Tigecycline Activity Tested Against Bacterial Isolates Causing Bloodstream Infections in European Medical Centers

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ABSTRACT

Objective:
To assess the activity of tigecycline against bloodstream infection (BSI) isolates from European hospitals. Tigecycline is a novel glycylcycline antimicrobial approved by the European Medicines Agency for the treatment of complicated skin and skin structure infections and intra-abdominal infections.

Methods:
Bacterial isolates (non-duplicates) were consecutively collected in the 2000-2007 period from documented BSI in patients hospitalized in 34 medical centers located in Europe (13 countries) and Israel. Frequency of occurrence of pathogens was determined and their antibiograms assessed using reference broth microdilution methods according to CLSI M7-A7 (2006). Tigecycline-susceptible (S) breakpoints (US-FDA/EUCAST) were defined as ≤2/≤1 mg/L for Enterobacteriaceae (ENT); ≤0.5/≤0.5 mg/L for staphylococci, and ≤0.25/≤0.25 mg/L for streptococci and enterococci.

Results:
A total of 25,401 strains were tested. Tigecycline was highly active against the 10 most frequent pathogens (Table), except for *P. aeruginosa* (PSA). Among the 5 most common pathogens (18,802 strains; 74% of the total), tigecycline was active against >99% at the established S breakpoints. The main resistance phenotypes detected were methicillin-resistant (R) *S. aureus* (MRSA; 28.3%) and CoNS (77.6%), ciprofloxacin-R *E. coli* (20.3%), extended-spectrum beta-lactamase (ESBL)-screen-positive *Klebsiella* spp. (22.8%) and *E. coli* (7.9%), imipenem-R PSA (IRPSA; 21.7%) and *Acinetobacter* spp. (ASP; 30.5%), and vancomycin-R enterococci (VRE; 5.0%). Tigecycline activity against MRSA (MIC_{90}, 0.25 mg/L; 99.8% S) was similar to that against methicillin-S *S. aureus* (MIC_{90},0.25 mg/L; 99.9% S), and 98.0% of VRE were S to tigecycline. ESBL-producing *E. coli* and KSP exhibited high rates of R to levofloxacin (62.4 and 31.8%, respectively) and gentamicin (31.7 and 45.1%), but were S to tigecycline (100.0 and 98.9%, by US-FDA breakpoints). 95.3% of ceftazidime-R ESP and 96.1% of imipenem-R ASP were inhibited at ≤2 mg/L of tigecycline.

Organism (no. tested / % of total)	Cumulative % inhibited at tigecycline MIC (mg/L) of: ≤0.12	0.25	0.5	1	2	4	% S (US-FDA /EUCAST)
E. coli (5,793 / 22.8)	66.5	95.7	99.6	99.9	>99.9	100.0	>99.9 / 99.9
S. aureus (5,642 / 22.6)	68.7	95.3	99.9	100.0	-	-	99.9 / 99.9
Coagulase-neg. staphylococci (CoNS; 3,396 / 13.4)	57.0	88.8	98.9	100.0	-	-	98.8 / 98.9
Enterococcus spp. (2,265 / 8.9)	75.3	97.0	99.9	100.0	-	-	97.0 / 97.0
Klebsiella spp. (KSP; 1,706 / 7.6)	8.5	58.7	87.3	96.2	99.4	>99.9	99.4 / 96.2
P. aeruginosa (PSA; 1,481 / 5.8)	0.1	0.3	1.1	2.4	11.1	45.9	- / -
Enterobacter spp. (ESP; 977 / 3.8)	2.3	44.8	81.9	92.2	97.9	100.0	97.9 / 92.2
S. pneumoniae (551 / 2.2)	99.5	100.0	-	-	-	-	100.0 / 100.0
Beta-haemolytic streptococci (535 / 2.1)	98.5	100.0	-	-	-	-	100.0 / 100.0
Acinetobacter spp. (ASP; 509 / 2.0)	18.7	39.3	55.8	83.5	97.6	100.0	97.6 / 83.5[a]

a. ENT breakpoints were applied for comparison purposes.

Conclusions:
Tigecycline exhibited a wide-spectrum of activity and potency versus contemporary BSI isolates collected in Europe, including multidrug-resistant organisms.

INTRODUCTION

The increased complexity of patients requiring hospitalization and the widespread use of indwelling devices has created higher risks for nosocomial bloodstream infection (BSI), which is one of the most serious nosocomial infections. Furthermore, the increasing rates of antimicrobial resistance are creating dilemmas for treatment of BSI patients, requiring the development of new therapeutic options, advanced diagnostic tests and preventive technologies. Despite such advances, accurate empiric treatment remains critical to minimize inappropriate antimicrobial therapy that may lead to poor clinical outcome.

Tigecycline is a semisynthetic derivative of minocycline which was recently (June, 2005) licensed by the United States (USA) Food and Drug Administration (FDA) as a parenteral agent for the treatment of complicated skin and skin structure and intra-abdominal infections. Tigecycline has the distinct advantage of enhanced stability to the major tetracycline resistance mechanisms, specifically an increased binding affinity to Tet M- and Tet O-protected tetracycline-resistant ribosomes and secondarily through the inhibition of tetracycline efflux determinants. In this presented study, we evaluated the activity of tigecycline against BSI isolates from European hospitals.

MATERIALS AND METHODS

Bacterial Isolates: Consecutively acquired, non-duplicate patient isolates were collected in 2000-2007 from documented BSI in patients hospitalized in 34 medical centers. All study sites were located in Europe (13 countries) and Israel, each following a common protocol.

Susceptibility Testing: The isolates were tested by the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines and interpretative criteria. Tigecycline was tested on fresh Mueller-Hinton broth and the breakpoints utilized were those recommended by the USA-FDA, which are ≤2 mg/L (susceptible) and ≥8 mg/L (resistant) for Enterobacteriaceae; ≤0.5 mg/L for staphylococci (susceptible only) and ≤0.25 mg/L for streptococci and enterococci (susceptible only). Concurrent quality control (QC) testing was performed using the following organisms: *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, *E. coli* ATCC 25923, and *P. aeruginosa* ATCC 27853. All QC results were within published ranges.

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RESULTS

- A total of 25,401 strains were tested and tigecycline was highly active against the 10 most frequently isolated pathogens, except for *P. aeruginosa* (Tables 1 and 2). Among the 5 most common pathogens (18,802 strains; 74% of the total), tigecycline was active against >99% of tested strains at the established susceptible breakpoints.
- *E. coli* was the most frequently isolated organism from BSI (22.8%), followed by *S. aureus* (22.6%), coagulase-negative staphylococci (CoNS; 13.4%), *Enterococcus* spp. (8.9%) and *Klebsiella* spp. (7.6%; Table 1).
- Tigecycline was highly active against *S. aureus* (MIC_{50}, ≤0.12 mg/L; MIC_{90}, 0.25 mg/L; 99.9% susceptible) and CoNS (MIC_{50}, ≤0.12 mg/L; MIC_{90}, 0.5 mg/L; 98.8% susceptible; Table 2). Linezolid and vancomycin were also active (>99.9% susceptibility), but less potent (MIC_{50}, 0.5 - 2 mg/L) than tigecycline against these pathogens (data not shown).
- *Enterococcus* spp. showed high rates of resistance to most antimicrobial agents tested. Tigecycline (MIC_{50}, ≤0.12 mg/L; MIC_{90}, 0.25 mg/L; 97.0% susceptible) and linezolid (MIC_{50}, 1 mg/L; MIC_{90}, 2 mg/L; 100.0% susceptible) were the most active compounds tested against this pathogen group, followed by vancomycin (MIC_{50}, 1 mg/L; MIC_{90}, 2 mg/L; 93.2% susceptible).
- Tigecycline was very potent (MIC_{90}, ≤0.12 mg/L and all isolates inhibited at ≤0.5 mg/L; Table 2) against the pneumococci; and it demonstrated a spectrum similar to that of ceftriaxone (98.5% susceptibility).
- Tigecycline and imipenem were the most active compounds tested against *E. coli* (>99.9% susceptible), *Klebsiella* spp. (98.8-99.4%) and *Enterobacter* spp. (97.9-98.2%; data not shown). Enterobacteriaceae organisms with ESBL phenotypes showed tigecycline MIC distributions very similar to non-ESBL producing organisms (Table 2).
- Tigecycline was also very active against *Acinetobacter* spp. (MIC_{50}, 0.5 mg/L; MIC_{90}, 2 mg/L) and was the second most active compound tested against this emerging pathogen, ranked after polymyxin B (99.6% susceptible). Only 69.5% of *Acinetobacter* spp. strains were susceptible to imipenem (Tables 2 and 3).
- The main resistance phenotypes detected were methicillin-resistant *S. aureus* (MRSA; 28.3%) and CoNS (77.6%), ciprofloxacin-resistant *E. coli* (20.3%), ESBL-screen-positive *Klebsiella* spp. (22.8%) and *E. coli* (7.9%), imipenem-non-susceptible *P. aeruginosa* (21.7%) and *Acinetobacter* spp. (30.5%), and vancomycin-resistant *E. faecium* (17.0%; Table 3).
- Tigecycline was the most active agent tested against ESBL-screen-positive *E. coli* (MIC_{90}, 0.25 mg/L; 100.0% susceptible), *Klebsiella* spp. (MIC_{90}, 1 mg/L; 98.9% susceptible) and *Enterobacter* spp. (MIC_{90}, 2 mg/L; 92.0% susceptible; Table 4).

Table 1. Frequency of occurrence of bacterial organisms isolated from bloodstream infections in European Medical centers (2000-2007).

Organism	No. of isolates	% of total
1. *E. coli*	5,793	22.8
2. *S. aureus*	5,642	22.6
3. Coagulase-negative staphylococci	3,396	13.4
4. *Enterococcus*	2,265	8.9
5. *Klebsiella* spp.	1,706	7.6
6. *P. aeruginosa*	1,481	5.8
7. *Enterobacter* spp.	977	3.8
8. *S. pneumoniae*	551	2.2
9. ß-haemolytic streptococci	535	2.1
10. *Acinetobacter* spp.	509	2.0
11. Viridans group streptococci	452	1.8
12. *Proteus mirabilis*	407	1.6
13. *Serratia* spp.	347	1.4
14. Indole-positive *Proteae*	265	1.0
15. *S. maltophilia*	201	0.8
16. Others	874	3.4

Table 3. Prevalence of selected resistance phenotypes.

Phenotype	Prevalence (%)[a]
Methicillin-resistant *S. aureus*	28.3
Methicillin-resistant CoNS	77.6
Vancomycin-resistant *E. faecium*	17.0
Penicillin-resistant pneumococci	19.4 (0.0)[b]
ESBL-producing *E. coli*	7.9
Ciprofloxacin-resistant *E. coli*	20.3
ESBL-producing *Klebsiella* spp.	22.8
Ciprofloxacin-resistant *Klebsiella* spp.	12.0
ESBL-producing *Enterobacter* spp.	12.8
Ceftazidime-resistant *Enterobacter* spp.	25.2
Imipenem-non-susceptible *Acinetobacter* spp.	30.5
Imipenem-non-susceptible *P. aeruginosa*	21.7

a. According to breakpoints published in M100-S18 (CLSI, 2008)
b. According to nonmeningitis breakpoints (CLSI, 2008).

Table 2. Tigecycline MIC distributions of bacterial organisms isolated from bloodstream infections in European Medical centers (2000-2007).

Organism (no. tested)	No. of isolates (cumulative %) inhibited at MIC (mg/L) of: ≤0.12	0.25	0.5	1	2	4	>4
S. aureus							
Oxacillin-susceptible (4,045)	2,896 (71.6)	986 (96.0)	160 (99.9)	3 (100.0)	-	-	-
Oxacillin-resistant (1,546)	978 (61.3)	517 (93.7)	98 (99.8)	3 (100.0)	-	-	-
Coagulase-negative staphylococci (3,396)	1,936 (57.0)	1,079 (88.8)	340 (98.8)	41 (100.0)	-	-	-
Enterococcus spp.							
Vancomycin-susceptible (2,112)	1,577 (74.7)	469 (96.9)	63 (99.9)	3 (100.0)	-	-	-
Vancomycin-resistant (153)	129 (84.3)	21 (98.0)	3 (100.0)	-	-	-	-
S. pneumoniae (551)	548 (99.5)	3 (100.0)	-	-	-	-	-
Viridans group streptococci (452)	442 (97.8)	9 (99.8)	1 (100.0)	-	-	-	-
ß-haemolytic streptococci (535)	527 (98.5)	8 (100.0)	-	-	-	-	-
E. coli							
All strains (5,793)	3,851 (66.5)	1,692 (95.7)	224 (99.6)	20 (99.9)	5 (>99.9)	1 (100.0)	-
ESBL phenotype (457)	222 (48.6)	198 (91.9)	34 (99.3)	3 (100.0)	-	-	-
Klebsiella spp.							
All strains (1,706)	145 (8.5)	857 (58.7)	487 (87.3)	153 (96.2)	54 (99.4)	9 (99.9)	1 (100.0)
ESBL phenotype (380)	23 (6.1)	112 (35.5)	134 (70.8)	84 (92.9)	23 (98.9)	4 (100.0)	-
Enterobacter spp.							
All strains (977)	22 (2.3)	416 (44.8)	362 (81.9)	101 (92.2)	55 (97.9)	21 (100.0)	-
ESBL phenotype (125)	1 (0.8)	18 (15.2)	40 (47.2)	26 (68.0)	30 (92.0)	10 (100.0)	-
Ceftazidime-non-susceptible (296)	3 (1.0)	80 (28.0)	95 (60.1)	63 (81.4)	41 (95.3)	14 (100.0)	-
P. mirabilis							
All strains (407)	0 (0.0)	3 (0.7)	15 (4.4)	68 (21.1)	173 (63.6)	124 (94.1)	24 (100.0)
ESBL phenotype (29)	0 (0.0)	0 (0.0)	2 (6.9)	3 (17.2)	9 (48.3)	11 (86.2)	4 (100.0)
Acinetobacter spp.							
All strains (509)	95 (18.7)	105 (39.3)	84 (55.8)	141 (83.5)	72 (97.6)	12 (100.0)	-
Imipenem-non-susceptible (155)	0 (0.0)	7 (4.5)	35 (27.1)	68 (71.0)	39 (96.1)	6 (100.0)	-
P. aeruginosa (1,481)	1 (0.1)	4 (0.3)	11 (1.1)	19 (2.4)	129 (11.1)	516 (45.9)	801 (100.0)

Table 4. Antimicrobial susceptibility of Enterobacteriaceae strains with an ESBL phenotype.

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) MIC_{50}	MIC_{90}	% susceptible	% resistant
E. coli (457)				
Tigecycline	0.25	0.25	100.0	0.0
Ciprofloxacin	>4	>4	30.9	68.9
Gentamicin	≤2	>8	66.1	31.7
Amikacin	≤4	16	95.0	1.1
Imipenem	≤0.5	≤0.5	99.6	0.0
Klebsiella spp. (380)				
Tigecycline	0.5	1	98.9	0.0
Ciprofloxacin	1	>4	52.4	42.9
Gentamicin	4	>8	50.4	45.1
Amikacin	4	32	85.3	7.4
Imipenem	≤0.5	2	94.5	3.2
Enterobacter spp. (125)				
Tigecycline	1	2	92.0	0.0
Ciprofloxacin	>4	>4	36.0	57.6
Gentamicin	>8	>8	45.2	50.8
Amikacin	≤4	>32	81.6	16.0
Imipenem	≤0.5	8	88.0	4.0
P. mirabilis (29)				
Tigecycline	4	8	48.3	13.8
Ciprofloxacin	>4	>4	13.8	79.3
Gentamicin	>8	>8	34.5	58.6
Amikacin	4	>32	72.4	27.6
Imipenem	1	4	100.0	0.0

CONCLUSIONS

- Tigecycline exhibited a wide-spectrum of activity and high potency tested against contemporary BSI isolates collected in European medical centers.
- Resistance to tetracyclines or other antimicrobial classes did not adversely influence tigecycline activity.
- Treatment options for serious multidrug-resistant organism infections in nosocomial environments should benefit from the availability of parenteral tigecycline.