# Spectrum and Potency of Dalbavancin Tested Against 3,322 Gram-Positive Cocci Isolated in the USA Surveillance Program (2004)

RN JONES, HS SADER, TR FRITSCHE, MG STILWELL
JMI Laboratories, North Liberty, IA, USA

IDSA 2005
JMI Laboratories
Phone: 319-665-3370
Fax: 319-665-3371
email:ronald-jones@jmilabs.com

## AMENDED ABSTRACT

**Background:** Dalbavancin (DAL) is an injectable, bactericidal lipoglycopeptide with pharmacokinetics permitting weekly dosing. This regimen has been successful for skin and skin structure (SSSI) and catheter-related bloodstream infections (CR-BSI). Concurrent with clinical trials, DAL resistance (R) surveillance was initiated; results are reported for 2004.
**Methods:** 3,322 Gram-positive cocci were tested by CLSI broth microdilution methods against DAL and comparators. Species tested included: *S. aureus* (SA; 2102, 49% methicillin-R [MR]), coag-neg staphylococci (CoNS; 255, 82% MR), ß-haemolytic (BHS; 241) and vir gr streptococci (VGS; 46), all SSSI pathogens; and *S. pneumoniae* (SPN; 678). Results were compared to earlier DAL surveillance results in the USA (2002-2003).
**Results:** SA were variably R to erythromycin (ER; 62%), clindamycin (CM; 29%) and levofloxacin (LEVO; 42%). DAL was comparable in spectrum to vancomycin (VAN; 100% S). CoNS were more MR (82%), ER/CM-R (76/49%), tetracycline-R (TET; 12%) and trimethoprim/sulfamethoxazole-R (42%). MR did not affect DAL activity ($MIC_{90}$, 0.06 [MS] vs 0.06 - 0.12 µg/ml [MR]). Streptococci had lower DAL MICs ($MIC_{90}$, 0.03 µg/ml).

| | Cum. % inhibited at MIC (µg/ml) | | | | | | |
|---|---|---|---|---|---|---|---|
| Organism (no.) | ≤0.016 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 |
| *S. aureus* (2,102) | 1 | 46 | 98 | >99 | >99 | 100 | |
| CoNS (255) | 11 | 62 | 89 | 96 | 98 | >99 | 100 |
| BHS (241) | 69 | 91 | >99 | 100 | | | |
| VGS (46) | 78 | 100 | | | | | |

DAL was more active than comparators versus SSSI pathogens (no MIC > 1 µg/ml): VAN (16-32X), linezolid (8-32X) and quinupristin/dalfopristin (4-32X). SPN DAL MICs did not exceed 0.12 µg/ml. All DAL $MIC_{90}$ results were unchanged from 2002-2003 samples.
**Conclusions:** DAL exhibited greater activity than comparison glycopeptides, streptogramins and oxazolidinones against Gram-positive pathogens associated with SSSI or CR-BSI. DAL wild-type MIC distributions remain stable compared to prior surveillance years.

## INTRODUCTION

Dalbavancin is an injectable, bactericidal lipglycopeptide with pharmacokinetics that permit weekly dosing ($T_{1/2}$, ca. 8.5 days). Success in clinical trials has been achieved with dalbavancin against skin and skin structure (SSSI) infections and catheter-related bloodstream infections (CR-BSI). Among glycopeptides, dalbavancin's spectrum most resembles that of teicoplanin; however, it has greater potency, in particular vs. staphylococci. Troublesome organisms inhibited in vitro by dalbavancin are: methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant CoNS, streptococcal species including penicillin- or macrolide-resistant isolates, many other Gram-positive cocci and vancomycin-resistant enterococci (VRE; other than *vanA*).

An in vitro resistance surveillance program for dalbavancin was initiated in 2002 and the year 2004 results for the United States (USA) are presented here. A total of 3,322 Gram-positive cocci were tested, 2,644 derived from organisms causing SSSI and CR-BSI, using reference methods of the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS). Results for 2004 were compared to the dalbavancin activity documented for 2002 and 2003.

## MATERIALS AND METHODS

Organisms tested. A total of 3,322 clinical isolates of Gram-positive cocci were tested, each isolated in 2004. The distribution of species was: *S. aureus* (2,102; 1,061 MRSA), CoNS (255; 209 MR-CoNS), ß-haemolytic streptococci (241; 20% erythromycin-resistant), viridans group streptococci (46; 30% penicillin-non-susceptible) and 678 *Streptococcus pneumoniae*, 39% penicillin-non-susceptible. The phenotypes of these organisms were such that it was possible to determine the influence of various resistances on the activity of dalbavancin (Tables 1 and 2).

The organisms were isolated in 24 medical centers in the USA, locally identified and forwarded to the central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) for processing. Organism identification was confirmed by routine methods as well as by the Vitek System (Hazelwood, MO, USA), where needed.

Susceptibility testing. All organisms were tested for antimicrobial susceptibility by CLSI methods (M7-A6, 2003) on validated, dry-form panels produced by TREK Diagnostics (Cleveland, OH, USA). These panels were manufactured to generate equivalent MIC results to those produced in frozen-form CLSI tests with dalbavancin in Mueller-Hinton base broths (MHB) supplemented with 0.002% polysorbate-80, a surfactant. MHB was supplemented with 2 - 5% lysed horse blood when testing the fastidious streptococci.

The following antimicrobials were used as comparison agents during this investigation (15 drugs): oxacillin, penicillin, ceftriaxone, clindamycin, erythromycin, gentamicin, levofloxacin, linezolid, rifampin, quinupristin/dalfopristin (Synercid®), teicoplanin, tetracycline, trimethoprim/sulfamethoxazole (TMP/SMX) and vancomycin. The antibiogram for the *S. pneumoniae* strains was: penicillin (61.4% susceptible, 18.7% resistant), erythromycin (69.3% susceptible, 62.9% *mefA* phenotype); amoxicillin/clavulanate (90.1% susceptible); ceftriaxone (96.2% susceptible); cefepime (95.0% susceptible); levofloxacin (99.1% susceptible); tetracycline and doxycycline (85.4% susceptible); TMP/SMX (74.9% susceptible); and 100% susceptible to vancomycin, linezolid and Synercid® (only co-resistance data is shown in Table 2). Daptomycin was added to the protocol in 2004.

The results were compared to dalbavancin surveillance data previously reported for 2002 and 2003 (Streit et al., 2004; Jones et al., 2004), and to in vitro data from Europe and South America (Gales et al., 2005; Mushtaq et al., 2004).

## RESULTS

- Dalbavancin was the most potent agent tested against *S. aureus* with the lowest $MIC_{90}$ (0.06 µg/ml) and concentration inhibiting all strains ($MIC_{100}$, 0.5 µg/ml; see Table 1).
- Dalbavancin's activity against CoNS isolates was similar to *S. aureus* and again it exhibited greater potency and lower $MIC_{100}$ (1 µg/ml) than comparators (Table 1).
- Streptococci were inhibited by very low concentrations of dalbavancin, with $MIC_{50}$ of ≤ 0.008 to 0.016 µg/ml for different groups of organisms.
- Dalbavancin was generally 16- to 32-fold more active than vancomycin, eight- to 16-fold more active than linezolid, four- to 32-fold more active than daptomycin and four- to 32-fold more active than Synercid® across all tested Gram-positive species in 2004.
- As summarized in Table 2, resistance to penicillins among staphylococci or streptococci had no effect on the dalbavancin MIC results.
- In the three (3) years of the dalbavancin surveillance program in the USA, the MIC values of the wild-type susceptible population has remained stable for those pathogens associated with SSSI and CR-BSI (Table 3).
- Figure 1 shows the distributions of the dalbavancin MIC results for the tested staphylococci (2,357 strains) and two groups of streptococci (287 strains) from the 2004 sample. A very narrow range of dalbavancin MICs (within 2 or 3 $\log_2$ dilutions for the great majority of isolates) was observed for each pathogen group.

**Table 1.** Antimicrobial activity of dalbavancin compared to 15 other antimicrobials against 2,644 Gram-positive cocci associated with SSSI and CR-BSI isolated in 2004 (USA).

| | Cumulative % of isolates inhibited at MIC (µg/ml) | | | | | | | | MIC (µg/ml) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Organism (no. tested) /antimicrobial agent | ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 50% | 90% |
| *S. aureus* (2,102) | | | | | | | | | | |
| Dalbavancin | 46 | 98 | 99 | 99 | 100 | 100 | 100 | 100 | 0.06 | 0.06 |
| Oxacillin | -[a] | - | - | 11 | 45 | 50 | 51 | -[a] | 1 | >2 |
| Ceftriaxone | - | - | - | - | <1 | <1 | 7 | 49 | 8 | >32 |
| Clindamycin | - | 20 | 70 | 71 | 71 | 71 | 71 | 71 | 0.12 | >8 |
| Daptomycin | 0 | 0 | 1 | 47 | 99 | >99 | 100 | 100 | 0.5 | 0.5 |
| Erythromycin | - | <1 | 1 | 37 | 38 | 38 | 38 | 39 | >8 | >8 |
| Gentamicin | - | - | - | - | - | - | 95 | 96 | ≤2 | ≤2 |
| Levofloxacin | <1 | 4 | 39 | 56 | 58 | 58 | 60 | 68 | 0.25 | >4 |
| Linezolid | - | - | - | - | <1 | 28 | 100 | 100 | 2 | 2 |
| Rifampin | - | - | - | - | 97 | 98 | 98 | - | ≤0.5 | ≤0.5 |
| Synercid® | - | - | - | 43 | 97 | >99 | >99 | - | 0.5 | 0.5 |
| Teicoplanin | - | - | <1 | 6 | 64 | 96 | >99 | >99 | 0.5 | 1 |
| Tetracycline | - | - | - | 63 | 92 | 94 | 95 | 95 | ≤0.25 | 0.5 |
| TMP/SMX[c] | - | - | - | - | 96 | 98 | 98 | - | ≤0.5 | ≤0.5 |
| Vancomycin | - | - | - | <1 | 14 | 98 | >99 | >99 | 1 | 1 |
| Coagulase-negative staphylococci (255) | | | | | | | | | | |
| Dalbavancin | 62 | 89 | 96 | 98 | 99 | 100 | 100 | 100 | 0.03 | 0.12 |
| Oxacillin | - | - | - | 18 | 21 | 28 | 40 | - | >2 | >2 |
| Ceftriaxone | - | - | - | - | 1 | 9 | 16 | 25 | 16 | >32 |
| Clindamycin | - | 42 | 49 | 50 | 51 | 51 | 52 | 52 | 0.5 | >8 |
| Daptomycin | 0 | 0 | 1 | 28 | 91 | >99 | 100 | 100 | 0.5 | 0.5 |
| Erythromycin | - | 1 | 11 | 24 | 24 | 24 | 24 | 24 | >8 | >8 |
| Gentamicin | - | - | - | - | - | - | 51 | 64 | 2 | >8 |
| Levofloxacin | 0 | 1 | 19 | 46 | 50 | 50 | 52 | 60 | 0.5 | >4 |
| Linezolid | - | - | - | <1 | 32 | 97 | 100 | 100 | 1 | 1 |
| Rifampin | - | - | - | - | 93 | 93 | 94 | - | ≤0.5 | ≤0.5 |
| Synercid® | - | - | - | 79 | 98 | 100 | 100 | - | ≤0.25 | 0.5 |
| Teicoplanin | - | - | 2 | 12 | 20 | 36 | 59 | 86 | 2 | 8 |
| Tetracycline | - | - | - | 42 | 57 | 70 | 88 | 90 | 0.5 | >8 |
| TMP/SMX[c] | - | - | - | - | 58 | 59 | 64 | - | ≤0.5 | >2 |
| Vancomycin | - | - | - | - | 4 | 56 | 100 | 100 | 1 | 2 |
| ß-haemolytic streptococci (241) | | | | | | | | | | |
| Dalbavancin | 91 | 99 | 100 | 100 | 100 | 100 | 100 | 100 | 0.016 | 0.03 |
| Penicillin | 80 | 99 | 100 | 100 | 100 | 100 | 100 | 100 | ≤0.016 | ≤0.016 |
| Ceftriaxone | - | - | - | 99 | 100 | 100 | 100 | 100 | ≤0.25 | ≤0.25 |
| Clindamycin | - | 91 | 91 | 91 | 91 | 91 | 91 | 92 | ≤0.06 | ≤0.06 |
| Daptomycin | - | 49 | 62 | 92 | 100 | 100 | 100 | 100 | 0.12 | 0.25 |
| Erythromycin | - | 79 | 80 | 80 | 80 | 82 | 88 | 89 | ≤0.06 | 8 |
| Levofloxacin | 0 | 0 | 0 | 5 | 80 | 96 | 98 | 98 | 0.5 | 1 |
| Linezolid | - | - | 0 | <1 | 8 | 99 | 100 | 100 | 1 | 1 |
| Rifampin | - | - | - | - | 100 | 100 | 100 | - | ≤0.5 | ≤0.5 |
| Synercid® | - | - | - | 68 | 97 | 100 | 100 | - | ≤0.25 | 0.5 |
| Teicoplanin | - | - | - | 99 | 100 | 100 | 100 | 100 | ≤0.12 | ≤0.12 |
| Tetracycline | - | - | - | 47 | 51 | 52 | 52 | 54 | 0.5 | >8 |
| TMP/SMX[c] | - | - | - | - | 99 | 100 | 100 | - | ≤0.5 | ≤0.5 |
| Vancomycin | - | - | - | 41 | 97 | 100 | 100 | 100 | 0.5 | 0.5 |
| viridans group streptococci (46) | | | | | | | | | | |
| Dalbavancin | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | ≤0.008 | 0.03 |
| Penicillin | 41 | 65 | 70 | 78 | 80 | 85 | 94 | 96 | 0.06 | 2 |
| Ceftriaxone | - | - | - | 78 | 85 | 94 | 98 | 98 | ≤0.25 | 1 |
| Clindamycin | - | 87 | 89 | 89 | 89 | 89 | 91 | 91 | ≤0.06 | 2 |
| Daptomycin | - | 9 | 22 | 52 | 89 | 100 | 100 | 100 | 0.25 | 0.5 |
| Erythromycin | - | 48 | 50 | 52 | 52 | 63 | 83 | 94 | 0.12 | 4 |
| Levofloxacin | 2 | 2 | 4 | 11 | 59 | 96 | 98 | 98 | 0.5 | 1 |
| Linezolid | - | - | 2 | 11 | 37 | 96 | 100 | 100 | 1 | 1 |
| Rifampin | - | - | - | - | 96 | 96 | 96 | - | ≤0.5 | >2 |
| Synercid® | - | - | - | 26 | 72 | 94 | 100 | - | 0.5 | 1 |
| Teicoplanin | - | - | 100 | 100 | 100 | 100 | 100 | 100 | ≤0.12 | ≤0.12 |
| Tetracycline | - | - | - | 30 | 50 | 59 | 67 | 72 | 0.5 | >8 |
| TMP/SMX[c] | - | - | - | - | 78 | 85 | 85 | - | ≤0.5 | >2 |
| Vancomycin | - | - | 2 | 17 | 76 | 100 | 100 | 100 | 0.5 | 1 |

a. - = MIC not tested.
b. Underline percentage is at the CLSI (2005) breakpoint, if on the test scale listed.
c. TMP/SMX = trimethoprim/sulfamethoxazole at a 1:19 ratio, only the TMP concentration is listed.

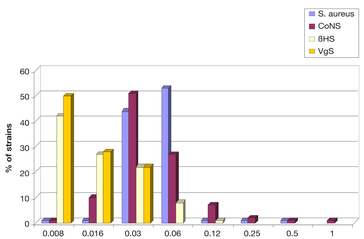
**Table 2.** Effect of resistance to penicillins on the activity of dalbavancin.

| | Dalbavancin (µg/ml) | | |
|---|---|---|---|
| Organism/resistance pattern (no. tested) | 50% | 90% | 100% |
| *S. aureus* | | | |
| oxacillin-resistant (1,061) | 0.06 | 0.06 | 0.25 |
| oxacillin-susceptible (1,041) | 0.06 | 0.06 | 0.5 |
| Coagulase-negative staphylococci | | | |
| oxacillin-resistant (209) | 0.03 | 0.06 | 0.25 |
| oxacillin-susceptible (46) | 0.03 | 0.12 | 1 |
| *S. pneumoniae* | | | |
| penicillin-resistant (127) | 0.016 | 0.016 | 0.03 |
| penicillin-intermediate (135) | 0.016 | 0.03 | 0.12 |
| penicillin-susceptible (416) | 0.016 | 0.03 | 0.06 |

**Table 3.** Comparisons of selected $MIC_{50/90}$ results for USA isolates in the dalbavancin surveillance programs for 2002 - 2004 (8,954 strains).

| | $MIC_{50/90}$ (µg/ml) by year of sample: | | |
|---|---|---|---|
| Organism (no. tested) | 2002 | 2003 | 2004 |
| *S. aureus* (6,634) | 0.06/0.06 | 0.03/0.06 | 0.06/0.06 |
| CoNS (1,424) | 0.03/0.06 | 0.03/0.06 | 0.03/0.12 |
| Streptococci | | | |
| ß-haemolytic (650) | ≤0.016/0.06 | ≤0.008/0.03 | 0.016/0.03 |
| viridans group (246) | ≤0.016/0.03 | ≤0.008/0.03 | ≤0.008/0.03 |

**Figure 1:** Dalbavancin MIC distributions of four pathogen groups associated with SSSI or CR-BSI (2,644 strains isolated in 2004).




## CONCLUSIONS

- Dalbavancin was the most potent agent tested against year 2004 USA isolates of Gram-positive pathogens that are associated with SSSI and CR-BSI indications.
- Dalbavancin showed no evidence of change in the susceptible wild-type population MIC values over the three (3) years of the surveillance program in the USA.
- Dalbavancin MIC distributions remain narrow and easy to monitor for emerging resistant organisms among potentially indicated genus or species groups.
- Dalbavancin resistance surveillance should be continued as this potent agent is approved for once-weekly regimens by regulatory agencies worldwide.

## SELECTED REFERENCES

Anderegg TR, Biedenbach DJ, Jones RN. (2003) The Quality Control Working Group. Initial quality control evaluations for susceptibility testing of dalbavancin (BI397), an investigational glycopeptide with potent Gram-positive activity. *Journal of Clinical Microbiology* 41:2795-2796.

Clinical and Laboratory Standards Institute. (2005) *Performance Standards for Antimicrobial Susceptibility Testing. Document M100-S15*. Wayne, PA:CLSI.

Gales AC, Sader HS, Jones RN. (2005) Antimicrobial activity of dalbavancin tested against Gram-positive clinical isolates from Latin American medical centers. *Clinical Microbiology Infection* 11:95-100.

Goldstein EJ, Citron DM, Merriam CV, Warren Y, Tyrrell K, Fernandez HT. (2003) In vitro activities of dalbavancin and nine-comparator agents against anaerobic Gram-positive species and corynebacteria. *Antimicrobial Agents and Chemotherapy* 47:1968-1971.

Jones RN, Biedenbach DJ, Johnson DM, Pfaller MA. (2001) In vitro evaluation of BI397, a novel glycopeptide antimicrobial agent. *Journal of Chemotherapy* 13:244-254.

Jones RN, Sader HS, Fritsche TR, Stilwell M. (2004) Comparative activity of dalbavancin tested against 7,771 isolates from the USA and Europe (2003), abstr #E-2009. In: *Programs and Abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Washington, DC:American Society for Microbiology.

Jones RN, Streit JM, Fritsche TR. (2004) Validation of commercial dry-form broth microdilution panels and test reproducibility for susceptibility testing of dalbavancin, a new very long-acting glycopeptide. *International Journal of Antimicrobial Agents* 23:197-199.

Malabarba A, Goldstein BP. (2005) Origin, structure and activity in vitro and in vivo of dalbavancin. *Journal of Antimicrobial Chemotherapy* 55(Suppl S2):ii15-ii-20.

Mushtaq S, Warner M, Johnson AP, Livermore DM. (2004) Activity of dalbavancin against staphylococci and streptococci, assessed by BSAC and NCCLS agar dilution methods. *Journal of Antimicrobial Chemotherapy* 54:617-620.

National Committee for Clinical Laboratory Standards. (2003) *Performance Standards for Antimicrobial Susceptibility Testing. Document M7-A6*. Wayne, PA:NCCLS.

Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H, Goldstein B, Henkel T, Seltzer E. (2005) Efficacy and safety of weekly dalbavancin in the treatment of catheter-related bloodstream infections. *Clinical Infectious Disease* 40:374-380.

Seltzer E, Dorr MB, Goldstein BP, Perry M, Dowell JA, Henkel T. (2003) Once-weekly dalbavancin versus standard of care antimicrobial regimens for treatment of skin and soft tissue infections. *Clinical Infectious Disease* 37:1298-1303.

Streit JM, Fritsche TR, Sader HS, Jones RN. (2004) Worldwide assessment of dalbavancin activity and spectrum against over 6,000 clinical isolates. *Diagnostic Microbiology and Infectious Disease* 48:137-143.