

# ANTIMICROBIAL ACTIVITY OF DAPTOMYCIN TESTED AGAINST *S. AUREUS* COLLECTED FROM OSTEOARTICULAR INFECTIONS

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## ABSTRACT

**Objectives:** To evaluate the antimicrobial activity of daptomycin and comparator agents tested against *S. aureus* from osteoarticular infections. *S. aureus* is a major cause of osteoarticular infections and those caused by oxacillin-resistant strains (MRSA) are particularly difficult to treat due to limited therapeutic options. MRSA osteoarticular infections are a primary indication for outpatient parenteral antimicrobial therapy.

**Methods:** As part of the Daptomycin Surveillance Program, 606 *S. aureus* causing osteoarticular infections were collected from 56 medical centers located in North America (NA; 29), Europe (EU; 17) and Latin America (LA; 10) in 2002-2009. Isolates were tested for susceptibility (S) against daptomycin and several comparators by CLSI broth microdilution method. Calcium content of the broth was adjusted (50 mg/L) for testing daptomycin. S breakpoint approved by the USA-FDA, CLSI and EUCAST ( $\leq 1$  mg/L) was applied.

**Results:** S to oxacillin was higher in EU (80.5%) and LA (76.0%) compared to NA (51.7%). Daptomycin was very active against *S. aureus* from osteoarticular infections independent of geographic region. Daptomycin activity was not adversely affected by resistance to oxacillin or other antimicrobials (Table). All isolates were S to daptomycin (MIC<sub>50</sub>/MIC<sub>90</sub> 0.25/0.5 mg/L) and 98.5% of strains were inhibited at  $\leq 0.5$  mg/L of daptomycin. Vancomycin (MIC<sub>50</sub>/MIC<sub>90</sub>, 1/1 mg/L) and linezolid (MIC<sub>50</sub>/MIC<sub>90</sub>, 2/2 mg/L) were also very active (both 100.0% S), but were four- to eight-fold less potent than daptomycin. Among MRSA, S to levofloxacin (LEV; 27.1% overall) ranged from only 16.0% in EU to 32.5% in NA; while S to clindamycin (CLI; 47.4% overall) varied from 19.2% in LA to 62.7% in NA and 72.0% in EU.

| Organism / Region (no.) | No. of strains (cumulative %) inhibited at DAP MIC (mg/L) of: |            |            |           | % susceptible |      |      |
|-------------------------|---|------------|------------|-----------|---------------|------|------|
|                         | $\leq 0.12$   | 0.25       | 0.5        | 1         | DAP           | LEV  | CLI  |
| All strains (606)       | 23 (3.8)  | 423 (73.6) | 151 (98.5) | 9 (100.0) | 100.0         | 72.4 | 83.3 |
| MSSA <sup>a</sup> (403) | 22 (5.5)  | 293 (78.2) | 80 (98.0)  | 8 (100.0) | 100.0         | 95.3 | 98.8 |
| MRSA (203)              | 1 (0.5)   | 130 (64.5) | 71 (99.5)  | 1 (100.0) | 100.0         | 27.1 | 52.7 |
| North America           | 9 (3.5)   | 188 (75.5) | 63 (99.6)  | 1 (100.0) | 100.0         | 63.6 | 80.8 |
| Europe                  | 6 (4.7)   | 98 (81.3)  | 23 (99.2)  | 1 (100.0) | 100.0         | 82.8 | 94.5 |
| Latin America           | 8 (3.7)   | 137 (66.8) | 65 (96.5)  | 7 (100.0) | 100.0         | 77.0 | 79.6 |

a. DAP = daptomycin; LEV = levofloxacin; CLI = clindamycin; MSSA = methicillin-susceptible *S. aureus*.

**Conclusion:** Daptomycin was highly active against a large collection of *S. aureus* from osteoarticular infections. Due to its excellent anti-*S. aureus* spectrum, high potency and rapid bactericidal activity, daptomycin may represent an excellent option for treatment of *S. aureus* osteoarticular infections, including those caused by MRSA.

## INTRODUCTION

Treatment of osteoarticular infections usually involves surgical procedures and prolonged antimicrobial therapy. *Staphylococcus aureus* is a major cause of osteoarticular infections and those caused by oxacillin-resistant strains (MRSA) are particularly difficult to treat due to limited therapeutic options. MRSA osteoarticular infections are a primary indication for outpatient parenteral antimicrobial therapy (OPAT).

Daptomycin is cyclic lipopeptide antimicrobial agent with potent bactericidal activity against a broad range of Gram-positive organisms, including MRSA. Daptomycin was approved in Europe for the treatment of complicated skin and soft tissue infections (cSSTIs) in 2006 and for the treatment of right-sided infective endocarditis (RIE) due to *S. aureus* and *S. aureus* bacteraemia when associated with RIE or with cSSTI in 2007. In the present study, we evaluated the antimicrobial activity of daptomycin and comparator agents tested against *S. aureus* from osteoarticular infections.

## MATERIALS AND METHODS

**Bacterial isolates:** 606 *S. aureus* isolates from osteoarticular infections were included in the study. The isolates were collected from 56 medical centers located in North America (29), Europe (17) and Latin America (10) in 2002-2009 as part of the Daptomycin Surveillance Program.

**Susceptibility Testing:** Daptomycin and various comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in validated, microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. European Committee on Antimicrobial Susceptibility Testing (EUCAST) and CLSI interpretive criteria were used to categorize the isolates as susceptible, intermediate and resistant. A daptomycin susceptibility breakpoint of  $\leq 1$  mg/L was applied, as recommended by the CLSI and USA-FDA for this organism. In addition, EUCAST has established daptomycin susceptible and resistant breakpoints for *S. aureus* ( $\leq 1$  and  $>1$  mg/L, respectively). *S. aureus* ATCC 29213 strain was concurrently tested for quality control (QC) purposes, and all QC results were within published limits.

## RESULTS

- Daptomycin was very active against *S. aureus* from osteoarticular infections independent of geographic region. MIC<sub>50</sub>, MIC<sub>90</sub> and highest MIC values were 0.25, 0.5 and 1 mg/L, respectively in all three geographic regions evaluated (Table 1).
- The overall oxacillin susceptibility rate was 66.5%, being higher in Europe (80.5%) and Latin America (76.0%) compared to North America (51.7%; Table 2).
- Daptomycin activity was not adversely affected by resistance to oxacillin or other antimicrobials (Table 1 and Table 2). All isolates were susceptible to daptomycin and 98.5% of strains were inhibited at  $\leq 0.5$  mg/L of daptomycin.
- Vancomycin (MIC<sub>50</sub> and MIC<sub>90</sub>, 1 mg/L) and linezolid (MIC<sub>50</sub> and MIC<sub>90</sub>, 2 mg/L) were also very active (both 100.0% susceptible), but were four- to eight-fold less potent than daptomycin (Table 2). Isolates with elevated vancomycin MIC value (2 mg/L) were very susceptible to daptomycin (MIC<sub>50</sub>, 0.5 mg/L and MIC<sub>90</sub>, 1 mg/L; Table 1)
- Among MRSA, susceptibility to levofloxacin (27.1% overall) ranged from only 16.0% in Europe to 32.5% in North America; while susceptibility to clindamycin (50.7% overall [CLSI]) varied from 19.2% in Latin America to 62.7% in North America and to 72.0% in Europe (data not shown).

## RESULTS

**Table 1.** Daptomycin MIC distributions when tested against *S. aureus* isolated from osteoarticular infections

| Subset / region (no. tested)                        | No. of strains (cumulative %) inhibited at DAP MIC (mg/L) of: |            |            |           |
|---|---|------------|------------|-----------|
|   | $\leq 0.12$   | 0.25       | 0.5        | 1         |
| All <i>S. aureus</i> strains (606)                  | 23 (3.8)  | 423 (73.6) | 151 (98.5) | 9 (100.0) |
| MSSA <sup>a</sup> (403)                             | 22 (5.5)  | 293 (78.2) | 80 (98.0)  | 8 (100.0) |
| MRSA <sup>a</sup> (203)                             | 1 (0.5)   | 130 (64.5) | 71 (99.5)  | 1 (100.0) |
| <i>S. aureus</i> with vancomycin MIC of 2 mg/L (16) | 0 (0.0)   | 5 (31.3)   | 9 (87.5)   | 2 (100.0) |
| North America (261)                                 | 9 (3.5)   | 188 (75.5) | 63 (99.6)  | 1 (100.0) |
| Europe (128)  | 6 (4.7)   | 98 (81.3)  | 23 (99.2)  | 1 (100.0) |
| Latin America (217)                                 | 8 (3.7)   | 137 (66.8) | 65 (96.5)  | 7 (100.0) |

Abbreviations: MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*

**Table 2.** Activity of daptomycin and comparator antimicrobial agents when tested against 606 isolates of *Staphylococcus aureus*

| Antimicrobial agent           | MIC <sub>50</sub> | MIC <sub>90</sub> | Range             | CLSI <sup>a</sup> %S / %R | EUCAST <sup>a</sup> %S / %R |
|-------------------------------|-------------------|-------------------|-------------------|---------------------------|-----------------------------|
| <b>All strains (606)</b>      |                   |                   |                   |                           |                             |
| Daptomycin                    | 0.25              | 0.5               | $\leq 0.06 - 1$   | 100.0 / -                 | 100.0 / 0.0                 |
| Oxacillin                     | 0.5               | $>2$              | $\leq 0.25 - >2$  | 66.5 / 33.5               | 66.5 / 33.5                 |
| Clindamycin                   | $\leq 0.25$       | $>2$              | $\leq 0.25 - >2$  | 83.3 / 16.5               | 82.1 / 16.7                 |
| Erythromycin                  | 0.5               | $>2$              | $\leq 0.25 - >2$  | 56.8 / 42.2               | 57.4 / 42.4                 |
| Levofloxacin                  | $\leq 0.5$        | $>4$              | $\leq 0.5 - >4$   | 72.4 / 26.1               | 72.4 / 26.1                 |
| Linezolid                     | 2                 | 2                 | 0.25 - 2          | 100.0 / 0.0               | 100.0 / 0.0                 |
| Teicoplanin                   | $\leq 2$          | $\leq 2$          | $\leq 2 - 4$      | 100.0 / 0.0               | 99.2 / 0.8                  |
| Tetracycline                  | $\leq 2$          | $\leq 2$          | $\leq 2 - >8$     | 92.6 / 6.8                | 92.4 / 7.6                  |
| Tigecycline <sup>b</sup>      | 0.12              | 0.25              | $\leq 0.03 - 0.5$ | 100.0 / -                 | 100.0 / 0.0                 |
| Trimethoprim/sulfamethoxazole | $\leq 0.5$        | $\leq 0.5$        | $\leq 0.5 - >2$   | 96.9 / 3.1                | 96.9 / 3.1                  |
| Vancomycin                    | 1                 | 1                 | 0.25 - 2          | 100.0 / 0.0               | 100.0 / 0.0                 |
| <b>MSSA (403)</b>             |                   |                   |                   |                           |                             |
| Daptomycin                    | 0.25              | 0.5               | $\leq 0.06 - 1$   | 100.0 / -                 | 100.0 / 0.0                 |
| Clindamycin                   | $\leq 0.25$       | $\leq 0.25$       | $\leq 0.25 - >2$  | 98.8 / 1.0                | 98.0 / 1.2                  |
| Erythromycin                  | $\leq 0.25$       | $>2$              | $\leq 0.25 - >2$  | 78.2 / 20.3               | 79.2 / 20.6                 |
| Levofloxacin                  | $\leq 0.5$        | $\leq 0.5 - >4$   | $\leq 0.5 - >4$   | 95.3 / 3.7                | 95.3 / 3.7                  |
| Linezolid                     | 2                 | 2                 | 0.25 - 2          | 100.0 / 0.0               | 100.0 / 0.0                 |
| Teicoplanin                   | $\leq 2$          | $\leq 2$          | $\leq 2$          | 100.0 / 0.0               | 100.0 / 0.0                 |
| Tetracycline                  | $\leq 2$          | $\leq 2$          | $\leq 2 - >8$     | 93.8 / 5.5                | 93.5 / 6.5                  |
| Tigecycline <sup>b</sup>      | 0.12              | 0.25              | $\leq 0.03 - 0.5$ | 100.0 / -                 | 100.0 / 0.0                 |
| Trimethoprim/sulfamethoxazole | $\leq 0.5$        | $\leq 0.5$        | $\leq 0.5 - >2$   | 99.8 / 0.2                | 99.8 / 0.2                  |
| Vancomycin                    | 1                 | 1                 | 0.25 - 2          | 100.0 / 0.0               | 100.0 / 0.0                 |
| <b>MRSA (203)</b>             |                   |                   |                   |                           |                             |
| Daptomycin                    | 0.25              | 0.5               | 0.12 - 1          | 100.0 / -                 | 100.0 / 0.0                 |
| Clindamycin                   | $\leq 0.25$       | $>2$              | $\leq 0.25 - >2$  | 52.7 / 47.3               | 50.7 / 47.3                 |
| Erythromycin                  | $>2$              | $>2$              | $\leq 0.25 - >2$  | 14.3 / 85.7               | 14.3 / 85.7                 |
| Levofloxacin                  | $>4$              | $>4$              | $\leq 0.5 - >4$   | 27.1 / 70.4               | 27.1 / 70.4                 |
| Linezolid                     | 1                 | 2                 | 0.5 - 2           | 100.0 / 0.0               | 100.0 / 0.0                 |
| Teicoplanin                   | $\leq 2$          | $\leq 2$          | $\leq 2 - 4$      | 100.0 / 0.0               | 97.5 / 2.5                  |
| Tetracycline                  | $\leq 2$          | $\leq 2$          | $\leq 2 - >8$     | 90.1 / 9.4                | 90.1 / 9.9                  |
| Tigecycline <sup>b</sup>      | 0.12              | 0.25              | 0.06 - 0.5        | 100.0 / -                 | 100.0 / 0.0                 |
| Trimethoprim/sulfamethoxazole | $\leq 0.5$        | 1                 | $\leq 0.5 - >2$   | 91.1 / 8.9                | 91.1 / 8.9                  |
| Vancomycin                    | 1                 | 1                 | 0.5 - 2           | 100.0 / 0.0               | 100.0 / 0.0                 |
| <b>North America (261)</b>    |                   |                   |                   |                           |                             |
| Daptomycin                    | 0.25              | 0.5               | 0.12 - 1          | 100.0 / -                 | 100.0 / 0.0                 |
| Oxacillin                     | 1                 | $>2$              | $\leq 0.25 - >2$  | 51.7 / 48.3               | 51.7 / 48.3                 |
| Clindamycin                   | $\leq 0.25$       | $>2$              | $\leq 0.25 - >2$  | 80.8 / 19.2               | 80.8 / 19.2                 |
| Erythromycin                  | $>2$              | $>2$              | $\leq 0.25 - >2$  | 39.1 / 60.5               | 39.1 / 60.9                 |
| Levofloxacin                  | $\leq 0.5$        | $>4$              | $\leq 0.5 - >4$   | 63.6 / 34.5               | 63.6 / 34.5                 |
| Linezolid                     | 1                 | 2                 | 0.25 - 2          | 100.0 / 0.0               | 100.0 / 0.0                 |
| Teicoplanin                   | $\leq 2$          | $\leq 2$          | $\leq 2 - 4$      | 100.0 / 0.0               | 99.6 / 0.4                  |
| Tetracycline                  | $\leq 2$          | $\leq 2$          | $\leq 2 - >8$     | 96.9 / 1.9                | 96.6 / 3.4                  |
| Tigecycline <sup>b</sup>      | 0.12              | 0.25              | $\leq 0.03 - 0.5$ | 100.0 / -                 | 100.0 / 0.0                 |
| Trimethoprim/sulfamethoxazole | $\leq 0.5$        | $\leq 0.5$        | $\leq 0.5 - >2$   | 98.9 / 1.1                | 98.9 / 1.1                  |
| Vancomycin                    | 1                 | 1                 | 0.5 - 2           | 100.0 / 0.0               | 100.0 / 0.0                 |

**Table 2.** Activity of daptomycin and comparator antimicrobial agents when tested against 606 isolates of *Staphylococcus aureus* (continued)

| Antimicrobial agent           | MIC <sub>50</sub> | MIC <sub>90</sub> | Range            | CLSI <sup>a</sup> %S / %R | EUCAST <sup>a</sup> %S / %R |
|-------------------------------|-------------------|-------------------|------------------|---------------------------|-----------------------------|
| <b>Europe (128)</b>           |                   |                   |                  |                           |                             |
| Daptomycin                    | 0.25              | 0.5               | 0.12 - 1         | 100.0 / -                 | 100.0 / 0.0                 |
| Oxacillin                     | 0.5               | $>2$              | $\leq 0.25 - >2$ | 80.5 / 19.5               | 80.5 / 19.5                 |
| Clindamycin                   | $\leq 0.25$       | $\leq 0.25$       | $\leq 0.25 - >2$ | 94.5 / 5.5                | 90.6 / 5.5                  |
| Erythromycin                  | $\leq 0.25$       | $>2$              | $\leq 0.25 - >2$ | 79.7 / 18.8               | 81.3 / 18.8                 |
| Levofloxacin                  | $\leq 0.5$        | $>4$              | $\leq 0.5 - >4$  | 82.8 / 14.8               | 82.8 / 14.8                 |
| Linezolid                     | 2                 | 2                 | 1 - 2            | 100.0 / 0.0               | 100.0 / 0.0                 |
| Teicoplanin                   | $\leq 2$          | $\leq 2$          | $\leq 2$         | 100.0 / 0.0               | 100.0 / 0.0                 |
| Tetracycline                  | $\leq 2$          | $\leq 2$          | $\leq 2 - >8$    | 93.8 / 5.5                | 93.8 / 6.3                  |
| Tigecycline <sup>b</sup>      | 0.12              | 0.25              | 0.06 - 0.25      | 100.0 / -                 | 100.0 / 0.0                 |
| Trimethoprim/sulfamethoxazole | $\leq 0.5$        | $\leq 0.5$        | $\leq 0.5 - 1$   | 100.0 / 0.0               | 100.0 / 0.0                 |
| Vancomycin                    | 1                 | 1                 | 0.5 - 2          | 100.0 / 0.0               | 100.0 / 0.0                 |
| <b>Latin America (217)</b>    |                   |                   |                  |                           |                             |
| Daptomycin                    | 0.25              | 0.5               | $\leq 0.06 - 1$  | 100.0 / -                 | 100.0 / 0.0                 |
| Oxacillin                     | 0.5               | $>2$              | $\leq 0.25 - >2$ | 76.0 / 24.0               | 76.0 / 24.0                 |
| Clindamycin                   | $\leq 0.25$       | $>2$              | $\leq 0.25 - >2$ | 79.6 / 19.9               | 78.7 / 20.4                 |
| Erythromycin                  | $\leq 0.25$       | $>2$              | $\leq 0.25 - >2$ | 64.5 / 34.1               | 65.4 / 34.1                 |
| Levofloxacin                  | $\leq 0.5$        | $>4$              | $\leq 0.5 - >4$  | 77.0 / 22.6               | 77.0 / 22.6                 |
| Linezolid                     | 2                 | 2                 | 0.5 - 2          | 100.0 / 0.0               | 100.0 / 0.0                 |
| Teicoplanin                   | $\leq 2$          | $\leq 2$          | $\leq 2 - 4$     | 100.0 / 0.0               | 98.2 / 1.8                  |
| Tetracycline                  | 0.12              | $>8$              | $\leq 2 - >8$    | 86.6 / 13.4               | 86.6 / 13.4                 |
| Tigecycline <sup>b</sup>      | $\leq 2$          | 0.25              | 0.06 - 0.5       | 100.0 / -                 | 100.0 / 0.0                 |
| Trimethoprim/sulfamethoxazole | $\leq 0.5$        | 1                 | $\leq 0.5 - >2$  | 92.6 / 7.4                | 92.6 / 7.4                  |
| Vancomycin                    | 1                 | 1                 | 0.25 - 2         | 100.0 / 0.0               | 100.0 / 0.0                 |

a. Criteria as published by the CLSI [2011] and EUCAST [2011].  $\beta$ -lactam susceptibility should be directed by the oxacillin test results.  
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2010].

## CONCLUSIONS

- Daptomycin was highly active against a large worldwide collection of *S. aureus* from osteoarticular infections.
- Due to its excellent anti-*S. aureus* spectrum, high potency and rapid bactericidal activity, daptomycin represents an excellent option for treatment (including OPAT) of *S. aureus* osteoarticular infections.

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