Daptomycin Activity Tested Against Gram-positive Bacteria Isolated from Medical Centers Located in China (2006)

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Daptomycin is registered in the USA and Europe as CUBICIN™

ABSTRACT

Background: Daptomycin, a novel cyclic lipopeptide, exhibits a unique mechanism of action that includes binding to, and depolarizing, the bacterial membrane resulting in rapid loss of cellular function and cell death. We evaluated the *in vitro* activity of daptomycin against recent clinical isolates collected in ten Chinese hospitals.

Methods: 924 consecutive strains were collected in Chinese medical centers in 2006. The organisms, one per patient, were isolated mainly from bloodstream and skin and soft tissue infections. The following pathogens were evaluated: *S. aureus* (SA; 37.5% oxacillin-resistant [MRSA]); coagulase-negative staphylococci (CoNS; 88.9% oxacillin-resistant), *Enterococcus* spp. (0.5% vancomycin-resistant [VRE]) and viridans group streptococci (VGS; 43.8% penicillin-susceptible). The strains were susceptibility tested by broth microdilution methods in cation-adjusted Mueller-Hinton broth supplemented to 50 mg/L of calcium for daptomycin tests. Numerous comparator agents were tested.

Results: All organisms tested were considered susceptible to daptomycin (see Table 1). Daptomycin was highly active against SA (MIC_{90}, 0.5 mg/L) and CoNS (MIC_{90}, 1 mg/L), and two- to four-fold more potent than vancomycin or linezolid against these organisms. MRSA showed high rates of resistance to clindamycin (92.4%), levofloxacin (96.2%) and gentamicin (95.5%), and daptomycin MIC values slightly higher compared to oxacillin-susceptible SA. All enterococcal strains were inhibited at the daptomycin susceptible breakpoint of ≤4 mg/L, including a few VRE strains. *E. faecalis* (MIC_{90}, 2 mg/L) exhibited daptomycin MIC values lower than *E. faecium* (MIC_{90}, 4 mg/L). Quinupristin/dalfopristin showed limited activity (61.7% susceptibility) against *E. faecium;* and *E. faecalis* showed high rate of high-level resistance to gentamicin (49.8%) and streptomycin (51.7%). Daptomycin was very active against VGS (MIC_{90}, 0.5 mg/L).

Conclusions: Daptomycin showed significant potency and broad-spectrum activity against recent clinical isolates of Gram-positive organisms isolated in Chinese medical centers, including multidrug-resistant subsets. All Gram-positive organisms tested were susceptible to daptomycin.

INTRODUCTION

Daptomycin, a novel cyclic lipopeptide, exhibits a unique mechanism of action that includes binding to, and depolarizing, the bacterial membrane resulting in rapid loss of cellular function and cell death. Daptomycin has been shown to be active against *Staphylococcus aureus* resistant to methicillin (oxacillin); linezolid-, quinupristin/dalfopristin- and vancomycin-resistant enterococci (VRE); and macrolide-resistant streptococci.

Daptomycin has been approved by the United States Food and Drug Administration (USA-FDA) and by the European Medicine Agency (EMEA) for the treatment of complicated skin and soft tissue infections (cSSTI) using a dose of 4 mg/kg every 24 hours, and for treatment of *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg every 24 hours. Daptomycin is not indicated for treatment of pneumonia due to its inhibition by naturally occurring pulmonary surfactants.

Antimicrobial resistance rates vary significantly by geographic regions and several resistance mechanisms are highly prevalent in various parts of the Asia-Pacific region. In the present study we evaluated the *in vitro* activity of daptomycin against recent clinical isolates collected from ten Chinese hospitals in 2006.

MATERIALS AND METHODS

Bacterial Strains: The isolates, one per patient, were consecutively collected, mainly from bloodstream and skin and soft tissue infections, from patients hospitalized in Chinese medical centers. Ten medical centers participated in the study and a total of 924 pathogens were evaluated: *S. aureus* (SA;419 strains; 37.5% oxacillin-resistant [MRSA]); coagulase-negative staphylococci (CoNS; 18 strains; 88.9% oxacillin-resistant), *Enterococcus* spp. (365 strains; 0.5% VRE) and viridans group streptococci (16 strains; VGS; 56.2% penicillin non-susceptible).

Susceptibility Testing: Daptomycin and comparator agents were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The test medium was Mueller-Hinton broth adjusted to contain physiologic levels of calcium (50 mg/L) when testing daptomycin. USA-FDA and CLSI approved daptomycin susceptible breakpoints of ≤1 mg/L for staphylococci and streptococci and ≤4mg/L for enterococci were used to categorize daptomycin susceptibility. The following quality control organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin was very active against oxacillin-susceptible (MSSA) and -resistant *S. aureus* (MIC_{50} and MIC_{90} of 0.5 mg/L for both pathogen groups; Tables 1 and 2). All staphylococcal isolates were inhibited at a daptomycin MIC of ≤1 mg/L, which is the susceptible breakpoint approved by the CLSI, USA-FDA and EUCAST
- Vancomycin (MIC_{50}, 1 mg/L and MIC_{90}, 1-2 mg/L) and linezolid (MIC_{50}, 1-2 mg/L and MIC_{90}, 2 mg/L) were also active against all *S. aureus* isolates at the current CLSI breakpoints, but were two to four-fold less active than daptomycin (Table 2)
- Erythromycin, clindamycin and tetracycline exhibited limited activity against MSSA (46.2%, 67.2% and 68.7% susceptibility, respectively) and MRSA (3.2%, 7.6% and 12.1% susceptibility, respectively)
- Daptomycin activity against CoNS was similar to that observed against *S. aureus* and all isolates were inhibited at daptomycin-susceptible breakpoint of ≤1 mg/L. Vancomycin (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) and linezolid (MIC_{50} and MIC_{90}, 1 mg/L) were also active against all strains
- Daptomycin was active against *E. faecalis* strains (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L). Ampicillin (MIC_{90}, 2 mg/L; 100.0% susceptible) and vancomycin (MIC_{90}, 2 mg/L; 100.0% susceptible) were also very active against *E. faecalis* and only one strain (0.5%) showed decreased susceptibility to linezolid. In contrast, approximately half of *E. faecalis* strains showed high-level resistance to gentamicin and/or streptomycin (Table 2)
- All *E. faecium* isolates were susceptible to daptomycin (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L), including VRE strains (only 1.2%). Quinupristin/dalfopristin was only active against 61.7% of *E. faecium* strains (Table 2)
- Daptomycin was very potent against viridans group streptococci (MIC_{50}, 0.25 mg/L and MIC_{90}, 1 mg/L) and all isolates were inhibited by daptomycin concentration of ≤1 mg/L (Table 1 and 2)

Table 1. Frequency of occurrence of daptomycin MIC among clinical strains collected from 10 Chinese medical centers in 2006.

	Cumulative % inhibited at daptomycin MIC (mg/L) of:					
Organism (no. tested)	≤0.25	0.5	1	2	4	%S[a]
MSSA (262)	42.0	98.5	100.0	-	-	100.0
MRSA (157)	19.1	95.5	100.0	-	-	100.0
CoNS (18)	38.9	88.9	100.0	-	-	100.0
E. faecalis (203)	1.0	12.3	75.4	100.0	-	100.0
E. faecium (162)	0.6	1.9	6.2	82.7	100.0	100.0
Viridans group streptococci (16)	68.7	87.5	100.0	-	-	100.0

[a]Percentage susceptible according to USA-FDA/CLSI interpretive criteria.

Table 2. Antimicrobial activity of daptomycin and comparator agents tested against Gram-positive organisms isolated in China.

	MIC (mg/L)			
Organism/antimicrobial agent (no. tested)	**50%**	**90%**	**% susceptible**	**% resistant**
S. aureus				
Oxacillin-susceptible (262)				
Daptomycin	0.5	0.5	100.0	-
Vancomycin	1	1	100.0	0.0
Linezolid	2	2	100.0	-
Erythromycin	>2	>2	46.2	53.8
Clindamycin	≤0.25	>2	67.6	32.4
Levofloxacin	≤0.5	≤0.5	92.7	6.9
Tetracycline	≤2	>8	68.7	30.5
Trimethoprim/sulfamethoxazole	≤0.5	1	93.1	6.9
Oxacillin-resistant (157)				
Daptomycin	0.5	0.5	100.0	-
Vancomycin	1	2	100.0	0.0
Linezolid	1	2	100.0	-
Erythromycin	>2	>2	3.2	95.5
Clindamycin	>2	>2	7.6	92.4
Levofloxacin	>4	>4	1.9	96.2
Tetracycline	>8	>8	12.1	87.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	80.9	19.1
CoNS (18)				
Daptomycin	0.5	1	100.0	-
Vancomycin	1	2	100.0	0.0
Linezolid	1	1	100.0	-
Erythromycin	>2	>2	16.7	83.3
Clindamycin	≤0.25	>2	50.0	50.0
Levofloxacin	4	>4	33.3	66.7
Tetracycline	≤2	>8	61.1	38.9
Trimethoprim/sulfamethoxazole	1	>2	61.1	38.9
E. Faecalis (203)				
Daptomycin	1	2	100.0	-
Vancomycin	1	2	100.0	0.0
Linezolid	1	2	99.5	0.5
Ampicillin	≤1	2	100.0	0.0
Levofloxacin	1	>4	67.0	33.0
Gentamicin (HL)	1000	>1000	49.8	50.2
Streptomycin (HL)	≤1000	>2000	51.7	48.3
E. faecium (162)				
Daptomycin	2	4	100.0	-
Vancomycin	1	2	98.8	1.2
Linezolid	1	2	100.0	0.0
Ampicillin	>16	>16	5.6	94.4
Levofloxacin	>4	>4	12.3	85.2
Quinupristin/dalfopristin	1	>2	61.7	16.0
Gentamicin (HL)	>1000	>1000	22.2	77.8
Streptomycin (HL)	≤1000	>2000	51.2	48.8
Viridans group streptococci (16)				
Daptomycin	0.25	1	100.0	-
Vancomycin	0.5	1	100.0	-
Linezolid	1	1	100.0	-
Penicillin	0.25	1	43.8	0.0
Ceftriaxone	≤0.25	≤0.25	100.0	0.0
Erythromycin	>2	>2	25.0	75.0
Clindamycin	>2	>2	43.8	56.3
Levofloxacin	1	>4	81.3	18.8

CONCLUSIONS

Daptomycin demonstrated significant potency and broad-spectrum activity against recent clinical isolates of Gram-positive organisms isolated in Chinese medical centers, including multidrug-resistant organism subsets.

All Gram-positive organisms tested were susceptible to daptomycin at internationally recognized breakpoints.

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