Antimicrobial Activity of Daptomycin and Comparator Agents Tested Against Gram-positive Organisms from Hong Kong, Indonesia, Philippines, Singapore and Thailand

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Daptomycin is registered in the USA and Europe as CUBICIN™

ABSTRACT

Background: Daptomycin is a cyclic lipopeptide with potent bactericidal activity against Gram-positive organisms. Daptomycin has been used in the USA and Europe for the treatment of complicated skin and soft tissue (cSSTI) and bloodstream infections (BSI) for several years. We evaluated the *in vitro* activity of daptomycin and comparators against recent (2006) clinical isolates collected in 5 Asia-Pacific (APAC) countries.

Methods: 523 consecutive strains were collected in (no. of strains; medical centers) Hong Kong (100; 1), Indonesia (63; 3), Philippines (124; 2), Singapore (119; 1) and Thailand (117; 2). Most isolates were from cSSTI and BSI. Organisms evaluated included: *S. aureus* (SA; 326 strains); coagulase-negative staphylococci (CoNS; 31), enterococci (92), viridans group streptococci (VGS; 32) and ß-haemolytic streptococci (BHS; 42). Antimicrobial susceptibility was evaluated by reference broth microdilution methods in cation-adjusted Mueller-Hinton broth with 50 mg/L of calcium for daptomycin tests.

Results: Daptomycin was highly active against SA (100.0% susceptibility) with minor variations among countries (see Table 1). Among SA, oxacillin resistance varied from 29.6% in Thailand to 80.4% in Singapore; while the highest rates of resistance to clindamycin and trimethoprim/sulfamethoxazole were observed in Indonesia (46.9 and 59.6% respectively), Thailand (28.3 and 39.1%) and Singapore (29.6 and 31.5%). Daptomycin inhibited all CoNS strains at ≤1 mg/L and was two- to four-fold more potent than vancomycin or linezolid against SA and CoNS. Enterococci were also very susceptible to daptomycin ($MIC_{50/90}$, 1/4 mg/L; 100.0% susceptible) and vancomycin resistance was observed only in Thailand (2.0%, VRE). VGS and BHS strains showed lower daptomycin MIC values (MIC_{90}, 1 and 0.25 mg/L respectively).

Conclusions: Antimicrobial susceptibility patterns of Gram-positive organisms varied substantially among the APAC nations evaluated and daptomycin exhibited complete coverage (100.0% susceptibility) and high potency against a large collection of contemporary clinical strains collected in 9 hospitals from 5 APAC countries.

INTRODUCTION

Daptomycin, a fermentation product produced by *Streptomyces roseosporus*, 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 bacterial cell death. The bactericidal effect of daptomycin is rapid and it is not adversely affected by oxacillin (methicillin) resistance. Furthermore, this rapid cell death does not result in rapid bacterial cell lysis. Daptomycin also remains bactericidal against stationary phase cultures of both oxacillin (methicillin)-susceptible (MSSA) and -resistant *S. aureus* (MRSA) present at high density (10^9 cfu) in a simulated endocarditis vegetation model.

We evaluated the *in vitro* activity of daptomycin and comparators against recent (2006) clinical isolates collected in five Asia-Pacific (APAC) countries.

MATERIALS AND METHODS

Bacterial isolates: A total of 523 consecutive strains were evaluated, including *S. aureus* (326 strains), coagulase-negative staphylococci (CoNS; 31), enterococci (92), viridans group streptococci (32) and ß-haemolytic streptococci (42). All isolates were collected from patients hospitalized in (no. of strains; no. of medical centers) Hong Kong (100; 1), Indonesia (63; 3), Philippines (124; 2), Singapore (119; 1) and Thailand (117; 2). Most isolates were from complicated skin and soft tissue infections (cSSTI) and blood stream infections (BSI).

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 USA-FDA, CLSI end EUCAST (≤1 mg/L for staphylococci and 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 *S. aureus* (overall MIC_{50} and MIC_{90} of 0.5 mg/L, 100.0% susceptible) with minor variations among countries (Tables 1 and 2)
- For *S. aureus*, oxacillin resistance varied from 29.6% in Thailand to 80.4% in Singapore (Table 3); while the highest rates of resistance to clindamycin and trimethoprim/sulfamethoxazole were observed in Indonesia (46.9 and 59.6%, respectively), Thailand (28.3 and 39.1%) and Singapore (29.6 and 31.5%)
- Overall, MRSA strains showed high rates of resistance to erythromycin (76.7%), clindamycin (36.0%), levofloxacin (77.9%), tetracycline (59.9%), and trimethoprim/sulfamethoxazole (43.6%; Table 2)
- Daptomycin inhibited all CoNS strains at ≤1 mg/L and was two- to four-fold more potent than vancomycin or linezolid against *S. aureus* and CoNS (Table 2)
- Enterococci were also very susceptible to daptomycin (MIC_{50}, 1 mg/L and MIC_{90}, 4 mg/L; 100.0% susceptible) and vancomycin resistance was observed only in Thailand (2.0%, one strain of *E. gallinarum*)
- Daptomycin was highly active against *E. faecalis* strains (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L). Ampicillin (MIC_{90}, 2 mg/L), vancomycin (MIC_{90}, 2 mg/L) and linezolid (MIC_{90}, 2 mg/L) were also very active (100.0% susceptible) against *E. faecalis*. In contrast, 32.7% *E. faecalis* strains showed high-level resistance to gentamicin and/or streptomycin (50.0 to 76.5% among *E. faecium*; Table 2)
- All *E. faecium* isolates were susceptible to daptomycin (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L; Table 2)
- ß-Haemolytic streptococci strains exhibited the lowest daptomycin MIC values (MIC_{90}, 0.25 mg/L).

Table 1. Frequency of daptomycin MIC values among *S. aureus* strains collected in the Asia-Pacific region in 2006

	No. (%) of *S. aureus* isolates inhibited at daptomycin MIC (mg/L) of:						
Country	0.12	0.25	0.5	1	2	MIC_{50}	MIC_{90}
Hong Kong (72)	1 (1.4)	41 (56.9)	30 (41.7)	0 (0.0)	0 (0.0)	0.25	0.5
Indonesia (32)	0 (0.0)	8 (25.0)	17 (53.1)	7 (21.9)	0 (0.0)	0.5	1
Philippines (76)	0 (0.0)	48 (63.2)	24 (31.6)	4 (5.3)	0 (0.0)	0.25	0.5
Singapore (92)	0 (0.0)	36 (39.1)	55 (59.8)	1 (1.1)	0 (0.0)	0.5	0.5
Thailand (54)	0 (0.0)	12 (22.2)	29 (53.7)	13 (24.1)	0 (0.0)	0.5	1
Overall (326)	1 (0.3)	145 (44.5)	155 (47.5)	25 (7.7)	0 (0.0)	0.5	0.5

CONCLUSIONS

- Antimicrobial susceptibility patterns of Gram-positive organisms varied substantially among the five sampled APAC nations evaluated
- No vancomycin-resistant *E. faecalis* or *E. faecium* was observed in the hospitals evaluated
- Daptomycin exhibited complete coverage (100.0% susceptibility) and high potency against a large collection of contemporary (2006) clinical strains collected in nine hospitals from five APAC countries

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Table 3. Frequency of important resistance phenotypes by country

Country	**Oxacillin-resistant *S. aureus* (%)**	**Vancomycin-non-susceptible *Enterococcus* spp.[a] (%)**
Hong Kong	37.5	0.0
Indonesia	65.7	0.0
Philippines	44.8	0.0
Thailand	29.6	2.0
Singapore	80.4	0.0
All regions	52.8	1.1

[a]Only one strain from Thailand (*E. Gallinarum*)

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms isolated in the Asia-Pacific region in 2006

Organism/antimicrobial agent (no. Tested)	MIC (mg/L) 50%	90%	% susceptible[a]	% resistant[a]
S. aureus				
Oxacillin-susceptible (154)				
Daptomycin	0.5	0.5	100.0	-
Vancomycin	1	1	100.0	0.0
Linezolid	2	2	100.0	-
Erythromycin	>2	>2	81.2	18.8
Clindamycin	≤0.25	>2	90.9	9.1
Levofloxacin	≤0.5	≤0.5	91.6	7.8
Tetracycline	≤2	>8	76.0	24.0
Trimethoprim/sulfamethoxazole	≤0.5	1	96.1	3.9
Oxacillin-resistant (172)				
Daptomycin	0.5	0.5	100.0	-
Vancomycin	1	2	100.0	0.0
Linezolid	1	2	100.0	-
Erythromycin	>2	>2	23.3	76.7
Clindamycin	>2	>2	64.0	36.0
Levofloxacin	>4	>4	22.1	77.9
Tetracycline	>8	>8	40.1	59.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	56.4	43.6
CoNS (31)				
Daptomycin	0.5	1	100.0	-
Vancomycin	2	2	100.0	0.0
Linezolid	1	1	100.0	-
Erythromycin	>2	>2	51.6	48.4
Clindamycin	≤0.25	>2	58.1	38.7
Levofloxacin	4	>4	71.0	25.8
Tetracycline	≤2	>8	58.1	41.9
Trimethoprim/sulfamethoxazole	1	>2	80.6	19.4
E. faecalis (55)				
Daptomycin	1	4	100.0	-
Vancomycin	1	2	100.0	0.0
Linezolid	1	2	100.0	0.5
Ampicillin	≤1	2	100.0	0.0
Levofloxacin	1	>4	60.0	40.0
Gentamicin (HL)[b]	1000	>1000	67.3	32.7
Streptomycin (HL)	≤1000	>2000	67.3	32.7
E. faecium (34)				
Daptomycin	2	4	100.0	-
Vancomycin	1	1	100.0	0.0
Linezolid	1	2	100.0	0.0
Ampicillin	>16	>16	2.9	97.1
Levofloxacin	>4	>4	0.0	97.1
Quinupristin/dalfopristin	1	>2	88.2	8.8
Gentamicin (HL)	>1000	>1000	23.5	76.5
Streptomycin (HL)	≤1000	>2000	50.0	50.0
Viridans group streptococci (32)				
Daptomycin	0.5	1	100.0	-
Vancomycin	0.5	1	100.0	-
Linezolid	1	1	100.0	-
Penicillin	0.12	2	56.3	6.3
Ceftriaxone	≤0.25	2	81.3	6.3
Erythromycin	>2	>2	81.3	18.8
Clindamycin	≤0.25	≤0.25	100.0	0.0
Levofloxacin	1	1	100.0	0.0
ß-haemolytic streptococci (42)				
Daptomycin	0.12	0.25	100.0	-
Vancomycin	0.5	0.5	100.0	-
Linezolid	1	1	100.0	-
Penicillin	0.03	0.06	100.0	-
Ceftriaxone	≤0.25	≤0.25	100.0	-
Erythromycin	≤0.25	>2	71.4	28.6
Clindamycin	≤0.25	>2	78.6	21.4
Levofloxacin	1	1	100.0	0.0

[a] CLSI interpretive criteria (2008)
[b] HL = High level resistance.

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