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In Vitro Activity of Tigecycline Tested Against Pneumonia Pathogens from Hospitalized Patients: Results from a Global Surveillance Program (2004-2005)

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IDSA 2006
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ABSTRACT

Background:

Emergence of resistance (R) among pneumonia-producing pathogens has been a variable that confounds empiric management. This report summarizes the activity of tigecycline (TIG), the sentinel approved glycylcycline, against leading bacterial pathogens recovered from patients hospitalized with pneumonia.

Methods:

6,594 consecutive, non-duplicate, lower respiratory tract isolates were submitted from >60 medical centers worldwide (North America, 44.3%; Europe, 34.5%; Latin America, 21.2%; 2004-2005). Ranking pathogens (91.3% of total) are summarized below. Susceptibility (S) tests were performed using CLSI methods (including ESBL confirmatory tests) and interpreted by US-FDA criteria.

Results:

Organism (no. tested)	TIG MIC (µg/ml) 50%	90%	RANGE	% S/R
S. aureus (SA; 1,880)	0.12	0.5	≤0.03 - 1	99.9/-
P. aeruginosa (PSA; 1,515)	8	16	0.12 - >32	-/-
Klebsiella spp (KSP; 626)	0.5	1	0.06 – 4	97.4/0.0
Acinetobacter spp. (ASP; 445)	1	4	≤0.03 - 8	-/-
E. coli (EC; 423)	0.12	0.25	0.03 - 2	100.0/0.0
Enterobacter spp. (ESP; 413)	0.5	1	0.06 - 4	97.8/0.0
Serratia spp. (SER; 253)	1	2	0.12 - 8	94.5/1.6
S. maltophilia (SM; 192)	1	2	0.12 - 8	-/-
S. pneumoniae (SPN; 145)	≤0.03	≤0.03	≤0.03 - 0.06	-/-
H. influenzae (HI; 131)	0.5	1	0.25 – 1	-/-

Ranking of the top-10 occurring pneumonia pathogens and key R characteristics were (see Table): SA (51.3% OXA-R) > PSA > KSP (27.1% ESBL) > ASP > EC (10.6% ESBL) > ESP (28.6% ceftazidime-R) > SPN (37.2% penicillin non-susceptible) > SER > SM > HI (18.0% ß-lactamase positive). Overall, TIG inhibited 98.9% of ranked pathogens having US-FDA breakpoints. While TIG was less active against PSA (MIC_{90}, 16 µg/ml), most ASP and SM were inhibited by ≤2 µg/ml (89.9 and 91.1%, respectively). Likewise, 96.5 and 100.0% of ESBL-confirmed KSP and EC, respectively, had TIG MIC values at ≤2 µg/ml (no R detected). All SPN and HI were inhibited by ≤1 µg/ml of TIG.

Conclusions: TIG is a promising agent targeting pneumonia pathogens displaying the most resistant phenotypes including SA, Enterobacteriaceae, SPN, HI, and some non-fermentative Gram-negative bacilli. Currently under investigation for this indication, empiric use of tigecycline may be prudent for patients less likely to have PSA as a causative pathogen or for directed therapy of indicated species.

INTRODUCTION

Pneumonia occurring in hospitalized patients, either community-acquired or nosocomial in origin, are significant causes of morbidity and mortality and have become much more difficult to manage with the escalating resistances being detected among all pathogen groups, including *S. pneumoniae* and *H. influenzae* among community-acquired pathogens and *S. aureus*, Enterobacteriaceae, and non-fermentative Gram-negative bacilli among nosocomial pathogens. The decrease in utility of many penicillins, cephalosporins, ß-lactamase inhibitor combinations and even carbapenems, among other classes of antimicrobics, has created a critical need for new agents. The search for compounds with greater potency, stability to common resistance mechanisms, favorable pharmacokinetic/pharmacodynamic features and lower potential to select for resistance is essential in addressing this situation.

Tigecycline is a derivative of minocycline that has become the sentinel representative of a new class of agent known as the glycylcyclines. Recently approved indications for this parenteral agent include skin and soft tissue infections and intra-abdominal infections. Tigecycline demonstrates potent activity against a broad range of commonly occurring species, including many resistant organisms such as penicillin-resistant *S. pneumoniae*, oxacillin-resistant *S. aureus*, vancomycin–resistant enterococci, and extended-spectrum ß-lactamase-producing strains of Enterobacteriaceae. The agent is also active against *H. influenzae, M. catarrhalis*, pathogenic *Neisserias* and many other Gram-negative species.

In this study, we evaluated the in vitro activity of tigecycline against a total of over 6,500 bacterial isolates originating from patients hospitalized with pneumonias to evaluate the spectrum of this agent against such species, and compared its activity to those agents commonly used in the directed or empiric therapy of respiratory tract infections.

MATERIALS AND METHODS

Organism Collection: To assess the spectrum of activity and potency of tigecycline against recent clinical isolates (consecutive, non-duplicate) recovered from patients hospitalized with pneumonia, a total of 6,594 Gram-positive and -negative bacterial isolates were processed by a reference laboratory (JMI Laboratories, North Liberty, Iowa) for testing. Consecutively acquired, non-duplicate, patient isolates were submitted from participating medical centers worldwide representing North America (44.3% of isolates), South America (21.2%) and Europe (34.5%). The collection consisted of those bacterial species and groups comprising the most commonly encountered respiratory tract pathogens (Table 1).

Isolates were identified by the submitting laboratory and confirmed by the monitoring facility (JMI Laboratories) using colonial characteristics on standard media, rapid tests (catalase, oxidase, coagulase, bile solubility, latex agglutination kits), and use of an automated identification system (Vitek bioMerieux, Hazelwood, MO), among others methods, as necessary.

Susceptibility Testing: MIC values for tigecycline (kindly supplied by Wyeth Pharmaceuticals, Inc., Collegeville, PA) and comparator agents (from their respective manufacturers or Sigma Chemical Co., St. Louis, MO), including those classes and examples of drugs most commonly used for the empiric or directed treatment of serious respiratory tract infections, were determined using validated broth microdilution panels with cation-adjusted Mueller-Hinton medium (TREK Diagnostics Inc., Cleveland, OH) according to Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) recommendations (M7-A7). When testing *Streptococcus* spp., supplemental lysed horse blood (2-5%) was added; Haemophilus Test Medium (HTM) was used when testing *Haemophilus* spp. Quality control (QC) was performed using American Type Culture Collection (ATCC) strains *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247 and *Pseudomonas aeruginosa* ATCC 27853. Enterobacteriaceae with elevated MIC values (≥2 µg/ml) for ceftazidime or ceftriaxone or aztreonam were considered as extended-spectrum ß-lactamase-producing phenotypes; confirmatory testing was performed using cefotaxime and ceftazidime alone and in combination with clavulanic acid using recommended QC strains (*Escherichia coli* ATCC 25922 and 35218, *K. pneumoniae* ATCC 700603).

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ACKNOWLEDGEMENT

This study was supported by an educational/research grant from Wyeth Pharmaceuticals.

RESULTS

- Ranking of the ten most-prevalent pathogens recovered from patients with pneumonia (91.3% of the total collection) and key resistance characteristics were (see Tables 1 to 4): *S. aureus* (51.3% oxacillin-resistant) > *P. aeruginosa* > *Klebsiella* spp. (27.1% ESBL) > *Acinetobacter* spp. > *E. coli* (10.6% ESBL) > *Enterobacter* spp. (28.6% ceftazidime-resistant) > *S. pneumoniae* (37.2% penicillin non-susceptible) > *Serratia* spp. > *S. maltophilia* > *H. influenzae* (18.0% ß-lactamase-positive).

- Tigecycline inhibited >99% of *S. aureus* at 0.5 µg/ml, including methicillin (oxacillin)-resistant strains. Comparable agents included linezolid, quinupristin/dalfopristin and glycopeptides (Table 2).

Table 1. Cumulative frequency distributions for the top ranked Gram-positive and -negative pathogens producing pneumonia in hospitalized patients (2004 - 2005).

Organisms (no. strains / % of total)	% inhibited at MIC (µg/ml): ≤0.12	0.25	0.5	1	2	4	8	16
S. aureus (1,880 / 28.5)	75	98	**>99**[a]	100				
P. aeruginosa (1,515 / 23.0)	<1	<1	2	3	7	30	66	94
Klebsiella spp. (626 / 9.5)	4	46	83	92	**97**	100		
Acinetobacter spp. (445 / 6.7)	11	23	38	64	90	>99	100	
E. coli (423 / 6.4)	62	93	>99	>99	**100**			
Enterobacter spp. (413 / 6.3)	<1	38	81	91	**98**	100		
Serratia spp. (253 / 3.8)	<1	2	24	79	**95**	98	100	
S. maltophilia (192 / 2.9)	2	12	39	71	91	98	100	
S. pneumoniae (145 / 2.2)	100							
H. influenzae (131 / 2.0)	0	6	72	100				

a. Underlined value = susceptible breakpoint found in the US-FDA product package insert.

Table 2. Antimicrobial activity of tigecycline and selected comparators tested against pneumonia pathogens including *S. aureus*, *S. pneumoniae* and *H. influenzae* (2004-2005).

Organism (no. tested) / antimicrobial agent	MIC (µg/ml): 50%	90%	Range	% by category:[a] Susceptible	Resistant
S. aureus (1,880)					
Tigecycline	0.12	0.25	≤0.03-1	99.9	-
Tetracycline	≤2	8	≤2->8	90.0	9.4
Oxacillin	>2	>2	≤0.25->2	48.7	51.3
Clindamycin	≤0.25	>8	≤0.25->8	61.5	38.1
Levofloxacin	4	>4	0.06->4	48.1	50.5
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	94.7	5.3
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25->2	99.8	0.1
Teicoplanin	≤2	≤2	≤2-4	100.0	0.0
Vancomycin	1	1	0.25-2	100.0	0.0
Linezolid	2	2	0.25-2	100.0	-
S. pneumoniae (145)					
Tigecycline	≤0.03	≤0.03	≤0.03-0.06	-	-
Tetracycline	≤2	>8	≤2->8	79.3	20.7
Penicillin	≤0.015	2	≤0.015-4	62.8	18.6
Amoxicillin/clavulanic acid	≤1	4	≤1-8	89.0	2.1
Ceftriaxone	≤0.25	1	≤0.25-2	98.6	0.0
Erythromycin	0.12	>8	≤0.06->8	62.8	36.6
Clindamycin	≤0.25	>2	≤0.25->2	82.1	17.2
Quinupristin/dalfopristin	0.5	0.5	≤0.25-1	100.0	0.0
Levofloxacin	1	1	0.25->4	99.3	0.7
Linezolid	1	1	0.5-2	100.0	-
Vancomycin	0.25	0.5	≤0.12-0.5	100.0	-
H. influenzae (131)					
Tigecycline	0.5	1	0.25-1	-	-
Tetracycline	≤2	≤2	≤2-8	98.5	0.8
Amoxicillin/clavulanic acid	≤1	≤1	≤1-2	100.0	0.0
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5	100.0	0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
Ciprofloxacin	≤0.03	≤0.03	≤0.03-0.06	100.0	-
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	77.9	17.6

a. Criteria as published by the CLSI [2006]; breakpoints for tigecycline are those of the US-FDA; - = no breakpoint established.

- Enterobacteriaceae were also readily inhibited by tigecycline (97.7% susceptible), varying from 94.5% for *Serratia* spp. to 100.0% for *E. coli*. Among comparators, only imipenem displayed a greater spectrum (98.6 to 100.0% susceptible; Table 3).

- ESBL-confirmed *Klebsiella* spp. and *E. coli* were broadly susceptible to tigecycline with 96.5 and 100.0%, respectively, having tigecycline MIC values at ≤2 µg/ml (no resistant strains were detected).

- Most *Acinetobacter* spp. and *S. maltophilia* were inhibited by ≤2 µg/ml of tigecycline (89.9 and 91.1%, respectively); only polymyxin B was more active against *Acinetobacter* spp. (MIC_{90}, 0.5 µg/ml; 98.9% susceptible) and trimethoprim/sulfamethoxazole more active against *S. maltophilia* (MIC_{90}, 1 µg/ml; 97.4%; Table 4).

- This agent is known to be less active against *P. aeruginosa* (MIC_{90}, 16 µg/ml); only amikacin (89.7% susceptible) and polymyxin B (99.9%) displayed consistent coverage against this species.

- Tigecycline was the most potent agent tested against *S. pneumoniae* (MIC_{90}, ≤0.03 µg/ml versus 0.5 to >8 µg/ml); 100% of this species and *H. influenzae* were inhibited by ≤0.06 and ≤1 µg/ml of tigecycline, respectively.

Table 3. Antimicrobial activity of tigecycline and selected comparators tested against the most prevalent Enterobacteriaceae producing pneumonia in hospitalized patients (2004 - 2005).

Organism (no. tested) / antimicrobial agent	MIC (µg/ml): 50%	90%	Range	% by category:[a] Susceptible	Resistant
E. coli (423)					
Tigecycline	0.12	0.25	0.03-2	100.0	0.0
Tetracycline	2	>8	1->8	57.1	42.4
Ceftriaxone	≤0.25	32	≤0.25->32	87.9	9.7
Ceftazidime	≤1	16	≤1->16	89.6	6.6
Cefepime	≤0.12	4	≤0.12->16	93.4	6.1
Piperacillin/tazobactam	2	32	≤0.5->64	88.2	5.9
Imipenem	≤0.12	0.25	≤0.12-1	100.0	0.0
Ciprofloxacin	≤0.03	>4	≤0.03->4	71.9	28.1
Gentamicin	≤2	>8	≤2->8	85.3	13.9
Amikacin	2	4	0.5->32	99.5	0.5
Klebsiella spp. (626)					
Tigecycline	0.5	1	0.06-4	97.4	0.0
Tetracycline	≤2	>8	≤2->8	78.3	18.8
Ceftriaxone	≤0.25	>32	≤0.25->32	74.4	17.7
Ceftazidime	≤1	>16	≤1->16	77.7	18.1
Cefepime	≤0.12	>16	≤0.12->16	85.6	11.8
Piperacillin/tazobactam	4	>64	≤0.5->64	78.9	16.1
Imipenem	≤0.12	0.25	≤0.12->8	98.6	1.1
Ciprofloxacin	≤0.03	>4	≤0.03->4	80.5	16.0
Gentamicin	≤2	>8	≤2->8	77.2	20.4
Amikacin	1	16	0.5->32	90.1	6.5
Enterobacter spp. (413)					
Tigecycline	0.5	1	0.06-4	97.8	0.0
Tetracycline	≤2	>8	≤2->8	81.4	13.1
Ceftriaxone	0.5	>32	≤0.25->32	68.3	19.6
Ceftazidime	≤1	>16	≤1->16	65.9	28.6
Cefepime	≤0.12	8	≤0.12->16	92.9	3.2
Piperacillin/tazobactam	4	>64	≤0.5->64	70.0	16.0
Imipenem	0.5	1	≤0.12-8	99.5	0.0
Ciprofloxacin	≤0.03	4	≤0.03->4	88.1	10.9
Gentamicin	≤2	>8	≤2->8	83.5	13.6
Amikacin	1	8	0.5->32	94.9	4.1
Serratia spp. (253)					
Tigecycline	1	2	0.12-8	94.5	1.6
Tetracycline	>8	>8	≤2->8	4.0	62.8
Ceftriaxone	≤0.25	8	≤0.25->32	91.2	4.4
Ceftazidime	≤1	≤1	≤1->16	98.0	1.2
Cefepime	≤0.12	1	≤0.12->16	96.4	2.8
Piperacillin/tazobactam	2	32	≤0.5->64	88.5	5.5
Imipenem	0.5	1	0.25-2	100.0	0.0
Ciprofloxacin	0.06	2	≤0.03->4	89.3	8.7
Gentamicin	≤2	8	≤2->8	88.5	8.7
Amikacin	2	4	0.5->32	98.0	0.8

a. Criteria as published by the CLSI [2006]; breakpoints for tigecycline are those of the US-FDA.

Table 4. Antimicrobial activity of tigecycline and selected comparators tested against the most prevalent non-fermentative Gram-negative bacilli producing pneumonia in hospitalized patients (2004 - 2005).

Organism (no. tested) / antimicrobial agent	MIC (µg/ml): 50%	90%	Range	% by category:[a] Susceptible	Resistant
P. aeruginosa (1,515)					
Tigecycline	8	16	0.12->32	-	-
Tetracycline	>8	>8	0.5->8	3.6	82.3
Ceftazidime	4	>16	≤1->16	73.1	20.9
Cefepime	4	>16	≤0.12->16	71.7	11.6
Piperacillin/tazobactam	8	>64	≤0.5->64	78.9	21.1
Imipenem	1	>8	≤0.12->8	72.4	13.4
Meropenem	1	>8	≤0.06->8	76.7	13.1
Ciprofloxacin	0.25	>4	≤0.03->4	64.2	29.5
Gentamicin	≤2	>8	≤2->8	73.2	23.1
Amikacin	4	32	≤0.25->32	89.7	9.8
Polymyxin B	0.5	1	≤0.12->4	99.9	0.1
Acinetobacter spp. (445)					
Tigecycline	1	4	≤0.03-8	-	-
Tetracycline	8	>8	1->8	34.8	46.1
Ceftazidime	>16	>16	≤1->16	22.0	71.9
Cefepime	>16	>16	≤0.12->16	28.5	50.1
Piperacillin/tazobactam	>64	>64	≤0.5->64	24.5	62.2
Imipenem	1	>8	≤0.12->8	73.9	22.0
Meropenem	2	>8	≤0.06->8	66.3	24.5
Ciprofloxacin	>4	>4	≤0.03->4	16.9	82.0
Gentamicin	>8	>8	≤2->8	26.7	67.4
Amikacin	>32	>32	≤0.25->32	41.6	53.9
Polymyxin B	0.5	0.5	≤0.12->8	98.9	1.1
S. maltophilia (192)					
Tigecycline	1	2	0.12-8	-	-
Tetracycline	>8	>8	≤0.25->8	4.7	65.6
Ceftazidime	16	>16	≤1->16	46.4	42.7
Cefepime	>16	>16	1->16	17.7	51.6
Piperacillin/tazobactam	>64	>64	8->64	7.8	64.1
Ticarcillin/clavulanic acid	32	128	≤16->128	45.3	21.9
Ciprofloxacin	2	>4	0.25->4	25.5	46.4
Levofloxacin	1	4	0.12->4	79.7	6.8
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5->2	97.4	2.6
Amikacin	>32	>32	1->32	12.0	80.7
Polymyxin B	0.5	2	0.25->8	92.7	7.3

a. Criteria as published by the CLSI [2006]; - = no breakpoint established.

CONCLUSIONS

- Tigecycline is a promising agent active in vitro against pneumonia pathogens displaying the most resistant phenotypes such as *S. aureus* (including methicillin-resistant strains), Enterobacteriaceae (including ESBL-producers), *S. pneumoniae*, *H. influenzae* and some non-fermentative Gram-negative bacilli.

- In this global surveillance sample of respiratory pathogens recovered from hospitalized patients with pneumonia, tigecycline inhibited 98.9% of ranked pathogens having US-FDA susceptibility breakpoints.

- Currently under investigation for this indication, empiric use of tigecycline may be prudent for patients less likely to have *P. aeruginosa* as a causative respiratory tract pathogen or for directed therapy of indicated species.