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Antistaphylococcal β-Lactams versus Vancomycin for Treatment of Infective Endocarditis Due to Methicillin-Susceptible Coagulase-Negative Staphylococci: a Prospective Cohort Study from the International Collaboration on Endocarditis

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The phenotypic expression of methicillin resistance among coagulase-negative staphylococci (CoNS) is heterogeneous regardless of the presence of the *mecA* gene. The potential discordance between phenotypic and genotypic results has led to the use of vancomycin for the treatment of CoNS infective endocarditis (IE) regardless of methicillin MIC values. In this study, we assessed the outcome of methicillin-susceptible CoNS IE among patients treated with antistaphylococcal β-lactams (ASB) versus vancomycin (VAN) in a multicenter cohort study based on data from the International Collaboration on Endocarditis (ICE) Prospective Cohort Study (PCS) and the ICE-Plus databases. The ICE-PCS database contains prospective data on 5,568 patients with IE collected between 2000 and 2006, while the ICE-Plus database contains prospective data on 2,019 patients with IE collected between 2008 and 2012. The primary endpoint was in-hospital mortality. Secondary endpoints were 6-month mortality and survival time. Of the 7,587 patients in the two databases, there were 280 patients with methicillin-susceptible CoNS IE. Detailed treatment and outcome data were available for 180 patients. Eighty-eight patients received ASB, while 36 were treated with VAN. In-hospital mortality (19.3% versus 11.1%; $P = 0.27$), 6-month mortality (31.6% versus 25.9%; $P = 0.58$), and survival time after discharge ($P = 0.26$) did not significantly differ between the two cohorts. Cox regression analysis did not show any significant association between ASB use and the survival time (hazard ratio, 1.7; $P = 0.22$); this result was not affected by adjustment for confounders. This study provides no evidence for a difference in outcome with the use of VAN versus ASB for methicillin-susceptible CoNS IE.

In addition to being a leading cause of catheter-related bloodstream infection (1), coagulase-negative staphylococci (CoNS) are an important cause of infective endocarditis (IE), accounting for 16% of prosthetic valve endocarditis (PVE) cases and 7.8% native valve endocarditis (NVE) cases (2). Although CoNS are generally considered low-virulence organisms, high rates of valvular abscess formation, congestive heart failure, and mortality are characteristic of CoNS IE (2).

The management of CoNS IE is complicated not only by the high level of methicillin resistance among CoNS strains but also by the heterogeneous expression of methicillin resistance (3). In staphylococci, including CoNS species, methicillin resistance is mediated by the expression of an additional penicillin-binding protein (PBP), designated PBP 2a, leading to resistance to most penicillins, cephalosporins, and carbapenems, except for the recently introduced cephalosporin agents ceftobiprole and ceftaroline. PBP 2a exhibits considerably reduced binding affinities for most β-lactam antibiotics compared to those of the intrinsic set of staphylococcal PBPs found in methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-susceptible *Staphylococcus epidermidis* strains (i.e., PBPs 1 to 4) (4–6). PBP 2a is encoded by the *mecA* gene, which is part of a mobile genetic element designated staphylococcal cassette chromosome *mec* (7). Conventional antimicrobial susceptibility testing of CoNS is based on the reference methods of the Clinical and Laboratory Standards Institute (CLSI; available at http://www.clsi.org) or of the European Committee on Antimicrobial Susceptibility Testing (EUCAST; available at http://www.eucast.org). Heteroresistance describes the phenom-

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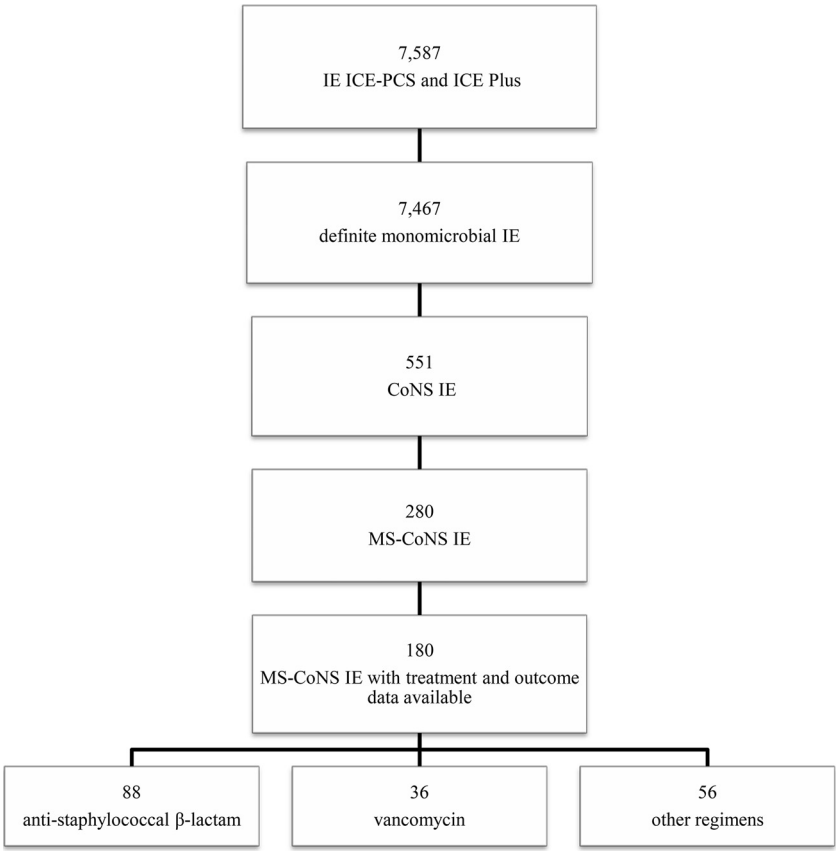

FIG 1 Study population. MS, methicillin susceptible.

enon in which only a minority of cells of a given isolate with genetically encoded methicillin resistance expresses resistance under *in vitro* conditions, thus creating a false-susceptible result (8). Heteroresistance in CoNS isolates can reduce the sensitivity and specificity of traditional phenotype-based methods for the detection of methicillin resistance. In the attempt to correct this inappropriate characterization of strains as being susceptible to methicillin, in 1995 the CLSI changed the susceptible breakpoint for CoNS strains from 2 μg/ml to 0.25 μg/ml (9). Despite the new lower breakpoints, false-susceptible results (*mecA*-positive strains classified as being susceptible by MIC testing) and false-resistant results (*mecA*-negative strains classified as being resistant by MIC testing) have been documented (10–13). Several factors may be responsible for these discrepancies between phenotypic and genotypic results. The results of phenotypic tests may be influenced by technical factors (e.g., inoculum size, addition of 2% NaCl to broth or agar for dilution) (12). Additionally, mechanisms not mediated by *mecA* may be responsible for the development of methicillin resistance among CoNS strains. In this regard, Suzuki et al. identified two strains lacking *mecA*, in spite of their resistance to methicillin. Gel electrophoretic analysis revealed some previously undescribed alterations in the PBP pattern (14). Moreover, the identification of a novel *mecA* homolog, *mecC*, in methicillin-resistant *Staphylococcus aureus and Staphylococcus saprophyticus* isolates lacking the classical *mecA* gene poses new questions about the genetic determinants of methicillin resistance among CoNS strains (15, 16).

Concern over the discordance between phenotypic and genotypic results has led some clinicians to use vancomycin (VAN) for the treatment of CoNS IE even if the methicillin MIC value falls within the susceptible range (17), exposing patients to the potential adverse effects of vancomycin treatment. The recently identified reversion from methicillin susceptibility to methicillin resistance among *mecA*-positive MSSA isolates within a patient during antibiotic therapy poses further questions regarding treatment strategies. Similar revertant strains may be found not only among MSSA isolates but also among methicillin-susceptible CoNS isolates (18).

In this observational prospective study, we assessed the influence of the antibiotic regimen (antistaphylococcal β-lactam [ASB] agents versus vancomycin) on the outcome of IE due to methicillin-susceptible CoNS.

MATERIALS AND METHODS

Study design. This observational study was based on data within the International Collaboration on Endocarditis (ICE) Prospective Cohort Study database and the ICE-Plus database. The ICE Prospective Cohort Study (ICE-PCS) database contains prospective data on 5,568 patients with IE from 64 sites in 28 countries collected between 1 January 2000 and 31 December 2006. The ICE-Plus database contains prospective data on 2,019 patients with IE from 29 sites in 16 countries collected between 1 September 2008 and 31 December 2012. A case report form was developed by the ICE group according to standard definitions (19–22). Data for each patient were collected prospectively by site investigators during the index hospitalization and were then sent to the coordinating center for data

TABLE 1 Baseline characteristics of patients with methicillin-susceptible coagulase-negative staphylococcal infective endocarditis according to treatment (univariate analysis)[a]

Characteristic	Result for the following treatment group:		
	ASB ($n = 88$)	VAN ($n = 36$)	*P* value[b]
Median (IQR) age (yr)	67.5 (47.0–74.5)	60.5 (46.0–72.0)	0.29
No. (%) of patients with the following characteristics:			
Male sex	63/88 (71.6)	30/36 (83.3)	0.25
Duration of symptoms of >1 mo before presentation	20/73 (27.4)	8/26 (30.8)	0.74
Presumed type of acquisition			
Community acquired	61/82 (74.4)	15/34 (44.1)	**<0.01**
Health care associated	21/82 (25.6)	19/34 (55.9)	
Type of IE			
Native valve IE	54/88 (61.4)	17/36 (47.2)	
Prosthetic valve IE	16/88 (18.2)	12/36 (33.3)	0.17
CEID-related IE	18/88 (20.5)	7/36 (19.4)	
IE location			
Left-sided IE	60/72 (83.3)	30/33 (90.9)	0.38
Right-sided IE	11/72 (15.3)	3/33 (9.1)	0.54
Left- and right-sided IE	1/72 (1.4)	0/33 (0.0)	1.00
Comorbidities			
Any comorbidity	23/88 (26.1)	14/36 (38.9)	0.16
Dialysis	3/77 (3.9)	7/34 (20.6)	**<0.01**
Diabetes mellitus	14/87 (16.1)	7/36 (19.4)	0.65
Malignancy	10/88 (11.4)	2/36 (5.6)	0.51
Immunosuppressive therapy	3/88 (3.4)	2/35 (5.7)	0.62
Predisposing conditions			
Endocavitary device	32/88 (36.4)	11/36 (30.6)	0.54
History of recent invasive procedure (60 days)	14/69 (20.3)	11/33 (33.3)	0.15
Previous IE episode	2/88 (2.3)	5/36 (13.9)	**0.02**
Clinical course			
Any complication	48/88 (54.6)	22/36 (61.1)	0.50
Stroke	3/88 (3.4)	5/36 (13.9)	**0.04**
Systemic embolization other than stroke	12/88 (13.6)	6/36 (16.7)	0.66
New or worsening heart failure	27/88 (30.7)	15/36 (41.7)	0.24
Intracardiac complications (abscess, fistula, perforation)	21/87 (24.1)	13/36 (36.1)	0.18
Paravalvular abscess	15/87 (17.2)	10/36 (27.8)	0.19
Paravalvular fistula	5/87 (5.8)	1/36 (2.8)	0.67
Paravalvular perforation	7/87 (8.1)	4/36 (11.1)	0.73
New conduction abnormality	8/88 (9.1)	3/34 (8.8)	1.00
Persistent bacteremia	5/88 (5.7)	3/36 (8.3)	0.69
Cardiovascular surgery	57/88 (64.8)	25/36 (69.4)	0.62
Outcomes			
In-hospital mortality	17/88 (19.3)	4/36 (11.1)	0.27
6-mo mortality	24//76 (31.6)	7/27 (25.9)	0.58

[a] Only percentages less than 1% are carried to the first decimal place. Abbreviations: IQR, interquartile range; IE, infective endocarditis; CEID, cardiac electronic implantable device.
[b] Statistically significant associations are presented in boldface.

entry. Both the ICE-PCS and the ICE-Plus databases are maintained at the Duke Clinical Research Institute, which serves as the coordinating center for the ICE studies, and approvals were obtained from the institutional review boards of the Duke University School of Medicine and the participating ICE sites. A detailed description of the ICE organization and the methodologies for data collection and cataloguing has been provided before (19).

Study population. Patients were included if they met all of the following criteria: (i) they were 18 years of age or older, (ii) they had a diagnosis of definite IE by the modified Duke criteria (19), (iii) they had monomicrobial IE caused by methicillin-susceptible CoNS, and (iv) they received treatment based on either an antistaphylococcal β-lactam (a penicillinase-resistant penicillin or cefazolin) or vancomycin. Patients treated with antistaphylococcal β-lactams were included in the ASB group, while patients treated with vancomycin were included in the VAN group. Patients simultaneously treated with both ASB and VAN were not included in the study.

Definitions. Susceptibility to methicillin was defined by MIC testing in accordance with EUCAST and CLSI breakpoints (MIC ≤ 0.25 μg/ml, except for *Staphylococcus lugdunensis* [MIC ≤ 2 μg/ml]) (available at http://www.clsi.org). The presence and expression of the *mecA* gene among CoNS strains were not used to define methicillin resistance. Persistent bacteremia was defined as persistence of positive blood cultures after 72 h of organism-specific targeted antibacterial treatment (23). Six-

TABLE 2 In-hospital mortality among patients with methicillin-susceptible CoNS IE (univariate analysis)[a]

Characteristic	Result for patients: Alive ($n = 103$)	Dead ($n = 21$)	P value[b]
Median (IQR) age (yr)	66.0 (47.0–73.0)	63.0 (47.0–74.0)	0.92
No. (%) of patients with the following characteristics:			
Male sex	77/103 (74.8)	16/21 (76.2)	0.89
Duration of symptoms of >1 mo before presentation	27/83 (32.5)	1/16 (6.3)	**0.04**
Presumed type of acquisition			
Community acquired	62/96 (64.6)	14/20 (70.0)	0.64
Health care associated	34/96 (35.4)	6/20 (30.0)	
Type of IE			
Native valve IE	56/103 (54.4)	15/21 (71.4)	
Prosthetic valve IE	22/103 (21.4)	6/21 (28.6)	**0.04**
CEID-related IE	25/103 (24.3)	0/21 (0.0)	
IE location			
Left-sided IE	70/84 (83.3)	20/21 (95.2)	0.29
Right-sided IE	13/84 (15.5)	1/21 (4.8)	0.29
Left- and right-sided IE	1/84 (1.2)	0/21 (0.0)	1.00
Comorbidities			
Any comorbidity	30/103 (29.1)	7/21 (33.3)	0.70
Dialysis	10/91 (11.0)	0/20 (0.0)	0.20
Diabetes mellitus	17/102 (16.7)	4/21 (19.1)	0.76
Malignancy	8/103 (7.8)	4/21 (19.1)	0.12
Immunosuppressive therapy	3/102 (2.9)	2/21 (9.5)	0.20
Predisposing conditions			
Endocavitary device	39/103 (37.9)	4/21 (19.1)	0.10
History of recent invasive procedure (60 days)	23/85 (27.1)	2/17 (11.8)	0.23
Previous IE episode	7/103 (6.8)	0/21 (0.0)	0.60
Clinical course			
Any complication	51/103 (49.5)	19/21 (90.5)	**<0.01**
Stroke	5/103 (4.9)	3/21 (14.3)	0.13
Systemic embolization other than stroke	13/103 (12.6)	5/21 (23.8)	0.19
New or worsening heart failure	29/103 (28.2)	13/21 (61.9)	**<0.01**
Intracardiac complications (abscess, fistula, perforation)	21/102 (20.6)	13/21 (61.9)	**<0.01**
Paravalvular abscess	17/102 (16.7)	8/21 (38.1)	**0.04**
Paravalvular fistula	2/102 (2.0)	4/21 (19.1)	**<0.01**
Paravalvular perforation	6/102 (5.9)	5/21 (23.8)	**0.02**
New conduction abnormality	8/101 (7.9)	3/21 (14.3)	0.40
Persistent bacteremia	8/103 (7.8)	0/21 (0.0)	0.35
Cardiovascular surgery	67/103 (65.1)	15/21 (71.4)	0.57
Treatment			
ASB	71/103 (68.9)	17/21 (80.9)	0.27
VAN	32/103 (31.1)	4/21 (19.1)	

[a] Only percentages less than 1% are carried to the first decimal place. Abbreviations: IQR, interquartile range; IE, infective endocarditis; CEID, cardiac electronic implantable device.
[b] Statistically significant associations are presented in boldface.

month mortality was defined as the mortality rate at 6 months from the time of hospital admission.

Study objectives. This study principally aimed to compare in-hospital mortality rates between patients treated with ASB and patients treated with VAN for IE due to methicillin-susceptible CoNS. The secondary objectives of the study included the following: (i) to compare the 6-month mortality rates of the ASB and VAN groups and (ii) to assess the overall survival time among patients in the ASB and VAN groups.

Statistical analysis. Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables are presented as frequencies and percentages of the specified group. Comparisons between groups were made with the Fisher exact test or the Kruskal-Wallis test, as appropriate. A two-sided P value of <0.05 was considered statistically significant. The log-rank test was used to estimate the equality of survival functions (24). To adjust for potential bias, a propensity score that reflected the probability that a patient would receive ASB therapy was generated. Factors associated with the receipt of ASB therapy with a P value of <0.2 in univariate analysis were entered into a logistic regression model (IE type, presence of comorbidities, and site of acquisition). The propensity score was derived from the product of all of the odds ratios in the model (25). For example, a patient with native valve IE (odds ratio, 0.8), at least one comorbidity (odds ratio, 1.7), and the community acquisition of IE (odds ratio, 3.2) would have a propensity score of $0.8 \times 1.7 \times 3.2 = 4.4$. The propensity score was then included as an additional value in the Cox analysis. Statistical

TABLE 3 Six-month mortality among patients with methicillin-susceptible CoNS IE (univariate analysis)[a]

Characteristic	Result for patients: Alive ($n = 72$)	Dead ($n = 31$)	P value[b]
Median (IQR) age (yr)	68.5 (46.5–74.0)	61.0 (47.0–74.0)	0.65
No. (%) of patients with the following characteristics:			
Male sex	55/72 (76.4)	20/31 (64.5)	0.21
Duration of symptoms of >1 mo before presentation	18/55 (32.7)	4/26 (15.4)	0.10
Presumed type of acquisition			
Community acquired	46/66 (69.7)	20/30 (66.7)	0.77
Health care associated	20/66 (30.3)	10/30 (33.3)	
Type of IE			
Native valve IE	38/72 (52.8)	20/31 (64.5)	
Prosthetic valve IE	14/72 (19.4)	8/31 (25.8)	0.13
CEID-related IE	20/72 (27.8)	3/31 (9.7)	
IE echocardiographic findings			
Left-sided IE	46/58 (79.3)	27/28 (96.4)	0.06
Right-sided IE	11/58 (19.0)	1/28 (3.6)	0.09
Left- and right-sided IE	1/58 (1.7)	0/28 (0.0)	1.00
Comorbidities			
Any comorbidity	25/72 (34.7)	8/31 (25.8)	0.37
Dialysis	8/61 (13.1)	0/29 (0.0)	0.06
Diabetes mellitus	16/71 (22.5)	4/31 (12.9)	0.26
Malignancy	6/72 (8.3)	5/31 (16.1)	0.30
Immunosuppressive therapy	3/72 (4.2)	2/31 (6.5)	0.64
Predisposing conditions			
Endocavitary device	31/72 (43.1)	8/31 (25.8)	0.10
History of recent invasive procedure (60 days)	12/59 (20.3)	4/23 (17.4)	1.00
Previous IE episode	3/72 (4.2)	1/31 (3.2)	1.00
Clinical course			
Any complication	33/72 (45.8)	25/31 (80.7)	**<0.01**
Stroke	3/72 (4.2)	4/31 (12.9)	0.19
Systemic embolization other than stroke	10/72 (13.9)	7/31 (22.6)	0.28
New or worsening heart failure	18/72 (25.0)	16/31 (51.6)	**<0.01**
Intracardiac complications (abscess, fistula, perforation)	13/72 (18.1)	15/31 (48.4)	**<0.01**
Paravalvular abscess	11/72 (15.3)	10/31 (32.3)	**0.04**
Paravalvular fistula	1/72 (1.4)	4/31 (12.9)	**0.03**
Paravalvular perforation	4/72 (5.6)	6/31 (19.4)	0.06
New conduction abnormality	6/70 (8.6)	4/31 (12.9)	0.49
Persistent bacteremia	6/72 (8.3)	1/31 (3.2)	0.67
Cardiovascular surgery	44/72 (61.1)	21/31 (67.7)	0.66
Treatment			
ASB	52/72 (72.2)	24/31 (77.4)	0.58
VAN	20/72 (27.8)	7/31 (22.6)	

[a] Six-month mortality data were available for 83% of the cohort. Only percentages less than 1% are carried to the first decimal place. Abbreviations: IQR, interquartile range; IE, infective endocarditis; CEID, cardiac electronic implantable device.
[b] Statistically significant associations are presented in boldface.

analyses were performed using SAS Enterprise Guide, version 5.1, software (SAS Institute, Cary, NC).

RESULTS

Of the 7,587 patients for whom data were available in the ICE-PCS and ICE-Plus databases, there were 7,467 patients with monomicrobial definite IE. IE was due to methicillin-susceptible CoNS in 280 of these patients, whereas it was due to methicillin-resistant CoNS IE in 271 patients. Detailed treatment and outcome data were available for only 180 patients with methicillin-susceptible CoNS IE. Of these, 88 received an ASB (an antistaphylococcal penicillin in 81 patients and cefazolin in 7 patients) and were included in the ASB group. Thirty-six patients were treated with vancomycin and were included in the VAN group. Patients treated with different antibiotic regimens (i.e., teicoplanin, daptomycin, penicillin, amoxicillin-clavulanate, quinolones) were excluded from the study ($n = 56$) (Fig. 1). Speciation data were available for 76.6% of the isolates. *S. epidermidis and S. lugdunensis* were isolated from 75 and 10 patients, respectively. Of the patients with *S. lugdunensis* IE, 5 were treated with ASB and 5 were treated with VAN. *S. capitis*, *S. haemolyticus*, and *S. hominis* each accounted for 0.02% of the isolates, whereas *S. cohnii* and *S. schleiferi* each represented 0.01% of the strains.

Patients in the ASB and VAN groups were from the following

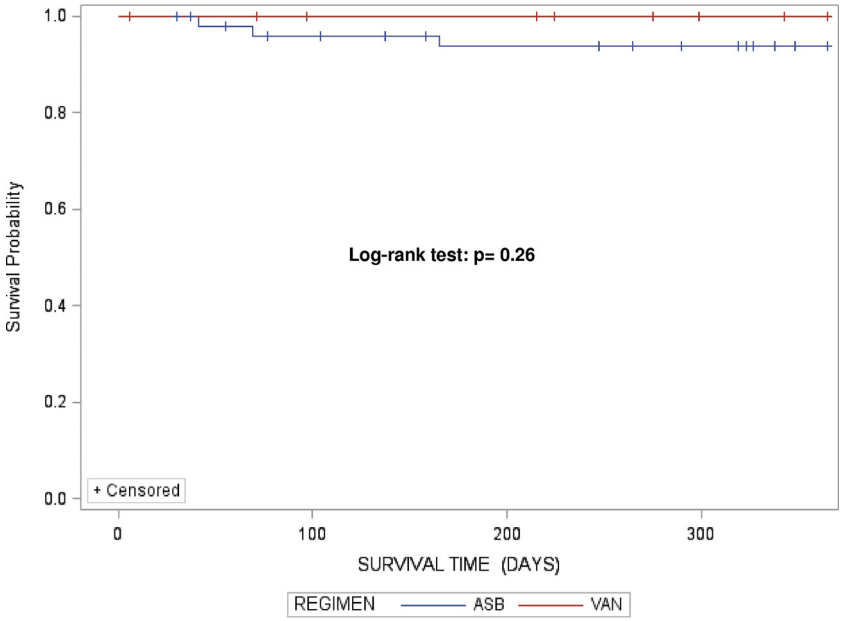

FIG 2 Product-limit survival estimates.

geographic regions: for the ASB group, 11.4% were from North America, 2.3% were from South America, 12.5% were from Australia/New Zealand, 65.9% were from Europe, and 8.0% were from Asia; for the VAN group, 34.9% were from North America, 4.7% were from South America, 11.6% were from Australia/New Zealand, and 48.8% were from Europe.

The majority of patients in the study were males (75.0%). The median age was 65.5 years (range 47.0 to 74.0 years). The health care-associated acquisition of CoNS IE was more common among patients treated with VAN than among those treated with an ASB (55.9% versus 25.6%, $P < 0.01$). Patients in the VAN group had higher rates of a previous episode of IE (14.0% for the VAN group versus 2.3% for the ASB group; $P < 0.01$) and hemodialysis (20.6% for the VAN group versus 3.9% for the ASB group, $P < 0.01$). The rate of complications was similar in the two cohorts, except for a higher incidence of stroke among patients treated with VAN (13.9% for the VAN group versus 3.4% for the ASB group, $P = 0.04$) (Table 1).

In-hospital mortality did not differ significantly among patients treated with ASB and patients treated with VAN (19.3% versus 11.1%, $P = 0.27$) (Table 1). However, in-hospital mortality was significantly higher overall among patients with new or worsening heart failure and with intracardiac complications of IE. The duration of symptoms for greater than 1 month and the presence of a cardiac implantable device were associated with lower in-hospital mortality rates (Table 2).

Similarly, 6-month mortality (data were available for 83% of the study population) did not differ significantly among patients treated with ASB and patients treated with VAN (31.6% versus 25.9%, $P = 0.58$) (Table 1). The presence of new or worsening heart failure and the development of intracardiac complications were associated with significantly higher 6-month mortality rates (Table 3).

When the overall survival time after discharge was assessed among patients receiving ASB and patients receiving VAN, no significant differences were identified, as shown by the log-rank test ($P = 0.26$) (Fig. 2). Similarly, Cox regression analysis did not show any significant association between ASB treatment and overall survival time (hazard ratio [HR], 1.7; $P = 0.22$); this result was not affected by inclusion of the propensity score in the model (HR, 1.7; $P = 0.40$).

DISCUSSION

The discordance between phenotypic and genotypic detection of methicillin resistance among CoNS strains has led some experts to recommend VAN use in the setting of all cases of CoNS IE regardless of methicillin MIC values. In order to understand the impact of this strategy on clinical outcomes, we assessed the in-hospital mortality, 6-month mortality, and survival time among methicillin-susceptible CoNS IE patients treated with either ASB or VAN.

This study demonstrated a number of interesting findings. First, there was a substantial clinical use of VAN for the treatment of methicillin-susceptible CoNS IE over a wide geographic area: VAN was used to treat 29.0% of the patients with methicillin-susceptible CoNS IE that fulfilled the study criteria. The use of VAN was also more common in patients with hemodialysis. This observation is not surprising, given the perceived convenience of administering VAN with hemodialysis. However, VAN was also more commonly used in patients with a previous episode of IE and health care-associated IE, which may reflect clinician perceptions regarding the resistance of the CoNS isolate to ASB, despite the MIC result.

Among patients treated with VAN and ASB for methicillin-susceptible CoNS IE, there was no significant difference in the in-hospital mortality, 6-month mortality, and overall survival time.

Although the difference was not statistically significant, there was a trend toward lower rate of in-hospital mortality among patients with methicillin-susceptible CoNS IE treated with VAN;

however, this trend did not carry forward to 6-month mortality, the rate of which was similar between groups. Our data suggest that while it is unclear whether antibiotic choice has an impact on short-term outcomes, the long-term outcomes in patients with CoNS infections are likely to be influenced more by other IE-related metrics, such as hemodynamic status (i.e., the presence of congestive heart failure) and valvular mechanical problems (i.e., significant valvular regurgitation). This is consistent with our current understanding of CoNS IE. Although CoNS are indolent pathogens, outcomes tend to be poor because of patient comorbidities and a high rate of heart failure. In our previous study of CoNS IE in the ICE-PCS, chronic illness and congestive heart failure were independently associated with in-hospital mortality (2).

In this study, patients with a longer duration of symptoms prior to presentation had a lower rate of in-hospital mortality. Although this seems counterintuitive, we previously demonstrated that patients with CoNS IE who had symptoms for >1 month prior to presentation were more likely to undergo surgery and had better in-hospital survival (2).

Our investigation has several noteworthy limitations. The small number of patients in this study limited our ability to detect significant differences between groups and to adjust our findings for the presence of confounders. Since this was an observational cohort study, we could not make any definitive inferences between treatment strategies and patient outcomes. Data for this study were derived from sites in the ICE collaboration, which are mostly tertiary care centers with extensive expertise in IE; therefore, the results of this study may be subject to center bias. Methicillin susceptibility was detected only by phenotypic methods, and the presence and the expression of the *mecA* gene among CoNS strains were not evaluated. Data about the vancomycin blood trough concentration, antimicrobial dosage, and antimicrobial side effects were not collected for inclusion in the database. Finally, combination regimens (including an aminoglycoside and/or rifampin) were used in approximately half of the patients and did not correlate with native versus prosthetic valve status, as is suggested in the current American Heart Association guidelines (26).

In conclusion, our data suggest that patients with methicillin-susceptible CoNS IE treated with ASB rather than VAN do not have significantly different long-term outcomes. Because of the small sample size and the lack of genotypic data, further studies are needed to validate these findings.

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