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Susceptibility among pathogens isolated from complicated skin and skin-structure infections in Europe; TEST program 2014-2016

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Revised Abstract

Background: Complicated skin and skin-structure infections (cSSSI) including diabetic foot, surgical site infections, deep soft tissue abscesses and cellulitis are difficult to manage therapeutically. Active antimicrobial agents are required to treat these infections which may be polymicrobial in some cases. Tigecycline (TGC) and other broad spectrum agents may be useful in cSSSI and continued monitoring of susceptibility rates to commonly used antimicrobials is critical. The TEST (Tigecycline European Surveillance Trial) program has provided surveillance on SSSI over the last 12 years in European (EU) hospitals. **Methods:** The TEST program 2014-2016 tested 8215 isolates of gram-positive (GP) and –negative (GN) isolates from species listed in the table. These were collected from patients with SSSI in EU hospitals. Susceptibility was determined against TGC and comparators locally using supplied broth micro dilution panels following CLSI guidelines and applying EUCAST breakpoint criteria. Phenotypic confirmation testing according to CLSI was performed to confirm ESBL-producing isolates at a central laboratory. **Results:** In this collection, the MRSA rate was 29.8%, the VRE rate was 6.2% and ESBL rates were 17.8% and 30.7% for *E. coli* and *K. pneumoniae*, respectively.

Antimicrobial*: % Susceptible

Organism (n)	AMK	AMC	CRO	LVX	MEM	TZP	TGC	VAN
S. aureus, MSSA (1645)	na	na	na	89.6	na	na	100	100
S. aureus, MRSA (698)	na	na	na	21.9	na	na	100	100
Enterococcus spp.(800)	na	72.1	na	55.6	na	na	99.9	93.7
S. agalactiae (494)	na	na	na	98	na	na	99.2	100
E. coli (1064)	97.9	32.2	77.5	63.4	99.7	90.6	99.5	na
K. pneumoniae (654)	91.9	3.2	58.7	62.8	89.1	67.7	82.6	na
Enterobacter spp. (1318)	98.6	6.1	68.1	88.6	98.6	78.2	92.7	na
Serratia spp. (492)	99	11.4	85.6	87.4	99.4	93.9	82.5	na
P. aeruginosa (1050)	92.1	na	na	61.7	74.1	82	na	na

*AMK=amikacin, AMC=ampicillin, CRO=ceftriaxone, LVX=levofloxacin, MEM=meropenem, TZP=piperacillin-tazobactam, TGC=tigecycline, VAN=vancomycin. na =no breakpoints defined, or results for the antibiotic not applicable to the organism

Conclusions: Among this large collection of EU SSSI isolates, *S. aureus* was the most common GP species and *Enterobacter* spp. were the most common GN pathogens. Susceptibility to TGC among all of the isolates in this study ranged from 82-100% using EUCAST breakpoint criteria. Considering that cSSSI is a very common cause of morbidity, diligent efforts are needed to monitor antimicrobial agents used in the treatment of these infections.

Introduction

Tigecycline has been approved for the treatment of complicated skin and skin structure infections (SSSIs) since 2006. Although target pathogens have not shown a propensity to develop resistance to tigecycline over this time period, continued monitoring of tigecycline's *in vitro* activity is prudent as both gram-positive and gram-negative pathogens continue to demonstrate increased resistance to first line antimicrobials. In this study data from The Tigecycline European Surveillance Trial (TEST) program were analyzed to assess the level of activity of tigecycline and relevant comparators against bacterial groups from European countries associated with skin and wound infections.

Materials & Methods

- A total of 8215 clinical isolates from SSSIs were collected and identified in hospitals in 21 European countries (Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Switzerland and the United Kingdom) from 2014 to 2016. Isolates were identified to the species level and MICs determined at each participating laboratory using supplied broth microdilution panels.
- Organism collection, transport, confirmation of organism identification, susceptibility testing, and development and management of a centralized database were coordinated by International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using MicroScan (Beckman Coulter, West Sacramento, CA) panels [1].
- MIC interpretive criteria followed EUCAST published guidelines [2].
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [3].

Results

Fig. 1 Distribution of All *S. aureus* and MRSA by Country

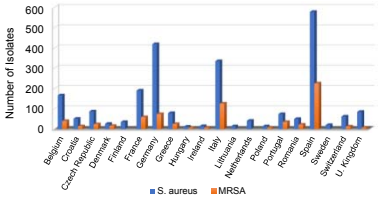

Table 1. *In vitro* activity of Tigecycline and Comparators Against *S. aureus*

Organism	Drug	%S	%I	%R	MIC_{50}	MIC_{90}	MIC range
S. aureus	Tigecycline	100	0	0	0.12	0.12	0.12 - 0.5
(2343)	Levofloxacin	69.4	0	30.6	0.25	16	0.25 - > 32
	Minocycline	95.4	1.4	3.2	≤0.25	≤0.25	≤0.25 - 8
	Penicillin	15.5	0	84.5	8	> 8	8 - > 8
	Vancomycin	100	0	0	0.5	1	0.5 - 2
S. aureus,	Tigecycline	100	0	0	0.12	0.25	0.12 - 0.5
MRSA	Levofloxacin	21.8	0	78.2	8	32	8 - > 32
(698)	Minocycline	92.8	1.43	5.7	≤0.25	≤0.25	≤0.25 - 8
	Penicillin	0	0	100	> 8	> 8	> 8 - > 8
	Vancomycin	100	0	0	0.5	1	0.5 - 2
S. aureus,	Tigecycline	100	0	0	0.12	0.12	0.12 - 0.5
MSSA	Levofloxacin	89.6	0	10.4	0.12	2	0.12 - > 32
(1645)	Minocycline	96.5	1.3	2.2	≤0.25	≤0.25	≤0.25 - 8
	Penicillin	22.1	0	77.9	2	> 8	2 - > 8
	Vancomycin	100	0	0	0.5	1	0.5 - 2

Table 2. *In vitro* activity of Tigecycline and Comparators Against *Enterococcus* spp.

Organism	Drug	%S	%I	%R	MIC_{50}	MIC_{90}	MIC Range
E. faecalis	Tigecycline	99.8	0.2	0	0.06	0.12	0.015 - 0.5
(533)	Ampicillin	99.3	0.2	0.6	1	1	≤0.06 - >16
	Ceftriaxone	na	na	na	>64	>64	≤0.03 - >64
	Levofloxacin	73.4	0	26.6	1	>32	≤0.06 - >32
	Meropenem	na	na	na	4	8	≤0.12 - >16
	Vancomycin	98.9	0	1.1	1	2	≤0.12 - >32
E. faecalis, VRE	Tigecycline	100	0	0	0.06	0.12	0.06 - 0.12
(6)	Ampicillin	100	0	0	1	2	0.5 - 2
	Ceftriaxone	na	na	na	>64	>64	64 - >64
	Levofloxacin	16.7	0	83.3	>32	>32	1 - >32
	Meropenem	na	na	na	8	8	4 - 8
	Vancomycin	0	0	100	>32	>32	32 - >32
E. faecalis, VSE	Tigecycline	99.8	0.2	0	0.06	0.12	0.015 - 0.5
(527)	Ampicillin	99.2	0.2	0.6	1	1	≤0.06 - >16
	Ceftriaxone	na	na	na	>64	>64	≤0.03 - >64
	Levofloxacin	74.0	0	26.0	1	>32	≤0.06 - >32
	Meropenem	na	na	na	4	8	≤0.12 - >16
	Vancomycin	100	0	0	1	2	≤0.12 - 2
E. faecium	Tigecycline	100	0	0	0.06	0.12	≤0.008 - 0.25
(242)	Ampicillin	12.4	0.8	86.8	>16	>16	≤0.06 - >16
	Ceftriaxone	na	na	na	>64	>64	1 - >64
	Levofloxacin	13.6	0	86.4	>32	>32	≤0.06 - >32
	Meropenem	na	na	na	>16	>16	≤0.12 - >16
	Vancomycin	81.8	0	18.2	0.5	>32	0.25 - >32
E. faecium, VRE	Tigecycline	100	0	0	0.06	0.25	0.03 - 0.25
(42)	Ampicillin	0	0	100	>16	>16	>16 - >16
	Ceftriaxone	na	na	na	>64	>64	64 - >64
	Levofloxacin	0	0	100	>32	>32	16 - >32
	Meropenem	na	na	na	>16	>16	>16 - >16
	Vancomycin	0	0	100	>32	>32	>32 - >32
E. faecium, VSE	Tigecycline	100	0	0	0.06	0.12	≤0.008 - 0.25
(200)	Ampicillin	15.0	1.0	84.0	>16	>16	≤0.06 - >16
	Ceftriaxone	na	na	na	>64	>64	1 - >64
	Levofloxacin	16.5	0	83.5	>32	>32	≤0.06 - >32
	Meropenem	na	na	na	>16	>16	≤0.12 - >16
	Vancomycin	99.0	0	1.0	0.5	1	0.25 - 16

* not available

Table 3. *In vitro* activity of Tigecycline and Comparators Against *Enterobacteriaceae* spp.

Organism	Drug	%S	%I	%R	MIC_{50}	MIC_{90}	MIC Range
Enterobacter spp	Tigecycline	92.7	4.0	3.3	0.5	1	≤0.008 - 8
(1318)	Amikacin	98.6	0.7	0.7	2	4	≤0.5 - >64
	Ampicillin	6.1	0	93.9	>32	>32	2 - >32
	Ceftriaxone	68.1	3.6	28.3	0.25	>32	≤0.06 - >32
	Levofloxacin	88.6	2.8	8.6	0.06	1	≤0.008 - >8
	Meropenem	98.6	1.2	0.2	≤0.06	0.25	≤0.06 - 16
	Pip-Tazo	78.2	4.8	17.1	2	64	0.12 - >128
E. coli	Tigecycline	99.5	0.5	0	0.12	0.25	≤0.008 - 2
(1064)	Amikacin	97.9	1.7	0.4	2	8	≤0.5 - 64
	Ampicillin	32.2	0	67.8	>32	>32	≤0.5 - >32
	Ceftriaxone	77.5	1.0	21.4	≤0.06	>32	≤0.06 - >32
	Levofloxacin	63.4	2.1	34.5	0.06	>8	≤0.008 - >8
	Meropenem	99.7	0.2	0.1	≤0.06	≤0.06	≤0.06 - 16
	Pip-Tazo	90.6	2.4	7.1	1	8	≤0.06 - >128
K. pneumoniae	Tigecycline	82.6	9.3	8.1	0.5	2	0.06 - >8
(654)	Amikacin	91.9	5.2	2.9	2	8	≤0.5 - >64
	Ampicillin	3.2	0	96.8	>32	>32	1 - >32
	Ceftriaxone	58.7	0.8	40.5	0.12	>32	≤0.06 - >32
	Levofloxacin	62.8	2.8	34.4	0.25	>8	0.015 - >8
	Meropenem	89.1	2.3	8.6	≤0.06	4	≤0.06 - >16
	Pip-Tazo	67.7	4.7	27.5	2	>128	0.12 - >128
Serratia spp	Tigecycline	82.5	15.0	2.4	1	2	0.06 - 4
(492)	Amikacin	99.0	0.6	0.4	2	4	≤0.5 - 64
	Ampicillin	11.4	0	88.6	>32	>32	≤0.5 - >32
	Ceftriaxone	85.6	4.9	9.6	0.25	2	≤0.06 - >32
	Levofloxacin	87.4	4.9	7.7	0.12	1	≤0.008 - >8
	Meropenem	99.4	0.6	0	0.12	0.12	≤0.06 - 8
	Pip-Tazo	93.9	2.9	3.3	1	8	0.12 - >128

Table 4. *In vitro* activity of Comparative Antimicrobials Against *P. aeruginosa*

Organism	Drug	%S	%I	%R	MIC_{50}	MIC_{90}	MIC Range
P. aeruginosa	Amikacin	92.1	2.5	5.4	4	8	≤0.5 - > 64
(1132)	Levofloxacin	61.7	0	38.3	1	> 8	0.03 - > 8
	Meropenem	74.1	12.8	13.1	1	16	≤0.06 - > 16
	Pip-Tazo	82.0	0	18.0	4	64	0.12 - > 128

Table 5. *In vitro* activity of Tigecycline and Comparators Against *S. agalactiae*

Organism	Drug	%S	%I	%R	MIC_{50}	MIC_{90}	MIC Range
S. agalactiae	Tigecycline	99.2	0	0.8	0.03	0.06	≤0.015 - 2
(494)	Levofloxacin	98.0	0	2.0	0.5	1	≤0.06 - 32
	Minocycline	20.5	1.6	77.9	8	8	≤0.25 - >8
	Penicillin	100	0	0	≤0.06	0.12	≤0.06 - 0.12
	Vancomycin	100	0	0	0.5	0.5	≤0.12 - 1

Conclusions

- Tigecycline demonstrated potent *in vitro* activity against the various organism groups from SSSIs in European countries including both gram-negative and gram-positive organisms.
- Tigecycline MIC_{90} values ranged from 0.06 - 2 mg/L for all the Gram-positive and Gram-negative species tested in this study.
- These current finding indicate that tigecycline has maintained a high level of *in vitro* activity against a wide variety of species associated with skin and wound infections in European countries.
- Given the propensity of many of these pathogens to develop resistance continued surveillance of the antimicrobial activities among both gram-positive and gram-negative pathogens causing SSSI in Europe is warranted.

References

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