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Dalbavancin Activity Tested Against Rarely Isolated Gram-positive Organism Species from Europe

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ABSTRACT

Objectives: To determine the in vitro dalbavancin activity against European isolates of Gram-positive species that may rarely be pathogens in significant infections. A large surveillance platform was utilized (SENTRY Antimicrobial Surveillance Program) to evaluate over 1,300 strains (≥10 isolates/species) tested by reference (CLSI) methods against dalbavancin and selected comparators.

Methods: A total of 1,314 strains were available for dalbavancin testing, all isolated since 2003. Only those species (26) with at least 10 isolates were considered representative. A total of 30 locations contributed strains from 13 countries, all tested by broth microdilution method (CLSI) with appropriate solvents and polysorbate-80 (0.002%). Quality control results with *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619 were within published ranges.

Results: The distribution of tested strains was: *Bacillus* spp. (19), *Corynebacterium* spp. (31), enterococci other than *E. faecalis/faecium* (82; 4 species), *Listeria* spp. (24), CoNS (699, 8 species), *Micrococcus* spp. (21) and streptococci not pneumococci or beta-haemolytic (439; 10 species). The overall dalbavancin MIC_{90} was ≤0.03 mg/L and the MIC_{90} results ranged from ≤0.03 (streptococci, micrococci) to 0.25 mg/L (*S. haemolyticus* and *S. warnerii*). These results were comparable to the MIC_{90} results for the most studied dalbavancin-indicated species (beta-haemolytic streptococci and *S. aureus*; MICs, 0.03-0.06 mg/L). Examples of specific species (≥50 strains) and their MIC_{90} (in mg/L) are: *Staphylococcus capitis* (0.06), *S. hominis* (0.06), *Streptococcus anginosus* (≤0.03), *S. bovis* (0.06), *S. mitis* (≤0.03), *S. oralis* (0.06) and *S. parasanguis* (≤0.03). All four enterococcal species (*avium*, *casseliflavus*, *durans*, and *gallinarum*) had the same MIC_{90} at 0.12 mg/L.

Table. Activity of dalbavancin against 1,314 uncommonly isolated Gram-positive species (Europe 2002-2006).

	MIC (mg/L)		
Organism (no. tested)	50%	90%	Range
B. cereus (19)	≤0.03	0.12	≤0.03-0.12
Corynebacterium spp. (31)	0.06	0.12	≤0.03-0.25
Enterococci (82; 4 spp.)	0.06	0.12	≤0.03-0.25
L. monocytogenes (24)	0.06	0.06	≤0.03-0.12
M. luteus (21)	≤0.03	≤0.03	≤0.03-0.06
CoNS (699; 8 spp.)	≤0.03	0.12	≤0.03-0.5
Streptococci (439; 10 spp.)	≤0.03	≤0.03	≤0.03-0.06

Conclusions: Dalbavancin exhibited a wide and potent spectrum of activity (MIC_{90} range, ≤0.03-0.25 mg/L) against European strains of 26 rarely isolated Gram-positive organisms other than the usual indicated species (e.g. *S. aureus* or *S. pyogenes*). Generally, the most dalbavancin-susceptible organisms were streptococci species (viridians group) and *M. luteus*; while *S. haemolyticus* showed the most elevated MIC values (0.5 mg/L). Dalbavancin demonstrated a wide potential application as therapy for Gram-positive infections encountered in European medical centers.

INTRODUCTION

Dalbavancin is a novel, lipoglycopeptide antimicrobial agent indicated for the treatment of moderate to severe skin and skin structure infections (SSSIs) caused by Gram-positive organisms. The most common and important Gram-positive pathogens associated with SSSIs are *Staphylococcus* spp. and *Streptococcus* spp. High staphylococcal prevalence and elevated oxacillin resistance rates have been detected from dalbavancin clinical trials studying SSSIs. A phase 2 proof-of-concept study conducted in the United States (USA) showed that *S. aureus* was the most commonly isolated pathogen (83%) with an oxacillin resistance rate of 38%, similar to surveillance data generated from the USA SENTRY Antimicrobial Surveillance Program for the same years.

Dalbavancin has an extremely long elimination half-life and is administered intravenously at one gram on day one followed by a 500 mg dose on day eight. This treatment regimen was shown to be clinically and microbiologically efficacious and comparable to twice daily linezolid therapy administered over a 14 day period. Dalbavancin exhibits excellent in vitro activity against *Staphylococcus* spp. (MIC_{90}, 0.06-0.12 mg/L), including strains resistant to oxacillin and has been shown to be bactericidal without a propensity towards development of resistance during in vitro serial-passage studies. This compound also has demonstrated activity against staphylococci that are resistant to other drug classes. The USA Food and Drug Administration (FDA) recently issued dalbavancin a marketable letter. Susceptible breakpoints have been proposed by the sponsor for staphylococci at ≤1 mg/L and for streptococci at ≤2 mg/L (no resistance criteria). Utilizing these tentative breakpoints, data generated by numerous published studies have assessed the activity of dalbavancin in multiple geographic regions, each showing that resistance to dalbavancin was extremely rare and does not readily develop in vitro.

These susceptibility criteria will also be helpful for clinical laboratories in guiding therapy for indicated Gram-positive infections; however, numerous other non-indicated Gram-positive pathogens could require dalbavancin as a treatment option due to potential intolerance of other agents or frank resistance. To address this therapeutic possibility, we expand the knowledge of dalbavancin activity and spectrum by studying the compound against 1,314 Gram-positive strains uncommonly isolated from contemporary clinical infections in European patients.

MATERIALS AND METHODS

The unusual organisms (1,314 strains; 26 species) were obtained by the SENTRY Program (2003-2006) from infections cultured in Europe (30 sites in 13 nations). All strains were processed in a central reference laboratory study design using CLSI M7-A7 broth microdilution methods. The cation-adjusted Mueller-Hinton broth was supplemented with 2-5% lysed horse blood when testing fastidious species and all panels contained 0.002% polysorbate-80 surfactant for accurate MIC testing of dalbavancin.

To interpret the susceptibility of these infrequently encountered species, tentative breakpoints for organisms of a similar genus (e.g. streptococci or staphylococci) were applied for comparative purposes only. Also, staphylococci and enterococci with dalbavancin MIC results of ≥0.5 mg/L were repeated to establish reproducible MIC values that occurred nearest to the proposed breakpoints. All tests had concurrent quality control (QC) performed with CLSI recommended strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619). All QC results were within established MIC ranges.

RESULTS

- Dalbavancin MIC values for the 26 Gram-positive species were distributed across a narrow range from ≤0.03 to 0.5 mg/L (Table 1).
- Generally, the lowest dalbavancin MIC_{90} results were reported for the streptococci (MIC_{50}, ≤0.03 mg/L) and *Micrococcus luteus* (MIC_{50}, ≤0.03 mg/L) with the highest MIC_{90} results for the four enterococcal species (0.12 mg/L).
- Among eight CoNS species, dalbavancin MIC results (MIC_{90} range, 0.06-0.25 mg/L) were similar to those found for *S. aureus* in earlier in vitro studies and clinical trials.
- The highest MIC and MIC_{90} results for dalbavancin were recorded for *S. haemolyticus* strains.

Table 1. Dalbavancin MIC distributions for uncommonly isolated Gram-positive pathogens from patients in Europe (1,314 strains).

	MIC occurrences at:						MIC (mg/L)	
Organism (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	50%	90%
Bacillus cereus (19)	9	4	6	0	0	0	≤0.03	0.12
Corynebacterium spp. (31)	14	10	6	1	0	0	0.06	0.12
Enterococcus avium (17)	2	9	6	0	0	0	0.06	0.12
Enterococcus casseliflavus (15)	2	11	1	1	0	0	0.06	0.12
Enterococcus durans (16)	10	4	2	0	0	0	≤0.03	0.12
Enterococcus gallinarum (34)	5	16	12	1	0	0	0.06	0.12
Listeria monocytogenes (24)	5	18	1	0	0	0	0.06	0.06
Micrococcus luteus (21)	20	1	0	0	0	0	≤0.03	≤0.03
Staphylococcus capitis (80)	68	11	1	0	0	0	≤0.03	0.06
Staphylococcus haemolyticus (237)	49	64	78	42	4	0	0.12	0.25
Staphylococcus hominis (180)	140	33	5	2	0	0	≤0.03	0.06
Staphylococcus lugdunensis (45)	33	12	0	0	0	0	≤0.03	0.06
Staphylococcus saprophyticus (43)	16	14	12	1	0	0	0.06	0.12
Staphylococcus simulans (29)	23	4	1	1	0	0	≤0.03	0.06
Staphylococcus warneri (44)	19	18	4	5	0	0	≤0.03	0.25
Staphylococcus xylosis (41)	22	16	3	0	0	0	≤0.03	0.06
Streptococcus anginosus (57)	56	1	0	0	0	0	≤0.03	≤0.03
Streptococcus bovis (56)	49	7	0	0	0	0	≤0.03	0.06
Streptococcus constellatus (38)	38	0	0	0	0	0	≤0.03	≤0.03
Streptococcus intermedius (13)	13	0	0	0	0	0	≤0.03	≤0.03
Streptococcus milleri (28)	28	0	0	0	0	0	≤0.03	≤0.03
Streptococcus mitis (95)	92	3	0	0	0	0	≤0.03	≤0.03
Streptococcus oralis (65)	57	8	0	0	0	0	≤0.03	0.06
Streptococcus parasanguis (10)	10	0	0	0	0	0	≤0.03	≤0.03
Streptococcus salivarius (36)	34	2	0	0	0	0	≤0.03	≤0.03
Streptococcus sanguis (40)	40	0	0	0	0	0	≤0.03	≤0.03

CONCLUSIONS

- The new lipoglycopeptide, dalbavancin, was very active against the 1,314 strains of uncommonly isolated Gram-positive species (overall MIC_{50}, ≤0.03 mg/L) having a potency comparable to indicated species such as *S. aureus* and ß-haemolytic streptococci.
- No dalbavancin non-susceptible strains (MIC, >2 mg/L) were identified. The highest MIC results were for CoNS, especially *S. haemolyticus* strains (MIC_{90}, 0.5 mg/L; Table 1).
- These results demonstrate the breadth of dalbavancin potency against contemporary Gram-positive species isolated from infected patients in European medical centers (30; 13 nations).

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