Tigecycline Activity Against Multidrug-resistant Enterobacteriaceae and *Acinetobacter* spp. Isolated in USA Hospitals (2005-2009)

269

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ABSTRACT

Background: High prevalence of Gram-negative strains producing broad-spectrum β-lactamases (such as ESBL, AmpC and KPC) coupled with elevated rates of resistance (R) to fluoroquinolones and aminoglicosides, forces increasing use of carbapenems. We evaluated the activity of tigecycline against Enterobacteriaceae (ENT) and *Acinetobacter* spp. (ASP) with various R phenotypes.

Methods: 10,398 clinical isolates (9,563 ENT and 835 ASP) were collected from 31 USA medical centers in the 2005-2009 period (1924-2264 organisms per year). The isolates were tested for susceptibility (S) by the CLSI microdilution broth method against tigecycline and many comparators. Tigecycline breakpoints established by the USA-FDA for ENT (≤2/≥8 µg/ml for S/R) were applied to ASP for comparison purpose.

Results: 6.8 and 15.4% of *E. coli* (EC) and *Klebsiella* spp. (KSP) exhibited an ESBL phenotype, respectively; and 22.2% of *Enterobacter* spp. (ESP) strains were R to ceftazidime (CAZ). Tigecycline was active against EC (100.0% S) independent of ESBL phenotype or R to other antimicrobials. Among KSP, tigecycline S ranged from 97.0 to 99.4%. Overall, 97.9% of ESBL-producing KSP were S to tigecycline, while among imipenem (IMI)-R KSP, tigecycline non-S strains were observed only in 2009 (3 strains). Tigecycline was active against ESP (97.2-99.5% S), including CAZ-R strains (94.7-98.8% S). R to ciprofloxacin/gentamicin among ESBL-EC, ESBL-KSP and CAZ-R ESP were 75.1/31.1, 75.1/38.5 and 23.5/25.5%, respectively. Tigecycline inhibited 94.4% of ASP overall and 86.2% of IMI-R ASP at ≤2 µg/ml. No trend of decreased tigecycline activity overtime was observed for any of the organisms or R subsets during the study period.

Conclusion: These results indicate that tigecycline has sustained potent in vitro activity and a broad-spectrum against clinically important ENT species and ASP causing infections in USA medical centers, including MDR organism subsets.

INTRODUCTION

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

Acinetobacter spp. represents a heterogenous group of organisms that are usually commensal, but in the past few decades they have emerged as important opportunistic pathogens. *Acinetobacter* spp. infections are usually restricted to the hospital setting, mainly affecting patients in the intensive care unit. These pathogens are capable of causing a range of nosocomial infections and usually are only susceptible to a very limited number of antimicrobial agents.

Tigecycline is a semisynthetic glycylcycline derived from the minocycline, a molecule, and 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 skin structure (cSSSI), complicated intra-abdominal (CIAI) and lower respiratory tract infections. We assessed the spectrum and potency of tigecycline tested against Enterobacteriaceae and *Acinetobacter* spp. from USA medical centers expressing various resistance phenotypes.

MATERIALS AND METHODS

Bacterial strains: The isolates were consecutively collected and only one strain per patient was included in the study (prevalence mode format). A total of 10,398 clinical isolates (9,563 Enterobacteriaceae and 835 *Acinetobacter* spp.) were collected from 31 USA medical centers in the 2005-2009 period (1,924-2,264 organisms per year). The sites of infection included the bloodstream, respiratory tract (mainly in hospitalized patients), cSSSI and urinary tract.

Antimicrobial susceptibility testing: All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical and Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains, including *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) criteria, when available. Tigecycline breakpoints established by the USA-FDA for Enterobacteriaceae (≤2/≥8 µg/ml for susceptible/resistant) were applied to *Acinetobacter* spp. for comparison purposes only.

ACKNOWLEDGMENT

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RESULTS

- Overall, 6.8 and 15.4% of *E. coli* and *Klebsiella* spp. exhibited an ESBL phenotype, respectively; and 22.2% of *Enterobacter* spp. strains were resistant to ceftazidime (MIC, ≥16 µg/ml). Among *Acinetobacter* spp., 29.5% of strains were non-susceptible to imipenem (MIC, ≥8 µg/ml; Table 1).
- Tigecycline was active against *E. coli* (MIC_{90}, 0.25 µg/ml, 100.0% susceptible), independent of ESBL phenotype or resistance to other antimicrobials. Among ESBL-producing strains, 75.1 and 31.1% were resistant to ciprofloxacin and gentamicin, respectively (Table 1).
- Among *Klebsiella* spp., tigecycline ($MIC_{50/90}$, 0.25/1 µg/ml) susceptibility varied from 99.4% in 2006 and 2007 to 97.0% in 2009 (Table 2). Tigecycline was also very active against *Klebsiella* spp. strains with an ESBL phenotype ($MIC_{50/90}$, 0.5/1 µg/ml; 97.9% susceptible) and all imipenem-non-susceptible strains were susceptible to tigecycline except for three strains (1.8%) isolated in 2009 (Tables 1 and 2).
- Resistance to ciprofloxacin and gentamicin were 75.1 and 38.5% among ESBL-producing *Klebsiella* spp., respectively; while among imipenem-non-susceptible *Klebsiella* spp., 89.0 and 32.3% were resistant to ciprofloxacin and gentamicin, respectively (Table 1).
- Tigecycline was active against *Enterobacter* spp. ($MIC_{50/90}$, 0.25/1 µg/ml; 98.4% susceptible overall), including ceftazidime-resistant strains ($MIC_{50/90}$, 0.5/2 µg/ml; 97.1% susceptible). Resistances to ciprofloxacin and gentamicin were observed among 23.5 and 25.5% of ceftazidime-resistant *Enterobacter* spp. (Table 1).
- Tigecycline inhibited 94.4% of *Acinetobacter* spp. overall and 86.2% of imipenem-non-susceptible at ≤2 µg/ml (Table 1); only 0.5-1.6% resistance.
- The occurrences of *E. coli* strains with an ESBL phenotype increased from 5.1 to 9.8% between 2005 and 2009. The prevalence of imipenem-non-susceptible *Klebsiella* spp. also increased (from 5.2 to 6.4%) in the same period of time. In contrast, the occurrence of *Klebsiella* spp. with an ESBL phenotype decreased from 17.6% in 2005 to 14.6% in 2006 and remained relatively stable between 14.0 and 15.9% in the 2006-2009 period (Figure 1).
- Imipenem resistance among *Acinetobacter* spp. increased from 7.6% in 2005 to as high as 44.3% in 2007, while rates of ceftazidime resistance among *Enterobacter* spp. remained relatively stable during the study period (Figure 1).
- No trend of decreased tigecycline activity overtime was observed for any of the organisms or resistant subsets assessed during the study period (Table 3).

Table 1. Activity of Tigecycline and comparator antimicrobial agents when tested against 10,398 Gram-negative isolates from USA medical centers.

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Escherichia coli (4,937)					
Tigecycline[b]	0.12	0.25	≤0.03 – 2	100.0 / 0.0	99.9 / 0.0
Ceftazidime	≤1	≤1	≤1 – >16	95.7 / 3.6	93.9 / 4.3
Ceftriaxone	≤0.25	≤0.25	≤0.25 – >32	94.4 / 5.4	94.4 / 5.4
Cefepime	≤0.12	0.25	≤0.12 – >16	97.7 / 1.9	95.8 / 2.9
Imipenem	≤0.12	0.25	≤0.12 – 4	99.9 / 0.1	99.9 / 0.0
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	76.3 / 23.6	76.0 / 23.7
Gentamicin	≤2	8	≤2 – >8	89.9 / 9.5	89.2 / 10.1
Amikacin	≤4	≤4	≤4 – >32	99.7 / 0.1	99.0 / 0.3
ESBL-phenotype *E. coli* (334)					
Tigecycline[b]	0.25	0.25	0.06 – 2	100.0 / 0.0	99.4 / 0.0
Ceftazidime	16	>16	≤1 – >16	36.8 / 53.6	9.3 / 63.2
Ceftriaxone	>32	>32	≤0.25 – >32	16.8 / 79.3	16.8 / 79.3
Cefepime	2	>16	≤0.12 – >16	65.9 / 27.8	43.1 / 43.1
Imipenem	0.25	0.5	≤0.12 – 4	98.5 / 0.9	99.1 / 0.0
Ciprofloxacin	>4	>4	≤0.5 – >4	24.6 / 75.1	24.6 / 75.4
Gentamicin	≤2	>8	≤2 – >8	66.5 / 31.1	63.8 / 33.5
Amikacin	≤4	8	≤4 – >32	97.3 / 0.6	91.3 / 2.7
Klebsiella pneumoniae (2,771)					
Tigecycline[b]	0.25	1	≤0.03 – >4	98.7 / 0.1	94.3 / 1.3
Ceftazidime	≤1	>16	≤1 – >16	86.2 / 13.4	85.0 / 13.8
Ceftriaxone	≤0.25	32	≤0.25 – >32	86.0 / 13.7	86.0 / 13.7
Cefepime	≤0.12	4	≤0.12 – >16	91.4 / 6.6	87.8 / 9.5
Imipenem	0.25	0.5	≤0.12 – >8	94.1 / 5.6	94.4 / 4.5
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	85.2 / 14.1	84.0 / 14.8
Gentamicin	≤2	≤2	≤2 – >8	91.4 / 7.0	90.2 / 8.6
Amikacin	≤4	≤4	≤4 – >32	97.3 / 1.0	92.0 / 6.3
ESBL-phenotype *K. pneumoniae* (426)					
Tigecycline[b]	0.5	1	0.06 – >4	97.9 / 0.2	90.6 / 2.1
Ceftazidime	>16	>16	≤1 – >16	10.1 / 87.1	2.3 / 89.9
Ceftriaxone	>32	>32	≤0.25 – >32	8.9 / 89.2	8.9 / 89.2
Cefepime	16	>16	≤0.12 – >16	43.9 / 43.2	21.1 / 61.7
Imipenem	0.5	>8	≤0.12 – >8	62.4 / 36.6	63.4 / 29.1
Ciprofloxacin	>4	>4	≤0.5 – >4	23.2 / 75.1	19.7 / 76.8
Gentamicin	4	>8	≤2 – >8	51.4 / 38.5	44.6 / 48.6
Amikacin	16	32	≤4 – >32	60.3 / 6.6	49.5 / 39.7
Imipenem-non-susceptible *K. pneumoniae* (164)					
Tigecycline[b]	0.5	1	0.12 – >4	98.2 / 0.6	92.1 / 1.8
Ceftazidime	>16	>16	≤1 – >16	2.4 / 95.7	2.4 / 97.6
Ceftriaxone	>32	>32	≤0.25 – >32	2.4 / 97.6	2.4 / 97.6
Cefepime	>16	>16	≤0.12 – >16	9.1 / 72.0	2.4 / 96.3
Imipenem	>8	>8	2 – >8	0.0 / 95.1	4.9 / 75.6
Ciprofloxacin	>4	>4	≤0.5 – >4	11.0 / 89.0	10.4 / 89.0
Gentamicin	4	>8	≤2 – >8	54.9 / 32.3	47.6 / 45.1
Amikacin	32	32	≤4 – >32	36.6 / 6.7	22.6 / 63.4
Enterobacter spp. (1,855)					
Tigecycline[b]	0.25	1	0.06 – >4	98.4 / 0.2	93.1 / 1.6
Ceftazidime	≤1	>16	≤1 – >16	75.8 / 22.2	72.0 / 24.2
Ceftriaxone	≤0.25	>32	≤0.25 – >32	72.9 / 25.0	72.9 / 25.0
Cefepime	≤0.12	2	≤0.12 – >16	96.8 / 2.2	86.6 / 5.1
Ciprofloxacin	≤0.5	1	≤0.5 – >4	91.4 / 6.6	89.9 / 8.6
Gentamicin	≤2	≤2	≤2 – >8	92.0 / 6.7	91.4 / 8.0
Amikacin	≤4	≤4	≤4 – >32	99.5 / 0.3	98.7 / 0.5
Ceftazidime-resistant *Enterobacter* spp. (412)					
Tigecycline[b]	0.5	2	0.06 – 4	97.1 / 0.0	83.3 / 2.9
Ceftazidime	>16	>16	16 – >16	0.0 / 100.0	0.0 / 100.0
Ceftriaxone	>32	>32	2 – >32	0.0 / 99.5	0.0 / 99.5
Cefepime	2	16	≤0.12 – >16	86.7 / 8.7	41.7 / 21.6
Imipenem	0.5	2	≤0.12 – >8	88.1 / 7.8	92.2 / 2.4
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	71.4 / 23.5	67.2 / 28.6
Gentamicin	≤2	>8	≤2 – >8	69.2 / 25.5	67.2 / 30.8
Amikacin	≤4	8	≤4 – >32	98.1 / 1.2	95.4 / 1.9
Acinetobacter spp. (835)					
Tigecycline[b]	0.5	2	≤0.03 – >4	94.4 / 0.5[c]	- / -
Amikacin	≤4	>32	≤4 – >32	70.5 / 23.2	65.6 / 29.5
Cefepime	16	>16	≤0.12 – >16	47.4 / 40.7	- / -
Ceftazidime	16	>16	≤1 – >16	45.5 / 49.5	- / -
Ceftriaxone	32	>32	≤0.25 – >32	23.1 / 46.9	- / -
Ciprofloxacin	>4	>4	≤0.5 – >4	46.8 / 52.7	46.8 / 53.2
Gentamicin	4	>8	≤2 – >8	53.4 / 43.1	53.4 / 46.6
Imipenem	0.5	>8	≤0.12 – >8	70.5 / 22.3	66.0 / 22.3
Imipenem-non-susceptible *Acinetobacter* spp. (246)					
Tigecycline[b]	1	4	0.25 – >4	86.2 / 1.6[c]	- / -
Amikacin	>32	>32	≤4 – >32	29.3 / 54.5	22.0 / 70.7
Cefepime	>16	>16	4 – >16	2.0 / 88.6	- / -
Ceftazidime	>16	>16	2 – >16	4.9 / 92.3	- / -
Ceftriaxone	>32	>32	8 – >32	0.8 / 91.1	- / -
Imipenem	>8	>8	8 – >8	0.0 / 75.6	0.0 / 75.6
Ciprofloxacin	>4	>4	0.06 – >4	0.8 / 99.2	0.8 / 99.2
Gentamicin	>8	>8	≤2 – >8	9.8 / 82.5	9.8 / 90.2

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2009].
c. Enterobacteriaceae breakpoints established by the USA-FDA were applied for comparison purposes only.

Table 2. Tigecycline MIC distributions of Enterobacteriaceae and *Acinetobacter* spp. strains with various antimicrobial susceptibility patterns from USA hospitals.

Organisms / resistance phenotype (no. tested)	No. of isolates (cumulative %) inhibited at MIC (µg/ml) of:								
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4
E. coli (4,937)	10 (0.2)	867 (17.8)	2,589 (70.2)	1,333 (97.2)	121 (99.7)	11 (99.9)	6 (100.0)	-	-
ESBL-phenotype (334)[a]	0 (0.0)	22 (6.7)	138 (47.9)	149 (92.5)	20 (98.5)	3 (99.4)	2 (100.0)	-	-
Klebsiella spp. (2,771)	1 (<0.1)	5 (0.2)	115 (4.4)	1,373 (53.9)	891 (86.1)	229 (94.3)	122 (98.7)	33 (99.9)	2 (100.0)
ESBL-phenotype (426)[a]	0 (0.0)	1 (0.2)	9 (2.4)	94 (24.4)	198 (70.9)	84 (90.6)	31 (97.9)	8 (99.8)	1 (100.0)
Imipenem-non-susceptible (164)[b]	0 (0.0)	0 (0.0)	2 (1.2)	24 (15.9)	92 (72.0)	33 (92.1)	10 (98.2)	2 (99.4)	1 (100.0)
Enterobacter spp. (1,855)	0 (0.0)	7 (0.4)	47 (2.9)	1,003 (57.0)	547 (86.5)	123 (93.1)	98 (98.4)	27 (99.8)	3 (100.0)
Ceftazidime-resistant (412)[c]	0 (0.0)	1 (0.2)	5 (1.5)	166 (41.8)	109 (68.2)	62 (83.3)	57 (97.1)	12 (100.0)	-
Acinetobacter spp. (835)	4 (0.5)	45 (5.9)	147 (23.5)	175 (44.4)	101 (56.5)	184 (78.6)	132 (94.4)	43 (99.5)	4 (100.0)
Imipenem-non-susceptible (246)[d]	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.4)	22 (11.4)	102 (52.9)	82 (86.2)	30 (98.4)	4 (100.0)

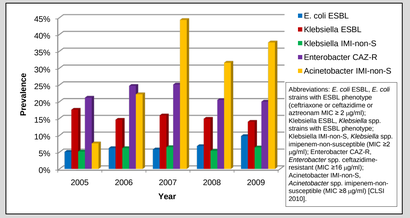
a. ESBL phenotype defined as ceftriaxone or ceftazidime or aztreonam MIC ≥2 µg/ml [CLSI 2010].
b. Imipenem MIC ≥2 µg/ml [CLSI 2010].
c. Ceftazidime MIC ≥16 µg/ml [CLSI 2010].
d. Imipenem MIC ≥8 µg/ml [CLSI 2010].

Table 3. Yearly variation of tigecycline antimicrobial activity when tested against Gram-negative organisms from USA medical centers with various resistance phenotypes.

Organisms / resistance phenotype (no. tested)	Tigecycline MIC_{50} / MIC_{90} / % Susceptible (no. tested)				
	2005	2006	2007	2008	2009
E. coli (4,937)	0.12/0.25/100 (1,008)	0.12/0.25/100 (974)	0.12/0.25/100 (875)	0.12/0.25/100(1,085)	0.12/0.25/100 (995)
ESBL[a] (334)	0.25/0.25/100 (51)	0.12/0.25/100 (60)	0.25/0.25/100 (51)	0.25/0.25/100 (74)	0.25/0.25/100 (98)
Klebsiella spp. (2,771)	0.25/1/99.1 (541)	0.25/1/99.4 (519)	0.25/1/99.4 (522)	0.5/1/99.0 (597)	0.5/1/97.0 (592)
ESBL[a] (426)	0.5/1/97.9 (95)	0.5/1/98.7 (76)	0.5/1/98.8 (83)	0.5/2/98.9 (89)	0.5/2/95.2 (83)
Imipenem-non-S[b] (164)	0.5/1/100 (28)	0.5/0.5/100 (32)	0.5/1/100 (34)	0.5/1/100 (32)	0.5/2/92.1 (38)
Enterobacter spp. (1,855)	0.25/1/97.2 (359)	0.25/1/99.5 (364)	0.25/1/98.8 (342)	0.25/1/98.5 (405)	0.5/1/97.9 (385)
Ceftazidime-R[c] (412)	0.5/2/94.7 (76)	0.5/1/97.8 (90)	0.5/2/98.8 (86)	0.5/2/97.6 (83)	0.5/2/96.1 (77)
Acinetobacter spp. (835)	0.5/2/93.1 (145)	0.5/2/97.7 (171)	1/4/88.7 (185)	0.5/2/97.2 (177)	0.5/2/95.5 (157)
Imipenem-non-S[d] (246)	1/2/100 (11)	1/2/92.1 (38)	2/475.6 (82)	1/2/91.1 (56)	1/4/89.8 (59)

a. ESBL phenotype defined as ceftriaxone or ceftazidime or aztreonam MIC ≥2 µg/ml [CLSI 2010].
b. Imipenem MIC ≥2 µg/ml [CLSI 2010].
c. Ceftazidime MIC ≥16 µg/ml [CLSI 2010].
d. Imipenem MIC ≥8 µg/ml [CLSI 2010].

Figure 1. Yearly occurrences of various resistance phenotypes in USA medical centers.



CONCLUSIONS

- Tigecycline demonstrated sustained potent in vitro activity and a broad-spectrum against clinically important Enterobacteriaceae species and *Acinetobacter* spp. causing infections in USA medical centers, including multidrug-resistant organism subsets.
- The results of this study indicated that tigecycline may have an evolving role in the treatment of infections caused by these increasingly resistant species.