

Evaluating Multi-Drug Resistant *Acinetobacter baumannii* in Critical Care Units

M. Hackel¹, S. Bouchillon¹, D. Hoban¹, B. Johnson¹, R. Badal¹, J. Johnson¹, S. Hawser², M. Dowzicky³

¹International Health Management Associates, Schaumburg, IL, USA

²IHMA Europe Sàrl, Epalinges, Switzerland

³Pfizer Inc., Collegetown, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: 847.303.5003
Fax: 847.303.5601

K9

Revised Abstract

Background: The increasing incidence of multi-drug resistant (MDR) *Acinetobacter baumannii* 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 *A. baumannii* resistant to three or more antibiotic classes isolated from intensive care units during 2004-2010. **Methods:** A total of 4,241 *A. baumannii* were isolated from ICUs, with 2,491 of these MDR. All isolates were identified to the species level by participating sites from 61 countries and confirmed by the central laboratory. Isolates came from medical, pediatric and surgical ICUs. Minimum inhibitory concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Susceptibilities of the 2,491 MDR isolates are shown below.

Drug	MIC ₅₀	MIC ₉₀	%S	%I	%R
Amikacin	>64	>64	21.04	9.23	69.73
Cefepime	32	>32	6.46	16.38	77.16
Ceftazidime	>32	>32	3.77	5.1	91.13
Ceftriaxone	>64	>64	0.48	3.41	96.11
Imipenem	16	>16	41.75	4.68	53.56
Levofloxacin	8	>8	4.7	12.81	82.5
Meropenem	>16	>16	16.85	7.1	76.05
Minocycline	2	8	75.39	16.3	8.31
PipTazo	>128	>128	2.29	5.58	92.13
Tigecycline	1	2	na	na	na

Conclusions: 58.7% of *A. baumannii* from ICUs were MDR. Tigecycline demonstrated excellent *in vitro* activity against MDR *A. baumannii*, with the lowest MIC_{50/90} values of 1/2 mcg/ml, followed by minocycline, levofloxacin, and imipenem.

Introduction

Infections resulting from *Acinetobacter* present a challenge to clinicians with increasing multi-drug resistance worldwide. Resistance of *Acinetobacter* to cephalosporins, aminoglycosides and ciprofloxacin is now widespread but carbapenems, colistin, sulbactam and minocycline have remained effective in over 80% of most strains [1, 2]. The emergence of imipenem resistance in this species is of considerable concern leaving relatively limited treatment options for infections due these resistant *Acinetobacter* and has led to a search for new compounds with activity against these problematic pathogens.

This study was undertaken to document the *in vitro* activity of tigecycline against multi-drug resistant *Acinetobacter baumannii* in a diverse population from multiple investigative sites globally. This study is part of the larger ongoing Tigecycline Evaluation and Surveillance Trial (TEST) program.

Materials & Methods

- A total of 4,241 clinical isolates were collected and tested between January 2004 and December 2010 from 1,667 cumulative sites in 61 countries. Isolates were identified to the species level and tested 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 [3]. MIC interpretive criteria followed published guidelines established by the CLSI [4], where available.
- 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

- Henwood, C.J., et al. 2002. *Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936)*. J. Antimicrob. Chemother. 49: 479-87.
- Hanberger, H., et al. 1999. *Antibiotic susceptibility among aerobic gram-negative bacilli in intensive care units in 5 European countries. French and Portuguese ICU Study Groups*. Jama. 281: 67-71.
- Clinical and Laboratory Standards Institute. 2009. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Eighth Edition, CLSI Document M7-A8*. Wayne, PA.
- Clinical and Laboratory Standards Institute. 2011. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-first Informational Supplement*. CLSI document M100-S21. Wayne, PA.

Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Surveillance Trial program group. This study was sponsored by Pfizer Inc.

Results

Table 1. Top ten species isolated in critical care units from a global population between 2004-2010.

Rank	Organism	N	% of Total N
1	<i>Pseudomonas aeruginosa</i>	5,120	12.8%
2	<i>Klebsiella pneumoniae</i>	4,774	11.9%
3	<i>Acinetobacter baumannii</i>	4,241	10.6%
4	<i>Enterobacter cloacae</i>	4,132	10.3%
5	<i>Escherichia coli</i>	3,972	9.9%
6	<i>Staphylococcus aureus</i>	3,949	9.9%
7	<i>Serratia marcescens</i>	2,409	6.0%
8	<i>Haemophilus influenzae</i>	1,952	4.9%
9	<i>Enterococcus faecalis</i>	1,906	4.8%
10	<i>Streptococcus pneumoniae</i>	1,759	4.4%
	All others*	5,760	14.4%
	Total	39,974	100.0%

* "All Others" includes the combined totals from 89 different species.

Table 3. *In vitro* activity of tigecycline and comparators against 2,491 multi-drug resistant *A. baumannii* from critical care units globally, 2004-2010.

Drug	CLSI Breakpoints	N	mcg/ml		%Sus ^a	%Int	%Res
			MIC ₅₀	MIC ₉₀			
Amikacin	≤16 32 ≥64	2491	>64	>64	21.0	9.2	69.7
Cefepime	≤8 16 ≥32	2491	32	>32	6.5	16.4	77.2
Ceftazidime	≤8 16 ≥32	2491	>32	>32	3.8	5.1	91.1
Ceftriaxone	≤8 16-32 ≥64	2491	>64	>64	0.5	3.4	96.1
Imipenem	≤4 8 ≥16	491	16	>16	41.8	4.7	53.6
Meropenem ^b	≤4 8 ≥16	2000	>16	>16	16.9	7.1	76.1
Levofloxacin	≤2 4 ≥8	2491	8	>8	4.7	12.8	82.5
Minocycline	≤4 8 ≥16	2491	2	8	75.4	16.3	8.3
PipTazo	≤16/4 32/4-64/4 ≥128/4	2491	>128	>128	2.3	5.6	92.1
Tigecycline	nbp	2491	1	2	—	—	—

^a Breakpoints defined in CLSI document M100-S21 (2011), where available; nbp = no breakpoints available.
^b Meropenem was substituted for imipenem in 2006.

Figure 1. Distribution of *A. baumannii* by specimen source for all isolates compared to MDR isolates from critical care units globally, 2004-2010.

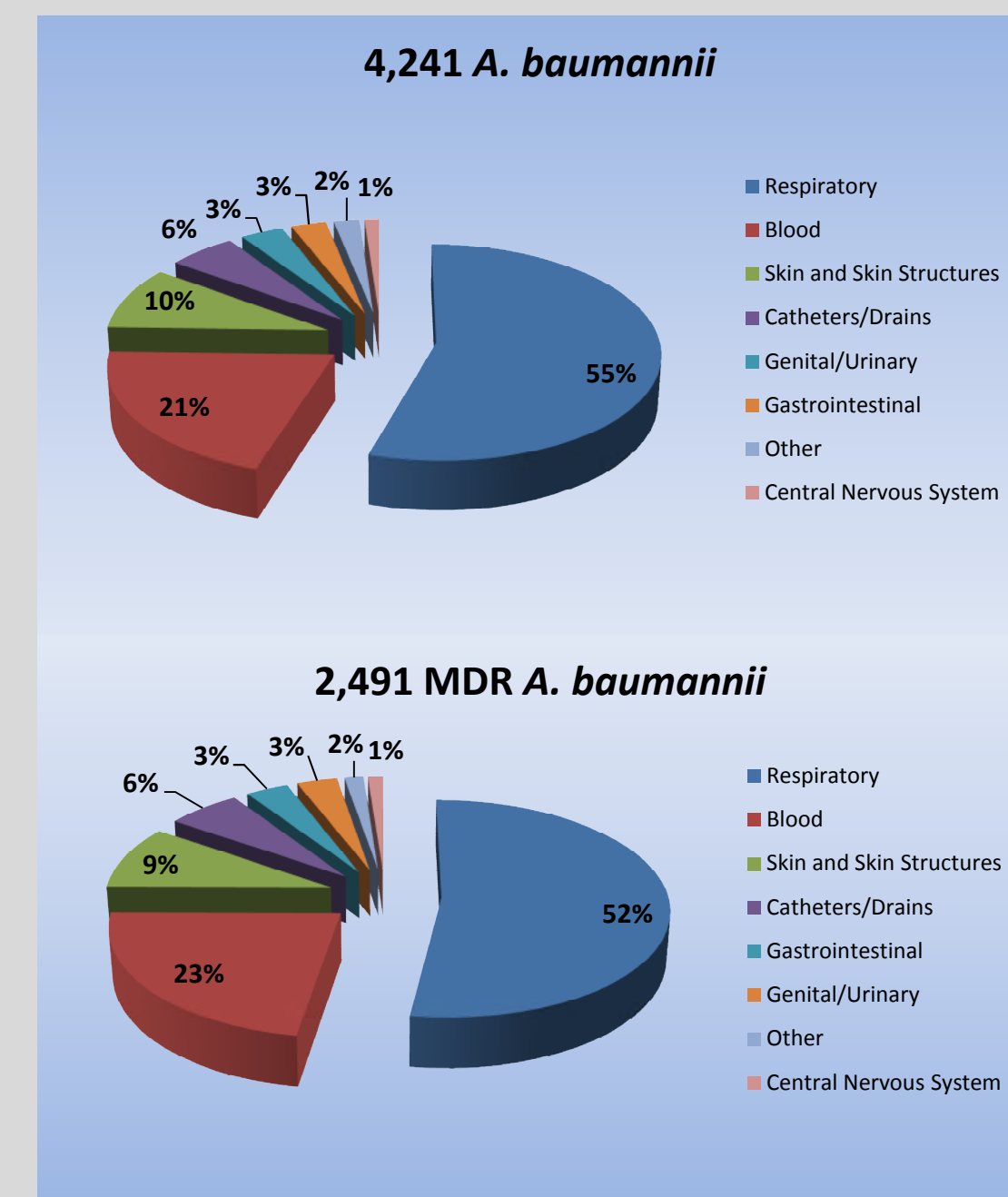


Figure 2. Percent (%) resistance by drug class for 2,491 multi-drug resistant *A. baumannii*.

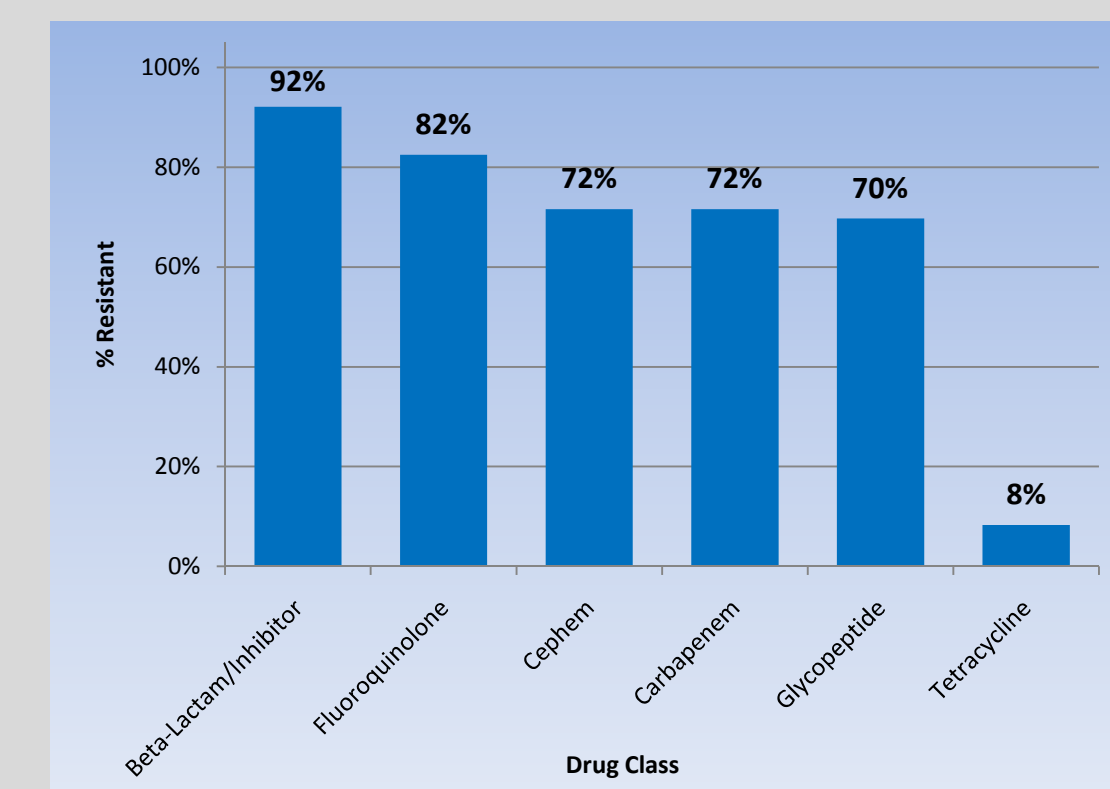


Table 2. *In vitro* activity of tigecycline and comparators against 4,241 *A. baumannii* from critical care units globally, 2004-2010.

Drug	CLSI Breakpoints	N	mcg/ml		%Sus ^a	%Int	%Res
			MIC ₅₀	MIC ₉₀			
Amikacin	≤16 32 ≥64	4241	32	>64	49.7	7.5	42.8
Cefepime	≤8 16 ≥32	4241	32	>32	33.6	15.6	50.8
Ceftazidime	≤8 16 ≥32	4241	>32	>32	30.4	6.7	62.9
Ceftriaxone	≤8 16-32 ≥64	4241	>64	>64	15.3	18.1	66.6
Imipenem	≤4 8 ≥16	1141	1	>16	73.2	3.5	23.3
Meropenem ^b	≤4 8 ≥16	3100	8	>16	44.8	5.7	49.6
Levofloxacin	≤2 4 ≥8	4241	8	>8	33.6	12.1	54.2
Minocycline	≤4 8 ≥16	4241	1	8	83.6	11.0	5.4
PipTazo	≤16/4 32/4-64/4 ≥128/4	4241	128	>128	32.0	10.4	57.5
Tigecycline	nbp	4241	0.5	2	—	—	—

^a Breakpoints defined in CLSI document M100-S21 (2011), where available; nbp = no breakpoints available.
^b Meropenem was substituted for imipenem in 2006.

Conclusions

Acinetobacter baumannii is the 3rd most common pathogen isolated from critical care units in this global study. Of the more than 4,000 *A. baumannii* studied, 58.7% were multi-drug resistant (resistant to 3 or more drug classes).

Half of all *A. baumannii*, as well as half of all MDR *A. baumannii*, came from respiratory sources; 75% of *A. baumannii* isolated came from the combined respiratory and blood sources.

Resistance of *A. baumannii* was extremely high to all antimicrobial drug classes except the tetracyclines (minocycline). The lowest MICs were seen with the glycylycylone, tigecycline, with MIC₅₀ and MIC₉₀ values of 0.5 and 2 mcg/ml, respectively. The MIC₉₀ of 2 mcg/ml for tigecycline was unaffected by any MDR phenotype or co-resistance factors.

The cepheems, beta-lactams (with beta-lactamase inhibitors), fluoroquinolones, carbapenems, and aminoglycosides are no longer therapeutic options for this difficult to treat pathogen. Minocycline is effective against 83% of *A. baumannii* but this rate drops to 75% against MDR *A. baumannii*. Tigecycline is currently the only marketed glycylycylone available and may be a viable clinical option.