

RESEARCH ARTICLE

Epidemiology and Prognosis of Coagulase-Negative Staphylococcal Endocarditis: Impact of Vancomycin Minimum Inhibitory Concentration

Cristina García de la Mària¹✉, Carlos Cervera¹✉, Juan M. Pericàs¹✉, Ximena Castañeda¹, Yolanda Armero¹, Dolors Soy³, Manel Almela², Salvador Ninot⁴, Carlos Falces⁵, Carlos A. Mestres⁴, Jose M. Gatell¹, Asuncion Moreno¹, Francesc Marco², José M. Miró^{1*}, Hospital Clinic Endocarditis Study Group[†]

1 Infectious Diseases Service, The Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona School of Medicine, Barcelona, Spain, **2** Microbiology Service, The Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona School of Medicine, Barcelona, Spain, **3** Pharmacy Service, The Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona School of Medicine, Barcelona, Spain, **4** Department of Cardiovascular Surgery, The Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona School of Medicine, Barcelona, Spain, **5** Cardiology Service, The Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona School of Medicine, Barcelona, Spain

✉ These authors contributed equally to this work.

† Membership of the Hospital Clinic Endocarditis Study Group is provided in the Acknowledgments.

* jmmiro@ub.edu



CrossMark
click for updates

OPEN ACCESS

Citation: García de la Mària C, Cervera C, Pericàs JM, Castañeda X, Armero Y, Soy D, et al. (2015) Epidemiology and Prognosis of Coagulase-Negative Staphylococcal Endocarditis: Impact of Vancomycin Minimum Inhibitory Concentration. PLoS ONE 10(5): e0125818. doi:10.1371/journal.pone.0125818

Academic Editor: Ulrich Nübel, Leibniz-Institute DSMZ, GERMANY

Received: November 23, 2014

Accepted: March 18, 2015

Published: May 11, 2015

Copyright: © 2015 García de la Mària et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This work was supported in part by a grant from the "Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III" (Madrid, Spain; <http://www.isciii.es/>), the Spanish Network for Research in Infectious Diseases (REIPI RD06/0008; <http://www.reipi.org/>), and the "Fundación Máximo Soriano Jiménez" (Barcelona, Spain; <http://www.fundSORIANO.es/>). JP received, during the period of manuscript elaboration, an "Emili Letang" Post-residency Scholarship (2013-14) from the Hospital Clinic, Barcelona (Spain) and a

Abstract

This study describes coagulase-negative staphylococcal (CoNS) infective endocarditis (IE) epidemiology at our institution, the antibiotic susceptibility profile, and the influence of vancomycin minimum inhibitory concentration (MIC) on patient outcomes. One hundred and three adults with definite IE admitted to an 850-bed tertiary care hospital in Barcelona from 1995-2008 were prospectively included in the cohort. We observed that CoNS IE was an important cause of community-acquired and healthcare-associated IE; one-third of patients involved native valves. *Staphylococcus epidermidis* was the most frequent species, methicillin-resistant in 52% of patients. CoNS frozen isolates were available in 88 patients. Vancomycin MICs of 2.0 µg/mL were common; almost all cases were found among *S. epidermidis* isolates and did not increase over time. Eighty-five patients were treated either with cloxacillin or vancomycin: 38 patients (Group 1) were treated with cloxacillin, and 47 received vancomycin; of these 47, 27 had CoNS isolates with a vancomycin MIC <2.0 µg/mL (Group 2), 20 had isolates with a vancomycin MIC ≥2.0 µg/mL (Group 3). One-year mortality was 21%, 48%, and 65% in Groups 1, 2, and 3, respectively ($P=0.003$). After adjusting for confounders and taking Group 2 as a reference, methicillin-susceptibility was associated with lower 1-year mortality (OR 0.12, 95% CI 0.02-0.55), and vancomycin MIC ≥2.0 µg/mL showed a trend to higher 1-year mortality (OR 3.7, 95% CI 0.9-15.2; $P=0.069$). Other independent variables associated with 1-year mortality were heart failure (OR 6.2, 95%

"Rio Hortega" Research Grant (CM14/00135; 2015-16) from the 'Instituto de Salud Carlos III' and the 'Ministerio de Economía and Competitividad', Madrid (Spain). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have read the journal's policy and the authors of this manuscript have the following competing interests: Dr. Jose M. Miro has received consulting honoraria and/or research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Cubist, Novartis, Glaxo Smith Kline, Gilead Sciences, Pfizer, Roche, Theravance, and ViiV. Dr. Francesc Marco has received consulting honoraria from Novartis and Janssen-Cilag. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials. All other authors have no competing interests to declare.

CI 1.5-25.2) and pacemaker lead IE (OR 0.1, 95%CI 0.02-0.51). In conclusion, methicillin-resistant *S.epidermidis* was the leading cause of CoNS IE, and patients receiving vancomycin had higher mortality rates than those receiving cloxacillin; mortality was higher among patients having isolates with vancomycin MICs ≥ 2.0 $\mu\text{g/mL}$.

Introduction

Coagulase-negative staphylococci (CoNS) have come to be recognized as important, commonly isolated pathogens [1,2]. Infections are usually associated with healthcare settings and occur in patients harbouring indwelling polymer or metallic devices [3]. CoNS cause >10% of all infective endocarditis (IE) cases [4] and are among the most frequent etiological agents of intracardiac prosthetic device infections, such as prosthetic valve endocarditis (PVE) and intracardiac device (ICD) endocarditis [5–7]. In addition, these microorganisms are becoming an important cause of native valve endocarditis (NVE) [8]. Among CoNS species, *Staphylococcus lugdunensis* is notable for its particular virulence [9].

Resistance to methicillin and other antibiotics is becoming more frequent among CoNS. A glycopeptide, such as vancomycin, is the recommended treatment for methicillin-resistant CoNS (MR-CoNS) NVE, while gentamicin and rifampin are typically added in PVE [10]. The emergence of CoNS with reduced susceptibility to vancomycin [3], together with the increasing prevalence of glycopeptide-intermediate *Staphylococcus epidermidis* (GISE) [11] and resistance to rifampin and gentamicin among methicillin-resistant *S. epidermidis* (MRSE), limits therapeutic options and warrants investigation of alternative bactericidal agents.

Among patients with *Staphylococcus aureus* bacteremia, increased vancomycin minimum inhibitory concentrations (MICs) have been associated with clinical failures [12], while vancomycin MICs >1 $\mu\text{g/mL}$ have been associated with higher mortality [13]. There currently are no data regarding the influence of vancomycin MIC on the outcome of CoNS IE.

This study aimed to characterize the epidemiology, clinical characteristics, and antibiotic susceptibility pattern of CoNS IE, and the influence of methicillin susceptibility and vancomycin MIC on outcomes.

Methods

This prospective cohort study was performed in an urban tertiary care hospital with 850 beds in Barcelona, Spain. All consecutive CoNS IE patients seen from 1995 to 2008 were recorded in a database using a standardized case report form. Only patients with a definite diagnosis of IE [14] were included. All survivors were followed ≥ 1 year. The Ethics Committee of our institution gave its approval to perform the current study.

The variables analyzed, including age, gender, history of chronic disease, calendar year, right- vs. left-sided IE, type of endocarditis (NVE, PVE, or ICD-associated), place of acquisition (community-acquired, nosocomial, or non-nosocomial healthcare-associated) [15], clinical complications (heart failure, renal failure, or systemic emboli, including stroke), need for surgery, and in-hospital and 1-year mortality, have been previously defined [16].

Due to the duration of the study period, antimicrobial treatment for CoNS IE was given according to the 1995 (originally) and 2005 (later) American Heart Association (AHA) recommendations [10,17], both of which recommend the same agents for CoNS IE. Methicillin-susceptible CoNS (MS-CoNS) IE was treated with cloxacillin, and MR-CoNS IE was treated with either vancomycin alone (NVE) or combined with other antibiotics (PVE or ICD IE). The

decision of using monotherapy or combination was at the discretion of the treating physician and influenced by factors related to patient' clinical status (ie, renal function, drug allergy, potential drug interactions, comorbidity, age). Per guidelines of the time [10,17], a vancomycin trough concentration of 10–15 µg/mL was targeted.

In order to analyze the impact of methicillin resistance and vancomycin MIC on outcomes, we divided patients into 3 groups: patients treated with cloxacillin for MS-CoNS IE (Group 1), vancomycin for CoNS with vancomycin MIC <2 µg/mL (Group 2), or vancomycin for CoNS with vancomycin MIC ≥2 µg/mL (Group 3). In the event of polyclonal or polymicrobial CoNS IE, we categorized patients per the higher vancomycin MIC.

Identification of CoNS Isolates

Isolates were stored at -80°C in skim milk. Isolates were identified using the API ID 32 Staph (bioMérieux, Marcy l'Etoile, France). Species were divided into 4 groups: *S. epidermidis*, *S. lugdunensis*, other CoNS, and polymicrobial IE. Polymicrobial infections were caused by different CoNS isolates. Polyclonal CoNS infections were caused by ≥2 isolates of the same species with different antibiotic susceptibilities and each isolate was counted separately.

Antibiotic Susceptibility Testing

Susceptibility was determined by Etest according to the manufacturer's recommendations (AB Biodisk-bioMérieux, Marcy l'Etoile, France). Etest strips were purchased from bioMérieux (Madrid, Spain). The following antimicrobials were evaluated: penicillin, oxacillin, erythromycin, clindamycin, gentamicin, ciprofloxacin, cotrimoxazole, rifampin, vancomycin, teicoplanin, linezolid, and daptomycin. The latter 2 agents were tested retrospectively after they became available and with emerging data about the impact of elevated vancomycin MICs. *S. aureus* ATCC 29213 was used as the test control strain. For vancomycin, isolates were divided according to MIC (<2 µg/mL or ≥2 µg/mL).

Statistical Analyses

Categorical variables were summarized as percentages and compared using the Chi-square or Fisher's exact test. Continuous variables were summarized as mean and SD. The Mantel-Haenszel test for trend was used if there were significant differences in vancomycin MIC over time among the isolates. The Kaplan-Meier estimator was used for survival analysis, and curves were compared using the log-rank test. For logistic regression analysis, predictors with a $P < 0.30$ were included, and it was performed by a likelihood ratio-based backward exclusion method. A 2-sided $P < 0.05$ was considered to be statistically significant. All statistics were calculated with SPSS statistical package version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical Characteristics of CoNS IE

There were 103 patients with CoNS IE during the study, representing 16% of the 620 IE cases diagnosed at our institution (Fig 1). Regarding the type of IE, 36 (35%) were ICD-associated, 31 (30%) were PVE, and 36 (35%) were NVE. Stored CoNS isolates were available for 88 patients, in whom 98 isolates were identified. Isolates could not be obtained in the others due to transfer from another institution.

The clinical characteristics and outcomes of these 103 patients are summarized by type of endocarditis in Table 1. The majority of infections were due to *S. epidermidis*, while the species was not identified in 15 (15%) patients. In 59 (57%) patients, isolates were susceptible to methicillin,

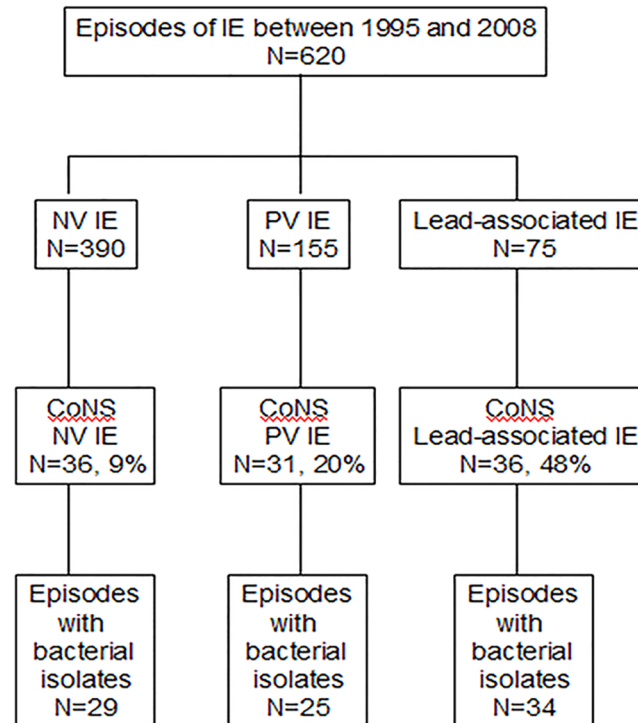


Fig 1. Patient disposition. Abbreviations: IE, infective endocarditis; NV, native valve; PV, prosthetic valve; CoNS, coagulase-negative staphylococci.

doi:10.1371/journal.pone.0125818.g001

with a lower rate in PVE (36%) compared with NVE (61%) or ICD IE (72%) ($P = 0.009$). The aortic valve was most commonly involved, but 13 (13%) patients had involvement of multiple valves. While vegetations were present in 82 (80%) patients, only 13 (13%) patients had evidence of systemic emboli. Median vegetation size was greatest in ICD IE ($P = 0.007$); perivalvular abscesses were most common among patients with PVE ($P < 0.001$). Sixty-six patients (64%) required surgery, including almost all patients with ICD IE. Mortality rates were similar within the NVE and PVE groups and lowest among patients with ICD IE ($P < 0.001$).

The clinical characteristics and outcomes of the 88 patients with available isolates are summarized by CoNS species in [S1 Table](#). In-hospital and 1-year mortality rates were similar among groups but were highest among patients infected with *S. lugdunensis* (55% for both).

CoNS Identification and Antibiotic Susceptibility Patterns

Ninety-eight isolates were identified in 88 patients: 70 *S. epidermidis* (71%), 11 *S. lugdunensis* (11%), 10 *S. hominis* (10%), and 7 other species ([S2 Table](#)). There were 6 and 4 patients with polymicrobial and polyclonal IE, respectively.

Susceptibility data are presented in [S2 Table](#). Overall, 44% of the CoNS isolates were methicillin-resistant, including 51% of *S. epidermidis*. One-third of MRSE also were resistant to gentamicin, rifampin, and ciprofloxacin. All isolates of *S. lugdunensis* remained methicillin-susceptible.

Forty-two isolates had a vancomycin MIC ≥ 2 $\mu\text{g/mL}$ (35 isolates at 2 $\mu\text{g/mL}$, 5 isolates at 3 $\mu\text{g/mL}$, and 2 isolates at 4 $\mu\text{g/mL}$). By species, 47% of the *S. epidermidis* isolates and 7% of other species ($P < 0.001$) had vancomycin MICs of 2 $\mu\text{g/mL}$. The clinical, microbiological and therapeutic characteristics, as well as the outcomes, of the 39 patients with strains with vancomycin MIC ≥ 2 $\mu\text{g/mL}$ can be seen in [S3 Table](#). Two *S. epidermidis* isolates (both with vancomycin

Table 1. Clinical characteristics and outcome of 103 consecutive patients with IE due to CoNS, according to the type of endocarditis (1995–2008).

	NVE (N = 36)	PVE (N = 31)	ICD IE (N = 36)	P value	
Mean age (SD), y	61.8 (16.7)	60.7 (11.3)	62.1 (19.4)	0.506	
Male gender	27 (75)	24 (77)	30 (83)	0.676	
Year of diagnosis				0.560	
	1995–1999	13 (36)	9 (29)	9 (25)	
	2000–2004	14 (39)	9 (29)	15 (42)	
	2005–2008	9 (25)	13 (42)	12 (33)	
CoNS species ^a				0.400	
	<i>S. epidermidis</i>	17 (47)	18 (58)	25 (69)	
	<i>S. lugdunensis</i>	4 (11)	2 (7)	5 (14)	
	Other CoNS ^b	4 (11)	4 (13)	3 (8)	
	Polymicrobial	4 (11)	1 (3)	1 (3)	
	Unknown	7 (20)	6 (19)	2 (6)	
Methicillin susceptibility	22 (61)	11 (36)	26 (72)	0.009	
Predisposing conditions and underlying diseases					
	Diabetes mellitus	1 (3)	8 (26)	4 (11)	0.015
	Chronic renal failure	4 (11)	2 (7)	1 (3)	0.386
	Hemodialysis	4 (11)	0	0	0.034
	History of cancer	4 (11)	5 (16)	2 (6)	0.239
	HIV infection	1 (3)	0	0	1.000
	Chronic liver disease	9 (25)	3 (10)	2 (6)	0.036
	Chronic lung disease	0	2 (7)	3 (8)	0.267
	Transplantation	1 (3)	0	0	1.000
Presumed mode of acquisition				0.004	
	Nosocomial	11 (31)	4 (13)	6 (17)	
	Non-nosocomial health care associated	11 (31)	18 (58)	7 (19)	
	Community acquired	14 (39)	9 (29)	23 (64)	
Valve involvement				<0.001	
	Aortic	14 (39)	12 (39)	1 (3) ^c	
	Mitral	13 (36)	11 (36)	0	
	Tricuspid	1 (3)	1 (3)	3 (8) ^c	
	PCM/ICD wire ^c	0	0	34 (94)	
	Unknown	1 (3)	1 (3)	0	
	Mitral + aortic	4 (11)	5 (16)	0	
	Tricuspid + aortic	2 (6)	0	0	
	Tricuspid + aortic + mitral	1 (3)	1 (3)	0	
Echocardiographic findings					
	Presence of vegetations	31 (86)	25 (81)	26 (72)	0.338
	Vegetation size in mm, median (IQR)	10 (7–15)	10 (6.5–15.5)	20 (10–25)	0.007
	Perivalvular abscess	4 (11)	15 (48)	0	<0.001
Complications					
	Heart failure	15 (42)	11 (36)	0	<0.001
	Renal failure	20 (56)	18 (58)	4 (11)	<0.001
	Systemic emboli	4 (11)	9 (29)	0	0.001
Antibiotic treatment				0.098	
	Cloxacillin alone	1 (3)	1 (3)	6 (17)	
	Cloxacillin in combination ^d	13 (36)	8 (26)	16 (44)	
	Vancomycin alone	4 (11)	5 (16)	3 (8)	
	Vancomycin in combination ^c	15 (42)	16 (52)	11 (31)	
	Other antibiotics ^e	3 (8)	1 (3)	0	

(Continued)

Table 1. (Continued)

Outcome	NVE (N = 36)	PVE (N = 31)	ICD IE (N = 36)	P value
Surgical treatment	11 (31)	22 (71)	33 (92)	<0.001
In-hospital mortality	16 (44)	14 (45)	2 (6)	<0.001
1-year mortality	20 (56)	16 (52)	3 (8)	<0.001

Unless otherwise noted, all values are shown as n (%). Abbreviations: CoNS, coagulase-negative staphylococci; HIV, human immunodeficiency virus; ICD, intracardiac device; IE, infective endocarditis; IQR, interquartile range; NVE, native valve endocarditis; PCM/ICD, pacemaker/implantable cardioverter-defibrillator; PVE, prosthetic valve endocarditis; SD, standard deviation.

^aOnly 88 patients had available isolates; these 88 patients served as the basis for the rest of the study (see Fig 1).

^b*S. hominis* (7), *S. capitis* (2), *S. schleiferi* (2).

^cPCM/ICD wire endocarditis was associated with tricuspid vegetations in 3 patients and aortic vegetations in 1 case.

^dAdministration of a second antibiotic, with or without a third, together with cloxacillin or vancomycin for >2 days.

^eTwo patients received teicoplanin, 1 received imipenem, and 1 received linezolid.

doi:10.1371/journal.pone.0125818.t001

MICs of 3 µg/mL) demonstrated intermediate resistance to teicoplanin (MIC 16 µg/mL). We did not find any isolates with intermediate susceptibility to vancomycin. Vancomycin MIC did not show a trend towards increase over time for overall CoNS isolates ($P = 0.49$) nor for *S. epidermidis* specifically ($P = 0.25$); this pattern did not change according to methicillin susceptibility. All isolates remained linezolid- and daptomycin-susceptible, but 1 strain each of *S. epidermidis* and *S. capitis* had daptomycin MICs of 1.5 µg/mL. Regarding other recommended antibiotics for PVE, we found that 14/31 (45%) of the CoNS isolates in patients with PVE were resistant to gentamicin, rifampin and/or ciprofloxacin.

Impact of Methicillin Susceptibility and Vancomycin MIC on Outcomes

Three of the 88 patients were excluded from the assessment of outcome because they were not treated with either cloxacillin or vancomycin, but instead were treated with teicoplanin (2) and linezolid (1). Cloxacillin was used in 38 (45%) patients (Group 1), and vancomycin was used in 47 (55%). Twelve of these 47 (26%) patients with MS-CoNS were treated with vancomycin because of penicillin allergy (3) or medical decision (9). Of these 12 patients, 2 died (17%). Among patients treated with vancomycin, 27 (32%) had CoNS isolates with vancomycin MICs <2 µg/mL (Group 2) and 20 (24%) had MICs ≥2 µg/mL (Group 3). The main clinical characteristics of the 3 groups are presented in Table 2.

In-hospital mortality was higher among those patients treated with vancomycin, regardless of vancomycin MIC, than in those treated with cloxacillin (47% vs 18%; $P = 0.012$). In-hospital mortality was 18%, 44%, and 50% for Groups 1, 2, and 3, respectively ($P = 0.021$), and 1-year mortality was 21%, 48%, and 65%, respectively ($P = 0.003$). Mortality was similar for patients treated with cloxacillin regardless of vancomycin MIC (Fig 2). Conversely, the highest mortality was among vancomycin-treated patients infected with CoNS isolates having vancomycin MICs ≥2 µg/mL ($P = 0.007$). One-year survival analysis according to the treatment received and vancomycin MIC is presented in Fig 3.

Table 3 shows the univariate and multivariate analyses of risk factors associated with one-year mortality. Using the group of patients with MR-CoNS IE with vancomycin MICs <2 µg/mL treated with vancomycin (Group 2) as the reference, Group 1 (MS-CoNS IE treated with cloxacillin) and Group 3 (MR-CoNS IE with vancomycin MICs ≥2 µg/mL) respectively had independently lower and higher mortality (OR 0.12, 95% CI 0.02–0.55 and OR 3.7, 95% CI 0.9–15.2,

Table 2. Clinical characteristics of 85 patients with CoNS IE according to treatment received (cloxacillin or vancomycin).^a

		Treated with cloxacillin (N = 38)	Treated with vancomycin		P value
			Vancomycin MIC <2 (N = 27)	Vancomycin MIC ≥2 (N = 20)	
Mean age, y		68.5 (55–77)	66.0 (59–73.5)	60.5 (44.5–72.5)	0.182
Male gender		28 (74)	20 (74)	17 (85)	0.645
CoNS species					0.471
	<i>S. epidermidis</i>	22 (58)	19 (70)	16 (80)	
	<i>S. lugdunensis</i>	7 (18)	4 (15)	0	
	Other	6 (16)	3 (11)	2 (10)	
	Polymicrobial ^b	3 (8)	1 (4)	2 (10)	
Predisposing conditions and underlying diseases					
	Diabetes mellitus	3 (8)	3 (11)	4 (20)	0.387
	Chronic renal failure	2 (5)	2 (7)	2 (10)	0.865
	Hemodialysis	2 (5)	1 (4)	0	0.792
	History of cancer	4 (11)	1 (4)	4 (20)	0.184
	HIV infection	0	1 (4)	0	0.553
	Chronic liver disease	2 (5)	3 (11)	5 (25)	0.090
	Chronic lung disease	1 (3)	3 (11)	0	0.168
	Transplantation	0	1 (4)	1 (5)	0.500
	History of IE	1 (3)	0	1 (5)	0.713
Presumed mode of acquisition					0.080
	Nosocomial	5 (13)	7 (26)	6 (30)	
	Non-nosocomial healthcare associated	11 (29)	8 (30)	10 (50)	
	Community acquired	22 (58)	12 (44)	4 (20)	
Type of endocarditis, n (%)					0.109
	NV	11 (29)	10 (37)	7 (35)	
	PV	7 (18)	8 (30)	9 (45)	
	Pacemaker lead	20 (53)	9 (33)	4 (20)	
Valve involvement					0.301
	Aortic	6 (16)	9 (33)	7 (35)	
	Mitral	8 (21)	4 (15)	4 (20)	
	Tricuspid	0	0	1 (5)	
	PCM/ICD wire	20 (53)	9	4 (20)	
	Unknown	0	1 (4)	1 (5)	
	Mitral + aortic	4 (11)	2 (7)	2 (10)	
	Tricuspid + aortic	0	1 (4)	0	
	Tricuspid + aortic + mitral	0	1 (4)	1 (5)	
Echocardiographic findings					
	Presence of vegetations	28 (74)	22 (82)	18 (90)	0.350
	Vegetation size in mm, median (IQR)	10 (0–19)	10 (1–16)	8 (2.5–10)	0.881
	Perivalvular abscess	5 (13)	5 (20)	5 (26)	0.436
Complications					
	Heart failure	9 (24)	9 (33)	5 (25)	0.670
	Renal failure	11 (29)	14 (52)	10 (50)	0.129
	Systemic emboli	3 (8)	1 (4)	4 (20)	0.178

(Continued)

Table 2. (Continued)

Outcomes	Treated with cloxacillin (N = 38)	Treated with vancomycin		P value
		Vancomycin MIC <2 (N = 27)	Vancomycin MIC ≥2 (N = 20)	
Surgery	28 (74)	16 (59)	12 (60)	0.394
In-hospital mortality	7 (18)	12 (44)	10 (50)	0.021
1-year mortality	8 (21)	13 (48)	13 (65)	0.003

Unless otherwise noted, all values are shown as n (%). Abbreviations: CoNS, coagulase-negative staphylococci; HIV, human immunodeficiency virus; IE, infective endocarditis; IQR, interquartile range; PCM/ICD, pacemaker/implantable cardioverter-defibrillator; MIC, minimum inhibitory concentration; NV, native valve; PV, prosthetic valve.

^aThree out of the 88 patients did not receive either cloxacillin or vancomycin and were not included.

^b*S. hominis* (7), *S. capitis* (2), *S. schleiferi* (2).

doi:10.1371/journal.pone.0125818.t002

respectively). Other independent variables associated with in-hospital mortality were heart failure and pacemaker lead endocarditis as a protective factor for mortality.

Discussion

Incidence, Types of IE, and Clinical Characteristics

CoNS are increasingly identified as a cause of NVE [8, 21] and caused 9% of all NVE in our cohort. In one recent multicenter investigation, nearly 8% of all NVE not associated with intravenous drug use (IVDU) were caused by CoNS, predominantly *S. epidermidis* [8]. A recent multinational prospective cohort study found that 16% of PVE not due to IVDU was attributed to CoNS [6]. *S. epidermidis* was isolated in 82% of cases, and 67% of these were methicillin-resistant. These results are similar to those seen in our series. In recent data provided by the International Collaboration on Endocarditis (ICE), CoNS was shown to be the second global cause of ICD IE immediately after *S. aureus*, being more often nosocomially-acquired than *S. aureus* [18].

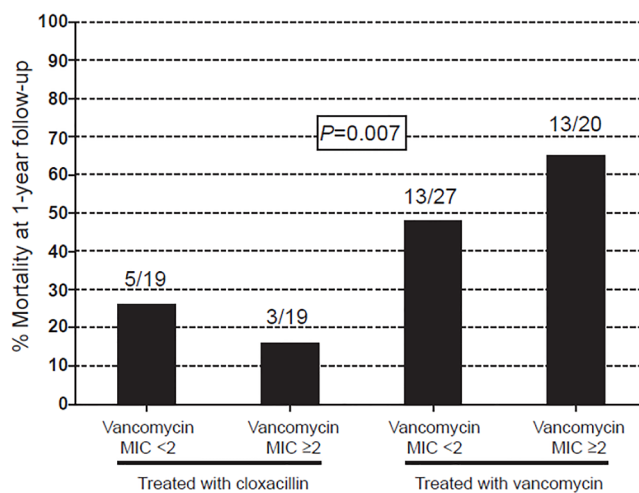


Fig 2. One-year mortality according to antibiotic treatment and vancomycin MIC. One-year mortality among 85 patients with coagulase-negative staphylococci infective endocarditis, according to antibiotic therapy and vancomycin minimum inhibitory concentration (MIC).

doi:10.1371/journal.pone.0125818.g002

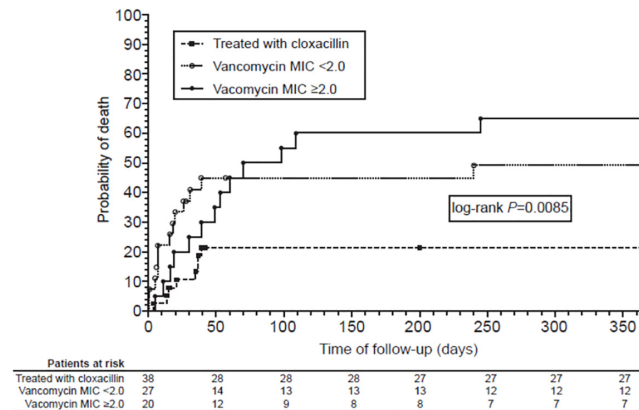


Fig 3. One-year survival analysis according to antibiotic therapy and vancomycin MIC. One-year survival analysis of 85 patients with coagulase-negative staphylococci infective endocarditis according to the treatment received and vancomycin minimum inhibitory concentration (MIC).

doi:10.1371/journal.pone.0125818.g003

Overall, we noted 44% of CoNS isolates were methicillin-resistant, a lower rate than documented in other surveys [19–22], and we did not find an association between methicillin-resistance and healthcare acquisition as did previous studies [8, 21]. Reduced susceptibility to vancomycin (MIC >2 µg/mL) was found in 3% of CoNS isolates in our study, similar to a 2% rate in a recent review of bloodstream infections caused by CoNS [23]. As was the case with other recent summaries of susceptibility data from Spain [20–22], no CoNS isolates were resistant to vancomycin, linezolid, or daptomycin.

Impact of Oxacillin Susceptibility and Vancomycin MIC on Outcome

Vancomycin treatment was associated with higher mortality, especially among patients with IE due to isolates with vancomycin MICs ≥2 µg/mL. A number of studies have found a correlation between vancomycin MIC and poorer outcomes among patients with methicillin-resistant *S. aureus* bacteremia [24]. The present study is, to our knowledge, the first to demonstrate the same correlation between poor outcomes and vancomycin MIC in CoNS IE. This finding could have important clinical implications. In addition, it suggests an important role for alternative antibacterial agents. In our series, higher vancomycin MICs had no impact on outcomes in patients with MS-CoNS IE receiving cloxacillin. In contrast, a recent study showed that among patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia treated with flucloxacillin, outcomes were less favourable among those with higher vancomycin MICs [25]. Our group recently found the same association of high vancomycin MIC and left-sided MSSA IE [26]. Higher vancomycin MICs could be a marker of bad prognosis in *S. aureus* bacteremia and IE regardless of the administered treatment, with the causative mechanism yet to be identified, but in light of our results, however, we cannot conclude that this hypothetical mechanism is common to all staphylococci.

Impact of Antibiotic Treatment on Outcome

Vancomycin monotherapy is the treatment of choice for MR-CoNS NVE [10,27]. However, we found very high mortality rates in vancomycin-treated patients. A vancomycin trough of 15–20 µg/mL is supposed to achieve the suggested target AUC/MIC ratios of ≥400 for organisms with MICs ≤1 µg/mL [28]. For patients infected with CoNS isolates having MICs ≥2 µg/mL, this ratio was likely not achieved in most cases; this may explain why patients with MR-CoNS

Table 3. Prognostic factors associated with one-year mortality in the 85 patients of CoNS endocarditis treated with either cloxacillin or vancomycin.

	Univariate analysis			Multivariate analysis		
	One-year mortality (N = 34)	Survived (N = 51)	P value	OR	95% CI	P value
Mean age (SD), y	63.5 (14.3)	62.6 (16.1)	0.795			
Male gender	25 (74)	40 (78)	0.602			
Year of diagnosis			0.929			
	1995	11 (32)	16 (31)			
	2000	12 (35)	20 (39)			
	2005	11 (32)	15 (29)			
CoNS species			0.773			
	<i>S. epidermidis</i>	22 (65)	35 (69)			
	<i>S. lugdunensis</i>	6 (18)	5 (10)			
	Other species ^a	4 (12)	7 (14)			
	Polymicrobial	2 (6)	4 (8)			
Predisposing conditions and underlying diseases						
	Diabetes mellitus	5 (15)	5 (10)	0.733		
	Chronic renal failure	4 (12)	2 (4)	0.212		
	Hemodialysis	1 (3)	2 (4)	1.000		
	History of cancer	3 (9)	6 (12)	0.735		
	HIV infection	1 (3)	0	0.400		
	Chronic liver disease	8 (24)	3 (6)	0.023		
	Chronic lung disease	1 (3)	3 (6)	0.647		
	Transplantation	0	1 (2)	1.000		
	History of IE	1 (3)	1 (2)	1.000		
Presumed mode of acquisition			0.619			
	Nosocomial	8 (24)	10 (20)			
	Non-nosocomial healthcare associated	13 (38)	16 (31)			
	Community acquired	13 (38)	25 (49)			
Type of endocarditis						
	NV	19 (56)	9 (18)	<0.001	0.1 0.02–0.51	0.006
	PV	13 (38)	11 (22)	0.094		
	Pacemaker lead	2 (6)	31 (61)	<0.001		
Valve involvement						
	Aortic	22 (65)	12 (24)	<0.001		
	Mitral	15 (44)	11 (22)	0.027		
	≥2 valves	8 (24)	3 (6)	0.023		
Complications						
	Heart failure	18 (53)	5 (10)	<0.001	6.2 1.5–25.2	0.011
	Renal failure	21 (62)	14 (28)	0.002		
	Systemic emboli	3 (9)	5 (10)	1.000		
	Perivalvular abscess	10 (29)	5 (10)	0.020		
Surgical treatment						
		16 (47)	40 (78)	0.003		
Treatment groups ^b				0.003		

(Continued)

Table 3. (Continued)

	Univariate analysis			Multivariate analysis		
	One-year mortality (N = 34)	Survived (N = 51)	P value	OR	95% CI	P value
Cloxacillin	8 (24)	30 (59)		0.12	0.02–0.55	0.008
Vancomycin (MIC <2 µg/mL)	13 (38)	14 (27)		1.0		
Vancomycin (MIC ≥2 µg/mL)	13 (38)	7 (14)		3.7	0.9–15.2	0.069

Unless otherwise noted, all values are shown as n (%). Abbreviations: CI, confidence interval; CoNS, coagulase-negative staphylococci; HIV, human immunodeficiency virus; IE, infective endocarditis; MIC, minimum inhibitory concentration; NV, native valve; OR, odds ratio; PV, prosthetic valve; SD, standard deviation.

^a*S. hominis* (7), *S. capitis* (2), *S. schleiferi* (2).

^bIn the multivariable regression analysis, cloxacillin treatment is the reference category. Vancomycin MIC <2 µg/mL effect on one-year mortality is compared to cloxacillin and Vancomycin MIC ≥2 µg/mL is compared to Vancomycin MIC <2 µg/mL.

doi:10.1371/journal.pone.0125818.t003

IE with vancomycin MIC ≥2 µg/mL had the highest mortality rates. At the time the AHA guidelines were published, higher vancomycin troughs were not yet recommended and so were not targeted in our patients. Nonetheless, Holmes et al [29] did not clearly find better outcomes in patients with *S. aureus* bacteremia achieving an AUC/MIC ratio >400. Thus, given these recent data and a lack of evidence regarding a correlation between AUC/MIC and CoNS bacteremia/IE outcomes, our results suggest the use of alternative agents to vancomycin.

For cases of MR-CoNS PVE, the recommended therapy is vancomycin in combination with rifampin and gentamicin [10,27]. Interestingly, we found that 45% of the CoNS causing PVE were resistant to at least one recommended drug associated to vancomycin (data not shown). Thus, in our setting, it may not be unusual that empirical treatment for CoNS-PVE is inappropriate. Therefore, better antibiotic options are needed for CoNS PVE since deciding the most suitable combination for CoNS PVE may result challenging in light of current evidence. Although clinical data supporting the use of ceftaroline for CoNS IE is lacking, some *in vitro* studies provide interesting results, showing a good susceptibility profile for ceftaroline against CoNS that includes methicillin-resistant, linezolid-resistant and daptomycin non-susceptible strains [30,31]. Besides, no emergence of ceftaroline-resistant strains has been described to date. Clinical evidence also lacks for telavancin, whose *in vitro* activity against CoNS is better than vancomycin due to its dual mechanism of action, which confers a rapid bactericidal activity [32, 33]. However, increased MICs for telavancin have been reported in some strains of *S. epidermidis* with reduced susceptibility to glycopeptides [33]. As occurred with the former agent, no clinical experience with tigecycline for the treatment of CoNS IE is yet available and experimental evidence from the IE model has been neither published. Linezolid use is limited in monotherapy due to its bacteriostatic activity. Noteworthy, emergence of resistance to linezolid among CoNS is increasingly reported [34]. Results derived from both *in vivo* studies and clinical experience with daptomycin are encouraging [35–38]. We have previously shown in animal models that daptomycin was a better therapeutic option than vancomycin [35, 39], particularly for IE caused by MR-CoNS with vancomycin MICs >1 µg/mL. Consequently, we believe that daptomycin should be considered as the preferred alternative for patients with NVE or PVE caused by MR-CoNS.

Study Limitations

This study has several limitations. First, it is a non-randomized, observational study. Second, it was conducted at a single, tertiary referral center for IE, so referral bias limits external validity,

as does the loss of some of the isolates of transferred patients. Third, while the total number of IE cases diagnosed in our center is large, the number of documented CoNS cases is relatively small and did not allow us to investigate the impact of vancomycin MIC in subpopulations of interest (eg, at the species level, according to IE type). As stated above, our study lacks pharmacokinetic and pharmacodynamic data, especially regarding the assessment of AUC/MIC ratios.

Conclusion

CoNS are well recognized as an important cause of IE, including infections of both native and prosthetic valves, as well as those involving pacemakers. Such infections are often acquired in healthcare settings, and are caused increasingly by pathogens less susceptible to agents like vancomycin that have long been standards of care. While several studies have documented poor outcomes among vancomycin-treated patients with serious *S. aureus* infections caused by isolates with higher vancomycin MICs, our report is the first to demonstrate a similar pattern among patients with MR-CoNS IE. Alternatives to currently recommended drugs should be considered in future studies. So, additional randomized, controlled studies are warranted.

Supporting Information

S1 Table. Clinical characteristics and outcomes of 88 patients with IE due to CoNS, according to the CoNS species.

(DOC)

S2 Table. Activity of 11 selected antibiotics as determined by Etest for 98 CoNS isolates from 88 patients with IE.

(DOC)

S3 Table. Basal characteristics, microbiological features and outcome of the 39 patients with CoNS strains with vancomycin ≥ 2 $\mu\text{g}/\text{mL}$.

(DOC)

Acknowledgments

This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP2 Guidelines." J.M.M. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analysis was conducted by Carlos Cervera of the Hospital Clinic Endocarditis Study Group (Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain).

Members of the Hospital Clínic Endocarditis Study Group, Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain are: J. M. Miro, J.M. Pericás, A. Tellez, A. Moreno, C. Cervera, and J. M. Gatell (Infectious Diseases Service); C. García-de-la-Mària, Y. Armero (Experimental Endocarditis Laboratory); F. Marco, M. Almela, and J. Vila (Microbiology Service); C. A. Mestres, J. C. Paré, C. Falces, R. Cartañá, S. Ninot, M. Azqueta, M. Sitges, B. Vidal, E. Quintana, J.M. Tolosana, D. Pereda and J. L. Pomar (Cardiovascular Institute); G. Fita, I. Rovira (Anesthesiology Department) J. Ramírez, T. Ribalta (Pathology Department); M. Brunet (Toxicology Service); D. Soy (Pharmacy Service); D. Fuster, U. Granados (Nuclear Medicine) and J. Llopis (Statistics).

Author Contributions

Conceived and designed the experiments: CGM CC JP XC YA DS MA SN CF CAM AM JG FM JMM. Performed the experiments: CGM XC YA. Analyzed the data: CC JP JMM. Contributed reagents/materials/analysis tools: DS MA JG AM FM. Wrote the paper: CGM CC XC JP JMM. Critical revision of the manuscript: DS MA CF SN CAM AM JG FM. Final approval: CGM CC JP XC YA DS MA SN CF CAM AM JG FM JMM.

References

1. Huebner J, Goldmann DA. Coagulase-negative staphylococci: role as pathogens. *Annu Rev Med* 1999; 50: 223–236. PMID: [10073274](#)
2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004; 39: 309–317. PMID: [15306996](#)
3. John JF, Harvin AM. History and evolution of antibiotic resistance in coagulase-negative staphylococci: Susceptibility profiles of new anti-staphylococcal agents. *Ther Clin Risk Manage* 2007; 3: 1143–1152. PMID: [18516271](#)
4. Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis—Prospective Cohort Study. *Arch Intern Med* 2009; 169: 463–473. doi: [10.1001/archinternmed.2008.603](#) PMID: [19273776](#)
5. Gandelman G, Frishman WH, Wiese C, Green-Gastwirth V, Hong S, Aronow WS, et al. Intravascular device infections: epidemiology, diagnosis, and management. *Cardiol Rev* 2007; 15: 13–23. PMID: [17172879](#)
6. Chu VH, Miro JM, Hoen B, Cabell CH, Pappas PA, Jones P, et al. Coagulase-negative staphylococcal prosthetic valve endocarditis—a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study. *Heart* 2009; 95: 570–576. doi: [10.1136/hrt.2008.152975](#) PMID: [18952633](#)
7. del Rio A, Anguera I, Miro JM, Mont L, Fowler VG Jr, Azqueta M, et al. Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. *Chest* 2003; 124: 1451–1459. PMID: [14555579](#)
8. Chu VH, Woods CW, Miro JM, Hoen B, Cabell CH, Pappas PA, et al. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis. *Clin Infect Dis* 2008; 46: 232–242. doi: [10.1086/524666](#) PMID: [18171255](#)
9. Anguera I, del Rio A, Miro JM, Matínez-Lacasa X, Marco F, Gumá JR, et al. Staphylococcus lugdunensis infective endocarditis: description of 10 cases and analysis of native valve, prosthetic valve, and pacemaker lead endocarditis clinical profiles. *Heart* 2005; 91: e10. PMID: [15657200](#)
10. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 111: e394–e434. PMID: [15956145](#)
11. Biavasco F, Vignaroli C, Varaldo PE. Glycopeptide resistance in coagulase-negative staphylococci. *Eur J Clin Microbiol Infect Dis* 2000; 19: 403–417. PMID: [10947214](#)
12. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004; 42: 2398–2402. PMID: [15184410](#)
13. Soriano A, Marco F, Martinez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008; 46: 193–200. doi: [10.1086/524667](#) PMID: [18171250](#)
14. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; 30: 633–638. PMID: [10770721](#)
15. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002; 137: 791–797. PMID: [12435215](#)
16. Benito N, Miro JM, De Lazzari E, Cabell CH, del Río A, Altclas J, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med* 2009; 150: 586–594. PMID: [19414837](#)

17. Wilson WR, Karchmer AW, Dajani AS, Taubert KA, Bayer A, Kaye D, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. American Heart Association. JAMA 1995; 274: 1706–1713. PMID: [7474277](#)
18. Athan E, Chu VH, Tattevin P, Selton-Suty C, Jones P, Naber C, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. JAMA 2012; 307: 1727–1735. doi: [10.1001/jama.2012.497](#) PMID: [22535857](#)
19. Fritsche TR, Sader HS, Jones RN. Antimicrobial activity of ceftobiprole, a novel anti-methicillin-resistant Staphylococcus aureus cephalosporin, tested against contemporary pathogens: results from the SENTRY Antimicrobial Surveillance Program (2005–2006). Diagn Microbiol Infect Dis 2008; 61: 86–95. doi: [10.1016/j.diagmicrobio.2008.02.008](#) PMID: [18385000](#)
20. Picazo JJ, Betriu C, Rodriguez-Avial I, Culebras E, Lopez-Fabal F, Gomez M. Comparative activities of daptomycin and several agents against staphylococcal blood isolates. Glycopeptide tolerance. Diagn Microbiol Infect Dis 2011; 70: 373–379. doi: [10.1016/j.diagmicrobio.2011.02.009](#) PMID: [21683269](#)
21. Loza E, Morosini MI, Pascual A, Tubau F, Alcalá J, Liñares J, et al. [Comparative in vitro activity of daptomycin against gram-positive microorganisms: SENTRY surveillance program, Spain (2002–2006)]. Enferm Infecc Microbiol Clín 2008; 26: 489–494.
22. Cuevas O, Cercenado E, Goyanes MJ, Vindel A, Trincado P, Boquete T, et al. [Staphylococcus spp. in Spain: present situation and evolution of antimicrobial resistance (1986–2006)]. Enferm Infecc Microbiol Clín 2008; 26: 269–277.
23. Natoli S, Fontana C, Favaro M, Bergamini A, Testore GP, Minelli S, et al. Characterization of coagulase-negative staphylococcal isolates from blood with reduced susceptibility to glycopeptides and therapeutic options. BMC Infect Dis 2009; 9: 83. doi: [10.1186/1471-2334-9-83](#) PMID: [19497104](#)
24. Holland TL, Fowler VG Jr. Vancomycin minimum inhibitory concentration and outcome in patients with Staphylococcus aureus bacteremia: pearl or pellet? J Infect Dis 2011; 204: 329–331. doi: [10.1093/infdis/jir275](#) PMID: [21742827](#)
25. Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, et al. Antibiotic choice may not explain poorer outcomes in patients with Staphylococcus aureus bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis 2011; 204: 340–347. doi: [10.1093/infdis/jir270](#) PMID: [21742831](#)
26. Cervera C, Castañeda X, de la Maria CG, del Rio A, Moreno A, Soy D, et al. Effect of vancomycin minimal inhibitory concentration on the outcome of methicillin-susceptible Staphylococcus aureus endocarditis. Clin Infect Dis 2014; 58: 1668–75. doi: [10.1093/cid/ciu183](#) PMID: [24647021](#)
27. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009; 30: 2369–2413. doi: [10.1093/eurheartj/ehp285](#) PMID: [19713420](#)
28. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC Jr, Craig WA, Billeter M, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2009; 29: 1275–1279. PMID: [19873687](#)
29. Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, et al. Vancomycin AUC/MIC ratio and 30-day mortality in patients with Staphylococcus aureus bacteremia. Antimicrob Agents Chemother 2013; 57: 1654–1663. doi: [10.1128/AAC.01485-12](#) PMID: [23335735](#)
30. Sader HS, Flamm RK, Jones RN. Antimicrobial Activity of Ceftaroline Tested against Staphylococci with Reduced Susceptibility to Linezolid, Daptomycin, or Vancomycin from U.S. Hospitals, 2008 to 2011. Antimicrob Agents Chemother 2013; 57: 3178–3181. doi: [10.1128/AAC.00484-13](#) PMID: [23629712](#)
31. Flamm RK, Sader HS, Farrell DJ, Jones RN. Ceftaroline potency among 9 US Census regions: report from the 2010 AWARE Program. Clin Infect Dis. 2012; 55 Suppl 3:S194–205. doi: [10.1093/cid/cis562](#) PMID: [22903952](#)
32. Hope R, Chaudhry A, Adkin R, Livermore DM. In vitro activity of telavancin and comparators against selected groups of Gram-positive cocci. Int J Antimicrob Agents 2013; 41: 213–217. doi: [10.1016/j.ijantimicag.2012.10.016](#) PMID: [23298432](#)
33. Stuart JI, John MA, Milburn S, Diagre D, Wilson B, Hussain Z, et al. Susceptibility patterns of coagulase-negative staphylococci to several newer antimicrobial agents in comparison with vancomycin and oxacillin. Int J Antimicrob Agents 2011; 37:248–52. doi: [10.1016/j.ijantimicag.2010.11.020](#) PMID: [21295951](#)
34. Gu B, Kelesidis T, Tsiodras S, Hindler J, Humphries RM. The emerging problem of linezolid-resistant Staphylococcus. J Antimicrob Chemother. 2013; 68:4–11 doi: [10.1093/jac/dks354](#) PMID: [22949625](#)

35. Garcia-de-la-Maria C, Marco F, Armero Y, Soy D, Moreno A, del Río A, et al. Daptomycin is effective for treatment of experimental endocarditis due to methicillin-resistant and glycopeptide-intermediate *Staphylococcus epidermidis*. *Antimicrob Agents Chemother* 2010; 54: 2781–2786. doi: [10.1128/AAC.01011-09](https://doi.org/10.1128/AAC.01011-09) PMID: [20421394](https://pubmed.ncbi.nlm.nih.gov/20421394/)
36. Duah M. Daptomycin for methicillin-resistant *Staphylococcus epidermidis* native-valve endocarditis: a case report. *Ann Clin Microb Antimicrob* 2010; 9: 9.
37. Durante-Mangoni E, Casillo R, Bernardo M, Caianiello C, Mattucci I, Pinto D, et al. High-dose daptomycin for cardiac implantable electronic device-related infective endocarditis. *Clin Infect Dis* 2012; 54: 347–354. doi: [10.1093/cid/cir805](https://doi.org/10.1093/cid/cir805) PMID: [22100575](https://pubmed.ncbi.nlm.nih.gov/22100575/)
38. Das I, Saluja T, Steeds R. Use of daptomycin in complicated cases of infective endocarditis. *Eur J Clin Microbiol Infect Dis* 2011; 30: 807–812. doi: [10.1007/s10096-011-1160-y](https://doi.org/10.1007/s10096-011-1160-y) PMID: [21327445](https://pubmed.ncbi.nlm.nih.gov/21327445/)
39. Dominguez-Herrera J, Docobo-Perez F, Lopez-Rojas R, Pichardo C, Ruiz-Valderas R, Lepe JA, et al. Efficacy of daptomycin versus vancomycin in an experimental model of foreign-body and systemic infection caused by biofilm producers and methicillin-resistant *Staphylococcus epidermidis*. *Antimicrob Agents Chemother* 2012; 56: 613–617. doi: [10.1128/AAC.05606-11](https://doi.org/10.1128/AAC.05606-11) PMID: [22123684](https://pubmed.ncbi.nlm.nih.gov/22123684/)