# Trends in Antimicrobial Susceptibility in European Gram-Positive Anaerobes: The Tigecycline European Surveillance Trial, 2007-2010

P 1120

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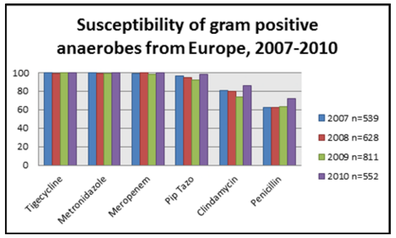
## Revised Abstract

**Objectives:** Antimicrobial resistance in anaerobic isolates is of increasing concern in clinical settings, with empiric treatment often employed. The Tigecycline European Surveillance Trial (TEST) has been monitoring susceptibility of anaerobes in Europe since 2007. This report compares the trends in susceptibility levels of gram-positive anaerobes from 2007 to 2010. **Methods:** 2,530 gram-positive anaerobic pathogens, including *Anaerococcus* spp., *Clostridium* spp., *Finegoldia magna*, *Peptoniphilus* spp., and *Peptostreptococcus* spp., were collected and identified from 44 cumulative sites in 6 countries in Europe, and sent to a central laboratory where MICs of tigecycline and five comparators were determined using CLSI agar dilution. Tigecycline MICs were interpreted using US FDA breakpoints, while EUCAST guidelines were used for all other drugs. **Results:** Overall % susceptibility for gram-positive anaerobes is shown below:




**Conclusions:** Tigecycline, metronidazole, meropenem and piperacillin-tazobactam showed excellent *in vitro* activity against gram-positive anaerobic bacteria isolated from European hospitals from 2007 to 2010, inhibiting nearly 100% of all isolates. Clindamycin and penicillin generally inhibited less than 80% of gram-positive isolates. No significant decreases in susceptibilities were noted over the four years surveyed.

## Introduction

Management of anaerobic infections can be problematical due to the emergence of antibiotic resistance strains. To counteract these trends, regular resistance surveillance in anaerobes, balanced antibiotic use and evaluation of new treatment alternatives are important. At present, metronidazole, penems, beta-lactam/beta-lactamase inhibitor combinations exhibit the most promising activity though reports of increasing resistance to these agents are emerging [1]. Recent reports also suggest tigecycline exhibits promising activity and high susceptibilities against a wide range of anaerobes [2].

The Tigecycline European Surveillance Trial (TEST) is an on-going surveillance study designed to monitor the *in vitro* activity of select antibiotics against a variety of gram-negative and gram-positive organisms. In this study, we compared the *in vitro* activity of six agents against gram-positive anaerobic isolates collected in Europe between 2007 and 2010.

## Materials & Methods

- All isolates were derived from blood, wounds, fluids, stool and intra-abdominal sources. Isolates were identified to genus and species by the local laboratory. Only one isolate per patient was accepted.
- For this study 2,530 clinical isolates were collected from 2007 to 2010 from 44 cumulative hospitals in six European countries (Belgium, Czech Republic, France, Germany, Hungary and the United Kingdom). The collection and transportation of organisms, confirmation of identification, and construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).
- Minimum inhibitory concentrations (MICs) were determined following CLSI guidelines for agar dilution [3] at the central laboratory (IHMA, Inc.). Tigecycline was supplied by Pfizer, Inc. (Collegeville, PA, USA). The following antimicrobial agents were tested with their dilution ranges (expressed in mcg/ml): tigecycline (0.06-32); clindamycin (0.25-8); metronidazole (0.12-16); piperacillin tazobactam (0.06/4-64/4); meropenem (0.06-8); and penicillin (0.25-32).
- MIC interpretive criteria followed published breakpoints established by EUCAST [4] where available and the FDA [5] for tigecycline.
- Quality control followed CLSI guidelines using the following ATCC strains: *Bacteroides fragilis* ATCC 25285, and *Bacteroides thetaiotaomicron* ATCC 29741.
- Fisher's exact test was used to compare percents suceptible between 2007 and 2010.

## References

1. Boyanova, L., R. Kolarov, and I. Mitov. 2007. *Antimicrobial resistance and the management of anaerobic infections.* Exp. Rev. Anti. Infect. Ther. 5: 685-701.
2. Nagy, E., and M.J. Dowzicky. 2010. *In vitro activity of tigecycline and comparators against a European compilation of anaerobes collected as part of the Tigecycline Evaluation and Surveillance Trial (TEST).* Scand. J. Infect. Dis. 42: 33-38.
3. Clinical and Laboratory Standards Institute. 2007. Methods for Antimicrobial Susceptibility Tests of Anaerobic Bacteria. Seventh Edition: Approved Standard. CLSI Document M100-S21. Wayne, PA.
4. The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints; http://www.eucast.org/clinical_breakpoints/
5. Tygacil®, 2011. Tigecycline FDA prescribing information. Pfizer, Inc., Philadelphia, PA.

## Acknowledgements

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

## Results

Figure 1. Number of isolates of each species tested of 2,530 gram-positive anaerobic isolates from Europe, 2007-2010.

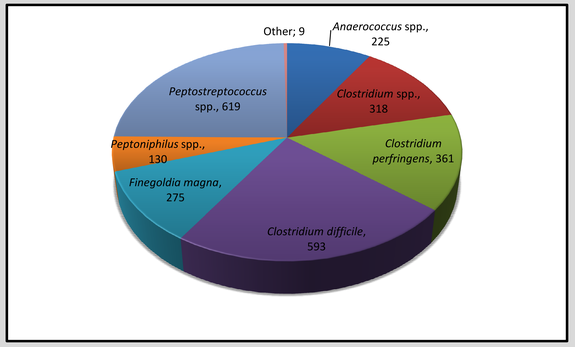
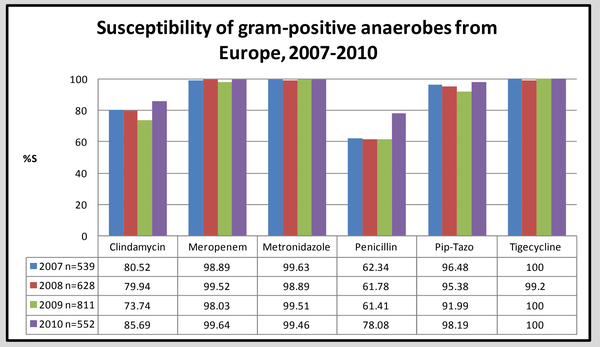
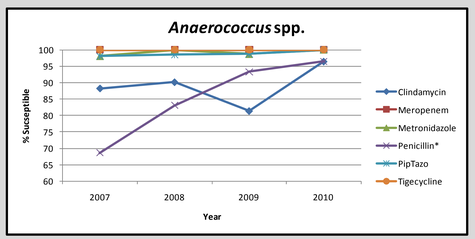



Figure 2. Susceptibility of 2,530 gram-positive anaerobic isolates from Europe, 2007-2010.




| | Clindamycin | Meropenem | Metronidazole | Penicillin | Pip-Tazo | Tigecycline |
|---|---|---|---|---|---|---|
| 2007 n=539 | 80.52 | 98.89 | 99.63 | 62.34 | 96.48 | 100 |
| 2008 n=628 | 79.94 | 99.52 | 98.89 | 61.78 | 95.38 | 99.2 |
| 2009 n=811 | 73.74 | 98.03 | 99.51 | 61.41 | 91.99 | 100 |
| 2010 n=552 | 85.69 | 99.64 | 99.46 | 78.08 | 98.19 | 100 |

Figure 3. Percent susceptibility of *Anaerococcus* spp. for 2007 (n=51), 2008 (n=71), 2009 (n=78) and 2010 (n=28).




* Indicates a significant increase in %S (p=.0037)

Figure 4. Percent susceptibility of *Clostridium* spp., not including *C. difficile*, for 2007 (n=174), 2008 (n=170), 2009 (n=196) and 2010 (n=139).

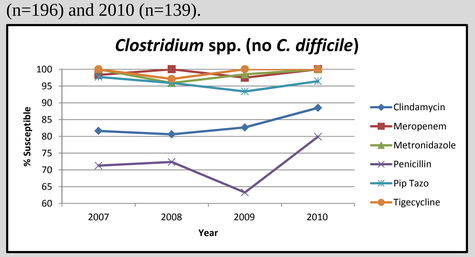



Figure 5. Percent susceptibility of *Clostridium difficile* for 2007 (n=113), 2008 (n=173), 2009 (n=217) and 2010 (n=90).

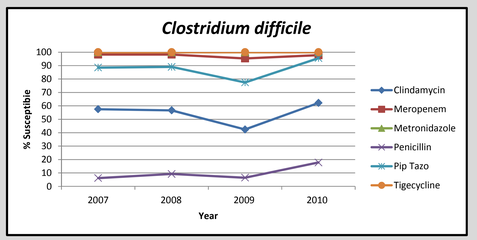
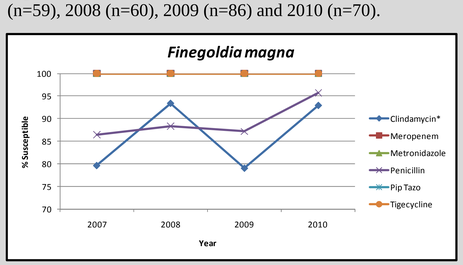
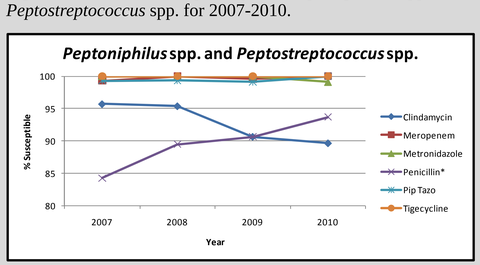



Figure 6. Percent susceptibility of *Finegoldia magna* for 2007 (n=59), 2008 (n=60), 2009 (n=86) and 2010 (n=70).




*Indicates a significant increase in %S (p=.0364)

Figure 7. Percent susceptibility of *Peptoniphilus* spp. and *Peptostreptococcus* spp. for 2007-2010.




*Peptoniphilus* spp. -2007(n=33), 2008 (n=30), 2009 (n=37), 2010 (n=30)
*Peptostreptococcus* spp.- 2007(n=107), 2008 (n=122), 2009 (n=198), 2010 (n=192)
*Indicates a significant increase in %S (p=.0061)

## Conclusions

- Over the four-year study period, tigecycline, metronidazole, meropenem and piperacillin tazobactam all exhibited excellent *in vitro* activity against gram-positive anaerobes with %S of ≥92%.
- Clindamycin and penicillin generally inhibited less than 80% of gram-positive isolates. While there was year to year fluctuation in % susceptible for these agents, no significant decreases in susceptibilities were noted over the four years surveyed, with significant increases in susceptibility of some anaerobic gram-positive cocci to penicillin and clindamycin.
- With the common use of empirical therapy for anaerobic infections, monitoring of antimicrobial agents and treatment strategies is warranted.