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Activity of Dalbavancin Against >6000 *S. aureus*, *S. epidermidis*, *S. pneumoniae* and *Enterococcus* spp. isolated from Canadian Hospitals: CANWARD 2007-2009

B.WESHNOWESKI[1], R. VASHISHT[2], F.TAILOR[2], L.BITTNER[2], L.SCHARIKOW[2], G.G. Zhanel[2] and D.J. HOBAN[1,2]

Diagnostic Services of Manitoba-Health Sciences Centre[1] and the University of Manitoba[2], Winnipeg, Manitoba, Canada

Barb Weshnoweski
Health Sciences Centre
MS673 - 820 Sherbrook St.
Winnipeg, MB, Canada R3A 1R9
Phone: (204) 787-4696
Email: bweshnoweski@hsc.mb.ca

ABSTRACT

Background: Dalbavancin (DAL) is a new teicoplanin-related lipoglycopeptide with activity against Gram-positive organisms. The purpose of this study was to assess the activity of DAL, linezolid (LZD) and vancomycin (VAN) against Gram-positive pathogens isolated from Canadian hospitals.

Methods: CANWARD is an ongoing (2007-present) national surveillance study involving tertiary care hospitals representing 8 of 10 provinces within Canada. A total of 7956 Gram-positive pathogens were collected from all hospital ward types. Susceptibility testing was performed using CLSI broth microdilution methods.

Results:
The activity (MIC50 and MIC90 µg/ml) of DAL, LZD and VAN against select pathogens is described below:

Organism (n)	DAL	LZD	VAN
SPN - PenS (1117)	≤0.03/≤0.03	0.5/1	≤0.25/≤0.25
SPN - Peni (200)	≤0.03/≤0.03	0.5/1	≤0.25/0.5
SPN - PenR (61)	≤0.03/≤0.03	0.5/1	≤0.25/0.5
MSSA (2697)	0.06/0.06	2/2	1/1
CA-MRSA (223)	0.06/0.06	2/2	1/1
HA-MRSA (629)	0.06/0.06	2/2	1/1
MSSE (268)	≤0.03/0.06	0.5/1	1/2
MRSE (45)	≤0.03/0.06	1/1	2/2
***E. faecalis* (381)**	0.06/0.06	2/2	1/2
***E. faecium* (150)**	0.06/2	2/2	0.5/4
***Enterococcus* spp.(578)**	0.06/0.06	2/2	1/2
VRE (34)	8/>16	2/2	>32/>32

SPN=S.pneumoniae, PenS=penicillin-susceptible, PenI=penicillin-intermediate, PenR=penicillin-resistant, MSSA=methicillin-susceptible S. aureus, MR=methicillin-resistant, CA=community-associated, HA=healthcare-associated, SE=S. epidermidis, VRE=vancomycin-resistant enterococci.

Conclusions: Dalbavancin is more active than linezolid and vancomycin versus S. pneumoniae, MSSA, MRSA, MSSE, MRSE and Enterococcus spp.

MATERIALS & METHODS

Bacterial Isolates
From 2007 to 2009, each participating Canadian hospital submitted consecutive bacterial isolates collected from four specimen sources: urines, lower respiratory tract, wounds and blood cultures. Each site submitted 730, 540 and 365 isolates per year respectively. Total isolates received each year were 7881, 5282 and 5375 respectively (overall total 18,538).

Antimicrobial Susceptibilities
A custom microtitre panel was prepared in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines. Polysorbate 80 (0.002% final concentration) was added to both the stock solution of dalbavancin and cation-adjusted broth used for panels.
The following interpretive breakpoints (FDA) were used for tigecycline (µg/ml): MSSA and MRSA <=0.5 (S); *Enterococcus faecalis* <=0.25 (S); *Streptococcus pneumoniae* <=0.06 (S). MIC interpretive standards for the remaining antimicrobial agents were defined according to CLSI breakpoints (M100-19, 2009).

RESULTS

Table 1. Activity of dalbavancin and comparators against gram-positive cocci from CANWARD 2007-2009

Organism (n), Antibiotic	% of Isolates per Category S[a]	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
S. aureus							
MSSA (2697)							
Cefazolin	99.9		0.1	0.5	1	≤ 0.5	32
Clarithromycin	75	0.3	24.7	0.25	>16	≤ 0.25	>16
Clindamycin	91.8	0.5	7.7	≤ 0.25	≤ 0.25	≤ 0.25	>8
Dalbavancin	no BP[b]			0.06	0.06	≤ 0.03	0.25
Daptomycin	100			0.12	0.25	≤ 0.06	1
Levofloxacin	90.1	0.3	9.6	1	1	≤ 0.06	>32
Linezolid	100			2	2	≤ 0.12	4
Meropenem	100			0.12	0.25	≤ 0.12	4
Pip-Tazo	99.9		0.1	≤1	≤1	≤1	32
Tigecycline	99.8[d]			0.25	0.25	≤ 0.03	1
TMP/SMX	99.3		0.7	≤ 0.12	≤ 0.12	≤ 0.12	>8
Vancomycin	100			1	1	≤ 0.25	2
MRSA (889)							
Cefazolin			100	64	>128	1	>128
Clarithromycin	11.7	0.1	88.2	>16	>16	≤ 0.25	>16
Clindamycin	44	0.1	55.9	>8	>8	≤ 0.25	>8
Dalbavancin	no BP[b]			0.06	0.06	≤ 0.03	0.12
Daptomycin	100			0.12	0.25	≤ 0.06	1
Levofloxacin	14.1		85.9	>32	>32	0.12	>32
Linezolid	100			2	2	≤ 0.12	4
Meropenem			100	8	32	0.12	>32
Pip-Tazo			100	64	128	≤1	512
Tigecycline	99.3[d]			0.25	0.5	0.06	≤0.5
TMP/SMX	90.3		9.7	≤ 0.12	1	≤ 0.12	>8
Vancomycin	99.9	0.1		1	1	≤ 0.25	4
CA-MRSA (223)							
Cefazolin			100[c]	16	64	1	>128
Clarithromycin	26.9	0.5	72.6	>16	>16	≤ 0.25	>16
Clindamycin	86.1		13.9	≤ 0.25	>8	≤ 0.25	>8
Dalbavancin				0.06	0.06	≤ 0.03	0.12
Daptomycin	100.0			0.25	0.25	0.12	1
Levofloxacin	39.9		60.1	4	8	0.12	32
Linezolid	100.0			2	2	1	4
Meropenem			100	2	4	0.12	16
Pip-Tazo			100	16	32	2	64
Tigecycline	99.6[d]			0.25	0.25	0.06	1
TMP/SMX	100.0			≤ 0.12	≤ 0.12	≤ 0.12	2
Vancomycin	100.0			1	1	0.5	2
HA-MRSA (629)							
Cefazolin			100[c]	128	>128	1	>128
Clarithromycin	4.3		95.7	>16	>16	≤ 0.25	>16
Clindamycin	27.8	0.2	72.0	>8	>8	≤ 0.25	>8
Dalbavancin				0.06	0.06	≤ 0.03	0.12
Daptomycin	100.0			0.12	0.25	0.06	1
Levofloxacin	2.9		97.1	>32	>32	0.12	>32
Linezolid	100.0			2	2	≤ 0.12	4
Meropenem			100	16	>32	0.25	>32
Pip-Tazo			100	64	128	≤1	512
Tigecycline	99.2[d]			0.25	0.5	0.12	1
TMP/SMX	86.5		13.5	≤ 0.12	>8	≤ 0.12	>8
Vancomycin	99.8	0.2		1	1	≤ 0.25	4

Organism (n), Antibiotic	% of Isolates per Category S[a]	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
S.epidermidis							
MSSE (268)							
Cefazolin	100			1	4	≤ 0.5	8
Clarithromycin	34.4	2.2	63.4	>16	>32	≤ 0.03	>32
Clindamycin	62.3	0.4	37.3	≤ 0.25	>8	≤ 0.25	>8
Dalbavancin	no BP[b]			≤ 0.03	0.06	≤ 0.03	1
Daptomycin	100			0.12	0.25	≤ 0.03	1
Levofloxacin	51.9	1.1	47	2	>32	0.12	>32
Linezolid	100			0.5	1	≤ 0.12	2
Meropenem	84.0	10.0	6.0	1	8	≤ 0.06	32
Pip-Tazo	98.9		1.1	≤ 1	2	≤ 1	16
Tigecycline	no BP[b]			0.25	0.5	≤ 0.03	1
TMP/SMX	64.9		35.1	0.25	8	≤ 0.12	>8
Vancomycin	100			1	2	≤ 0.12	2
MRSE (45)							
Cefazolin			100	64	128	32	128
Clarithromycin	11.1		88.9	>16	>16	≤ 0.25	>16
Clindamycin	13.3		86.7	>8	>8	≤ 0.25	>8
Dalbavancin	no BP[b]			≤ 0.03	0.06	≤ 0.03	0.06
Daptomycin	100			0.12	0.25	≤ 0.06	0.5
Levofloxacin	2.2	2.2	95.6	>32	>32	1	>32
Linezolid	100			1	1	0.25	1
Meropenem			100	32	32	8	>32
Pip-Tazo			100	32	64	8	128
Tigecycline	no BP[b]			0.25	0.25	0.06	0.5
TMP/SMX	24.4		85.6	4	8	≤ 0.12	>8
Vancomycin	100			2	2	1	2
***S.pneumoniae* (1391)**							
Ceftriaxone	99.4	0.4	0.2	≤ 0.12	0.12	≤ 0.12	4
Clarithromycin	81.2	4.3	14.5	≤ 0.03	2	≤ 0.03	>32
Clindamycin	93.5	0.6	5.9	≤ 0.12	≤ 0.12	≤ 0.12	>8
Dalbavancin	no BP[b]			≤ 0.03	≤ 0.03	≤ 0.03	0.12
Doxycycline[e]	93.2	2.8	4	≤ 0.25	1	≤ 0.25	>16
Levofloxacin	99.0	0.2	0.8	1	1	≤ 0.06	32
Linezolid	100			0.5	1	≤ 0.12	2
Meropenem	96.4	2.5	1.1	≤ 0.06	≤ 0.06	≤ 0.06	2
Penicillin	81.1	14.5	4.4	≤ 0.03	0.25	≤ 0.03	>8
Tigecycline	100[d]			≤ 0.03	0.06	≤ 0.03	0.06
TMP/SMX	84.7	7	8.3	≤ 0.12	1	≤ 0.12	>8
Vancomycin	100			≤ 0.25	≤ 0.25	≤ 0.25	1
Penicillin-resistant *S.pneumoniae* (61)							
Ceftriaxone	90.1	6.6	3.3	0.5	1	≤ 0.12	4
Clarithromycin	41	3.3	55.7	I	>32	≤ 0.03	>32
Clindamycin	62.3	3.3	34.4	≤ 0.12	>8	≤ 0.12	>8
Dalbavancin	no BP[b]			≤ 0.03	≤ 0.03	≤ 0.03	≤ 0.03
Doxycycline	no BP[b]			I	4	≤ 0.25	>16
Levofloxacin	100			1	1	0.25	2
Linezolid	100			0.5	1	0.25	2
Meropenem	36.1	42.6	21.3	0.5	1	≤ 0.06	2
Penicillin			100	2	4	2	>8
Tigecycline	100[d]			0.03	0.06	≤ 0.03	0.06
TMP/SMX	21.3	8.2	70.5	4	>8	≤ 0.12	>8
Vancomycin	100			≤ 0.25	0.5	≤ 0.25	1

Organism (n), Antibiotic	% of Isolates per Category S[a]	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
***E. faecalis* (381)**							
Ciprofloxacin	45.4	19.2	35.4	2	>16	0.25	>16
Clarithromycin	no BP[b]			>16	>16	≤ 0.25	>16
Clindamycin	no BP[b]			>8	>8	≤ 0.12	>8
Dalbavancin	no BP[b]			0.06	0.06	≤ 0.03	0.25
Daptomycin	100			0.5	1	≤ 0.06	4
Ertapenem	no BP[b]			8	16	0.25	>32
Levofloxacin	65.6	1.1	33.3	2	>32	0.12	>32
Linezolid	99.5	0.5		2	2	0.5	4
Meropenem	no BP[b]			4	8	≤ 0.06	>32
Pip-Tazo	no BP[b]			4	8	≤1	512
Tigecycline	97.9[d]			0.12	0.25	0.06	0.5
Vancomycin	100			1	2	0.5	4
***E.faecium* (150)**							
Ciprofloxacin	6	4	90	>16	>16	0.5	>16
Clarithromycin	no BP[b]			>16	>16	0.12	>16
Clindamycin	no BP[b]			>8	>8	≤ 0.25	>8
Dalbavancin	no BP[b]			0.06	2	≤ 0.03	>16
Daptomycin	100			1	2	≤ 0.03	4
Ertapenem	no BP[b]			>4	>4	4	>4
Levofloxacin	10	1.3	88.7	>32	>32	1	>32
Linezolid	96	4		2	2	0.5	4
Meropenem	no BP[b]			>32	>32	2	>32
Pip-Tazo	no BP[b]			>512	>512	2	>512
Tigecycline	no BP[b]			0.12	0.12	≤ 0.03	2
Vancomycin	82.7		17.3	0.5	>32	≤ 0.25	>32
***Enterococcus*, non-speciated (578)**							
Ciprofloxacin	39.6	21.3	39.1	2	>16	≤ 0.06	>16
Clarithromycin	no BP[b]			>16	>16	≤ 0.25	>16
Clindamycin	no BP[b]			>8	>8	≤ 0.25	>8
Dalbavancin	no BP[b]			0.06	0.06	≤ 0.03	>16
Daptomycin	100			0.5	1	≤ 0.06	4
Ertapenem	no BP[b]			16	32	≤ 0.06	>32
Levofloxacin	62.1	0.5	37.4	2	>32	≤ 0.06	>32
Linezolid	97.8	2.2		2	2	≤ 0.12	4
Meropenem	no BP[b]			4	16	≤ 0.06	>32
Pip-Tazo	no BP[b]			4	8	≤1	>512
Tigecycline	no BP[b]			0.12	0.25	≤ 0.03	1
Vancomycin	98.6	0.1	1	2	≤ 0.25	≤ 0.25	>32
Vancomycin resistant *Enterococcus* (34)							
Ciprofloxacin			100	>16	>16	>16	>16
Clarithromycin	no BP[b]			>16	>16	0.25	>16
Clindamycin	no BP[b]			>8	>8	≤ 0.25	>8
Dalbavancin	no BP[b]			8	>16	≤ 0.03	>16
Daptomycin	100			1	2	≤ 0.06	2
Ertapenem	no BP[b]			>4	>4	>4	>4
Levofloxacin			100	>32	>32	32	>32
Linezolid	94.1	5.9		2	2	0.5	4
Meropenem	no BP[b]			>32	>32	>32	>32
Pip-Tazo	no BP[b]			>512	>512	64	>512
Tigecycline	no BP[b]			0.12	0.12	0.06	0.25
Vancomycin			100	>32	>32	32	>32

[a] S, susceptible; I, intermediate; R, resistant; [b] No BP, no breakpoint defined; [c] based on oxacillin susceptibility, [d] FDA breakpoints; [e] Tetracycline breakpoints used to interpret MIC values

MIC, minimum inhibitory concentration (µg/ml); Pip-Tazo, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole

Table 2:MIC distribution of dalbavancin against gram-positive cocci from CANWARD

Organism	No. tested	MIC <=0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Methicillin-susceptible *S. aureus*	2697	755	1898	41	3	-	-	-	-	-	-	-
Methicillin-resistant *S. aureus*	889	208	659	22	-	-	-	-	-	-	-	-
Community-associated MRSA	223	36	184	3	-	-	-	-	-	-	-	-
Hospital-associated MRSA	629	164	447	18	-	-	-	-	-	-	-	-
Methicillin-susceptible *S. epidermidis*	268	178	81	8	-	-	-	-	-	-	-	-
Methicillin-resistant *S. epidermidis*	45	34	11	-	-	-	-	-	-	-	-	-
S. pneumoniae	1391	1371	16	4	-	-	-	-	-	-	-	-
Penicillin-resistant *S. pneumoniae*	61	61	-	-	-	-	-	-	-	-	-	-
E. faecalis	381	147	221	12	1	-	-	-	-	-	-	-
E. faecium	150	28	57	37	6	4	-	3	1	3	11	-
***Enterococcus* spp.**	578	225	309	35	2	1	-	2	-	-	4	-
VRE	34	3	1	2	-	4	-	5	1	3	15	-

CONCLUSIONS

- Dalbavancin is more active than comparators against both methicillin-susceptible and -resistant strains of *S. aureus*, including community-associated and hospital-associated strains.
- Dalbavancin is more active than comparators against both methicillin-susceptible and -resistant strains of *S. epidermidis*.
- Dalbavancin is more active than comparators against *S. pneumoniae*, including penicillin-resistant strains.
- Dalbavancin is as or more active than comparators against *E. faecalis*, *E. faecium* and non-speciated *Enterococcus*.

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