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In vitro Activity of Tigecycline and Comparators Against Gram-Negative Pathogens in France from Patients with Complicated Intra-Abdominal (IAI) and Skin and Soft Tissue Infections (SSTI)

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Revised Abstract

Background: The Tigecycline European Surveillance Trial (TEST) monitors the in vitro activity of tigecycline and other antimicrobials against clinically-relevant pathogens collected in multiple European countries. This study reports on the activity of tigecycline and comparators against IAI and SSTI isolates collected in France during 2013-2016 during the course of this surveillance study.

Methods: Non-duplicate clinical gram-negative isolates (1118) from multiple medical centers in France were collected during 2013-2016 from IAI and SSTI infection sources. Organism identification and antibiotic susceptibility testing was performed by the local laboratories. Susceptibility testing was performed using supplied broth micro dilution panels according to CLSI guidelines and categorical interpretation of results was done using EUCAST breakpoints.

Results: The table provides % Susceptibility and ($MIC_{50/90}$) data for tigecycline and comparators against key pathogens.

Organism	Tigecycline	Amikacin	Levofloxacin	Meropenem	Pip-Tazo
Citrobacter spp. (110)	100(0.25/0.5)	100(2/2)	93.6(0.03/0.5)	100(≤0.06/≤0.06)	82.7(1/32)
Enterobacter spp. (206)	87.4(0.5/2)	98.1(2/8)	79.1(0.06/8)	99.5(≤0.06/0.25)	68(4/128)
E. coli (252)	99.6(0.12/0.25)	98.4(2/4)	81.4(0.03/8)	100(≤0.06/≤0.06)	93.3(1/4)
K. oxytoca (72)	98.6(0.25/0.5)	98.6(2/4)	94.4(0.03/0.06)	100(≤0.06/≤0.06)	93.1(1/4)
K. pneumoniae (141)	87.9(0.5/2)	97.2(2/4)	80.1(0.06/8)	99.3(≤0.06/0.12)	84.4(2/32)
Serratia spp (67)	85.1(1/2)	100(2/4)	94(0.12/0.5)	100(≤ 0.06/0.12)	94.0(1/4)
Acinetobacter spp. (107)	na(0.12/0.5)	88.8(2/16)	76.6(0.12/8)	86(0.5/>16)	na(0.5/>128)
P. aeruginosa (163)	na(8/>8)	96.3(4/8)	72.4(0.5/>8)	78.5(1/8)	84.1(4/64)

na:breakpoints not available

Conclusions: Based on percent susceptibility, meropenem, amikacin, and tigecycline exhibited the most potent *in vitro* activity against the studied Enterobacteriaceae from France. Tigecycline was the most active agent, based on MIC_{90}, against *A. baumannii* and activities of other agents against *P. aeruginosa* were variable with amikacin demonstrating the highest percent susceptibility. Country specific monitoring of susceptibility patterns among common gram-negative pathogens associated with IAI and SSTI infections provides useful information for determining if changes in treatment strategies should be considered on both a local and country specific level.

Introduction

The Tigecycline European Surveillance Trial (TEST) monitors the *in vitro* activity of tigecycline and other comparator antimicrobials against clinically-relevant pathogens collected globally from a variety of infectious processes including skin and soft tissue (SSTI) and intra-abdominal infections (IAI). This study reports on the activity of tigecycline and comparators against IAI and SSTI gram-negative isolates collected in multiple hospitals in France during 2013-2016.

Materials & Methods

- Non-duplicate clinical isolates of gram-negative pathogens (*E. coli, Klebsiella pneumoniae/oxytoca*, *Citrobacter* spp., *Enterobacter* spp., *Serratia* spp., *Acinetobacter* spp. and *P. aeruginosa* were collected during 2013-2016 in France from IAI and SSTI.
- 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]. All antimicrobials were supplied by the panel manufacturers.
- MIC interpretive criteria followed published EUCAST 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

Table 1. Susceptibility and MIC values observed among gram-negative pathogens collected from patients with IAI

Organism	Drug	% S	% I	% R	MIC_{50}	MIC_{90}	MIC Range
E. coli (n=162)	Tigecycline	99.4	0.6	0	0.12	0.25	0.03 - 2
	Amikacin	98.8	1.2	0	2	4	≤0.5 - 16
	Ampicillin	46.9	0	53.1	>32	>32	1 - >32
	Cefepime	82.7	5.6	11.7	≤0.5	8	≤0.5 - >32
	Ceftriaxone	83.3	0.6	16.1	≤0.06	>32	≤0.06 - >32
	Levofloxacin	82.1	0.6	17.3	0.03	8	≤0.008 - >8
	Meropenem	100	0	0	≤0.06	≤0.06	≤0.06 - 0.5
	Pip - Tazo	93.2	1.2	5.6	1	4	≤0.06 - >128
Enterobacter spp (n=81)	Tigecycline	87.7	11.1	1.2	0.5	2	0.25 - 4
	Amikacin	98.8	1.2	0	2	4	1 - 16
	Ampicillin	7.4	0	92.6	>32	>32	2 - >32
	Cefepime	58.0	17.3	24.7	≤0.5	>32	≤0.5 - >32
	Ceftriaxone	43.2	2.5	54.3	4	>32	≤0.06 - >32
	Levofloxacin	77.8	1.2	21.0	0.06	8	0.015 - >8
	Meropenem	98.8	0	1.2	0.12	0.25	≤0.06 - >16
	Pip - Tazo	63.0	2.5	34.6	8	128	0.5 - >128
K. pneumoniae (n=80)	Tigecycline	90.0	3.8	6.3	0.5	1	0.12 - 4
	Amikacin	98.8	1.3	0	2	4	≤0.5 - 16
	Ampicillin	2.5	0	97.5	>32	>32	8 - >32
	Cefepime	68.8	2.5	28.8	≤0.5	32	≤0.5 - >32
	Ceftriaxone	68.8	0	31.3	≤0.06	>32	≤0.06 - >32
	Levofloxacin	82.5	1.3	16.3	0.06	2	0.03 - >8
	Meropenem	100	0	0	≤0.06	0.12	≤0.06 - 0.5
	Pip - Tazo	85.0	2.5	12.5	2	32	0.25 - >128
Citrobacter spp (n=36)	Tigecycline	100	0	0	0.25	0.5	0.06 - 1
	Amikacin	100	0	0	2	2	≤0.5 - 8
	Ampicillin	19.4	0	80.6	>32	>32	8 - >32
	Cefepime	91.7	5.6	2.8	≤0.5	1	≤0.5 - 8
	Ceftriaxone	61.1	2.8	36.1	0.12	32	≤0.06 - >32
	Levofloxacin	91.7	2.8	5.6	0.06	0.5	≤0.008 - >8
	Meropenem	100	0	0	≤0.06	0.12	≤0.06 - 0.25
	Pip - Tazo	72.2	8.3	19.4	2	64	≤0.06 - 128
K. oxytoca (n=36)	Tigecycline	97.2	0	2.8	0.25	0.5	0.12 - 4
	Amikacin	97.2	2.8	0	2	4	≤0.5 - 16
	Ampicillin	8.3	0	91.7	>32	>32	8 - >32
	Cefepime	91.7	5.6	2.8	≤0.5	1	≤0.5 - 8
	Ceftriaxone	91.7	0	8.3	≤0.06	1	≤0.06 - >32
	Levofloxacin	91.7	2.8	5.6	0.03	0.5	0.015 - >8
	Meropenem	100	0	0	≤0.06	≤0.06	≤0.06 - 0.12
	Pip - Tazo	91.7	0	8.3	1	4	0.25 - >128
P. aeruginosa (n=48)	Amikacin	93.8	0	6.3	4	8	1 - 64
	Cefepime	85.4	0	14.6	2	16	≤0.5 - >32
	Levofloxacin	81.3	0	18.8	0.5	>8	0.03 - >8
	Meropenem	85.4	2.1	12.5	0.5	16	≤0.06 - >16
	Pip - Tazo	79.2	0	20.8	4	64	0.25 - >128
Acinetobacter spp (n=26)	Tigecycline	na	na	na	0.12	1	0.015 - 1
	Amikacin	73.1	3.9	23.1	2	>64	≤0.5 - >64
	Levofloxacin	57.7	0	42.3	0.12	>8	0.03 - >8
	Meropenem	69.2	3.9	26.9	1	>16	≤0.06 - >16
	Pip - Tazo	na	na	na	4	>128	≤0.06 - >128

na:beakpoints not available
Serratia spp., n=5 not in the table

Figure 1. Species Distribution of Isolates collected from Patients with IAI

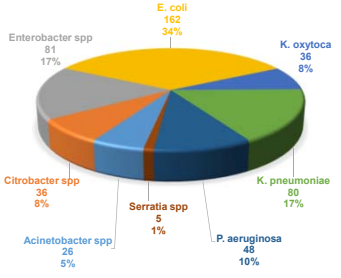

Figure 2. Species Distribution of Isolates collected from Patients with SSTI

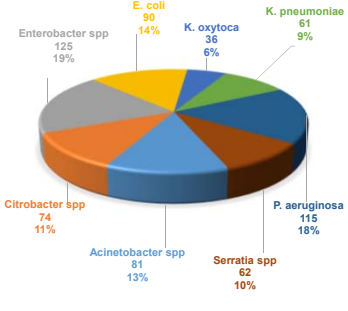

Table 2. Susceptibility and MIC Values observed among gram-negative pathogens collected from patients with SSTI

Organism	Drug	% S	% I	% R	MIC_{50}	MIC_{90}	MIC Range
E. coli (n=90)	Tigecycline	100	0	0	0.12	0.25	0.06 - 0.5
	Amikacin	97.8	2.2	0	2	4	1 - 16
	Ampicillin	34.4	0	65.6	>32	>32	1 - >32
	Cefepime	84.4	2.2	13.3	≤0.5	16	≤0.5 - >32
	Ceftriaxone	81.1	2.2	16.7	≤0.06	>32	≤0.06 - >32
	Levofloxacin	80.0	2.2	17.8	0.03	8	0.015 - >8
	Meropenem	100	0	0	≤0.06	≤0.06	≤0.06 - 0.12
	Pip - Tazo	93.3	1.1	5.6	1	8	0.5 - >128
Enterobacter spp (n=125)	Tigecycline	87.2	10.4	2.4	0.5	2	0.06 - 4
	Amikacin	97.6	0.8	1.6	≤0.5	8	1 - >64
	Ampicillin	2.4	0	97.6	>32	>32	2 - >32
	Cefepime	68.8	12.8	18.4	≤0.5	32	≤0.5 - >32
	Ceftriaxone	54.4	6.4	39.2	1	>32	≤0.06 - >32
	Levofloxacin	80.0	2.4	17.6	0.06	8	0.015 - >8
	Meropenem	100	0	0	≤0.06	0.25	≤0.06 - 2
	Pip - Tazo	71.2	7.2	21.6	2	128	0.5 - >128
K. pneumoniae (n=61)	Tigecycline	85.3	6.6	8.2	0.5	2	0.12 - 4
	Amikacin	95.1	3.3	1.6	2	4	≤0.5 - >64
	Ampicillin	4.9	0	95.1	>32	>32	2 - >32
	Cefepime	73.8	1.6	24.6	≤0.5	>32	≤0.5 - >32
	Ceftriaxone	73.8	0	26.2	≤0.06	>32	≤0.06 - >32
	Levofloxacin	77.1	4.9	18.0	0.06	8	0.03 - >8
	Meropenem	98.4	0	1.6	≤0.06	0.12	≤0.06 - 16
	Pip - Tazo	83.6	6.6	9.8	2	16	0.5 - >128
Citrobacter spp (n=74)	Tigecycline	100	0	0	0.12	0.5	0.03 - 1
	Amikacin	100	0	0	1	4	≤0.5 - 8
	Ampicillin	13.5	0	86.5	32	>32	4 - >32
	Cefepime	90.5	2.7	6.8	≤0.5	1	≤0.5 - >32
	Ceftriaxone	78.4	1.4	20.3	≤0.06	32	≤0.06 - >32
	Levofloxacin	94.6	1.4	4.1	0.03	0.25	0.015 - >8
	Meropenem	100	0	0	≤0.06	≤0.06	≤0.06 - 0.25
	Pip - Tazo	87.8	5.4	6.8	1	16	0.5 - 128
K. oxytoca (n=36)	Tigecycline	100	0	0	0.25	1	0.12 - 1
	Amikacin	5.6	0	94.4	>32	>32	8 - >32
	Amikacin	100	0	0	2	4	≤0.5 - 4
	Cefepime	91.7	2.8	5.6	≤0.5	1	≤0.5 - 32
	Ceftriaxone	91.7	2.8	5.6	≤0.06	0.5	≤0.06 - >32
	Levofloxacin	97.2	0	2.8	0.03	0.06	0.03 - 8
	Meropenem	100	0	0	≤0.06	0.12	≤0.06 - 1
	Pip - Tazo	94.4	0	5.6	1	4	0.25 - 128
Serratia spp (n=62)	Tigecycline	83.9	16.1	0	1	2	0.12 - 2
	Amikacin	100	0	0	2	4	1 - 8
	Ampicillin	4.8	0	95.2	>32	>32	4 - >32
	Cefepime	93.6	6.5	0	≤0.5	≤0.5	≤0.5 - 4
	Ceftriaxone	87.1	1.6	11.3	0.25	4	≤0.06 - >32
	Levofloxacin	93.6	1.6	4.8	0.12	0.5	0.015 - >8
	Meropenem	100	0	0	≤0.06	0.12	≤0.06 - 0.25
	Pip - Tazo	93.6	3.2	3.2	1	4	0.5 - 32
P. aeruginosa (n=115)	Amikacin	97.4	0.9	1.7	4	8	≤0.5 - >64
	Cefepime	86.1	0	13.9	4	16	1 - >32
	Levofloxacin	68.7	0	31.3	1	>8	0.12 - >8
	Meropenem	75.7	15.7	8.7	1	8	≤0.06 - >16
	Pip - Tazo	86.1	0	13.9	4	64	2 - >128
Acinetobacter spp (n=81)	Tigecycline	na	na	na	0.12	0.5	0.015 - 2
	Amikacin	93.8	2.5	3.7	2	4	≤0.5 - >64
	Levofloxacin	82.7	1.2	16.1	0.12	4	≤0.008 - >8
	Meropenem	91.4	1.2	7.4	0.5	2	≤0.06 - >16
	Pip - Tazo	na	na	na	0.25	32	≤0.06 - >128

na:breakpoints not available

Conclusions

- **Tigecycline, meropenem and amikacin overall were the most active against species of *Enterobacteriaceae.***
- **Based on MIC_{90} tigecycline was the most active agent against *Acinetobacter* spp. while amikacin was the most active agent against *P. aeruginosa* based on percent susceptible.**
- **Minimal differences among the drugs tested were noted between the same species when isolated from either IAI or SSTI.**
- **Given the ability of many of these species to develop antimicrobial resistance, ongoing monitoring of activity on a country specific basis is warranted.**

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