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Susceptibility Pattern of Gram-positive Organisms Isolated in Australian Medical Centers (2004, 2006-2007): Results from a Multi-center Prospective Surveillance Program

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ABSTRACT

Background: Antimicrobial susceptibility (S) patterns of Gram-positive (GP) organisms most commonly associated with hospital- and community-acquired infections in Australia were evaluated.

Methods: Bacterial isolates were consecutively collected from patients in 8 Australian medical centers in the 2004-2007 period and tested for S by CLSI broth microdilution methods with appropriate supplements.

Results: 1,603 organisms were tested, most from bacteremia and skin/skin structure infections. Resistance (R) to erythromycin, levofloxacin (LEV), trimethoprim/sulfamethoxazole (TMP/SMX) and tetracycline (TET; 39.6%) were high among MRSA (24.4% of *S. aureus*). Vancomycin (VAN), linezolid (LZD) and daptomycin (DAP) were very active against MRSA and DAP was 4-fold more potent than VAN or LZD (Table). TMP/SMX-R was also elevated among CoNS (37.8%). CoNS strains with decreased S to teicoplanin (TEI; 98.0% S) and quinupristin/dalfopristin (Q/D; 99.0% S) were observed. *E. faecium* showed very low S to ampicillin (14.3%) and Q/D (71.4%), and elevated high-level R to gentamicin (50.0%); in contrast, all strains were S to DAP (MIC range, 1-4 μg/ml) and TEI. Among viridans gr. strep., 75.4 and 92.8% were S to penicillin and ceftriaxone, respectively. All GP tested were S to DAP except for 1 MRSA (VISA) with DAP MIC of 2 μg/ml (1 $\log_2$ dilution above S breakpoint). Only 58.4% of β-haemolytic strep. were S to TET.

Organism (no tested)	MIC_{90} (μg/ml) /% S					
	LEV	Clindamycin	TMP/SMX	VAN	LZD	DAP
MSSA (877)	≤0.5/99.3	≤0.25/99.1	≤0.5/98.9	1/100	2/100	0.5/100
MRSA (283)	>4/35.7	>2/72.8	>2/60.4	2/99.6	2/100	0.5/>99.6
CoNS (98)	>4/63.3	>2/88.8	>2/62.2	2/100	1/100	1/100
E. faecalis (86)	>4/67.4	-	-	2/98.8	2/100	2/100
E. faecium (28)	>4/7.1	-	-	4/92.9	2/100	4/100
β-haemolytic strep. (161)	1/99.4	≤0.25/99.4	≤0.5/-	0.5/100	1/100	0.25/100
Viridans gr. strep. (65)	1/100	≤0.25/93.8	-	1/100	1/100	1/-

Conclusion: Antimicrobial R among GP appears to be relatively low in Australia compared to those published from other Asia-Pacific countries. DAP and LZD showed greatest in vitro activity against GP organisms (1,603) collected in Australian hospitals.

INTRODUCTION

Daptomycin is a cyclic lipopeptide with potent bactericidal activity against most Gram-positive organisms including multidrug-resistant (MDR) organisms. The unique structure of daptomycin confers a novel mechanism of action, which involves insertion of the lipophilic daptomycin tail into the bacterial cell membrane, causing rapid membrane depolarization and a potassium ion efflux, resulting in rapid 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 for the treatment of complicated skin and skin structure infections (cSSSI) since 2003 (USA), and was later approved for the treatment of right sided infective endocarditis (RIE) due to *S. aureus* and for *S. aureus* bacteraemia when associated with RIE or cSSSI. Daptomycin has also been used in many European countries and, has more recently been licensed in other nations. We evaluated the in vitro activity of daptomycin and comparators against contemporary clinical isolates collected in eight hospitals across Australia.

MATERIALS AND METHODS

Bacterial Isolates: Bacterial isolates were consecutively collected from patients in eight Australian medical centers in the 2004-2007 period. The majority of isolates were from bloodstream infections (BSI) and cSSSI.

Susceptibility Testing: The strains were susceptibility tested against daptomycin and numerous comparator agents by reference broth microdilution methods performed according to Clinical and Laboratory Standards Institute (CLSI) documents. 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 μg/ml for staphylococci and β-haemolytic streptococci and ≤4 μg/ml 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 (MIC_{90}, 0.5 μg/ml) and its activity was not adversely influenced by resistance to oxacillin. All staphylococcal isolates were susceptible to daptomycin except for one vancomycin-intermediate MRSA strain (Tables 1 and 2).
- Linezolid (MIC_{50} and MIC_{90}, 2 μg/ml) and vancomycin (MIC_{50} 1 μg/ml and MIC_{90}, 1-2 μg/ml) were also very active against *S. aureus*, but four- to eight-fold less potent than daptomycin.
- MRSA strains exhibited high resistance rates to many antimicrobials, including erythromycin (69.3%), levofloxacin (64.0%), trimethoprim/sulfamethoxazole (TMP/SMX; 39.6%) and clindamycin (26.9%).
- Daptomycin activity against CoNS (MIC_{50} of 0.5 μg/ml and MIC_{90} of 1 μg/ml) was similar to that observed against *S. aureus* and all isolates were inhibited at daptomycin susceptible breakpoint of ≤1 μg/ml. CoNS strains with decreased susceptibility to teicoplanin (MIC_{90}, 4 μg/ml, 98.0% susceptible) and quinupristin/dalfopristin (MIC_{90}, 0.5 μg/ml, 99.0% susceptible) were observed.
- Daptomycin was highly active against *E. faecalis* strains (MIC_{50}, 1 μg/ml and MIC_{90}, 2 μg/ml; 100.0% susceptible). Ampicillin (MIC_{90}, 2 μg/ml) and linezolid (MIC_{90}, 2 μg/ml) were also active against all *E. faecalis* strains tested and only one strain was resistant to vancomycin (MIC_{90}, 2 μg/ml and 98.8% susceptible; Table 1).
- All *E. faecium* isolates were susceptible to daptomycin (MIC_{50}, 2 μg/ml and MIC_{90}, 4 μg/ml) and linezolid (MIC_{50} and MIC_{90}, 2 μg/ml). Two strains (7.1%) were vancomycin-nonsusceptible (Table 2).
- Only three vancomycin-nonsusceptible enterococci were observed and all three strains were susceptible to daptomycin (MIC range, 0.5 – 2 μg/ml; Table 1) and linezolid (MIC range, 1 – 2 μg/ml; Table 2).
- Daptomycin was highly active against β-haemolytic streptococci (MIC_{90}, 0.25 μg/ml) as were most comparison agents tested. Viridans group streptococci (MIC_{50}, 0.25 μg/ml and MIC_{90}, 1 μg/ml) showed daptomycin MIC values slightly higher (two-fold) than β-haemolytic streptococci (Table 2).

Table 1. Daptomycin MIC distributions of Gram-positive organisms from Australian medical centers (2004-2007).

	No. of strain (cumulative %) inhibited at daptomycin MIC (μg/ml) of:						
Organism (no. tested)	≤0.06	0.12	0.25	0.5	1	2	4
MSSA (877)	0(0.0)	6(0.7)	505(58.3)	351(98.3)	15(100.0)	-	-
MRSA (283)	0(0.0)	0(0.0)	124(43.8)	146(95.4)	12(99.7)	1(100.0)	-
CoNS (98)	2(2.0)	3(5.1)	33(38.8)	47(86.7)	13(100.0)	-	-
E. faecalis (86)	0(0.0)	1(1.2)	0(1.2)	16(19.8)	51(79.1)	16(97.7)	2(100.0)
E. faecium (28)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(17.9)	17(78.6)	6(100.0)
Vancomycin-nonsusceptible enterococci (3)[a]	0(0.0)	0(0.0)	0(0.0)	1(33.3)	1(66.7)	1(100.0)	-
β-haemolytic streptococci (161)	108(67.1)	14(75.8)	35(97.5)	4(100.0)	-	-	-
Viridans group streptococci (65)	1(1.5)	8(13.9)	25(52.3)	18(80.0)	12(98.5)	1(100.0)	-

a. Includes one *E. faecalis* and two *E. faecium* isolates.
Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; CoNS, coagulase-negative staphylococci.

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms from Australian medical centers.

Antimicrobial agent/ organism (no. tested)	MIC (μg/ml): MIC_{50}	MIC_{90}	% susceptible	% resistant[b]
MSSA (877)				
Daptomycin	0.25	0.5	100.0	-
Clindamycin	≤0.25	≤0.25	99.1	0.9
Erythromycin	≤0.25	>4	89.2	10.7
Levofloxacin	≤0.5	≤0.5	99.3	0.6
Linezolid	2	2	100.0	-
Q/D	≤0.25	0.5	100.0	0.0
Tetracycline	≤2	≤2	97.3	2.7
TMP/SMX	≤0.5	≤0.5	98.9	1.1
Teicoplanin	≤2	≤2	100.0	100.0
Vancomycin	1	1	100.0	0.0
MRSA (283)				
Daptomycin	0.5	0.5	99.6	-
Clindamycin	≤0.25	>2	72.8	26.9
Erythromycin	>4	>4	26.9	69.3
Levofloxacin	4	>4	35.7	64.0
Linezolid	2	2	100.0	-
Q/D	≤0.25	0.5	100.0	0.0
Tetracycline	≤2	>8	60.4	39.6
TMP/SMX	≤0.5	>2	60.4	39.6
Teicoplanin	≤2	≤2	100.0	0.0
Vancomycin	1	2	99.6	0.0
CoNS (98)				
Daptomycin	0.5	1	100.0	-
Oxacillin	>2	>2	15.3	84.7
Clindamycin	≤0.25	>2	88.8	10.2
Erythromycin	>2	>2	40.8	57.1
Levofloxacin	≤0.5	>4	63.3	33.7
Linezolid	1	1	100.0	-
Q/D	≤0.25	0.5	99.0	1.0
Tetracycline	≤2	>8	89.8	10.2
TMP/SMX	≤0.5	>2	62.2	37.8
Teicoplanin	≤2	4	98.0	0.0
Vancomycin	2	2	100.0	0.0
E. faecalis (86)				
Daptomycin	1	2	100.0	-
Ampicillin	≤1	2	100.0	0.0
Gentamicin (HL)	≤500	>1000	52.3	47.7
Levofloxacin	1	>4	67.4	31.4
Linezolid	1	2	100.0	0.0
Q/D	>2	>2	0.0	95.3
Streptomycin (HL)	≤1000	≤1000	90.7	93
Teicoplanin	≤2	≤2	100.0	0.0
Vancomycin	1	2	98.8	1.2
E. faecium (28)				
Daptomycin	2	4	100.0	-
Ampicillin	>16	>16	14.3	85.7
Gentamicin (HL)	≤500	>1000	50.0	50.0
Levofloxacin	>4	>4	7.1	85.7
Linezolid	2	2	100.0	0.0
Q/D	0.5	2	71.4	7.1
Streptomycin (HL)	2000	>2000	46.4	53.6
Teicoplanin	≤2	≤2	100.0	0.0
Vancomycin	1	4	92.9	3.6

Table 2. Continued.

Antimicrobial agent/ organism (no. tested)	MIC (μg/ml): MIC_{50}	MIC_{90}	% susceptible	% resistant[a]
β-haemolytic streptococci (161)				
Daptomycin	≤0.06	0.25	100.0	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Clindamycin	≤0.25	≤0.25	99.4	0.6
Erythromycin	≤0.25	≤0.25	95.0	4.3
Levofloxacin	≤0.5	1	99.4	0.6
Linezolid	1	1	100.0	-
Penicillin	≤0.015	0.06	100.0	-
Tetracycline	≤2	>8	58.4	39.1
Vancomycin	0.5	0.5	100.0	-
Viridans group streptococci (65)				
Daptomycin	0.25	1	-	-
Ceftriaxone	≤0.25	1	92.3	4.6
Clindamycin	≤0.25	≤0.25	93.8	6.2
Erythromycin	≤0.25	>2	61.5	38.5
Levofloxacin	1	1	100.0	0.0
Linezolid	1	1	100.0	-
Penicillin	0.06	2	75.4	6.2
Tetracycline	≤2	>8	67.7	32.3
Vancomycin	0.5	1	100.0	-

a. According to CLSI (2009) breakpoints.
Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; CoNS, coagulase-negative staphylococci; Q /D, quinupristin/dalfopristin; TMP/SMX, trimethoprim/sulfamethoxazole and HL, high-level resistance.

CONCLUSIONS

- Daptomycin showed significant potency and broad-spectrum activity against contemporary isolates of Gram-positive pathogens in Australian medical centers.
- All organisms tested, except for one VISA strain, were susceptible to daptomycin.
- Daptomycin could represent an important treatment option for serious infections caused by Gram-positive cocci in Australia.

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