DAPTOMYCIN ACTIVITY TESTED AGAINST GRAM-POSITIVE COCCI ISOLATED IN CANADIAN MEDICAL CENTERS (2004-2007)

D ROSCOE*, DJ HOBAN, MA DESJARDINS, KR FORWARD, R RENNIE, HS SADER

Vancouver Hospital, Vancouver, BC, Canada; Health Sciences Centre, Winnipeg, MB, Canada;
Ottawa Hospital, General Campus, Ottawa, ON, Canada; Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada;
University of Alberta Hospital, Alberta, AB, Canada; and JMI Laboratories, North Liberty, IA, USA

Dr. Diane Roscoe
Vancouver Hospital
Vancouver, BC
diane.roscoe@vch.ca

ABSTRACT

BACKGROUND: Daptomycin is a cyclic lipopeptide with broad spectrum and potent antimicrobial activity against Gram-positive pathogens. Daptomycin is approved by Health Canada for the treatment of complicated skin and skin structure infections (cSSSI) and *S. aureus* bacteremia, including right-sided endocarditis.

METHODS: 2,737 bacterial isolates were consecutively collected in 2004-2007 in 5 Canadian hospitals from various types of infections, mainly bacteremia and cSSSI. Isolates were tested for susceptibility to daptomycin (50 mg/L calcium) and comparators using CLSI broth microdilution methods.

RESULTS: All isolates were susceptible to daptomycin – see table. Daptomycin was the most potent (lowest MIC_{90}) among selected antimicrobials commonly used to treat Gram-positive infections, including vancomycin, teicoplanin, linezolid, and ß-lactam and fluoroquinolone compounds.

Organism (no tested)	Cumulative % inhibited at MIC mg/L): ≤0.12	0.25	0.5	1	2	4
Methicillin-susceptible *S. aureus* (MSSA; 747)	4.7	80.9	99.9	100.0	-	-
Methicillin-resistant *S. aureus* (MRSA; 368)	1.6	75.4	98.6	100.0	-	-
Coagulase-negative staphylococci (CoNS; 589)	7.5	58.2	97.3	100.0	-	-
E. faecalis (432)	0.7	4.6	54.2	94.9	99.1	100.0
Vancomycin-susceptible *E. faecium* (106)	0.0	1.9	4.7	28.3	79.3	100.0
Vancomycin-resistant *E. faecium* (18)	0.0	0.0	0.0	44.4	100.0	-
ß-haemolytic streptococci (246)	78.1	97.6	100.0	-	-	-
Viridans group streptococci (209)	35.4	65.1	92.8	100.0	-	-

33.0 and 70.1% of *S. aureus* and CoNS were resistant to methicillin, respectively, and daptomycin demonstrated excellent activity against both methicillin-susceptible and methicillin-resistant staphylococci ($MIC_{50/90}$, 0.25/0.5 mg/L). Vancomycin resistance (VRE) was detected among 12.9% of *E. faecium*, but daptomycin remained highly active against these strains (MIC_{90}, 2 mg/L).

CONCLUSIONS: Resistance to methicillin or vancomycin did not adversely influence daptomycin activity against staphylococci or enterococci. Daptomycin demonstrated significant potency and spectrum against contemporary Gram-positive bacteria isolated in Canada, including MRSA and VRE.

INTRODUCTION

Increasing antimicrobial resistance has created a need for development of new antimicrobial agents. Daptomycin is a novel cyclic lipopeptide which has a mechanism of action distinct from other antibiotics. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential and potassium loss causing inhibition of protein, DNA and RNA synthesis and rapid cell death. Daptomycin has rapid in vitro bactericidal activity against a wide spectrum of Gram-positive organisms, including multidrug-resistant strains of staphylococci, streptococci and enterococci. It is important to note that daptomycin in vitro activity is dependent upon the presence of physiologic levels of calcium in the culture medium, making accurate testing of this agent challenging for clinical microbiology laboratories not using commercial automated systems.

Daptomycin was approved by the Health Canada, the United States Food and Drug Administration (US-FDA) and the European Medicine Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24 hours and for treatment of *Staphylococcus aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg every 24 hours. We evaluated the in vitro activity of daptomycin and comparator agents tested against Gram-positive organisms collected in Canadian hospitals.

MATERIALS AND METHODS

The isolates were consecutively collected mainly from bloodstream and skin and soft tissue infections according to a common protocol as part of a worldwide surveillance platform. In this study, we evaluated 2,737 bacterial isolates collected in 2004-2007 in 5 Canadian hospitals.

Susceptibility testing was performed by broth microdilution methods in validated microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, OH, USA). The test medium was Mueller-Hinton broth adjusted to contain physiologic levels of calcium (50 mg/L) for testing daptomycin. Susceptibility was defined according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints.

The daptomycin susceptible breakpoint of ≤1 mg/L was used for staphylococci and streptococci, while ≤4 mg/L was used for enterococci, as established by the US-FDA, Health Canada and the CLSI. The following quality control organisms were concurrently tested: *Streptococcus pneumoniae* ATCC strain 49619, *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213.

RESULTS

- Daptomycin was highly active against all Gram-positive organisms collected in Canadian medical centers in the 2004-2007 period and no daptomycin-resistant strains were observed (Tables 1 and 2).
- *S. aureus* strains were very susceptible to daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L). Daptomycin was also very potent against coagulase-negative staphylococci (CoNS; MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; Tables 1 and 2).
- All staphylococcal strains were considered susceptible to daptomycin based on the susceptible breakpoints approved by the US-FDA, Health Canada and CLSI (≤1 mg/L) for these pathogens. Furthermore, daptomycin was equally active against both methicillin-resistant and -susceptible staphylococci (Table 1).
- Daptomycin, linezolid and vancomycin were the most active compounds tested against *E. faecalis* with 100.0% of isolates being susceptible to these compounds. Ampicillin (99.8% susceptible) was also very active against this organism (Table 2).
- *E. faecium* showed high rates of resistance to most compounds tested, including vancomycin (14.5%). Daptomycin (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L) and linezolid (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) were the most active compounds against this pathogen with 100.0% of isolates being susceptible to both drugs (Table 2).
- Daptomycin activity against *E. faecium* was not affected by vancomycin resistance patterns (Table 1).
- ß-haemolytic streptococcal strains were very susceptible to daptomycin (MIC_{90}, 0.25 and 0.12 mg/L, respectively) and the majority of compounds tested; however, 21.5% of strains were resistant to erythromycin and 50.8% were resistant to tetracycline (Table 2).
- All viridans group streptococci were susceptible to daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L), linezolid (MIC_{50} and MIC_{90} at 1 mg/L) and vancomycin (MIC_{50} and MIC_{90}, 0.5 mg/L).

Table 1. Activity of daptomycin tested by reference broth microdilution (CLSI) methods against eight analysis groups of Gram-positive cocci isolated from Canadian medical centers (2004-2007).

Organism (no tested)	Number of isolates (%) inhibited at MIC (mg/L): ≤0.06	0.12	0.25	0.5	1	2	4	>4
Methicillin-susceptible *S. aureus* (747)	-[a]	35 (4.7)	569 (76.2)	142 (19.0)	1 (0.1)	-	-	-
Methicillin-resistant *S. aureus* (368)	-	6 (1.6)	264 (71.4)	93 (25.3)	5 (1.4)	-	-	-
Methicillin-susceptible CoNS (176)	5 (2.8)	18 (10.2)	87 (49.4)	57 (32.4)	9 (5.1)	-	-	-
Methicillin-resistant CoNS (413)	1 (0.2)	20 (4.8)	212 (51.3)	173 (41.9)	7 (1.7)	-	-	-
Enterococcus faecalis (432)	1 (0.2)	2 (0.5)	17 (3.9)	214 (49.5)	176 (40.7)	18 (4.2)	4 (0.9)	-
Vancomycin-susceptible *E. faecium* (106)	-	-	2 (1.9)	3 (2.8)	25 (23.6)	54 (50.9)	22 (20.8)	-
Vancomycin-resistant *E. faecium* (18)	-	-	-	-	8 (44.4)	10 (55.6)	-	-
ß-haemolytic streptococci (246)	145 (58.9)	47 (19.1)	48 (19.5)	6 (2.4)	-	-	-	-
Viridans group streptococci (209)	34 (16.3)	40 (19.1)	62 (29.7)	58 (27.8)	15 (7.2)	-	-	-

a. - = No isolate showed this MIC value.

Table 2. Activity of daptomycin and comparator agents tested against Gram-positive organisms from Canadian hospitals.

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
S. aureus				
Methicillin-susceptible (747)				
Daptomycin	0.25	0.5	0.12-1	100.0 / -[b]
Erythromycin	≤0.25	>4	≤0.25->4	77.4 / 22.5
Clindamycin	≤0.25	≤0.25	≤0.25->2	94.5 / 5.2
Levofloxacin	≤0.5	≤0.5	≤0.5->4	92.8 / 6.7
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	99.5 / 0.5
Tetracycline	≤2	≤2	≤2->8	96.4 / 3.3
Linezolid	2	2	0.25-4	100.0 / -
Vancomycin	1	1	0.25-2	100.0 / 0.0
Methicillin-resistant (368)				
Daptomycin	0.25	0.5	0.12-1	100.0 / -
Erythromycin	>4	>4	≤0.25->4	9.2 / 90.5
Clindamycin	>2	>2	≤0.25->2	34.2 / 65.8
Levofloxacin	>4	>4	≤0.5->4	10.9 / 86.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	85.3 / 14.7
Tetracycline	≤2	>8	≤2->8	81.3 / 18.5
Linezolid	1	2	0.5-2	100.0 / -
Vancomycin	1	1	0.5-2	100.0 / 0.0
Coagulase-negative staphylococci				
Oxacillin-susceptible (176)				
Daptomycin	0.25	0.5	≤0.06-1	100.0 / -
Erythromycin	≤0.25	>2	≤0.25->2	65.9 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25->2	92.6 / 6.8
Levofloxacin	≤0.5	≤0.5	≤0.5->4	90.3 / 9.1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	88.6 / 11.4
Tetracycline	≤2	≤2	≤2->8	93.8 / 6.3
Linezolid	1	1	0.25-2	100.0 / -
Vancomycin	1	2	0.25-4	100.0 / 0.0
Oxacillin-resistant (413)				
Daptomycin	0.25	0.5	≤0.06-1	100.0 / -
Erythromycin	>2	>2	≤0.25->2	20.6 / 0.0
Clindamycin	>2	>2	≤0.25->2	46.0 / 53.5
Levofloxacin	>4	>4	≤0.5->4	37.0 / 60.3
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	47.7 / 52.3
Tetracycline	≤2	>8	≤2->8	88.1 / 11.1
Linezolid	1	1	0.25-2	100.0 / -
Vancomycin	1	2	0.25-2	100.0 / 0.0
E. faecalis (432)				
Daptomycin	0.5	1	≤0.06-4	100.0 / -
Ampicillin	≤1	2	≤1->16	99.8 / 0.2
Levofloxacin	1	>4	≤0.5->4	58.6 / 41.0
Gentamicin (HL)	≤500	>1000	≤500->1000	67.6 / 32.4
Streptomycin (HL)	≤1000	>2000	≤1000->2000	74.3 / 25.7
Quinupristin/dalfopristin	>2	>2	≤0.25->2	0.9 / 96.5
Linezolid	1	2	0.25-2	100.0 / 0.0
Vancomycin	1	2	0.25-4	100.0 / 0.0

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
E. faecium				
Vancomycin-susceptible (106)				
Daptomycin	2	4	0.25-4	100.0 / -
Ampicillin	>16	>16	≤1->16	19.8 / 80.2
Levofloxacin	>4	>4	≤0.5->4	12.3 / 77.4
Gentamicin (HL)	≤500	≤500	≤500->1000	97.2 / 2.8
Streptomycin (HL)	≤1000	>2000	≤1000->2000	73.6 / 26.4
Quinupristin/dalfopristin	0.5	2	≤0.25->2	80.2 / 9.4
Linezolid	2	2	0.25-2	100.0 / 0.0
Vancomycin-resistant (18)				
Daptomycin	2	2	1-2	100.0 / -
Ampicillin	>16	>16	>16	0.0 / 100.0
Levofloxacin	>4	>4	>4	0.0 / 100.0
Gentamicin (HL)	1000	>1000	≤500->1000	44.4 / 55.6
Streptomycin (HL)	2000	>2000	≤1000->2000	22.2 / 77.8
Quinupristin/dalfopristin	0.5	1	0.5-2	94.4 / 0.0
Linezolid	1	2	1-2	100.0 / 0.0
ß-haemolytic streptococci (246)				
Daptomycin	≤0.06	0.25	≤0.06-0.5	100.0 / -
Penicillin	≤0.015	0.06	≤0.015-0.12	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -
Erythromycin	≤0.25	>2	≤0.25->2	78.5 / 21.5
Clindamycin	≤0.25	≤0.25	≤0.25->2	93.1 / 6.9
Levofloxacin	≤0.5	1	≤0.5->4	98.4 / 1.2
Tetracycline	8	>8	≤2->8	47.6 / 50.8
Linezolid	1	1	0.25-2	100.0 / -
Vancomycin	0.25	0.5	0.25-1	100.0 / -
Viridans group streptococci (209)				
Daptomycin	0.25	0.5	≤0.06-1	100.0 / -
Penicillin	0.06	0.5	≤0.015-4	76.1 / 1.4
Ceftriaxone	≤0.25	≤0.25	≤0.25-4	99.5 / 0.5
Erythromycin	≤0.25	>2	≤0.25->2	56.9 / 39.2
Clindamycin	≤0.25	≤0.25	≤0.25->2	96.7 / 3.3
Levofloxacin	1	2	≤0.5->4	95.2 / 3.8
Tetracycline	≤2	>8	≤2->8	70.8 / 25.8
Linezolid	0.5	1	0.12-1	100.0 / -
Vancomycin	0.5	0.5	≤0.12-1	100.0 / -

a. According to CLSI breakpoint criteria.
b. - = no breakpoint has been established by the CLSI.

CONCLUSIONS

- Daptomycin demonstrated potent in vitro activity and broad spectrum against Gram-positive organisms collected in five Canadian medical centers in 2004-2007.
- The in vitro activity of daptomycin was not associated with resistance to vancomycin, macrolides, quinupristin/dalfopristin and oxacillin or penicillin when tested against enterococci, staphylococci or streptococci with a wide range of resistance patterns (Table 2).
- Daptomycin appears to represent a potential therapeutic option for complicated infections caused by both susceptible Gram-positive cocci, and multi-resistant Gram-positive pathogens (especially MRSA) that occur in this geographic area.

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