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# Worldwide Activity of Tigecycline against Community-Acquired Respiratory Tract Infection (CARTI) Pathogens Collected During 2006-2008

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## ABSTRACT

**Objectives:** To assess the contemporary potency and spectrum of tigecycline tested against Gram-positive and -negative CARTI pathogens, including strains with various resistant (R) phenotypes. Tigecycline is a glycylcycline antimicrobial with proven activity against numerous bacterial species, including staphylococci and streptococci. Based upon in vitro activity and demonstrated clinical trial efficacy, tigecycline has received approval in the USA and Europe (EU) for treating complicated skin and skin structure and intra-abdominal infections.

**Methods:** A total of 9,235 clinically-significant non-duplicate isolates from patients with CARTI were collected from North and Latin America and EU medical centers participating in surveillance of tigecycline (2006-2008). Susceptibility (S) testing was performed by a central laboratory (JMI Laboratories) using CLSI methods (M7-A7, 2006) and all quality control tests were within published ranges.

**Results:** Tigecycline was active against all (≤2 mg/L) tested strains as summarized in Table 1. Tigecycline inhibited *S. aureus* at ≤0.5 mg/L, with a $MIC_{90}$ at 0.25 mg/L, regardless of S or R to oxacillin. Tigecycline also had good activity against *S. pneumoniae* isolates ($MIC_{90}$, 0.06 mg/L), including penicillin-R strains. The $MIC_{90}$ for fastidious Gram-negative pathogens was 1 mg/L for *H. influenzae* (HI) and 0.12 mg/L for *M. catarrhalis* (MCAT). There was no significant difference in tigecycline activity between the three monitored regions for any of CARTI pathogens.

**Table 1.**

| Organism (no. tested) | TIG MIC (mg/L) 50% | 90% | Cum. % inhibited at tigecycline MIC (mg/L): ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 |
|---|---|---|---|---|---|---|---|---|---|
| *S. aureus* (714) | 0.12 | 0.25 | 0.6 | 27.6 | 80.1 | 99.4 | 100.0 | - | - |
| Oxacillin-S (450) | 0.12 | 0.25 | 0.7 | 28.4 | 80.4 | 99.8 | 100.0 | - | - |
| Oxacillin-R (264) | 0.12 | 0.25 | 0.4 | 26.1 | 79.6 | 98.9 | 100.0 | - | - |
| *S. pneumoniae* (5,375) | ≤0.03 | 0.06 | 80.3 | 96.3 | 99.3 | 99.9 | >99.9 | 100.0 | |
| Penicillin-S (3,519)[a] | ≤0.03 | 0.06 | 81.7 | 96.5 | 99.4 | 100.0 | - | - | - |
| Penicillin-I (881)[b] | ≤0.03 | 0.06 | 83.9 | 96.8 | 99.6 | 100.0 | - | - | - |
| Penicillin-R (975)[c] | ≤0.03 | 0.06 | 72.1 | 95.1 | 98.7 | 99.8 | 99.9 | 100.0 | - |
| *H. influenzae* (3,129) | 0.5 | 1 | 0.1 | 0.1 | 0.2 | 11.7 | 73.7 | 99.6 | 100.0 |
| ß-lactamase-neg. (2,486) | 0.5 | 1 | 0.1 | 0.1 | 0.2 | 12.4 | 74.1 | 99.6 | 100.0 |
| ß-lactamase-pos. (642) | 0.5 | 1 | 0.3 | 0.3 | 0.5 | 9.0 | 72.0 | 99.7 | 100.0 |
| *M. catarrhalis* (17) | 0.12 | 0.12 | 23.5 | 47.1 | 100.0 | - | - | - | - |

a. MIC, ≤0.06 mg/L
b. MIC, 0.12 – 1 mg/L
c. MIC, ≥2 mg/L

**Conclusions:** Tigecycline demonstrated broad antimicrobial activity against pathogens associated with CARTI. Tigecycline was active against antimicrobial-R strains including oxacillin-R staphylococci and penicillin-R *S. pneumoniae*, as well as HI and MCAT isolates, including those producing ß-lactamase enzymes. Tigecycline potency and spectrum shown here for 2006-2008 confirms that this agent may have a role in treating CARTI.

## INTRODUCTION

Tigecycline, a glycycycline derivative of a tetracycline class agent, was first licensed by the United States (USA) Food and Drug Administration (FDA) in 2005 and the European Medicines Agency (EMEA) in 2006. This parenteral agent has been approved for the treatment of complicated skin and skin structure infections (cSSSI) and intra-abdominal infections (IAI). Unique to the class, tigecycline has stability against mechanisms of tetracycline resistance including increased binding affinity to tetracycline-resistant ribosomes and inhibition of efflux determinants. Tigecycline is a broad-spectrum, bacteriostatic agent which inhibits protein synthesis without killing the organism.

Tigecycline has activity against numerous bacterial pathogens, including aerobic and anaerobic species. In this study, we evaluated the activity of tigecycline tested against over 9,200 isolates of Gram-positive and -negative bacterial species commonly associated with community-acquired respiratory tract infections (CARTI). Isolates were collected from patient infections from the USA, Europe (EU) and Latin America (LA) between 2006 and 2008. The isolates targeted for this presentation were the four most common CARTI pathogens and included *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates; MRSA and MSSA, respectively), *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*.

## MATERIALS AND METHODS

Bacterial isolates. Medical centers from 18 countries in the USA, LA and EU referred isolates for this global surveillance study. Thirteen countries in EU contributed 3,915 strains (42.4%) and included hospitals in Belgium, France (five), Germany (four), Greece (two), Ireland (two), Israel, Italy (three), Poland, Spain (two), Sweden (two), Switzerland, Turkey (two) and the United Kingdom (two). In the USA, 25 medical centers from diverse geographic regions contributed 4,248 isolates (46.0%). Ten centers in four countries in LA, including Argentina (two), Chile (two), Brazil (four) and Mexico (two) referred 1,072 isolates (11.6%) for this investigation.

A total of 9,235 isolates were collected from patients infected with common causes of CARTI. The majority of isolates were cultured from lower pulmonary samples (66.4%). Isolates collected from upper respiratory tract infections, ear, nose, throat and eye cultures represented 26.6% of the samples and 2.2% of the strains came from blood cultures. This study reports the antimicrobial activity against the most common bacterial causes of CARTI collected between 2006 and 2008. The isolates included in this study were *S. aureus* (714 strains; 37.0% MRSA), *S. pneumoniae* (5,375; 34.5% penicillin-non-susceptible), *H. influenzae* (3,129; 20.5% ß-lactamase-positive) and a small sample of ß-lactamase-positive *M. catarrhalis* (17 strains).

Susceptibility testing. All isolates were tested by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI, M7-A7) in validated panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Freshly prepared Mueller-Hinton broth (MHB) or Haemophilus Test Media, necessary for testing tigecycline, was used for testing all isolates. MHB was adjusted with 3-5% lysed-horse blood when testing *S. pneumoniae*. CLSI approved breakpoints were used to categorize susceptibility (M100-S18). American Type Culture Collection (ATCC) quality control organisms were tested concurrently and included *S. aureus* ATCC 29213, *H. influenzae* ATCC 49427 and *S. pneumoniae* ATCC 49619.

## ACKNOWLEDGEMENT

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## RESULTS

- Tigecycline was very active (100% susceptibility) against both MSSA and MRSA with 99.8 and 98.9% of isolates inhibited by ≤0.25 mg/L, respectively (Table 1).
- Tigecycline had similar activity against *S. aureus* in all regions, with $MIC_{50}$ and $MIC_{90}$ values of 0.12 and 0.25 mg/L, respectively (Table 2). All *S. aureus* isolates were susceptible to tigecycline using the susceptibility breakpoint criteria (≤0.5 mg/L) for this agent. In contrast, tetracycline susceptibility rates ranged from 89.9% (LA) to 95.3% (USA).
- The MRSA rate (Table 2) was highest among isolates collected from the USA (41.5%) compared to LA (37.0%) and EU (27.5%). This resulted in lower susceptibility rates for some of the comparator agents among the USA isolates. Tigecycline, vancomycin and linezolid were active against 100% of *S. aureus* isolates tested in this study.

**Table 2. Antimicrobial activity of tigecycline and comparator agents tested against *S. aureus* isolates collected from patients hospitalized in North America, Latin America and Europe (2006-2008).**

| Region (no. tested) | MIC (mg/L) 50% | 90% | % Susceptible[a] | % Resistant[a] |
|---|---|---|---|---|
| North America (402) | | | | |
| Tigecycline | 0.12 | 0.25 | 100.0 | -[b] |
| Oxacillin | 0.5 | >2 | 58.5 | 41.5 |
| Erythromycin | >2 | >2 | 37.6 | 62.2 |
| Clindamycin | ≤0.25 | >2 | 74.4 | 25.4 |
| Levofloxacin | ≤0.5 | >4 | 62.2 | 37.1 |
| Gentamicin | ≤2 | ≤2 | 97.0 | 3.0 |
| Quinupristin/dalfopristin | 0.5 | 0.5 | 99.5 | 0.0 |
| Tetracycline | ≤2 | ≤2 | 95.3 | 4.5 |
| Trim/sulfa[c] | ≤0.5 | ≤0.5 | 98.3 | 1.7 |
| Linezolid | 2 | 2 | 100.0 | - |
| Vancomycin | 1 | 1 | 100.0 | 0.0 |
| Latin America (119) | | | | |
| Tigecycline | 0.12 | 0.25 | 100.0 | - |
| Oxacillin | 0.5 | >2 | 63.0 | 37.0 |
| Erythromycin | 0.5 | >2 | 56.3 | 43.7 |
| Clindamycin | ≤0.25 | >2 | 64.7 | 35.3 |
| Levofloxacin | ≤0.5 | >4 | 62.2 | 37.0 |
| Gentamicin | ≤2 | >8 | 68.9 | 30.3 |
| Quinupristin/dalfopristin | 0.5 | 1 | 100.0 | 0.0 |
| Tetracycline | ≤2 | >8 | 89.9 | 10.0 |
| Trim/sulfa[c] | ≤0.5 | ≤0.5 | 97.5 | 2.5 |
| Linezolid | 2 | 2 | 100.0 | - |
| Vancomycin | 1 | 1 | 100.0 | 0.0 |
| Europe (193) | | | | |
| Tigecycline | 0.12 | 0.25 | 100.0 | - |
| Oxacillin | 0.5 | >2 | 72.5 | 27.5 |
| Erythromycin | ≤0.25 | >2 | 66.3 | 32.6 |
| Clindamycin | ≤0.25 | >2 | 87.1 | 12.9 |
| Levofloxacin | ≤0.5 | >4 | 67.9 | 31.6 |
| Gentamicin | ≤2 | ≤2 | 92.2 | 6.7 |
| Quinupristin/dalfopristin | ≤0.25 | 0.5 | 100.0 | 0.0 |
| Tetracycline | ≤2 | ≤2 | 90.7 | 8.8 |
| Trim/sulfa[c] | ≤0.5 | ≤0.5 | 99.5 | 0.5 |
| Linezolid | 2 | 2 | 100.0 | - |
| Vancomycin | 1 | 1 | 100.0 | 0.0 |

a. According to CLSI or USA-FDA.
b. - = no breakpoints have been established by the CLSI or the USA-FDA.
c. Trimethoprim/sulfamethoxazole.

**Table 3. Antimicrobial activity of tigecycline and comparator agents tested against *S. pneumoniae* and *H. influenzae* isolates collected from patients hospitalized in North America, Latin America, and Europe (2006-2008).**

| Organism/Region (no. tested) | MIC (mg/L) 50% | 90% | % Susceptible[a] | % Resistant[a] |
|---|---|---|---|---|
| *S. pneumoniae* | | | | |
| North America (2,441) | | | | |
| Tigecycline | ≤0.03 | 0.06 | -[b] | - |
| Penicillin | ≤0.03 | 4 | 59.7 (87.9)[c] | 19.9 (0.9)[c] |
| Cefuroxime | ≤1 | 8 | 74.7 | 21.9 |
| Ceftriaxone | ≤0.25 | 1 | 93.2 | 0.8 |
| Amoxacillin/clavulanate | ≤1 | 8 | 85.1 | 11.3 |
| Erythromycin | ≤0.25 | >2 | 62.4 | 37.3 |
| Clindamycin | ≤0.25 | >2 | 80.3 | 19.2 |
| Levofloxacin | 1 | 1 | 99.3 | 0.6 |
| Tetracycline | ≤2 | >8 | 76.3 | 23.4 |
| Trim/sulfa[d] | ≤0.5 | >2 | 68.3 | 23.5 |
| Vancomycin | ≤1 | ≤1 | 100.0 | - |
| Latin America (590) | | | | |
| Tigecycline | ≤0.03 | 0.06 | - | - |
| Penicillin | ≤0.03 | 2 | 66.1 (94.2)[c] | 16.3 (1.5)[c] |
| Cefuroxime | ≤1 | 4 | 82.2 | 16.5 |
| Ceftriaxone | ≤0.25 | 1 | 95.9 | 0.2 |
| Amoxacillin/clavulanate | ≤1 | 2 | 93.6 | 1.4 |
| Erythromycin | ≤0.25 | >2 | 80.5 | 18.6 |
| Clindamycin | ≤0.25 | ≤0.25 | 94.2 | 5.6 |
| Levofloxacin | 1 | 1 | 99.3 | 0.7 |
| Tetracycline | ≤2 | >8 | 82.2 | 14.9 |
| Trim/sulfa[d] | ≤0.5 | >2 | 58.3 | 30.4 |
| Vancomycin | ≤1 | ≤1 | 100.0 | - |
| Europe (2,344) | | | | |
| Tigecycline | ≤0.03 | 0.06 | - | - |
| Penicillin | ≤0.03 | 2 | 71.3 (96.2)[c] | 16.7 (0.1)[c] |
| Cefuroxime | ≤1 | 4 | 79.8 | 18.4 |
| Ceftriaxone | ≤0.25 | 1 | 96.5 | 0.3 |
| Amoxacillin/clavulanate | ≤1 | 2 | 94.3 | 2.7 |
| Erythromycin | ≤0.25 | >2 | 68.4 | 31.2 |
| Clindamycin | ≤0.25 | >2 | 79.1 | 20.6 |
| Levofloxacin | 1 | 1 | 98.1 | 1.7 |
| Tetracycline | ≤2 | >8 | 75.5 | 23.4 |
| Trim/sulfa[d] | ≤0.5 | >2 | 69.3 | 20.2 |
| Vancomycin | ≤1 | ≤1 | 100.0 | - |
| *H. influenzae* | | | | |
| North America (1,400) | | | | |
| Tigecycline | 0.5 | 1 | - | - |
| Ampicillin | ≤1 | >16 | 73.4 | 25.6 |
| Cefuroxime | ≤2 | ≤2 | 99.4 | 0.2 |
| Ceftriaxone | ≤0.25 | ≤0.25 | 100.0 | 0.0 |
| Levofloxacin | ≤0.5 | ≤0.5 | 100.0 | 0.0 |
| Tetracycline | ≤2 | ≤2 | 98.5 | 1.1 |
| Trim/sulfa[d] | ≤0.5 | >2 | 78.2 | 19.1 |
| Latin America (359) | | | | |
| Tigecycline | 0.5 | 1 | - | - |
| Ampicillin | ≤1 | 16 | 82.2 | 17.3 |
| Cefuroxime | ≤2 | ≤2 | 100.0 | 0.0 |
| Ceftriaxone | ≤0.25 | ≤0.25 | 100.0 | 0.0 |
| Levofloxacin | ≤0.5 | ≤0.5 | 100.0 | 0.0 |
| Tetracycline | ≤2 | ≤2 | 97.5 | 2.2 |
| Trim/sulfa[d] | ≤0.5 | >2 | 73.8 | 24.0 |
| Europe (1,370) | | | | |
| Tigecycline | 0.5 | 1 | - | - |
| Ampicillin | ≤1 | 8 | 84.3 | 14.4 |
| Cefuroxime | ≤2 | ≤2 | 99.5 | 0.2 |
| Ceftriaxone | ≤0.25 | ≤0.25 | 100.0 | 0.0 |
| Levofloxacin | ≤0.5 | ≤0.5 | 100.0 | 0.0 |
| Tetracycline | ≤2 | ≤2 | 98.0 | 1.5 |
| Trim/sulfa[d] | ≤0.5 | >2 | 77.3 | 19.9 |

a. According to CLSI criteria.
b. - = no breakpoints have been established by the CLSI or the USA-FDA.
c. Penicillin results in parentheses represent the respiratory breakpoint criteria.
d. Trimethoprim/sulfamethoxazole.

- Tigecycline had excellent potency against *S. pneumoniae* in all geographic regions, regardless of susceptibility to penicillin with >99.9% of isolates inhibited at ≤0.25 mg/L (Table 1).
- Penicillin susceptibility (MIC, ≤0.06 mg/L) among *S. pneumoniae* was lowest in the USA (59.7%) compared to LA (66.1%) and EU (71.3%), see Table 3. Susceptibility to erythromycin was lower in the USA (62.4%) and EU (68.4%), compared to LA (80.5%). Tetracycline resistance ranged from 14.9 to 23.4% in these regions.
- Tetracycline resistance was low (1.1 to 2.2%) among the *H. influenzae* isolates tested in this study and tigecycline had a $MIC_{90}$ value of 1 mg/L against this species in all regions (Table 3).
- As shown in Table 3, ampicillin-resistant (ß-lactamase-positive) *H. influenzae* isolates were more commonly isolated in the USA (25.6%) when compared to the other regions (14.4 - 17.3%).
- *M. catarrhalis* isolates (all ß-lactamase producers) were very susceptible to tigecycline with 100.0% inhibited by ≤0.12 mg/L (Table 1).

## CONCLUSIONS

- ß-lactam resistance varied considerably between geographic regions with higher rates of MRSA, penicillin-resistant *S. pneumoniae* and ampicillin-resistant *H. influenzae* being observed in USA medical centers.
- No geographic potency variation was observed for tigecycline tested against the four CARTI pathogens reported in this investigation.
- Tigecycline was documented to have excellent potency against MSSA and MRSA in all geographic regions and all strains were considered susceptible using breakpoint criteria recommended by the USA-FDA and EMEA.
- Although tigecycline is not indicated for the treatment of CARTI, this antimicrobial agent was demonstrated to have excellent potency against the most common bacterial causes of this type of infection.