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Activity of Daptomycin and Selected Antimicrobial Agents against *Staphylococcus aureus* Isolated from Patients with Bacteremia in North America: A Four-Year Analysis

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IDSA 2006
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ABSTRACT

Background: Daptomycin (DAP) has been approved by the US-FDA for the treatment of complicated skin and soft tissue infections and a supplemental filing has been submitted to the FDA for *S. aureus* (SA) bacteremia and infectious endocarditis. We evaluated the activity of DAP against SA (5,894 strains) from patients with bloodstream infections (BSI) hospitalized in North American (NA) hospitals.

Methods: 5,894 SA causing BSI were collected from 29 medical centers located in the United States (24) and Canada (5) in 2002-2005. The strains were susceptibility (S) tested against DAP and numerous comparator agents by reference broth microdilution methods according to CLSI guidelines. Test medium was supplemented with calcium (50 mg/L) for testing DAP only.

Results: The highest DAP MIC observed was 2 µg/ml (only 3 strains). No significant variation was noted in the DAP activity ($MIC_{50/90}$) over the years evaluated. In contrast, oxacillin (OXA) resistance (R) increased from 39.1-41.0% in 2002-3 to 48.3-49.8% in 2004-5. DAP was equally active against OXA-S and OXA-R strains. S rates to other compounds were: erythromycin (41.4%), ciprofloxacin (55.3%), clindamycin (68.8%), trimethoprim-sulfamethoxazole (96.9%), quinupristin-dalfopristin (>99.9%; QD; 1 non-S strain), linezolid (>99.9%; 1 non-S strain) and vancomycin (>99.9%; 2 non-S strains).

	Year (no. of isolates tested) 2002 (1,270)	2003 (1,813)	2004 (1,452)	2005 (1,359)	All strains (5,894)	OXA-R strains (2,617)
DAP MIC_{50} (µg/ml)	0.25	0.25	0.25	0.25	0.25	0.25
DAP MIC_{90} (µg/ml)	0.5	0.5	0.5	0.5	0.5	0.5
% S to DAP	99.92	100.00	99.93	99.93	99.95	99.96
DAP non-S isolates[a]	1	0	1	1	3	1
% of S to oxacillin	60.9	59.0	50.2	51.7	55.6	0.0

a. All 3 isolates had DAP MIC at 2 µg/ml.

Conclusions: DAP was highly active against SA isolates from BSI and its activity remained stable during the 4 year period evaluated (2002-2005). Increased R has not been observed since US-FDA approval of DAP for treatment of skin and soft tissue infection in September 2003. R to OXA did not adversely influence DAP activity. R to QD, linezolid, vancomycin and DAP remain extremely low among SA isolated from BSI in NA.

INTRODUCTION

Staphylococcus aureus represents an important cause of bloodstream infections and the increasing prevalence of resistance exhibited by this pathogen is of particular concern. Infections caused by methicillin (oxacillin)-resistant *S. aureus* (MRSA) strains are associated with longer hospital stay, more days of antimicrobial therapy and higher costs than infections caused by methicillin-susceptible *S. aureus* (MSSA) strains. Vancomycin remains the standard for treating most MRSA bloodstream infections; however, concerns over increases in the rates of heteroresistance and tolerance to this agent, combined with its safety and clinical shortcomings have motivated the development of newer agents.

Daptomycin is a novel lipopeptide with potent in vitro activity against Gram-positive cocci. Daptomycin does not exhibit cross resistance with other known classes of antimicrobials and also has a low risk for development of spontaneous mutational resistance. Indeed, daptomycin has been shown to be active against MRSA, *S. aureus* resistant to linezolid or quinupristin/dalfopristin, vancomycin-resistant enterococci (VRE), and macrolide-resistant streptococci.

Daptomycin was approved by the United States Food and Drug Administration (US-FDA) and by the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure infections (SSSI) caused by MSSA and MRSA, groups A and B ß-haemolytic streptococci, and for vancomycin-susceptible *Enterococcus faecalis*. This compound has also been recently approved for the treatment of *S. aureus* bacteremia including right-sided endocarditis.

In the present study, we evaluated the activity of daptomycin against *S. aureus* from patients with bloodstream infections (BSI) hospitalized in North American (NA) hospitals.

MATERIALS AND METHODS

Bacterial strains: A total of 5,894 strains of *S. aureus* causing bloodstream infections were consecutively collected from medical centers located in the United States (24 sites) and Canada (five sites) in 2002-2005. Only one strain per patient was included in the study.

Susceptibility testing: Daptomycin and more than 20 comparator agents were tested using the Clinical Laboratory Standards Institute (CLSI) M7-A7 broth microdilution method. All strains were tested in validated, broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton Broth (MHB) adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. US-FDA and CLSI approved daptomycin susceptibility breakpoints of ≤1 µg/ml for staphylococci and ß-haemolytic streptococci and ≤4 µg/ml for enterococci were used to categorize these Gram-positive organisms as susceptible. The following quality control organisms were concurrently tested: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Daptomycin was highly active against the *S. aureus* strains tested with MIC_{50} of 0.25 µg/ml, MIC_{90} of 0.5 µg/ml and >99.9% susceptibility (Table 1).
- The vast majority of strains (>99%) were inhibited at ≤0.5 µg/ml of daptomycin and only three strains (0.05%) showed elevated daptomycin MIC values (2 µg/ml; Tables 1 and 2).

Table 1. In vitro activity of daptomycin and comparator agents tested against *S. aureus* strains from bloodstream infections.

Organisms (no. tested)/ Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% Susceptible	% Resistant
All strains (5,894)					
Daptomycin	0.25	0.5	≤0.12-2	>99.9	-[a]
Oxacillin	1	>8	≤0.5-8	55.6	44.4
Ciprofloxacin	0.5	>4	≤0.03->4	55.3	43.7
Levofloxacin	≤0.5	>4	≤0.5->4	56.4	42.4
Clindamycin	0.12	>8	≤0.06->8	68.8	31.0
Erythromycin	8	>8	≤0.06->8	41.4	50.4
Gentamicin	≤2	≤2	≤2->8	95.4	4.1
Linezolid	2	2	0.12-16	>99.9	-[a]
Quinupristin/dalfopristin	0.25	0.5	≤0.25-2	>99.9	0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	96.9	3.1
Vancomycin	1	1	0.25-4	>99.9	0.0
Oxacillin-susceptible (3,277)					
Daptomycin	0.25	0.5	≤0.12-2	>99.9	-[a]
Ciprofloxacin	0.25	2	≤0.03->4	89.7	8.8
Levofloxacin	≤0.5	≤0.5	≤0.5->4	91.2	8.1
Clindamycin	≤0.25	≤0.25	≤0.25->8	94.0	5.7
Erythromycin	0.25	>8	≤0.06->8	71.1	24.6
Gentamicin	≤2	≤2	≤2->8	98.7	1.0
Linezolid	2	2	0.12-4	100.0	-[a]
Quinupristin/dalfopristin	0.25	0.5	≤0.25-2	>99.9	0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	98.0	2.0
Vancomycin	1	1	0.25-2	100.0	0.0
Oxacillin-resistant (2,617)					
Daptomycin	0.25	0.5	≤0.12-2	>99.9	-[a]
Ciprofloxacin	>4	>4	≤0.03->4	12.3	87.4
Levofloxacin	>4	>4	≤0.5->8	12.9	85.3
Clindamycin	>2	>2	≤0.06->2	37.1	62.7
Erythromycin	>8	>8	≤0.06->8	4.3	82.8
Gentamicin	≤2	≤2	≤2->8	91.2	8.1
Linezolid	2	2	0.5-16	>99.9	-[a]
Quinupristin/dalfopristin	0.25	0.5	≤0.25-1	100.0	0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	95.5	4.5
Vancomycin	1	1	0.25-4	>99.9	0.0

a. Resistant breakpoints have not been established by the CLSI for these antimicrobials.

- Daptomycin was equally active against MSSA and MRSA (Tables 1 and 2).
- MSSA showed high rates of susceptibility (>90%) to most antimicrobials tested, except erythromycin (71.1%). On the other hand, MRSA strains showed high rates of co-resistance to clindamycin (62.7% resistant), erythromycin (82.8% resistant), ciprofloxacin (87.4% resistant) and levofloxacin (85.3% resistant; Table 1).
- Linezolid, quinupristin/dalfopristin and vancomycin were also very active (>99.9% susceptibility) against *S. aureus* (Table 1).
- No significant variation was noted in the daptomycin activity (MIC_{50} of 0.25 µg/ml, MIC_{90} of 0.5 µg/ml and MIC range of ≤0.12 to 2 µg/ml) over the four years evaluated (Table 2).
- In contrast, oxacillin susceptibility decreased from 59.0-60.9% in 2002-2003 to 50.2-51.7% in the 2004-2005 period; and ciprofloxacin susceptibility rates declined from 56.4-58.3% in 2002-2003 to 51.7-52.1% in 2004-2005 (Table 3).

Table 2. Daptomycin MIC distributions among 5,894 *S. aureus* strains listed by year of isolation.

Year/Organisms (no. tested)	No. of isolates (cumulative %) inhibited at daptomycin MIC (µg/ml) of: ≤0.12	0.25	0.5	1	2
2002					
Oxacillin-susceptible (774)	45 (5.8)	590 (82.0)	138 (99.9)	0 (99.9)	1 (100.0)
Oxacillin-resistant (496)	17 (3.4)	33 (70.6)	142 (99.2)	4 (100.0)	
2003					
Oxacillin-susceptible (1,007)	113 (10.6)	877 (92.5)	76 (99.6)	4 (100.0)	
Oxacillin-resistant (743)	13 (1.7)	492 (68.0)	235 (99.6)	3 (100.0)	
2004					
Oxacillin-susceptible (729)	15 (2.1)	397 (56.5)	312 (99.3)	4 (99.9)	1 (100.0)
Oxacillin-resistant (723)	6 (0.8)	320 (45.0)	381 (97.8)	16 (100.0)	
2005					
Oxacillin-susceptible (704)	40 (5.7)	523 (80.0)	140 (99.9)	1 (100.0)	
Oxacillin-resistant (655)	13 (2.0)	424 (66.7)	208 (98.5)	9 (99.8)	1 (100.0)
All years					
Oxacillin-susceptible (3,277)	213 (6.5)	2,387 (79.3)	666 (99.7)	9 (99.9)	2 (100.0)
Oxacillin-resistant (2,617)	49 (1.9)	1,569 (61.8)	966 (98.7)	32 (99.9)	1 (100.0)

Table 3. Yearly variation of the antimicrobial susceptibility profile of *S. aureus* strains isolated from bloodstream infections in North American medical centers.

Antimicrobial	% susceptible (no. tested) 2002 (1,270)	2003 (1,813)	2004 (1,452)	2005 (1,359)	All Years (5,894)
Daptomycin	99.9	100.0	99.9	99.9	>99.9
Oxacillin	60.9	59.0	50.2	51.7	55.6
Ciprofloxacin	58.3	56.4	52.1	51.7	55.3
Clindamycin	67.7	66.9	67.9	73.1	68.8
Vancomycin	100.0	99.9	99.9	100.0	>99.9

CONCLUSIONS

- Daptomycin was highly active against *S. aureus* isolates from patients with BSI hospitalized in North American medical centers.
- Daptomycin activity remained stable during the 4 year period evaluated (2002-2005) and increased resistance has not been observed since US-FDA approval of daptomycin for treatment of SSSI in September 2003.
- Resistance to oxacillin did not adversely influence daptomycin activity.
- Resistance to quinupristin/dalfopristin, linezolid, vancomycin and daptomycin remain extremely rare among *S. aureus* isolated from BSI in North America.

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This study was funded by Cubist Pharmaceuticals.

44th Annual meeting of the Infecious Disease Society of America

October 12-15, 2006, Toronto, Canada