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Activities of Dalbavancin against a Worldwide Collection of 81,673 Gram-Positive Bacterial Isolates▽

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Dalbavancin, a long-acting lipoglycopeptide, was evaluated against 81,673 isolates of staphylococci, enterococci, and streptococci collected from 33 countries during worldwide resistance surveillance (2002 to 2007). Regardless of susceptibility to oxacillin, comparable potencies for dalbavancin against *Staphylococcus aureus* and coagulase-negative staphylococci from all countries were noted (MIC_{90}, 0.06 to 0.12 μg/ml). Vancomycin-susceptible *Enterococcus* spp. had dalbavancin MIC_{90}s comparable to those for staphylococci, whereas vancomycin-resistant strains were more resistant (MIC_{50}, >4 μg/ml). β-Hemolytic and viridians group streptococci were very susceptible to dalbavancin (MIC_{90}, ≤0.03 μg/ml). Overall, dalbavancin was ≥16-fold more active than vancomycin against the monitored gram-positive species.

Skin and skin structure infections (SSSI) are most commonly caused by gram-positive pathogens, and the most significant organism is *Staphylococcus aureus* (9). This species has become increasingly resistant to numerous antimicrobial classes over the last several decades. Oxacillin (β-lactam)-resistant *S. aureus* presents a serious treatment dilemma for both community-acquired and nosocomial SSSI since most strains are multidrug resistant. Macrolide-lincosamide-streptogramin B (MLS_B) resistance, including inducible clindamycin resistance, in this species has also become problematic. Glycopeptide resistance at high and detectible levels (vancomycin-resistant *S. aureus*) has been documented, and vancomycin-intermediate *S. aureus* and heteroresistant vancomycin-intermediate *S. aureus* have been observed in many countries. β-Hemolytic streptococci (βHS) are also commonly isolated from wound cultures, and, although these species have remained susceptible to penicillins and advanced-generation cephalosporins, resistance to other antimicrobial classes such as MLS_B agents and tetracyclines is more prevalent (4, 9). Enterococci and coagulase-negative staphylococci (CoNS) can also be associated with SSSI, and viridians group streptococci (VGS) can be causes of oral abscesses and bacteremias (4, 9).

Dalbavancin is a novel lipoglycopeptide antimicrobial agent for which approval in the United States for the treatment of SSSI caused by selected gram-positive pathogens is being sought (8, 10). This long-acting agent is administered once weekly and is highly potent against the common species associated with SSSI, including many antimicrobial-resistant strains (14). Clinical trials have established that dalbavancin is comparable to "standard of care" therapies for the treatment of SSSI and yields successful microbiological responses (5, 12). Previous in vitro studies have documented that dalbavancin is a potent antimicrobial agent with activity against gram-positive clinical isolates (1, 6, 13). This investigation defines the activity of dalbavancin against a very large collection of recently collected gram-positive pathogens collected from medical centers located throughout the world and confirms the potency advantage that this new antimicrobial agent has over the commonly used vancomycin.

During a 6-year period (2002 to 2007), a total of 81,673 isolates of staphylococci, enterococci, βHS, and VGS were collected from 210 medical centers in 33 countries. North America contributed 37,085 isolates (45.4% of the collection) from 86 sites located in the United States (80) and Canada (6). European medical centers also provided a significant number of isolates (30.5%), with a total of 24,932 strains from 35 sites in 14 countries. Hospitals in the Asia-Pacific region (77 sites in 12 countries) and Latin America (12 sites in 5 countries) provided a smaller number of isolates, representing 11.9 and 12.2% of the collection, respectively. The majority (55.9%) of the isolates were collected from 2006 to 2007 (45,670 strains). Isolates were confirmed for appropriate species identification by each of the reference, monitoring laboratories, which included JMI Laboratories (North Liberty, IA) and Women's and Children's Hospital (North Adelaide, Australia).

MIC testing was performed with validated panels (TREK Diagnostics, Cleveland, OH) using the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) reference broth microdilution method (2, 7, 11). Categorization of susceptibility and resistance followed the CLSI criteria (3). Differentiation of vancomycin-resistant *Enterococcus* sp. isolates into VanA and VanB phenotypes excluded isolates with intermediate MICs for teicoplanin or vancomycin. Quality control utilized appropriate American Type Culture Collection (ATCC) strains, including *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619, to ensure the validity of all test results (3).

Dalbavancin (MIC_{90}, 0.06 μg/ml) was 16-fold more active than vancomycin (MIC_{90}, 1 μg/ml) against both oxacillin-susceptible and -resistant *S. aureus* isolates (Table 1). Dalbavancin displayed a similar potency advantage over vancomycin (16- to 32-fold) against the CoNS in this collection. Resistance to other antimicrobial classes, particularly among the oxacillin-resistant population, had no effect on the activity of dalbavan-

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TABLE 1. Activities of dalbavancin and comparator agents against 81,673 gram-positive cocci isolated from 33 countries worldwide

Organism or group and susceptibility subset (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[a]	% Resistant[b]
		50%	90%	Range		
S. aureus						
Oxacillin susceptible (27,052)	Dalbavancin	0.06	0.06	≤0.03–0.25	100.0	—
	Vancomycin	1	1	≤0.12–4	>99.9	0.0
	Erythromycin	≤0.25	>2	≤0.25–>2	78.7	20.7
	Clindamycin	≤0.25	≤0.25	≤0.25–>2	95.8	4.0
	Levofloxacin	≤0.5	≤0.5	≤0.5–>4	92.8	6.7
	Gentamicin	≤2	≤2	≤2–>8	97.1	2.6
	Tetracycline	≤4	≤4	≤4–>8	93.7	5.8
	Linezolid	2	2	0.12–4	100.0	—
Oxacillin resistant (19,721)	Dalbavancin	0.06	0.06	≤0.03–0.5	>99.9	—
	Vancomycin	1	1	0.25–4	>99.9	0.0
	Erythromycin	>2	>2	≤0.25–>2	10.9	88.8
	Clindamycin	>2	>2	≤0.25–>2	47.8	52.1
	Levofloxacin	>4	>4	≤0.5–>4	18.3	80.1
	Gentamicin	≤2	>8	≤2–>8	74.1	24.8
	Tetracycline	≤4	>8	≤4–>8	81.1	18.4
	Linezolid	1	2	≤0.25–>8	>99.9	0.04
CoNS						
Oxacillin susceptible (2,836)	Dalbavancin	≤0.03	0.06	≤0.03–1	99.8	—
	Vancomycin	1	2	≤0.12–4	100.0	0.0
	Erythromycin	≤0.25	>2	≤0.25–>2	66.0	33.6
	Clindamycin	≤0.25	≤0.25	≤0.25–>2	93.5	5.7
	Levofloxacin	≤0.5	4	≤0.5–>4	87.5	11.1
	Gentamicin	≤2	≤2	≤2–>8	95.0	3.1
	Tetracycline	≤4	>8	≤4–>8	86.7	12.6
	Linezolid	1	1	≤0.25–>8	99.9	—
Oxacillin resistant (9,472)	Dalbavancin	≤0.03	0.12	≤0.03–2	99.2	—
	Vancomycin	1	2	≤0.12–8	>99.9	0.0
	Erythromycin	>2	>2	≤0.25–>2	24.1	75.4
	Clindamycin	≤0.25	>2	≤0.25–>2	57.0	41.7
	Levofloxacin	4	>4	≤0.5–>4	31.8	61.4
	Gentamicin	4	>8	≤2–>8	50.7	35.3
	Tetracycline	≤4	>8	≤4–>8	83.4	15.8
	Linezolid	1	1	≤0.25–>8	99.5	—
E. faecalis						
Vancomycin susceptible (10,025)	Dalbavancin	≤0.03	0.06	≤0.03–0.5	>99.9	—
	Ampicillin	≤2	≤2	≤2–>16	99.6	0.2
	Ciprofloxacin	1	>4	0.06–>4	62.2	33.6
	Gentamicin (HL[c])	≤500	>1000	≤500–>1000	68.5	31.5
	Linezolid	1	2	≤0.25–>8	99.8	0.1
Vancomycin nonsusceptible (349)	Dalbavancin	>4	>4	≤0.03–>4	27.8	—
	Ampicillin	≤2	4	≤2–>16	96.0	4.0
	Ciprofloxacin	>4	>4	0.5–>4	3.7	96.3
	Gentamicin (HL)	>1000	>1000	≤500–>1000	28.4	71.6
	Linezolid	1	2	0.25–>8	98.6	1.4
E. faecium						
Vancomycin susceptible (2,578)	Dalbavancin	0.06	0.12	≤0.03–2	99.6	—
	Ampicillin	>16	>16	≤2–>16	15.6	84.4
	Ciprofloxacin	>4	>4	0.06–>4	8.1	83.7
	Gentamicin (HL)	≤500	>1000	≤500–>1000	61.8	38.2
	Linezolid	1	2	≤0.25–>8	99.6	0.3
Vancomycin nonsusceptible (2,176)	Dalbavancin	>4	>4	≤0.03–>4	11.4	—
	Ampicillin	>16	>16	≤2–>16	0.8	99.2
	Ciprofloxacin	>4	>4	≤0.03–>4	0.7	98.3
	Gentamicin (HL)	≤500	>1000	≤500–>1000	64.3	35.7
	Linezolid	1	2	0.5–>8	97.6	1.8
βHS (5,316)	Dalbavancin	≤0.03	≤0.03	≤0.03–0.25	100.0	—
	Vancomycin	0.5	0.5	≤0.12–1	100.0	—

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TABLE 1—*Continued*

Organism or group and susceptibility subset (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[a]	% Resistant[b]
		50%	90%	Range		
	Penicillin	≤0.015	0.06	≤0.015–1	99.9	—
	Ceftriaxone	≤0.25	≤0.25	≤0.25–4	99.9	—
	Erythromycin	≤0.25	>2	≤0.25–>2	79.6	19.9
	Clindamycin	≤0.25	≤0.25	≤0.25–>2	91.4	8.2
	Levofloxacin	≤0.5	1	≤0.5–>4	98.6	1.3
	Linezolid	1	1	≤0.25–2	100.0	—
VGS (2,148)	Dalbavancin	≤0.03	≤0.03	≤0.03–0.12	100.0	—
	Vancomycin	0.5	1	≤0.12–2	>99.9	—
	Penicillin	0.06	1	≤0.03–>32	71.7	6.0
	Ceftriaxone	≤0.25	1	≤0.25–>32	92.5	4.3
	Erythromycin	≤0.25	>2	≤0.25–>2	56.0	41.7
	Clindamycin	≤0.25	0.5	≤0.25–>2	89.8	9.5
	Levofloxacin	1	2	≤0.5–>4	95.7	3.6
	Linezolid	1	1	≤0.25–8	>99.9	—

[a] Susceptibility criteria of the CLSI (M100-S18 [3]) were used where available. For dalbavancin, a proposed susceptible breakpoint of ≤0.25 μg/ml for all species was applied for comparisons only with vancomycin.
[b] —, no resistant breakpoint criteria have been recommended.
[c] HL, high-level resistance.

cin against staphylococci. However, oxacillin-resistant CoNS had a slightly higher MIC_{90} (0.12 μg/ml), as demonstrated in Table 1.

Dalbavancin activity against vancomycin-susceptible *Enterococcus* sp. isolates was similar to that against *Staphylococcus* spp., with MIC_{90}s of 0.06 and 0.12 μg/ml for *E. faecalis* and *Enterococcus faecium*, respectively (Table 1). Overall, dalbavancin was less active against vancomycin-resistant strains although this agent was more potent against isolates exhibiting a VanB phenotype (MIC_{50}s, 0.06 to 0.12 μg/ml) than against those with a VanA phenotype (Table 2).

Dalbavancin was very active against VGS and βHS, with all MICs at ≤0.25 μg/ml, and only MLS_B agents (56.0 to 91.4%) and penicillin (71.7%, VGS only) had reduced activity against these species (Table 1). Group B streptococci (*Streptococcus agalactiae*) had slightly elevated dalbavancin MICs, with 90.3% of strains inhibited by ≤0.03 μg/ml, compared to group A, C, G, and F isolates, which were inhibited by ≤0.03 μg/ml at rates of 95.6 to 99.4% (Table 2).

Significant variation in the rates of oxacillin resistance among *S. aureus* isolates between geographic regions was observed, with higher rates detected in the United States (46.1%) and Asia-Pacific countries (44.2%) (Table 3). Medical centers in the United States had significantly higher rates of vancomycin-resistant *E. faecium* (73.3%) and *E. faecalis* (5.7%) isolates than those in Canada and sampled countries on other continents (Table 3).

In conclusion, dalbavancin was 8- to 32-fold more active than vancomycin overall against this large collection of commonly isolated gram-positive pathogens (81,673 strains) collected from diverse geographic regions. Resistance to other antimicrobial classes had no effect on the activity of dalbavancin, with the exception of resistance to vancomycin among *Enterococcus* spp., particularly those with a VanA resistance

TABLE 2. Activity of dalbavancin against vancomycin-resistant *Enterococcus* spp. and β-hemolytic *Streptococcus* spp.

Organism or group and resistance phenotype or serogroup (no. tested)	Cumulative % inhibited at MIC (μg/ml) of:							
	≤0.03	0.06	0.12	0.25	0.5	1	2	4
E. faecalis								
VanA (230)	0.4	0.9	2.6	3.9	4.3	4.3	7.4	14.8
VanB (84)	9.5	33.3	70.2	70.2	75.0	78.6	85.7	91.7
E. faecium								
VanA (1,744)	0.1	0.3	1.2	3.1	6.6	11.5	18.3	33.1
VanB (134)	26.1	56.0	71.6	77.6	85.1	90.3	94.0	97.8
βHS								
Group A (2,182)	98.8	99.9	>99.9	100.0				
Group B (2,265)	90.3	98.0	99.6	100.0				
Group C (174)	99.4	100.0						
Group G (502)	95.6	99.6	100.0					
Group F (35)	97.1	97.1	100.0					

TABLE 3. Variation in oxacillin and vancomycin resistance rates between geographic regions

Isolate type	% Resistance by country or continent[a]			
	Canada/United States	Europe	Latin America	Asia-Pacific
Oxacillin-resistant *S. aureus*	26.5/46.1	27.9	38.6	44.2
Vancomycin-resistant *E. faecalis*	0.8/5.7	1.6	4.4	0.9
Vancomycin-resistant *E. faecium*	13.2/73.3	22.1	30.7	15.8

[a] Resistance rates are based upon the CLSI-recommended breakpoints (M100-S18 [3]).

phenotype pattern. The potency advantage of dalbavancin compared to some class comparators, coupled with infrequent patient dosing, provides a unique therapeutic alternative for treating serious gram-positive infections, including those by oxacillin-resistant staphylococci and other species which are common causes of SSSI (5, 13).

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