Antimicrobial Activity of Dalbavancin against Clinical Isolates of Coagulase-Negative Staphylococci (CoNS) from United States and Europe Stratified by Species

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INTRODUCTION

- Changes in patient populations, such as increased numbers of chronically ill, immunocompromised patients, premature newborns, and elderly, coupled with the increasing use of inserted foreign bodies, led to a recognition of the large variety of infections caused by coagulase-negative staphylococci (CoNS).
- The development and widespread use of MALDI-TOF-MS allowed a better understanding of the clinical importance of different CoNS species.
- *S. epidermidis* by far is the most prevalent CoNS in microbiological samples and the primary cause of CoNS-related infections, particularly in nosocomial settings; however, the clinical relevance of many other CoNS species, such as *Staphylococcus lugdunensis*, *S. haemolyticus*, *S. hominis*, *S. simulans*, and *S. warneri*, is increasing continuously.
- Dalbavancin allows for the very convenient parenteral administration in a single dose of 1500 mg or a dose of 1000 mg followed by 500 mg a week later to treat ABSSSI.
- Single or multiple dalbavancin doses have been demonstrated to be a potential strategy for the treatment of endocarditis, osteomyelitis, septic arthritis, pneumonia, prosthetic joint infections, intra-abdominal infections, and bacteremia, although it is not approved for these indications.
- We evaluated the *in vitro* activity of dalbavancin and comparators against a large collection of CoNS from US and European hospitals.

MATERIALS AND METHODS

- A total of 5,088 CoNS isolates considered clinically significant (multiple infection types) were collected from 79 medical centers in the US (n=2,707) and 43 medical centers in 21 European countries (n=2,381) over 6 years (2014-2019) (one/patient episode).
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) as part of the International Dalbavancin Evaluation of Activity (IDEA) Surveillance Program.
- The participating laboratory initially identified isolates, and the reference monitoring laboratory confirmed bacterial identifications by standard algorithms and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).
- Isolates were tested for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07 document.

RESULTS

- Overall, 2,721 (53.5%) isolates were from bloodstream infections (BSI), 1,451 (28.5%) from SSSI, 348 (6.8%) from UTI, and 568 (11.2%) from other infection sites.
  - Among isolates from BSI, the most common species were *S. epidermidis* (61.3%), *S. hominis* (14.7%), *S. hemolyticus* (8.9%), and *S. capitis* (6.5%; Figure 1A).
  - Among non-BSI isolates, the most common species were *S. epidermidis* (46.9%), *S. lugdunensis* (23.0%), *S. hemolyticus* (8.8%), and *S. capitis* (6.5%; Figure 1B).
  - Moreover, 60.0% of *S. epidermidis* and 53.7% of *S. haemolyticus* were from BSI, 82.2% of *S. saprophyticus* isolates were from UTI, and 74.9% of *S. lugdunensis* isolates were from SSSI (data not shown).
- Dalbavancin ($MIC_{50/90}$, 0.03/0.06 mg/L) inhibited >99.9% of CoNS at ≤0.25 mg/L (CLSI and US FDA susceptible breakpoint for *S. aureus*) and 99.1% at ≤0.12 mg/L (EUCAST breakpoint; Table 1).
  - All isolates from the US were inhibited at the dalbavancin MIC of ≤0.25 mg/L (US FDA), and 99.0% of isolates from Europe were inhibited at ≤0.12 mg/L (EUCAST; Table 1).
- Vancomycin (>99.9% susceptibility), daptomycin (99.9%), linezolid (98.7%), and teicoplanin (98.6%) were very active against all CoNS species per CLSI and EUCAST criteria (Table 2).
- Teicoplanin susceptibility rates ranged from (CLSI/EUCAST) 95.3/80.2% for *S. haemolyticus* to 100.0/100.0% for *S. lugdunensis, S. saprophyticus*, and *S. simulans* (CLSI; Table 2).
- Susceptibility to daptomycin was 99.9%, with only 3 daptomycin non-susceptible strains (all with a daptomycin MIC of 2 mg/L) being observed, 2 *S. pettenkoferi* and 1 *S. epidermidis* (Table 2).
- Linezolid was active against 97.8% of BSI isolates and 99.7% on non-BSI isolates (MIC_{50}, 0.5 mg/L and MIC_{90}, 1 mg/L for both groups; Table 3).
- Overall, 60.7% of isolates were oxacillin-resistant (MRCoNS).
  - MRCoNS rates were 57.1% in US isolates and 64.6% among isolates from Europe (Table 2).
  - Oxacillin-resistance rates varied from as low as 4.6% for *S. lugdunensis* and 33.0% for *S. capitis* to as high as 84.0% for *S. haemolyticus* and 97.0% for *S. saprophyticus* (Table 2).
- BSI isolates were less susceptible (CLSI) to oxacillin (32.3% versus 47.4%), clindamycin (69.4% versus 77.7%), erythromycin (35.6% versus 48.5%), levofloxacin (47.3% versus 67.9%), tetracycline (85.0% versus 87.9%), and trimethoprim-sulfamethoxazole (TMP-SMX; 64.3% versus 76.9%) than non-BSI isolates (Table 3).

CONCLUSIONS

- Dalbavancin demonstrated potent *in vitro* activity against all clinically significant CoNS species, including many uncommonly isolated species for which very limited susceptibility information is available to guide contemporary therapy.
- Dalbavancin, daptomycin, and vancomycin were equally active against BSI and non-BSI isolates.
- Clinical studies of dalbavancin for treatment of CoNS infections should be considered based on these *in vitro* data.

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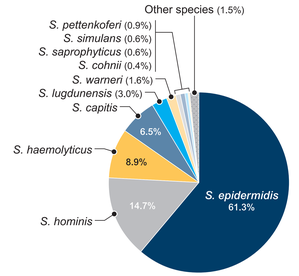
Figure 1. Frequency of CoNS species

A. BSI isolates



B. Non-BSI isolates

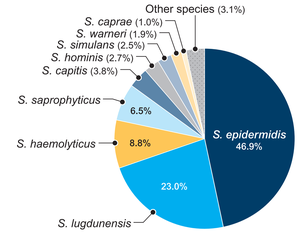


Table 1. MIC distribution of dalbavancin tested against coagulase-negative staphylococci (CoNS) from the United States and Europe (2014–2018)

Organism (no. tested)	No. of isolates and cumulative % inhibited at dalbavancin MIC (mg/L) of:									MIC (mg/L)	
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	>0.25	50%	90%
S. epidermidis (2,777)	0	9	43	534	1529	555	92	14	1	0.03	0.06
	0.0%	0.3%	1.9%	21.1%	76.2%	96.1%	99.5%	>99.9%	100.0%		
S. lugdunensis (625)	1	0	7	210	379	27	1			0.03	0.03
	0.2%	0.2%	1.3%	34.9%	95.5%	99.8%	100.0%				
S. haemolyticus (449)		0	2	17	60	197	154	19		0.06	0.12
		0.0%	0.4%	4.2%	17.6%	61.5%	95.8%	100.0%			
S. hominis (462)	0	1	7	146	246	54	8			0.03	0.06
	0.0%	0.2%	1.7%	33.3%	86.6%	98.3%	100.0%				
S. capitis (267)	1	10	65	106	68	15	1	1		0.015	0.03
	0.4%	4.1%	28.5%	68.2%	93.6%	99.3%	99.6%	100.0%			
S. saprophyticus (169)			0	2	16	67	77	7		0.06	0.12
			0.0%	1.2%	10.7%	50.3%	95.9%	100.0%			
S. warneri (88)	0	1	5	25	31	18	6	1	1	0.03	0.06
	0.0%	1.1%	6.8%	35.2%	70.5%	90.9%	97.7%	98.9%	100.0%		
S. simulans (76)		0	6	37	30	3				0.015	0.03
		0.0%	7.9%	56.6%	96.1%	100.0%					
Other species (175)	0	4	21	46	64	30	8	2		0.03	0.06
	0.0%	2.3%	14.3%	40.6%	77.1%	94.3%	98.9%	100.0%			
All CoNS (5,088)	2	25	156	1123	2423	966	347	44	2	0.03	0.06
	<0.1%	0.5%	3.7%	25.7%	73.3%	92.3%	99.1%	>99.9%	100.0%		
BSI isolates (2,721)	2	14	84	620	1312	506	159	23	1	0.03	0.06
	0.1%	0.6%	3.7%	26.5%	74.7%	93.3%	99.1%	>99.9%	100.0%		
Non-BSI isolates (2,367)		11	72	503	1111	460	188	21	1	0.03	0.06
		0.5%	3.5%	24.8%	71.7%	91.1%	99.1%	>99.9%	100.0%		
US (2,707)	1	14	80	647	1358	457	129	21		0.03	0.06
	<0.1%	0.6%	3.5%	27.4%	77.6%	94.5%	99.2%	100.0%			
Europe (2,381)	1	11	76	476	1065	509	218	23	2	0.03	0.12
	<0.1%	0.5%	3.7%	23.7%	68.4%	89.8%	99.0%	99.9%	100.0%		

Abbreviations: CoNS, coagulase-negative staphylococci; BSI, bloodstream infection; US, United States.

Table 2. Susceptibility rates for dalbavancin and comparators against coagulase-negative staphylococci (CoNS) stratified by species and geographic region

Species (no. tested)	% Susceptible[a]								
	Dalba[b]	Vanco	Teico	Dapto	Linez	Clinda	Levo	TMP-SMX	Oxa
S. epidermidis (2,777)	>99.9	>99.9	99.0	>99.9	97.7	62.5	42.7	60.5	26.3
S. lugdunensis (625)	100.0	100.0	100.0	100.0	100.0	92.5	98.9	99.5	95.4
S. hominis (462)	100.0	100.0	97.4	100.0	99.6	84.6	69.3	67.1	49.6
S. haemolyticus (449)	100.0	100.0	95.3	100.0	99.8	79.3	25.2	46.8	16.0
S. capitis (267)	100.0	100.0	97.4	100.0	100.0	87.3	74.5	98.5	67.0
S. saprophyticus (169)	100.0	100.0	100.0	100.0	100.0	84.6	99.4	98.2	3.0
S. warneri (88)	100.0	100.0	94.3	100.0	100.0	92.0	95.5	98.9	58.0
S. simulans (76)	100.0	100.0	100.0	100.0	100.0	85.3	76.3	98.7	61.8
Other species (175)	100.0	100.0	100.0	98.9	99.4	82.9	84.6	90.3	53.7
All CoNS (5,088)	>99.9	>99.9	98.6	99.9	98.7	73.3	56.9	70.2	39.3
US (2,707)	100.0	>99.9	98.6	>99.9	98.6	70.2	61.2	71.7	42.9
Europe (2,381)	>99.9	100.0	98.5	99.9	98.8	76.7	52.0	68.4	35.4

[a] Per CLSI criteria.
[b] Percentage inhibited at *S. aureus* breakpoint of ≤0.25 mg/L.
Abbreviations: Dalba, dalbavancin; Vanco, vancomycin; Teico, teicoplanin; Linez, linezolid; Clinda, clindamycin; TMP-SMX, trimethoprim-sulfamethoxazole; Oxa, oxacillin; US, United States.

Table 3. Activity of dalbavancin and comparator antimicrobial agents tested against 5,088 coagulase-negative staphylococci isolates (2014–2019)

Antimicrobial agent	MIC in mg/L		CLSI[a]		EUCAST[b]	
	MIC_{50}	MIC_{90}	%S	%R	%S	%R
BSI isolates (2,721)						
Dalbavancin	0.03	0.06	>99.9[b]		99.1	0.9
Daptomycin	0.25	0.5	99.9		99.9	0.1
Vancomycin	1	2	100.0	0.0	100.0	0.0
Teicoplanin	≤2	4	98.3	0.1	90.1	9.9
Linezolid	0.5	1	97.8	2.2	97.8	2.2
Oxacillin	>2	>2	32.3	67.7	32.9	67.1
Clindamycin	≤0.25	>2	69.4	28.7	68.2	30.6
Erythromycin	>8	>8	35.6	61.5	36.2	62.7
Levofloxacin	1	>4	47.3	49.7	[c]	52.7
Tetracycline	≤0.5	>8	85.0	13.3	77.1	16.2
TMP-SMX[d]	≤0.5	>4	64.3	35.7	64.3	16.4
Non-BSI isolates (2,367)						
Dalbavancin	0.03	0.06	>99.9[b]		99.1	0.9
Daptomycin	0.25	0.5	100.0		100.0	0.0
Vancomycin	1	2	>99.9	0.0	>99.9	<0.1
Teicoplanin	≤2	4	98.9	0.3	93.7	6.3
Linezolid	0.5	1	99.7	0.3	99.7	0.3
Oxacillin	1	>2	47.4	52.6	53.2	46.8
Clindamycin	≤0.25	>2	77.7	20.9	76.0	22.3
Erythromycin	4	>8	48.5	49.4	48.7	50.7
Levofloxacin	0.25	>4	67.9	30.1	[c]	32.1
Tetracycline	≤0.5	>8	87.9	10.8	82.5	13.2
TMP-SMX[d]	≤0.5	>4	76.9	23.1	76.9	12.5

[a] CLSI (2020) and EUCAST (2020) published criteria.
[b] Percentage inhibited at *S. aureus* breakpoint of ≤0.25 mg/L.
[c] An arbitrary susceptible breakpoint of ≤0.001 mg/L has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure (EUCAST 2020).
[d] TMP-SMX, trimethoprim-sulfamethoxazole.

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