

## Revised Abstract

**Background:** The Tigecycline Evaluation and Surveillance Trial (TEST) has tracked the *in vitro* activity of tigecycline and comparators against gram-negative organisms from a broad range of infections since 2004. This report summarizes that activity against *Escherichia coli* and extended-spectrum beta-lactamase (ESBL) producing *E. coli* collected from 2005-2009 in the United States.

**Methods:** 543 clinically significant *E. coli* were obtained from intra-abdominal infections from 456 labs. Seven isolates (1.3%) were ESBL producers. MICs were determined using supplied broth microdilution panels. Results were interpreted according to CLSI or FDA (tigecycline) guidelines.

**Results:** The %Susceptible/Intermediate/Resistant for tigecycline and comparators is shown in the following table:

Drug	<i>Escherichia coli</i> (n=543)			<i>Escherichia coli</i> , ESBL (n=7)		
	MIC <sub>50</sub>   MIC <sub>90</sub>	%S   %I   %R	MIC Range	%S   %I   %R		
Amikacin	2   4	99.4   0.4   0.4	1 - 16	100   0   0		
Amox-Clav	4   16	76.1   14   9.9	8 - >32	14.3   28.6   57.1		
Ampicillin	4   >32	56.2   1.8   4.2	>32 - >32	0   0   100		
Cefepime	≤0.5   ≤0.5	98.2   0.7   1.1	2 - >32	28.6   42.9   28.6		
Ceftriaxone	≤0.06   0.25	93.9   1.1   5	2 - >64	0   14.3   85.7		
Imipenem	0.25   0.5	99.5   0   0.5	0.12 - 0.12	100   0   0		
Levofloxacin	0.03   >8	80.7   1.3   18.1	8 - >8	0   0   100		
Meropenem	≤0.06   ≤0.06	98.5   0.9   0.6	≤0.06 - 0.5	100   0   0		
Minocycline	1   8	83.4   8.3   8.3	≤0.5 - >16	42.9   14.3   42.9		
Pip-Tazo	1   4	97.6   0.6   1.8	2 - >128	71.4   0   28.6		
Tigecycline	0.12   0.25	100   0   0	0.06 - 0.25	100   0   0		

**Conclusions:** The ESBL positive rate among *E. coli* from IAI in the United States was 1.3% from 2005-2009. Overall, there has been a modest but steady increase in ESBLs each year from 0.8% in 2005 to 2.8% in 2009. Amoxicillin-clavulanic acid, ampicillin, levofloxacin, and minocycline each demonstrated *in vitro* %S values <90%, while all remaining study drugs demonstrated activity >93%. Amikacin, imipenem, meropenem, and tigecycline each inhibited 100% of ESBL producing *E. coli* at their respective CLSI or FDA susceptible breakpoints.

## Introduction

*Escherichia coli* is the leading pathogen in intra-abdominal infections (IAIs), accounting for almost half of all IAIs globally [1]. There has been a steady increase in resistance to *E. coli* in the past decade due primarily to the emergence of extended-spectrum beta-lactamase (ESBL) producing strains and, in more recent years, to carbapenemases [2]. This increase in drug resistance demands frequent surveillance to keep the clinician informed of epidemiological and resistance patterns. This study looked at the susceptibility of *E. coli* to a number of antimicrobial agents from IAIs in the United States from 2005 through 2009. This study is part of the larger ongoing Tigecycline Evaluation and Surveillance Trial.

## Materials & Methods

- Clinical isolates:** Isolates were identified to the species level and tested at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria. All isolates were from intra-abdominal infections with only one isolate per patient accepted. Isolates were collected during the years 2005 - 2009 by 456 cumulative sites from the United States.
- Susceptibility testing:** Minimum inhibitory concentrations (MICs) were determined using broth microdilution plates manufactured by MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and Trek Diagnostics (TREK Diagnostic Systems, Cleveland, OH, USA), following manufacturer and Clinical and Laboratory Standards Institute (CLSI) instructions for broth microdilution testing [3]. Susceptibility was determined using clinical breakpoints published by the CLSI [4] and the FDA (tigecycline) [5]. ESBLs were determined using the CLSI disk Confirmation Test for ESBLs [4].
- Quality Control:** QC of broth microdilution panels followed manufacturers' and CLSI guidelines using the following ATCC strains as needed and applicable: *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, and *Klebsiella pneumoniae* ATCC 700603 as ESBL-positive control.

## References

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## Acknowledgements

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## Results

Figure 1. Distribution of clinical isolates from IAIs in the United States, 2005 – 2009.

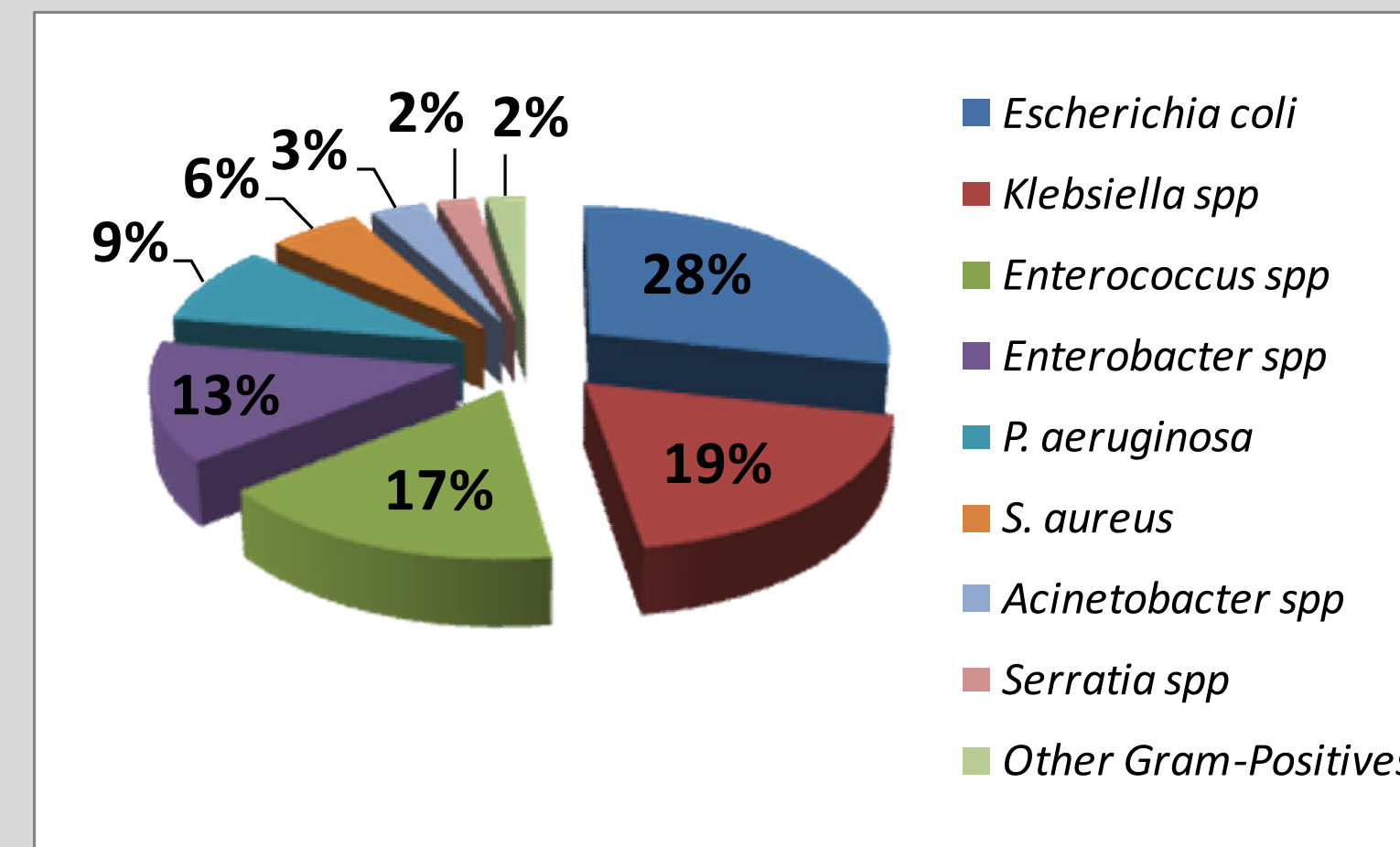
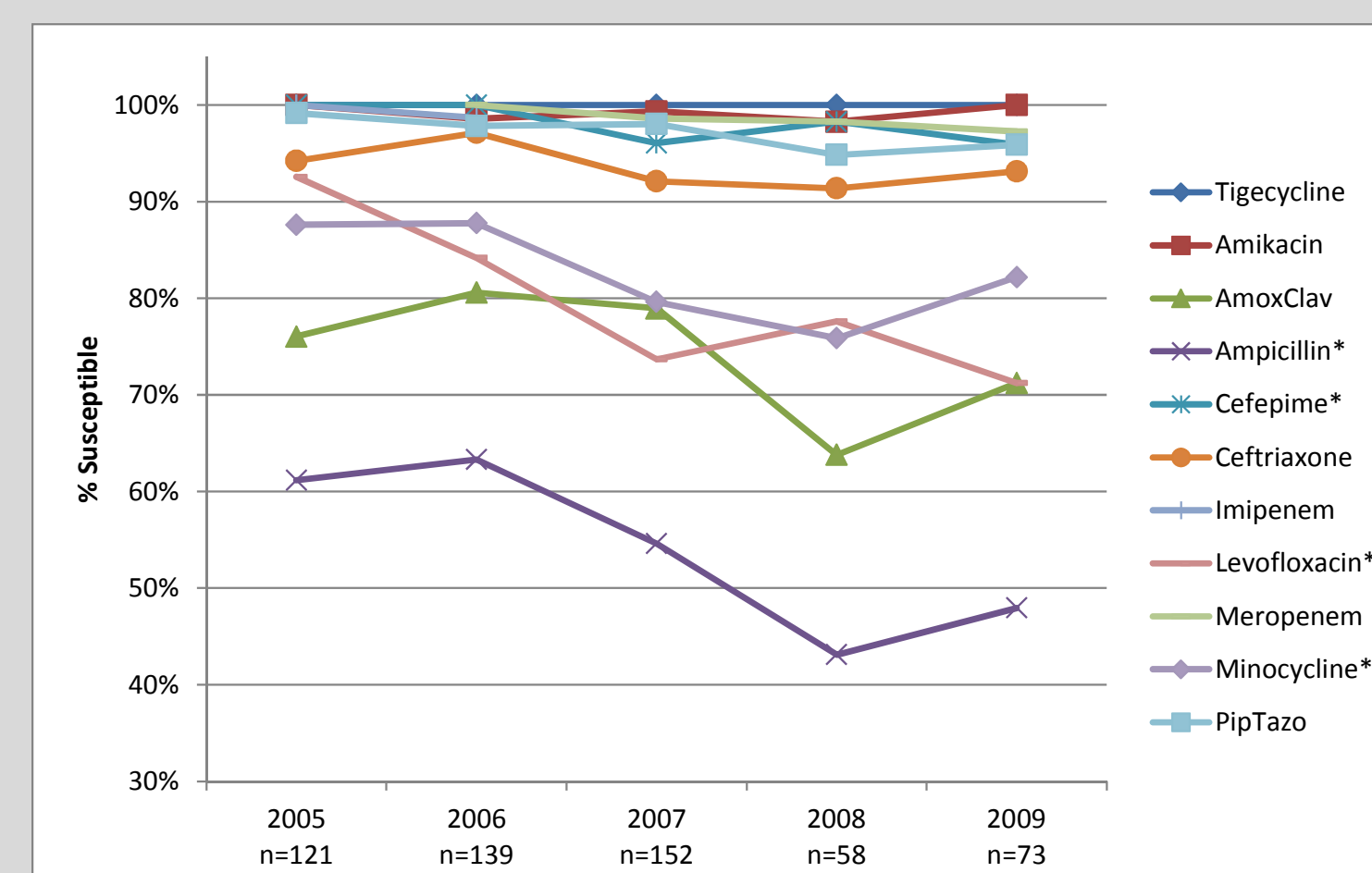


Table 1. Comparison of ESBL-positive phenotype from IAIs in the United States vs Rest of World, 2005 – 2009.

Organism/Phenotype	North America	Rest of World	Total
<i>E. coli</i>	543	1501	2044
ESBL-positive	7	225	232
Non-ESBL	536	1276	1812
% ESBL-Positive	1.3%	15.0%	11.4%

Figure 2. Longitudinal trend of percents susceptible by year for 543 IAI *E. coli* isolates from the United States, 2005 – 2009.



\* p-value significant at <0.05; Cochran-Armitage Trend Test, two-tailed.  
\*\* p-value significant at <0.001; ibid.

Table 2. *In vitro* susceptibility for tigecycline and comparators against *E. coli* and ESBL-positive phenotypes from IAIs in the United States, 2005 – 2009.

Organism	Drug	mcg/ml			%Sus*	%Int	%Res
		Range	MIC <sub>50</sub>	MIC <sub>90</sub>			
<i>E. coli</i> n=543	Amikacin	≤0.5 - 64	2	4	99.4	0.4	0.4
	Amox-Clav	≤0.12 - >32	4	16	76.1	14	9.9
	Ampicillin	≤0.5 - >32	4	>32	56.2	1.8	4.2
	Cefepime	≤0.5 - >32	≤0.5	≤0.5	98.2	0.7	1.1
	Ceftriaxone	≤0.06 - >64	≤0.06	0.25	93.9	1.1	5
	Imipenem	≤0.06 - 4	0.25	0.5	99.5	0	0.5
	Levofloxacin	≤0.008 - >8	0.03	>8	80.7	1.3	18.1
	Meropenem	≤0.06 - 8	≤0.06	≤0.06	98.5	0.9	0.6
	Minocycline	≤0.5 - >16	1	8	83.4	8.3	8.3
	PipTazo	≤0.06 - >128	1	4	97.6	0.6	1.8
	Tigecycline	≤0.008 - 2	0.12	0.25	100	0	0
	<i>E. coli</i> ESBL-Positive n=7	Amikacin	1 - 16	--	--	100	0
Amox-Clav		8 - >32	--	--	14.3	28.6	57.1
Ampicillin		>32 - >32	--	--	0	0	100
Cefepime		2 - >32	--	--	28.6	42.9	28.6
Ceftriaxone		2 - >64	--	--	0	14.3	85.7
Imipenem		0.12 - 0.12	--	--	100	0	0
Levofloxacin		8 - >8	--	--	0	0	100
Meropenem		≤0.06 - 0.5	--	--	100	0	0
Minocycline	≤0.5 - >16	--	--	42.9	14.3	42.9	
PipTazo	2 - >128	--	--	71.4	0.0	28.6	
Tigecycline	0.06 - 0.25	--	--	100	0	0	

\* Interpretive criteria defined by CLSI document M100-S21 (2011), where breakpoints were available; tigecycline breakpoints defined by the FDA (Tygacil®). For n<10, MIC<sub>50/90</sub> are not shown.

## Conclusions

- The ESBL positive rate among *E. coli* from IAI in the United States was 1.3% from 2005-2009. Overall, there has been a modest but steady increase in ESBLs each year from 0.8% in 2005 to 2.8% in 2009. The 1.3% ESBL rate for *E. coli* from IAIs in the United States compares favorably to the ESBL rate of the Rest of World isolates (also from TEST), which is significantly higher at 15.0%. (p<0.0001, Fisher's exact test).
- Amoxicillin-clavulanic acid, ampicillin, levofloxacin, and minocycline each demonstrated *in vitro* %S values <90%, while all remaining study drugs demonstrated activity >93%. Amikacin, imipenem, meropenem, and tigecycline each inhibited 100% of ESBL producing *E. coli* at their respective CLSI or FDA susceptible breakpoints.
- Longitudinal analysis demonstrated significant decreases in susceptibility for ampicillin (61% to 48%; p<0.05), cefepime (100 to 96%; p<0.01), levofloxacin (93% to 71%; p<0.001), and minocycline (88% to 82%; p<0.05) during the 5 year period of the study (2005-2009; Cochran-Armitage Trend Test/Two-tailed).
- Continued surveillance is warranted in the monitoring of antimicrobial resistance and providing clinicians with current trends in order to make informed decisions on empiric therapy.