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Activity of Telavancin against Gram-Positive Cocci from Canadian Hospitals using Revised CLSI Guidelines: CANWARD 2013 and 2014

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ABSTRACT

Background: Telavancin (TLV) is a bactericidal lipoglycopeptide with activity against methicillin-resistant *Staphylococcus aureus* and other Gram-positive pathogens. In 2014, CLSI published revised guidelines for broth microdilution (BMD) susceptibility testing of TLV which recommend the use of DMSO as solvent/diluent for stock solution preparation/dilution and the addition of 0.002% polysorbate-80 (P-80) to the BMD test medium. Using this revised methodology, we assessed the in vitro activity of TLV against Gram-positive cocci associated with infections in Canadian hospitals.

Methods: From 2013-2014, more than 2,500 Gram-positive cocci were collected from tertiary-care medical centres across Canada as part of the ongoing national CANWARD surveillance study. Vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) isolates from the Network on Antimicrobial Resistance in *S. aureus* (NARSA) repository were also included in this comparison. TLV activity was evaluated using the revised BMD method and MICs were interpreted using updated FDA-approved breakpoint criteria. Susceptibility testing of comparator agents was performed by BMD following CLSI guidelines.

Results: The activity of TLV and select comparators (vancomycin [VAN], daptomycin [DAP], linezolid [LZD]) against Gram-positive cocci is summarized below:

Organism (n)	TLV MIC_{50}/MIC_{90}/Range (μg/mL)	Comparator MIC_{50}/MIC_{90} (μg/mL)		
		VAN	DAP	LZD
MSSA (1250)	0.03/0.06/0.008-0.12	0.5/1	0.25/0.5	2/2
MRSA (293)	0.06/0.06/0.03-0.12	0.5/1	0.25/0.5	2/2
- HA-MRSA (179)	0.06/0.06/0.03-0.12	1/1	0.25/0.5	2/2
- CA-MRSA (114)	0.03/0.06/0.03-0.12	0.5/1	0.25/0.5	2/2
hVISA (8)	0.06/0.12/0.03-0.12	2/2	0.25/0.5	1/2
VISA (11)	0.12/0.25/0.06-0.25	4/8	0.5/1	1/2
VRSA (7)	0.5/1/0.5-1	32/>32	0.25/0.25	2/2
S. epidermidis (130)	0.06/0.12/0.03-0.25	1/2	0.25/0.25	0.5/1
S. pneumoniae (334)	0.008/0.015/≤0.002-0.03	0.25/0.25	0.12/0.12	1/2
S. pyogenes (87)	0.03/0.06/0.015-0.06	0.25/0.5	0.12/0.12	1/2
S. agalactiae (124)	0.03/0.06/0.03-0.06	0.5/0.5	0.25/0.25	1/2
E. faecalis (112)	0.12/0.12/0.015-0.25	1/2	1/2	2/2
E. faecium (45)	0.03/>2/0.015->2	0.5/>32	2/2	2/2
- VanS (34)	0.03/0.06/0.015-0.12	0.5/1	2/2	2/2
- VanR (11)	2/>2/0.25->2	>32/>32	1/2	2/4

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; HA-MRSA, healthcare-associated MRSA; CA-MRSA, community-associated MRSA; hVISA, heterogeneous vancomycin-intermediate *S. aureus*.

Conclusions: TLV was more active in vitro than VAN, DAP and LZD against MSSA and MRSA, including CA-MRSA and HA-MRSA genotypes. TLV was also the most active agent tested against hVISA and VISA. Although VRSA had TLV MICs above the susceptible breakpoint, TLV remained more active than VAN and LZD against these isolates. Against *S. epidermidis*, *S. pneumoniae* and b-hemolytic streptococci, TLV demonstrated activity comparable to or greater than DAP and superior than VAN and LZD.

BACKGROUND

Telavancin is a semisynthetic lipoglycopeptide with a dual mechanism of action against a broad spectrum of clinically relevant Gram-positive bacteria, including both susceptible and multidrug-resistant staphylococci and streptococci as well as enterococci. The rapid bactericidal activity of telavancin is derived from its ability to inhibit synthesis of the bacterial cell wall as well as to disrupt bacterial membrane integrity and increase cell membrane permeability.

In January 2014, the Clinical and Laboratory Standards Institute (CLSI) published revised guidelines for broth microdilution susceptibility testing of telavancin. This method utilizes DMSO as both solvent and diluent for stock solution preparation/dilution to increase drug solubility and incorporates 0.002% polysorbate-80 (P-80) in the broth microdilution test medium to minimize binding of the drug to plastic panels (M100-S24, CLSI 2014).

The purpose of this study was to assess the activity of telavancin against Gram-positive cocci associated with infections in Canadian hospitals using the revised CLSI broth microdilution method.

MATERIALS & METHODS

CANWARD Study Design

Between January 2013 and December 2014, 6,685 clinical isolates, including more than 2,500 Gram-positive cocci, were collected as part of the ongoing CANWARD study assessing pathogen prevalence and antibiotic resistance in Canadian hospitals. Isolates were received from tertiary-care medical centres (15 in 2013, 13 in 2014) that were geographically distributed in a population-based fashion in eight of the ten Canadian provinces. Annually, 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. Isolates were collected from patients attending hospital clinics, emergency rooms, medical/surgical wards and intensive care units. All organisms were identified by the submitting centre and were deemed clinically significant using local site criteria.

Additional Test Isolates

Eight heterogeneous vancomycin-intermediate *S. aureus* (hVISA) identified as part of the CANWARD study, as well as 11 vancomycin-intermediate *S. aureus* (VISA) and 7 vancomycin-resistant *S. aureus* (VRSA) isolates from the Network on Antimicrobial Resistance in *S. aureus* (NARSA) repository were also included in this comparison.

Antimicrobial Susceptibility Testing

The *in vitro* activities of comparator agents, including cefazolin, ceftriaxone, clarithromycin, clindamycin, ciprofloxacin, daptomycin, doxycycline, ertapenem, levofloxacin, linezolid, meropenem, moxifloxacin, penicillin, piperacillin-tazobactam, tigecycline, trimethoprim-sulfamethoxazole and vancomycin, were determined by broth microdilution in accordance with CLSI guidelines (M7-A7, CLSI 2012). Telavancin susceptibility testing was performed by the revised broth microdilution method, which utilizes DMSO as both solvent and diluent for stock solution preparation/dilution and incorporates 0.002% P-80 in the test medium. MIC interpretive standards were defined according to CLSI breakpoints for comparator agents (M100-S24, CLSI 2014). The following interpretive breakpoints (FDA) were used for telavancin susceptible: *S. aureus*, ≤0.12 μg/ml; *S. pyogenes*, ≤0.12 μg/ml; *S. agalactiae*, ≤0.12 μg/ml; and *E. faecalis* (vancomycin-susceptible) ≤0.25 μg/ml.

CONCLUSIONS

Telavancin was more active than the comparator agents vancomycin, daptomycin and linezolid against MSSA and MRSA, including both community- and healthcare-associated strains.

Telavancin remained active against hVISA (100% susceptible), but exhibited reduced activity against VISA strains (81.8% susceptible). All VRSA were telavancin non-susceptible.

Telavancin had greater activity than vancomycin, daptomycin and linezolid against hVISA and VISA strains and was more active than vancomycin and linezolid against VRSA.

Televancin was more active than vancomycin, daptomycin and linezolid against *S. epidermidis*.

Telavancin demonstrated comparable activity to penicillin and superior activity to vancomycin and linezolid against *S. pyogenes* and *S. agalactiae,* and was the most potent agent tested against *S. pneumoniae*.

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RESULTS

Table 1. Activity of telavancin and comparators against Gram-positive cocci

Organism (n), Antibiotic	% of Isolates per Category			MIC (μg/mL)		
	S	I	R	50%	90%	Range
S. aureus						
MSSA (1250)						
Telavancin[a]	100			0.03	0.06	0.008 - 0.12
Vancomycin	100			0.5	1	≤0.12 - 2
Cefazolin	No BP			≤0.5	≤0.5	≤0.5 - 8
Clarithromycin	76.7	1.0	22.3	0.12	>32	≤0.03 - >32
Clindamycin	94.1	0.4	5.5	≤0.12	≤0.12	≤0.12 - >8
Daptomycin	100			0.25	0.5	0.06 - 1
Linezolid	99.9		0.1	2	2	≤0.12 - 8
Meropenem	No BP			0.12	0.25	≤0.03 - 2
Moxifloxacin	90.8	1.1	8.1	≤0.06	0.25	≤0.06 - >16
Pip-Tazo	No BP			≤1	≤1	≤1 - 16
Tigecycline[a]	99.7			0.25	0.25	≤0.03 - 1
TMP/SMX	99.5		0.5	≤0.12	≤0.12	≤0.12 - >8
MRSA (293)						
Telavancin[a]	100			0.06	0.06	0.03 - 0.12
Vancomycin	100			0.5	1	≤0.12 - 2
Cefazolin			100[b]	32	>128	1 - >128
Clarithromycin	20.3	1.9	77.8	>32	> 32	≤0.03 - >32
Clindamycin	64.8		35.2	≤0.12	> 8	≤0.12 - >8
Daptomycin	100			0.25	0.25	0.12 - 0.5
Linezolid	100			2	2	1 - 4
Meropenem			100[b]	4	32	0.12 - >32
Moxifloxacin	21.6	7.6	70.8	4	>16	≤0.06 - >16
Pip-Tazo			100[b]	32	128	≤1 - 256
Tigecycline[a]	96.8			0.25	0.5	0.06 - 2
TMP/SMX	92.5		7.5	≤0.12	≤0.12	≤0.12 - >8
CA-MRSA (114)						
Telavancin[a]	100			0.03	0.06	0.03 - 0.12
Vancomycin	100			0.5	1	0.5 - 2
Cefazolin			100[b]	8	64	1 - >128
Clarithromycin	27.2	1.8	71.1	32	>32	0.12 - >32
Clindamycin	88.6		11.4	≤0.12	>8	≤0.12 - >8
Daptomycin	100			0.25	0.5	0.25 - 0.5
Linezolid	100			2	2	1 - 4
Meropenem			100[b]	2	4	0.12 - 32
Moxifloxacin	26.3	19.3	54.4	2	2	≤0.06 - 16
Pip-Tazo			100[b]	16	32	2 - 256
Tigecycline[a]	100			0.25	0.25	≤0.03 - 0.5
TMP/SMX	100			≤0.12	≤0.12	≤0.12 - 1
HA-MRSA (179)						
Telavancin[a]	100			0.06	0.06	0.03 - 0.12
Vancomycin	100			1	1	≤0.12 - 2
Cefazolin			100[b]	128	>128	1 - >128
Clarithromycin	12.3	2.2	85.5	>32	>32	≤0.03 - >32
Clindamycin	46.9		53.1	>8	>8	≤0.12 - >8
Daptomycin	100			0.25	0.5	0.12 - 0.5
Linezolid	100			2	2	1 - 4
Meropenem			100[b]	16	>32	0.25 - >32
Moxifloxacin	3.5	0.2	96.3	8	>16	≤0.06 - >16
Pip-Tazo			100[b]	64	128	≤1 - 256
Tigecycline[a]	94.4		5.6	0.25	0.5	0.06 - 1
TMP/SMX	93.9		6.1	≤0.12	≤0.12	≤0.12 - >8

Organism (n), Antibiotic	% of Isolates per Category			MIC (μg/mL)		
	S	I	R	50%	90%	Range
S. aureus						
CANWARD hVISA (8)						
Telavancin[a]	100			0.06	0.12	0.03 - 0.12
Vancomycin	100			2*	2	2
Cefazolin			100[b]	>128*	>128	1 - >128
Clarithromycin			100	>32*	>32	>32
Clindamycin	25.0		75.0	>8*	>8	≤0.12 - >8
Daptomycin	100			0.25*	0.25	0.12 - 0.5
Linezolid	100			1*	2	0.5 - 2
Meropenem			100[b]	>32*	>32	0.5 - >32
Moxifloxacin	12.5		87.5	>16*	>16	≤0.06 - >16
Pip-Tazo			100[b]	256*	512	8 - 512
Tigecycline[a]	100			0.12*	0.25	0.06 - 0.25
TMP/SMX	100			≤0.12*	≤0.12	≤0.12
NARSA VISA (11)						
Telavancin[a]	81.8			0.12*	0.25	0.06 - 0.25
Vancomycin		100		4*	8	4 - 8
Cefazolin			100[b]	>64*	>128	4 - >128
Clarithromycin	9.1		90.9	>32*	>32	0.12 - >32
Clindamycin	9.1		90.9	>8*	>8	≤0.12 - >8
Daptomycin	100			0.5*	1	0.25 - 1
Linezolid	100			1*	2	1 - 2
Meropenem			100[b]	8*	16	1 - >32
Moxifloxacin			100	4*	8	2 - 8
Pip-Tazo			100[b]	128*	128	32 - 256
Tigecycline[a]	100			0.25*	0.5	0.12 - 0.5
TMP/SMX	72.7		27.3	0.25*	>8	≤0.12 - >8
NARSA VRSA (7)						
Telavancin[a]	0.0			0.5*	1	0.5 - 1
Vancomycin			100	32*	>32	16 - >32
Cefazolin			100[b]	>128*	>128	≤0.5 - >128
Clarithromycin			100	>32*	>32	>32
Clindamycin			100	>8*	>8	>8
Daptomycin	100			0.25*	0.25	0.12 - 0.25
Linezolid	100			2*	2	1 - 2
Meropenem			100[b]	16*	>32	0.12 - >32
Moxifloxacin			100	4*	>16	4 - >16
Pip-Tazo			100[b]	64*	128	≤1 - 128
Tigecycline[a]	100			0.12*	0.5	0.12 - 0.5
TMP/SMX	100			≤0.12*	2	≤0.12 - 2
***S. epidermidis* (130)**						
Telavancin	No BP			0.06	0.12	0.03 - 0.25
Vancomycin	100			1	2	≤0.25 - 2
Cefazolin	No BP			1	16	≤0.5 - >128
Clarithromycin	41.1	1.6	57.4	32	>32	≤0.0.03 - >32
Clindamycin	55.8	3.9	40.3	≤0.12	>8	≤0.12 - >8
Daptomycin	100			0.25	0.25	≤0.06 - 0.5
Linezolid	100			0.5	1	0.25 - 2
Meropenem	No BP			1	32	≤0.0.03 - >32
Moxifloxacin	54.3	8.5	37.2	0.5	>16	≤0.06 - >16
Pip-Tazo	No BP			≤1	8	≤1 - 64
Tigecycline	No BP			0.12	0.25	≤0.03 - 1
TMP/SMX	65.1		34.9	0.5	8	≤0.12 - >8

Organism (n), Antibiotic	% of Isolates per Category			MIC (μg/mL)		
	S	I	R	50%	90%	Range
***S. pneumoniae* (334)**						
Telavancin	No BP			0.008	0.015	≤0.002 - 0.03
Vancomycin	100			0.25	0.25	≤0.12 - 0.5
Ceftriaxone	99.4	0.6		≤0.12	0.25	≤0.12 - 2
Clarithromycin	75.2	3.6	21.2	≤0.03	2	≤0.03 - >32
Clindamycin	92.7	0.6	6.7	≤0.12	≤0.12	≤0.12 - >64
Doxycycline	84.8	0.9	14.2	≤0.25	4	≤0.25 - 16
Levofloxacin	98.5		1.5	1	1	≤0.06 - 16
Linezolid	100			1	2	≤0.12 - 2
Meropenem	93.0	4.2	2.7	≤0.06	≤0.06	≤0.06 - 1
Penicillin	85.8	9.7	4.5	≤0.03	0.25	≤0.03 - 4
Tigecycline[a]	100			≤0.015	0.03	≤0.015 - 0.06
TMP/SMX	83.2	5.8	11	≤0.12	4	≤0.12 - >8
***S. pyogenes* (87)**						
Telavancin[a]	100			0.03	0.06	0.015 - 0.06
Vancomycin	100			0.25	0.5	0.25 - 0.5
Ceftriaxone	98.9			≤0.12	≤0.12	≤0.12 - 1
Clarithromycin	94.3		5.7	≤0.03	≤0.03	≤0.03 - 4
Clindamycin	98.9		1.1	≤0.12	≤0.12	≤0.12 - >64
Doxycycline	No BP			≤0.25	0.5	≤0.25 - 16
Levofloxacin	100			0.5	1	0.25 - 2
Linezolid	97.7		2.3	1	2	0.25 - 4
Meropenem	100			≤0.06	≤0.06	≤0.06 - 0.12
Penicillin	100			≤0.03	≤0.03	≤0.03 - 0.06
Tigecycline[a]	100			≤0.015	0.06	≤0.015 - 0.06
TMP/SMX	No BP			≤0.12	0.25	≤0.12 - >8
***S. agalactiae* (124)**						
Telavancin[a]	100			0.03	0.06	0.03 - 0.06
Vancomycin	100			0.5	0.5	0.25 - 1
Ceftriaxone	100			≤0.12	≤0.12	≤0.12
Clarithromycin	70.2	3.2	26.6	≤0.03	32	≤0.03 - >32
Clindamycin	83.9	0.8	15.3	≤0.12	>64	≤0.12 - >64
Doxycycline	No BP			8	16	≤0.25 - >16
Levofloxacin	96.8		3.2	0.5	1	0.25 - >32
Linezolid	100			1	2	1 - 2
Meropenem	100			≤0.06	≤0.06	≤0.06 - 0.12
Penicillin	100			≤0.03	0.06	≤0.03 - 0.12
Tigecycline[a]	99.2			0.06	0.12	≤0.015 - 1
TMP/SMX	No BP			≤0.12	0.25	≤0.12 - 1

[a] Interpretive breakpoint defined by the FDA; only susceptible criteria assigned
[b] Based on oxacillin susceptibility
* Median MIC value

Abbreviations:
No BP, no breakpoints defined
S, susceptible; I, intermediate; R, resistant
MSSA, methicillin-susceptible *S. aureus*
MRSA, methicillin-resistant *S. aureus*
CA-MRSA, community-associated methicillin-resistant *S. aureus*
HA-MRSA, healthcare-associated methicillin-resistant *S. aureus*
hVISA, heterogeneous vancomycin-intermediate *S. aureus*
VISA, vancomycin-intermediate *S. aureus*
VRSA, vancomycin-resistant *S. aureus*

Table 2. MIC distribution for telavancin against Gram-positive cocci

Organism (no. tested)	Number (cumulative percentage) inhibited at telavancin MIC (μg/mL)								
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
Methicillin-susceptible *S. aureus* (1250)		2 (0.2)	6 (0.6)	641 (51.9)	571 (97.6)	30 (100)			
Methicillin-resistant *S. aureus* (293)				144 (49.1)	140(96.9)	9 (100)			
Community-associated MRSA (114)				58 (50.9)	54 (98.2)	2 (100)			
Healthcare-associated MRSA (179)				86 (48.0)	86 (96.1)	7 (100)			
CANWARD hVISA (8)				1 (12.5)	6 (87.5)	1 (100)			
NARSA VISA (11)					2 (18.2)	7 (81.8)	2 (100)		
NARSA VRSA (7)								4 (57.1)	3 (100)
S. epidermidis (130)				27 (20.8)	73 (76.9)	27 (97.7)	3 (100)		
S. pneumoniae (334)	23 (6.9)	183 (61.7)	127 (99.7)	1 (100)					
S. pyogenes (87)			4 (4.6)	71 (86.2)	12 (100)				
S. agalactiae (124)				81 (65.3)	43 (100)				

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