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Longitudinal Assessment of Tigecycline Activity Tested Against Gram-positive and -negative Organisms from European Medical Centres: Results from the SENTRY Programme (2004-2012)

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ABSTRACT

Objective: To evaluate the in vitro activity of tigecycline and comparators agents overtime tested against key bacterial pathogens isolated from European (EU) medical centres. Tigecycline presents a therapy option for emerging multidrug-resistant (MDR) Gram-positive (GP) and -negative (GN) organisms and was approved by the European Medicines Agency for the treatment of complicated skin and soft tissue (cSSTI) as well as intra-abdominal infections (IAI) in April 2006.

Methods: A total of 59,612 GP and GN clinically-significant non-duplicate isolates from multiple types of infections were collected from 18 EU countries from January 2004 to September 2012. Susceptibility (S) testing was performed by a central monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) against a large panel of antimicrobials using CLSI methods (M07-A9, 2012). S interpretations were performed according to EUCAST breakpoint criteria.

Results: Staphylococci ($MIC_{50/90}$, 0.12/0.25 mg/L), enterococci ($MIC_{50/90}$, 0.06-0.12/0.12-0.25 mg/L), and streptococci (β-haemolytic and viridans group; $MIC_{50/90}$, ≤0.03/≤0.03-0.06 mg/L) S rates were ≥99.6% (Table 2). Tigecycline activity was not adversely affected by oxacillin resistance (R) among staphylococci or vancomycin-R among enterococci. Among Enterobacteriaceae species (22,103 strains), S rates varied from 93.9% for *S. marcescens* to 100.0% for *C. koseri* (98.2% overall), and MIC_{90} values ranged from 0.25 mg/L (*C. koseri* and *E. coli*) to 1 mg/L (*E. aerogenes*, *E. cloacae, K. pneumoniae* and *S. marcescens*). Tigecycline retained activity against ESBL-phenotype strains as well as carbapenem-non-S Enterobacteriaceae. Tigecycline inhibited 95.0, 72.7 and 95.3% of *Acinetobacter* spp., *B. cepacia* and *S. maltophilia* strains at ≤2 mg/L, respectively; and MIC_{50} and MIC_{90} values for these organisms ranged from 0.5 to 1, and 2 to 4 mg/L, respectively.

Conclusions: Tigecycline continues to demonstrate quality antimicrobial activity against common pathogens associated with cSSSI and IAI occurring in EU patients. Tigecycline was active against antimicrobial-R as well as MDR strains, including MRSA, VRE and ESBL-phenotype Enterobacteriaceae. No tendency towards increasing tigecycline MIC values was observed across 9 years for any of the pathogens or R subsets evaluated. Based on the potency and spectrum exhibited here, tigecycline continues to have an important role for treating indicated bacterial pathogens in EU nations (Table 2).

INTRODUCTION

Tigecycline was approved by the United States Food and Drug Administration (USA-FDA; 2005) and by the European Medicines Agency (EMA; 2006) for acute bacterial skin and skin structure infections and complicated intra-abdominal infections, and in 2009 for treatment of community-acquired bacterial pneumonia. Sentinel monitoring through surveillance programs has provided information on the continuing activity of tigecycline tested against antimicrobial-resistant Gram-positive and -negative bacteria over time.

The purpose of this study is to evaluate the in vitro activity of tigecycline tested against bacterial isolates collected from medical centres located in Europe from January 2004 to September 2012 through the SENTRY Antimicrobial Surveillance Programme. This programme tested tigecycline and various comparator agents against pathogens causing clinically significant infections in a prevalence study design.

MATERIALS AND METHODS

Organism collection: A total of 59,612 Gram-positive and -negative clinically-significant non-duplicate isolates from multiple types of infections were collected from 18 EU countries from January 2004 to September 2012. Countries sampled and number of isolates per country are listed in Table 1. Isolates were collected from patients with bloodstream infections, community-acquired and nosocomial respiratory tract infections, and wound or skin and skin structure infections.

Methods: Broth microdilution susceptibility testing was performed according to Clinical Laboratory and Standards Institute (CLSI) methods using validated broth microdilution panels produced by ThermoFisher Scientific Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). Tigecycline MIC breakpoints were those established by EUCAST (version 2.0, January 2012). *E. coli* and *Klebsiella* spp. isolates were grouped as "ESBL-phenotype" and "non-ESBL-phenotype" based on the CLSI screening criteria for ESBL production (CLSI, 2012). Those isolates with positive ESBL screening test, ie. MIC of ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam were categorized as "ESBL-phenotype" for the purpose of susceptibility testing results analysis. Quality control was performed according to CLSI (M07-A9) methods using *Escherichia coli* ATCC 25922 and 35218, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212.

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RESULTS

- Tigecycline MIC_{50} and MIC_{90} values were 0.12 and 0.25 mg/L, respectively for both MSSA and MRSA. The highest tigecycline MIC value for *S. aureus* was only 1 mg/L, and >99.9% of strains were susceptible to tigecycline when applying the EUCAST breakpoint of ≤0.5 mg/L (Table 2 and Figure 1).
- Tigecycline MIC_{50} and MIC_{90} values were 0.12 and 0.25 mg/L, respectively for both methicillin-susceptible and –resistant *S. epidermidis* and for *S. haemolyticus*. The highest tigecycline MIC value was 1 mg/L for *S. epidermidis* (>99.9% susceptibility) and 0.5 mg/L for *S. haemolyticus* (100.0% susceptible; Table 2).
- *E. faecium* strains (MIC_{50}, 0.06 mg/L and MIC_{90}, 0.12 mg/L; 99.9% susceptible) showed tigecycline MIC values slightly lower (one doubling dilution) than those of *E. faecalis* strains (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L; 99.6% susceptible). Vancomycin-susceptible subsets exhibited tigecycline MIC_{50} and MIC_{90} values identical to those of vancomycin-resistant subsets (Table 2 and Figure 1).
- β-haemolytic and viridans group streptococci were highly susceptible to tigecycline with MIC_{50} of ≤0.03 mg/L and MIC_{90} of ≤0.03-0.06 mg/L (Table 2).
- Tigecycline was generally active against Enterobacteriaceae (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; 22,103 strains tested) and 98.2% of strains were inhibited at ≤1 mg/L (EUCAST breakpoints for indicated Enterobacteriaceae species; Table 2 and Figure 2).
- Among the Enterobacteriaceae species/subsets tested, MIC_{50} values varied from 0.12 mg/L for *C. koseri* and *E. coli,* to 0.5 mg/L for *S. marcescens* and ESBL-phenotype *K. pneumoniae*; whereas MIC_{90} values varied from 0.25 mg/L for *C. koseri* and *E. coli,* to 1 mg/L for *E. aerogenes, E. cloacae, K. pneumoniae* and *S. marcescens* (Table 2).
- Highest percentage of tigecycline non-susceptible strains among the Enterobacteriaceae species/subsets tested were observed for *S. marcescens* (6.1%), followed by *E. cloacae* (5.9%), *K. pneumoniae* (4.5%; 6.9% among strains with ESBL-phenotype) and *E. aerogenes* (4.1%); whereas *C. koseri, E. coli* and *K. oxytoca* showed 99.0-100.0% tigecycline susceptibility rates at EUCAST breakpoints (Table 2).
- Tigecycline exhibited good activity against *Acinetobacter* spp. (MIC_{50}, 0.5 mg/L and MIC_{90}, 2 mg/L; Table 2 and Figure 2), *B. cepacia* (MIC_{50}, 1 mg/L and MIC_{90}, 4 mg/L; Table 2), and *S. maltophilia* (MIC_{50}, 0.5 mg/L and MIC_{90}, 2 mg/L; Table 2).
- Tigecycline MIC distributions remained stable across the monitored period evaluated in this investigation, with no tendency of increasing MIC values overtime eg. MIC creep (data not shown).

Table 1. Demographics of European surveillance study isolates (SENTRY Programme, 2004-2012)

Nation	No. of Isolates (n)	Percent of Total Isolates (%)	Nation	No. of Isolates (n)	Percent of Total Isolates (%)
Belgium	1,996	3.35	Poland	2,535	4.25
Bulgaria	76	0.13	Portugal	1,244	2.09
Czech Republic	498	0.84	Romania	386	0.65
France	12,599	21.14	Slovakia	143	0.24
Germany	9,510	15.95	Slovenia	407	0.68
Greece	2,095	3.51	Spain	6,698	11.24
Hungary	280	0.47	Sweden	4,931	8.27
Ireland	4,594	7.71	UK	4,913	8.24
Italy	6,605	11.08	**Total**	**59,612**	**100**
Netherlands	102	0.17			

Figure 1. Frequency distribution of tigecycline MICs (mg/L) against *Staphylococcus aureus* (n=20,323) and *Enterococcus* spp. (n=7,132; SENTRY Programme, Europe, 2004-2012)

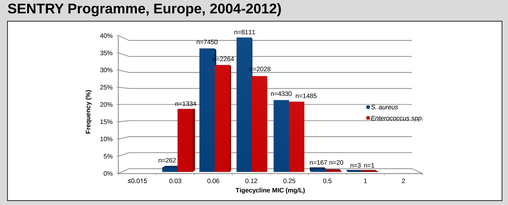
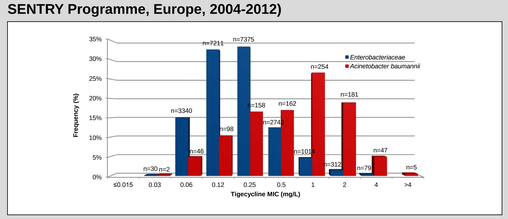


Figure 2. Frequency distribution of tigecycline MICs (mg/L) against Enterobacteriaceae (n=22,103) and *Acinetobacter baumannii* (n=953; SENTRY Programme, Europe, 2004-2012)



CONCLUSIONS

- Tigecycline continues to demonstrate a high level of antimicrobial activity when tested against common pathogens causing patient infections in European hospitals.
- Tigecycline was active against many antimicrobial-resistant as well as MDR strains, including MRSA, VRE and ESBL-phenotype Enterobacteriaceae.
- No tendency towards increasing tigecycline MIC values was observed across 9 years for any of the pathogens or resistant subsets evaluated.
- Based on the potency and spectrum exhibited here, tigecycline continues to have an important role for treating indicated bacterial pathogens found in European nations.

ACKNOWLEDGMENT

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Table 2. Summary of tigecycline in vitro activity against Gram-positive and -negative[a] organisms from European medical centres (SENTRY Programme, 2004-2012)

Organism	N	MIC (mg/L) Range	MIC_{50}	MIC_{90}	%S[b]	%I[b]	%R[b]
Staphylococcus aureus	20323	≤0.03 – 1	0.12	0.25	>99.9	0.0	<0.1
methicillin-susceptible	14839	≤0.03 – 1	0.12	0.25	>99.9	0.0	<0.1
methicillin-resistant	5484	≤0.03 – 1	0.12	0.25	>99.9	0.0	<0.1
Staphylococcus epidermidis	2844	≤0.03 – 1	0.12	0.25	>99.9	0.0	<0.1
methicillin-susceptible	630	≤0.03 – 0.5	0.12	0.25	100.0	0.0	0.0
methicillin-resistant	2214	≤0.03 – 1	0.12	0.25	>99.9	0.0	<0.1
Staphylococcus haemolyticus	533	≤0.03 – 0.5	0.12	0.25	100.0	0.0	0.0
Enterococcus faecalis	4767	≤0.03 – 1	0.12	0.25	99.6	0.4	<0.1
vancomycin-susceptible	4702	≤0.03 – 1	0.12	0.25	99.6	0.4	<0.1
vancomycin-resistant	65	≤0.03 – 0.25	0.12	0.25	100.0	0.0	0.0
Enterococcus faecium	2365	≤0.03 – 0.5	0.06	0.12	99.9	0.1	0.0
vancomycin-susceptible	1773	≤0.03 – 0.25	0.06	0.12	100.0	0.0	0.0
vancomycin-resistant	592	≤0.03 – 0.5	0.06	0.12	99.7	0.3	0.0
Group A *Streptococcus*	1596	≤0.03 – 0.25	≤0.03	≤0.03	100.0	0.0	0.0
Group B *Streptococcus*	1703	≤0.03 – 0.25	≤0.03	0.06	100.0	0.0	0.0
Streptococcus anginosus group	345	≤0.03 – 0.12	≤0.03	≤0.03	-	-	-
other Viridans group streptococci	1302	≤0.03 – 0.5	≤0.03	0.06	-	-	-
Enterobacteriaceae	22103	≤0.03 – 4	0.25	0.5	98.2	1.3	0.4
Citrobacter freundii	387	0.06 – 4	0.25	0.5	97.9	1.8	0.3
Citrobacter koseri	257	0.06 – 0.5	0.12	0.25	100.0	0.0	0.0
Enterobacter aerogenes	563	0.06 – 4	0.25	1	95.9	2.9	1.2
Enterobacter cloacae	2008	0.06 – 4	0.25	1	94.1	4.7	1.2
Escherichia coli	13194	≤0.03 – 2	0.12	0.25	>99.9	<0.1	0.0
non-ESBL-phenotype	11797	≤0.03 – 2	0.12	0.25	>99.9	<0.1	0.0
ESBL-phenotype	1397	≤0.03 – 2	0.12	0.25	99.9	0.1	0.0
Klebsiella oxytoca	1086	0.06 – 2	0.25	0.5	99.0	1.0	0.0
Klebsiella pneumoniae	3516	0.06 – 4	0.25	1	95.5	3.6	0.9
Non-ESBL-phenotype	2516	0.06 – 4	0.25	0.5	96.5	3.0	0.5
ESBL-phenotype	1000	0.06 – 4	0.5	1	93.1	5.2	1.7
Serratia marcescens	1092	0.12 – 4	0.5	1	93.9	4.5	1.6
Acinetobacter spp.	1200	≤0.03 – >4	0.5	2	-	-	-
Acinetobacter baumannii	953	≤0.03 – >4	1	2	-	-	-
Burkholderia cepacia	22	0.25 – 8	1	4	-	-	-
Stenotrophomonas maltophilia	509	0.12 – >4	0.5	2	-	-	-

a. Tigecycline does not cover *Pseudomonas aeruginosa*. b. Criteria as published by EUCAST [2012].