

## Revised Abstract

**Background:** Development of bacterial resistance has become an important concern world-wide, but availability of newer agents offers clinicians options for therapy. Tigecycline (Tig) exhibits potent activity against a broad spectrum of bacteria, including strains resistant to other drugs. As part of the global Tigecycline Evaluation Surveillance Trial, strains collected in Iberia from 2004 to 2009 were evaluated for susceptibility to several antimicrobials. **Methods:** Strains were collected and identified at 49 cumulative sites in Spain and Portugal. MICs were determined at each site using microdilution panels following EUCAST guidelines. **Results:** The following table summarizes MIC<sub>90</sub> results for all isolates, and for specific key pathogens.

|              | All gram-positives<br>n=1683 | <i>S. aureus</i> (MR)<br>n=203 | <i>S. aureus</i> (MS)<br>n=500 | Enterococci<br>n=459 | <i>S. pneumoniae</i><br>n=271 |
|--------------|------------------------------|--------------------------------|--------------------------------|----------------------|-------------------------------|
| Tigecycline  | 0.25                         | 0.25                           | 0.25                           | 0.25                 | 0.12                          |
| Amox/Clav    | >8                           | >8                             | 1                              | >8                   | 2                             |
| Ampicillin   | >16                          | >16                            | >16                            | >16                  | 4                             |
| Ceftriaxone  | >64                          | >64                            | 4                              | >64                  | 1                             |
| Imipenem     | 4                            | >16                            | 0.25                           | >16                  | 0.5                           |
| Levofloxacin | 32                           | 32                             | 0.5                            | >32                  | 1                             |
| Linezolid    | 2                            | 4                              | 2                              | 2                    | 1                             |
| Minocycline  | 8                            | 1                              | 0.5                            | >8                   | 8                             |
| Penicillin   | 8                            | >8                             | >8                             | >8                   | 2                             |
| Pip/Tazo     | 16                           | >16                            | 2                              | >16                  | 2                             |
| Vancomycin   | 1                            | 2                              | 1                              | 2                    | 0.5                           |

  

|              | All gram-negatives<br>n=4174 | <i>E. coli</i><br>n=815 | <i>K. pneumoniae</i><br>n=604 | <i>Enterobacter</i> spp.<br>n=780 | <i>Acinetobacter</i> spp.<br>n=451 |
|--------------|------------------------------|-------------------------|-------------------------------|-----------------------------------|------------------------------------|
| Tigecycline  | 4                            | 0.5                     | 1                             | 1                                 | 2                                  |
| Amikacin     | 8                            | 8                       | 4                             | 4                                 | >64                                |
| Amox/Clav    | >32                          | 32                      | 32                            | >32                               | >32                                |
| Ampicillin   | >32                          | >32                     | >32                           | >32                               | >32                                |
| Cefepime     | 16                           | 8                       | 16                            | 4                                 | 32                                 |
| Ceftazidime  | 32                           | <8                      | 16                            | >32                               | >32                                |
| Ceftriaxone  | >64                          | 64                      | 64                            | 64                                | >64                                |
| Imipenem     | 2                            | 0.5                     | 0.5                           | 1                                 | >16                                |
| Levofloxacin | 8                            | >8                      | >8                            | 4                                 | >8                                 |
| Minocycline  | 16                           | 16                      | >16                           | 8                                 | 8                                  |
| Pip/Tazo     | >64                          | 32                      | 128                           | 64                                | >128                               |

**Conclusions:** Tig had the lowest MIC<sub>90</sub> vs. gram-positive isolates (incl. MRSA), and was nearly as active as imipenem vs. gram-negative strains (incl. ESBL+). It was also 4 to 128-fold more active than all comparators vs. *Acinetobacter*.

## Introduction

Resistance rates of bacteria to modern-era antimicrobials are increasing worldwide. Portugal and Spain have experienced particularly high resistance rates for a number of key pathogens, which in recent years seems to have stabilized [1-3]. This study examined the changes in resistance among selected gram-positive and gram-negative bacteria in these two countries from the TEST program from its inception in 2004 through the latest compiled data in 2009.

## Materials & Methods

- 5851 clinical isolates were collected and tested between January 2004 and March 2009 from 49 cumulative total investigative sites (51% participated in more than one year) from Spain and Portugal. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of 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 [4]. MIC interpretive criteria followed published guidelines established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), where applicable [5]. Breakpoints used for tigecycline against *S. pneumoniae* are defined by the FDA [6].
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *K. pneumoniae* ATCC 700603 (positive ESBL control); *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *P. aeruginosa* ATCC 27853; *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2009) guidelines [7].

## References

- Cuevas O, Cercenado E, Goyanes MJ, Vindel A, et al. 2008. [Staphylococcus spp. in Spain: present situation and evolution of antimicrobial resistance (1986-2006)] *Enferm Infecc Microbiol Clin.* 26(5):269-77.
- Boucher HW, Talbot GH, Bradley JS et al. 2009. *Bad bugs, no drugs: no ESCAPE! An update from the Infectious Diseases Society of America.* *Clin Infect Dis*; 48:1-12.
- Rodloff AC, Leclercq R, Debbia EA, Cantón R, et al. 2008. *Comparative analysis of antimicrobial susceptibility among organisms from France, Germany, Italy, Spain and the UK as part of the tigecycline evaluation and surveillance trial.* *Clin Microbiol Infect.* 2008 Apr;14(4):307-14.
- CLSI. 2008. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition*, in Document M7-A7. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.
- European Committee on Antimicrobial Susceptibility Testing (EUCAST), Clinical Breakpoints. <http://www.srga.org/eucastwt/MICTAB/index.html>, July 21, 2009.
- Tygacil®, March 2009. FDA Product Information, Wyeth Pharmaceuticals Inc., Philadelphia, PA 19101, USA.
- CLSI. 2009. *Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement.* Document M100-S19. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA, USA.

## Acknowledgements

This study was sponsored by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge the contributions of all investigators, laboratory personnel and from the members of the Tigecycline Evaluation Surveillance Trial program group worldwide.

## Results

Table 1. *In vitro* activity of tigecycline and comparators against all gram-positive pathogens from 2004 to 2009.

| Organism                          | Drug         | MIC (mcg/ml)      |                   |       |       |       |
|-----------------------------------|--------------|-------------------|-------------------|-------|-------|-------|
|                                   |              | MIC <sub>50</sub> | MIC <sub>90</sub> | %SUS* | %INT  | %RES  |
| <i>S. aureus</i><br>MRSA<br>n=203 | Tigecycline  | 0.12              | 0.25              | 100   | 0     | 0     |
|                                   | Amox/Clav    | >8                | >8                | 0     | 0     | 100   |
|                                   | Ampicillin   | >16               | >16               | 0     | 0     | 100   |
|                                   | Ceftriaxone  | >64               | >64               | 0     | 0     | 100   |
|                                   | Imipenem     | 4                 | >16               | 0     | 0     | 100   |
|                                   | Levofloxacin | 8                 | 32                | 8.37  | 0.99  | 90.64 |
|                                   | Linezolid    | 2                 | 4                 | 100   | 0     | 0     |
|                                   | Minocycline  | ≤0.25             | 1                 | 87.19 | 3.94  | 8.87  |
|                                   | Penicillin   | >8                | >8                | 0     | 0     | 100   |
|                                   | Pip/Taz      | >16               | >16               | 0     | 0     | 100   |
| <i>S. aureus</i><br>MSSA<br>n=500 | Tigecycline  | 0.12              | 0.25              | 100   | 0     | 0     |
|                                   | Amox/Clav    | 0.5               | 1                 | 99.2  | 0     | 0.8   |
|                                   | Ampicillin   | 4                 | >16               | 13.6  | 0     | 86.4  |
|                                   | Ceftriaxone  | 2                 | 4                 | 99.2  | 0.6   | 0.2   |
|                                   | Imipenem     | ≤0.12             | 0.25              | 100   | 0     | 0     |
|                                   | Levofloxacin | 0.12              | 0.5               | 94.2  | 3     | 2.8   |
|                                   | Linezolid    | 2                 | 2                 | 100   | 0     | 0     |
|                                   | Minocycline  | ≤0.25             | 0.5               | 98    | 1     | 1     |
|                                   | Penicillin   | 8                 | >8                | 10.4  | 0     | 89.6  |
|                                   | Pip/Taz      | 1                 | 2                 | 99.8  | 0     | 0.2   |
| <i>E. faecalis</i><br>n=343       | Tigecycline  | 0.12              | 0.25              | 100   | 0     | 0     |
|                                   | Amox/Clav    | 0.5               | 1                 | 99.71 | 0.29  | 0     |
|                                   | Ampicillin   | 1                 | 2                 | 99.42 | 0.58  | 0     |
|                                   | Ceftriaxone  | >64               | >64               | na    | na    | na    |
|                                   | Imipenem     | 1                 | 2                 | 99.07 | 0.93  | 0     |
|                                   | Levofloxacin | 1                 | >32               | 62.68 | 1.17  | 36.15 |
|                                   | Linezolid    | 1                 | 2                 | 100   | 0     | 0     |
|                                   | Meropenem    | 4                 | 8                 | na    | na    | na    |
|                                   | Minocycline  | 8                 | >8                | 35.57 | 29.15 | 35.28 |
|                                   | Penicillin   | 2                 | 4                 | 100   | 0     | 0     |
| <i>E. faecium</i><br>n=109        | Amox/Clav    | >8                | >8                | 21.1  | 5.5   | 73.39 |
|                                   | Ampicillin   | >16               | >16               | 20.18 | 0     | 79.82 |
|                                   | Ceftriaxone  | >64               | >64               | na    | na    | na    |
|                                   | Imipenem     | >16               | >16               | 20.83 | 4.17  | 75    |
|                                   | Levofloxacin | >32               | >32               | 22.02 | 4.59  | 73.39 |
|                                   | Linezolid    | 2                 | 2                 | 100   | 0     | 0     |
|                                   | Meropenem    | >16               | >16               | na    | na    | na    |
|                                   | Minocycline  | ≤0.25             | >8                | 76.15 | 8.26  | 15.6  |
|                                   | Penicillin   | >8                | >8                | 25.69 | 0     | 74.31 |
|                                   | Pip/Tazo     | >16               | >16               | na    | na    | na    |
| <i>S. agalactiae</i><br>n=250     | Tigecycline  | 0.03              | 0.12              | 99.6  | 0     | 0.4   |
|                                   | Ampicillin   | ≤0.06             | 0.12              | 100   | 0     | 0     |
|                                   | Ceftriaxone  | 0.06              | 0.12              | 100   | 0     | 0     |
|                                   | Imipenem     | 0.25              | 0.5               | 100   | 0     | 0     |
|                                   | Levofloxacin | 0.5               | 1                 | 97.2  | 2.4   | 0.4   |
|                                   | Linezolid    | 1                 | 1                 | 100   | 0     | 0     |
|                                   | Minocycline  | 8                 | >8                | 12.8  | 0.8   | 86.4  |
|                                   | Penicillin   | ≤0.06             | 0.12              | 100   | 0     | 0     |
|                                   | Pip/Taz      | ≤0.25             | ≤0.25             | na    | na    | na    |
|                                   | Vancomycin   | 0.5               | 0.5               | 100   | 0     | 0     |

\* SUS, INT or RES are defined by EUCAST. <http://www.srga.org/eucastwt/MICTAB/index.html> (July 2009).  
\* na = not available; intermediate and resistant breakpoints are undefined.

Table 2. *In vitro* activity of tigecycline and comparators against all *Enterobacteriaceae* pathogens from 2004 to 2009.

| Organism   | Drug         | MIC (mcg/ml)      |                   |       |       |       |
|--|--------------|-------------------|-------------------|-------|-------|-------|
|  |              | MIC <sub>50</sub> | MIC <sub>90</sub> | %SUS* | %INT  | %RES  |
| ESBL producers<br>combined<br>( <i>E. coli</i> ,<br><i>K. pneumoniae</i> ,<br><i>K. oxytoca</i> )<br>n=173 | Tigecycline  | 0.5               | 1                 | 93.06 | 4.62  | 2.31  |
|  | Amikacin     | 2                 | 16                | 89.02 | 8.67  | 2.31  |
|  | Amox/Clav    | 16                | >32               | 36.42 | 0     | 63.58 |
|  | Ampicillin   | >32               | >32               | 0.58  | 0     | 99.42 |
|  | Cefepime     | 8                 | >32               | 13.29 | 39.88 | 46.82 |
|  | Ceftazidime  | 16                | >32               | 0     | 49.13 | 50.87 |
|  | Ceftriaxone  | >64               | >64               | 1.73  | 1.16  | 97.11 |
|  | Imipenem     | 0.5               | 0.5               | 100   | 0     | 0     |
|  | Levofloxacin | 8                 | >8                | 35.84 | 1.73  | 62.43 |
|  | Minocycline  | 4                 | >16               | 61.85 | 13.87 | 24.28 |
| <i>Enterobacter</i> spp.<br>n=780  | Tigecycline  | 0.5               | 1                 | 95.13 | 2.44  | 2.44  |
|  | Amikacin     | 2                 | 4                 | 97.69 | 1.28  | 1.03  |
|  | Amox/Clav    | >32               | >32               | 0.9   | 0     | 99.1  |
|  | Ampicillin   | >32               | >32               | 0     | 0     | 100   |
|  | Cefepime     | ≤0.5              | 4                 | 82.44 | 13.33 | 4.23  |
|  | Ceftazidime  | ≤8                | >32               | 0     | 74.49 | 25.51 |
|  | Ceftriaxone  | 0.25              | 64                | 66.54 | 3.08  | 30.38 |
|  | Imipenem     | 0.5               | 1                 | 99.01 | 0.99  | 0     |
|  | Levofloxacin | 0.06              | 4                 | 88.97 | 0.77  | 10.26 |
|  | Minocycline  | 2                 | 8                 | 83.33 | 8.97  | 7.69  |
| <i>Klebsiella</i> spp.<br>n=788  | Tigecycline  | 0.5               | 1                 | 91.75 | 5.2   | 3.05  |
|  | Amikacin     | 1                 | 4                 | 96.19 | 1.65  | 2.16  |
|  | Amox/Clav    | 4                 | 32                | 69.16 | 0     | 30.84 |
|  | Ampicillin   | >32               | >32               | 0.13  | 0     | 99.87 |
|  | Cefepime     | ≤0.5              | 8                 | 80.84 | 9.64  | 9.52  |
|  | Ceftazidime  | ≤8                | 16                | 0     | 87.69 | 12.31 |
|  | Ceftriaxone  | ≤0.06             | 64                | 78.17 | 1.4   | 20.43 |
|  | Imipenem     | 0.5               | 0.5               | 100   | 0     | 0     |
|  | Levofloxacin | 0.06              | 8                 | 79.95 | 3.55  | 16.5  |
|  | Minocycline  | 2                 | >16               | 75    | 8.38  | 16.62 |
| <i>E. coli</i><br>n=815  | Tigecycline  | 0.12              | 0.5               | 99.39 | 0.61  | 0     |
|  | Amikacin     | 2                 | 8                 | 96.32 | 2.58  | 1.1   |
|  | Amox/Clav    | 8                 | 32                | 62.21 | 0     | 37.79 |
|  | Ampicillin   | >32               | >32               | 24.17 | 0     | 75.83 |
|  | Cefepime     | ≤0.5              | 8                 | 82.33 | 10.18 | 7.48  |
|  | Ceftazidime  | ≤8                | ≤8                | 0     | 91.41 | 8.59  |
|  | Ceftriaxone  | ≤0.06             | 64                | 78.41 | 1.72  | 19.88 |
|  | Imipenem     | 0.25              | 0.5               | 100   | 0     | 0     |
|  | Levofloxacin | 0.12              | >8                | 60.49 | 2.94  | 36.56 |
|  | Minocycline  | 2                 | 16                | 78.16 | 9.69  | 12.15 |
| <i>Serratia</i> spp.<br>n=305  | Tigecycline  | 1                 | 2                 | 86.56 | 11.48 | 1.97  |
|  | Amikacin     | 2                 | 4                 | 98.69 | 1.31  | 0     |
|  | Amox/Clav    | >32               | >32               | 3.93  | 0     | 96.07 |
|  | Ampicillin   | >32               | >32               | 4.26  | 0     | 95.74 |
|  | Cefepime     | ≤0.5              | ≤0.5              | 95.74 | 2.3   | 1.97  |
|  | Ceftazidime  | ≤8                | ≤8                | 0     | 97.05 | 2.95  |
|  | Ceftriaxone  | 0.25              | 1                 | 92.13 | 1.97  | 5.9   |
|  | Imipenem     | 0.5               | 2                 | 100   | 0     | 0     |
|  | Levofloxacin | 0.12              | 0.5               | 94.75 | 1.31  | 3.93  |
|  | Minocycline  | 4                 | 8                 | 77.7  | 15.74 | 6.56  |

| Organism   | Drug         | MIC (mcg/ml)      |                   |       |       |       |
|--|--------------|-------------------|-------------------|-------|-------|-------|
|  |              | MIC <sub>50</sub> | MIC <sub>90</sub> | %SUS* | %INT  | %RES  |
| <i>S. pneumoniae</i><br>n=271                                    | Tigecycline  | 0.03              | 0.12              | 82.22 | na    | na    |
|  | Amox/Clav    | ≤0.03             | 2                 | 92.59 | 4.81  | 2.59  |
|  | Ampicillin   | ≤0.06             | 4                 | 76.3  | 11.85 | 11.85 |
|  | Ceftriaxone  | ≤0.03             | 1                 | 85.19 | 14.44 | 0.37  |
|  | Imipenem     | ≤0.12             | 0.5               | 100   | 0     | 0     |
|  | Levofloxacin | 0.5               | 1                 | 99.26 | 0     | 0.74  |
|  | Linezolid    | ≤0.5              | 1                 | 100   | 0     | 0     |
|  | Minocycline  | ≤0.25             | 8                 | 60.37 | 7.78  | 31.85 |
|  | Penicillin   | ≤0.06             | 2                 | 60.74 | 35.56 | 3.7   |
|  | Pip/Taz      | ≤0.25             | 2                 | na    | na    | na    |
| <i>Haemophilus influenzae</i><br>n=377                           | Tigecycline  | 0.25              | 0.5               | 65.25 | na    | na    |
|  | Amikacin     | 4                 | 8                 | Na    | na    | na    |
|  | Amox/Clav    | 0.5               | 1                 | 90.98 | 0     | 9.02  |
|  | Ampicillin   | ≤0.5              | 32                | 79.58 | 0     | 20.42 |
|  | Cefepime     | ≤0.5              | ≤0.5              | 0     | 0     | 100   |
|  | Ceftazidime  | ≤8                | ≤8                | na    | na    | na    |
|  | Ceftriaxone  | ≤0.06             | ≤0.06             | 97.35 | 0     | 2.65  |
|  | Imipenem     | 0.5               | 1                 | 98.41 | 0     | 1.59  |
|  | Levofloxacin | 0.015             | 0.03              | 100   | 0     | 0     |
|  | Minocycline  | ≤0.5              | 2                 | 89.92 | 6.37  | 3.71  |
| <i>Haemophilus influenzae</i><br>β-Lactamase<br>Positive<br>n=65 | Tig          |                   |                   |       |       |       |