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Activity of Daptomycin, Vancomycin and Linezolid against 6,951 Gram-positive Pathogens Isolated from Canadian Hospitals: CANWARD 2007-2009

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ABSTRACT

Background:
Daptomycin (DAP) is a cyclic lipopeptide with activity against gram-positive organisms. We compared the activity of DAP, vancomycin (VAN) and linezolid (LZD) against Gram-positive pathogens causing infections in Canadian hospitals.
Methods:
From January 2007 through December 2009, sentinel hospitals representing 8 of 10 provinces across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. 6,951 Gram-positive pathogens were collected and available for susceptibility testing. Susceptibility testing was performed using CLSI broth microdilution methods.
Results:
The activity (µg/ml) of DAP, VAN and LZD against select pathogens is described below:

Organism (# isolates)	DAP MIC_{50}/MIC_{90}	LZD MIC_{50}/MIC_{90}	VAN MIC_{50}/MIC_{90}
***S. pyogenes* (273)**	≤0.06/0.06	1/1	0.5/0.5
MSSA (2697)	0.12/0.25	2/2	1/1
MRSA (889)	0.12/0.25	2/2	1/1
CA-MRSA (223)	0.25/0.5	2/2	1/1
HA-MRSA (629)	0.12/0.25	2/2	1/1
***S. epidermidis* (321)**	0.12/0.25	0.5/1	1/2
MSSE (268)	0.12/0.25	0.5/1	1/2
MRSE (45)	0.12/0.25	1/1	2/2
***Enterococcus* spp. (578)**	0.5/1	2/2	1/2
***E. faecalis* (381)**	0.5/1	2/2	1/2
***E. faecium* (150)**	1/2	2/2	0.5/>32
VRE (34)	1/2	2/2	>32/>32
***VISA (12)**	1/2	1/2	4/4
***VRSA (7)**	0.5**	2**	>32**

MSSA-methicillin-susceptible *Staphylococcus auerus*, CA-community-associated; HA-healthcare-associated, MSSE-methicillin-susceptible *Staphylococcus epidermidis*, VRE-vancomycin-resistant enterococci, VISA-vancomycin-intermediate *S. aureus*, VRSA-vancomycin-resistant *S. aureus*.
*Isolates obtained through the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) program: supported under NIAID, NIH Contract No. N01-AI-95359.
**median MIC
Conclusions:
Daptomycin is more active than vancomycin and linezolid versus MSSA, MRSA, MSSE, MRSE, *E. faecalis*, *E. faecium* and VRE.

REFERENCES

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BACKGROUND

Methicillin-resistant *S. aureus* (MRSA), whether community-acquired or healthcare-acquired continue to increase in North America[1-3]. These strains are usually resistant to all β-lactam antibiotics and to several other antimicrobial classes1, further complicating the treatment of MRSA infections. Glycopeptides, such as vancomycin, have widely been used as first-line therapy for the treatment of these infections, but the emergence of glycopeptide resistance has prompted the need for new antibiotics with activity against MRSA and other Gram positive pathogens[1-3].
Daptomycin, a cyclic lipopeptides, is highly active *in vitro* against a range of Gram positive pathogens, including both susceptible and multidrug-resistant staphylococci, and enterococci[3]. Daptomycin is indicated for the treatment of complicated skin and skin structure infections (SSSIs), *S. aureus* bacteremia and right-sided endocarditis.
PURPOSE:
The purpose of this study was to compare the activity of daptomycin and several comparators, against Gram-positive pathogens in Canadian hospitals.

MATERIALS & METHODS

Bacterial Isolates:
Tertiary-care medical centres (12 in 2007, 10 in 2008, 15 in 2009) representing 8 of 10 provinces across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. The sites were geographically distributed in a population-based fashion. From January 2007 through December 2009, 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. In 2007, 2008, and 2009, 7881, 5282, and 5375 isolates were collected, respectively.
Antimicrobial Susceptibilities:
Following 2 subcultures from frozen stock, the in vitro activity of selected antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2006 M7-A7 and M100-S16). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (CLSI, 2010). Susceptibility testing could not be performed with all agents due to lack of space on the susceptibility panels. Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (M7-A7, 2006). The MICs of the antimicrobial agents for the isolates 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; *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

RESULTS

Activity of daptomycin and comparators against gram-positive cocci from CANWARD 2007-2009

Table 1. *Staph aureus*

Organism (n)Antibiotic	% of Isolates per Category						
(MSSA, n=2696)	S[a]	I	R	MIC_{50}	MIC_{90}	Range Min	Range Max
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
Daptomycin	**100**			**0.12**	**0.25**	**≤ 0.06**	**1**
Levofloxacin	90.1	0.3	9.6	0.25	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, n=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
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	1
TMP/SMX	90.3		9.7	≤ 0.12	1	≤ 0.12	>8
Vancomycin	99.9	0.1		1	1	≤ 0.25	4
CA-MRSA, n=223							
Cefazolin			100	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
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, n=629							
Cefazolin			100	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
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

Tabel 2. *Enterococcus*

Organism (n)Antibiotic	% of Isolates per Category			MIC_{50}	MIC_{90}	Range Min	Range Max
***E. faecalis* n=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
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	0.25	>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	97.6[d]			0.12	0.25	0.06	0.5
Vancomycin	100			1	2	0.5	4
***E. faecium* n=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
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
Non speciated *Enterococcus* n=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
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	>32
Vancomycin resistant *Enterococcus* n=34)							
Ciprofloxacin			100	>16	>16	>16	>16
Clarithromycin	no BP[b]			>16	>16	1	>16
Clindamycin	no BP[b]			>8	>8	≤ 0.25	>8
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

Table 3. *Staph epidermidis*

Organism (n)Antibiotic	% of Isolates per Category			MIC_{50}	MIC_{90}	Range Min	Range Max
MSSE, n=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
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, n=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
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

Table 4. MIC distribution of daptomycin against gram-positive cocci from CANWARD 2007-09

Organism	Isolates Tested	% of isolates with MIC (Minimal Inhibitory Concentration µg/mL)									
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Methicillin-susceptible *S. aureus*	2697	1.1	64.0	31.0	3.7	0.2	-	-	-	-	-
Methicillin-resistant *S. aureus*	889	0.3	51.8	41.2	6.3	0.4	-	-	-	-	-
Community-associated MRSA	223	0.0	49.8	42.2	7.6	0.4	-	-	-	-	-
Healthcare-associated MRSA	629	0.5	52.0	41.2	5.9	0.4	-	-	-	-	-
Methicillin-susceptible *S. epidermidis*	268	11.2	59.7	28.4	0.4	0.3	-	-	-	-	-
Methicillin-resistant *S. epidermidis*	45	2.2	75.6	20.0	2.2	-	-	-	-	-	-
Streptococcus pyogenes	273	98.9	0.7	0.4	-	-	-	-	-	-	-
E. faecalis	381	0.8	2.4	20.2	42.8	30.2	2.4	1.3	-	-	-
E. faecium	150	0.7	2.0	7.3	16.0	56.7	16.0	1.3	-	-	-
Enterococcus spp.	578	1.2	3.6	22.5	39.5	24.9	7.4	0.7	-	-	-
VRE	34	2.9	-	2.9	11.8	64.7	17.7	-	-	-	-

CONCLUSIONS

Daptomycin was more active than comparators against methicillin- susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) both community-associated (CA) and healthcare-associated (HA) strains.
Daptomycin was more active than comparators against coagulase-negative staphylococci, and *S. epidermidis*, including methicillin-resistant (MRSE) strains.
Daptomycin was more active than comparators against *Enterococcus* species, *E. faecalis*, *E. faecium* and vancomycin-resistant enterococci (VRE)
Daptomycin was more active than comparators against vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* VRSA.
Daptomycin demonstrates excellent activity against common Gram-positive pathogens isolated from Canadian hospitals.

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