Comparison of Tigecycline Activity Tested Against Multidrug-resistant Bacteria Isolated from European Medical Centres in Two Time Periods: 2003-2005 and 2008-2010

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AMENDED ABSTRACT

Objectives: To compare the activities of tigecycline and comparators tested against bacteria with clinically important resistance (R) phenotypes isolated in Europe (EU) in 2003-2005 (before tigecycline was approved for clinical use) with those isolated in 2008-2010 (contemporary strains).

Methods: 6,345 clinical isolates, including 3,881 oxacillin-R *S. aureus* (MRSA), 501 vancomycin (VAN)-R enterococci (VRE), 581 *E. coli* with ESBL phenotype (ESBL-EC), 647 *K. pneumoniae* with ESBL phenotype (ESBL-KPN), 112 meropenem (MER)-R Enterobacteriaceae and 466 imipenem-R *Acinetobacter* spp. (IMI-R-ASP), were collected from 48 hospitals in 18 EU countries and Israel. The isolates were tested for susceptibility (S) by the CLSI microdilution broth method and EUCAST breakpoint criteria were used for MIC result interpretations.

Results: Overall, 96.6% of strains were tigecycline-S and tigecycline MIC distributions were very similar in the two time periods evaluated. Two-thirds of tigecycline non-S strains were IMI-R-ASP with tigecycline MIC at >1 mg/L (EUCAST breakpoint for enterics). MRSA showed low S to levofloxacin (LEV; 8.1-11.4%) and clindamycin (50.2-64.7%), and high S to tigecycline (>99.9%), VAN (100.0%), daptomycin (DAP; 100.0%), linezolid (LZD; 99.9-100.0%) and cotrimoxazole (93.4-97.6%) in both periods. Against VRE, tigecycline ($MIC_{50/90}$, 0.06-0.12/0.25 mg/L), DAP ($MIC_{50/90}$, 2-4/4 mg/L) and LZD ($MIC_{50/90}$, 1/2 mg/L) were the most active compounds (>99% S). 99.5% of ESBL-EC were S (MIC, ≤1 mg/L) to tigecycline ($MIC_{50/90}$, 0.25/0.5 mg/L). ESBL-EC exhibited low S to LEV (24.5-31.7%) and gentamicin (GEN; 54.2-59.9%) in both time periods, but >99% of strains were S to MER. Tigecycline inhibited 89.7-91.7% of ESBL-KPN and 88.1-88.6% of MER-R-Enterobacteriaceae at ≤1 mg/L. Only 29.6-35.8% of ESBL-KPN was S to GEN, and S to LEV and MER dropped from 55.2 and 93.9% in 2003-2005 to 26.7 and 86.0% in 2008-2010, respectively. Among MER-R-KPN, S to amikacin and LEV fell from 59.5 and 42.9% in 2003-2005 to 28.6 and 8.6% in 2008-2010, respectively. Only 67.1% of MER-R-Enterobacteriaceae isolated in 2008-2010 were S to colistin. Tigecycline ($MIC_{50/90}$, 1/2 mg/L; 66.7-73.1% inhibited at ≤1 mg/L) and the polymyxins (>99% S) were the most active compounds tested against IMI-R-ASP.

Conclusions: Tigecycline was very active against this large collection of multidrug-R organisms and no trend toward decreased tigecycline activity overtime was observed for any of the organisms or R subsets. Tigecycline demonstrated sustained potent in vitro activity and a broad-spectrum against clinically important R organisms from EU hospitals.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are frequently multidrug-resistant (MDR) and represent major causes of serious bacterial infections in many European hospitals. Treatment of infections caused by these organisms especially VRE strains, is becoming increasingly difficult mainly because of limited therapeutic options.

The emergence and dissemination of Enterobacteriaceae producing extended spectrum β-lactamases (ESBLs), stably derepressed AmpC enzymes and, more recently, carbapenemases, has compromised the use of many β-lactam agents in various geographic regions. Furthermore, strains producing these enzymes usually have elevated rates of resistance to fluoroquinolones and aminoglycosides.

Acinetobacter spp. have emerged as important opportunistic pathogens in the past two decades. These pathogens are capable of causing a range of nosocomial infections and usually are susceptible to a very limited number of antimicrobial agents.

Tigecycline is a newer semisynthetic glycylcycline derived from minocycline, which has been approved by the United States Food and Drug Administration (USA-FDA) and by the European Medicines Agency (EMEA) for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections and community-acquired pneumonia. In the present study, we evaluated the activities of tigecycline and comparators tested against bacteria with clinically important resistance phenotypes isolated in Europe in 2003-2005 (before tigecycline was approved for clinical use) and compared with those isolated in 2008-2010 (contemporary strains).

MATERIALS AND METHODS

Bacterial isolates: A total of 6,345 clinical isolates, including 3,881 oxacillin-resistant *S. aureus* (MRSA), 501 vancomycin-resistant enterococci (VRE), 581 *Escherichia coli* with an ESBL phenotype (ESBL-*E. coli*), 647 *Klebsiella pneumoniae* with an ESBL phenotype (ESBL-*K. pneumoniae*), 112 meropenem-resistant Enterobacteriaceae and 466 imipenem-resistant *Acinetobacter* spp. were collected from 48 hospitals in 18 European countries and Israel.

E. coli and *K. pneumoniae* isolates with elevated MIC values (≥2 mg/L) for ceftazidime or ceftriaxone or aztreonam were categorized as ESBL phenotype. Enterobacteriaceae strains displaying meropenem MIC values at ≥4 mg/L were considered meropenem-resistant and *Acinetobacter* spp. strains with imipenem MIC values at ≥16 mg/L were considered imipenem-resistant.

Susceptibility testing. All isolates were tested by reference broth microdilution methods using the Clinical and Laboratory Standards Institute recommendations (CLSI, M07-A8). All isolates were tested using validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio USA) and freshly prepared Mueller-Hinton broth (MHB) which is necessary for testing tigecycline. EUCAST approved susceptible breakpoints were used to categorize susceptibility (2011). The following American Type Culture Collection (ATCC) quality control organisms were concurrently tested confirming test quality assurance: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, *E. coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

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RESULTS

- Overall, 96.6% of strains were tigecycline-susceptible and tigecycline MIC distributions were very similar in the two time periods evaluated (Table 1).
- Two-thirds of tigecycline non-susceptible strains overall were imipenem-resistant *Acinetobacter* spp. with tigecycline MIC at >1 mg/L (EUCAST breakpoint for Enterobacteriaceae; Table 1).
- MRSA showed low susceptibility to levofloxacin (8.1-11.4%) and clindamycin (50.2-64.7%), and high susceptibility to tigecycline (>99.9%), vancomycin (100.0%), daptomycin (>99.9-100.0%), linezolid (99.9-100.0%) and sulfamethoxazole/trimethoprim (93.4-97.6%) in both time periods (Table 2).
- Against VRE, tigecycline ($MIC_{50/90}$, 0.06-0.12/0.25 mg/L), daptomycin ($MIC_{50/90}$, 2-4/4 mg/L) and linezolid ($MIC_{50/90}$, 1/2 mg/L) were the most active compounds (>99% susceptibility; Table 2).
- Among *E. coli* with an ESBL-phenotype, 99.5% of strains were susceptible (MIC, ≤1 mg/L) to tigecycline ($MIC_{50/90}$, 0.25/0.5 mg/L). *E. coli* strains with ESBL phenotype exhibited low susceptibility to levofloxacin (24.5-31.7%) and gentamicin (54.2-59.9%) in both time periods. In contrast, >99% of strains were susceptible to meropenem (Table 2).
- Tigecycline inhibited 89.7-91.7% of *K. pneumoniae* strains with ESBL phenotype and 88.1-88.6% of meropenem-resistant Enterobacteriaceae at ≤1 mg/L. Only 29.6-35.8% of *K. pneumoniae* strains with ESBL phenotype were susceptible to gentamicin. Furthermore, susceptibility to levofloxacin and meropenem dropped from 55.2 and 93.9% in 2003-2005 to 26.7 and 86.0% in 2008-2010, respectively (Table 2).
- Among meropenem-resistant Enterobacteriaceae, susceptibility to amikacin and levofloxacin fell from 59.5 and 42.9% in 2003-2005 to only 28.6 and 8.6% in 2008-2010, respectively. A more limited number (67.1%) of meropenem-resistant Enterobacteriaceae isolated in 2008-2010 were susceptible to colistin (Table 2).
- Tigecycline ($MIC_{50/90}$, 1/2 mg/L; 66.7-73.1% inhibited at ≤1 mg/L) and the polymyxins (>99% susceptible) were the most active compounds tested against imipenem-resistant *Acinetobacter* spp. (Table 2).

Table 2. Antimicrobial activities of tigecycline and comparator antimicrobial agents tested against resistant subsets of organisms from two time periods.

Organism / (no. tested: 2003-2005 / 2008-2010)	% susceptible[a]		% resistant[a]	
	2003-2005	2008-2010	2003-2005	2008-2010
MRSA (1,700/2,181)				
Tigecycline	99.9	>99.9	0.1	<0.1
Clindamycin	50.2	64.7	49.4	34.6
Erythromycin	25.1	32.1	74.4	67.1
Levofloxacin	8.1	11.4	88.8	87.4
Tetracycline	77.6	81.9	22.4	17.9
TMP/SMX	93.4	97.7	6.6	2.3
Linezolid	100.0	100.0	0.0	0.0
Daptomycin	100.0	>99.9	0.0	<0.1
Vancomycin	100.0	100.0	0.0	0.0
VRE (147/354)				
Tigecycline	98.6	99.4	0.0	0.0
Ampicillin	27.9	13.3	71.4	86.7
Linezolid	100.0	99.4	0.0	0.6
Daptomycin	100.0[b]	100.0[b]	-	-
Teicoplanin	28.6	21.2	71.4	78.8
ESBL-*E. coli* (227/585)				
Tigecycline	100.0	99.5	0.0	0.2
Meropenem	99.1	99.7	0.0	0.2
Ertapenem	96.4	95.9	3.6	2.9
Levofloxacin	31.7	24.5	68.3	74.7
Gentamicin	54.2	59.9	44.1	38.6
Amikacin	81.9	87.5	10.1	4.1
ESBL-*K. pneumoniae* (261/386)				
Tigecycline	89.7	91.7	0.8	1.3
Meropenem	93.9	86.0	1.9	10.9
Ertapenem	86.2	76.6	10.3	19.7
Levofloxacin	55.2	26.7	40.6	70.2
Gentamicin	29.6	35.8	66.9	62.2
Amikacin	53.3	66.3	25.7	17.1
Colistin/Polymyxin B	96.9	94.0	2.3	5.2
Meropenem-R-Enterics (42[c]/70[d])				
Tigecycline	88.1	88.6	0.0	0.0
Levofloxacin	42.9	8.6	45.2	88.6
Gentamicin	50.0	60.0	47.6	34.3
Amikacin	59.5	28.6	9.5	51.4
Colistin/Polymyxin B	78.6	67.1	21.4	32.9
Imipenem-R-*Acinetobacter* (120/346)				
Tigecycline[e]	66.7	73.1	7.5	6.1
Levofloxacin	0.8	1.7	95.0	97.7
Gentamicin	5.9	11.8	94.1	88.2
Tobramycin	12.5	29.2	87.5	70.8
Colistin/Polymyxin B	100.0	99.7	0.0	0.3

a. According to EUCAST breakpoint criteria (EUCAST, 2011), unless noted.
b. According to CLSI susceptible breakpoint of ≤4 mg/L.
c. Includes: *Enterobacter aerogenes* (5 strains), *Enterobacter cloacae* (16 strains), *Escherichia coli* (two strains), *Klebsiella pneumoniae* (16 strains), *Proteus mirabilis* (one strain), and *Serratia marcescens* (two strains).
d. Includes: *Enterobacter aerogenes* (two strains), *Enterobacter cloacae* (nine strains), *Escherichia coli* (two strains), *Klebsiella oxytoca* (two strains), *Klebsiella pneumoniae* (54 strains), and *Proteus mirabilis* (one strain).
e. According to EUCAST breakpoints for *Enterobacteriaceae*, i.e. susceptible, ≤1 mg/L and resistant, ≥4 mg/L.
Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus* , VRE = vancomycin-resistant enterococci.

CONCLUSIONS

- Tigecycline was very active against this large collection of multidrug-resistant organisms and no significant trend toward decreased tigecycline activity over time was observed for any of the organisms or resistant subsets. In fact, for five of six (83.3%) compared subsets the tigecycline susceptibility rates increased.
- Tigecycline demonstrated sustained potent in vitro activity and a broad-spectrum against clinically important resistant organisms from European hospitals (Tables 1 and 2).

Table 1. Tigecycline activity tested against resistant subsets of organisms from two time periods.

Organism	Time period (no. tested)	No. of isolates (cumulative %) inhibited at tigecycline MIC (mg/L) of:						
		≤0.06	0.12	0.25	0.5	1	2	4
MRSA	2003-2005 (1,700)	214 (12.6)	856 (62.9)	558 (95.8)	71 (>99.9)	1 (100.0)		
	2008-2010 (2,181)	455 (20.9)	906 (62.4)	773 (97.9)	46 (>99.9)	1 (100.0)		
VRE	2003-2005 (147)	81 (55.1)	39 (81.6)	25 (98.6)	2 (100.0)			
	2008-2010 (354)	158 (44.6)	120 (78.6)	74 (99.4)	2 (100.0)			
ESBL-*E. coli*	2003-2005 (227)	10 (4.4)	71 (35.7)	117 (87.2)	28 (99.6)	1 (100.0)		
	2008-2010 (584)	60 (10.3)	169 (39.2)	275 (86.3)	72 (98.6)	5 (99.5)	2 (99.8)	0 (99.8)[a]
ESBL-*K. pneumoniae*	2003-2005 (261)	0 (0.0)	10 (3.8)	68 (29.9)	97 (67.1)	59 (89.7)	25 (99.2)	2 (100.0)
	2008-2010 (386)	1 (0.3)	18 (4.9)	133 (39.4)	151 (78.5)	51 (91.7)	27 (98.7)	5 (100.0)
Meropenem-R-Enterics	2003-2005 (42)[b]	1 (2.4)	1 (4.8)	11 (31.0)	10 (54.8)	14 (88.1)	5 (100.0)	
	2008-2010 (70)[c]	0 (0.0)	2 (2.9)	11 (18.6)	31 (62.9)	18 (88.6)	8 (100.0)	
Imipenem-R-*Acinetobacter*	2003-2005 (120)	0 (0.0)	0 (0.0)	2 (1.7)	20 (18.3)	58 (66.7)	31 (92.5)	9 (100.0)
	2008-2010 (346)	0 (0.0)	2 (0.6)	44 (13.3)	74 (34.7)	133 (73.1)	72 (93.9)	20 (99.7)[a]

a. Only one strain with tigecycline MIC at >4 mg/L
b. Includes: *Enterobacter aerogenes* (five strains), *Enterobacter cloacae* (16 strains), *Escherichia coli* (two strains), *Klebsiella pneumoniae* (16 strains), *Proteus mirabilis* (one strain), and *Serratia marcescens* (two strains).
c. Includes: *Enterobacter aerogenes* (two strains), *Enterobacter cloacae* (nine strains), *Escherichia coli* (two strains), *Klebsiella oxytoca* (two strains), *Klebsiella pneumoniae* (54 strains), and *Proteus mirabilis* (one strain).
Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*, VRE = vancomycin-resistant enterococci.