Daptomycin Antimicrobial Activity and Spectrum When Tested Against Gram-positive Organisms from Australia and New Zealand (2008-2009)

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ABSTRACT

Background: Daptomycin (DAP) is a cyclic lipopeptide with a unique mechanism of action that includes binding to, and depolarizing the bacterial membrane, resulting in rapid cell death. Antimicrobial susceptibility (S) patterns of Gram-positive (GP) organisms commonly associated with hospital- and community-acquired infections in Australia (AU) and New Zealand (NZ) were evaluated.

Methods: 2,529 strains were consecutively collected from patients in 8 AU (1,826) and 3 NZ (703) medical centres in the 2008-2009 period. The strains were S tested by CLSI broth microdilution methods with 50 mg/L of calcium for daptomycin tests. Organisms evaluated included: *S. aureus* (SA: 1,818 strains), coagulase-negative staphylococci (CoNS; 90), enterococci (ENT; 251), β-haemolytic streptococci (BHS; 301), and viridans group streptococci (VGS; 69).

Results: Rates of oxacillin-resistance (R) among SA (MRSA) were 31.1% in AU and 11.3% in NZ. DAP was highly active against SA (oxacillin-S and MRSA; MIC_{90}, 0.5 mg/L for both groups). CoNS strains were also DAP-S (MIC_{90}; 0.5-1 mg/L). The highest DAP MIC value among SA and CoNS was only 1 mg/L. DAP was two- to four-fold more active than vancomycin (VAN) or linezolid against SA and CoNS. All ENT were inhibited at the DAP breakpoint of ≤4 mg/L, including VAN-R strains. 40% of *E. faecium* from AU were VAN-R; all *van*B genotype by PCR. DAP was equally active against VAN-S and -R ENT. *E. faecalis* (MIC_{90}, 2 mg/L) exhibited DAP MIC values lower than *E. faecium* (MIC_{90}, 4 mg/L). BHS and VGS were very S to DAP (MIC_{90}, 0.25 and 0.5 mg/L respectively).

Conclusions: DAP showed 100.0% S and high potencies against recent clinical isolates of GP organisms from AU and NZ medical centres. R to other antimicrobial classes did not adversely influence the DAP activity against these troublesome organisms.

INTRODUCTION

Daptomycin is a cyclic lipopeptide with potent bactericidal activity against most Gram-positive bacteria and a unique mechanism of action, which involves insertion of the lipophilic daptomycin tail into the bacterial cell membrane, causing rapid membrane depolarization and bacterial death. Furthermore, daptomycin remains bactericidal against stationary-phase cultures of both oxacillin (methicillin)-susceptible (MSSA) and -resistant *Staphylococcus aureus* (MRSA) present at high density (10^9 cfu) in a simulated endocarditis vegetation model.

Daptomycin has been used in the United States (USA) for the treatment of complicated skin and skin structure infections (cSSSI) since 2003 and for treatment of right-sided infective endocarditis (RIE) due to *S. aureus* and for *S. aureus* bacteraemia when associated with RIE or cSSSI since 2005. Daptomycin is approved by the European Medicines Agency (EMEA) for use in many countries in Europe for same indications and has more recently been licensed in various nations in other continents. We evaluated the antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms associated with hospital- and community-acquired infections in Australia and New Zealand.

MATERIALS AND METHODS

Organism collection: A total of 2,529 strains were consecutively collected from patients in eight Australian (1,826) and three New Zealand (703) medical centres in the 2008-2009 period. Organisms evaluated included: *S. aureus* (1,818 strains), coagulase-negative staphylococci (CoNS; 90), enterococci (251), β-haemolytic streptococci (301) and viridans group streptococci (69).

Susceptibility testing: All strains were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. Daptomycin susceptible breakpoints approved by the United States (USA) Food and Drug Administration (FDA), CLSI and EUCAST (≤1 mg/L for staphylococci and β-haemolytic streptococci and ≤4 mg/L for enterococci) were applied. The following quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin was highly active against MSSA and MRSA from Australia and New Zealand (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L for isolates from both countries) and its activity was not adversely influenced by resistance to oxacillin. All *S. aureus* isolates were susceptible to daptomycin (Tables 1 and 2).
- Linezolid (MIC_{50} and MIC_{90}, 2 mg/L) and vancomycin (MIC_{50} and MIC_{90}, 1 mg/L) were also very active against *S. aureus*, but four- to eight-fold less potent than daptomycin (Table 2).
- Daptomycin activity against CoNS (MIC_{50}, 0.25 mg/L and MIC_{90}, 1 mg/L) was similar to that observed against *S. aureus* and all isolates were inhibited at daptomycin susceptible breakpoint of ≤1 mg/L (Tables 1 and 2).
- Daptomycin was highly active against *E. faecalis* strains (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L; 100.0% susceptible). Ampicillin (MIC_{90}, 2 mg/L) and linezolid (MIC_{90}, 2 mg/L) were also active against all *E. faecalis* strains tested and only one strain (Australia) was resistant to vancomycin (MIC_{90}, 2-4 mg/L; Table 2).
- All *E. faecium* isolates were susceptible to daptomycin (MIC_{50}, 2-4 mg/L and MIC_{90}, 4 mg/L) and linezolid (MIC_{50} and MIC_{90}, 2 mg/L). Two strains (7.1%) were vancomycin-non-susceptible (Table 2).
- Among *E. faecium*, 40.0 and 10.0% of strains were resistant to vancomycin (VRE) in Australia and New Zealand (only 10 isolates tested), respectively (Table 2). Daptomycin MIC distributions among VRE were very similar to that of vancomycin-susceptible strains, indicating that daptomycin activity was not adversely affected by resistance to vancomcyin (Table 1).
- Daptomycin was highly active against β-haemolytic streptococci (MIC_{90}, 0.25 mg/L) as were most comparison agents tested. Viridans group streptococci (MIC_{50} and MIC_{90}, 0.5 mg/L) showed daptomycin MIC values slightly higher (two- to four-fold) than β-haemolytic streptococci (Table 2).
- Daptomycin was equally active against isolates from Australia and New Zealand for all organisms evaluated (Table 2).

Table 1. Antimicrobial activity of daptomycin tested against 2,529 Gram-positive organisms from Australia and New Zealand (2008-2009).

Organisms (no. tested)	No. of organisms (cumulative %) inhibited at daptomycin MIC (mg/L) of:						
	≤0.06	0.12	0.25	0.5	1	2	4
SA (1,818)	-	19 (1.1)	913 (51.3)	843 (97.6)	43 (100.0)	-	-
MSSA (1,341)	-	14 (1.0)	733 (55.7)	585 (99.3)	9 (100.0)	-	-
MRSA (477)	-	5 (1.1)	180 (38.8)	258 (92.9)	34 (100.0)	-	-
CoNS (90)	2 (2.2)	4 (6.7)	39 (50.0)	35 (88.9)	10 (100.0)	-	-
ENT (251)	-	-	6 (2.4)	41 (18.7)	116 (64.9)	67 (91.6)	21 (100.0)
VS (225)	-	-	5 (2.2)	34 (17.3)	111 (66.7)	58 (92.4)	17 (100.0)
VR (26)	-	-	1 (3.9)	7 (30.8)	5 (50.0)	9 (84.6)	4 (100.0)
BHS (301)	210 (69.8)	45 (84.7)	39 (97.7)	6 (99.7)	1 (100.0)	-	-
VGS (69)	6 (8.7)	7 (18.8)	21 (49.3)	29 (91.3)	6 (100.0)	-	-

ENT = *Enterococcus* spp.; VS/VR = Vancomycin susceptible/resistant; BHS = β-haemolytic streptococci; VGS = Viridans group streptococci.

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms from Australia and New Zealand (2008-2009).

Organism (no.)/ Antimicrobial agent	Australia			New Zealand		
	MIC_{50}	MIC_{90}	% Susceptible[a]	MIC_{50}	MIC_{90}	% Susceptible[a]
S. aureus	(1,375)			(443)		
Daptomycin	0.25	0.5	100.0	0.25	0.5	100.0
Oxacillin	0.5	>2	68.9	0.5	>2	88.7
Clindamycin	≤0.25	>2	86.7	≤0.25	≤0.25	99.3
Erythromycin	0.5	>2	72.0	≤0.25	0.5	91.6
Levofloxacin	≤0.5	>4	80.0	≤0.5	≤0.5	96.4
Linezolid	2	2	100.0	2	2	100.0
TMP/SMX	≤0.5	>2	85.7	≤0.5	≤0.5	97.7
Vancomycin	1	1	100.0	1	1	100.0
CoNS	(58)			(32)		
Daptomycin	0.25	1	100.0	0.5	0.5	100.0
Oxacillin	>2	>2	5.2	2	>2	31.3
Clindamycin	≤0.25	>2	69.0	≤0.25	>2	81.3
Erythromycin	>2	>2	29.3	≤0.25	>2	59.4
Levofloxacin	4	>4	43.1	≤0.5	4	65.6
Linezolid	1	1	100.0	1	2	100.0
TMP/SMX	>2	>2	46.6	≤0.5	>2	62.5
Vancomycin	2	2	100..0	2	2	100.0
E. faecalis	(99)			(74)		
Daptomycin	1	2	100.0	1	2	100.0
Ampicillin	≤1	2	100.0	≤1	2	100.0
Levofloxacin	1	>4	75.8	1	>4	71.6
Linezolid	2	2	100.0	2	2	100.0
Teicoplanin	≤2	≤2	100.0	≤2	≤2	100.0
Vancomycin	2	4	99.0	1	2	100.0
E. faecium	(60)			(10)		
Daptomycin	2	4	100.0	4	4	100.0
Ampicillin	>16	>16	11.7	>16	>16	30.0
Levofloxacin	>4	>4	16.7	>4	>4	100.0
Linezolid	2	2	96.7	2	2	100.0
Q/D	1	2	80.0	1	>2	50.0
Teicoplanin	≤2	≤2	100.0	≤2	≤2	100.0
Vancomycin	1	>16	60.0	1	1	90.0
BHS	(183)			(118)		
Daptomycin	≤0.06	0.25	100.0	≤0.06	0.25	100.0
Penicillin	≤0.015	0.06	100.0	≤0.015	0.06	100.0
Clindamycin	≤0.25	≤0.25	98.4	≤0.25	≤0.25	98.3
Levofloxacin	≤0.5	1	100.0	1	1	100.0
Linezolid	1	1	100.0	1	1	100.0
Tetracycline	≤2	>8	67.2	≤2	>8	72.9
Vancomycin	0.5	0.5	100.0	0.5	0.5	100.0
VGS	(45)			(24)		
Daptomycin	0.5	0.5	100.0	0.5	0.5	100.0
Penicillin	0.06	0.5	82.2	0.06	0.12	95.8
Ceftriaxone	≤0.25	0.5	95.6	≤0.25	≤0.25	95.8
Clindamycin	≤0.25	>2	86.7	≤0.25	≤0.25	95.8
Levofloxacin	1	2	97.8	1	2	100.0
Linezolid	1	2	100.0	1	2	100.0
Vancomycin	1	1	100.0	0.5	1	100.0

a. According to CLSI (M100-S20-U) breakpoint criteria.
TMP/SMX = Trimethoprim/sulfamethoxazole; Q/D = Quinupristin/dalfopristin; BHS = β-haemolytic streptococci; VGS = Viridans group streptococci.

CONCLUSIONS

- Daptomycin showed 100.0% susceptibility and high potencies against recent clinical isolates of Gram-positive organisms from Australia and New Zealand medical centres.
- Resistance to other antimicrobial classes did not adversely influence the daptomycin activity against these troublesome organisms.
- Daptomycin could represent an important treatment option for serious infections caused by Gram-positive cocci in Australia and New Zealand.

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