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In Vitro Activity of Tigecycline Tested Against Pneumonia Pathogens from Patients Hospitalized in European Medical Centers, Including Multidrug-resistant *Acinetobacter* spp.

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ABSTRACT

Objectives:
Emergence of resistance (R) among pneumonia-producing pathogens has been a variable that confounds empiric management. We evaluated the activity of tigecycline against leading bacterial pathogens recovered from patients hospitalized with pneumonia. Tigecycline was approved by the European Medicines Agency and US-FDA for the treatment of complicated skin and skin structure infections and intra-abdominal infections and is currently under investigation for treatment of hospital acquired pneumonia.

Methods:
Consecutive, non-duplicate, lower respiratory tract isolates (3,864) were submitted from 34 medical centers located in Europe (13 countries) and Israel in the 2000-2007 period. Susceptibility (S) tests were performed using CLSI methods (including ESBL confirmatory tests) and interpreted by US-FDA and EUCAST criteria.

Results:
Ranking of the top-10 occurring pneumonia pathogens and key resistance (R) characteristics were (see Table): *S. aureus* (28.3% oxacillin-R [MRSA]) > *P. aeruginosa* (19.6 imipenem [IMI]-R) > *E. coli* (8.5% ESBL) > *Klebsiella* spp. (28.9% ESBL) > *Enterobacter* spp. (25.6% ceftazidime [CAZ]-R) > *Acinetobacter* spp. > *S. pneumoniae* (23.1% penicillin-R) > *Serratia* spp. > *S. maltophilia* > *H. influenzae* (12.8% ß-lactamase positive). *Acinetobacter* spp. exhibited high R rates to IMI (43.1%), CAZ (77.0%), ciprofloxacin (CIP; 82.8%) and amikacin (AMK; 65.1%); while 34.9% of strains were R to all 4 drugs (MDR). R to these antimicrobials did not adversely affect tigecycline activity, which inhibited > 95% of strains non-S to CAZ, CIP or AMK, 93.3% of strains non-S to IMI and 91.8% of MDR strains at ≤2 mg/L. Tigecycline was also very active against *S. maltophilia* (MIC_{90}, 2 mg/L; 99.2% inhibited at ≤2 mg/L), MRSA (MIC_{90}, 0.25 mg/L; 99.5% S) and Enterobacteriaceae with an ESBL-phenotype, but showed limited activity against PSA.

	Tigecycline MIC (mg/L)			
Organism (no. tested / % of total)	50%	90%	Range	% S (US-FDA /EUCAST)
S. aureus (1,067 / 27.6)	≤0.12	0.5	≤0.12 - 1	99.8/99.8
P. aeruginosa (786 / 20.3)	>4	>4	≤0.12 - >4	-/-
E. coli (366 / 9.5)	≤0.12	0.25	≤0.12 - 1	100.0/100.0
Klebsiella spp (353 / 9.1)	0.25	1	≤0.12 - 4	98.6/92.4
Enterobacter spp. (223 / 5.8)	0.5	1	0.06 - 4	99.1/96.0
Acinetobacter spp. (209 / 5.4)	1	2	≤0.12 - 4	97.1/77.5[a]
S. pneumoniae (121 / 3.1)	≤0.12	≤0.12	≤0.12	-/-
Serratia spp. (121 / 3.1)	1	2	≤0.12 - 4	99.2/92.6
S. maltophilia (114 / 3.0)	1	2	≤0.12 - 4	99.2/77.2[a]
H. influenzae (109 / 2.8)	0.5	1	≤0.12 - 1	-/-

a. Enterobacteriaceae breakpoints were used for comparison purposes only.

Conclusions:
Tigecycline is a potent agent targeting pneumonia pathogens displaying highly resistant phenotypes including *S. aureus*, Enterobacteriaceae, *S. pneumoniae*, *H. influenzae*, and some non-fermentative Gram-negative bacilli. Only tigecycline and the polymyxins showed reasonable in vitro activity against *Acinetobacter* spp.

INTRODUCTION

Several multi-drug resistance (MDR) mechanisms have disseminated among key pathogens associated with pneumonia. Oxacillin-resistant staphylococci and penicillin-resistant streptococci are prevalent among the Gram-positive pathogens. Gram-negative pathogens can produce ß-lactamases (extended-spectrum and metallo ß-lactamase) including stably derepressed Amp-C enzymes; each causing serious problems for empiric therapy. Alternative antimicrobial therapies are needed to address the increasing prevalence of MDR bacterial pathogens, including those commonly causing pneumonia.

Tigecycline, a semisynthetic minocycline derivative, provides excellent activity against many bacterial species and is stable against mechanisms of tetracycline resistance. This compound inhibits protein translation by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This agent was approved by the European Medicines Agency and the United States (USA) Food and Drug Administration (FDA) for the treatment of complicated skin and skin structure infections and intra-abdominal infections. In this study, the antimicrobial activities of tigecycline and comparator agents are presented for the 10 most frequently isolated pathogens from patients with pneumonia hospitalized in European medical centers.

MATERIALS AND METHODS

Between 2000 and 2007, a total of 3,864 bacterial pathogens were collected from patients diagnosed with pneumonia in European medical centers. A total of 34 medical centers located within 13 countries contributed isolates for this study. The isolates were collected and identified locally and forwarded to a central laboratory for confirmation of species identification and reference susceptibility testing against numerous antimicrobial classes. Isolates were tested by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M7-A7, 2006). Commercially prepared panels (TREK Diagnostics, Cleveland, OH, USA) using Mueller-Hinton (MH), Haemophilus Test Media and MH supplemented with 2 - 5% lysed horse blood (*Streptococcus* spp.) were used to determine all MIC values.

For tigecycline, susceptibility breakpoints utilized were those recommended by the USA-FDA as follows: ≤2 mg/L (susceptible) and ≥8 mg/L (resistant) for Enterobacteriaceae; ≤0.5 mg/L for staphylococci (susceptible only). Susceptibility breakpoint criteria currently do not exist for some species reported in this study. However, for comparative purposes, the enteric breakpoints were utilized for *Acinetobacter* spp. and *S. maltophilia*; and the streptococci breakpoint (≤0.25 mg/L; susceptible only) was used for *S. pneumoniae*. Susceptibility breakpoints for the other antimicrobial agents presented were those recommended by the CLSI (M100-S18, 2008) and EUCAST (where available).

ACKNOWLEDGEMENT

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SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement.* Wayne, PA: CLSI.
3. Fraise AP (2006). Tigecycline: The answer to ß-lactam and fluoroquinolone resistance? *J Infect* 53: 293-300.
4. Frampton JE, Curran MP (2005). Tigecycline. *Drugs* 65: 2623-2635; Discussion 2636-2627.
5. Hoban DJ, Bouchillon SK, Dowzicky MJ (2007). Antimicrobial susceptibility of extended-spectrum ß-lactamase producers and multidrug-resistant *Acinetobacter baumannii* throughout the United States and comparative in vitro activity of tigecycline, a new glycylcycline antimicrobial. *Diagn Microbiol Infect Dis* 57: 423-428.
6. Rodloff AC, Leclercq R, Debbia EA, Canton R, Oppenheim BA, Dowzicky MJ (2008). Comparative analysis of antimicrobial susceptibility among organisms from France, Germany, Italy, Spain and the UK as part of the tigecycline evaluation and surveillance trial. *Clin Microbiol Infect* 14: 307-314.
7. Stein GE, Craig WA (2006). Tigecycline: A critical analysis. *Clin Infect Dis* 43: 518-524.
8. Tygacil Package Insert (2005). Philadelphia (PA): Wyeth Pharmaceuticals Inc. (June, 2005).

RESULTS

- As shown in Table 1, nearly one-half (47.9%) of the isolates collected from patients with pneumonia were *S. aureus* (27.6%) and *P. aeruginosa* (20.3%). Enterobacteriaceae were also isolated with high frequency at a rate of 24.4% for *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. combined. *Acinetobacter* spp. ranked sixth in frequency of occurrence at a rate of 5.4%. All other species were isolated at ≤3%. The top 10 pathogens accounted for nearly 90% of all causative/reported organisms (Table 1).
- Based upon the cumulative MIC distribution shown in Table 2, oxacillin-resistant strains of *S. aureus* had slightly higher tigecycline MIC values than oxacillin-susceptible isolates. Tigecycline showed limited activity against *P. aeruginosa*.
- Variability of tigecycline activity was noted among enteric species with highest potency against *E. coli* (third-ranked pathogen), compared to the other three species groups listed in Table 2.
- Tested against the fastidious pathogens, tigecycline showed excellent potency against *S. pneumoniae* (MIC_{90}, ≤0.12 mg/L). The highest tigecycline MIC value for *H. influenzae* was 1 mg/L and 81.7% of the isolates were inhibited at a MIC of ≤0.5 mg/L (see Table 2).
- Tigecycline exhibited good activity against *Acinetobacter* spp. and *S. maltophilia* (MIC_{90}, 2 mg/L for both organisms, Tables 2 and 3). No co-resistance between tigecycline and the four other listed agents was observed when testing *Acinetobacter* spp. with various resistance phenotypes (Table 3).
- Tigecycline was highly active against *S. aureus* (99.8% susceptible), key Gram-negative enteric pathogens (92.4 - 100.0% susceptible) and *S. pneumoniae* (all isolates inhibited at ≤0.12 mg/L) utilizing either USA-FDA or EUCAST interpretative criteria (Table 3).

Table 1. Rank order of pathogen frequency among bacterial species causing pneumonia in European patients.

Rank	Organism	Number	Percent of total
1	*S. aureus*	1,067	27.6
2	*P. aeruginosa*	786	20.3
3	*E. coli*	366	9.5
4	*Klebsiella* spp.	353	9.1
5	*Enterobacter* spp.	223	5.8
6	*Acinetobacter* spp.	209	5.4
7	*S. pneumoniae*	121	3.1
8	*Serratia* spp.	121	3.1
9	*S. maltophilia*	114	3.0
10	*Haemophilus* spp.	110	2.8
11	Other species[a]	394	10.3

a. All other species or species groups were collected at 4.1% occurrence.

Table 2. Cumulative percentage MIC distributions of tigecycline tested against the 10 most common pathogens isolated from European patients hospitalized with pneumonia.

	MIC (mg/L)					
Organism/ resistance phenotype	≤0.12	0.25	0.5	1	2	4
S. aureus						
Oxacillin-susceptible	71.4	96.8	100.0	-	-	-
Oxacillin-resistant	60.9	91.4	99.5	100.0	-	-
P. aeruginosa	0.3	0.9	2.0	3.7	10.9	44.9
E. coli	63.7	95.6	99.7	100.0	-	-
Klebsiella spp.	11.3	64.3	86.1	92.4	98.6	100.0
Enterobacter spp.	4.5	52.9	84.3	96.0	99.1	100.0
Acinetobacter spp.	12.4	24.4	44.5	77.5	97.1	100.0
Ceftazidime-non-susceptible (161)	1.2	7.5	32.3	72.0	96.3	100.0
Ciprofloxacin-non-susceptible (173)	2.3	10.4	33.5	73.4	96.5	100.0
Amikacin-non-susceptible (136)	1.5	9.6	36.0	75.0	95.6	100.0
Imipenem-non-susceptible (90)	2.2	11.1	36.7	68.9	93.3	100.0
MDR[a] (73)	2.7	11.0	39.7	71.2	91.8	100.0
S. pneumoniae	100.0	-	-	-	-	-
Serratia spp.	0.8	6.6	47.1	92.6	99.2	100.0
S. maltophilia	1.8	14.0	45.6	77.2	92.1	100.0
H. influenzae	0.9	12.8	81.7	100.0	-	-

a. Isolates non-susceptible to ceftazidime (MIC, ≥16 mg/L), ciprofloxacin (MIC, ≥2 mg/L), amikacin (MIC, ≥32 mg/L) and imipenem (MIC, ≥8 mg/L).

Table 3. Potency and susceptibility of tigecycline and comparator agents tested against the 10 most common pathogens collected from patients with pneumonia in Europe.

		MIC (mg/L)		% susceptible[a]	
Organism (no.)	Antimicrobial agent	50%	90%	CLSI/USA-FDA	EUCAST
S. aureus (1,067)	Tigecycline	≤0.12	0.25	99.8	99.8
	Oxacillin	1	>2	61.7	61.7
	Clindamycin	≤0.25	>2	80.4	80.4
	Levofloxacin	≤0.5	>4	58.2	58.2
	Vancomycin	1	1	100.0	100.0
P. aeruginosa (658)	Tigecycline	>4	>4	-[b]	-
	Piperacillin/ tazobactam	8	>64	80.3	-
	Ceftazidime	4	>16	73.2	73.2
	Imipenem	2	>8	69.3	69.3
	Ciprofloxacin	0.25	>4	66.9	61.1
	Amikacin	≤4	32	87.9	83.6
E. coli (366)	Tigecycline	0.12	0.25	100.0	100.0
	Ceftazidime	≤1	≤1	94.0 (8.2)[c]	91.5
	Ciprofloxacin	≤0.03	>4	77.6	76.5
	Gentamicin	≤2	≤2	92.3	92.1
Klebsiella spp. (353)	Tigecycline	0.25	1	98.6	92.4
	Ceftazidime	≤1	>16	81.6 (26.3)[c]	73.7
	Ciprofloxacin	≤0.03	>4	81.0	79.0
	Gentamicin	≤2	>8	84.1	83.3
Enterobacter spp. (223)	Tigecycline	0.25	1	99.1	96.0
	Ceftazidime	≤1	>16	65.5	53.8
	Ciprofloxacin	≤0.03	>4	82.5	82.5
	Gentamicin	≤2	≤2	92.4	91.9
Acinetobacter spp. (209)	Tigecycline	1	2	97.1[d]	77.5[d]
	Ampicillin/sulbactam	>16	>16	34.0	-
	Ceftazidime	>16	>16	23.0	-
	Ciprofloxacin	>4	>4	17.2	17.2
	Amikacin	>8	>8	34.9	33.0
S. pneumoniae (121)	Tigecycline	≤0.12	≤0.12	100.0[e]	100.0[e]
	Penicillin	0.03	2	64.5 (94.2)[f]	-
	Erythromycin	≤0.25	>2	58.7	58.7
	Clindamycin	≤0.25	>2	71.9	73.6
	Levofloxacin	1	1	96.7	96.7
Serratia spp. (121)	Tigecycline	1	1	99.2	92.6
	Ceftazidime	≤1	≤1	98.3	92.6
	Ciprofloxacin	0.06	1	95.0	86.8
	Gentamicin	≤2	4	90.9	89.3
S. maltophilia (114)	Tigecycline	1	2	92.1	77.2[d]
	Ceftazidime	16	>16	44.7	-
	Levofloxacin	1	>4	78.9	-
	Trimethoprim/ sulfamethoxazole	≤0.5	1	99.1	-
H. influenzae (109)	Tigecycline	0.5	1	-	-
	Ampicillin	≤1	4	87.2	-
	Ceftriaxone	≤0.25	≤0.25	100.0	100.0
	Ciprofloxacin	≤0.03	≤0.03	100.0	100.0

a. Susceptibility percentages were based upon the USA-FDA or CLSI (M100-S18, 2008) and EUCAST clinical MIC breakpoints.
b. - = no interpretable breakpoints.
c. Percentage in parenthesis represents the rate of isolates with an ESBL phenotype (MIC, ≥2 mg/L) according to the CLSI (M100-S18, 2008).
d. Susceptibility percentages were calculated using Enterobacteriaceae breakpoints. These figures are for comparison purposes only.
e. Susceptibility percentages were calculated using a breakpoint of ≤0.25 mg/L. These figures are for comparison purposes only.
f. Susceptibility percentage according to non-meningitis breakpoints recently published in the CLSI document M100-S18.

CONCLUSIONS

- The ten most frequent pathogens causing pneumonia in European patients were highly susceptible to tigecycline, with the exception of *P. aeruginosa*.
- Resistance to other commonly prescribed antimicrobial classes does not appear to affect the activity of tigecycline.