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Activity of Tigecycline Tested Against an International Collection (2000-2004) of AmpC-Producing Enterobacteriaceae

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AMENDED ABSTRACT

Objective:

To evaluate the activity and potency of tigecycline (TIG) when tested against an international collection of Enterobacteriaceae (ENT) with chromosomal AmpC enzymes, including subsets predictive of extended-spectrum ß-lactamase (ESBL) production. TIG is the first-in-class glycylcycline to be approved (US-FDA) as a parenteral agent indicated for intra-abdominal and skin and skin structure infections, and has demonstrated activity against a variety of Gram-positive and –negative pathogens, including anaerobes.

Methods:

Non-duplicate clinically-significant bacterial isolates (2,413) were collected from 2000 to 2004 in >60 medical centers participating in the global TIG surveillance program. Isolates included *Citrobacter freundii* (CF), *Enterobacter aerogenes* (EA), *E. cloacae* (EC) and *Serratia marcescens* (SM). All isolates were tested using NCCLS (2003) broth microdilution methods against TIG and representative comparator agents. Ceftazidime (CTZ) resistance (R) was used as a marker for stably derepressed AmpC production, and cefepime (CPM) elevated MIC values (>= 4 mg/L) as a predictive marker for concomitant ESBL-production.

Results:

TIG results for the R organism subsets are in the table.

Organism (no. tested)	MIC (mg/L) 50%	MIC (mg/L) 90%	% inhibited at MIC (mg/L) <=1	<=2	<=4
EC (1246)	0.5	1	90	95	>99
CTZ-S (924)	0.5	1	96	97	>99
CTZ -R (276)	0.5	4	70	88	>99
CPM at < 4 mg/L (218)	0.5	4	71	87	>99
CPM at >= 4 mg/L (39)	1	2	71	94	100
EA (336)	0.5	1	93	97	>99
CTZ -S (236)	0.5	1	94	98	100
CTZ -R (83)	0.5	2	89	96	98
CPM at < 4 mg/L (77)	0.5	2	88	96	98
CPM at >= 4 mg/L (2)	1	-	100	-	-
CF (186)	0.25	1	94	98	100
CTZ -S (148)	0.25	0.5	96	99	100
CTZ -R (32)	0.5	2	87	96	100
CPM at < 4 mg/L (25)	0.5	2	88	100	-
CPM at >= 4 mg/L (5)	0.5	-	80	100	-
SM (645)	1	2	82	95	98
CTZ -S (618)	1	2	83	95	98
CTZ -R (13)	1	2	69	92	100
CPM at < 4 mg/L (12)	1	2	75	91	100
CPM at >= 4 mg/L (1)	-	-	0	100	-
Cumulative % Inhibited			88	96	>99

Stably-derepressed AmpC- and ESBL-production were evident in, respectively: 22.2 and 3.1% of EC; 24.7 and 0.6% of EA; 17.2 and 2.7% of CF; and 2.0 and 0.2% of SM. Slightly decreased potency (MIC_{90} values) of TIG among the CTZ-R subsets was noted and varied from 0- (SM) to 4-fold (EC and CF). Overall, 97.4 and 90.8% of CTZ-S and -R isolates, respectively, were inhibited by <= 2 mg/L of TIG. The presence of additional ESBL phenotypes among these isolates did not affect the potency of TIG, and >95% of CTZ- and CPM-R isolates remained S, indicative of the broad-spectrum of activity retained by this agent against highly-R ENT.

Conclusions:

Among EC, EA, CF and SM, including those strains that express AmpC and ESBL-enzymes, 96% were inhibited by <= 2 mg/L of TIG (the current USFDA breakpoint) and >99% were inhibited by 4 mg/L. TIG is highly stable to most R determinants affecting multiple drug classes, and may represent a significant choice among parenteral agents for broad-spectrum coverage, including the most commonly occurring - and problematic - resistance phenotypes.

INTRODUCTION

Tigecycline, a semisynthetic glycylcycline derived from the minocycline molecule, is a recently approved, broad-spectrum agent with documented activity against many Gram–negative and Gram-positive pathogens including Enterobacteriaceae, *Acinetobacter* spp., oxacillin-resistant staphylococci, vancomycin-resistant enterococci, penicillin-resistant *Streptococcus pneumoniae*, anaerobic wound pathogens, *Neisseria gonorrhoeae,* and commonly occurring respiratory pathogens. Only *P. aeruginosa* and certain Proteae regularly display elevated MIC values to tigecycline.

The findings from several large studies of Gram-negative isolates have also demonstrated that tigecycline possesses remarkable stability against tetracycline refractory strains (both efflux and ribosomal protection mechanisms) and against extended spectrum ß-lactamase (ESBL)-producing Enterobacteriaceae. The present study was conducted to further evaluate the activity and potency of tigecycline when tested against an international collection of Enterobacteriaceae with inducible or constitutively expressed chromosomal AmpC (Bush Group 1) enzymes, including subsets predictive of co-existent extended-spectrum ß-lactamase (ESBL) production.

MATERIALS AND METHODS

Specimen collection: Consecutively acquired, non-duplicate clinically-significant bacterial isolates (2,413) were collected from 2000 to 2004 in >60 medical centers representing 29 countries in the five continents of Asia, Australia, Europe, South America and North America that participated in a global tigecycline surveillance program. Species studied included *Enterobacter cloacae, E. aerogenes, Citrobacter freundii* and *Serratia marcescens*. Ceftazidime resistance was used as a marker for stably derepressed AmpC production in these species, and elevated cefepime MIC values (≥ 4 mg/L) were a predictive marker for concomitant ESBL-production.

Susceptibility testing: All isolates were identified by the participant laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, Iowa). Each strain was tested by a standardized broth microdilution method against more than 30 antimicrobial agents; only selected (peer) agents with the widest potential clinical utility and in vitro activity are reported here. All isolates were tested using standardized broth microdilution methods against tigecycline and representative comparator agents. Interpretation of quantitative MIC results was in accordance with Clinical and Laboratory Standards Institute (CLSI) methods and criteria. Tigecycline breakpoints utilized were those recommended by the US-FDA (≤ 2/4/≥ 8 mg/L for S/I/R, respectively). Concurrent quality control (QC) testing was performed using *E. coli* ATCC 25923; all QC results were within CLSI specified ranges.

SELECTED REFERENCES

1. Biedenbach DJ, Beach ML, Jones RN (2001). In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases. *Diagn Microbiol Infect Dis* 40: 173-177.

2. Bratu S, Tolaney P, Karumudi U, Quale J, Mooty M, Nichani S, Landman D (2005). Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents. *J Antimicrob Chemother* 56: 128-132.

3. Clinical and Laboratory Standards Institute. (2006). *Approved Standard M7-A7: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed*. Wayne, PA: CLSI.

4. Clinical and Laboratory Standards Institute. (2006). *Performance standards for antimicrobial susceptibility testing, 16th informational supplement M100-S16*. Wayne, PA: CLSI.

5. Felmingham D (2005). Tigecycline-the first glycylcycline to undergo clinical development: an overview of in vitro activity compared to tetracycline. *J Chemother* 17 (Suppl) 1: 5-11.

6. Fritsche TR, Strabala PA, Sader HS, Dowzicky MJ, Jones RN (2005). Activity of tigecycline tested against a global collection of Enterobacteriaceae, including tetracycline-resistant isolates. *Diagn Microbiol Infect Dis* 52: 209-213.

7. Jones CH, Petersen PJ (2005). Tigecycline: A review of preclinical and clinical studies of the first-in-class glycylcycline antibiotic. *Drugs Today* 41: 637-659.

8. Livermore DM (2005). Tigecycline: What is it, and where should it be used? *J Antimicrob Chemother* 56: 611-614.

9. Milatovic D, Schmitz FJ, Verhoef J, Fluit AC (2003). Activities of the glycylcycline tigecycline (GAR-936) against 1,924 recent European clinical bacterial isolates. *Antimicrob Agents Chemother* 47: 400-404.

10. Sader HS, Jones RN, Dowzicky MJ, Fritsche TR (2005). Antimicrobial activity of tigecycline tested against nosocomial bacterial pathogens from patients hospitalized in the intensive care unit. *Diagn Microbiol Infect Dis* 52: 203-208.

11. Sader HS, Jones RN, Stilwell MG, Dowzicky MJ, Fritsche TR (2005). Tigecycline activity tested against 26,474 bloodstream infection isolates: a collection from 6 continents. *Diagn Microbiol Infect Dis* 52: 181-186.

12. Wilcox MH (2005). Efficacy of tigecycline in complicated skin and skin structure infections and complicated intra-abdominal infections. *J Chemother* 17 Suppl 1: 23-29.

13. Zhanel GG, Karlowsky JA, Rubinstein E, Hoban DJ (2006). Tigecycline: A novel glycylcycline antibiotic. *Expert Rev Anti Infect Ther* 4: 9-25.

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RESULTS

- Agents providing more than 94% coverage of tested *Enterobacter* spp., *C. freundii* and *S. marcescens* included imipenem (97.9 – 100.0%) > tigecycline > amikacin > cefepime (94.0 – 97.9%) (Table 1).
- Despite variable resistance to tetracycline (10.4 to 13.8% for *E. cloacae, E. aerogenes* and *C. freundii*; 69.3% for *S. marcescens*), tigecycline resistance rates remained very low (0.0 to 1.9%) at the US-FDA breakpoint of ≥ 8 mg/L.
- Stably-derepressed AmpC- and ESBL-production were evident in: 22.2 and 3.1% of *E. cloacae*; 24.7 and 0.6% of *E. aerogenes*; 17.2 and 2.7% of *C. freundii*; and 2.0 and 0.2% of *S. marcescens*, respectively (Table 2).
- Slightly decreased potency (MIC_{90} values) of tigecycline among the ceftazidime-resistant subsets was noted among *E. cloacae* (four-fold), *E. aerogenes* (two-fold) and *C. freundii* (four-fold) isolates; no difference was noted among *S. marcescens* isolates (Table 2).
- Among strains expressing resistance to ceftazidime, greater than 96% of *E. aerogenes* and *C. freundii*, 92% of *S. marcescens* and 88% of *E. cloacae* remained susceptible to tigecycline, whereas 92% of *E. aerogenes* and *S. marcescens*, 79% of *E. cloacae* and 78% of *C. freundii* were susceptible to cefepime, an agent inherently stable to most cephalosporinases (Table 2; data not shown).
- Overall, 97.4 and 90.8% of ceftazidime-susceptible and -resistant isolates, respectively, were inhibited by ≤ 2 mg/L of tigecycline.

Table 1. Antimicrobial activity of tigecycline against select Enterobacteriaceae with inducible or constitutive AmpC production.

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) 50%	MIC (mg/L) 90%	Range	% susceptible[a]	% resistant[a]
E. cloacae (1,246)					
Tigecycline	0.5	1	0.06-8	95.7	0.2
Tetracycline	≤2	>8	≤2->8	82.5	13.8
Ceftriaxone	≤0.25	>32	≤0.25->32	74.6	21.7
Ceftazidime	≤1	>16	≤1->16	74.2	22.2
Cefepime	≤0.12	4	≤0.12->16	94.0	4.3
Piperacillin/Tazobactam	2	>64	0.25->64	78.4	12.0
Imipenem	0.25	1	≤0.12->8	99.5	0.2
Ciprofloxacin	≤0.03	4	≤0.03-4	87.0	10.6
Gentamicin	≤2	>8	≤2->8	86.3	11.7
Amikacin	2	4	0.5->32	95.7	2.5
E. aerogenes (336)					
Tigecycline	0.5	1	0.12-8	97.9	0.3
Tetracycline	≤2	>8	≤2->8	81.8	10.4
Ceftriaxone	≤0.25	32	≤0.25->32	81.5	6.8
Ceftazidime	≤1	>16	≤1->16	70.2	24.7
Cefepime	≤0.12	2	≤0.12->16	97.9	0.9
Piperacillin/Tazobactam	4	64	≤0.12->64	75.9	6.5
Imipenem	0.5	1	≤0.12->8	97.9	0.3
Ciprofloxacin	≤0.03	>4	≤0.03->4	87.2	11.9
Gentamicin	≤2	≤2	≤2->8	94.0	4.8
Amikacin	2	4	0.5->32	96.1	2.7
C. freundii (186)					
Tigecycline	0.25	1	0.06-4	98.9	0.0
Tetracycline	≤2	>8	≤2->8	83.9	13.4
Ceftriaxone	≤0.25	32	≤0.25->32	80.6	9.7
Ceftazidime	≤1	>16	≤1->16	79.6	17.2
Cefepime	≤0.12	2	≤0.12->16	95.2	3.2
Piperacillin/Tazobactam	2	>64	0.5->64	80.6	10.8
Imipenem	0.5	1	≤0.12->8	99.5	0.5
Ciprofloxacin	≤0.03	4	≤0.03->4	86.0	12.4
Gentamicin	≤2	>8	≤2->8	86.6	10.8
Amikacin	2	4	≤0.25->32	96.8	1.6
S. marcescens (645)					
Tigecycline	1	2	0.25-16	95.3	1.9
Tetracycline	>8	>8	≤2->8	3.6	69.3
Ceftriaxone	≤0.25	8	≤0.25->32	90.2	3.9
Ceftazidime	≤1	2	≤1->16	95.8	2.0
Cefepime	≤0.12	0.5	≤0.12->16	96.6	2.8
Piperacillin/Tazobactam	2	16	≤0.5->64	90.4	2.9
Imipenem	0.5	1	≤0.12->8	99.4	0.6
Ciprofloxacin	0.06	1	≤0.03->4	93.0	5.6
Gentamicin	≤2	8	≤2->8	89.8	8.2
Amikacin	2	4	0.5->32	96.1	2.0

a. Criteria as published by the CLSI [2005]; breakpoints for tigecycline are those of the US-FDA (2/4/8 mg/L for S/I/R).

Table 2. Potency of tigecycline against select Enterobacteriaceae displaying resistances to ceftazidime and cefepime.

Organism (no. tested)	MIC (mg/L) 50%	MIC (mg/L) 90%	Cumulative % inhibited at (mg/L): ≤0.12	0.25	0.5	1	2[a]	4	8	16
E. cloacae (1,246)	0.5	1	1	31	79	90	95	>99	100	
Ceftazidime-susceptible (924)	0.5	1	1	35	88	96	97	>99	100	
Ceftazidime-resistant (276)	0.5	4	1	19	53	70	88	>99	100	
Cefepime-susceptible (218)	0.5	4	1	20	54	71	87	>99	100	
Cefepime-resistant (39)	1	2		20	48	71	94	100		
E. aerogenes (336)	0.5	1	2	44	82	93	97	>99	100	
Ceftazidime-susceptible (236)	0.5	1	2	49	89	94	98	100		
Ceftazidime-resistant (83)	0.5	2	1	31	61	89	96	98	100	
Cefepime-susceptible (77)	0.5	2	1	31	59	88	96	98	100	
Cefepime-resistant (2)	1	-		50	50	100				
C. freundii (186)	0.25	1	10	51	85	94	98	100		
Ceftazidime-susceptible (148)	0.25	0.5	12	56	90	96	99	100		
Ceftazidime-resistant (32)	0.5	2	3	28	62	87	96	100		
Cefepime-susceptible (25)	0.5	2	4	24	64	88	100			
Cefepime-resistant (5)	0.5	-		40	60	80	80	100		
S. marcescens (645)	1	2		1	24	82	95	98	>99	100
Ceftazidime-susceptible (618)	1	2		1	24	83	95	98	100	
Ceftazidime-resistant (13)	1	2		7	7	69	92	100		
Cefepime-susceptible (12)	1	2		8	8	75	91	100		
Cefepime-resistant (1)	-	-					100			

a. Susceptible breakpoint found in the US-FDA product package insert.

- The presence of additional ESBL phenotypes among these isolates did not further affect the potency of tigecycline, and >95% of ceftazidime- and cefepime-resistant isolates remained susceptible to tigecycline (Table 2).
- Given the importance of the Enterobacteriaceae in causing intra-abdominal and complicated skin and skin structure infections, the approved indications for use of tigecycline, the results presented here demonstrate that tigecycline retains broad coverage and activity against commonly occurring resistant enteric bacilli.

CONCLUSIONS

- Among tested Enterobacteriaceae (*E. cloacae, E. aerogenes, C. freundii,* and *S. marcescens*) including strains that express AmpC- and ESBL-enzymes, and tetracycline resistance mechanisms, 96% were inhibited by 2 mg/L of tigecycline (the current US-FDA breakpoint) and >99% were inhibited by 4 mg/L.
- Our findings confirm that tigecycline exhibits potency, breadth of spectrum, and stability to the commonly occurring resistance mechanisms found in Enterobacteriaceae, attributes that make this parenteral agent an attractive candidate for use against indicated serious infections produced by these species.
- Given the recent introduction of this novel agent, a critical need exists for antimicrobial resistance surveillance, to provide continued guidance of its usefulness against contemporary pathogens and to detect emerging resistance patterns both temporally and geographically.