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Daptomycin Activity against Uncommonly Isolated Streptococcal and Other Gram-Positive Species Groups

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A total of 1,356 clinical isolates were tested against daptomycin by broth microdilution methods. Daptomycin was active against seven groups of viridans group streptococci (MIC_{50} and MIC_{90} values ranging from ≤0.06 and ≤0.06 μg/ml [*Streptococcus bovis* and *Streptococcus dysgalactiae*] to 0.5 and 1 μg/ml [*Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus parasanguinis*], respectively), beta-hemolytic streptococci serogroups C, F, and G (MIC_{50} and MIC_{90}, ≤0.06 to 0.25 and 0.12 to 0.25 μg/ml, respectively), *Corynebacterium* spp. (MIC_{50} and MIC_{90}, ≤0.06 and 0.12 μg/ml, respectively), and *Micrococcus* spp. (MIC_{50} and MIC_{90}, ≤0.06 and 0.25 μg/ml, respectively). *Listeria monocytogenes* exhibited higher daptomycin MICs (MIC_{50} and MIC_{90}, 2 and 4 μg/ml, respectively) than other tested organisms.

Daptomycin is a natural cyclic lipopeptide with rapid *in vitro* bactericidal activity against a wide spectrum of Gram-positive organisms. Daptomycin was initially approved by the U.S. Food and Drug Administration (FDA) in 2003 and by the European Medicines Agency (EMA) in 2005 for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria, using a dose of 4 mg/kg of body weight every 24 h (1). In 2006 (United States) and 2007 (Europe), daptomycin received approval for the treatment of *Staphylococcus aureus* bloodstream infections (bacteremia), including right-sided infective endocarditis, at a dose of 6 mg/kg every 24 h (2, 3).

Daptomycin has demonstrated potent *in vitro* activity against many common staphylococci and streptococci, such as *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]; MIC_{90}, 0.5 μg/ml), coagulase-negative staphylococci (*Staphylococcus epidermidis* [MIC_{90}, 0.5 μg/ml] and less frequently isolated species), group A and B β-hemolytic streptococci (MIC_{90}, ≤0.03 μg/ml), *Enterococcus faecalis* (MIC_{90}, 1 μg/ml), and *Enterococcus faecium* (MIC_{90}, 2 μg/ml), in numerous investigations (4, 5). However, limited information exists on the activity of daptomycin tested against less frequently isolated Gram-positive species. We evaluated daptomycin activity tested against uncommonly isolated streptococci and three other Gram-positive groups derived from recent global surveillance programs.

A total of 1,356 unique isolates (one per patient) were collected from documented infections and submitted to a monitoring reference laboratory (JMI Laboratories; North Liberty, IA, USA) where species identifications were confirmed using standard algorithms, Vitek systems (bioMérieux, Hazelwood, MO), matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany), or 16S sequencing methods, when necessary. The organisms were obtained from the SENTRY Antimicrobial Surveillance Program platform from infections cultured in 112 medical centers located worldwide from 2008 to 2011 and stored in Trypticase soy broth with 15% glycerol in temperature-monitored −80°C freezers. The collection included viridans group streptococci (675 isolates; seven groups or species), β-hemolytic streptococci (BHS) other than *Streptococcus pyogenes* and *Streptococcus agalactiae* (598 isolates), *Corynebacterium* spp. (18 isolates; five species), *Listeria monocytogenes* (39 isolates), and *Micrococcus* spp. (26 isolates). The majority of isolates were from 77 U.S. medical centers, whereas four less common species isolates were obtained from worldwide hospital locations, including *Streptococcus equisimilis*, *Streptococcus mutans*, *Corynebacterium* spp., and *L. monocytogenes*.

Daptomycin and comparators were tested for susceptibility by the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (6, 7). The cation-adjusted Mueller-Hinton broth was supplemented with 2.5 to 5% lysed horse blood when fastidious streptococcal species were tested. Also, the test medium was adjusted to contain physiological levels of calcium (50 mg/liter) when daptomycin was tested (6). All quality control results were within published ranges for daptomycin when *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 were tested (7).

Daptomycin exhibited potent *in vitro* activity when tested against seven groups of viridans group streptococci tested with MIC_{50} and MIC_{90} results ranging from ≤0.06 and ≤0.06 μg/ml (*Streptococcus bovis* and *Streptococcus dysgalactiae* groups) to 0.5 and 1 μg/ml (*Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus parasanguinis*), respectively (Table 1). The highest daptomycin MIC value among viridans group streptococci was 2 μg/ml, which was observed in only two strains (0.3%): one *Streptococcus anginosus* strain and one *S. oralis* strain (Table 1).

Daptomycin was highly active against β-hemolytic streptococci serogroups C (MIC_{50} and MIC_{90}, ≤0.06 and 0.25 μg/ml, respectively), F (MIC_{50} and MIC_{90}, 0.25 and 0.25 μg/ml, respectively), and G (MIC_{50} and MIC_{90}, ≤0.06 and 0.12 μg/ml, respectively). The highest daptomycin MIC value among β-hemolytic streptococci was only 0.5 μg/ml (Table 1). Daptomycin MIC results were slightly lower among β-hemolytic streptococci serogroups G and C (MIC_{50}, ≤0.06 μg/ml for both groups) than among serogroup F (MIC_{50}, 0.25 μg/ml) (Table 1).

Corynebacterium spp. (MIC_{50} and MIC_{90}, ≤0.06 and 0.12

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TABLE 1 Uncommonly isolated streptococcal species and three other Gram-positive species groups (1,356 strains) tested against daptomycin

Group and organism (no. of isolates tested)	No. (cumulative % inhibited) with a daptomycin MIC (μg/ml) of:							MIC (μg/ml)	
	≤0.06	0.12	0.25	0.5	1	2	4	50%	90%
Viridans group streptococci (675)									
S. anginosus group									
S. anginosus (124)	13 (10.5)	15 (22.6)	63 (73.4)	31 (98.4)	1 (99.2)	1 (100.0)		0.25	0.5
S. constellatus (44)	3 (6.8)	13 (36.4)	21 (84.1)	7 (100.0)				0.25	0.5
S. intermedius (22)	1 (4.6)	4 (22.7)	13 (81.8)	3 (95.5)	1 (100.0)			0.25	0.5
S. milleri group (14)[a]	0 (0.0)	4 (28.6)	5 (64.3)	5 (100.0)				0.25	0.5
S. bovis group (47)[b]	43 (91.5)	3 (97.9)	1 (100.0)					≤0.06	≤0.06
S. dysgalactiae group									
S. dysgalactiae (32)	29 (90.6)	3 (100.0)						≤0.06	≤0.06
S. equisimilis (18)	17 (94.4)	1 (100.0)						≤0.06	≤0.06
S. mitis group									
S. mitis (197)	6 (3.1)	15 (10.7)	62 (42.1)	74 (79.7)	40 (100.0)			0.5	1
S. gordonii (13)	1 (7.7)	1 (15.4)	5 (53.9)	4 (84.6)	2 (100.0)			0.25	1
S. oralis (25)	0 (0.0)	1 (4.0)	10 (44.0)	8 (76.0)	5 (96.0)	1 (100.0)		0.5	1
S. parasanguinis (35)	1 (2.9)	0 (2.9)	3 (11.4)	24 (80.0)	7 (100.0)			0.5	1
S. sanguinis (35)	2 (5.7)	11 (37.1)	14 (77.1)	6 (94.3)	2 (100.0)			0.25	0.5
S. mutans group									
S. mutans (20)	6 (30.0)	1 (35.0)	10 (85.0)	3 (100.0)				0.25	0.5
S. salivarius/*S. vestibularis* group (49)	17 (34.7)	24 (83.7)	7 (98.0)	1 (100.0)				0.12	0.25
β-Hemolytic streptococci (598)									
Serogroup C (207)	118 (57.0)	33 (73.0)	42 (93.2)	14 (100.0)				≤0.06	0.25
Serogroup F (56)	4 (7.1)	16 (35.7)	32 (92.9)	4 (100.0)				0.25	0.25
Serogroup G (335)	294 (87.8)	23 (94.6)	13 (98.5)	5 (100.0)				≤0.06	0.12
Other species (83)									
Corynebacterium spp. (18)	13 (72.2)	4 (94.4)	1 (100.0)					≤0.06	0.12
Listeria monocytogenes (39)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	8 (23.1)	25 (87.2)	5 (100.0)	2	4
Micrococcus spp. (26)	13 (50.0)	8 (80.8)	5 (100.0)					≤0.06	0.25

[a] Taxonomy unclear but most closely related to the *Streptococcus anginosus* group.
[b] Includes *Streptococcus bovis* group NOS (31 isolates), *Streptococcus gallolyticus* (13 isolates), and *Streptococcus infantarius* (3 isolates).

μg/ml, respectively) and *Micrococcus* spp. (MIC_{50} and MIC_{90}, ≤0.06 and 0.25 μg/ml, respectively) were very susceptible to daptomycin, whereas *L. monocytogenes* exhibited elevated daptomycin MIC values (MIC_{50} and MIC_{90}, 2 and 4 μg/ml, respectively) compared to those of all other tested Gram-positive organisms (Table 1).

Although uncommonly isolated in the clinical microbiology laboratory, the organisms evaluated in the present study may cause life-threatening infections, and limited data about their antimicrobial susceptibility patterns are available to guide therapy. Viridans group *Streptococcus* spp. represent a major cause of endocarditis as well as bacteremia with septic shock in neutropenic patients (8), whereas serogroup C, F, and G beta-hemolytic streptococci can cause a wide array of infections, including upper respiratory tract infections, skin and soft tissue infections, necrotizing fasciitis, bacteremia, and endocarditis (9). *Corynebacterium* spp. are increasingly being recognized as causing opportunistic disease under specific circumstances, such as in patients who are immunocompromised, have prosthetic devices, or have been in hospitals/nursing homes for long periods of time (10). *Micrococcus* spp. are usually acknowledged as nonpathogenic, commensal microorganisms but can also act as opportunistic pathogens and may cause valve endocarditis, folliculitis, bacteremia, meningitis, pneumonia, and even fatal infections as nosocomial pathogens (11). Lastly, *Listeria* spp. are also considered opportunistic pathogens, and the majority of listeriosis cases occur among individuals with underlying conditions that lead to suppression of cell-mediated immunity; however, epidemic common-source infections in immunocompetent individuals are increasingly being reported (12).

These daptomycin susceptibility results presented here document the wider potential clinical application to uncommonly isolated Gram-positive species. The results of this study coupled with documented daptomycin clinical efficacy and safety experience in the treatment of severe staphylococcal infections, including bacteremia and endocarditis (2, 3), indicate that this antimicrobial represents a valuable option for treatment of infections caused by a wide variety of Gram-positive species as guided by reference MIC test results and/or published surveillance literature.

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