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Update of the in vitro activity of daptomycin tested against 6710 Gram-positive cocci isolated in North America (2006)

Mariana Castanheira[a,*], Ronald N. Jones[a,b], Hélio S. Sader[a,c]

[a]*JMI Laboratories, North Liberty, IA 52317, USA*
[b]*Tufts University School of Medicine, Boston, MA 02111, USA*
[c]*Division of Infectious Diseases, Universidade Federal de São Paulo, São Paulo, SP 04023-900, Brazil*

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Abstract

Gram-positive bacterial strains (6710) consecutively collected during 2006 in hospitals located in the United States and Canada were tested by reference broth microdilution methods against daptomycin and comparison agents. Only 1 *Staphylococcus aureus* strain (0.01%) had nonsusceptible daptomycin MIC value as specified by published break points. *S. aureus* daptomycin MIC distributions from 2006 as compared with those of previous years did not show "MIC creep". Resistance to other compounds, such as vancomycin, oxacillin, and penicillin, did not adversely influence daptomycin activity. Daptomycin remains highly active against clinical Gram-positive isolates collected in North America.

Keywords: Daptomycin; MRSA; Vancomycin resistance

Daptomycin is a rapidly bactericidal lipopeptide produced by *Streptomyces roseosporus* that acts at the level of the cytoplasmic membrane with potent activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* and ampicillin- and vancomycin-resistant enterococci (Sader and Jones, 2006; Sader et al., 2006). Daptomycin is approved by the US Food and Drug Administration for the treatment of *S. aureus*, as well as MRSA bacteremia and right-sided endocarditis. As an intravenous agent that is administered once per day, it offers a convenient regimen for therapy that may be continued after hospital discharge, with an adverse event profile that appears safe or manageable (Carpenter and Chambers, 2004). Daptomycin bactericidal activity, favorable pharmacologic and side effect profiles, and low potential for resistance make it an attractive alternative to vancomycin (Kanafani and Corey, 2007). The daptomycin mechanism of action is novel compared with classes of antimicrobial agents currently used in clinical practice (Boucher and Sakoulas, 2007). Its activity is dependent on physiologic levels of free calcium ions (50 mg/L) (Carpenter and Chambers, 2004), and the mechanism of daptomycin resistance is not completely elucidated (Friedman et al., 2006; Pillai et al., 2007).

The Daptomycin Surveillance Program was implemented in North America in 2002 to evaluate and follow the in vitro activity of this compound against principal Gram-positive organisms causing infections in hospitalized patients. We report here the results of the 5th year (2006) of the program in North America and compare daptomycin MIC results of *S. aureus* with those collected in previous years.

A total of 6710 organisms were collected during 2006 from 28 medical centers distributed across North America (23 located in the United States and 5 in Canada). The isolates were consecutively collected from bloodstream infections, skin and soft tissue infections, and pneumonia (only *S. aureus*) in hospitalized patients according to a common surveillance design. All organisms were isolated from documented human infections, and only 1 strain per patient infection episode was included in the study. Species identifications were confirmed by standard biochemical tests and the Vitek System (bioMérieux, Hazelwood, MO), when necessary.

* Corresponding author. Tel.: +1-319-665-3370; fax: +1-319-665-3371.
E-mail address: mariana-castanheira@jmilabs.com (M. Castanheira).

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Isolates were tested against 20 antimicrobial agents by broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI, 2006). Cation-adjusted Mueller–Hinton broth was used in validated panels manufactured by TREK Diagnostics, Cleveland, OH. Categoric interpretations for all antimicrobials were those of M100-S17 (CLSI, 2007). The susceptible break points applied for daptomycin were ≤1 μg/mL for staphylococci and streptococci, and ≤4 μg/mL for enterococci (CLSI, 2007). *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619 were concurrently tested for quality assurance purposes, and results obtained were within the expected ranges (CLSI, 2007).

Daptomycin MIC distributions by organism group are listed in Table 1. The vast majority of *S. aureus* strains had a daptomycin MIC of 0.25 μg/mL (79.2%) or 0.5 μg/mL (15.3%). Daptomycin MIC distribution for MRSA (77.9% at 0.25 μg/mL and 18.3% at 0.5 μg/mL) was very similar to that for oxacillin-susceptible *S. aureus* (MSSA) (80.7% at 0.25 μg/mL and 11.9% at 0.5 μg/mL). Coagulase-negative staphylococci (CoNSs) exhibit a daptomycin MIC distribution like that of *S. aureus*, with 61.5% of strains with MIC values of 0.25 μg/mL. Daptomycin activity against oxacillin-resistant CoNS was essentially identical to that against oxacillin-susceptible CoNS (62.3 versus 59.2%, respectively, at an MIC of 0.25 μg/mL).

The majority of *E. faecalis* strains showed daptomycin MIC values of 0.5 (52.2%) or 1 μg/mL (38.2%), whereas *Enterococcus faecium* strains exhibit daptomycin MIC values slightly higher. Furthermore, daptomycin MIC distributions for vancomycin-susceptible and vancomycin-resistant strains were almost identical within each species. Streptococci displayed daptomycin MIC values generally lower than those of staphylococci or enterococci, with a modal result at ≤0.06 μg/mL for β-hemolytic streptococci and 0.25 μg/mL for viridans group streptococci.

The in vitro activity of daptomycin in comparison to selected Gram-positive active antimicrobial agents tested is summarized in Table 2. Daptomycin was very active against MSSA and MRSA (MIC_{50}, 0.25 μg/mL, and MIC_{90}, 0.5 μg/mL, for both groups). Only 1 *S. aureus* strain was considered nonsusceptible to daptomycin (MIC values, 2 μg/mL), which was only 1 doubling dilution above the susceptible break point (≤1 μg/mL) for this organism (CLSI, 2007). This strain was isolated from a wound infection and a bacteremia case in medical centers located in New York City. Furthermore, the strain was MRSA, and showed a concurrent decreased susceptibility to vancomycin (4 μg/mL, intermediate category).

Although some reports have suggested that decreased susceptibility to vancomycin could be associated with decreased susceptibility to daptomycin in *S. aureus*, the correlation between vancomycin and daptomycin resistance has not been completely elucidated. One recent study suggested that under experimental conditions, physiologic changes occurring during vancomycin exposure may lead to reduced daptomycin susceptibility in MRSA (Sakoulas et al., 2006). Daptomycin, however, remains very active and demonstrates potent bactericidal activity against both vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous VISA (hVISA) strains (Sader and Jones, 2006; Sader et al., 2006). The mechanism of daptomycin resistance is unknown; thickening of the bacterial cell wall, which is the mechanism of vancomycin-intermediate resistance in *S. aureus*, does not consistently affect daptomycin activity (Friedman et al., 2006). In addition, there are a limited number of isolates demonstrating decreased susceptibility to vancomycin, and not all of those demonstrate concomitant increases of daptomycin MIC values (Sader and Jones, 2006; Sader et al., 2006).

Only daptomycin (MIC_{90}, 0.5 μg/mL) and vancomycin (MIC_{90}, 2 μg/mL) were active against all CoNS strains at the current susceptible break point. CoNS with reduced susceptibility to linezolid (4 strains [0.7%]; MIC, >8 μg/mL),

Table 1
Frequency of occurrence of daptomycin MIC values for the organisms collected in US medical centers (2006)

Organisms/resistance group (no. tested)	No. (%) of isolates inhibited at daptomycin MIC (μg/mL) of						
	≤0.06	0.12	0.25	0.5	1	2	4
S. aureus (4288)	12 (0.3)	207 (4.8)	3398 (79.2)	656 (15.3)	14 (0.3)	1 (<0.1)	0 (0.0)
Oxacillin susceptible (2037)	9 (0.4)	137 (6.7)	1644 (80.7)	243 (11.9)	4 (0.2)	0 (0.0)	0 (0.0)
Oxacillin resistant (2251)	3 (0.1)	70 (3.1)	1754 (77.9)	413 (18.3)	10 (0.4)	1 (<0.1)	0 (0.0)
CoNS (585)	11 (1.9)	48 (8.2)	360 (61.5)	153 (26.2)	13 (2.2)	0 (0.0)	0 (0.0)
Oxacillin susceptible (142)	3 (2.1)	16 (11.3)	84 (59.2)	22 (23.2)	6 (4.2)	0 (0.0)	0 (0.0)
Oxacillin resistant (443)	8 (1.8)	32 (7.2)	276 (62.3)	120 (27.1)	7 (1.6)	0 (0.0)	0 (0.0)
Enterococcus spp. (1231)	2 (0.2)	8 (0.6)	60 (4.9)	459 (37.3)	527 (42.8)	169 (13.7)	6 (0.5)
E. faecalis (782)	2 (0.3)	8 (1.0)	49 (6.3)	408 (52.2)	299 (38.2)	16 (2.0)	0 (0.0)
Vancomycin susceptible (750)	2 (0.3)	8 (1.1)	46 (6.1)	391 (52.1)	289 (38.5)	14 (1.9)	0 (0.0)
Vancomycin nonsusceptible (32)	0 (0.0)	0 (0.0)	3 (9.4)	17 (53.1)	10 (31.3)	2 (6.3)	0 (0.0)
E. faecium (399)	0 (0.0)	0 (0.0)	6 (1.5)	33 (8.3)	213 (53.4)	142 (35.6)	5 (1.3)
Vancomycin susceptible (111)	0 (0.0)	0 (0.0)	2 (1.8)	9 (8.1)	60 (54.1)	39 (35.1)	1 (0.9)
Vancomycin nonsusceptible (288)	0 (0.0)	0 (0.0)	4 (1.4)	24 (8.3)	153 (53.1)	103 (35.8)	4 (1.4)
β-Hemolytic streptococci (424)	234 (55.2)	121 (28.5)	65 (15.3)	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Viridans group streptococci (182)	46 (25.3)	35 (19.2)	49 (26.9)	43 (23.6)	9 (4.9)	0 (0.0)	0 (0.0)