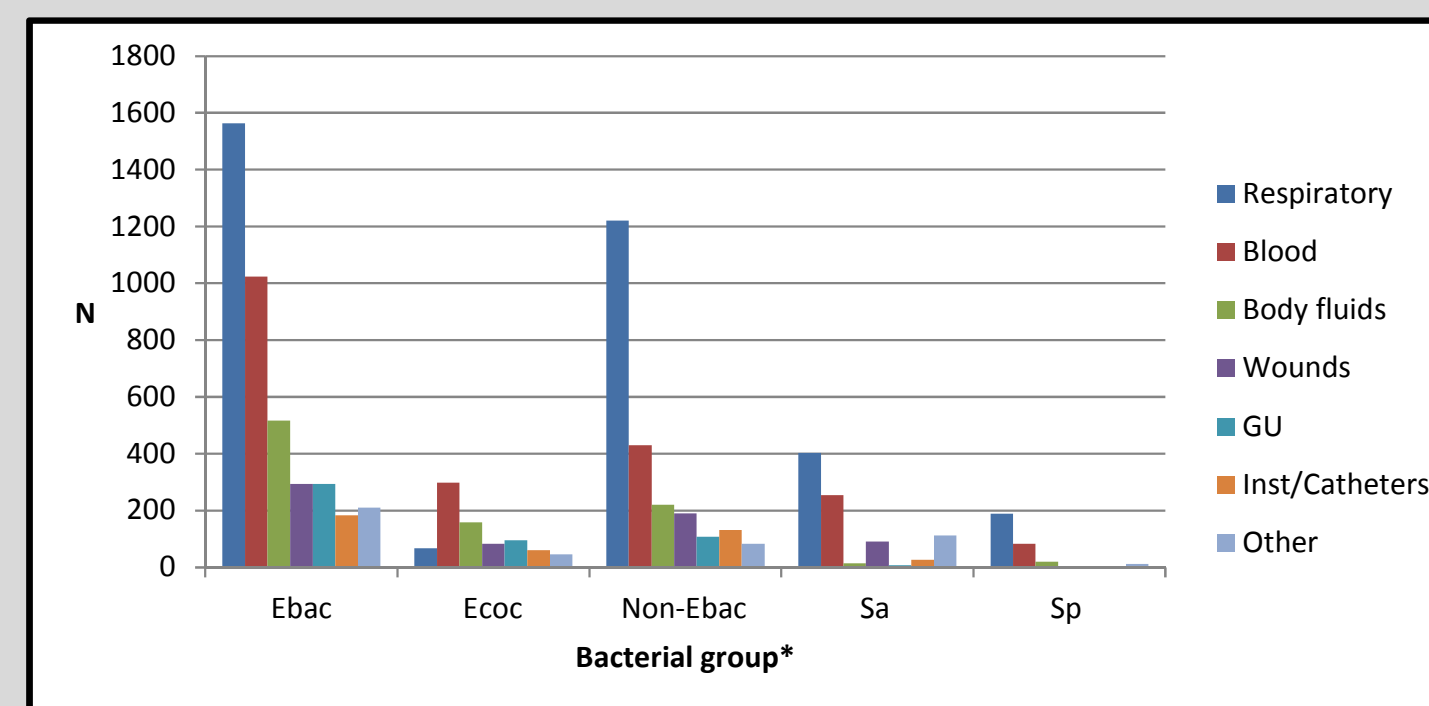
Results

Figure 1. Distribution of isolates by specimen source from surgical and medical intensive care units globally, 2009-2010.



HEENT = head, ears, eyes, nose, throat

Figure 2. Distribution of bacterial groups by specimen source for isolates from surgical and medical intensive care units globally, 2009-2010.



*Ebac = *Enterobacteriaceae*, Ecoc = *Enterococcus* spp., Non-Ebac = non-*Enterobacteriaceae* (*P. aeruginosa* and *A. baumannii*), Sa = *Staphylococcus aureus*, Sp = *Streptococcus pneumoniae*

Table 2. *In vitro* activity of tigecycline and comparators against 3,527 *Enterobacteriaceae* from surgical and medical ICUs globally, 2009-2010.

Organism	Drug	Breakpoints (S R)*	MIC ₅₀	MIC ₉₀	%S ^b	%I	%R	
All <i>Enterobacteriaceae</i> N= 3,512	Meropenem	≤1 2 ≥4	≤0.06	0.25	96.6	1.5	1.9	
	Amikacin	≤16 32 ≥64	1	8	95.1	1.1	3.9	
	Tigecycline	≤2 4 ≥8	0.5	2	94.1	4.8	1.1	
	Cefepime	≤8 16 ≥32	≤0.5	16	87.6	2.8	9.6	
	Levofloxacin	≤2 4 ≥8	0.06	> 8	81.8	4.1	14.1	
	Pip-tazo	≤16/4 32/4-64/4 ≥128/4	8	> 128	62.8	14.1	23.1	
	Minocycline	≤4 8 ≥16	4	> 16	54.7	23.5	21.8	
	Ceftriaxone	≤1 2 ≥4	4	> 64	47.1	2.1	50.8	
	ESBL ⁺ <i>E. coli</i> N=189	Tigecycline	≤1 2 ≥4	0.25	0.5	100	0	0
		Meropenem	≤16 32 ≥64	≤0.06	≤0.06	98.4	1.1	0.5
Amikacin		≤2 4 ≥8	4	16	93.1	2.7	4.2	
Pip-tazo		≤8 16 ≥32	8	128	65.6	20.1	14.3	
Minocycline		≤2 4 ≥8	4	> 16	56.6	19.1	24.3	
Cefepime		≤16/4 32/4-64/4 ≥128/4	32	> 32	36.5	10.6	52.9	
ESBL+ <i>K. pneumoniae</i> N=300	Levofloxacin	≤4 8 ≥16	> 8	> 8	18.0	1.1	81.0	
	Ceftriaxone	≤1 2 ≥4	> 64	> 64	2.1	0.5	97.4	
	Tigecycline	≤1 2 ≥4	0.5	2	92.7	4.7	2.7	
	Meropenem	≤16 32 ≥64	≤0.06	1	90.0	3.7	6.3	
All <i>Enterobacteriaceae</i> N= 3,512	Amikacin	≤2 4 ≥8	8	> 64	82.7	4.3	13.0	
	Pip-tazo	≤8 16 ≥32	64	> 128	35.3	21.7	43.0	
	Minocycline	≤2 4 ≥8	8	> 16	34.0	19.0	47.0	
	Levofloxacin	≤16/4 32/4-64/4 ≥128/4	8	> 8	31.0	5.3	63.7	
	Cefepime	≤4 8 ≥16	> 32	> 32	23.0	13.3	63.7	
	Ceftriaxone	≤1 2 ≥4	> 64	> 64	1.0	0	99.0	

*Breakpoints and MIC values in mcg/mL.
*Breakpoints defined in CLSI document M100-S21 (2011), where available; tigecycline breakpoint defined by the FDA.
*ESBL = extended spectrum beta-lactamase

Table 3. *In vitro* activity of tigecycline and comparators against 2,443 non-*Enterobacteriaceae* from surgical and medical ICUs globally, 2009-2010.

Organism	Drug	Breakpoints (S R)*	MIC ₅₀	MIC ₉₀	%S ^b	%I	%R	
<i>P. aeruginosa</i> N=1,271	Amikacin	≤16 32 ≥64	4	64	84.1	4.6	11.3	
	Pip-tazo	≤64/4 -- ≥128/4	16	> 128	76.0	0	24.1	
	Meropenem	≤4 8 ≥16	1	> 16	67.6	11.9	20.5	
	Cefepime	≤8 16 ≥32	8	32	66.9	14.0	19.1	
	Ceftazidime	≤8 16 ≥32	≤8	> 32	61.7	10.9	27.4	
	Levofloxacin	≤2 4 ≥8	2	> 8	58.3	7.4	34.4	
	Ceftriaxone	≤8 16-32 ≥64	> 64	> 64	6.6	17.9	75.5	
	Tigecycline	No Breakpoints Defined	8	16	-	-	-	
	<i>A. baumannii</i> N=1,172	Minocycline	≤4 8 ≥16	1	8	76.3	17.0	6.7
		Amikacin	≤16 32 ≥64	64	> 64	42.2	6.4	51.4
Meropenem		≤4 8 ≥16	16	> 16	42.2	4.4	53.3	
Cefepime		≤8 16 ≥32	32	> 32	32.7	15.6	51.7	
Levofloxacin		≤2 4 ≥8	8	> 8	29.4	11.9	58.8	
Ceftazidime		≤8 16 ≥32	> 32	> 32	28.3	5.6	66.1	
Pip-tazo		≤16/4 32/4-64/4 ≥128/4	> 128	> 128	25.9	6.9	67.2	
Ceftriaxone		≤8 16-32 ≥64	> 64	> 64	14.2	15.1	70.7	
Tigecycline		No Breakpoints Defined	0.5	2	-	-	-	

*Breakpoints and MIC values in mcg/mL.
*Breakpoints defined in CLSI document M100-S21 (2011), where available; tigecycline breakpoint defined by the FDA.

Table 4. *In vitro* activity of tigecycline and comparators against 2,026 gram-positive isolates from surgical and medical ICUs globally, 2009-2010.

Organism	Drug	Breakpoints (S R)*	MIC ₅₀	MIC ₉₀	%S ^b	%I	%R	
<i>S. aureus</i> MRSA ^c N=362	Tigecycline	≤0.5 -- ≥1	0.25	0.5	100	0	0	
	Linezolid	≤4 -- ≥8	2	2	100	0	0	
	Vancomycin	≤2 4-8 ≥16	1	1	99.5	0.6	0	
	Minocycline	≤4 8 ≥16	≤0.25	8	77.4	14.1	8.6	
	Levofloxacin	≤1 2 ≥4	16	> 32	8.3	0.6	91.2	
	Amox-clav	≤4/2 -- ≥8/4	> 8	> 8	0	0	100	
	Ampicillin	≤0.25 -- ≥0.5	> 16	> 16	0	0	100	
	Ceftriaxone	≤8 16-32 ≥64	> 64	> 64	0	0	100	
	Meropenem	≤4 8 ≥16	16	> 16	0	0	100	
	Penicillin	≤0.12 -- ≥0.25	> 8	> 8	0	0	100	
	Pip-tazo	≤8/4 -- ≥16/4	> 16	> 16	0	0	100	
	<i>S. aureus</i> MSSA ^c N=547	Tigecycline	≤0.5 -- ≥1	0.12	0.25	100	0	0
		Linezolid	≤4 -- ≥8	2	4	100	0	0
Meropenem		≤4 8 ≥16	≤0.12	≤0.12	100	0	0	
Pip-tazo		≤8/4 -- ≥16/4	1	2	100	0	0	
Amox-clav		≤4/2 -- ≥8/4	0.5	1	100	0	0	
Vancomycin		≤2 4-8 ≥16	1	1	99.8	0.2	0	
Minocycline		≤4 8 ≥16	≤0.25	0.5	98.7	0.9	0.4	
Ceftriaxone		≤8 16-32 ≥64	4	4	98.2	1.8	0	
Levofloxacin		≤1 2 ≥4	0.25	2	89.8	1.5	8.8	
Ampicillin		≤0.25 -- ≥0.5	4	> 16	22.5	0	77.5	
<i>Enterococcus</i> spp. N=809	Penicillin	≤0.12 -- ≥0.25	4	> 8	21.2	0	78.8	
	Tigecycline	≤0.25 -- ≥0.5	0.12	0.25	99.6	0	0.4	
	Linezolid	≤2 4 ≥8	2	2	99.6	0.3	0.1	
	Vancomycin	≤4 8-16 ≥32	1	> 32	88.5	0.5	11.0	
	Ampicillin	≤8 -- ≥16	2	> 16	63.3	0	36.7	
	Penicillin	≤8 -- ≥16	4	> 8	62.1	0	38.0	
	Minocycline	≤4 8 ≥16	8	> 8	40.3	16.3	43.4	
	Levofloxacin	≤2 4 ≥8	32	> 32	38.7	2.5	58.8	
	<i>S. pneumoniae</i> N=308	Linezolid	≤2 -- --	1	1	100	0	0
		Vancomycin	≤1 -- --	0.5	0.5	100	0	0
Levofloxacin		≤2 4 ≥8	1	1	99.7	0.3	0	
Tigecycline		≤0.015 -- --	0.015	0.03	99.4	0	0.7	
Amox-clav		≤2/1 4/2 ≥8/4	≤0.03	2	91.6	3.9	4.6	
Ceftriaxone		≤1 2 ≥4	≤0.03	1	90.6	7.8	1.6	
Meropenem		≤0.25 0.5 ≥1	≤0.12	0.5	84.4	7.5	8.1	
Clindamycin		≤0.25 0.5 ≥1	0.06	> 64	82.1	0.7	17.2	
Erythromycin		≤0.25 0.5 ≥1	0.06	64	66.2	1.4	32.4	
Penicillin		≤0.06 0.12-1 ≥2	≤0.06	2	61.4	24.0	14.6	

*Breakpoints and MIC values in mcg/mL.
*Breakpoints defined in CLSI document M100-S21 (2011), where available; tigecycline breakpoint defined by the FDA.
*MRSA = methicillin-resistant *S. aureus*, MSSA = methicillin-susceptible *S. aureus*

Conclusions

- Gram-negative organisms accounted for approximately 76% of pathogens in this study, with *P. aeruginosa* and *A. baumannii* the most frequently isolated (26.7%). *S. aureus* accounted for another 10% (MRSA 4%).
- Linezolid and tigecycline were the most active agents against the gram-positive pathogens, inhibiting >99% of all isolates. Tigecycline had the lowest MIC₉₀ against gram-positive organisms.
- Meropenem, amikacin and tigecycline had percents susceptible of >94% against all *Enterobacteriaceae*, and maintained this activity against ESBL-positive *E. coli*. ESBL-positive *K. pneumoniae* was more resistant *in vitro*, with only tigecycline and meropenem able to inhibit >90% of these isolates.
- Amikacin was the only agent with activity of >80% susceptible for *P. aeruginosa*, while *A. baumannii* exhibited <80% susceptibility to all agents with published breakpoints tested in this study.
- Tigecycline's *in vitro* activity was comparable to or greater than most commonly prescribed broad