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Tigecycline Activity Tested against Resistant Surveillance Subsets of Clinical Bacteria Collected Worldwide (2011)

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AMENDED ABSTRACT

Background: Tigecycline (TIG) was approved by the USA-FDA in 2005 and has generally retained activity against resistant (R) Gram-positive and -negative organisms. This glycylcycline was monitored in 2011 for continued potency worldwide.

Methods: 20,950 unique clinical isolates were consecutively collected in North America (NA; 7,985), Europe (EU; 6,908), Latin America (LA; 2,220) and Asia-Pacific region (APAC; 3,387) and tested for susceptibility (S) by the CLSI broth microdilution method against TIG and numerous comparators. TIG breakpoints established by the USA-FDA for Enterobacteriaceae (ENT; ≤2/≥8 µg/ml for S/R) were also applied to *Acinetobacter* spp. (ASP) and *Stenotrophomonas maltophilia* (XM) for comparison purpose only.

Results: MRSA/vancomycin-R enterococci (VRE) rates were 49.3/27.0, 30.2/11.3, 42.9/6.3 and 37.8/4.0% in NA, EU, LA and APAC, respectively. All MRSA (2,839) and >99% of VRE were S to TIG. Among *E. coli*, ESBL rates varied from 12.6% in the NA to 57.4% in APAC and one strain was non-S to TIG. TIG was active against ESBL phenotype (96.5-98.4% S) and MER-non-S *Klebsiella* spp. (KSP; 94.3-100.0% S). Only 4 of 213 (1.9%) MER-non-S KSP were TIG-non-S, all with TIG MIC of 4 µg/ml. 94.7-98.2% of CAZ-non-S *Enterobacter* spp. (ESP) were TIG-S. MER-non-S ASP varied from 51.2% in the NA to 80.9% in APAC, and 83.8 (LA) to 93.9% (APAC) were inhibited at a TIG MIC of ≤2 µg/ml. TIG showed limited activity against *P. aeruginosa*, but good activity was maintained against XM (89.3-98.3% inhibited at ≤2 µg/ml).

Conclusion: MRSA and VRE rates were highest in the NA while R among ENT and ASP were generally higher in APAC and LA compared to NA and EU. TIG has sustained potent activity and a broad-spectrum against clinically important bacteria causing infections worldwide, including MDR organism subsets (Table).

Organism	Tigecycline MIC_{90} in µg/ml / %S (no. tested) NA	EU	LA	APAC
MRSA	0.12/100.0 (1538)	0.12/100.0 (619)	0.12/100.0 (211)	0.25/100.0 (471)
VRE	0.06/99.4 (318)	0.06/100.0 (46)	-/100.0 (5)	0.06/100.0 (10)
E. coli ESBL	0.25/100.0 (198)	0.25/100.0 (371)	0.25/100.0 (134)	0.25/99.7 (395)
KSP ESBL	2/96.5 (200)	1/98.4 (378)	1/97.6 (170)	1/97.4 (233)
MER-non-S KSP	1/98.3 (58)	1/98.8 (82)	2/94.3 (35)	1/100.0 (38)
CAZ-non-S ESP	1/96.5 (141)	2/96.6 (145)	2/94.7 (75)	2/98.2 (111)
MER-non-S ASP	4/88.8 (107)	2/93.1 (233)	4/83.8 (315)	2/93.9 (310)
S. maltophilia	2/90.6 (170)	2/92.5 (106)	4/89.3 (28)	1/98.3 (58)

INTRODUCTION

Tigecycline was approved by the United States Food and Drug Administration (USA-FDA) in 2005 for acute bacterial skin and skin structure infections and complicated intra-abdominal infections, and in 2009 for treatment of community-acquired bacterial pneumonia. Sentinel monitoring through surveillance programs including the global SENTRY Antimicrobial Surveillance Program has provided information on the continuing activity of tigecycline against resistant Gram-positive and -negative bacteria over time.

The occurrence of multidrug-resistant (MDR) Gram-positive and -negative bacteria continues to increase. This problem has brought about recommendations from professional societies such as IDSA and governmental agencies to encourage the development of new antimicrobial agents. However, therapeutic options for the treatment of resistant pathogens remain limited as diverse regional and local resistance patterns evolve.

In this study, the activity of tigecycline tested against resistant subsets of Gram-positive and -negative bacteria from the SENTRY Program was evaluated (2011, 20,950 clinical isolates).

MATERIALS AND METHODS

Organism collection: A total of 20,950 unique clinical isolates were consecutively collected in 2011 in North America (NA; 7,985), Europe (EU; 6,908), Latin America (LA; 2,220) and Asia-Pacific region (APAC; 3,387). Countries sampled were NA (United States, Canada), EU (Belgium, Czech Republic, France, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Turkey, United Kingdom, Ukraine), LA (Argentina, Brazil, Chile, Mexico), and APAC (Australia, China, Hong Kong, India, Japan, Korea, Malaysia, New Zealand, Singapore, Taiwan, Thailand). Isolates were from clinically significant infections from patients with bloodstream infections, community-acquired and nosocomial respiratory tract infections, and wound or skin and skin structure infections.

Methods: Broth microdilution susceptibility testing was performed according to Clinical Laboratory and Standards Institute (CLSI) methods using validated broth microdilution panels produced by ThermoFisher Scientific Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). Susceptibility interpretive criteria were those of CLSI (M100-S22, 2012). Tigecycline MIC breakpoints were those found in the USA-FDA approved package insert (Tygacil Product Insert, 2011). The tigecycline breakpoints established by the USA-FDA for Enterobacteriaceae (ENT; ≤2/≥8 µg/ml for S/R) were also applied to *Acinetobacter* spp. and *Stenotrophomonas maltophilia* for comparison purposes only. Quality control was performed according to CLSI (M07-A9 and M100-S22) methods using 1) *Escherichia coli* ATCC 25922 and 35218, 2) *Staphylococcus aureus* ATCC 29213, 3) *Pseudomonas aeruginosa* ATCC 27853, and 4) *Enterococcus faecalis* ATCC 29212.

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RESULTS

- Regional MRSA rates varied at 49.3, 30.2, 42.9 and 37.8% in NA, EU, LA and APAC, respectively. All MRSA were susceptible to tigecycline and ≥99.9% were susceptible to linezolid, daptomycin, and vancomycin. Resistance to levofloxacin varied by region, ranging from 65.2% in NA to 81.9% in EU. Erythromycin resistance varied from 66.4 in EU to 88.1% in NA (Tables 1 and 2).
- The global vancomycin-resistant enterococci (VRE) rate was 19.7% with regional rates at 27.0, 11.3, 6.3 and 4.0% in NA, EU, LA and APAC, respectively. Susceptibility was high for tigecycline (99.5%), daptomycin (100.0%), and linezolid (98.7%; Table 2).
- The overall penicillin resistance rate (MIC, ≥2 µg/ml) for *Streptococcus pneumoniae* was at 23.9%. Tigecycline exhibited potent activity with regional susceptibility rates ranging from 98.7-100.0%. Overall the ceftriaxone and levofloxacin susceptibility rates were 46.3 and 97.1% respectively against penicillin-resistant pneumococci (Table 2).
- The global *E. coli* ESBL-phenotype rate was 24.1% with regional rates at 12.6, 19.4, 35.7, and 57.4%, respectively for NA, EU, LA and APAC. Overall, tigecycline (99.9%) and meropenem (98.7%) were highly active against these organisms (Table 3).
- The global *Klebsiella* spp. ESBL-phenotype rate was 32.5%. Tigecycline was uniformly active across the regions (96.5-98.4% susceptible). It was active against meropenem-non-susceptible *Klebsiella* spp. (94.3-98.8% susceptible). Only 4 of 213 (1.9%) of the meropenem-non-susceptible *Klebsiella* spp. were not susceptible to tigecycline, all with a tigecycline MIC of 4 µg/ml (Table 3).
- Overall, 27.6% of *Klebsiella* spp. were ceftazidime-non-susceptible. For these strains, regional rates of tigecycline susceptibility ranged from 94.7-98.2%. Only one other agent had regional susceptibility rates >90%; meropenem (90.1-93.3% susceptible; Table 3).
- Percentages of *Acinetobacter* spp. strains with tigecycline MIC values at ≤2 µg/ml rate were 88.8, 93.1, 83.8, and 93.9%, respectively for NA, EU, LA and APAC. Overall, 70.1% of *Acinetobacter* spp. were meropenem-non-susceptible. Regional rates varied from 51.2% in the NA to 80.9% in APAC. Regional colistin susceptibility rates for meropenem-non-susceptible *Acinetobacter* spp. ranged from 97.8-100.0% with an overall rate of 98.8% (Table 3).
- Tigecycline showed limited activity against *P. aeruginosa* and potent activity against *S. maltophilia* (89.3-98.3% across the regions inhibited at ≤2 µg/ml). In addition, trimethoprim/sulfamethoxazole (94.5% susceptible) and colistin (98.5% susceptible) also exhibited potent activity against *S. maltophilia* (Table 3).

CONCLUSIONS

- High levels of resistance for Gram-positive organisms (MRSA, VRE, MDR-*S. pneumoniae*) and Gram-negative-organisms (Enterobacteriaceae and non-fermenters) varied regionally and compromise the use of many available antimicrobials.
- In the 2011 global SENTRY Program, MRSA and VRE rates were highest in NA while resistance among Enterobacteriaceae and *Acinetobacter* spp. were generally higher in APAC and LA compared to NA and EU.
- Tigecycline demonstrated sustained potent activity across the regions when tested against clinically important bacteria causing infections worldwide, including MDR organism subsets.

Table 1. MIC distribution and cumulative frequency (%) of tigecycline against bacterial pathogens (2011).

Organism (no. tested)	Tigecycline MIC in µg/ml: ≤0.03	0.06	0.12	0.25	0.5	1	2	≥4	MIC_{50}	MIC_{90}	% S
Staphylococcus aureus (6910)	139 (2.0)	5675 (84.1)	849 (96.4)	216 (99.6)	31 (100.0)	-	-	-	0.06	0.12	100.0
MSSA (4071)	96 (2.4)	3530 (89.1)	385 (98.5)	57 (99.9)	3 (100.0)	-	-	-	0.06	0.12	100.0
MRSA (2839)	43 (1.5)	2145 (77.1)	464 (93.4)	159 (99.0)	28 (100.0)	-	-	-	0.06	0.12	100.0
Enterococcus spp. (1920)	919 (47.9)	881 (93.8)	89 (98.4)	28 (99.8)	0 (99.8)	1 (99.9)	2 (100.0)	-	0.06	0.06	99.9
vancomycin-susceptible (1541)	704 (45.7)	741 (93.8)	70 (98.3)	25 (99.9)	0 (99.9)	1 (100.0)	-	-	0.06	0.06	100.0
vancomycin-non-susceptible (379)	215 (56.7)	140 (93.7)	19 (98.7)	3 (99.5)	0 (99.5)	0 (99.5)	2 (100.0)	-	≤0.03	0.06	99.5
Escherichia coli (4553)	11 (0.2)	2065 (45.6)	2011 (89.8)	410 (98.8)	47 (99.8)	7 (100.0)	1 (100.0)	1 (100.0)	0.12	0.25	100.0
non-ESBL-phenotype (3455)	6 (0.2)	1732 (50.3)	1442 (92.0)	242 (99.0)	29 (99.9)	4 (100.0)	-	-	0.06	0.12	100.0
ESBL-phenotype (1098)	5 (0.5)	333 (30.8)	569 (82.6)	168 (97.9)	18 (99.5)	3 (99.8)	1 (99.9)	1 (100.0)	0.12	0.25	99.9
Klebsiella spp. (3020)	-	23 (0.8)	640 (22.0)	1515 (72.1)	499 (88.6)	210 (95.6)	90 (98.6)	43 (100.0)	0.25	1	98.6
meropenem-non-susceptible (213)	-	2 (0.9)	9 (5.2)	55 (31.0)	92 (74.2)	43 (94.4)	8 (98.1)	4 (100.0)	0.5	1	98.1
meropenem-susceptible (2807)	-	21 (0.7)	631 (23.2)	1460 (75.2)	407 (89.7)	167 (95.7)	82 (98.6)	39 (100.0)	0.25	1	98.6
non-ESBL-phenotype (2039)	-	16 (0.8)	542 (27.4)	1131 (82.8)	209 (93.1)	78 (96.9)	43 (99.0)	20 (100.0)	0.25	0.5	99.0
ESBL-phenotype (981)	-	7 (0.7)	98 (10.7)	384 (49.8)	290 (79.4)	132 (92.9)	47 (97.7)	23 (100.0)	0.5	1	97.7
Enterobacter spp. (1713)	-	5 (0.3)	223 (13.3)	1093 (77.1)	240 (91.1)	74 (95.4)	54 (98.6)	24 (100.0)	0.25	0.5	98.6
ceftazidime-susceptible (1241)	-	3 (0.2)	182 (14.9)	844 (82.9)	154 (95.3)	30 (97.7)	20 (99.4)	8 (100.0)	0.25	0.5	99.4
ceftazidime-non-susceptible (472)	-	2 (0.4)	41 (9.1)	249 (61.9)	86 (80.1)	44 (89.4)	34 (96.6)	16 (100.0)	0.25	2	96.6
Acinetobacter spp. (1377)	6 (0.4)	64 (5.1)	150 (16.0)	134 (25.7)	219 (41.6)	416 (71.8)	276 (91.9)	112 (100.0)	1	2	91.9
meropenem-non-susceptible (965)	-	3 (0.3)	22 (2.6)	71 (9.9)	167 (27.3)	366 (65.2)	238 (89.8)	98 (100.0)	1	4	89.8
meropenem-susceptible (412)	6 (1.5)	61 (16.3)	128 (47.3)	63 (62.6)	52 (75.2)	50 (87.4)	38 (96.6)	14 (100.0)	0.25	2	96.6
Stenotrophomonas maltophilia (362)	-	-	14 (3.9)	64 (21.5)	128 (56.9)	83 (79.8)	45 (92.3)	28 (100.0)	0.5	2	92.3

Table 2. Regional and global activity of tigecycline and comparator antimicrobial agents when tested against Gram-positive pathogens (2011).

Antimicrobial agent	North America (n) CLSI[a] %S / %R	North America (n) EUCAST[a] %S / %R	Europe (n) CLSI[a] %S / %R	Europe (n) EUCAST[a] %S / %R	LA (n) CLSI[a] %S / %R	LA (n) EUCAST[a] %S / %R	APAC (n) CLSI[a] %S / %R	APAC (n) EUCAST[a] %S / %R	Global (n) CLSI[a] %S / %R	Global (n) EUCAST[a] %S / %R
MRSA	(1538)		(619)		(211)		(471)		(2839)	
Tigecycline[b]	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0
Daptomycin	100.0 / -	100.0 / 0.0	99.8 / -	99.8 / 0.2	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	>99.9 / -	>99.9 / <0.1
Erythromycin	10.4 / 88.1	10.5 / 89.2	28.6 / 66.4	29.1 / 69.0	16.1 / 83.9	16.1 / 83.9	23.1 / 70.5	23.4 / 75.6	16.9/ 80.1	17.1/ 82.1
Levofloxacin	31.2 / 65.2	31.2 / 65.2	15.5 / 81.9	15.5 / 81.9	19.0 / 80.1	19.0 / 80.1	21.0 / 76.2	21.0 / 76.2	25.2 / 71.8	25.2 / 71.8
Linezolid	99.8 / 0.2	99.8 / 0.2	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	99.9 / 0.1	99.9 / 0.1
Teicoplanin	100.0 / 0.0	99.9 / 0.1	100.0 / 0.0	99.5 / 0.5	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	96.2 / 3.8	100.0 / 0.0	99.2 / 0.8
TMP/SMX[c]	97.7 / 2.3	97.7 / 2.2	97.6 / 2.4	97.6 / 2.3	97.2 / 2.8	97.2 / 2.8	86.8 / 13.2	86.8 / 12.7	95.8 / 4.2	95.8 / 4.0
Vancomycin	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	99.8 / 0.0	99.8 / 0.2	>99.9 / 0.0	>99.9 / <0.1
Enterococcus spp[d] (vancomycin non-susceptible	(318)		(46)		(5)		(10)		(379)	
Tigecycline[b]	99.4 / -	99.4 / 0.6	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	99.5 / -	99.5 / 0.5
Ampicillin	11.6 / 88.4	11.6 / 88.4	15.2 / 84.8	15.2 / 84.8	40.0 / 60.0	40.0 / 60.0	20.0 / 80.0	10.0 / 80.0	12.7 / 87.3	12.4 / 87.3
Daptomycin	100.0 / -	- / -	100.0 / -	- / -	100.0 / -	- / -	100.0 / -	- / -	100.0 / -	- / -
Levofloxacin	1.6 / 98.1	- / -	8.7 / 91.3	- / -	20.0 / 80.0	- / -	10.0 / 90.0	- / -	2.9 / 96.8	- / -
Linezolid	99.1 / 0.3	99.7 / 0.3	95.7 / 4.3	95.7 / 4.3	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	98.7 / 0.8	99.2 / 0.8
Teicoplanin	6.9 / 89.6	5.3 / 94.7	15.2 / 82.6	13.0 / 87.0	20.0 / 80.0	20.0 / 80.0	50.0 / 50.0	50.0 / 50.0	9.2 / 87.6	7.7 / 92.3
TMP/SMX[c]	- / -	8.8 / 91.2	- / -	17.4 / 82.6	- / -	40.0 / 60.0	- / -	30.0 / 70.0	- / -	10.8 / 89.2
Vancomycin	0.0 / 97.5	0.0 / 100.0	0.0 / 89.1	0.0 / 100.0	0.0 / 100.0	0.0 / 100.0	0.0 / 60.0	0.0 / 100.0	0.0 / 95.5	0.0 / 100.0
S. pneumoniae (PenR)	(218)		(78)		(31)		(187)		(514)	
Tigecycline[b]	100.0 / -	- / -	98.7 / -	- / -	100.0 / -	- / -	98.9 / -	- / -	99.4 / -	- / -
Amox/clav[e]	17.9 / 65.1	- / -	35.9 / 37.2	- / -	54.8 / 25.8	- / -	35.8 / 51.3	- / -	29.4 / 53.5	- / -
Ceftriaxone	48.6 / 5.0	3.7 / 5.0	51.3 / 20.5	6.4 / 20.5	58.1 / 0.0	9.7 / 0.0	39.6 / 21.9	4.3 / 21.9	46.3 / 13.2	4.7 / 13.2
Erythromycin	7.8 / 92.2	7.8 / 92.2	14.1 / 85.9	14.1 / 85.9	45.2 / 54.8	45.2 / 54.8	4.3 / 95.7	4.3 / 95.7	9.7 / 90.3	9.7 / 90.3
Levofloxacin	98.2 / 1.8	98.2 / 1.8	96.2 / 3.8	96.2 / 3.8	100.0 / 0.0	100.0 / 0.0	95.7 / 3.7	95.7 / 4.3	97.1 / 2.7	97.1 / 2.9
Penicillin[f]	31.2 / 8.7	- / -	46.2 / 7.7	- / -	51.6 / 0.0	- / -	38.5 / 11.8	- / -	37.4 / 9.1	- / -
Penicillin[g]	0.0 / 100.0	0.0 / 68.8	0.0 / 100.0	0.0 / 53.8	0.0 / 100.0	0.0 / 48.4	0.0 / 100.0	0.0 / 61.5	0.0 / 100.0	0.0 / 62.6
TMP/SMX[c]	22.5 / 75.7	24.3 / 75.7	14.1 / 67.9	29.5 / 67.9	3.2 / 90.3	3.2 / 90.3	9.1 / 83.9	13.4 / 83.9	15.2 / 78.4	19.9 / 78.4
Vancomycin	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2011].
c. Trimethoprim/sulfamethoxazole.
d. Includes: *Enterococcus faecalis* (38 strains), *E. faecium* (327 strains), *E. gallinarum* (9 strains), *E. raffinosus* (3 strains), and unspeciated *Enterococcus* (2 strains).
e. Amoxicillin/clavulanate.
f. Criteria as published by the CLSI [2012] for 'Penicillin parenteral (non-meningitis)'.
g. Criteria as published by the CLSI [2012] for 'Penicillin (oral penicillin V)'.

Table 3. Regional and global activity of tigecycline and comparator antimicrobial agents when tested against Gram-negative pathogens (2011).

Antimicrobial agent	North America (n) CLSI[a] %S / %R	North America (n) EUCAST[a] %S / %R	Europe (n) CLSI[a] %S / %R	Europe (n) EUCAST[a] %S / %R	LA (n) CLSI[a] %S / %R	LA (n) EUCAST[a] %S / %R	APAC (n) CLSI[a] %S / %R	APAC (n) EUCAST[a] %S / %R	Global (n) CLSI[a] %S / %R	Global (n) EUCAST[a] %S / %R
E. coli ESBL-phenotype	(198)		(371)		(134)		(395)		(1098)	
Tigecycline[b]	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	99.7 / 0.0	99.5 / 0.3	99.9 / 0.0	99.8 / 0.1
Piperacillin/tazobactam	79.3 / 14.1	66.2 / 20.7	75.2 / 11.6	60.1 / 24.8	70.1 / 7.5	45.5 / 29.9	81.3 / 8.4	74.2 / 18.7	77.5 / 10.4	64.5 / 22.5
Amikacin	95.5 / 2.0	88.4 / 4.5	94.3 / 2.4	84.4 / 5.7	95.5 / 1.5	81.3 / 4.5	93.9 / 4.6	88.4 / 6.1	94.5 / 3.0	86.2 / 5.5
Cefepime	47.5 / 44.4	26.3 / 61.1	33.2 / 59.3	17.0 / 72.5	21.6 / 64.2	3.0 / 85.8	23.5 / 65.8	4.6 / 85.1	30.9 / 59.6	12.5 / 76.6
Ceftazidime	35.9 / 53.5	11.1 / 64.1	31.8 / 58.0	8.6 / 68.2	18.7 / 74.6	7.5 / 81.3	36.5 / 53.4	15.2 / 63.5	32.6 / 57.6	11.3 / 67.4
Colistin	100.0 / 0.0	100.0 / 0.0	99.9 / 0.1	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	100.0 / 0.0	99.2 / 0.8	>99.9 / <0.1	99.7 / 0.3
Levofloxacin	19.7 / 79.3	19.2 / 80.3	25.9 / 70.9	25.1 / 74.1	13.4 / 84.3	13.4 / 86.6	18.5 / 78.2	17.5 / 81.5	20.6 / 76.7	19.9 / 79.4
Meropenem	97.0 / 2.0	98.0 / 0.5	99.5 / 0.3	99.7 / 0.3	100.0 / 0.0	100.0 / 0.0	97.5 / 2.3	97.7 / 1.3	98.4 / 1.3	98.7 / 0.6
Klebsiella spp. ESBL-phenotype[c]	(200)		(378)		(170)		(233)		(981)	
Tigecycline[b]	96.5 / 0.0	88.5 / 3.5	98.4 / 0.0	93.7 / 1.6	97.6 / 0.0	92.4 / 2.4	97.4 / 0.4	95.7 / 2.6	97.7 / 0.1	92.9 / 2.3
Piperacillin/tazobactam	26.5 / 64.0	18.5 / 73.5	31.5 / 51.9	17.2 / 68.5	31.8 / 55.3	22.9 / 68.2	56.7 / 30.5	47.2 / 43.3	36.5 / 49.8	25.6 / 63.5
Amikacin	69.0 / 6.5	62.5 / 31.0	77.2 / 8.2	63.2 / 22.8	80.6 / 11.8	65.3 / 19.4	79.8 / 18.5	73.4 / 20.2	76.8 / 10.9	65.9 / 23.2
Cefepime	46.0 / 45.0	23.0 / 61.0	28.8 / 64.6	13.0 / 77.2	27.1 / 65.3	7.1 / 78.8	37.3 / 53.6	12.4 / 72.5	34.0 / 58.1	13.9 / 73.1
Ceftazidime	20.5 / 76.0	10.5 / 79.5	14.8 / 78.6	6.9 / 85.2	21.2 / 71.2	8.8 / 78.8	21.5 / 64.4	14.6 / 78.5	18.7 / 73.4	9.8 / 81.3
Colistin	99.5 / 0.5	92.5 / 7.5	99.0 / 1.0	94.2 / 5.8	100.0 / 0.0	90.6 / 9.4	99.6 / 0.4	99.1 / 0.9	99.5 / 0.5	94.4 / 5.6
Levofloxacin	32.5 / 65.0	31.0 / 67.5	33.9 / 55.8	30.4 / 66.1	38.8 / 59.4	34.7 / 61.2	52.8 / 41.6	50.6 / 47.2	38.9 / 54.9	36.1 / 61.1
Meropenem	71.0 / 28.0	72.0 / 23.5	78.3 / 21.2	78.8 / 17.5	79.4 / 17.1	82.9 / 11.2	83.7 / 15.0	85.0 / 12.9	78.3 / 20.4	79.6 / 16.5
Klebsiella spp. MER-non-S[d]	(58)		(82)		(35)		(38)		(213)	
Tigecycline[b]	98.3 / 0.0	94.8 / 1.7	98.8 / 0.0	95.1 / 1.2	94.3 / 0.0	88.6 / 5.7	100.0 / 0.0	97.4 / 0.0	98.1 / 0.0	94.4 / 1.9
Piperacillin/tazobactam	0.0 / 100.0	0.0 / 100.0	1.2 / 98.8	1.2 / 98.8	0.0 / 100.0	0.0 / 100.0	7.9 / 92.1	7.9 / 92.1	1.9 / 98.1	1.9 / 98.1
Amikacin	25.9 / 17.2	15.5 / 74.1	35.4 / 15.9	20.7 / 64.6	62.9 / 20.0	48.6 / 37.1	36.8 / 57.9	18.4 / 63.2	37.6 / 24.4	23.5 / 62.4
Cefepime	5.2 / 82.8	0.0 / 98.3	2.4 / 93.9	1.2 / 98.8	11.4 / 80.0	0.0 / 94.3	10.5 / 89.5	0.0 / 97.4	6.1 / 87.8	0.5 / 97.7
Ceftazidime	1.7 / 96.6	0.0 / 98.3	1.2 / 98.8	0.0 / 98.8	5.7 / 88.6	0.0 / 94.3	0.0 / 100.0	0.0 / 100.0	1.9 / 96.7	0.0 / 98.1
Colistin	- / -	79.3 / 20.7	- / -	85.4 / 14.6	- / -	68.6 / 31.4	- / -	100.0 / 0.0	- / -	83.6 / 16.4
Levofloxacin	10.3 / 89.7	10.3 / 89.7	4.9 / 92.7	2.4 / 95.1	14.3 / 85.7	11.4 / 85.7	15.8 / 78.9	15.8 / 84.2	9.9 / 88.3	8.5 / 90.1
Meropenem	0.0 / 96.6	3.4 / 81.0	0.0 / 97.6	2.4 / 80.5	0.0 / 82.9	17.1 / 54.3	0.0 / 92.1	7.9 / 78.9	0.0 / 93.9	6.1 / 76.1
CAZ-non-S ESP[e]	(141)		(145)		(75)		(111)		(472)	
Tigecycline[b]	96.5 / 0.0	90.1 / 3.5	96.6 / 0.0	89.0 / 3.4	94.7 / 0.0	89.3 / 5.3	98.2 / 0.0	89.2 / 1.8	96.6 / 0.0	89.4 / 3.4
Piperacillin/tazobactam	19.9 / 36.9	11.3 / 80.1	32.4 / 30.3	22.1 / 67.6	42.7 / 29.3	29.3 / 57.3	37.8 / 37.8	21.6 / 62.2	31.6 / 33.9	19.9 / 68.4
Amikacin	99.3 / 0.7	97.2 / 0.7	88.3 / 11.0	84.1 / 11.7	89.3 / 8.0	73.3 / 10.7	82.9 / 13.5	78.4 / 17.1	90.5 / 8.1	85.0 / 9.5
Cefepime	84.4 / 12.1	46.8 / 22.7	69.7 / 25.5	42.8 / 34.5	60.0 / 34.7	32.0 / 52.0	55.9 / 36.9	32.4 / 50.5	69.3 / 25.6	39.8 / 37.5
Ceftazidime	0.0 / 91.5	0.0 / 100.0	0.0 / 90.3	0.0 / 100.0	0.0 / 93.3	0.0 / 100.0	0.0 / 93.7	0.0 / 100.0	0.0 / 91.9	0.0 / 100.0
Colistin	- / -	85.8 / 14.2	- / -	96.6 / 3.4	- / -	80.0 / 20.0	- / -	84.7 / 15.3	- / -	87.9 / 12.1
Levofloxacin	79.4 / 17.7	77.3 / 20.6	72.4 / 23.4	65.5 / 27.6	56.0 / 40.0	54.7 / 44.0	62.2 / 32.4	62.2 / 37.8	69.5 / 26.5	66.5 / 30.5
Meropenem	90.1 / 7.8	92.2 / 1.4	92.4 / 4.1	95.9 / 1.4	93.3 / 5.3	94.7 / 1.3	90.1 / 8.1	91.9 / 7.2	91.3 / 6.4	93.6 / 2.8
MER Non-S *Acinetobacter* spp[f]	(107)		(233)		(315)		(310)		(965)	
Amikacin	21.5 / 67.3	17.8 / 78.5	25.8 / 70.8	24.9 / 74.2	19.0 / 75.6	17.1 / 81.0	9.4 / 88.4	8.4 / 90.6	17.8 / 77.6	16.3 / 82.2
Ceftazidime	5.6 / 90.7	- / -	1.3 / 94.9	- / -	1.3 / 96.5	- / -	4.2 / 94.8	- / -	2.7 / 94.9	- / -
Colistin	98.1 / 1.9	98.1 / 1.9	98.7 / 1.3	98.7 / 1.3	97.8 / 2.2	97.8 / 2.2	100.0 / 0.0	100.0 / 0.0	98.8 / 1.2	98.8 / 1.2
Levofloxacin	0.9 / 91.6	0.9 / 99.1	3.0 / 86.3	1.3 / 97.0	1.0 / 94.0	0.6 / 99.0	5.2 / 73.9	3.2 / 94.8	2.8 / 85.4	1.7 / 97.2
Meropenem	0.0 / 95.3	0.0 / 95.3	0.0 / 89.3	0.0 / 89.3	0.0 / 98.1	0.0 / 98.1	0.0 / 100.0	0.0 / 100.0	0.0 / 96.3	0.0 / 96.3
S. maltophilia	(170)		(106)		(28)		(58)		(362)	
Ceftazidime	42.4 / 45.3	- / -	28.3 / 54.7	- / -	25.0 / 50.0	- / -	41.4 / 46.6	- / -	36.7 / 48.6	- / -
Colistin	97.6 / 2.4	97.6 / 2.4	98.9 / 1.1	98.9 / 1.1	97.5 / 2.5	97.5 / 2.5	99.7 / 0.3	99.7 / 0.3	98.5 / 1.5	98.5 / 1.5
Doxycycline	67.9 / 30.6	67.9 / 30.6	52.4 / 47.4	52.4 / 47.4	79.4 / 20.4	79.4 / 20.4	41.0 / 57.4	41.0 / 57.4	59.6 / 39.7	59.6 / 39.7
Levofloxacin	71.6 / 16.0	- / -	81.1 / 14.2	- / -	75.0 / 14.3	- / -	87.9 / 5.2	- / -	77.3 / 13.6	- / -
Meropenem	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -	- / -
Trimethoprim/sulfamethoxazole	97.6 / 2.4	98.8 / 1.2	94.3 / 5.7	94.3 / 5.7	78.6 / 21.4	78.6 / 21.4	93.1 / 6.9	93.1 / 6.9	94.5 / 5.5	95.0 / 5.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2011].
c. Includes: *Klebsiella oxytoca* (94 strains), *K. ozaenae* (3 strains), *K. pneumoniae* (859 strains), and unspeciated *Klebsiella* (25 strains).
d. Includes: *Klebsiella oxytoca* (5 strains), and *Klebsiella pneumoniae* (208 strains).
e. Includes: *Enterobacter aerogenes* (86 strains), *E. amnigenus* (2 strains), *E. asburiae* (1 strain), *E. cloacae* (356 strains), *E. sakazakii* (1 strain), and unspeciated *Enterobacter* (26 strains).
f. Includes: *Acinetobacter baumannii* (896 strains), *A. lwoffii* (5 strains), *A. ursingii* (1 strain), and unspeciated *Acinetobacter* (63 strains).