

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 ($\mu\text{g/ml}$) 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
<i>S. pyogenes</i> (273)	$\leq 0.06/0.06$	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
<i>S. epidermidis</i> (321)	0.12/0.25	0.5/1	1/2
MSSSE (268)	0.12/0.25	0.5/1	1/2
MRSE (45)	0.12/0.25	1/1	2/2
<i>Enterococcus</i> spp. (578)	0.5/1	2/2	1/2
<i>E. faecalis</i> (381)	0.5/1	2/2	1/2
<i>E. faecium</i> (150)	0.5/32	2/2	0.5/32
VRE (44)	1/2	2/2	>32/32
VISA (12)	1/2	1/2	4/4
VRSA (7)	0.5**	2**	>32**

MSSA-methicillin-susceptible *Staphylococcus aureus*, CA-community-associated, HA-healthcare-associated, MSSSE-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-AY-95359.

**Median MIC

Conclusions: Daptomycin is more active than vancomycin and linezolid versus MSSA, MRSA, MSSSE, 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 lipopeptides¹, is highly active *in vitro* against a range of Gram positive pathogens, including both susceptible and multidrug-resistant staphylococci, and enterococci². 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 100 μl volume of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5×10^6 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.

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

Table 1. *Staph aureus*

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max		
MSSA, n=2696					
Cefazolin	99.9	0.1	0.5	< 0.05	32
Clarithromycin	75	0.3	24.7	0.25	>16
Clinidamycin	91.8	0.5	7.7	<0.25	>0.25
Daptomycin	100	1.02	0.25	0.06	1
Levofloxacin	90.1	0.3	9.6	0.25	>16
Linezolid	100	2	2	>12	>16
Meropenem	100	0.12	0.25	>12	4
Pip-Tazo	99.9	0.1	>1	1.5	>16
Tigecycline	99.6*	0.25	0.25	>0.03	1
Vancomycin	99.3	0.7	<0.12	<0.12	>8
					>16

MRSA, n=889

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max		
Cefazolin	117	0.1	88.2	>16	>128
Clarithromycin	44	0.1	65.9	>8	>0.25
Clinidamycin	100	0.12	0.25	0.06	1
Daptomycin	100	1.41	>32	>32	>32
Levofloxacin	100	100	84	>28	>1
Linezolid	100	84	>28	>1	>512
Meropenem	99.3*	0.25	0.5	0.06	1
Pip-Tazo	99.3	0.7	<0.12	<0.12	>8
Tigecycline	90.9	0.1	>1.2	1	>0.25

CA-MRSA, n=223

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max		
Cefazolin	26.9	0.5	72.6	>16	>0.25
Clarithromycin	81.0	0.1	19.9	<0.25	>8
Clinidamycin	100.0	0.12	0.25	0.12	1
Daptomycin	100.0	60.1	4	2	1
Levofloxacin	100.0	100	2	4	0.12
Linezolid	100.0	100	2	4	0.12
Meropenem	99.6*	0.25	0.25	0.06	1
Pip-Tazo	100.0	<0.12	<0.12	<0.12	>2
Tigecycline	99.8	0.2	>1	0.5	>2

HA-MRSA, n=629

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max		
Cefazolin	4.3	>16	66.7	>16	>0.25
Clarithromycin	27.8	0.2	72.0	>8	>0.25
Clinidamycin	100.0	0.12	0.25	0.06	1
Daptomycin	100.0	2	>32	>32	>32
Levofloxacin	100.0	97.1	>32	>32	>32
Linezolid	100.0	2	>12	>4	>16
Meropenem	100	100	16	>2	>2
Pip-Tazo	100	64	>16	>16	>16
Tigecycline	99.2*	0.25	0.5	0.12	1
Vancomycin	88.5	0.2	13.5	<0.12	>8
VRE	99.8	0.2	>1	>1	>0.25

Table 2. MIC distribution of daptomycin against gram-positive cocci from CANWARD 2007-2009

Organism	Tested	% of Isolates with MIC	2	4	8	16	>16
Methicillin-susceptible <i>S. aureus</i>	2697	1.1	64.0	31.0	3.7	0.2	-
Methicillin-resistant <i>S. aureus</i>	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 <i>S. epidermidis</i>	328	11.2	59.7	28.4	0.4	0.3	-
Methicillin-resistant <i>S. epidermidis</i>	45	2.2	75.6	20.0	2.2	-	-
Streptococcus pyogenes	273	98.9	0.7	0.4	-	-	-
<i>E. faecalis</i>	381	0.8	2.4	20.2	42.8	30.2	2.4
<i>E. faecium</i>	150	0.7	2.0	7.3	16.0	56.7	16.0
<i>Enterococcus</i> spp.	578	1.2	3.6	22.5	39.5	24.9	7.4
VRE	34	2.9	-	2.9	11.8	64.7	17.7

RESULTS

Table 2. *Enterococcus*

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max	
<i>E. faecalis</i> n=381				
Ciprofloxacin	48.4	19.2	35.4	2
Clarithromycin	no BP*	>16	>16	>16
Clinidamycin	no BP*	>16	>16	>16
Daptomycin	no BP*	>8	>8	>12
Levofloxacin	100	0.5	1	0.06
Linezolid	no BP*	8	7.25	>32
Meropenem	65.8	1.1	33.3	2
Pip-Tazo	99.5	0.5	2	2
Tigecycline	no BP*	4	8	>0.06
Vancomycin	no BP*	4	8	>1
VRE	97.9*	0.12	0.25	0.06
	100	1	2	0.5

E. faecium n=150

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max	
Ciprofloxacin	6	4	90	>16
Clarithromycin	no BP*	>16	>16	>16
Clinidamycin	no BP*	>8	>8	>12
Daptomycin	100	1	2	0.06
Levofloxacin	no BP*	>4	>4	>4
Linezolid	10	1.3	88.7	>32
Meropenem	96	4	2	0.5
Pip-Tazo	no BP*	>32	>32	>2
Tigecycline	no BP*	>512	>512	>2
Vancomycin	no BP*	0.12	0.12	<0.03
VRE	82.7	0.5	>2	>0.25

Non specified *Enterococcus* n=578

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max	
Ciprofloxacin	39.8	21.3	39.1	2
Clarithromycin	no BP*	>16	>16	>16
Clinidamycin	no BP*	>8	>8	>12
Daptomycin	100	0.5	1	0.06
Levofloxacin	no BP*	8	32	>0.06
Linezolid	62.1	0.5	37.4	2
Meropenem	97.8	2.2	2	>12
Pip-Tazo	no BP*	2	0.06	>4
Tigecycline	no BP*	4	8	>1
Vancomycin	no BP*	0.1	0.12	<0.03
VRE	82.7	0.5	>2	>0.25

Vancomycin resistant *Enterococcus* n=34

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max	
Ciprofloxacin	100	>16	>16	>16
Clarithromycin	no BP*	>16	>16	>16
Clinidamycin	no BP*	>8	>8	>12
Daptomycin	100	1	2	0.06
Levofloxacin	no BP*	>4	>4	>4
Linezolid	100	>32	>32	>32
Meropenem	94.1	5.9	2	0.5
Pip-Tazo	no BP*	>32	>32	>2
Tigecycline	no BP*	>512	>512	>4
Vancomycin	no BP*	0.12	0.12	<0.06
VRE	100	>32	>32	>32

Table 3. *Staph epidermidis*

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max
MSSSE, n=268			
Cefazolin	100	1	4
Clarithromycin	34.4	2.2	63.4
Clinidamycin	62.3	0.4	37.3
Daptomycin	100	0.12	0.25
Levofloxacin	51.9	1.1	47
Linezolid	100	10.0	47
Meropenem	84.0	1.0	6.0
Pip-Tazo	98.9	1.1	<1
Tigecycline	no BP*	0.25	0.5
Vancomycin	no BP*	35.1	1

MRSE, n=45

Organism (n)Antibiotic	% of Isolates per Category	Range	Range Max
Cefazolin	100	64	128
Clarithromycin	11.1	88.9	>16
Clinidamycin	13.3	86.7	>8
Daptomycin	100	0.12	0.25
Levofloxacin	2.2	2.2	95.6
Linezolid	100	1	1
Meropenem	100	32	32
Pip-Tazo	no BP*	100	32
Tigecycline	no BP*	100	32
Vancomycin	100	2	2

CONCLUSIONS

Daptomycin was more active than comparators against methicillin-susceptible *S. aure*