Susceptibility of *Clostridium difficile* from Europe: 2007-2010

OB014

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Revised Abstract

Background: *Clostridium difficile* is an anaerobic, gram-positive, spore-forming bacillus that causes a spectrum of diseases, ranging from uncomplicated mild diarrhea to pseudomembranous colitis. *C. difficile* infection (CDI) is a growing problem worldwide and is the most common cause of hospital-acquired infectious diarrhea in recent years. Numerous outbreaks in North America and Europe have been reported as particularly virulent strains have emerged, resulting in changes in the clinical presentation, response to treatment, and outcome of CDI. In this study, we compared the *in vitro* activity of six agents against *C. difficile* collected from 2007-2010 in the Tigecycline European Surveillance Trial (TEST)**. Methods:** 354 *C. difficile* isolates from stool were collected from sites in 4 countries in Europe. MICs of tigecycline and five comparators were determined per CLSI guidelines using agar dilution at a central laboratory. Percents susceptible (%S) are based on CLSI breakpoints where available (clindamycin, meropenem, metronidazole, piperacillin-tazobactam, penicillin), and the FDA (tigecycline). **Results:** Results are shown below, with MIC values in mcg/ml:

	MIC_{50}	MIC_{90}	%S	%I	%R	Minimum MIC	Maximum MIC
Tigecycline	≤ 0.06	0.12	100	0	0	≤ 0.06	2
Metronidazole	0.5	2	100	0	0	≤ 0.12	4
Meropenem	1	2	99.7	0.3	0	≤0.06	8
PipTazo	4	8	99.7	0	0.3	≤ 0.06	> 64
Clindamycin	4	> 8	39.6	15.3	45.2	≤ 0.25	> 8
Penicillin	1	4	15.3	43.8	41.0	≤0.25	> 32

Conclusions: Tigecycline, metronidazole, meropenem and piperacillin-tazobactam all exhibited excellent *in vitro* activity against *C. difficile*, with %S of >99%. Tigecycline had the lowest MIC_{90}, at 0.12 mcg/ml, followed by metronidazole and meropenem, both with MIC_{90} values of 2 mcg/ml. With increasing reports that standard treatments for CDI are not always successful, monitoring of antimicrobial agents and treatment strategies is warranted.

Introduction

Clostridium difficile is an anaerobic, gram-positive, spore-forming bacillus that causes a spectrum of diseases, ranging from uncomplicated mild diarrhea to pseudomembranous colitis [1]. *C. difficile* infection (CDI) is a growing problem worldwide and is the most common cause of hospital-acquired infectious diarrhea in recent years. Numerous outbreaks in North America and Europe have been reported as particularly virulent strains have emerged, resulting in changes in the clinical presentation, response to treatment, and outcome of CDI [2,3]. The risk of developing CDI appears to be greater with certain antimicrobial agents and may increase if strains are resistant to administered antimicrobials [4]. The Tigecycline Evaluation and Surveillance Trial (TEST) is an on-going worldwide 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 *C. difficile* collected between 2007 and 2010.

Materials & Methods

- All isolates were derived from stool sources. Isolates were identified to genus and species by the local laboratory. Only one isolate per patient was accepted.
- For this study 354 clinical isolates were collected from 2007 to 2010 from hospitals in four European countries (Belgium, France, Germany, and Hungary). 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 [5] 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 CLSI [6] and the FDA [7].
- Quality control followed CLSI guidelines using the following ATCC strains: *Bacteroides fragilis* ATCC 25285 and *Bacteroides thetaiotaomicron* ATCC 29741.

References

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Acknowledgements

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Results

Table 1. *In vitro* activity of six antibiotics against 354 *C. difficile* from Europe, 2007-2010.

	MIC_{50} [a]	MIC_{90}	%S [b]	%I	%R	Minimum MIC	Maximum MIC
Tigecycline	≤ 0.06	0.12	100	0	0	≤ 0.06	2
Metronidazole	0.5	2	100	0	0	≤ 0.12	4
Meropenem	1	2	99.7	0.3	0	≤ 0.06	8
PipTazo	4	8	99.7	0	0.3	≤ 0.06	> 64
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[a] MICs reported in mcg/ml; [b] Interpretive criteria are defined according to CLSI breakpoints (M100-S21, 2011), where available; Tigecycline breakpoints defined by FDA (Tygacil®, 2010).

Figure 1. Percent susceptible of 354 *C. difficile* from Europe by year, 2007-2010.

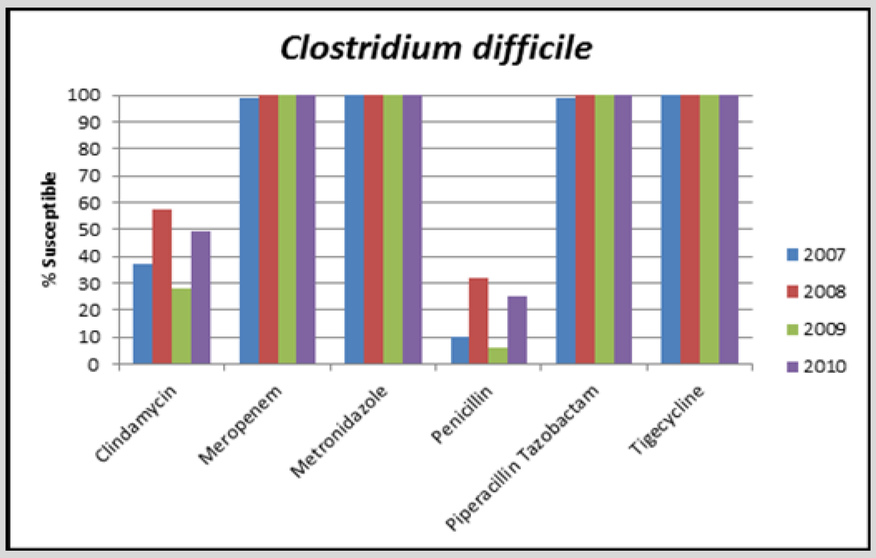


Figure 2. Frequency distribution of metronidazole MICs (mcg/ml) against 354 isolates of *C. difficile*.

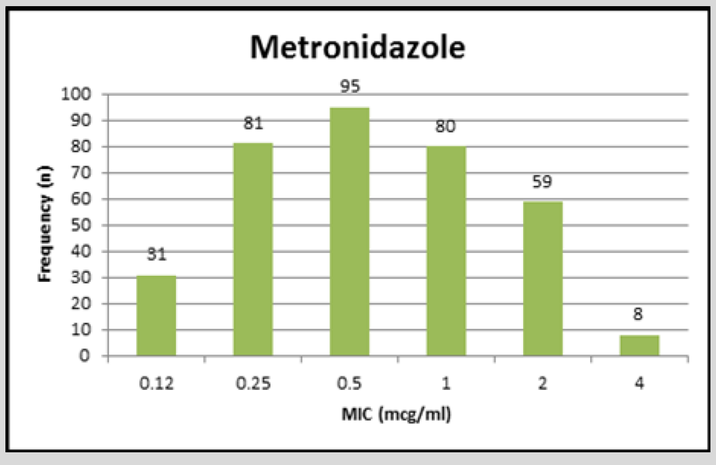
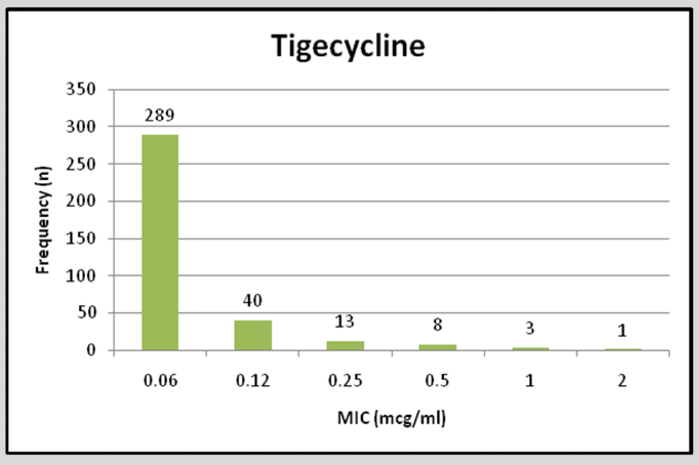


Figure 3. Frequency distribution of tigecycline MICs (mcg/ml) against 354 isolates of *C. difficile*.



Conclusions

- Over the four-year study period, tigecycline, metronidazole, meropenem and piperacillin-tazobactam all exhibited excellent *in vitro* activity against *C. difficile*, with %S of >99%.
- Tigecycline had the lowest MIC_{90}, at 0.12 mcg/ml, followed by metronidazole and meropenem, both with MIC_{90} values of 2 mcg/ml.
- Metronidazole remains a first-line drug associated with no *in vitro* resistance in *C. difficile*.
- With increasing reports that standard treatments for CDI are not always successful, monitoring of antimicrobial agents and treatment strategies is warranted.