1828

# Update on Daptomycin Activity and Spectrum When Tested Against Gram-Positive Strains Collected in European Medical Centers (2006)

HS SADER, PR RHOMBERG, TR FRITSCHE, RN JONES
JMI Laboratories, North Liberty, IA, USA

JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370
fax 319.665.3371
helio-sader@jmilabs.com

## ABSTRACT

**Objective**: As part of the Daptomycin Surveillance Program, we evaluated the in vitro activity of daptomycin against recent clinical isolates collected in Europe (2006). Daptomycin is a novel cyclic lipopeptide recently approved by European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI).

**Methods**: A total of 2,907 consecutive strains were collected in 24 medical centers located in nine European countries, Turkey and Israel. The organisms were isolated mainly from bloodstream infections (52%) and cSSSI (18%). The following pathogens were evaluated: *S. aureus* (SA; 31% oxacillin [OXA]-resistant [R]); coagulase-negative staphylococci (CoNS; 75% OXA-R), *E. faecalis* (EF; 1% vancomycin [VAN]-R), *E. faecium* (EFM; 14% VAN-R), beta-haemolytic *Streptococcus* spp. (BHS; 235), and viridans group *Streptococcus* spp. (VGS; 119). The strains were susceptibility (S) tested by broth microdilution methods in cation-adjusted Mueller-Hinton broth, additionally supplemented to 50 mg/L of calcium for daptomycin tests. Numerous comparators were also tested.

**Results**: Daptomycin was highly active against SA and CoNS ($MIC_{90}$, 0.5 mg/L) and its activity was not adversely affected by resistance to OXA or VAN. All staphylococcal strains were inhibited at the daptomycin S breakpoint of ≤1 mg/L. Daptomycin and linezolid were the only compounds active against all enterococci. Daptomycin was highly active against BHS ($MIC_{90}$, 0.25 mg/L) as were most comparison agents tested. Daptomycin was also very active against VGS ($MIC_{90}$, 0.5 mg/L).

| Organism (no. tested) | | Cumulative % inhibited at daptomycin MIC (mg/L) of: ≤0.25 | 0.5 | 1 | 2 | 4 | %S[a] |
|---|---|---|---|---|---|---|---|
| SA | OXA-S (1,014) | 88.4 | 99.5 | 100.0 | - | - | 100.0 |
| | OXA-R (465) | 75.7 | 99.4 | 100.0 | - | - | 100.0 |
| CoNS | OXA-S (131) | 72.0 | 96.2 | 100.0 | - | - | 100.0 |
| | OXA-R (388) | 68.3 | 98.7 | 100.0 | - | - | 100.0 |
| *Enterococcus* spp. | | | | | | | |
| | VAN-S (526) | 4.0 | 44.6 | 87.1 | 99.4 | 100.0 | 100.0 |
| | VAN-R (28) | 7.1 | 14.3 | 71.4 | 100.0 | - | 100.0 |
| BHS (235) | | 100.0 | - | - | - | - | 100.0 |
| VGS (119) | | 75.8 | 97.5 | 100.0 | - | - | 100.0 |

a. US-FDA/CLSI interpretive criteria.

**Conclusions**: Daptomycin was highly active (100.0% S) against the most clinically important Gram-positive pathogens causing cSSSI in European medical centers, including multi-drug resistant organisms. Continued wide geographic monitoring would be preferred to detect emerging daptomycin-R strains, especially among strains with compromised VAN activity.

## INTRODUCTION

With the increasing occurrence of vancomycin-resistant enterococci (VRE) and the emergence of *Staphylococcus aureus* strains with decreased susceptibility to vancomycin (hVISA, VISA and VRSA), new antimicrobial agents focused against Gram-positive cocci are required for therapy of infections caused by these multidrug-resistant (MDR) strains.

Daptomycin is a naturally occurring cyclic lipopeptide produced by *Streptomyces roseosporus* which has demonstrated activity against most Gram-positive bacterial species. A once-daily dosing regimen with a minimal side effect profile has made daptomycin a promising alternative for nosocomial infections. Daptomycin is active against a wide range of MDR strains for which there are few therapeutic alternatives, including VRE, methicillin-resistant *S. aureus* (MRSA), and *S. aureus* with decreased susceptibility to vancomycin.

Daptomycin has been approved by the United States Food and Drug Administration (US-FDA) and by the European Medicine Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24 hours. Daptomycin has a rapid bactericidal effect and has been approved for treatment of *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg every 24 hours. Despite the absence of human studies, daptomycin has also been used successfully to treat osteomylitis having minimal adverse events and low potential for the development of drug resistance. In contrast, daptomycin is not indicated for treatment of pneumonia due to its inhibition by naturally occurring pulmonary surfactants.

In the present study, we evaluated the antimicrobial susceptibility patterns of recent (2006) clinical Gram-positive bacteria collected from Europe and Middle East regions.

## MATERIALS AND METHODS

Bacterial isolates: A total of 2,907 non-duplicate Gram-positive pathogens were consecutively collected from patients hospitalized in 24 European medical centers in 2006. The medical centers are located in France (5), Germany (4), Ireland (2), Israel (1), Italy (3), Poland (1), Spain (2), Sweden (2), Switzerland (1), Turkey (2) and the United Kingdom (1). The main pathogens evaluated were: *S. aureus* (1,479 strains, 31.4% oxacillin-resistant); coagulase-negative staphylococci (CoNS; 519, 74.6% oxacillin-resistant), *Enterococcus* spp. (554, 5.1% vancomycin-resistant), ß- haemolytic streptococci (235), and viridans group streptococci (119).

Susceptibility testing: Daptomycin and more than 20 comparator agents were tested using the Clinical and Laboratory Standards Institute (CLSI) M7-A7 broth microdilution method. All strains were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. US-FDA and CLSI approved daptomycin susceptible breakpoints of ≤1 mg/L for staphylococci and streptococci and ≤4 mg/L for enterococci were used to categorize these Gram-positive organisms as susceptible. The following quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

## RESULTS

- Daptomycin was very active against oxacillin-susceptible and -resistant *S. aureus* ($MIC_{50}$ of 0.25 mg/L and $MIC_{90}$ of 0.5 mg/L for both pathogen groups). All staphylococcal isolates were inhibited at a daptomycin MIC of 1 mg/L or less, which is the susceptible breakpoint approved by the CLSI and US-FDA.
- Linezolid ($MIC_{50}$ and $MIC_{90}$, 2 mg/L), teicoplanin ($MIC_{50}$ and $MIC_{90}$, ≤2 mg/L), and vancomycin ($MIC_{50}$ and $MIC_{90}$, 1 mg/L) were also active against all isolates at the CLSI breakpoint. Decreased susceptibility to quinupristin/dalfopristin was observed, but restricted to one medical center located in France (seven strains).
- Daptomycin activity against CoNS was similar to that observed against *S. aureus* and all isolates were inhibited at daptomycin susceptible breakpoint of ≤1 mg/L. Vancomycin ($MIC_{50}$, 1 mg/L and $MIC_{90}$, 2 mg/L) was also active against all strains, while decreased susceptibility for teicoplanin was noted in several countries.
- Daptomycin was highly active against *E. faecalis* strains ($MIC_{50}$, 0.5 mg/L and $MIC_{90}$, 1 mg/L). All vancomycin-non-susceptible strains (only three tested) were susceptible to daptomycin with MIC values of 0.25 (two strains) and 1 mg/L (one strain). Ampicillin ($MIC_{90}$, 2 mg/L; 98.9% susceptible) was also very active against *E. faecalis* and only 0.5% of strains showed high-level resistance to either or both tested glycopeptides.
- All *E. faecium* isolates were susceptible to daptomycin ($MIC_{50}$, 1 mg/L and $MIC_{90}$, 2 mg/L) and vancomycin resistance (16.1%) did not adversely influence daptomycin activity.
- *E. faecium*, especially vancomycin-resistant strains (16.1%), showed high rates of resistance to most antimicrobial agents tested. In general, only 67.8% of *E. faecium* strains were susceptible to quinupristin/dalfopristin and 42.6% of strains showed high-level resistance to gentamicin. The majority of strains with decreased susceptibility to quinupristin/dalfopristin were observed in Germany and Italy.
- Daptomycin was very potent against ß-haemolytic streptococci with an MIC range of ≤0.06 to 0.25 mg/L. This organism group was also very susceptible to most antimicrobial agents tested.
- Viridans group streptococci ($MIC_{50}$, 0.12 mg/L and $MIC_{90}$, 0.5 mg/L) showed daptomycin MIC values slightly higher (two-fold) than ß-haemolytic streptococci and all isolates were inhibited by daptomycin concentration of 1 mg/L or less.

**Table 1.** Antimicrobial activity of daptomycin and comparator agents tested against bacterial isolates collected from patients hospitalized in European hospitals (2006).

| Organism (no. tested) | MIC (mg/L) 50% | 90% | % Susceptible[a] | % Resistant[a] |
|---|---|---|---|---|
| *S. aureus* | | | | |
| Oxacillin-susceptible (1,014) | | | | |
| Daptomycin | 0.25 | 0.5 | 100.0 | -[b] |
| Erythromycin | ≤0.25 | >4 | 85.5 | 13.7 |
| Clindamycin | ≤0.25 | ≤0.25 | 97.6 | 2.3 |
| Levofloxacin | ≤0.5 | ≤0.5 | 91.8 | 7.5 |
| Quinupristin/dalfopristin | ≤0.25 | 0.5 | 99.8 | 0.2 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | 99.8 | 0.2 |
| Linezolid | 2 | 2 | 100.0 | - |
| Teicoplanin | ≤2 | ≤2 | 99.9 | 0.1 |
| Vancomycin | 1 | 1 | 100.0 | 0.0 |
| Oxacillin-resistant (465) | | | | |
| Daptomycin | 0.25 | 0.5 | 100.0 | - |
| Erythromycin | >4 | >4 | 27.7 | 71.8 |
| Clindamycin | ≤0.25 | >2 | 61.7 | 38.1 |
| Levofloxacin | >4 | >4 | 6.2 | 92.5 |
| Quinupristin/dalfopristin | 0.5 | 1 | 98.9 | 0.9 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | 96.6 | 3.4 |
| Linezolid | 2 | 2 | 100.0 | - |
| Teicoplanin | ≤2 | ≤2 | 100.0 | 0.0 |
| Vancomycin | 1 | 1 | 100.0 | 0.0 |
| CoNS | | | | |
| Oxacillin-susceptible (131) | | | | |
| Daptomycin | 0.25 | 0.5 | 100.0 | - |
| Erythromycin | ≤0.25 | >4 | 62.9 | 37.1 |
| Clindamycin | ≤0.25 | ≤0.25 | 94.7 | 4.5 |
| Levofloxacin | ≤0.5 | ≤0.5 | 93.1 | 5.3 |
| Quinupristin/dalfopristin | ≤0.25 | ≤0.25 | 100.0 | 0.0 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | 93.2 | 6.8 |
| Linezolid | 1 | 1 | 100.0 | - |
| Teicoplanin | ≤2 | ≤2 | 100.0 | 0.0 |
| Vancomycin | 1 | 2 | 100.0 | 0.0 |
| Oxacillin-resistant (388) | | | | |
| Daptomycin | 0.25 | 0.5 | 100.0 | - |
| Erythromycin | >4 | >4 | 24.0 | 75.5 |
| Clindamycin | ≤0.25 | ≤0.25 | 69.6 | 29.1 |
| Levofloxacin | 4 | >4 | 27.8 | 59.3 |
| Quinupristin/dalfopristin | ≤0.25 | 0.5 | 98.5 | 0.5 |
| Trimethoprim/sulfamethoxazole | 2 | >2 | 50.5 | 49.5 |
| Linezolid | 1 | 1 | 99.7[c] | - |
| Teicoplanin | ≤2 | 4 | 99.0 | 0.3 |
| Vancomycin | 1 | 2 | 100.0 | 0.0 |
| *E. faecalis* (399) | | | | |
| Daptomycin | 0.5 | 1 | 100.0 | - |
| Ampicillin | ≤1 | 2 | 98.2 | 1.8 |
| Gentamicin (HL) | ≤500 | >1000 | 64.2 | 35.8 |
| Quinupristin/dalfopristin | >2 | >2 | 2.3 | 94.0 |
| Linezolid | 1 | 2 | 100.0 | 0.0 |
| Teicoplanin | ≤2 | ≤2 | 99.2 | 0.5 |
| Vancomycin | 1 | 2 | 99.2 | 0.8 |
| *E. faecium* | | | | |
| Vancomycin-susceptible (130) | | | | |
| Daptomycin | 1 | 2 | 100.0 | - |
| Ampicillin | >16 | >16 | 9.2 | 90.8 |
| Gentamicin (HL) | ≤500 | >1000 | 56.2 | 43.8 |
| Quinupristin/dalfopristin | 1 | >2 | 67.7 | 20.8 |
| Linezolid | 1 | 2 | 100.0 | 0.0 |
| Teicoplanin | ≤2 | ≤2 | 100.0 | 0.0 |
| Vancomycin-resistant (25) | | | | |
| Daptomycin | 1 | 2 | 100.0 | - |
| Ampicillin | >16 | >16 | 0.0 | 100.0 |
| Gentamicin (HL) | ≤500 | >1000 | 64.0 | 36.0 |
| Quinupristin/dalfopristin | 1 | >2 | 68.0 | 20.0 |
| Linezolid | 1 | 2 | 100.0 | 0.0 |
| Teicoplanin | >16 | >16 | 28.0 | 72.0 |
| ß-haemolytic streptococci (235) | | | | |
| Daptomycin | ≤0.06 | 0.25 | 100.0 | - |
| Penicillin | ≤0.015 | 0.06 | 100.0 | - |
| Erythromycin | ≤0.25 | >2 | 80.0 | 19.6 |
| Clindamycin | ≤0.25 | 0.5 | 89.8 | 10.2 |
| Tetracycline | ≤2 | >8 | 51.9 | 46.4 |
| Levofloxacin | ≤0.5 | 1 | 100.0 | 0.0 |
| Linezolid | 1 | 1 | 100.0 | - |
| Viridans group streptococci (119) | | | | |
| Daptomycin | 0.12 | 0.5 | 100.0 | - |
| Penicillin | 0.06 | 0.5 | 85.7 | 3.4 |
| Erythromycin | ≤0.25 | >2 | 68.9 | 26.1 |
| Clindamycin | ≤0.25 | >2 | 86.6 | 13.4 |
| Tetracycline | ≤2 | >8 | 59.7 | 38.7 |
| Levofloxacin | 1 | 1 | 97.5 | 2.5 |
| Linezolid | 0.5 | 1 | 100.0 | - |

a. According to CLSI criteria.
b. - = no breakpoints have been established by the CLSI.
c. One isolate from Italy with MIC of 8 mg/L.

## CONCLUSIONS

- Daptomycin showed excellent in vitro activity against a wide variety of European Gram-positive pathogens and resistance to vancomycin, quinupristin/dalfopristin or oxacillin did not compromise its activity against enterococci or staphylococci.
- Daptomycin represents a valuable alternative for the treatment of serious infections caused by Gram-positive cocci, including MDR strains.

## SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2007). *M100-S17, Performance standards for antimicrobial susceptibility testing, 17th informational supplement*. Wayne, PA: CLSI.
2. Fuchs PC, Barry AL, Brown SD (2000). Daptomycin susceptibility tests: Interpretive criteria, quality control, and effect of calcium on in vitro tests. *Diagn Microbiol Infect* Dis 38: 51-58.
3. Johnson AP, Mushtaq S, Warner M, Livermore DM (2004). Calcium-supplemented daptomycin Etest strips for susceptibility testing on Iso-Sensitest agar. *J Antimicrob Chemother* 53: 860-862.
4. Package insert. Cubicin (daptomycin for injection). Lexington MA. (Cubist Pharmaceuticals, Inc) 2003. Available at http://www.cubist.com/prescribe.htm Accessed on March 9, 2006.
5. Sader HS, Jones RN (2006). The activity of daptomycin against wild-type *Staphylococcus aureus* and strains with reduced susceptibility to vancomycin. *Clin Infect Dis* 43: 798-799.
6. Sader HS, Streit JM, Fritsche TR, Jones RN (2006). Antimicrobial activity of daptomycin tested against Gram-positive strains colleced from European medical centers in 2005: Results of the Daptomycin Surveillance Programme. 16th European Congress of Clinical Microbiology and Infectious Diseases, Nice, April 1-4.
7. Streit JM, Jones RN, Sader HS (2004). Daptomycin activity and spectrum: A worldwide sample of 6,737 clinical Gram-positive organisms. *J Antimicrob Chemother* 53: 669-674.

This study was funded by Novartis Pharmaceuticals