

The NOVA Score: A Proposal to Reduce the Need for Transesophageal Echocardiography in Patients With Enterococcal Bacteremia

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(See the Editorial Commentary by Stryjewski and Corey on pages 536–8.)

Background. Frequency of enterococcal bloodstream infection (E-BSI) is increasing, and the number of episodes complicated by infective endocarditis (IE) varies. Performing transesophageal echocardiography (TEE) in all patients with E-BSI is costly and time-consuming. Our objectives were to identify patients with E-BSI who are at very low risk of enterococcal IE (and therefore do not require TEE) and to compare the outcome of E-BSI in patients with/without IE.

Methods. Between September 2003 and October 2012, we performed a prospective cohort study (all patients with E-BSI) and a case-control study (patients with/without enterococcal IE) in our center.

Results. We detected 1515 patients with E-BSI and 65 with enterococcal IE (4.29% of all episodes of E-BSI, 16.7% of patients with E-BSI who underwent transthoracic echocardiography, and 35.5% of all patients with E-BSI who underwent TEE). We developed a bedside predictive score for enterococcal IE—Number of positive blood cultures, Origin of the bacteremia, previous Valve disease, Auscultation of heart murmur (NOVA) score—based on the following variables: Number of positive blood cultures (3/3 blood cultures or the majority if more than 3), 5 points; unknown Origin of bacteremia, 4 points; prior heart Valve disease, 2 points; Auscultation of a heart murmur, 1 point (receiver operating characteristic = 0.83). The best cutoff corresponded to a score ≥ 4 (sensitivity, 100%; specificity, 29%). A score < 4 points suggested a very low risk for enterococcal IE and that TEE could be obviated.

Conclusions. Enterococcal IE may be more frequent than generally thought. Depending on local prevalence of endocarditis, application of the NOVA score may safely obviate echocardiography in 14%–27% of patients with E-BSI.

Keywords. endocarditis; *Enterococcus* spp.; bacteremia.

Enterococcus species is an increasingly common cause of bloodstream infections (E-BSI) in many institutions. The percentage of patients with E-BSI who have infective endocarditis (IE) is estimated to be between 3% and

10% [1–3]. The difference in these values is partially due to the study population selected and the methods used to confirm endocarditis. Some authors analyzed all patients with E-BSI [4–6], whereas others only included patients with at least 2 positive blood cultures [2, 7–9].

Establishing a diagnosis of enterococcal IE frequently requires transesophageal echocardiography (TEE) [10, 11]. However, use of TEE in all patients with E-BSI is costly, time consuming, and subject to complications.

Here, our objectives were to identify factors that enable early selection of a subgroup of patients with E-BSI who are at very low risk for enterococcal IE and in whom TEE could be avoided. We also compared the

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outcome of E-BSI in patients with and without IE in order to assess the potential consequences of misdiagnosis.

MATERIALS AND METHODS

Our design included 2 studies. In the first one, we aimed to assess the frequency of enterococcal IE by analyzing a prospective cohort that included all patients with E-BSI. In the second, we performed a case-control study and compared patients with and without enterococcal IE. Both studies were performed in a 1550-bed tertiary center attending a population of 715 000.

Prospective Cohort Study

The study sample comprised all cases of E-BSI diagnosed in our institution from September 2003 to October 2012. During this period, we identified 2 phases that differed with respect to the diagnosis of IE. From 2003 to 2007, patients with E-BSI were managed by the attending physician who requested consultation with the infectious diseases department or the laboratory of echocardiography [3] according to his/her own criteria (period A). From 2008 to 2012 (period B), a physician from the infectious diseases department visited the patients with E-BSI and promoted the systematic use of echocardiography. We recommended the systematic performance of TEE in most patients, provided the patient consented to and the attending physician agreed with the indication. Occasionally, the cardiologist indicated the need for TEE in patients referred for transthoracic echocardiography (TTE). Accordingly, in some patients, only TTE was performed, in some TTE and TEE, and in others neither of the 2 techniques was performed. From September 2003 onward, clinical data on all patients with enterococcal IE were collected prospectively as part of a preestablished protocol.

Case-Control Study

We designed a case-control study to identify a subgroup of patients at very low risk of enterococcal IE in whom systematic TEE could safely be deemed unnecessary. All patients fulfilling the modified Duke criteria [12] for IE were considered cases, and patients with E-BSI and a TEE result that ruled out IE were considered controls. Control patients were randomly selected from among patients with E-BSI and a negative TEE result and no criteria for IE according to the modified Duke criteria [12]. Both groups were independently selected from the period in which they presented.

To evaluate the possibility of misdiagnosed IE, we reviewed the clinical records of a randomly selected significant sample (176/1127) of patients with enterococcal bacteremia who did not undergo TEE. We analyzed primary clinical characteristics and duration of therapy. The selected parameters were previous valve disease; origin of bacteremia; number of positive blood

cultures; recurrence of bacteremia; clinical, microbiological, and/or radiological findings suggestive of septic embolism; NOVA score (Number of positive blood cultures, Origin of the bacteremia, previous Valve disease, Auscultation of heart murmur); and treatment and outcome during admission and follow-up. Patients were followed up for a mean of 653 days after discharge.

Definitions and Evaluation Criteria

We used the following definitions:

Blood culture was defined as a volume of blood obtained under aseptic conditions and inoculated into 2 bottles for microbiologic isolation [8].

BSI episode, episode of bacteremia, refers only to patients, not to number of blood cultures. All microorganisms isolated from blood from the same patient within 1 week were considered a single episode [8].

Continuous bacteremia is a positive result in all of 3 blood cultures, or the majority if more than 3 blood cultures (with the first and last sample drawn at least 1 hour apart) [13].

Infective endocarditis was diagnosed according to the modified Duke criteria [12]. Patients with IE were followed for 1 year after discharge.

Underlying diseases were classified according to the McCabe and Jackson scale [14]. *Comorbidities* were assessed using the Charlson comorbidity score [15].

Ethical Issues

The Institutional Review Board and Ethics Committee of Hospital Gregorio Marañón, Madrid, Spain, approved the study (EC 106/13).

Statistical Analysis

In the descriptive study, qualitative variables are presented as percentages with their confidence interval (CI) and quantitative variables are presented as the mean and CI and/or median with the interquartile range, depending on the distribution. Clinical and microbiological variables were studied to obtain a predictive model for enterococcal endocarditis. Differences between groups were analyzed using the *t* test, median test, χ^2 test, or Fisher exact test, depending on the characteristics of the variables and their distribution between groups. The sensitivities of TTE and TEE were compared using a McNemar test for pair samples. The evolution of the variables during the study period was assessed using the autoregressive integrated moving average test.

In order to develop a reliable algorithm that made it possible to rule out the need for TEE, we designed a strategy based on bootstrapping. Given that the same case-control dataset was used for developing the model, testing, assessing goodness of fit, and establishing threshold values, we implemented bootstrapping techniques to avoid overfitting. The association

between individual predictors and the risk of IE was assessed using binary multivariate logistic regression, including variables selected from the exploratory univariate analysis. Final variables in the model were selected using a backward stepwise approach based on Akaike information criterion [16] and clinical judgment. This logistic regression model was validated by 2 runs of 2000 bootstrap replications [17] with IE prevalence values of 50% (as in the case-control group) and 4.3% (as in the prospective cohort). After validation, we developed a quantitative score for the risk of endocarditis by rounding the estimated odds ratio (OR) values of the model. This synthetic univariate prediction score was tested in a second logistic regression model and again validated by 2 bootstrap runs, as described above. Additionally, the logistic regression model was calibrated by plotting predicted vs observed probabilities. Finally, bootstrap-based 95% CIs were obtained for sensitivity and specificity and overlaid on the receiver operating characteristic (ROC) plot [18, 19]. A conservative cutoff for the predictive score was based on the maximization of sensitivity, as recommended for screening methods. Data were analyzed using SPSS, version 18.0 (SPSS Inc., Chicago, Illinois) and R [20].

RESULTS

Incidence of Enterococcal Endocarditis

During the study period (2003–2012), we detected 1515 episodes of E-BSI. The annual distribution is shown in Table 1. Of these, 679 (2.1 episodes/1000 admissions) occurred in period A (2003–2007) and 836 (3.1 episodes/1000 admissions) in period B (2008–2012). This increase was statistically significant ($P < .001$). The annual increase in E-BSI was 0.167 episodes/1000 admissions (95% CI, .100–.234; $P < .001$) see [Supplementary Data](#). Overall, 388 patients underwent TEE after the

episode of E-BSI: 100 during period A (14.7% of all E-BSI) and 288 during period B (34.4% of all E-BSI).

Enterococcal IE was detected in 65 patients, who accounted for 4.29% of all patients with E-BSI (3.76% in period A and 4.54% in period B). The increase in the annual incidence of enterococcal IE was 0.012 episodes/1000 admissions (95% CI, .004–.020; $P = .004$). IE was diagnosed in 16.7% of patients who underwent TTE and 35.5% of the patients who underwent TEE. Of all the episodes of enterococcal IE, only 18 cases (27.7%) were detected by TTE; the remaining 47 (72.3%) were demonstrated only after TEE. Sensitivity of TTE and TEE for the diagnosis of enterococcal IE was 32% vs 95% ($P < .01$).

Comparison of E-BSI Patients With and Without Endocarditis

In order to identify characteristics that could help to identify IE among patients with E-BSI, the 65 cases were compared with the 65 controls. The epidemiological, microbiological, and clinical characteristics of both groups are shown in Table 2. No differences were detected in age or sex, but patients with IE more frequently presented with a history of stroke (27.7% vs 13.8%, $P = .05$), immunosuppressive therapy (24.2% vs 10.8%, $P = .03$), previous heart valve disease (63.0% vs 29.2%, $P < .01$), and previous heart valve surgery (44.6% vs 24.6%, $P = .03$). Malignancy, however, was more frequent in controls (23% vs 41.5%, $P = .02$).

Episodes of IE were caused mainly by *Enterococcus faecalis* (86.2% vs 58.5%, $P < .01$). In addition, they were associated with continuous bacteremia (93.8% vs 69.2%, $P < .01$), community acquisition (43.1% vs 20%, $P < .01$), and unknown source of infection (38.4% vs 10.7%, $P < .01$). In the control group, however, E-BSI was mainly nosocomial (69.2% vs 46.2%, $P = .01$) and had a gastrointestinal origin (48.4% vs 13.8%, $P < .01$). As for outcome, patients with IE presented more complications (Table 3) and had significantly higher mortality (38.4% vs 15.4%, $P < .01$).

Score for Identifying Bacteremic Patients With a Low Risk of IE

The multivariate analysis showed that enterococcal IE is 9-fold more probable in patients with positive blood cultures in all of 3 blood cultures or the majority of more than 3 blood cultures (OR, 9.9; 95% CI, 2.2–40.6). Other factors independently associated with enterococcal IE were a history of heart valve disease (OR, 3.7; 95% CI, 1.6–8.7) and an unknown source of bacteremia (OR, 7.7; 95% CI, 2.5–23.8). We developed a score using the variables selected in the multivariate model by including those that improved sensitivity and specificity for predicting enterococcal IE (Table 4). This model validated both very well using bootstrap resampling based on prevalence values of 50% (slope shrinkage factor for the agreement between the training and test samples, 0.88; maximum absolute error in predicted probability, 0.03) and 4.3% (slope shrinkage factor = 0.90;

Table 1. Enterococcal Bloodstream Infections and Enterococcal Endocarditis During the Study Period

Year	E-BSI Episodes	E-BSI/1000 Admissions	EE Episodes	EE/E-BSI (%)	EE/1000 Admissions
2003	109	2.0	2	1.8	0.04
2004	114	1.9	8	7.0	0.13
2005	129	2.1	3	2.3	0.05
2006	149	2.3	5	3.3	0.08
2007	178	2.6	8	4.4	0.12
2008	177	3.0	5	2.8	0.12
2009	170	3.2	9	5.2	0.15
2010	149	2.7	3	2.0	0.05
2011	181	3.4	14	7.7	0.26
2012	159	3.2	8	5.0	0.14

Abbreviations: E-BSI, *Enterococcus* caused bloodstream infection; EE, enterococcal endocarditis.

Table 2. Epidemiological, Clinical, and Microbiological Characteristics of Patients With and Without Enterococcal Endocarditis

Characteristic	Endocarditis (%)	No Endocarditis (%)	P Value
Mean age (SD)	71.2 (11.3)	70.3 (13.6)	.7
Females	18 (27.7)	23 (35.4)	.34
Males	47 (72.3)	42 (64.6)	
Underlying disease			
Congestive heart failure			
Yes	27 (41.5)	19 (29.2)	.09
No	38 (58.5)	46 (70.8)	
Stroke			
Yes	18 (27.7)	9 (13.8)	.05
No	47 (72.3)	56 (86.2)	
Transplant			
Yes	6 (9.2)	7 (10.8)	.77
No	59 (90.8)	58 (89.2)	
Immunosuppression			
Yes	15 (23)	7 (10.8)	.03
No	50 (76.9)	58 (89.2)	
Neoplasm			
Yes	14 (21.5)	27 (41.5)	.02
No	51 (78.5)	38 (58.5)	
Renal failure			
Yes	23 (35.4)	21 (32.3)	.41
No	42 (64.6)	44 (67.7)	
Previous endocarditis			
Yes	8 (12.3)	4 (6.2)	.17
No	57 (87.7)	61 (93.8)	
Heart valve disease			
Yes	41 (63.1)	19 (29.2)	<.01
No	24 (36.9)	46 (70.8)	
Prosthetic valve			
Yes	31 (47.7)	17 (26.2)	.18
No	34 (52.3)	48 (73.8)	
Native valve disease			
Yes	10 (15.4)	2 (3.1)	.07
No	55 (84.6)	63 (96.9)	
Previous cardiac valve surgery			
Yes	25 (38.5)	16 (24.6)	.03
No	40 (61.5)	49 (75.4)	
Mean Charlson index (SD)	5.47 (2.3)	6.5 (2.9)	.02
Clinical presentation			
Fever			
Yes	59 (90.7)	58 (89.2)	.36
No	6 (9.2)	7 (10.8)	
Heart murmur			
Yes	37 (56.9)	19 (29.2)	<.01
No	28 (43.1)	46 (70.8)	
Etiology			
<i>Enterococcus faecalis</i>			
Yes	56 (86.2)	38 (58.5)	<.01
No	9 (13.8)	27 (41.5)	

Table 2 continued.

Characteristic	Endocarditis (%)	No Endocarditis (%)	P Value
<i>Enterococcus faecium</i>			
Yes	7 (10.8)	24 (36.9)	<.01
No	58 (89.2)	41 (63.1)	
<i>Enterococcus</i> spp.			
Yes	2 (3.1)	3 (4.6)	.65
No	63 (96.9)	62 (95.4)	
Continuous bacteremia			
Yes	61 (93.8)	45 (69.2)	<.01
No	4 (6.2)	20 (30.8)	
Site of acquisition			
Community			
Yes	28 (43.1)	13 (20)	<.01
No	37 (56.9)	52 (80)	
Nosocomial			
Yes	30 (46.2)	45 (69.2)	.01
No	35 (53.8)	20 (30.8)	
Healthcare-associated			
Yes	7 (10.8)	7 (10.8)	.03
No	58 (89.2)	58 (89.2)	
Source of bloodstream infection			
Gastrointestinal			
Yes	9 (13.8)	31 (47.7)	<.01
No	56 (86.2)	34 (52.3)	
Unknown ^a			
Yes	25 (38.5)	7 (10.8)	<.01
No	40 (61.5)	58 (89.2)	

Abbreviation: SD, standard deviation.

^aOverall 16/32 (50%) had colonoscopy (4/7 patients without endocarditis and 12/25 patients with endocarditis).

maximum error = 0.02). The ORs of these models were used to obtain representative weights by rounding to develop a synthetic score on a scale of 0 to 12 for the risk of IE in patients with E-BSI. The score, which we called the NOVA score, was based on the following variables: number of positive blood cultures (N) suggestive of continuous bacteremia (3/3 blood cultures or the majority if more than 3), 5 points; unknown origin of bacteremia (O), 4 points; prior valve disease (V), 2 points; and auscultation of a heart murmur (A), 1 point (Table 4). The area under the ROC curve for the NOVA score was 0.829 (95% CI, .758–.901). Again, this model was accurately validated by bootstrapping (slope shrinkage factor = 0.99 and 1; maximum error = 0.003 and 0.002, for the resampling runs each stratified by the IE prevalence values of 50% and 4.3%, respectively). The best binary cutoff value for ruling out IE without the need for TEE was established at a NOVA score < 4 points (Figure 1). Using this cutoff, the model calibration curve excluded the risk of false negatives (Figure 2). The probability of enterococcal

Table 3. Outcome of Patients With and Without Endocarditis

Outcome	Endocarditis N = 65 (%)	No Endocarditis N = 65 (%)	P Value
Complications			
Cardiac failure	23 (35.9)	6 (9.2)	<.01
Persistent bloodstream infection	13 (21.7)	9 (13.8)	.09
Central nervous system vascular event	5 (7.9)	0	.02
Other than central nervous system embolic event	10 (15.9)	2 (3.1)	.007
Treatment			
Empiric adequate treatment	54 (96.4)	13 (20.0)	<.01
Mean days of overall treatment (SD)	34 (17.1)	15 (8.2)	<.01
Death			
Mean days of hospital stay (SD)	25 (38.4)	10 (15.4)	<.01
Mean days of hospital stay (SD)	47.3 (29.7)	36.2 (33.0)	.04

Abbreviation: SD, standard deviation.

IE with different scores is as follows: 5 points, 23.3%; 6 points, 45.5%; 7 points, 82.4%; 8 points, 66.7%; 9 points, 60.0%; 10 points, 100%; 11 points, 83.3%; 12 points, 80%.

None of the 65 patients with enterococcal IE had a NOVA score <4 points in our series (Figure 3). According to this model, the percentage of patients with E-BSI who would not require echocardiography (score <4 points) ranged from 14.6% in

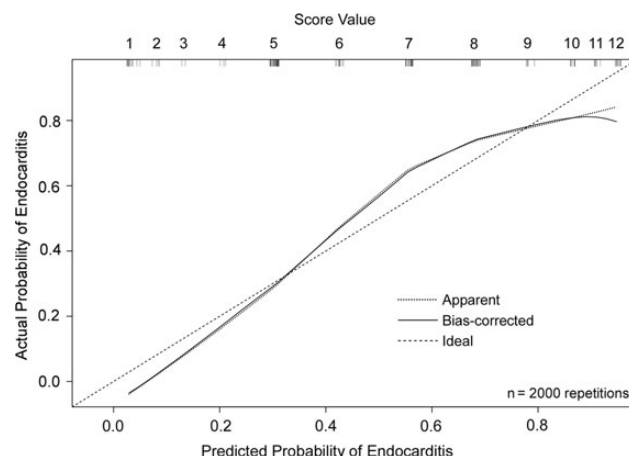


Figure 2. Model calibration curve for predicting enterococcal endocarditis based on the 12-point score obtained by bootstrapping the case-control population. The curve replicates the 4.3% prevalence of infective endocarditis observed in the prospective cohort. Values and number of cases in the original case-control dataset for each score value are shown on the top horizontal axis. Notice that a false-negative diagnosis (actual probability > predicted probability) is not expected for a Number of positive blood cultures, Origin of the bacteremia, previous Valve disease, Auscultation of heart murmur (NOVA) score <4 points.

a setting with a prevalence of endocarditis of 50%, such as our case-control study, to 27.7% in a setting with a 5% prevalence of endocarditis. Therefore, according to our model, in populations with a low prevalence (5%) and high prevalence (20%) of IE, the

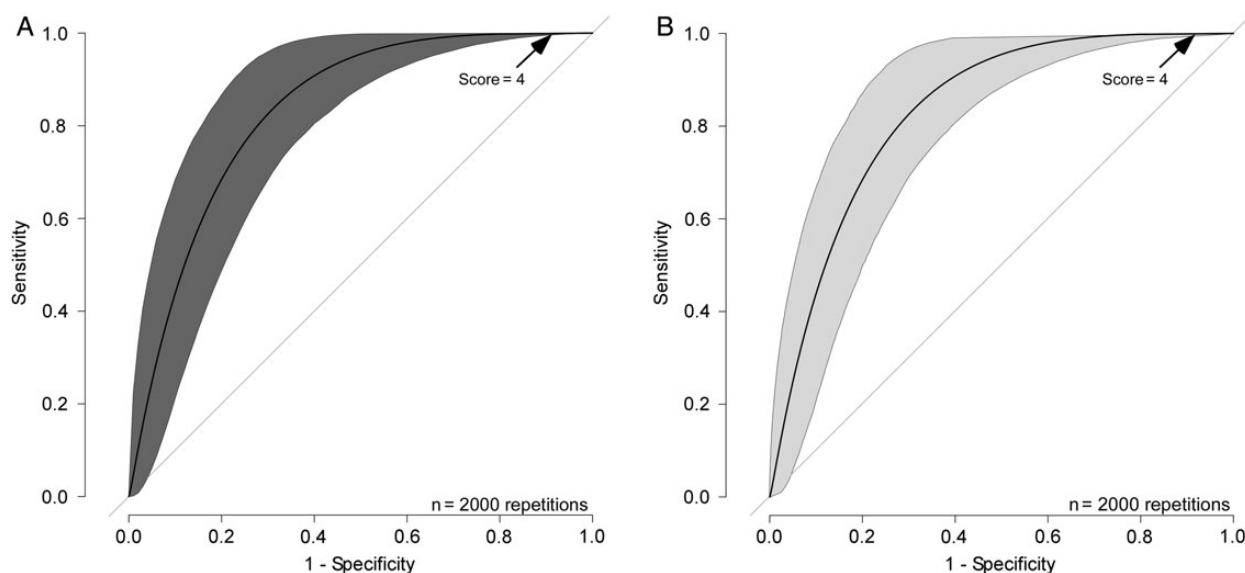


Figure 1. Receiver operating characteristic curves for the prediction of enterococcal endocarditis in patients with enterococcal bacteremia as a function of the 12-point score defined in Table 4. Areas of 95% confidence intervals for test sensitivity (panel A, shaded areas) and specificity (panel B, shaded areas) were obtained by 2000 bootstrap replications using a random prevalence of disease.

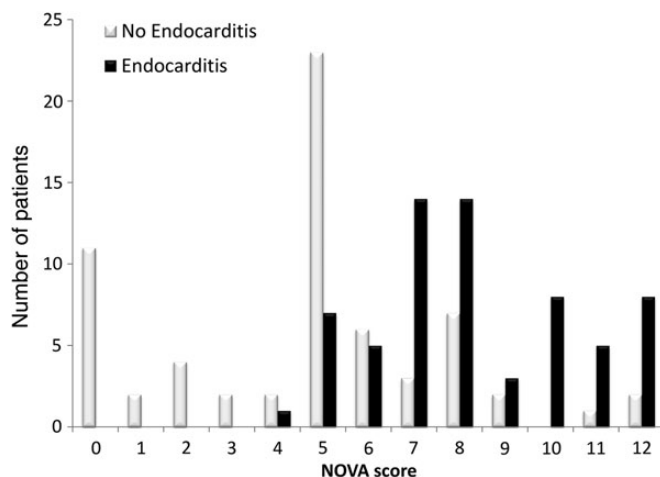


Figure 3. Patients with and without enterococcal endocarditis distributed according to the score in our case-control study (50% endocarditis and 50% no endocarditis). The score was as follows: heart murmur, 1 point; prior valve disease, 2 points; unknown source of bacteremia, 4 points; and continuous bacteremia, 5 points. Abbreviation: NOVA, Number of positive blood cultures, Origin of the bacteremia, previous Valve disease, Auscultation of heart murmur.

proportion of patients with E-BSI in whom TEE may not be necessary is 27.7% and 23.4%, respectively (Figure 4).

Analysis of a Sample of E-BSI Patients Who Did Not Undergo Echocardiography

After a careful record review, only 3/176 patients (1.70%) without TEE could have had IE according to the selected clinical criteria. All 3 had been treated for at least 4 weeks. Regarding length of treatment with appropriate regimens, only 12/176 patients received more than 2 weeks of therapy (3 with bacteremia of unknown origin, 6 with cholangitis, 1 with osteomyelitis, 1 with infected knee prosthesis, and 1 with fecal peritonitis).

As for occurrence of embolic episodes, only 2 patients presented with clinical, microbiological, and/or radiological

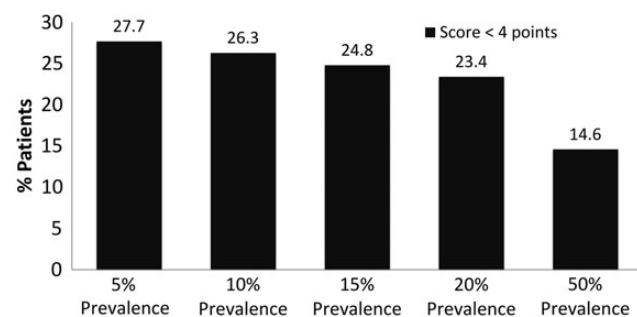


Figure 4. Estimated percentage of patients in whom transesophageal echocardiography could be obviated, with a score <4 points, according to different prevalence values for infective endocarditis in the population.

Table 4. Score for Assessing the Risk of Infective Endocarditis in Patients With Enterococcal Bloodstream Infections

Variable	Points	Odds Ratio (95% Confidence Interval)
Number of positive blood cultures (N)	5	9.9 (2.2–40.6)
Unknown origin of bacteremia (O)	4	7.7 (2.5–23.8)
Prior valve disease (V)	2	3.7 (1.6–8.7)
Auscultation of a heart murmur (A)	1	1.8 (.77–4.3)
Total	12	

evidence of septic embolism: a 79-year-old patient with multiple bilateral pulmonary consolidations who refused to undergo TEE and a 92-year-old man with severe Alzheimer disease and L4-S1 osteomyelitis whose family refused TEE. Both patients had been treated for at least 4 weeks before discharge.

Finally, we classified the 176 patients according to the NOVA score. Overall, 106 had a score < 4 points and were treated for a mean of 14 (standard deviation, 5.2) days. None of them presented clinical, microbiological, or radiological signs of embolism or IE during follow-up. Seventy patients had a NOVA score ≥ 4 points. Three of these patients were thought to have had IE and 2 presented with an embolic complication, as previously mentioned; all had been treated for more than 2 weeks. We cannot rule out the possibility of endocarditis in patients who died early after E-BSI.

DISCUSSION

The frequency of E-BSI is growing, and a significant percentage of cases are associated with IE. In our institution, enterococcal IE is present in 4.3% of all patients with E-BSI, 16.7% of patients undergoing echocardiography, and 35.5% of those who undergo TEE. We describe a simple, bedside predictive score to identify a subgroup of patients with E-BSI in whom the risk of enterococcal IE is very low and who therefore would not require systematic TEE. Our results confirm that, as indicated in the American guidelines, TEE should be the test of choice when the indication is to detect IE, especially if the pretest probability is high, such as in patients with staphylococcal bacteremia, fungemia, prosthetic heart valve, or intracardiac device [21]. Although systematic performance of TEE is not recommended in patients with enterococcal bacteremia in current guidelines, our relatively small percentage of patients with enterococcal bacteremia who underwent TEE (25.6%) reflects the real daily practice and, to date, is the only figure in the literature. In our opinion, TEE should also be performed in patients with enterococcal IE and a NOVA score >4 points.

In many institutions, *Enterococcus* species is the third most common cause of BSI. The main origins are the gastrointestinal tract and catheter-related infections [22]. The need to rule out

IE in patients with staphylococcal bacteremia remains open to debate [23], although some authors suggest that it may be unnecessary in 26%–28% of patients who fulfill specific criteria of uncomplicated BSI [24, 25]. The indication for echocardiography is even less clear in episodes of bacteremia caused by *Streptococcus*, *Candida*, and *Enterococcus* species [26].

Current guidelines for the diagnosis of IE [26] include echocardiography as a key test for the diagnosis and management of patients with IE; however, whether TTE or TEE should be performed first depends on the interpretation of a series of complex clinical, microbiological, and radiological findings. Although the detection rate for TTE is approximately 50% [10], the efficiency of the technique is affected by factors such as image quality, presence of previous valve disease or prosthetic material, skill of the examiner, and pretest probability of endocarditis. It has been proposed that for patients with a high probability of endocarditis, performance of TEE provides the highest quality-adjusted survival [23]. Our study suggests that most patients with E-BSI (those with a score ≥ 4 points) should undergo TEE (16.7% positive). We also show that TTE misses more than 70% of episodes of IE and that those patients should undergo TEE.

Our risk prediction score (NOVA) provides physicians with an easy-to-use system that could rapidly determine which patients with E-BSI may require further studies to detect IE. This is done by examining the number of positive blood cultures, the origin of the bacteremia, previous history of valve disease, and auscultation of a heart murmur.

Our study is subject to a series of limitations. First, as it was performed in a single center, and the sample size was not as large as it might have been. Nevertheless, it is the largest sample reported to date and was collected over a long period. Second, since an infectious diseases specialist previously evaluated patients with bacteremia, selection bias should be taken into consideration. Interestingly, despite the intervention of the infectious diseases department, the rate of compliance with echocardiography recommendations remains low (34.4%), and a significant number of patients (1127) with enterococcal bacteremia did not undergo TEE, thus limiting the ability of the study to estimate the real prevalence of IE. However, a further analysis of this population showed that only a very small proportion of patients (1.7%) could have had IE and that even without TEE, they were treated for at least 4 weeks. Finally, ours is a case-control study, and the results should be validated in a second cohort and/or prospective study.

Overall, the NOVA score is particularly useful for identifying a subgroup of patients with enterococcal bacteremia who may not need to undergo TEE (sensitivity 100%) because of an extremely low risk of endocarditis. We do not aim to put forward a hypothesis on the treatment of bacteremia or endocarditis. However, we do believe that treatment should be established according to guidelines, predisposing conditions, or clinical

presentation (eg, stroke and embolic phenomena) independently of the NOVA score.

In conclusion, our study shows that the prevalence of enterococcal IE depends on whether the sample comprised all cases among those with E-BSI (4.3%), only patients undergoing echocardiography (16.7%), or only patients undergoing TEE (35.5%). Use of TEE in all patients with E-BSI is difficult, costly, time consuming, and subject to complications. Depending on the local prevalence of endocarditis, application of the NOVA bedside prediction score could safely obviate echocardiography in 14%–27% of patients with enterococcal bacteremia.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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References

- Shlaes DM, Levy J, Wolinsky E. Enterococcal bacteremia without endocarditis. *Arch Intern Med* **1981**; 141:578–81.
- Malone DA, Wagner RA, Myers JP, Watanakunakorn C. Enterococcal bacteremia in two large community teaching hospitals. *Am J Med* **1986**; 81:601–6.
- Patterson JE, Sweeney AH, Simms M, et al. An analysis of 110 serious enterococcal infections. Epidemiology, antibiotic susceptibility, and outcome. *Medicine (Baltimore)* **1995**; 74:191–200.
- Garrison RN, Fry DE, Berberich S, Polk HC Jr. Enterococcal bacteremia: clinical implications and determinants of death. *Ann Surg* **1982**; 196:43–7.
- Barie PS, Christou NV, Dellinger EP, Rout WR, Stone HH, Waymack JP. Pathogenicity of the enterococcus in surgical infections. *Ann Surg* **1990**; 212:155–9.
- Fernandez-Guerrero ML, Herrero L, Bellver M, Gadea I, Roblas RF, de Gorgolas M. Nosocomial enterococcal endocarditis: a serious hazard for hospitalized patients with enterococcal bacteraemia. *J Intern Med* **2002**; 252:510–5.

7. Anderson DJ, Murdoch DR, Sexton DJ, et al. Risk factors for infective endocarditis in patients with enterococcal bacteremia: a case-control study. *Infection* **2004**; 32:72–7.
8. Rodriguez-Creixems M, Alcala L, Munoz P, Cercenado E, Vicente T, Bouza E. Bloodstream infections: evolution and trends in the microbiology workload, incidence, and etiology, 1985–2006. *Medicine (Baltimore)* **2008**; 87:234–49.
9. Fernandez-Cruz A, Marin M, Kestler M, Alcala L, Rodriguez-Creixems M, Bouza E. The value of combining blood culture and SeptiFast data for predicting complicated bloodstream infections caused by Gram-positive bacteria or *Candida* species. *J Clin Microbiol* **2013**; 51:1130–6.
10. Evangelista A, Gonzalez-Alujas MT. Echocardiography in infective endocarditis. *Heart* **2004**; 90:614–7.
11. Baddour LM. 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: e394–434.
12. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* **2000**; 30:633–8.
13. Murdoch DR, Corey GR, Hoen B, 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**; 169:463–73.
14. McCabe W, Jackson G. Gram-negative bacteremia: I. etiology and ecology. *Arch Intern Med* **1962**; 110:847–55.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* **1987**; 40:373–83.
16. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* **1999**; 15:816–22; discussion 22–3.
17. Harrell FE. Regression modeling strategies, with applications to linear models, survival analysis and logistic regression. New York, NY: Springer, **2001**.
18. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. *Stat Med* **2000**; 19: 1141–64.
19. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* **2011**; 12:77.
20. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, **2008**. Available at: <http://www.R-project.org>.
21. Douglas PS, Garcia MJ, Haines DE, et al. ACCF/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. *J Am Soc Echocardiogr* **2011**; 24:229–67.
22. Reigadas E, Rodriguez-Creixems M, Guembe M, Sanchez-Carrillo C, Martin-Rabadan P, Bouza E. Catheter-related bloodstream infection caused by *Enterococcus* spp. *Clin Microbiol Infect* **2013**; 19:457–61.
23. Incani A, Hair C, Purnell P, et al. *Staphylococcus aureus* bacteraemia: evaluation of the role of transesophageal echocardiography in identifying clinically unsuspected endocarditis. *Eur J Clin Microbiol Infect Dis* **2013**; 32:1003–8.
24. Kaasch AJ, Fowler VG Jr, Rieg S, et al. Use of a simple criteria set for guiding echocardiography in nosocomial *Staphylococcus aureus* bacteremia. *Clin Infect Dis* **2011**; 53:1–9.
25. Khatib R, Sharma M. Echocardiography is dispensable in uncomplicated *Staphylococcus aureus* bacteremia. *Medicine (Baltimore)* **2013**; 92:182–8.
26. Habib G, Hoen B, Tornos P, 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**; 30:2369–413.