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Antimicrobial Activity of Daptomycin (DAP) Against Multi–Drug-Resistant (MDR) Gram-positive Strains Collected Worldwide

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Abstract

Daptomycin (DAP) is a cyclic lipopeptide currently in Phase III clinical trials for the treatment of Gram-positive infections in hospitalized patients. We evaluated the *in vitro* activity of DAP against recent multi–drug-resistant (MDR) Gram-positive clinical strains. A total of 386 isolates were selected from a large collection of clinical strains from more than 70 centers located in Europe, North America, and South America, most of them in 2002. The strains were tested by NCCLS broth microdilution methods (M7-A6) in Mueller-Hinton broth with 50 mg/L Ca^{2+} against DAP. More than 20 comparators were also tested by reference methods. The activity of DAP is summarized in the following table:

	DAP activity (µg/mL)		
Organisms (no. tested)	MIC_{50}	MIC_{90}	Range
Vancomycin (VAN)-resistant (R) *Enterococcus faecium* (EFM; 55)	2	4	0.25-4
VAN-R *Enterococcus faecalis* (EF; 20)	1	1	0.25-1
VAN-intermediate staphylococci (13)	0.5	1	0.5-2
Coagulase-negative staphylococci (CNS) with VAN MIC of 4 µg/mL (4)	0.5	–	0.25-1
Teicoplanin (TEIC)–non-susceptible CNS (20)	0.25	0.5	≤0.12-0.5
Quinupristin-dalfopristin (Q-D)–R EFM (41)	2	4	≤0.12-8
Q-D–R staphylococci (11)	0.5	1	0.25-1
Penicillin (PEN)-R *Staphylococcus pneumoniae* (203)	≤0.12	0.25	≤0.12-0.5
PEN-R viridans group streptococci (5)	0.5	-	≤0.12-1
Linezolid-R Gram-positive cocci (LZD; 14)	1	2	≤0.12-4

DAP activity was not influenced by R to VAN, TEIC, Q-D, or PEN among the Gram-positive isolates tested. DAP showed a significant potency and spectrum against Gram-positive species including MDR strains, and may represent a reasonable therapeutic option for infections caused by these important MDR pathogens. Tests with appropriate media (50 mg/L) will be required.

Introduction

The emergence of multi–drug-resistant (MDR) *Streptococcus pneumoniae* and increasing resistances in enterococci and staphylococci have created a need for the development of new antimicrobial agents to treat Gram-positive infections. Daptomycin (DAP) is a cyclic lipopeptide currently in Phase III trials for the treatment of serious Gram-positive infections. DAP has an unique mechanism of action that targets the bacterial membrane, and cross-resistance has not been observed with any other drug class. Gram-positive strains resistant to other compounds – such as vancomycin (VAN), streptogramin combinations (quinupristin-dalfopristin [Q-D]), linezolid (LZD) and telithromycin – are proving to be susceptible to DAP.

DAP has rapid *in vitro* bactericidal activity against a wide spectrum of Gram-positive organisms, including MDR strains of staphylococci, streptococci, and enterococci. We evaluated the *in vitro* activity of DAP against a contemporary worldwide collection of MDR Gram-positive strains.

Materials and Methods

Bacterial Isolates

A total of 386 strains with variable resistance to common Gram-positive antimicrobial agents were evaluated from a large collection of clinical isolates from more than 70 centers located in Europe, North America, and South America in 2001 and 2002. The collection included penicillin (PEN)-resistant (R) (MIC, ≥2 µg/mL) *S. pneumoniae* (203 strains), PEN-R viridans group streptococci (5 strains), VAN-R *Enterococcus faecium* (55 strains), VAN-R *Enterococcus faecalis* (20 strains), Q-D–R *E. faecium* (41 strains), teicoplanin (TEIC)–non-susceptible coagulase-negative staphylococci (CNS) (20 strains), VAN-intermediate staphylococci (13 strains), CNS with VAN MIC of 4 µg/mL (4 strains), Q-D–R staphylococci (11 strains) and linezolid (LZD)-R Gram-positive cocci (14 strains).

Susceptibility Testing

The strains were tested by NCCLS M7-A6 broth microdilution methods (NCCLS, 2003). Mueller-Hinton broth adjusted to contain physiologic levels of Ca^{2+} (50 mg/L) for testing DAP as recommended by previous investigators was used as a test medium.

DAP was tested along with more than 20 comparator agents in microdilution panels manufactured by TREK Diagnostic Systems, Inc. (Cleveland, Ohio). Comparator agents included PEN, oxacillin, VAN, TEIC, Q-D, LZD, levofloxacin, chloramphenicol, erythromycin, amoxicillin-clavulanate, ceftriaxone, and gentamicin. ATCC quality control organisms were tested concurrently with the clinical isolate collection.

Results

- DAP was very active against this worldwide collection of MDR organisms. All isolates were inhibited at ≤1 µg/mL of DAP, except the enterococci (Tables 1 and 2)
- DAP was the most potent compound tested against PEN-R *S. pneumoniae* with MIC_{50}/MIC_{90} values at ≤0.12 and 0.25 µg/mL, respectively. All isolates were inhibited at ≤0.5 µg/mL of DAP (Table 1)
- DAP was highly active against VAN-R enterococci. *E. faecium* showed higher DAP MIC values (MIC_{90}, 4 µg/mL) than *E. faecalis* (MIC_{90}, 1 µg/mL). All isolates were inhibited at ≤4 µg/mL of DAP except for one *E. faecium* strain which showed a DAP MIC of 8 µg/mL (Table 1)
- DAP (MIC_{90}, 4 µg/mL) and LZD (MIC_{90}, 2 µg/mL) were the most active compounds tested against Q-D–R enterococci (Table 1)
- TEIC–non-susceptible CNS were highly susceptible to DAP with all isolates being inhibited at ≤0.5 µg/mL. VAN (MIC_{90}, 2 µg/mL), Q-D (MIC_{90}, 0.5 µg/mL), and LZD (MIC_{90}, 1 µg/mL) were also active against all isolates at the susceptible breakpoint (Table 1)

Table 1. Antimicrobial Activity of Several Antimicrobial Agents Tested Against MDR Gram-positive Strains Collected Worldwide

	MIC µg/ml			Category:	
Organism/antimicrobial agent (no. tested)	50%	90%	Range	% Susceptible	% Resistant
Penicillin-resistant *S. pneumoniae* (203)					
Daptomycin	≤0.12	0.25	≤0.12-0.5	—[a]	—[a]
Amoxicillin-clavulanate	≤2	8	≤2-16	79.2	11.9
Ceftriaxone	1	1	≤0.25-8	91.6	4.0
Vancomycin	0.25	0.5	0.12-0.5	100.0	0.0
Clindamycin	≤0.06	>8	≤0.06->8	64.0	34.0
Eythromycin	4	>32	≤0.25->32	25.6	72.9
Quinupristin-dalfopristin	0.25	0.5	0.12-1	100.0	0.0
Linezolid	1	1	≤0.25-2	100.0	0.0
Levofloxacin	1	1	0.5->4	98.5	1.5
Vancomycin-resistant *E. faecium* (55)					
Daptomycin	2	4	0.25-4	—[a]	—[a]
Penicillin	>32	>32	1->32	3.6	96.7
Chloramphenicol	8	8	≤2->16	92.7	3.6
Teicoplanin	>16	>16	≤2->16	14.5	69.1
Quinupristin-dalfopristin	1	1	0.25-8	98.2	1.8
Linezolid	2	2	0.5-16	8.2	1.8
Levofloxacin	>4	>4	1->4	3.6	96.4
Vancomycin-resistant *E. faecalis* (20)					
Daptomycin	1	1	0.25-1	—[a]	—[a]
Penicillin	4	16	2-32	80.0	20.0
Chloramphenicol	8	>16	4->16	55.0	35.0
Teicoplanin	>16	>16	≤0.12->16	30.0	70.0
Quinupristin-dalfopristin	>8	>8	4->8	5.0	95.0
Linezolid	1	2	0.5-2	100.0	0.0
Levofloxacin	>4	>4	1->4	5.0	95.0
Quinupristin-dalfopristin-resistant *E. faecium* (41)					
Daptomycin	2	4	≤0.12-8	—[a]	—[a]
Penicillin	16	>32	1-32	43.9	56.1
Vancomycin	1	8	0.25->16	87.8	9.8
Chloramphenicol	8	16	≤2->16	85.4	4.9
Doxycycline	≤0.5	>4	≤0.5->4	58.5	41.5
Teicoplanin	≤2	≤2	≤2->16	90.2	9.8
Linezolid	2	2	1-2	100.0	0.0
Levofloxacin	2	>4	0.25->4	61.0	29.3
Teicoplanin–non-susceptible CNS[b] (20)					
Daptomycin	0.25	0.5	≤0.12-0.5	—[a]	—[a]
Oxacillin	>8	>8	0.12->8	15.0	85.0
Vancomycin	2	2	1-4	100.0	0.0
Chloramphenicol	4	>16	≤2->16	70.0	25.0
Tetracycline	≤4	4	≤4->8	90.0	10.0
Quinupristin-dalfopristin	0.25	0.5	≤0.25-1	100.0	0.0
Linezolid	1	1	0.5-1	100.0	0.0
Levofloxacin	4	>4	0.25->4	30.0	40.0

[a]No breakpoint has been established by NCCLS or FDA for these organisms.
[b]CNS=coagulase-negative staphylococci.

- All staphylococcal strains with decreased susceptibility to VAN were inhibited at ≤1 µg/ml of DAP (Table 2)

Table 2. DAP Activity Against Subsets of MDR Gram-positive Strains

	DAP MIC (µg/mL)		
Organisms	50%	90%	Range
Vancomycin-intermediate staphylococci[a] (13)	0.5	1	0.5-1
CNS[b] with vancomycin MIC of 4 µg/mL (4)	0.5	–	0.5-1
Quinupristin-dalfopristin–resistant staphylococci (11)	0.5	1	0.25-1
Linezolid-resistant Gram-positive cocci[c] (14)	1	2	≤0.12-4
Penicillin-resistant viridans group streptococci (5)	0.5	–	≤0.12-1

[a]Includes: *S. aureus* (10 strains) and CNS (3 strains).
[b]CNS=coagulase-negative staphylococci.
[c]Includes: *S. aureus* (3 strains), *Staphylococcus epidermidis* (1 strain), *Streptococcus oralis* (1 strain), *E. faecium* (6 strains), and *E. faecalis* (3 strains).

Conclusions

- DAP was highly active against MDR Gram-positive pathogens
- DAP activity was not influenced by resistance to VAN, TEIC, PEN, Q-D, or LZD
- DAP exhibited potent *in vitro* activity against a wide spectrum of multi–drug-resistant Gram-positive pathogens and may represent an excellent therapeutic option for infections caused by these pathogens.

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