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Activity of Dalbavancin against *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. Isolated by Clinical Laboratories in Canadian Hospitals: CANWARD 2007-2017

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Introduction

Dalbavancin is a semisynthetic lipoglycopeptide structurally related to teicoplanin (1, 2). Like other glycopeptides, dalbavancin inhibits growth of Gram-positive bacterial pathogens. Dalbavancin inhibits cell wall synthesis in Gram-positive bacteria by forming complexes with C-terminal d-alanyl-d-alanine residues of growing peptidoglycan chains. In addition, dalbavancin appears to have the unique ability to form dimers and to anchor its lipophilic side chain in bacterial membranes which increases its target affinity and increases its potency. Consequently, dalbavancin possesses more potent *in vitro* bactericidal activity than vancomycin or teicoplanin against many resistant Gram-positive organisms. Dalbavancin is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms. Dalbavancin can be used as a single dose regimen of 1500mg administered via intravenous infusion, using a total infusion time of 30 minutes.

The purpose of this study was to compare the activity of dalbavancin, vancomycin and comparators against Gram-positive pathogens causing infections in patients in Canadian hospitals.

Materials and Methods

Participating Sites: From January 2007 to October 2017, tertiary-care medical centres in major population centres in 8 of the 10 provinces in Canada were recruited (2, 3). These sites were geographically distributed in a population based fashion.

Bacterial Isolates: Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. From January 2007 through October 2017, inclusive, each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. The medical centres submitted clinically significant isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media, and stocked in skim milk at -80˚ C until minimum inhibitory concentration (MIC) testing was carried out.

Antimicrobial Susceptibilities: The *in vitro* activity of selected antimicrobials was determined by broth microdilution in accordance with (CLSI) guidelines (4). Antimicrobial MIC interpretive standards were defined according to CLSI breakpoints (5). The MICs of the antimicrobial agents were determined using 96-well custom designed microtitre plates. These plates contained doubling antimicrobial dilutions in 100µL/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10^5 CFU/mL then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms including *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212.

CLSI breakpoints were used for dalbavancin: *Staphylococcus aureus* (including methicillin-resistant isolates) susceptible (S) ≤0.25µg/mL; *Streptococcus pyogenes* and *Streptococcus agalactiae* (S) ≤0.25µg/mL; and *Enterococcus faecalis* , (S) ≤0.25µg/mL.

Results

Table 1. Activity of dalbavancin and comparators against Gram-positive cocci from CANWARD 2007-2017

Organism (no. tested) / Antimicrobial Agent	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
Methicillin-susceptible *S. aureus* (MSSA, n=5280)							
Cefazolin	NA[a]			≤ 0.5	1	≤ 0.5	32
Clarithromycin	75.3	0.6	24.1	0.25	> 32	≤ 0.03	> 32
Clindamycin	93.0	0.5	6.5	≤ 0.25	≤ 0.25	≤ 0.25	> 8
Dalbavancin	100.0			0.06	0.06	≤ 0.03	0.25
Daptomycin	100.0			0.25	0.25	≤ 0.03	1
Levofloxacin	90.1	0.3	9.6	0.25	1	≤ 0.06	> 32
Linezolid	100.0			2	4	≤ 0.12	4
Meropenem	NA[a]			0.12	0.25	≤ 0.03	16
Pip-Tazo	NA[a]			≤ 1	≤ 1	≤ 1	64
Tigecycline	99.8		0.2	0.25	0.25	≤ 0.03	2
TMP/SMX	99.5		0.5	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	100.0			1	1	≤ 0.12	2
Methicillin-resistant *S. aureus* (MRSA, n=1482)							
Cefazolin	NA[a]			64	> 128	≤ 0.5	> 128
Clarithromycin	14.0	0.1	85.9	> 32	> 32	≤ 0.03	> 32
Clindamycin	51.1	0.1	48.8	0.25	> 8	≤ 0.12	> 8
Dalbavancin	99.9		0.1	0.06	0.06	≤ 0.03	1
Daptomycin	99.9		0.1	0.25	0.5	0.06	4
Levofloxacin	14.1		85.9	> 32	> 32	0.12	> 32
Linezolid	100.0			2	4	≤ 0.12	4
Meropenem	NA[a]			4	32	0.12	> 64
Pip-Tazo	NA[a]			32	128	≤ 1	512
Tigecycline	99.7		0.3	0.25	0.5	0.06	1
TMP/SMX	93.3		6.7	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	99.8	0.2		1	1	≤ 0.25	4
Community-associated methicillin resistant *S. aureus* (CA-MRSA, n=484)							
Cefazolin	NA[a]			16	64	≤ 0.5	> 128
Clarithromycin	24.8	0.2	75.0	> 32	> 32	0.12	> 32
Clindamycin	86.0		14.0	≤ 0.12	> 8	≤ 0.12	> 8
Dalbavancin	99.8		0.2	0.06	0.06	≤ 0.03	1
Daptomycin	100.0			0.25	0.5	0.12	1
Levofloxacin	40.0		60.0	4	8	0.12	32
Linezolid	100.0			2	2	0.5	4
Meropenem	NA[a]			2	4	0.12	32
Pip-Tazo	NA[a]			16	64	≤ 1	256
Tigecycline	100.0			0.25	0.25	0.06	0.5
TMP/SMX	99.8		0.2	≤ 0.12	≤ 0.12	≤ 0.12	4
Vancomycin	99.8	0.2		1	1	0.5	4
Healthcare-associated methicillin resistant *S. aureus* (HA-MRSA, n=949)							
Cefazolin	NA[a]			128	> 128	≤ 0.5	> 128
Clarithromycin	5.9		94.1	> 32	> 32	≤ 0.03	> 32
Clindamycin	31.5	0.1	68.4	> 8	> 8	≤ 0.12	> 8
Dalbavancin	100.0			0.06	0.06	≤ 0.03	0.25
Daptomycin	99.9		0.1	0.25	0.5	0.06	4
Levofloxacin	2.9		97.1	> 32	> 32	0.12	> 32
Linezolid	100.0			2	4	≤ 0.12	4
Meropenem	NA[a]			16	> 32	0.12	> 64
Pip-Tazo	NA[a]			64	128	≤ 1	512
Tigecycline	99.6		0.4	0.25	0.5	0.06	1
TMP/SMX	89.7		10.3	≤ 0.12	8	≤ 0.12	> 8
Vancomycin	99.8	0.2		1	1	≤ 0.25	4
Methicillin-susceptible[b] *S. epidermidis* (MSSE, n=637)							
Cefazolin	NA[a]			1	4	≤ 0.5	8
Clarithromycin	35.5	2.0	62.5	> 16	> 32	≤ 0.03	> 32
Clindamycin	65.3	1.1	33.6	≤ 0.12	> 8	≤ 0.12	> 8
Dalbavancin	NA[a]			≤ 0.03	0.06	≤ 0.03	1
Daptomycin	100.0			0.12	0.25	≤ 0.03	1
Levofloxacin	51.9	1.1	47.0	0.25	> 32	0.12	> 32
Linezolid	100.0			0.5	2	≤ 0.12	2
Meropenem	NA[a]			1	8	≤ 0.03	> 32
Pip-Tazo	NA[a]			≤ 1	4	≤ 1	64
Tigecycline	99.5		0.5	0.12	0.5	≤ 0.03	1
TMP/SMX	67.2		32.8	≤ 0.12	8	≤ 0.12	> 8
Vancomycin	100.0			1	2	≤ 0.12	4
Methicillin-resistant[c] *S. epidermidis* (MRSE, n=90)							
Cefazolin	NA[a]			128	> 128	32	> 128
Clarithromycin	16.7		83.3	> 32	> 32	≤ 0.03	> 32
Clindamycin	18.9		81.1	> 8	> 8	≤ 0.12	> 8
Dalbavancin	NA[a]			≤ 0.03	0.06	≤ 0.03	0.06
Daptomycin	100.0			0.12	0.25	≤ 0.03	0.5
Levofloxacin	2.2	2.2	95.6	> 32	> 32	1	> 32
Linezolid	100.0			1	1	≤ 0.12	2
Meropenem	NA[a]			32	32	4	64
Pip-Tazo	NA[a]			32	64	8	128
Tigecycline	100.0			0.12	0.25	0.06	0.5
TMP/SMX	20.0		80.0	4	8	≤ 0.12	> 8
Vancomycin	100.0			1	2	≤ 0.12	2

Organism (no. tested) / Antimicrobial Agent	% of Isolates per Category S	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
***S. pneumoniae* (n=1744)**							
Ceftriaxone	99.4	0.4	0.2	≤ 0.12	≤ 0.12	≤ 0.12	4
Clarithromycin	79.5	4.1	16.4	≤ 0.03	4	≤ 0.03	> 32
Clindamycin	93.4	0.6	6.0	≤ 0.12	≤ 0.12	≤ 0.12	> 64
Dalbavancin	NA[a]			≤ 0.03	≤ 0.03	≤ 0.03	0.12
Doxycycline	87.1	1.4	11.5	≤ 0.25	1	≤ 0.25	> 16
Levofloxacin	99.1	0.1	0.8	1	1	≤ 0.06	32
Linezolid	100.0			0.5	1	≤ 0.12	2
Meropenem	95.9	2.7	1.3	≤ 0.06	≤ 0.06	≤ 0.06	2
Penicillin	81.3	14.4	4.3	≤ 0.03	0.25	≤ 0.03	> 8
Tigecycline	99.7		0.3	0.03	0.06	≤ 0.015	0.25
TMP/SMX	84.7	6.7	8.6	≤ 0.12	2	≤ 0.12	> 8
Vancomycin	100.0			≤ 0.25	≤ 0.25	≤ 0.25	1
Penicillin-resistant *S. pneumoniae* (Pen-R, n=75)							
Ceftriaxone	89.3	8.0	2.7	0.5	2	≤ 0.06	4
Clarithromycin	34.7	2.7	62.7	4	> 32	≤ 0.03	> 32
Clindamycin	54.7	2.7	42.7	≤ 0.12	> 64	≤ 0.12	> 64
Dalbavancin	NA[a]			≤ 0.03	≤ 0.03	≤ 0.03	≤ 0.03
Doxycycline	38.7		61.3	1	4	≤ 0.25	> 16
Levofloxacin	98.7		1.3	1	1	0.25	16
Linezolid	100.0			0.5	1	0.25	2
Meropenem	29.3	42.7	28.0	0.5	1	≤ 0.06	2
Penicillin	≤ 1		100.0	2	4	2	> 8
Tigecycline	98.7		1.3	0.03	0.06	≤ 0.015	0.12
TMP/SMX	18.7	6.7	74.7	4	> 8	≤ 0.12	> 8
Vancomycin	100.0			≤ 0.25	0.5	≤ 0.25	1
***E. faecalis* (n=899)**							
Ciprofloxacin	59.7	12.6	27.7	1	> 16	≤ 0.06	> 16
Clarithromycin	NA[a]			2	> 32	≤ 0.03	> 32
Clindamycin	NA[a]			> 8	> 8	≤ 0.12	> 8
Dalbavancin	99.9		0.1	0.06	0.06	≤ 0.03	0.5
Daptomycin	92.3	7.7		0.5	1	≤ 0.03	4
Ertapenem	NA[a]			8	16	0.25	> 32
Levofloxacin	65.6	1.0	33.3	2	> 32	0.25	> 32
Linezolid	90.2	9.8		2	2	0.5	4
Meropenem	NA[a]			4	8	≤ 0.06	> 32
Pip-Tazo	NA[a]			4	8	≤ 1	> 512
Tigecycline	98.1		1.9	0.12	0.25	≤ 0.03	0.5
Vancomycin	100.0			1	2	0.25	4
***E. faecium* (n=338)**							
Ciprofloxacin	6.5	2.7	90.8	> 16	> 16	0.5	> 16
Clarithromycin	NA[a]			> 32	> 32	≤ 0.03	> 32
Clindamycin	NA[a]			> 8	> 8	≤ 0.12	> 8
Dalbavancin	NA[a]			0.06	4	≤ 0.03	> 16
Daptomycin	65.1	34.6	0.3	1	2	≤ 0.03	8
Ertapenem	NA[a]			> 32	> 32	4	> 32
Levofloxacin	9.5	1.3	89.2	> 32	> 32	1	> 32
Linezolid	89.3	10.4	0.3	2	4	≤ 0.12	8
Meropenem	NA[a]			> 32	> 32	1	> 64
Pip-Tazo	NA[a]			> 512	> 512	≤ 1	> 512
Tigecycline	98.5		1.5	0.12	0.12	≤ 0.03	2
Vancomycin	79.6	0.3	20.1	0.5	> 32	≤ 0.12	> 32
Non-speciated *Enterococcus* (n=570)							
Ciprofloxacin	40.2	21.6	38.2	2	> 16	≤ 0.06	> 16
Clarithromycin	NA[a]			> 16	> 32	≤ 0.03	> 32
Clindamycin	NA[a]			> 8	> 8	≤ 0.12	> 8
Dalbavancin	NA[a]			0.06	0.06	≤ 0.03	0.25
Daptomycin	91.9	8.1		0.5	1	≤ 0.03	4
Ertapenem	NA[a]			16	32	≤ 0.06	> 32
Levofloxacin	63.0	0.5	36.5	2	> 32	≤ 0.06	> 32
Linezolid	97.7	2.3		2	2	≤ 0.12	4
Meropenem	NA[a]			4	16	≤ 0.06	> 64
Pip-Tazo	NA[a]			4	8	≤ 1	> 512
Tigecycline	97.7		2.3	0.12	0.25	≤ 0.03	1
Vancomycin	100.0			1	2	≤ 0.25	4
Vancomycin-resistant Enterococci (VRE, n=68)							
Ciprofloxacin			100.0	> 16	> 16	16	> 16
Clarithromycin	NA[a]			> 32	> 32	0.12	> 32
Clindamycin	NA[a]			> 8	> 8	≤ 0.12	> 8
Dalbavancin	NA[a]			4	> 16	≤ 0.03	> 16
Daptomycin	75.0	25.0		1	2	≤ 0.03	4
Ertapenem	NA[a]			> 32	> 32	32	> 32
Levofloxacin			100.0	> 32	> 32	32	> 32
Linezolid	91.2	8.8		2	2	0.5	4
Meropenem	NA[a]			> 32	> 32	> 32	> 64
Pip-Tazo	NA[a]			> 512	> 512	64	> 512
Tigecycline	98.5		1.5	0.12	0.12	0.06	0.5
Vancomycin			100.0	> 32	> 32	32	> 32

[a] NA, no breakpoints defined; [b] MSSE= Cefazolin MIC ≤ 8µg/mL; [c] MSSE= Cefazolin MIC ≥ 32µg/mL.

Table 2. MIC distribution of dalbavancin against Gram-positive cocci from CANWARD

Organism	No. tested	MIC (Minimum Inhibitory Concentration µg/mL) ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Methicillin-susceptible *S. aureus*	5280	1798	3383	94	5							
Methicillin-resistant *S. aureus*	1482	435	1013	30	3		1					
Community-associated MRSA	484	123	351	8	1		1					
Healthcare-associated MRSA	949	303	623	21	2							
Methicillin-susceptible *S. epidermidis*	637	416	206	14			1					
Methicillin-resistant *S. epidermidis*	90	70	20									
S. pneumoniae	1744	1718	21	5								
Penicillin-resistant *S. pneumoniae*	75	75										
E. faecalis	899	394	472	30	2	1						
E. faecium	338	56	126	85	11	8	3	10	7	6	4	22
***Enterococcus* spp. ***	570	224	309	35	2							
VRE	68	3	2	4	2	6	3	9	7	6	4	22

* Not speciated CANWARD 2007-2010

Conclusions

1. Dalbavancin is more active than comparators against both methicillin-susceptible and -resistant strains of *S. aureus*, including community-associated and healthcare-associated strains.
2. Dalbavancin is more active than comparators against both methicillin-susceptible and -resistant strains of *S. epidermidis*.
3. Dalbavancin is more active than comparators against *Streptococcus* spp., including *S. pneumoniae*, *S. pyogenes* and *S. agalactiae*.
4. Dalbavancin is active against *E. faecalis* and *E. faecium,* but is not active versus VRE.

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References

1. Salem AH, Zhanel GG, Ibrahim SA, Noreddin AM. Monte Carlo simulation analysis of ceftobiprole, dalbavancin, daptomycin, tigecycline, linezolid, and vancomycin pharmacodynamics against intensive care unit-isolated methicillin-resistant *Staphylococcus aureus*. Clin Exp Pharmacol Physiol. 2014 Jun;41(6):437-43.
2. Karlowsky JA, Adam HJ, Poutanen SM, Hoban DJ, Zhanel GG; Canadian Antimicrobial Resistance Alliance (CARA). *In vitro* activity of dalbavancin and telavancin against staphylococci and streptococci isolated from patients in Canadian hospitals: results of the CANWARD 2007-2009 study. Diagn Microbiol Infect Dis. 2011 Mar;69(3):342-7.
3. Zhanel GG, Adam H, Baxter M, Fuller J, Nichol K, Denisuik AJ, Golden A, Hink R, Lagacé-Wiens P, Walkty A, Mulvey M, Schweizer F, Bay D, Hoban DJ, Karlowsky JA, the Canadian Antimicrobial Resistance Alliance (CARA). 42,936 pathogens from Canadian hospitals: 10 years of results (2007-2016) from the CANWARD surveillance study. Journal of Antimicrobial Chemotherapy 2019 (in press).
4. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Eleventh Edition: Approved Standard M07-A11. CLSI, Wayne, PA, USA, 2018.
5. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-eighth Informational Supplement M100-S28. CLSI, Wayne, PA, USA; 2018.