Antimicrobial Activity of Daptomycin Tested Against *Staphylococcus aureus* and *Enterococcus* spp. Clinical Strains Isolated in European Medical Centers (2002-2005)

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AMENDED ABSTRACT

Background: Daptomycin is a cyclic lipopeptide approved for use by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure infections. We evaluated the in vitro activity of daptomycin and many comparator agents tested against recent clinical isolates collected in Europe.

Methods: A total of 9,517 strains from 31 medical centers located in 12 European countries, Turkey and Israel were evaluated. The bacterial isolates were consecutively collected during the 2002-2005 period from patients with documented infections. Susceptibility (S) testing was performed by reference broth microdilution methods according to CLSI (formerly NCCLS) guidelines and interpretative criteria against daptomycin and >20 comparators. Mueller-Hinton broth was supplemented to a 50 mg/L Ca^{++} concentration for testing daptomycin.

Results: Rates of oxacillin-resistant *S. aureus* (ORSA) varied from 1.2% in Sweden to >40% in Belgium, Greece, Ireland and the UK; while the highest rates of vancomycin (VAN)-resistant (R) *E. faecium* were observed in Ireland (56.5%) and the UK (42.5%). Daptomycin and selected comparator activities are summarized in the table:

	MIC_{90} (mg/L)/% S					
Organism (no.)	Daptomycin	Linezolid	Synercid	Teicoplanin	VAN	Levofloxacin
Oxacillin-S *S. aureus* (5,148)	0.5/>99.9	2/100	0.5/99.9	≤2/>99.9	1/>99.9	≤0.5/93.5
ORSA (2,021)	0.5/>99.9	2/>99.9	1/98.8	≤2/99.6	1/100	>4/8.6
VAN-S *E. faecalis* (1,645)	1/100	2/100	>2/1.9	≤2/100	2/100	>4/69.8
VAN-R *E. faecalis* (40)	1/100	2/100	>2/0.0	>16/15.0	>16/0.0	>4/20.0
VAN-S *E. faecium* (540)	4/99.6	2/100	>2/69.8	≤2/100	1/100	>4/25.2
VAN-R *E. faecium* (123)	4/99.2	2/100	>2/79.7	>16/23.6	>16/0.0	>4/12.2

Daptomycin was highly active against the most clinically important Gram-positive organisms causing nosocomial infections in European medical centers with MIC_{90} varying from 0.5 mg/L for *S. aureus* to 4 mg/L for *E. faecium*. Daptomycin and linezolid showed the broadest spectrum of activity (>99% S) among the antimicrobial agents tested.

Conclusions: Resistance to other compounds did not adversely influence the high daptomycin activity against staphylococci, enterococci or streptococci. Daptomycin showed high potency and broad spectrum against recent clinical isolates of Gram-positive cocci isolated in European medical centers, including multi-drug resistant subsets.

INTRODUCTION

Daptomycin is a cyclic lipopeptide approved by the United States Food and Drug Administration (US-FDA) in September 2003 for the treatment of complicated skin and skin structure infections (cSSSI) and a supplemental filing has been presented to the US-FDA for the treatment of *S. aureus* bacteremia and infectious endocarditis. Daptomycin has also been recently approved by the European Medicines Agency (EMEA) for the treatment of cSSSI in Europe. In addition, the European Committee for Antimicrobial Susceptibility Testing (EUCAST) has assigned daptomycin breakpoints for staphylococci and streptococci, which are ≤1 mg/L for susceptible (similar to CLSI and US-FDA breakpoints) and ≥2 mg/L for resistance.

Daptomycin is active against a wide range of multidrug-resistant (MDR) strains for which there are very few therapeutic alternatives, such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Daptomycin acts on the cytoplasmic membrane in the presence of physiological levels of calcium ions and in vitro susceptibility testing requires appropriate supplementation of calcium (50 mg/L) to the test medium.

In the present study, we evaluated the activity of daptomycin and many comparator agents tested against clinical isolates of *S. aureus* and enterococci collected in Europe.

MATERIALS AND METHODS

Bacterial isolates. A total of 9,517 strains from 31 medical centers located in 12 European countries, Turkey and Israel were evaluated. The collection included *S. aureus* (7,169 strains), *Enterococcus faecalis* (1,685 strains) and *E. faecium* (663 strains).

Susceptibility Testing. The strains were tested by Clinical and Laboratory Standards Institute (CLSI) M7-A7 broth microdilution methods. Daptomycin and more than 20 comparator agents were tested in validated, dry-form broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin only. The isolates were categorized as susceptible, intermediate and resistant according to CLSI guidelines [2006]. A daptomycin susceptible breakpoint of ≤ 1 mg/L was used for staphylococci and ß-haemolytic streptococci, while ≤ 4 mg/L was used for enterococci, as approved by the FDA and CLSI. The following quality control organisms were concurrently tested: *Streptococcus pneumoniae* ATCC 49619, *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213.

RESULTS

- Daptomycin was highly active against *S. aureus* (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; >99.9% susceptible) with only two non-susceptible strains observed in 4 years of surveillance program testing, both with a daptomycin MIC at 2 mg/L (susceptible breakpoint at 1 mg/L). Resistance to oxacillin did not adversely affect daptomycin activity (Table 1).

- Oxacillin-resistant *S. aureus* showed high rates of co-resistance with levofloxacin (88.6%), erythromycin (74.0%) and clindamycin (48.7%). None of the antimicrobials tested was active against all *S. aureus* strains.

- Daptomycin was the most active compound tested against *E. faecalis* (MIC_{50}, 0.5 mg/L and MIC_{90}, 1 mg/L; 100.0% susceptible) followed by linezolid (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L; >99.9% susceptible).

- Daptomycin was also very active against vancomycin-susceptible and -resistant *E. faecium* (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L). Only three daptomycin non-susceptible *E. faecium* isolates were observed (99.5% susceptible). Resistance to vancomycin did not adversely affect daptomycin activity against this population of enterococci (Table 1).

- Vancomycin-resistant *E. faecium* showed high rates of resistance to most antimicrobials, including teicoplanin (82.4%), gentamicin (high-level, 56.9%) and quinupristin/dalfopristin (12.2%, only 79.7% susceptible). However, daptomycin was active against 99.2% and linezolid was active against all isolates at published susceptible breakpoints.

- MRSA rates varied from only 1.2% in Sweden to 46.2% in Ireland, 43.9% in Israel, 43.2% in Greece, 42.5% in the UK, and 41.0% in Belgium (Table 2).

- VRE rates were generally low (0.0-1.5%) among *E. faecalis* in nine of the countries evaluated, but relatively high in Greece (10.4%), Russia (13.3%) and the UK (14.6%; Table 2). In contrast, among *E. faecium*, VRE rates varied from 0.0% in Switzerland and Russia to as high as 56.5% in Ireland and 42.5% in the UK with an overall rate of 18.5%.

Table 1. Antimicrobial activity of daptomycin and comparator agents against *S. aureus* and enterococci isolated in Europe (2002-2005).

	MIC (mg/L)			
Organism (no. tested)/antimicrobial	50%	90%	% Susceptible	% Resistant
S. aureus				
Oxacillin-susceptible (5,148)				
Daptomycin	0.25	0.5	>99.9[a]	-[b]
Levofloxacin	≤0.5	≤0.5	93.5	5.7
Erythromycin	≤0.25	>2	85.2	14.0
Clindamycin	≤0.25	≤0.25	97.0	2.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	99.3	0.7
Quinupristin/dalfopristin	≤0.25	0.5	99.9	0.1
Teicoplanin	≤2	≤2	>99.9[a]	0.0
Vancomycin	1	1	>99.9[a]	0.0
Linezolid	2	2	100.0	-[b]
Oxacillin-resistant (2,021)				
Daptomycin	0.25	0.5	>99.9[a]	-
Levofloxacin	>4	>4	8.6	88.6
Erythromycin	>2	>2	24.9	74.0
Clindamycin	0.5	>2	51.1	48.7
Trimethoprim/sulfamethoxazole	≤0.5	1	93.5	6.5
Quinupristin/dalfopristin	0.5	1	98.8	1.0
Teicoplanin	≤2	≤2	99.6	0.0
Vancomycin	1	1	100.0	0.0
Linezolid	2	2	>99.9[a]	-
E. faecalis				
Vancomycin-susceptible (1,645)				
Daptomycin	0.5	1	100.0	-
Ampicillin	≤2	≤2	99.2	0.8
Levofloxacin	1	>4	69.8	29.3
Gentamicin (HL)[c]	≤500	>1000	68.3	31.7
Streptomycin (HL)[c]	≤1000	>2000	61.2	38.8
Quinupristin/dalfopristin	>2	>2	1.9	91.5
Teicoplanin	≤2	≤2	100.0	0.0
Linezolid	1	2	>99.9[a]	0.0
Vancomycin-resistant (40)				
Daptomycin	0.5	1	100.0	-
Ampicillin	≤2	8	100.0	0.0
Levofloxacin	>4	>4	20.0	80.0
Gentamicin (HL)[c]	>1000	>1000	22.5	77.5
Streptomycin (HL)[c]	>2000	>2000	27.5	72.5
Quinupristin/dalfopristin	>2	>2	0.0	100.0
Teicoplanin	>16	>16	15.0	85.0
Linezolid	1	2	100.0	0.0
E. faecium				
Vancomycin-susceptible (540)				
Daptomycin	2	4	99.6	-
Ampicillin	>16	>16	16.1	83.9
Levofloxacin	>4	>4	25.2	66.3
Gentamicin	≤500	>1000	64.8	35.2
Streptomycin	>2000	>2000	43.9	56.1
Quinupristin/dalfopristin	1	>2	69.8	13.0
Teicoplanin	≤2	≤2	100.0	0.0
Linezolid	1	2	100.0	0.0
Vancomycin-resistant(123)				
Daptomycin	2	4	99.2[a]	-
Ampicillin	>16	>16	2.4	97.6
Levofloxacin	>4	>4	12.2	86.2
Gentamicin (HL)[c]	>1000	>1000	43.1	56.9
Streptomycin (HL)[c]	>2000	>2000	39.8	60.2
Quinupristin/dalfopristin	0.5	>2	79.7	12.2
Teicoplanin	>16	>16	23.6	82.4
Linezolid	1	2	100.0	0.0

a. Only one non-susceptible isolate.
b. - = No breakpoint has been established by CLSI or US-FDA.
c. High level resistance.

Table 2. Frequency (%) of important resistance phenotypes by country.

Country	% Oxacillin-resistant *S. aureus*	% Vancomycin-resistant *E. faecalis*	% Vancomycin-resistant *E. faecium*
Belgium	41.0	0.0	7.7
France	29.6	0.0	4.3
Germany	12.1	1.5	13.2
Greece	43.2	10.4	30.8
Ireland	46.2	1.3	56.5
Israel	43.9	6.3	31.6
Italy	35.5	5.1	28.9
Poland	30.3	0.0	6.1
Russia	33.3	13.3	0.0
Spain	21.1	0.0	9.4
Sweden	1.2	0.0	10.3
Switzerland	17.5	0.0	0.0
Turkey	28.4	0.0	9.0
UK	42.5	14.6	42.5
Overall	28.2	2.4	18.5

CONCLUSIONS

- Daptomycin demonstrated excellent in vitro activity against recent clinical isolates of *S. aureus* and enterococci isolated in hospitals in Europe, Turkey and Israel.

- In general, countries with high rates of MRSA, e.g. Greece, Ireland, Israel, Italy and the UK, also showed elevated rates of vancomycin-resistant *E. faecium* (possible CC17 clones).

SELECTED REFERENCES

Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI (2004). The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 38: 1673-1681.

Clinical and Laboratory Standards Institute. (2006). *Performance standards for antimicrobial susceptibility testing, 16th informational supplement M100-S16*. Wayne, PA: CLSI.

Cubicin Product Information. European Medicines Agency. http://www.emea.eu.int/humandocs/Humans/EPAR/cubicin/cubicin.htm Accessed on May 11, 2006.

Package insert. Cubicin (daptomycin for injection). Lexington MA. (Cubist Pharmaceuticals, Inc) 2003. Available at http://www.cubist.com/prescribe.htm Accessed on March 9, 2006.

Sader HS, Streit JM, Fritsche TR, Jones RN (2004). Antimicrobial activity of daptomycin against multidrug-resistant Gram-positive strains collected worldwide. *Diagn Microbiol Infect Dis* 50: 201-204.