Tigecycline Activity Tested Against More than 11,000 Isolates of *Acinetobacter* spp. Collected Worldwide in 2004-2013

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INTRODUCTION

Acinetobacter spp. represent an important cause of health-care associated infections worldwide. These organisms may cause a range of infections, but most commonly affect the lower respiratory tract and at-risk patients in the intensive care unit. Furthermore, these organisms generally exhibit intrinsically decreased susceptibility to a range of antimicrobials and possesses a great ability to develop resistance to multiple classes of agents. Thus, selection of antimicrobial therapy for serious *Acinetobacter* spp. infections can be very challenging.

Tigecycline, a derivative of minocycline, is the first agent in the glycylcycline class to be approved and market for clinical use. Tigecycline is approved for treatment of complicated intra-abdominal infections and complicated skin and skin structure infections in the United States (USA) and Europe and also for treatment of community-acquired pneumonia in the USA. Tigecycline is not approved for treatment of *Acinetobacter* spp. infections, but has been sporadically used to treat infections caused by extensively- or pan-drug resistant strains.

The SENTRY Antimicrobial Surveillance Program has been monitoring the in vitro activity of tigecycline worldwide since 2004. In this investigation, we assessed the in vitro activity of tigecycline and comparator agents tested against a large collection (n=11,033) of clinical isolates of *Acinetobacter* spp. collected worldwide during a 10-year period, from January 2004 to December 2013.

METHODS

Organism collection: A total of 11,033 clinically-significant non-duplicate *Acinetobacter* spp. isolates were collected over a decade (2004-2013) in hospitals from Europe (25.3%), USA (19.3%), Latin America (LA; 24.0%) and Asia-Pacific region (APAC; 31.5%) via the SENTRY Program. The isolates were mainly from pneumonias (42.1%), bacteremias (35.4%) and skin and skin structure infections (15.7%), and were collected from a total of 260 medical centers in 49 countries.

Methods: Susceptibility testing was performed by broth microdilution method in a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) according to Clinical Laboratory and Standards Institute (CLSI) methods using validated broth microdilution panels produced by ThermoFisher Scientific Inc. (Cleveland, Ohio, USA). Susceptibility interpretations were performed according to EUCAST breakpoint criteria (version 5.0, January 2015) and CLSI (M100-S15, 2015). Quality control was performed according to CLSI (M07-A10 and M100-S25) methods using *Escherichia coli* ATCC 25922 and 35218 and *Pseudomonas aeruginosa* ATCC 27853.

RESULTS

- Tigecycline exhibited similar in vitro activity against *Acinetobacter* spp. isolates from all four geographic regions combined, with MIC_{50} of 0.5-1 mg/L and MIC_{90} of 2 mg/L (Figure 1 and Table 1).
- Tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 52.0, 80.8 and 96.1% inhibited at ≤0.5, ≤1 and ≤2 mg/L, respectively) and colistin ($MIC_{50/90}$, ≤0.5/1 mg/L; 97.9% susceptible) were the most active agents in all regions (Tables 1 and 2).
- Among the aminoglycosides, tobramycin ($MIC_{50/90}$, 8/>16 mg/L; 48.2% susceptible) was slightly more active than amikacin ($MIC_{50/90}$, >32/>32 mg/L; 39.1% susceptible [EUCAST]) overall, but with regional variations. Tobramycin was the most active (highest susceptibility rate) aminoglycoside in Europe (50.9%) and Latin America (47.5%); whereas in the USA and Asia-Pacific region, amikacin and tobramycin exhibited similar susceptibility rates by EUCAST criteria (Table 1).
- The highest susceptibility rates to aminoglycosides were observed in the USA (52.4-63.8%) and the lowest in Latin America (24.4-47.5%) and Asia-Pacific (31.0-38.0%; Table 1).
- Tigecycline and colistin activities did not vary significantly by geographic region; whereas tobramycin susceptibility varied from 38.0% in the Asia-Pacific region to 62.2% in the USA, and imipenem susceptibility rates varied from 37.7% in Latin America to 60.0% in the USA (Table 1).
- Overall, imipenem and tobramycin susceptibility decreased from 72.2 and 59.0% in 2004-2005 to 31.0 and 44.8% in 2012-2013, respectively; whereas susceptibility to colistin decreased from 99.8% in 2006-2007 to 95.9% in 2012-2013. Imipenem susceptibility rates decreased significantly in all geographic regions (Table 2).
- Although the percentage of isolates inhibited at ≤2 mg/L of tigecycline (current FDA susceptible breakpoint for Enterobacteriaceae) remained relatively stable during the study period (94.8-97.3% worldwide and 95.1-97.6% in Europe); the percentages of strains inhibited at ≤0.5 and ≤1 mg/L of tigecycline decreased in all geographic regions during the study period; e.g. from 57.2 and 79.4% in 2004-2005 to 42.0 and 73.4% in 2012-2013 worldwide, and from 50.8 and 80.9 in 2004-2005 to 38.5 and 68.8% in 2012-2013 in Europe (Table 2).

Table 1. Activity of tigecycline and comparator antimicrobial agents when tested against 11,033 isolates of *Acinetobacter* spp.[a]

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[b] %S / %R
All regions (11,033)					
Tigecycline	0.5	2	≤0.03 – >4	- / - / -	- / - / -
Ceftazidime	>16	>16	≤1 – >16	28.1 / 4.6 / 67.3	- / - / -
Cefepime	>16	>16	≤0.5 – >16	30.1 / 8.6 / 61.3	- / - / -
Imipenem	>8	>8	≤0.12 – >8	43.7 / 3.2 / 53.1	43.7 / 3.2 / 53.1
Amp/sulbactam[c]	>16	>16	≤2 – >16	35.0 / 10.2 / 54.8	- / - / -
Levofloxacin	>4	>4	≤0.5 – >4	29.7 / 7.0 / 63.3	28.7 / 1.0 / 70.3
Amikacin	>32	>32	≤4 – >32	41.6 / 4.0 / 54.4	39.1 / 2.5 / 58.4
Gentamicin	>8	>8	≤2 – >8	35.5 / 4.4 / 60.1	35.5 / 0.0 / 64.5
Tobramycin	8	>16	≤0.25 – >16	48.2 / 2.5 / 49.3	48.2 / 0.0 / 51.8
Colistin	≤0.5	1	≤0.5 – >4	97.9 / 0.0 / 2.1	97.9 / 0.0 / 2.1
Europe (2,789)					
Tigecycline	1	2	≤0.03 – >4	- / - / -	- / - / -
Ceftazidime	>16	>16	≤1 – >16	24.4 / 5.7 / 69.9	- / - / -
Cefepime	>16	>16	≤0.5 – >16	28.7 / 12.0 / 59.3	- / - / -
Imipenem	>8	>8	≤0.12 – >8	42.7 / 2.3 / 55.0	42.7 / 2.3 / 55.0
Amp/sulbactam[c]	>16	>16	≤2 – >16	32.6 / 9.8 / 57.6	- / - / -
Levofloxacin	>4	>4	≤0.5 – >4	26.0 / 8.7 / 65.3	24.3 / 1.7 / 74.0
Amikacin	>32	>32	≤4 – >32	38.3 / 3.9 / 57.8	36.3 / 2.0 / 61.7
Gentamicin	>8	>8	≤2 – >8	32.3 / 3.9 / 63.8	32.3 / 0.0 / 67.7
Tobramycin	4	>16	≤0.25 – >16	50.9 / 3.0 / 46.1	50.9 / 0.0 / 49.1
Colistin	≤0.5	2	≤0.5 – >4	97.5 / 0.0 / 2.5	97.5 / 0.0 / 2.5
USA (2,131)					
Tigecycline	0.5	2	≤0.03 – >4	- / - / -	- / - / -
Ceftazidime	16	>16	≤1 – >16	44.9 / 5.7 / 49.4	- / - / -
Cefepime	16	>16	≤0.5 – >16	45.7 / 9.6 / 44.7	- / - / -
Imipenem	0.5	>8	≤0.12 – >8	60.0 / 4.2 / 35.8	60.0 / 4.2 / 35.8
Amp/sulbactam[c]	8	>16	≤2 – >16	55.6 / 12.6 / 31.8	- / - / -
Levofloxacin	>4	>4	≤0.5 – >4	47.3 / 2.5 / 50.2	46.4 / 0.9 / 52.7
Amikacin	≤4	>32	≤4 – >32	68.0 / 5.6 / 26.4	63.8 / 4.2 / 32.0
Gentamicin	4	>8	≤2 – >8	52.4 / 3.8 / 43.8	52.4 / 0.0 / 47.6
Tobramycin	2	>16	≤0.25 – >16	62.2 / 4.3 / 33.5	62.2 / 0.0 / 37.8
Colistin	≤0.5	2	≤0.5 – >4	96.5 / 0.0 / 3.5	96.5 / 0.0 / 3.5
Latin America (2,643)					
Tigecycline	0.5	2	≤0.03 – >4	- / - / -	- / - / -
Ceftazidime	>16	>16	≤1 – >16	15.1 / 5.0 / 79.9	- / - / -
Cefepime	>16	>16	≤0.5 – >16	18.7 / 10.0 / 71.3	- / - / -
Imipenem	>8	>8	≤0.12 – >8	37.7 / 2.6 / 59.7	37.7 / 2.6 / 59.7
Amp/sulbactam[c]	>16	>16	≤2 – >16	24.3 / 15.4 / 60.3	- / - / -
Levofloxacin	>4	>4	≤0.5 – >4	16.4 / 5.8 / 77.8	16.0 / 0.4 / 83.6
Amikacin	>32	>32	≤4 – >32	27.8 / 6.4 / 65.8	24.4 / 3.4 / 72.2
Gentamicin	>8	>8	≤2 – >8	31.3 / 9.7 / 59.0	31.3 / 0.0 / 68.7
Tobramycin	8	>16	≤0.25 – >16	47.5 / 2.7 / 49.8	47.5 / 0.0 / 52.5
Colistin	≤0.5	1	≤0.5 – >4	98.3 / 0.0 / 1.7	98.3 / 0.0 / 1.7
Asia-Pacific (3,470)					
Tigecycline	0.5	2	≤0.03 – >4	- / - / -	- / - / -
Ceftazidime	>16	>16	≤1 – >16	30.5 / 2.9 / 66.6	- / - / -
Cefepime	>16	>16	≤0.5 – >16	30.3 / 4.2 / 65.5	- / - / -
Imipenem	>8	>8	≤0.12 – >8	39.0 / 4.0 / 57.0	39.0 / 4.0 / 57.0
Amp/sulbactam[c]	>16	>16	≤2 – >16	32.5 / 5.1 / 62.4	- / - / -
Levofloxacin	>4	>4	≤0.5 – >4	31.9 / 9.4 / 58.7	31.0 / 0.9 / 68.1
Amikacin	>32	>32	≤4 – >32	38.5 / 1.3 / 60.2	37.2 / 1.3 / 61.5
Gentamicin	>8	>8	≤2 – >8	31.0 / 1.2 / 67.8	31.0 / 0.0 / 69.0
Tobramycin	>16	>16	≤0.12 – >16	38.0 / 0.9 / 61.1	38.0 / 0.0 / 62.0
Colistin	≤0.5	1	≤0.5 – >4	98.7 / 0.0 / 1.3	98.7 / 0.0 / 1.3

a. Includes: *Acinetobacter baumannii* (9,508 strains), *A. berezinae* (nine strains), *A. calcoaceticus* (one strain), *A. calcoaceticus* (75 strains), *A. guillouiae* (one strain), *A. haemolyticus* (35 strains), *A. johnsonii* (four strains), *A. junii* (79 strains), *A. lwoffii* (325 strains), *A. nosocomialis* (11 strains), *A. pittii* (93 strains), *A. radioresistens* (nine strains), *A. soli* (three strains), *A. ursingii* (39 strains), *Acinetobacter* Genospecies 13 (one strain), and unspeciated *Acinetobacter* (840 strains).
b. Criteria as published by the CLSI [2015] and EUCAST [2015].
c. Ampicillin/sulbactam.

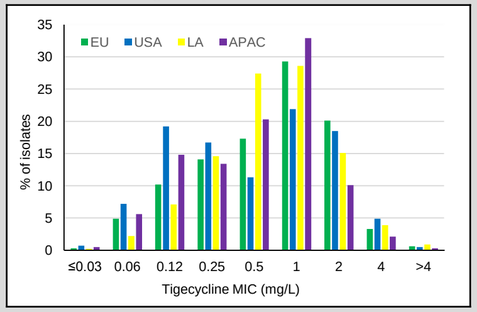
Table 2. Antimicrobial activities of imipenem, tobramycin, colistin and tigecycline tested against *Acinetobacter* spp. isolates collected over a 10 year period.

Region / year (no. tested)	% Susceptible (EUCAST criteria) IMI	TOB	Colistin	Tigecycline[a]
All regions				
2004-2005 (1,112)	72.2	59.0	(99.7)[b]	57.2 / 79.4 / 95.2
2006-2007 (2,568)	59.0	55.5	99.8	63.0 / 87.0 / 97.3
2008-2009 (2,105)	40.7	43.6	98.4	53.6 / 85.3 / 96.8
2010-2011 (2,864)	31.6	43.6	98.4	47.2 / 78.7 / 94.8
2012-2013 (2,384)	31.0	44.8	95.9	42.0 / 73.4 / 96.1
All years combined (11,033)	43.7	48.2	97.9	52.0 / 80.8 / 96.1
Europe				
2004-2005 (382)	60.0	55.8	(99.2)[b]	50.8 / 80.9 / 95.5
2006-2007 (454)	57.5	53.5	99.3	53.5 / 81.7 / 97.6
2008-2009 (487)	42.1	48.5	98.8	46.2 / 77.7 / 95.1
2010-2011 (707)	40.3	56.7	98.2	49.8 / 77.1 / 95.9
2012-2013 (759)	27.9	42.8	95.1	38.5 / 68.8 / 96.6
All years combined (2,789)	42.7	50.9	97.5	46.8 / 76.1 / 96.2
USA				
2004-2005 (287)	84.0	72.8	(100.0)[b]	56.4 / 71.1 / 89.5
2006-2007 (397)	63.5	67.8	98.0	57.2 / 77.1 / 93.5
2008-2009 (337)	62.6	58.8	97.9	57.0 / 83.4 / 96.4
2010-2011 (414)	50.7	53.1	96.4	52.2 / 73.4 / 93.5
2012-2013 (696)	52.2	61.6	95.0	54.2 / 78.3 / 97.0
All years combined (2,131)	60.0	62.2	96.5	55.1 / 77.0 / 94.6
Latin America				
2004-2005 (382)	76.4	50.4	(99.7)[b]	61.4/ 81.9 / 98.7
2006-2007 (454)	56.8	48.8	99.2	59.1 / 82.6 / 95.9
2008-2009 (487)	31.0	45.7	98.7	60.0 / 87.4 / 96.1
2010-2011 (707)	24.0	48.1	98.5	41.6 / 75.0 / 92.1
2012-2013 (759)	12.8	43.8	95.3	40.0 / 75.4 / 95.6
All years combined (2,643)	37.7	47.5	98.3	51.5 / 80.1 / 95.2
Asia-Pacific				
2004-2005 (62)	67.7	67.7	(100.0)[b]	74.2 / 93.5 / 98.4
2006-2007 (1,199)	59.0	55.1	99.2	70.2 / 94.1 / 99.0
2008-2009 (743)	36.9	31.9	98.3	52.2 / 89.9 / 98.7
2010-2011 (943)	23.0	25.9	99.6	47.7 / 85.4 / 96.7
2012-2013 (523)	21.4	26.4	98.3	31.9 / 87.4 / 94.5
All years combined (3,470)	39.0	38.0	98.7	44.5 / 87.5 / 97.6

Abbreviations: IMI = Imipenem; TOB = Tobramycin.

a. Percentage inhibited at ≤0.5/≤1/≤2 mg/L for comparison purpose only.
b. Polymyxin B was tested instead of colistin in 2004-2005; number in parenthesis indicates percentage of strains inhibited at ≤2 mg/L.

Figure 1. Tigecycline MIC distributions when tested against 11,033 *Acinetobacter* spp. clinical isolates from four geographic regions (2004-2013), including Europe (EU; n= 2,789), USA (2,131), Latin America (LA; 2,643) and the Asia-Pacific region (APAC; 3,470).



CONCLUSIONS

- The activity of key antimicrobials used to treat *Acinetobacter* spp. infections decreased substantially in all geographic regions during the 2004-2013 period, and the most significant decrease was observed with the carbapenems.
- Tigecycline and the polymyxins remain among the most active compounds against *Acinetobacter* spp. worldwide at published or suggested breakpoints.

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