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ANTIMICROBIAL ACTIVITY OF DAPTOMYCIN IN COMPARISON TO GLYCOPEPTIDES AND OTHER ANTIMICROBIALS WHEN TESTED AGAINST NUMEROUS SPECIES OF COAGULASE-NEGATIVE *STAPHYLOCOCCUS* (CoNS)

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AMENDED ABSTRACT

Background: CoNS represent a major cause of bloodstream infections, especially in patients with prosthetic devices and intravenous catheters. We evaluated the activity of daptomycin (DAP) in comparison to vancomycin (VAN) and teicoplanin (TEI) against a large collection of CoNS.

Methods: 22,024 CoNS isolates causing clinically significant infections were collected worldwide from 283 medical centers over 9 years (2002-2010) and tested for susceptibility (S) by CLSI broth microdilution methods against DAP and numerous comparators. Species identification was performed at the local laboratory and confirmed at JMI Laboratories when necessary.

Results: Overall, DAP ($MIC_{50/90}$, 0.25/0.5 μg/ml) inhibited 99.8% of CoNS at the S breakpoint of ≤1 μg/ml and was four- to 16-fold more active than VAN ($MIC_{50/90}$, 1/2 μg/ml; >99.9% S) and TEI ($MIC_{50/90}$, ≤2/8 μg/ml; 97.5% S). All species showed ≥99.6% DAP-S except *S. auricularis* (95.1% S), *S. capitis* (99.0%), *S. warneri* (98.8%) and *S. sciuri*. *S. sciuri* represented only 0.2% of the collection (46 strains) and exhibited atypically decreased S to DAP ($MIC_{50/90}$, 1/2 μg/ml, 71.7% S). In contrast, *S. sciuri* exhibited high S to VAN and TEI (highest MIC at 2 μg/ml for both drugs) when compared to other CoNS species. The species with highest MIC values for VAN and TEI (eg. *S. epidermidis*, *S. haemolyticus* and *S. xylosis*) were very DAP-S ($MIC_{50/90}$, 0.25/0.5 μg/ml; 99.9-100.0% S). Other agents active against CoNS were tigecycline ($MIC_{50/90}$, ≤0.12/0.25 μg/ml; 99.8% S), linezolid ($MIC_{50/90}$, 1/1 μg/ml; 99.5% S) and quinupristin/dalfopristin ($MIC_{50/90}$, ≤0.5/≤0.5 μg/ml; 99.2% S).

Conclusions: DAP exhibited species-specific activity among CoNS, especially versus *S. sciuri*. No correlation between decreased DAP-S and the glycopeptides tested was observed.

Species/no. tested	Daptomycin % of strains at MIC[a] of: ≤1	2	4	MIC_{50}[a]	MIC_{90}[a]	% at VAN MIC[a] ≥2	% at TEI MIC[a] ≥4
S. sciuri (46)	71.7	23.9	4.4	1	2	15.2	0.0
S. auricularis (81)	95.1	3.7	1.2	0.5	1	25.9	12.3
S. warneri (323)	98.8	1.2	-	0.5	1	29.4	31.9
S. capitis (490)	99.0	0.8	0.2	0.5	1	13.1	10.2
S. saprophyticus (223)	99.6	0.4	-	0.25	0.5	7.6	23.8
S. hominis (1,134)	99.8	0.2	-	0.25	0.5	18.7	15.3
S. epidermidis (7,653)	99.9	<0.1	<0.1	0.25	0.5	55.3	34.2
S. haemolyticus (1,291)	100.0	-	-	0.25	0.5	45.3	48.2
S. simulans (138)	100.0	-	-	0.25	0.5	9.4	15.2
S. xylosus (143)	100.0	-	-	0.25	0.5	40.6	25.9
S. lugdenensis (280)	100.0	-	-	0.25	0.25	3.2	3.6
All CoNS[b] (22,024)	99.8	0.2	<0.1	0.25	0.5	29.9	43.1

a. MIC in μg/ml. b. Includes strains from 24 species and 10,098 unspeciated CoNS strains.

INTRODUCTION

Coagulase-negative staphylococci (CoNS) have long been regarded as culture contaminants but their important role as true pathogens, and their increasing incidence, have been recognized in recent years. CoNS are by far the most common cause of bacteremia related to indwelling devices and most of these infections are hospital-acquired. Other important infections caused by CoNS include central nervous system shunt infections, native or prosthetic valve endocarditis, urinary tract infections, and endophthalmitis.

CoNS infections are characterized by their indolence and usually require the removal of the catheter or device. Resistance to multiple antimicrobial agents further complicates treatment of systemic infections. Resistance to oxacillin and other β-lactams is widespread among CoNS associated with human infections. Although CoNS are usually susceptible to glycopeptides, increased MIC values for teicoplanin (≥4 μg/ml) and/or vancomcyin (≥2 μg/ml) are frequently reported and may be related to poor clinical outcome.

Daptomycin is a cyclic lipopeptide antimicrobial with a novel mode of action against Gram-positive organisms. Daptomycin is rapidly bactericidal and has shown excellent *in vitro* activity against the most commonly isolated CoNS organisms. We evaluated the activity of daptomycin in comparison to vancomycin and teicoplanin against a large collection of clinical CoNS isolates.

MATERIALS AND METHODS

Bacterial isolates.

A total of 22,024 clinically-significant isolates of CoNS (24 species) were collected from 283 hospitals in 42 countries as part of the SENTRY Antimicrobial Surveillance Program over a 9-year period (2002-2010). The isolates were collected from medical centers located in Europe (37.6%), North America (37.0%), Latin America (15.5%) and Asia-Pacific region (9.9%). The majority of strains (>75%) were from bloodstream infections. Species identification was performed at the local laboratory and confirmed at JMI Laboratories, when necessary, using algorithms and the automated Vitek systems (Vitek and Vitek 2; bioMérieux, Hazelwood, Missouri, USA).

Antimicrobial susceptibility testing.

All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed using validated broth microdilution panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). Categorical interpretation of MIC values was performed according to CLSI (M100-S21, 2011) and validation of MIC values was performed by concurrent testing of CLSI-recommended (M100-S21, 2011) quality control (QC) strains: *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.

RESULTS

Table 1. Antimicrobial activity of daptomycin and comparators tested against 22,024 clinical isolates of coagulase-negative staphylococci.

Antimicrobial	MIC_{50}[a]	MIC_{90}[a]	MIC range[a]	% Susc.[b]	% Resistant[b]
Daptomycin	0.25	0.5	≤0.06-4	99.8	-
Vancomycin	1	2	≤0.12-8	>99.9	0.0
Teicoplanin	≤2	8	≤2->16	97.5	0.4
Linezolid	1	1	≤0.25->8	99.5	0.5
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25->4	99.2	0.4
Tigecycline	≤0.12	0.25	≤0.12-2	99.8	-
Oxacillin	>2	>2	≤0.25->2	23.6	76.4

a. MIC in μg/ml.
b. According to CLSI breakpoints [CLSI, 2011].

- Overall, daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/ml) inhibited 99.8% of CoNS at the susceptible breakpoint of ≤1 μg/ml and was four- to 16-fold more active than vancomycin ($MIC_{50/90}$, 1/2 μg/ml; >99.9% susceptible) and teicoplanin ($MIC_{50/90}$, ≤2/8 μg/ml; 97.5% susceptible; Table 1).
- All species showed ≥99.6% susceptibility to daptomycin, except *S. auricularis* (95.1% susceptible), *S. capitis* (99.0%), *S. warneri* (98.8%) and *S. sciuri* (71.7%; Table 2).
- *S. sciuri* represented only 0.2% of the collection (46 strains) and exhibited atypically decreased susceptibility to daptomycin ($MIC_{50/90}$, 1/2 μg/ml, 71.7% susceptible). In contrast, *S. sciuri* exhibited high susceptibility to vancomycin and teicoplanin (highest MIC at 2 μg/ml for both drugs) when compared to other CoNS species (Table 2).
- The species with highest MIC values for vancomycin and teicoplanin (eg. *S. epidermidis*, *S. haemolyticus* and *S. xylosis*) were very susceptible to daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/ml; 99.9-100.0% susceptible).
- Other agents active against CoNS were tigecycline ($MIC_{50/90}$, ≤0.12/0.25 μg/ml; 99.8% susceptible), linezolid ($MIC_{50/90}$, 1/1 μg/ml; 99.5% susceptible) and quinupristin/dalfopristin ($MIC_{50/90}$, ≤0.25/0.5 μg/ml; 99.2% susceptible; Table 1).
- The CoNS species with lowest susceptibility rates to oxacillin were *S. sciuri* (2.2%), *S. cohnii* (3.1%), *S. saprophyticus* (6.7%) and *S. haemolyticus* (10.4%; Table 2).

Table 2. Daptomycin MIC distribution when tested against various species of CoNS.

Species/no. tested	No. of isolates (cumulative %) inhibited at daptomycin MIC[a] of: ≤0.12	0.25	0.5	1	2	4	daptomycin MIC_{50}[a]	daptomycin MIC_{90}[a]	% at VAN MIC[a] ≥2	% at TEI MIC[a] ≥4	% S to oxacillin[c]
S. sciuri (46)	3 (6.5)	2 (10.9)	7 (26.1)	21 (71.7)	11 (95.7)	2(100.0)	1	2	15.2	0.0	2.2
S. auricularis (81)	14 (17.3)	20 (42.0)	24 (71.6)	19 (95.1)	3 (98.8)	1 (100.0)	0.5	1	25.9	12.3	48.2
S. warneri (323)	23 (7.1)	86 (33.8)	160 (83.3)	50 (98.8)	4 (100.0)	-	0.5	1	29.4	31.9	35.3
S. capitis (490)	19 (3.9)	75 (19.2)	266 (73.5)	125 (99.0)	4 (99.8)	1 (100.0)	0.5	1	13.1	10.2	55.1
S. cohnii (32)	3 (9.4)	10 (40.6)	16 (90.6)	3 (100.0)	-	-	0.5	0.5	12.5	3.1	3.1
S. saprophyticus (223)	21 (9.4)	101 (54.7)	88 (94.2)	12 (99.6)	1 (100.0)	-	0.25	0.5	7.6	23.8	6.7
S. hominis (1,134)	259 (22.8)	683 (83.1)	176 (98.3)	17 (99.8)	2 (100.0)	-	0.25	0.5	18.7	15.3	27.4
S. epidermidis (7,653)	353 (4.6)	4,053 (57.6)	3,090 (98.0)	152 (99.9)	3 (>99.9)	2 (100.0)	0.25	0.5	55.3	34.2	20.5
S. haemolyticus (1,291)	133 (10.3)	659 (61.4)	472 (97.9)	27 (100.0)	-	-	0.25	0.5	45.3	48.2	10.4
S. simulans (138)	53 (38.4)	52 (76.1)	27 (95.7)	1 (100.0)	-	-	0.25	0.5	9.4	15.2	34.8
S. xylosus (143)	14 (9.8)	72 (60.1)	54 (97.9)	3 (100.0)	-	-	0.25	0.5	40.6	25.9	14.7
S. caprae (12)	-	8 (66.7)	4 (100.0)	-	-	-	0.25	0.5	8.3	0.0	75.0
S. intermedius (32)	11 (34.4)	14 (78.3)	6 (96.9)	1 (100.0)	-	-	0.25	0.5	12.5	3.1	65.6
S. lugdenensis (280)[c]	95 (33.9)	161 (91.4)	22 (99.3)	2 (100.0)	-	-	0.25	0.25	3.2	3.6	92.1[c]
S. schleiferi (18)	10 (55.6)	5 (83.3)	3 (100.0)	-	-	-	0.12	0.5	11.1	11.1	72.2
Other CoNS species (30)[b]	7 (23.3)	11 (60.0)	10 (93.3)	2 100.0)	-	-	0.25	0.5	43.3	26.7	26.7
Unspecified CoNS (10,098)	971 (9.6)	5,150 (60.6)	3,568 (95.9)	400 (99.9)	9 (100.0)		0.25	0.5	40.7	29.0	25.6
All CoNS[b] (22,024)	1,989 (9.0)	11,162 (59.7)	7,990 (96.0)	840 (99.8)	37 (>99.9)	6 (100.0)	0.25	0.5	43.1	29.9	23.6

a. MIC in μg/ml.
b. Includes *S. arlettae* (5), *S. carnosus* (1), *S. chromogenes* (8), *S. delphini* (1), *S. equorum* (4), *S hycus* (1), *S. lentus* (6), *S. saccharolyticus* (2) and *S. succinus* (2).
c. Susceptible at ≤0.25 μg/ml of oxacillin except for *S. lugdenensis* for which a susceptible breakpoint of ≤2 μg/ml was applied [CLSI, 2011].

CONCLUSIONS

- Daptomycin exhibited excellent in vitro activity against a large collection (22,024) of CoNS clinical isolates, with 99.8% of strains being susceptible.
- Daptomycin exhibited species-specific activity among CoNS. *S. sciuri* exhibited atypically decreased susceptibility to daptomycin ($MIC_{50/90}$, 1/2 μg/ml, 71.7% susceptible), but represented only a very small proportion (0.2%) of CoNS isolated from clinical infections.
- No correlation between decreased susceptibility to daptomycin and to glycopeptides tested was observed.

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DISCLOSURE

CUBICIN® (daptomycin for injection) is not indicated for the treatment of coagulase-negative staphylococcal infections. Although daptomycin has shown to be active *in vitro*, the efficacy of CUBICIN® in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

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