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# Update on Daptomycin Activity and Spectrum when Tested against Gram-positive Strains Collected in European Medical Centers (2007-2008)

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## ABSTRACT

**Objective**: To evaluate the in vitro activity and spectrum of daptomycin (DAP) tested against recent clinical isolates collected in European hospitals. DAP is a cyclic lipopeptide approved by European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) and *S. aureus* (SA) endocarditis.
**Methods**: 10,430 consecutive strains were collected in 28 medical centers located in 11 European countries, Turkey and Israel. The following pathogens were evaluated: SA (27.4% oxacillin [OXA]-resistant [R]); coagulase-negative staphylococci (CoNS; 76.3% OXA-R), *E. faecalis* (EF; 1.2% vancomycin [VAN]-R), *E. faecium* (EFM; 25.6% VAN-R), beta-haemolytic *Streptococcus* spp. (BHS; 807), and viridans group *Streptococcus* spp. (VGS; 274). The organisms were isolated mainly from bloodstream infections (49%) and cSSSI (20%). The strains were susceptibility (S) tested against DAP and numerous comparators by CLSI broth microdilution methods in cation-adjusted Mueller-Hinton broth supplemented to 50 mg/L of calcium for DAP tests.
**Results**: DAP was highly active against SA and CoNS ($MIC_{50/90}$, 0.25/0.5 mg/L for both organisms) and its activity was not adversely influenced by resistance to OXA (see Table). MRSA varied from 1.4 in Sweden to 55.9% in Greece and showed high R rates to levofloxacin (87.7) and clindamycin (34.0%). DAP ($MIC_{50/90}$, 0.25/0.5 mg/L) and VAN ($MIC_{50/90}$, 1/1 mg/L) were active against all MRSA (100.0% S), and linezolid (99.9% S) and TMP/SMX (98.6% S) was also very active against this pathogen. All EF were S to DAP ($MIC_{50/90}$, 1/1 mg/L). VAN-R EFM was observed in 10 of 12 countries evaluated and was highest in Ireland (58.7%) and Greece (46.0%). Among VAN-R EFM isolates, only 80% were S to quinupristin/dalfopristin and 43.3% showed high-level R to gentamicin. DAP was highly active against BHS ($MIC_{90}$, 0.25 mg/L) as were most comparison agents tested. DAP was also very active against VGS ($MIC_{90}$, 0.5 mg/L).

| Organism | Cumulative % inhibited at daptomycin MIC (mg/L) of: | | | | | | |
|---|---|---|---|---|---|---|---|
| (no. tested) | ≤0.12 | 0.25 | 0.5 | 1 | 2 | 4 | %S |
| SA | | | | | | | |
| OXA-S (4,047) | 5.7 | 86.5 | 99.7 | 100.0 | - | - | 100.0 |
| OXA-R (1,531) | 4.0 | 76.5 | 99.1 | 100.0 | - | - | 100.0 |
| CoNS (1,665) | 10.2 | 65.3 | 96.0 | 99.9 | 100.0 | - | 99.9 |
| EF (1,306) | 0.5 | 3.2 | 37.3 | 92.2 | 99.9 | 100.0 | 100.0 |
| EFM | | | | | | | |
| VAN-S (533) | 0.9 | 2.1 | 7.1 | 32.7 | 94.0 | 100.0 | 100.0 |
| VAN-R (210) | 0.0 | 1.4 | 4.3 | 42.9 | 96.2 | 100.0 | 100.0 |
| BHS (807) | 83.9 | 99.4 | 100.0 | - | - | - | 100.0 |
| VGS (274) | 31.4 | 65.7 | 92.3 | 100.0 | - | - | 100.0 |

**Conclusions**: DAP showed significant potency and broad-spectrum activity against recent clinical isolates of Gram-positive organisms isolated in European medical centers, including R subsets. All organisms tested except for 2 CoNS were S to DAP and R to other compounds did not adversely influence the DAP potency against staphylococci, enterococci or streptococci.

## INTRODUCTION

Daptomycin is a naturally occurring cyclic lipopeptide produced by *Streptomyces roseosporus* which has demonstrated activity against all clinically significant Gram-positive bacterial species. Daptomycin is active against a wide range of multidrug-resistant (MDR) organisms for which there are few therapeutic alternatives, including vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and *S. aureus* with decreased susceptibility to vancomycin. A once-daily dosing regimen with a minimal side effect profile has made daptomycin a promising alternative for nosocomial infections.

Daptomycin was approved by the United States Food and Drug Administration (US-FDA) and by the European Medicine Agency (EMEA) for the treatment of complicated skin and skin structure infections (cSSSI) using a dose of 4 mg/kg every 24 hours. Daptomycin has a rapid bactericidal effect and has been approved for treatment of *S. aureus* bacteremia and right-sided endocarditis at a dose of 6 mg/kg every 24 hours. Additional studies of pharmacokinetics/pharmacodynamics and efficacy in pediatric patients with cSSSI and prosthetic joint infections in adults are underway.

In the present study, we evaluated the antimicrobial susceptibility patterns of recent (2007-2008) clinical Gram-positive bacteria collected in European medical centers.

## MATERIALS AND METHODS

Bacterial isolates. A total of 10,430 consecutive strains were collected in 28 medical centers located in 11 European countries, Turkey and Israel. The medical centers are located in Belgium (1), France (5), Germany (4), Greece (2), Ireland (2), Israel (1), Italy (3), Poland (1), Spain (2), Sweden (2), Switzerland (1), Turkey (2) and the United Kingdom (2). The pathogens evaluated were *S. aureus* (5,578); coagulase-negative staphylococci (CoNS; 1,665), *Enterococcus faecalis* (1,306), *E. faecium* (743), β-haemolytic *Streptococcus* spp. (807), and viridans group *Streptococcus* spp. (274). The organisms were isolated mainly from bloodstream infections (49%) and cSSSI (20%).

Susceptibility testing. Daptomycin and comparator agents were tested using the Clinical and Laboratory Standards Institute (CLSI) M07-A8 broth microdilution method. All strains were tested in validated broth microdilution panels manufactured by TREK Diagnostics (Cleveland, OH). Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. US-FDA and CLSI approved daptomycin susceptible breakpoints of ≤1 mg/L for staphylococci and β-haemolytic *Streptococcus* spp. and ≤4 mg/L 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 oxacillin-susceptible and -resistant *S. aureus* ($MIC_{50}$ of 0.25 mg/L and $MIC_{90}$ of 0.5 mg/L for both pathogen groups) and its activity was not adversely influenced by resistance to oxacillin (Table 1). All staphylococcal isolates were inhibited at a daptomycin MIC of 1 mg/L or less, which is the susceptible breakpoint approved by the CLSI, US-FDA and EUCAST.
- Linezolid ($MIC_{50}$ 1 mg/L and $MIC_{90}$, 2 mg/L), teicoplanin ($MIC_{50}$ and $MIC_{90}$, ≤2 mg/L) and vancomycin ($MIC_{50}$ and $MIC_{90}$, 1 mg/L) were also active against all isolates at the CLSI breakpoint. Decreased susceptibility to quinupristin/dalfopristin was observed among *S. aureus*, but restricted to medical centers located in France (12 strains), Belgium (1 strain) and Israel (1 strain).
- MRSA rates varied from 1.4% in Sweden to 44.0 and 55.9% in Ireland and Greece, respectively (Table 2). MRSA strains exhibited high resistance rates to levofloxacin (87.7%), erythromycin (67.1%) and clindamycin (34.0%; Table 1).
- Daptomycin activity against CoNS ($MIC_{50}$ of 0.25 mg/L and $MIC_{90}$ of 0.5 mg/L) was similar to that observed against *S. aureus* and all isolates, except for two isolates (0.12%, one each from Italy and Switzerland), were inhibited at daptomycin susceptible breakpoint of ≤1 mg/L. Vancomycin ($MIC_{50}$, 1 mg/L and $MIC_{90}$, 2 mg/L) was active against all CoNS strains, while decreased susceptibility for teicoplanin was noted in several countries.
- Daptomycin was highly active against *E. faecalis* strains ($MIC_{50}$ and $MIC_{90}$, 1 mg/L; 100.0% susceptible). Daptomycin MIC values ranged from 0.25 to 2 mg/L among vancomycin-non-susceptible strains. Ampicillin ($MIC_{90}$, 2-4 mg/L; 100.0% susceptible) was also very active against *E. faecalis* while 34.0% of vancomycin susceptible and 86.7% of vancomycin-resistant strains showed high-level resistance to gentamicin (Table 1).
- Vancomycin-resistant *E. faecium* was observed in 10 of 12 countries evaluated and was highest in Ireland (58.7%), Greece (46.0%), Poland (27.8%) and Germany (27.4%; Table 2).
- All *E. faecium* isolates were susceptible to daptomycin ($MIC_{50}$, 1-2 mg/L and $MIC_{90}$, 2 mg/L) and vancomycin resistance did not adversely influence daptomycin activity.
- *E. faecium*, especially vancomycin-resistant strains, showed high rates of resistance to most antimicrobial agents tested. Only 80.0% of strains were susceptible to quinupristin/dalfopristin and 43.3% of strains showed high-level resistance to gentamicin.
- Decreased susceptibility to quinupristin/dalfopristin (MIC ≥2 mg/L) among *E. faecium* was observed in all countries and was more common in Sweden (62.3 %), Germany (47.4%) and France (45.7%).
- Daptomycin was highly active against β-haemolytic streptococci ($MIC_{90}$, 0.25 mg/L) as were most comparison agents tested.
- Viridans group streptococci ($MIC_{50}$, 0.25 mg/L and $MIC_{90}$, 0.5 mg/L) showed daptomycin MIC values slightly higher (two-fold) than β-haemolytic streptococci and all isolates were inhibited by daptomycin concentration of 1 mg/L or less.

**Table 1**. Antimicrobial activity of daptomycin and comparator agents tested against bacterial isolates collected from patients hospitalized in European hospitals (2007-2008).

| Organism (no. tested) | MIC (mg/L) 50% | MIC (mg/L) 90% | % susceptible[a] | % resistant[a] |
|---|---|---|---|---|
| *S. aureus* | | | | |
| Oxacillin-susceptible (4,047) | | | | |
| Daptomycin | 0.25 | 0.5 | 100.0 | -[b] |
| Erythromycin | ≤0.25 | >4 | 85.3 | 14.1 |
| Clindamycin | ≤0.25 | ≤0.25 | 97.6 | 2.3 |
| Levofloxacin | ≤0.5 | ≤0.5 | 94.4 | 5.3 |
| Quinupristin/dalfopristin | ≤0.25 | 0.5 | 99.9 | 0.0 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | 99.6 | 0.4 |
| Linezolid | 1 | 2 | 100.0 | - |
| Teicoplanin | ≤2 | ≤2 | 100.0 | 0.1 |
| Vancomycin | 1 | 1 | 100.0 | 0.0 |
| Oxacillin-resistant (1,531) | | | | |
| Daptomycin | 0.25 | 0.5 | 100.0 | - |
| Erythromycin | >4 | >4 | 31.7 | 67.1 |
| Clindamycin | ≤0.25 | >2 | 65.8 | 34.0 |
| Levofloxacin | >4 | >4 | 11.5 | 87.7 |
| Quinupristin/dalfopristin | 0.5 | 1 | 99.3 | 0.5 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | 98.4 | 1.6 |
| Linezolid | 1 | 2 | 100.0 | - |
| Teicoplanin | ≤2 | ≤2 | 100.0 | 0.0 |
| Vancomycin | 1 | 1 | 100.0 | 0.0 |
| CoNS (1,665) | | | | |
| Daptomycin | 0.25 | 0.5 | 99.9 | - |
| Oxacillin | >2 | >2 | 23.7 | 76.3 |
| Erythromycin | >4 | >4 | 36.6 | 63.1 |
| Clindamycin | ≤0.25 | >2 | 71.2 | 27.9 |
| Levofloxacin | 4 | >4 | 43.2 | 53.6 |
| Quinupristin/dalfopristin | ≤0.25 | 0.5 | 98.5 | 1.1 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | >2 | 61.7 | 38.3 |
| Linezolid | 1 | 1 | 100.0 | - |
| Teicoplanin | ≤2 | 8 | 97.7 | 0.4 |
| Vancomycin | 1 | 2 | 100.0 | 0.0 |
| *E. faecalis* | | | | |
| Vancomycin-susceptible (1,290) | | | | |
| Daptomycin | 1 | 1 | 100.0 | - |
| Ampicillin | ≤1 | 2 | 98.8 | 0.2 |
| Gentamicin (HL) | ≤500 | >1000 | 66.0 | 34 |
| Quinupristin/dalfopristin | >2 | >2 | 0.7 | 95.8 |
| Linezolid | 1 | 2 | 100.0 | 0.0 |
| Teicoplanin | ≤2 | <2 | 100.0 | 0.0 |
| Vancomycin-resistant (16) | | | | |
| Daptomycin | 1 | 1 | 100.0 | - |
| Ampicillin | 2 | 4 | 100.0 | 0.0 |
| Gentamicin (HL) | >1000 | >1000 | 13.3 | 86.7 |
| Quinupristin/dalfopristin | >2 | >2 | 0.0 | 93.8 |
| Linezolid | 1 | 2 | 100.0 | 0.0 |
| Teicoplanin | >16 | >16 | 18.8 | 81.3 |

| Organism (no. tested) | MIC (mg/L) 50% | MIC (mg/L) 90% | % susceptible[a] | % resistant[a] |
|---|---|---|---|---|
| *E. faecium* | | | | |
| Vancomycin-susceptible (533) | | | | |
| Daptomycin | 2 | 2 | 100.0 | - |
| Ampicillin | >16 | >16 | 10.1 | 89.9 |
| Gentamicin (HL) | ≤500 | >1000 | 63.0 | 37.0 |
| Quinupristin/dalfopristin | 1 | >2 | 69.2 | 23.3 |
| Linezolid | 1 | 2 | 99.8 | 0.0 |
| Teicoplanin | ≤2 | ≤2 | 100.0 | 0.0 |
| Vancomycin-resistant (210) | | | | |
| Daptomycin | 1 | 2 | 99.5 | - |
| Ampicillin | >16 | >16 | 0.0 | 100.0 |
| Gentamicin (HL) | ≤500 | >1000 | 56.7 | 43.3 |
| Quinupristin/dalfopristin | 1 | 2 | 80.0 | 9.5 |
| Linezolid | 1 | 2 | 99.0 | 0.0 |
| Teicoplanin | >16 | >16 | 28.6 | 70.0 |
| *Enterococci* spp. (57)[c] | | | | |
| Daptomycin | 1 | 4 | 100.0 | - |
| Ampicillin | ≤1 | >16 | 86.0 | 14.0 |
| Gentamicin (HL) | ≤500 | >1000 | 89.5 | 10.5 |
| Quinupristin/dalfopristin | 2 | >2 | 17.5 | 40.4 |
| Linezolid | 1 | 2 | 100.0 | 0.0 |
| Teicoplanin | ≤2 | ≤2 | 96.5 | 1.8 |
| Vancomycin | 1 | 4 | 91.2 | 3.5 |
| β-haemolytic streptococci (807) | | | | |
| Daptomycin | ≤0.06 | 0.25 | 100.0 | - |
| Penicillin | ≤0.015 | 0.06 | 100.0 | - |
| Erythromycin | ≤0.25 | >2 | 82.3 | 16.9 |
| Clindamycin | ≤0.25 | 0.5 | 91.9 | 7.6 |
| Tetracycline | ≤2 | >8 | 50.8 | 46.8 |
| Levofloxacin | ≤0.5 | 1 | 99.4 | 0.6 |
| Linezolid | 1 | 1 | 100.0 | - |
| Viridans group streptococci (274) | | | | |
| Daptomycin | 0.25 | 0.5 | - | - |
| Penicillin | 0.06 | 2 | 72.6 | 8.4 |
| Ceftraixone | ≤0.25 | 2 | 89.8 | 5.5 |
| Erythromycin | ≤0.25 | >2 | 60.6 | 35.8 |
| Clindamycin | ≤0.25 | >2 | 89.1 | 10.6 |
| Tetracycline | ≤2 | >8 | 67.9 | 29.6 |
| Levofloxacin | 1 | 1 | 96.7 | 1.8 |
| Linezolid | 1 | 1 | 100.0 | - |
| Vancomycin | 0.5 | 1 | 100.0 | - |

a. According to CLSI criteria.
b. - = no breakpoints have been established by the CLSI.
c. Includes: *E. avium* (23 strains), *E. cassiluflavus* (9 strains), *E. durans* (8 strains), *E. gallinarum* (11 strains), *E. hirae* (4 strains), *E. raffinosus* (1 strain), and unspecified *Enterococcus* (1 strain).

**Table 2**. Rates of MRSA and vancoymcin-resistant *E. faecium* (VREFM) by country.

| Country | % (no. tested) MRSA | % (no. tested) VREFM |
|---|---|---|
| Belgium | 34.9 (198) | 11.1 (9) |
| France | 26.3 (1,087) | 1.4 (70) |
| Germany | 15.7 (776) | 27.4 (175) |
| Greece | 55.9 (222) | 46.0 (63) |
| Ireland | 44.0 (500) | 58.7 (109) |
| Israel | 38.6 (184) | 15.4 (13) |
| Italy | 28.3 (460) | 18.5 (27) |
| Poland | 32.8 (171) | 27.8 (36) |
| Spain | 23.8 (458) | 7.9 (38) |
| Sweden | 1.4 (351) | 0 (54) |
| Switzerland | 12.1 (182) | 0 (23) |
| Turkey | 21.9 (320) | 24.0 (104) |
| UK | 36.9 (669) | 22.7 (22) |
| Overall | 27.4 (5,578) | 25.6 (743) |

## CONCLUSIONS

- Daptomycin showed significant potency and broad-spectrum activity against recent clinical isolates of Gram-positive organisms isolated in European medical centers, including resistant subsets.
- All organisms tested, except for two CoNS isolates, were susceptible to daptomycin and resistance to other compounds did not adversely influence the daptomycin potency against staphylococci, enterococci or streptococci.
- Daptomycin is a valuable treatment alternative for serious infections caused by Gram-positive cocci, including MDR strains.

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