In Vitro Activity of Tigecycline and Comparators Against Extended Spectrum Beta- Lactamase (ESBL) Positive Isolates of *Escherichia coli* and *Klebsiella pneumoniae* from Germany

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D. Biedenbach[1], D. Sahm[1], M. Hackel[1], H. Leister-Tebbe[2]
[1]International Health Management Associates, Schaumburg, IL, USA
[2]Pfizer Inc., Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
Phone: +1.847.303.5003
Fax: +1.847.303.5601
www.ihmainc.com

Revised Abstract

Objectives: Worldwide dissemination of gram-negative bacteria producing extended-spectrum b-lactamases (ESBLs) has proved problematic in many countries. The Tigecycline European Surveillance Trial (TEST) monitors the activity of tigecycline and other antimicrobials against clinically-relevant pathogens collected globally. This study reports the activity of tigecycline in TEST isolates collected in Germany during the course of this surveillance study with a focus on populations exhibiting the ESBL phenotype. **Methods**: Non-duplicate clinical isolates of *E. coli* and *K. pneumoniae* from German medical centers were collected during 2004-2015 from defined infection sites. Organism identification and antibiotic susceptibility testing was performed by the local laboratories. Susceptibility testing was performed using broth microdilution according to CLSI guidelines and categorical interpretation of results was done using EUCAST breakpoints. **Results**: The table provides MIC and susceptibility data for tigecycline and comparators against ESBL-positive populations.

Organism (n)	Drug	% Susceptible	% Resistant	$MIC_{50/90}$	MIC range
***E. coli*, ESBL-Positive (445)**	Amikacin	92.8	2.5	2/8	≤0.5->64
	Levofloxacin	31.2	68.5	8/>8	≤0.008->8
	Meropenem	99.5	0.0	≤0.06/0.12	≤0.06-4
	Pip/Tazo	74.4	15.7	2/64	0.25->128
	Tigecycline	98.4	0.0	0.25/0.5	0.03-2
***K. pneumoniae*, ESBL-Positive (274)**	Amikacin	88.7	4.4	2/16	≤0.5->64
	Levofloxacin	37.2	54.0	4/>8	0.015->8
	Meropenem	94.6	3.1	≤0.06/1	≤0.06->16
	Pip/Tazo	49.3	39.4	16/>128	0.5->128
	Tigecycline	75.9	8.4	0.5/2	0.12-8

Conclusions: Tigecycline and meropenem provided similar activity (>98% susceptible) against ESBL-positive *E. coli* isolates from Germany. ESBL-positive *K. pneumoniae* isolates were less susceptible to most agents tested when compared to *E. coli* isolates. Country specific monitoring is essential to follow the susceptibility patterns of ESBL isolates for common gram-negative pathogens.

Introduction

The Tigecycline European Susceptibility Testing Study (TEST) is now in the 13th year of antimicrobial resistance surveillance and has evaluated the incidence of ESBL-producing *Enterobacteriaciae* in multiple countries worldwide. This report focuses on the evaluation of *E. coli* and *K. pneumonia*, including ESBL-producing isolates of from Germany during 2004-2015 surveillance.

Materials & Methods

- Non-duplicate clinical isolates of *E. coli* and *K. pneumoniae* from German medical centers were collected during 2004-2015 from defined infection sites. Organism identification and antibiotic susceptibility testing was performed by the local laboratories.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA) or TREK (TREK Diagnostic Systems, Cleveland, OH) panels. MIC interpretive criteria followed published EUCAST guidelines.
- Quality control isolates (QC) were tested on each day 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.

Results

Table 1. *In vitro* susceptibility of all *E. coli* and *K. pneumoniae* collected from Germany during TEST surveillance 2004-2015.

Organism (n)	Drug	MIC_{50}	MIC_{90}	MIC range	% Susceptible	% Intermediate	% Resistant
E. coli (2,785)	Ceftriaxone	≤ 0.06	> 32	≤ 0.06 - >64	80.2	0.5	19.3
	Cefepime	≤ 0.5	32	≤ 0.5 - >32	80.1	4.7	15.2
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - >16	99.4	0.3	0.3
	Piperacillin-tazobactam	1	16	≤ 0.06 - >128	89.6	2.6	7.8
	Amikacin	2	8	≤ 0.5 - >64	97.3	1.8	0.9
	Levofloxacin	0.06	> 8	≤ 0.008 - >8	69.7	0.9	29.4
	Tigecycline	0.12	0.5	≤ 0.008 - 4	99.4	0.5	0.1
K. pneumoniae (1,752)	Ceftriaxone	≤ 0.06	> 32	≤ 0.06 - >64	80.8	1.0	18.2
	Cefepime	≤ 0.5	16	≤ 0.5 - >32	82.1	3.6	14.3
	Meropenem	≤ 0.06	0.12	≤ 0.06 - >16	98.6	0.6	0.9
	Piperacillin-tazobactam	2	32	≤ 0.06 - >128	85.2	4.1	10.8
	Amikacin	1	4	≤ 0.5 - >64	97.8	1.3	0.9
	Levofloxacin	0.06	4	≤ 0.008 - >8	83.7	3.3	13.0
	Tigecycline	0.5	2	≤ 0.008 - 8	86.8	7.9	5.3

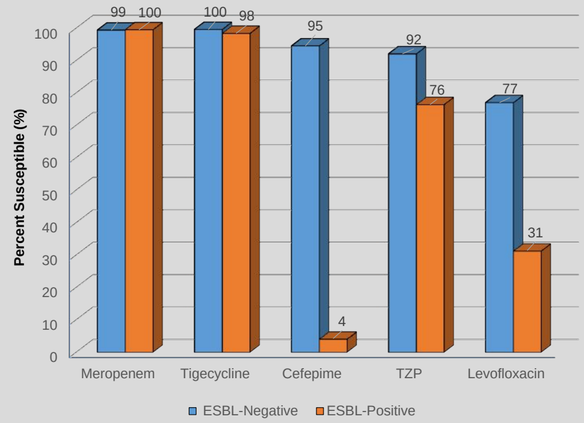
Table 2. *In vitro* susceptibility of ESBL-negative *E. coli* and *K. pneumoniae* collected from Germany during TEST surveillance 2004-2015.

Organism (n)	Drug	MIC_{50}	MIC_{90}	MIC range	% Susceptible	% Intermediate	% Resistant
E. coli, ESBL-negative (2,340)	Ceftriaxone	≤ 0.06	0.25	≤ 0.06 - >64	95.1	0.5	4.4
	Cefepime	≤ 0.5	≤ 0.5	≤ 0.5 - >32	94.5	3.0	2.4
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - >16	99.4	0.2	0.3
	Piperacillin-tazobactam	1	8	≤ 0.06 ->128	92.1	1.6	6.3
	Amikacin	2	4	≤ 0.5 - >64	98.2	1.3	0.6
	Levofloxacin	0.03	> 8	≤ 0.008 - >8	77.0	1.0	22.0
	Tigecycline	0.12	0.5	≤ 0.008 - 4	99.6	0.3	0.0
K. pneumoniae, ESBL-negative (1,478)	Ceftriaxone	≤ 0.06	0.25	≤ 0.06 - >64	95.6	0.8	3.6
	Cefepime	≤ 0.5	≤ 0.5	≤ 0.5 - >32	96.3	1.8	2.0
	Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - >16	99.3	0.2	0.5
	Piperacillin-tazobactam	2	8	≤ 0.06 - >128	91.8	2.7	5.5
	Amikacin	1	2	≤ 0.5 - >64	99.5	0.3	0.3
	Levofloxacin	0.06	1	≤ 0.008 - >8	92.3	2.3	5.4
	Tigecycline	0.5	2	≤ 0.008 - 8	88.8	6.5	4.7

Table 3. *In vitro* susceptibility of ESBL-positive *E. coli* and *K. pneumoniae* collected from Germany during TEST surveillance 2004-2015.

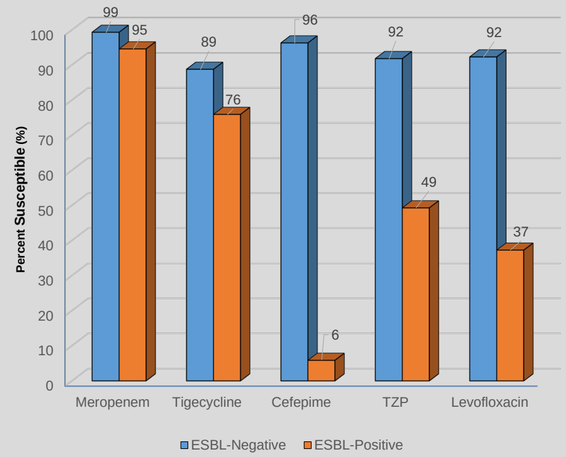
Organism (n)	Drug	MIC_{50}	MIC_{90}	MIC range	% Susceptible	% Intermediate	% Resistant
E. coli, ESBL-positive (445)	Ceftriaxone	> 32	> 64	≤ 0.06 - >64	1.6	0.7	97.8
	Cefepime	32	> 32	≤ 0.5 >32	4.0	13.3	82.7
	Meropenem	≤ 0.06	0.12	≤ 0.06 - 4	99.5	0.5	0.0
	Piperacillin-tazobactam	2	64	0.25 - >128	76.4	7.9	15.7
	Amikacin	2	8	≤ 0.5 - >64	92.8	4.7	2.5
	Levofloxacin	8	> 8	≤ 0.008 - >8	31.2	0.2	68.5
	Tigecycline	0.25	0.5	0.03 - 2	98.4	1.6	0.0
K. pneumoniae, ESBL-positive (274)	Ceftriaxone	> 32	> 64	0.25 - >64	1.1	1.8	97.1
	Cefepime	32	> 32	≤ 0.5 - >32	5.8	13.5	80.7
	Meropenem	≤ 0.06	1	≤ 0.06 - >16	94.6	2.3	3.1
	Piperacillin-tazobactam	16	> 128	0.5 - >128	49.3	11.3	39.4
	Amikacin	2	16	≤ 0.5 - >64	88.7	6.9	4.4
	Levofloxacin	4	> 8	0.015 - >8	37.2	8.8	54.0
	Tigecycline	0.5	2	0.12 - 8	75.9	15.7	8.4

Figure 1. Susceptibility Percentages Observed Among 2,340 ESBL-Negative and 445 ESBL- Positive *E. coli* from Germany.



*** 10% of the *E. coli* isolates were ESBL-positive by phenotypic tests.**

Figure 2. Susceptibility Percentages Observed Among 1,478 ESBL-Negative and 274 ESBL- Positive *K. pneumoniae* from Germany.



*** 6% of the *K. pneumoniae* isolates were ESBL-positive by phenotypic tests.**

Conclusions

- Tigecycline and meropenem provided similar activity against ESBL-positive *E. coli* isolates from Germany.
- ESBL-positive *K. pneumoniae* isolates were less susceptible to most agents tested when compared to *E. coli* isolates from Germany.
- Country specific monitoring is essential to follow the susceptibility patterns of ESBL producing isolates for common gram-negative pathogens.

References and Acknowledgments:

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