

Revised Abstract

Background: The Tigecycline Evaluation surveillance trial (TEST) has been monitoring the susceptibility of pathogens worldwide since 2004. Dramatic increases in resistance over the past 10 years have challenged empirical treatment regimens for many infectious processes. This report summarizes global data from T.E.S.T. in 2009-2010 for *Enterobacteriaceae* spp. isolated from intra-abdominal infections.

Methods: 407 cumulative hospital sites in 51 countries collected consecutive isolates of gram-negative aerobic bacilli from IAI in 2009-2010. Isolate identification and susceptibility testing was performed at a central laboratory and interpreted using CLSI M100-S21 guidelines and FDA guidelines for tigecycline.

Results: 1288 isolates were collected, of which 42% were *E. coli*, 23% *K. pneumoniae* and 16% *E. cloacae*. Of all IAI pathogens 14% of *E. coli* and 20% of *K. pneumoniae* were ESBL+ and exhibited reduced susceptibility profiles. Susceptibility of organisms with n>20 are shown in the table below. Shading denotes % susceptible values >90%.

| Organism | N | Ak | Cpe | Cax | Lvx | Mer | PT | Tig |
|----------------------------|-----|----|-----|-----|-----|-----|----|-----|
| <i>E. coli</i> , all | 559 | 96 | 88 | 76 | 65 | 98 | 87 | 99 |
| <i>E. coli</i> ESBL+ | 79 | 87 | 41 | 3 | 18 | 96 | 66 | 100 |
| <i>E. coli</i> ESBL- | 480 | 98 | 96 | 89 | 73 | 99 | 90 | 99 |
| <i>K. pneumoniae</i> , all | 302 | 94 | 80 | 69 | 73 | 97 | 72 | 94 |
| <i>K. pneumo.</i> ESBL+ | 61 | 80 | 25 | 2 | 25 | 95 | 30 | 95 |
| <i>K. pneumo.</i> ESBL- | 241 | 98 | 94 | 86 | 86 | 98 | 82 | 94 |
| <i>E. cloacae</i> | 216 | 96 | 91 | 49 | 79 | 97 | 67 | 95 |
| <i>K. oxytoca</i> | 60 | 97 | 88 | 77 | 88 | 97 | 87 | 98 |
| <i>E. aerogenes</i> | 54 | 94 | 98 | 63 | 83 | 94 | 72 | 98 |
| <i>S. marcescens</i> | 43 | 93 | 95 | 65 | 81 | 98 | 86 | 98 |

Ak=amikacin, Cpe=cefepime, Cax=ceftriaxone, Lvx=levofloxacin, Mer=meropenem, PT=piperacillin-tazobactam, Tig=tigecycline NA=No breakpoints

Conclusions: In 2009-2010 two species that accounted for 2/3 of all IAI pathogens (*E. coli* and *K. pneumoniae*) were <90% susceptible to all study drugs except meropenem, tigecycline and amikacin. Beta-lactamase + *E. coli* and *K. pneumoniae* exhibited significantly lower susceptibility to most studied agents except meropenem and tigecycline. Increasing resistance requires ongoing monitoring to help control the rapid spread of multi-drug resistant pathogens.

Introduction

Pathogens belonging to the family *Enterobacteriaceae* are commonly isolated from patients presenting with intra-abdominal infections. Increasingly these organisms display reduced antimicrobial susceptibility profiles to agents recommended for the treatment of IAIs. Today the global prevalence of extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* continues to grow with resultant resistance and reduced susceptibility to fluoroquinolones and cephalosporins.

Although ESBLs occur worldwide with varying but increasing prevalence, they are most commonly found in *Escherichia coli*, *Klebsiella pneumoniae* and *K. oxytoca*. The carbapenems, including imipenem, ertapenem and meropenem are some of the most commonly prescribed therapeutic agents for infections caused by ESBL-producing isolates and are used clinically in many countries. Tigecycline has previously been shown to be active against ESBL-producing isolates.

The purpose of this study was to examine the *in vitro* activity of tigecycline and comparator antibiotics against *Enterobacteriaceae* isolated from intra-abdominal infections collected as part of the multi-year, ongoing global Tigecycline Evaluation and Surveillance Trial (TEST).

Materials & Methods

- ❖ Isolates were collected from clinical specimens (one isolate per patient only) according to site criteria and deemed clinically significant.
- ❖ Isolates were derived from intra-abdominal sources only.
- ❖ Isolates were collected between 2009-2010 from 407 cumulative sites in 51 countries.
- ❖ Isolates were identified to the species level at each site using local laboratory criteria.
- ❖ Isolate collection, transport, confirmatory identification and database management were coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (Schaumburg, IL, USA).
- ❖ Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method. Tigecycline was supplied by Pfizer Inc (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers; MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH, USA).
- ❖ The following agents were included on the gram-negative panel with expressed dilution ranges (mcg/ml): amikacin (0.5-64), cefepime (0.5-32), ceftriaxone (0.06-64), meropenem (0.06-16), levofloxacin (0.008-8), tigecycline (0.008-16) and piperacillin-tazobactam (0.06/4-128/4).
- ❖ QC of broth microdilution panels followed manufacturers' and CLSI guidelines using the following ATCC strains as needed and applicable: *E. coli* (ATCC 25922), *Haemophilus influenzae* (ATCC 49247), *H. influenzae* (ATCC 49766) and *K. pneumoniae* (ATCC 700603 as ESBL positive control).
- ❖ ESBLs were initially screened using ceftazidime and/or ceftriaxone (microbroth panels) and confirmed using ceftazidime +/- clavulanic acid and cefotaxime +/- clavulanic acid as described by the CLSI.

Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Surveillance Trial program group. This study was sponsored by Pfizer Inc.

Results

Figure 1. Distribution (%) of *Enterobacteriaceae* species isolated from IAI sources in 2009-2010.

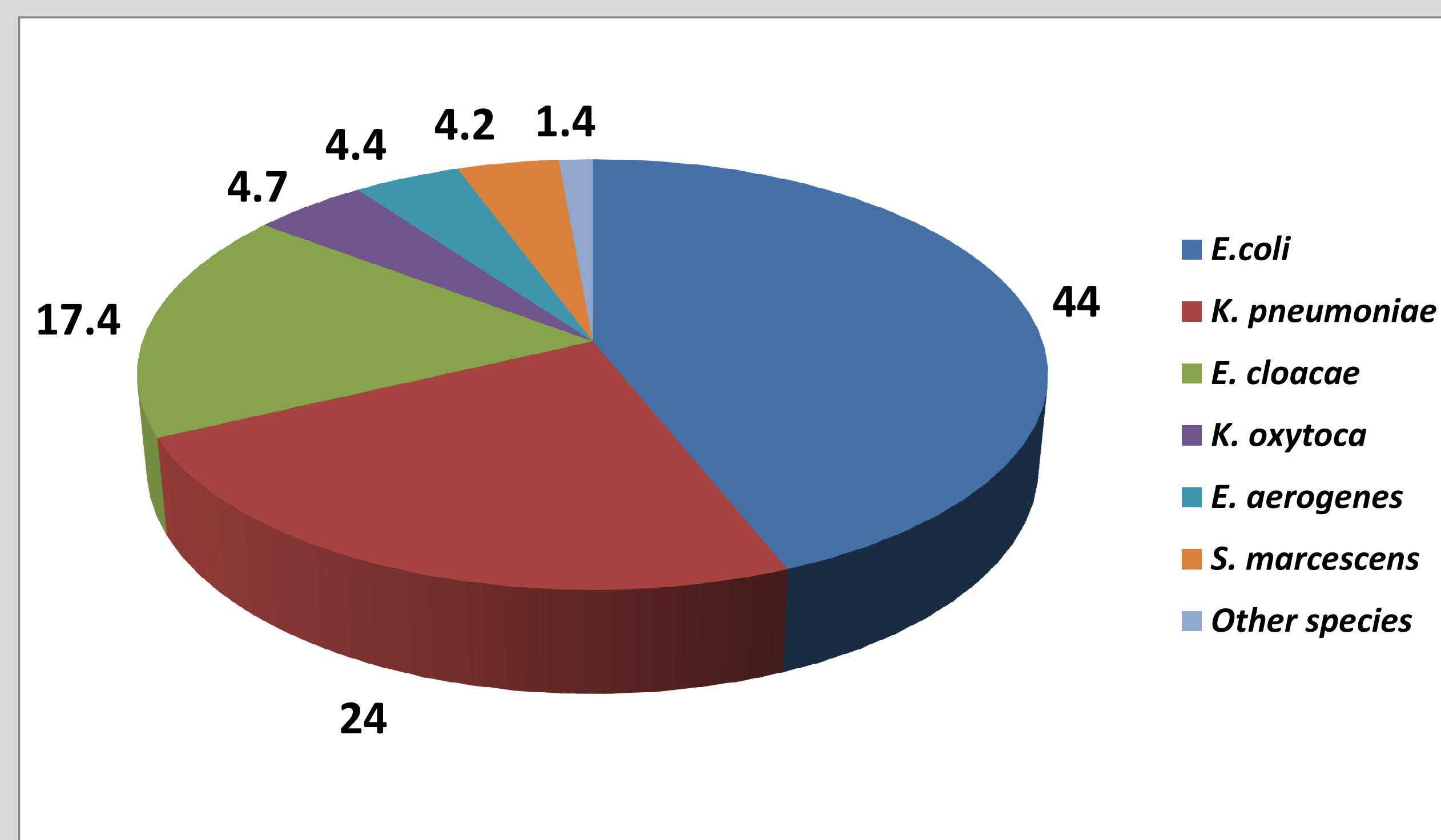


Table 1. *In vitro* activity of tigecycline and comparators against 1288 clinical isolates of *Enterobacteriaceae* from 2009-2010.

| Drug | mcg/ml | | | | |
|--------------|-------------------|-------------------|-----------------|-----|------|
| | MIC ₅₀ | MIC ₉₀ | %S ^a | %I | %R |
| Amikacin | 2 | 8 | 95.6 | 1.7 | 2.6 |
| Cefepime | ≤0.5 | 16 | 87.8 | 3.3 | 8.9 |
| Ceftriaxone | 0.12 | >64 | 69.3 | 1.4 | 29.3 |
| Levofloxacin | 0.12 | >8 | 72.9 | 3.2 | 23.9 |
| Meropenem | ≤0.06 | 0.12 | 97.6 | 0.5 | 2.0 |
| PipTazo | 4 | 128 | 79.1 | 8.2 | 12.7 |
| Tigecycline | 0.5 | 1 | 97.1 | 2.1 | 0.9 |

^a % S, I, R defined by CLSI M100-S21 (2011); Tigecycline % S, I, R defined by FDA breakpoints, Tygacil® package insert, 2009.

Table 3. *In vitro* activity of tigecycline and comparators against 304 levofloxacin-resistant isolates of *Enterobacteriaceae* from 2009-2010.

| Drug | mcg/ml | | | | |
|--------------|-------------------|-------------------|-----------------|------|------|
| | MIC ₅₀ | MIC ₉₀ | %S ^a | %I | %R |
| Amikacin | 4 | 64 | 85.9 | 3.6 | 10.5 |
| Cefepime | 4 | >32 | 61.8 | 9.5 | 28.6 |
| Ceftriaxone | 64 | >64 | 31.6 | 2.9 | 65.5 |
| Levofloxacin | >8 | >8 | 0 | 0 | 100 |
| Meropenem | ≤0.06 | 1 | 92.8 | 1.0 | 6.3 |
| PipTazo | 16 | >128 | 55.3 | 16.1 | 28.6 |
| Tigecycline | 0.5 | 2 | 93.1 | 3.6 | 3.3 |

^a % S, I, R defined by CLSI M100-S21 (2011); Tigecycline % S, I, R defined by FDA breakpoints, Tygacil® package insert, 2009.

Table 2. *In vitro* activity of tigecycline and comparators against 140 ESBL-producing *Enterobacteriaceae* from 2009-2010.

| Drug | mcg/ml | | | | |
|--------------|-------------------|-------------------|-----------------|------|------|
| | MIC ₅₀ | MIC ₉₀ | %S ^a | %I | %R |
| Amikacin | 4 | >64 | 84.7 | 3.7 | 11.8 |
| Cefepime | 32 | >32 | 33.3 | 13.2 | 53.5 |
| Ceftriaxone | >64 | >64 | 2.1 | 0 | 97.9 |
| Levofloxacin | >8 | >8 | 20.8 | 5.6 | 73.6 |
| Meropenem | ≤0.06 | 0.5 | 95.8 | 0 | 4.2 |
| PipTazo | 16 | >128 | 51.4 | 22.2 | 26.4 |
| Tigecycline | 0.5 | 2 | 97.9 | 2.1 | 0 |

^a % S, I, R defined by CLSI M100-S21 (2011); Tigecycline % S, I, R defined by FDA breakpoints, Tygacil® package insert, 2009.

Table 4. *In vitro* activity of tigecycline and comparators against 33 amikacin-resistant isolates of *Enterobacteriaceae* from 2009-2010.

| Drug | mcg/ml | | | | |
|--------------|-------------------|-------------------|-----------------|------|------|
| | MIC ₅₀ | MIC ₉₀ | %S ^a | %I | %R |
| Amikacin | >64 | >64 | 0 | 0 | 100 |
| Cefepime | 32 | >32 | 24.2 | 12.1 | 63.6 |
| Ceftriaxone | >64 | >64 | 3.0 | 10.0 | 97.0 |
| Levofloxacin | >8 | >8 | 3.0 | 0 | 97.0 |
| Meropenem | 0.5 | >16 | 69.7 | 3.0 | 27.3 |
| PipTazo | 128 | >128 | 21.2 | 18.2 | 60.6 |
| Tigecycline | 1 | 4 | 87.9 | 3.0 | 9.1 |

^a % S, I, R defined by CLSI M100-S21 (2011); Tigecycline % S, I, R defined by FDA breakpoints, Tygacil® package insert, 2009.

Conclusions

- ❖ In the past 2 years of the TEST study, tigecycline has maintained an MIC₅₀ and MIC₉₀ profile of 0.5 and 1 mcg/ml, respectively, against more than 1200 *Enterobacteriaceae* isolated from intra-abdominal infections. The overall percent susceptible of 97% for tigecycline against all isolates is comparable to that of amikacin (96%) and meropenem (97%).
- ❖ Tigecycline has maintained potent *in vitro* activity (susceptible %) against isolates with multiple resistant phenotypes including ESBL-producing *Enterobacteriaceae* (98%), levofloxacin-resistant (93%), and amikacin-resistant (88%) phenotypes.
- ❖ Tigecycline continues to demonstrate minimal *in vitro* cross-resistance among the antimicrobial agents from multiple drug classes in this on-going study.