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The VIRSTA score, a prediction score to estimate risk of infective endocarditis and determine priority for echocardiography in patients with *Staphylococcus aureus* bacteremia

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1 **Original article**

2 **The VIRSTA score, a prediction score to estimate risk of infective endocarditis and**

3 **determine priority for echocardiography in patients with *Staphylococcus aureus***

4 **bacteremia**

5

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13

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41

42 **Structured abstract (199 words)**

43 **Objectives.** To develop and validate a prediction score, to quantify, within 48 hours of *Staphylococcus*
44 *aureus* bacteremia (SAB) diagnosis, the risk of IE, and therefore determine priority for urgent
45 echocardiography.

46 **Methods.** Consecutive adult patients with SAB in 8 French university hospitals between 2009 and 2011
47 were prospectively enrolled and followed-up 3 months. A predictive model was developed and internally
48 validated using bootstrap procedures.

49 **Results.** Among the 2,008 patients enrolled, 221 (11.0%) had definite IE of whom 39 (17.6%) underwent
50 valve surgery, 25% of them within 6 days of SAB diagnosis. Ten predictors independently associated with IE
51 were used to build up the prediction score: intracardiac device or previous IE, native valve disease,
52 intravenous drug use, community or non-nosocomial-acquisition, cerebral or extracerebral emboli,
53 vertebral osteomyelitis, severe sepsis, meningitis, C-reactive protein above 190 mg/L, and H48-persistent
54 bacteremia. Patients with a score ≤ 2 (n=792, 39.4%) were at low IE-risk (1.1%; negative predictive value:
55 98.8% (95% CI, 98.4-99.4)) compared to those ≥ 3 who were at higher risk (17.4%).

56 **Conclusions.** Physicians must be strongly encouraged to urgently perform echocardiography in SAB
57 patients with a score ≥ 3 to establish IE diagnosis, to orient antimicrobial therapy and to help determine
58 the need for valvular surgery.

59
60 **Key words:** *Staphylococcus aureus* Bacteremia; Infective endocarditis; prognostic score;
61 echocardiography, VIRSTA score.

62

63

64 **Abbreviations list**

65 CI, confidence interval;

66 CRP, C-reactive protein;

67 ICD, implantable cardioverter defibrillator;

68 IE, infective endocarditis;

69 IQR, interquartile range;

70 SAB, *Staphylococcus aureus* bacteremia;71 *S aureus*, *Staphylococcus aureus*;

72 TEE , trans-esophageal echocardiography;

73 TTE, transthoracic echocardiography;

74

75 Introduction

76 *Staphylococcus (S) aureus* is among the most frequent causes of both healthcare-associated and
77 community-acquired bloodstream infections worldwide, with incidence rates of between 20 and 50 cases /
78 100,000 population per year in industrialized countries [1,2]. One of the most severe complications of *S.*
79 *aureus* bloodstream infection (SAB) is infective endocarditis (IE), reported to occur in 5-17% of cases [3].

80 Echocardiography plays a key role in IE diagnosis [4]. Recommendations on the systematic use of
81 echocardiography in SAB patients are not consistent in the literature[4–10]. Even in situations for which
82 most guidelines recommend echocardiography, it is not performed in a substantial number of SAB
83 patients: in a recent pooled analysis of SAB prospective studies, echocardiography was performed in only
84 56% of patients despite being strongly recommended to investigators [11] . In this context, some authors
85 have proposed criteria to guide the use of echocardiography. However, none of these studies were
86 prospectively designed with a large number of patients who underwent echocardiography in all subset of
87 community and health-care associated SAB patients.

88 In the present study, we developed and validated a simple score-based prediction rule to quantify
89 the risk of IE within 48 hours after SAB diagnosis in patients with community- acquired or healthcare-
90 associated SAB, using the largest prospective cohort of SAB patients reported to date [12–14]. This score
91 could be used for the early identification of urgent echocardiography candidates, for rapid IE diagnosis,
92 and early initiation of specific interventions for IE, including appropriate antimicrobial therapy, and
93 multidisciplinary evaluation of indications for valvular surgery.

94

95 **Methods**

96 ***Setting and subjects***

97 VIRSTA is an observational prospective cohort study previously described [15] conducted between April
98 2009 and January 2012 which included all consecutive adult patients having at least one blood culture
99 positive for *S. aureus* in 8 tertiary-care university hospitals in France. Patients with catheter colonization
100 without SAB, defined as positive blood cultures only through vascular access device specimen and those
101 referred to the hospitals for the management of IE were excluded.

102 Trained research assistants prospectively collected clinical, biological (CRP measured at inclusion) and
103 therapeutic data through a standardized case report form in each center. Clinical data included
104 demographics, background characteristics (comorbidities, IE-predisposing conditions), healthcare contacts
105 within the 90 days preceding hospitalization including invasive procedures, and setting of acquisition.
106 Investigations for SAB complications present and/or occurring during the first 48 hours (including
107 meningitis, vertebral osteomyelitis, cerebral emboli, and extracerebral emboli) as well as presence of
108 severe sepsis or septic shock were recorded. Therapeutic data included antibiotics, catheter removal,
109 surgery, and admission to intensive care unit.

110 Transthoracic echocardiography (TTE) and/or TEE were strongly encouraged. Patients, their relatives or
111 physicians were contacted 12 weeks after the beginning of the SAB to check the patient's status.

112 ***Data acquisition and definitions***

113 SAB was classified as healthcare-associated (nosocomial or non-nosocomial), or as community-acquired
114 [16] (see in Appendix). Patients were considered as having a permanent intracardiac device in the
115 presence of prosthetic heart valve, and/or pacemaker and/or implantable cardioverter defibrillator (ICD).
116 Persistent bacteremia was defined as positive blood cultures more than 48 hours after the first positive
117 blood culture result (Figure 1).

118 ***Infective endocarditis classification***

119 The primary endpoint was the diagnosis of definite IE according to modified Duke classification [17] within
120 12 weeks established by a local adjudication committee made up of cardiologists, infectious diseases
121 specialists and bacteriologists.

122 ***Statistical analysis***

123 ***Predictive factors***

124 First, a descriptive analysis of patients was performed. Potential IE predictors were then selected based on
125 the literature [6,13,14,18–21], categorized as 1/ patient background characteristics, 2/ initial SAB
126 presentation characteristics, and 3/ early extracardiac events (Table 1). Only SAB characteristics and
127 extracardiac events present and/or occurring during the first 48 hours following the T0 blood sample
128 collection were considered, as well as the result of the T48 hour blood sample collection.

129 Categorical variables were summarized using percentages and compared using Fisher exact test.
130 Continuous variables were summarized using medians with interquartile ranges and compared using
131 Wilcoxon test. All variables with a P value of < 0.20 in the bivariate analysis were entered into a
132 multivariate logistic regression with a stepwise backward approach and a significance level at $P < 0.05$. All
133 significant variables in the logistic model were used to build a predictive score of IE.

134

135 ***Model validation***

136 To improve the final reduced model's stability, a validation was performed using a ".632 bootstrap
137 procedure"[22]. One thousand bootstrap samples were drawn from the original sample, estimating the
138 overfitting-corrected regression coefficients from the final model and the overfitting-corrected measures
139 of the model performance on subjects not sampled. To quantify the model performance, we determined
140 the discrimination computing the C statistic (area under the receiver operating characteristic curve) and its
141 95% confidence interval (CI) and the calibration using Hosmer-Lemeshow's test.

142

143 **Scoring system**

144 Median β coefficients from the bootstrap procedure were rounded to the nearest half, and then multiplied
145 by 2 to build corresponding weights. For each patient, the score was then calculated by adding up the
146 weights corresponding to each variable. Intrinsic (sensitivity, specificity) and extrinsic (positive and
147 negative predictive value) qualities were then assessed using a classic bootstrap procedure for different
148 values of the score. Finally, to ensure model performance consistency among subgroups, we applied the
149 score separately according to 1/ setting of acquisition and 2/ the presence of predisposing cardiac
150 conditions.). Analyses were performed with SAS software (version 9.3) and R software, version 2.13.0.

151

152 **Sensitivity analyses**

153 To assess the robustness of the model, two sensitivity analyses were performed. The first one was
154 performed in the subpopulation of patients, who underwent echocardiography, or in whom
155 echocardiography was not performed but for whom the addition of an echocardiographic major criterion
156 would not have upgraded the modified Duke classification to a definite IE case (hereafter referred to as
157 “echo sensitivity analysis”). In the second one, we excluded all definite IE in which definite classification
158 was based on the presence of modified Duke Criteria which were included in the statistical model as
159 potential predictors of IE to avoid the resulting tautology (hereafter referred to as “modified Duke criteria
160 sensitivity analysis

161 A third sensitivity analysis was performed to evaluate the performance of the score among patients with
162 highest diagnostic uncertainty. We excluded from our population patients with definite IE, based on duke
163 criteria determined within the first 48 hours (patients with the microbiological major criteria AND ≥ 3
164 minor criteria).

165

166 **Ethics**

167 The VIRSTA study was approved by the French institutional review board for the protection of human
168 subjects (CPP Sud-Méditerranée IV) and registered in the European Clinical Trials Database (EUDRACT
169 2,008-A00680-55).

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171 **Results**

172 *Patient characteristics*

173 During the 30-month study period, 2,091 consecutive patients with SAB were enrolled. Background
174 characteristics, initial SAB features, and extracardiac events occurring in the first 48 hours in the 2,008
175 patients not referred for the management of IE are presented in Table 1.

176 Echocardiography was performed in 1,348 patients (67.1%), and 605 patients (30.1%) underwent
177 TEE. According to setting of acquisition, echocardiography was performed in 678 patients with nosocomial
178 SAB (63.1%), and in 641 patients with community-acquired or non-nosocomial healthcare-related SAB
179 (73.3%). The extracardiac events which were present and/or occurred within the first 48 hours are listed in
180 Table 1. The 30-day and the 12-week mortality rates were respectively 22.2% (445 patients) and 32.2%
181 (646 patients).

182

183 *Endocarditis classification*

184 The adjudication committee categorized 221 (11.0%) (95% CI 9.6%-12.4%) patients as definite IE cases.
185 Table 2 presents the distribution of the modified Duke criteria in the 2,008 patients. The rate of definite IE
186 was 15.6% (n=211) in the 1,348 subjects in whom echocardiography was performed. Among them,
187 echocardiography revealed one major criterion of IE in 80.6% (n=170), including vegetation in 139 patients
188 (65.9%), abscess in 32 patients (15.1%), and new dehiscence of a prosthetic valve in 13 patients (6.2%).
189 Valve surgery was performed in 39 of the 221 patients with definite IE (17.7%), with a median time interval
190 of 12 days [IQR; 6-29] after T0 blood sample collection, and 6 days [IQR; 2-28] after echocardiography. In
191 those patients, echocardiographic findings showed valvular regurgitations in 48.7%, vegetations at high
192 risk of embolism in 56.4%, and cardiac abscesses in 30.8 %.

193

194 Predictive factors

195 Ten predictive factors were independently associated with definite IE (Table 3). The Hosmer-Lemeshow's
196 test p-value for the final model was 0.60 and the median area under the curve after bootstrap procedure
197 was equal to 0.85 (95% CI 0.84–0.86).

198 The “echo sensitivity analysis”, performed in 1,728 patients yielded a comparable final model with
199 the same ten independent predictive factors. The “modified Duke criteria sensitivity analysis” performed
200 in 1,950 patients also provided closely related results, with the exception of vertebral osteomyelitis, which
201 was removed from the final model (see Table 1 in Appendix).

202

203 Scoring system

204 Score building is detailed in Table 4. After 1000 resampling iterations using a .632 bootstrap procedure,
205 median β coefficients of the ten predictive factors were estimated. The weights varied from 1 to 5 points,
206 leading to a theoretical score ranging from 0 to 30 for a given patient. In the VIRSTA cohort, the score
207 ranged from 0 to 20. For instance a patient who presents vertebral osteomyelitis or a community acquired
208 SAB without any other criteria or a patient with severe sepsis with or without CRP>190 mg/L have a score
209 ≤ 2 . A patient with cerebral emboli (or with pre-existing native valve disease or with meningitis or with
210 persistent bacteremia or with history of injection drug use) no needs to have more criteria to have a
211 score ≥ 3 (Figure 2).

212 The rate of endocarditis increased significantly from 1.1% (9/792) when the score was ≤ 2 to 17.4%
213 (212/1216) when the score was ≥ 3 and up to 70.8% (63/89) when the score was ≥ 10 (Figure 3).

214 TTE performance rate rose from 54.2% with a score ≤ 2 to 89.9% when the score was ≥ 10 . Score
215 performance according to different cutoffs is presented in Table 4. For a score ≤ 2 , the negative predictive
216 value was 98.8% (95% CI 98.4; 99.4) and the sensitivity was 95.8% (95% CI 94.3; 97.8).

217 After exclusion of (n=28) patients with definite IE as established within the first 48 hours (third sensitivity
218 analysis), the performance of the VIRSTA score was similar (95.3 % for sensitivity and 98.9% for negative
219 predictive value).”

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221 Discussion

222 In this large multicenter prospective cohort study on adult patients with SAB, we have developed and
223 assessed the performance of an IE prediction model taking into account patients' background and initial
224 SAB characteristics. The VIRSTA score provides an accurate estimation of IE probability in patients with
225 SAB, whatever the setting of SAB acquisition and may be used by physicians to decide on the early use of
226 echocardiography.

227 Our study is based on the largest prospective cohort of SAB patients reported to date. To enhance
228 the generalizability of our results, we enrolled all patients in hospitals from different French regions with a
229 large population pool and a representation of multiple medical specialties. Most SAB characteristics
230 observed in our study are consistent with those reported in other SAB studies [11], including
231 predominance of elderly individuals and men, the high proportion of nosocomial SAB, the rate of
232 methicillin-resistant strains, and the 30-day and 12-week mortality rates. Although echocardiography use
233 differs between studies, impacting IE diagnosis rate, the 15.6% or 11% endocarditis rates (according to
234 restriction of analysis to patients with echocardiography), are also similar to those reported in the
235 literature [11]. Our rate of 67.1 % echocardiography (1,348 of our 2,008 patients underwent
236 echocardiography), is among the highest reported in the literature (43 to 79%) [6,10,12,23]. Furthermore,
237 the establishment of IE diagnosis in each case by an adjudication committee using a validated classification
238 (modified Duke) and follow-up data reinforces the study's validity.

239 Our goal was to quantify, as early as possible, the risk of IE among SAB patients and thus the
240 indication for echocardiography for adjustment of antibacterial treatment, and early multidisciplinary
241 evaluation of indication(s) for cardiac surgery. This is particularly critical for IE patients with, valvular or
242 paravalvular complications, or high embolic risk [5,24]. Of note, 25% of VIRSTA patients who were
243 operated on for IE underwent surgery before day 6 (after first blood sample collection), and 50% before
244 day 12.

245 Our study shows several readily available predictors independently associated with IE such as
246 patient background characteristics, including predisposing cardiac conditions. These findings agree with
247 previous reports who proposed criteria to assess predictors of IE among SAB patients [6,13,18,21,25,26].

248 Other factors classified as initial SAB presentation – i.e IV drug use and community-acquired SAB - are IE
249 predictors in our final model, as in previous studies [6,7,13,14]. Interestingly, CRP, another predictor of IE
250 in our population, has been proposed to be an additional minor criteria of Duke modified classification by
251 Lamas and colleagues [27] because it improved Duke classification sensitivity in patients with
252 pathologically proven IE. To our knowledge, our VIRSTA study is the first who reported an independent
253 association between CRP level and IE in patients with suspected IE in multivariable analysis. To our
254 knowledge, this study is the first to report the CRP level as an independent predictor of IE. Some early
255 extracardiac events such as embolic events, vertebral osteomyelitis, meningitis and severe sepsis or shock
256 were associated with a higher frequency of IE. Persistent bacteremia was strongly associated with definite
257 IE, and has been shown to be a predictor of complicated SAB [14,16,17,19,24].

258 The two sensitivity analyses, which found quite similar determinants of IE, argue for the
259 robustness of the model. With the “echo sensitivity analysis”, we tested the risk that some IE cases may
260 have been undetected in patients without echocardiography even with 12 weeks of follow-up data. Thanks
261 to the “modified Duke criteria sensitivity analysis,” we ensured that ascertainment of candidate predictors
262 was fully independent of ascertainment of criteria taken into account for the end-point; of note, to the
263 best of our knowledge, such sensitivity analysis has never been performed before by authors developing
264 prediction score in SAB patients. The excellent performance of the final predictive model also proved its
265 reliability, which constitutes a strong argument for supporting its application in clinical practice.

266 The proportion of IE increases concomitantly with the score, from 1% for a score ≤ 2 to more than
267 70 % for a score ≥ 10 . For a score ≤ 2 , the negative predictive value was excellent (98.8%). The threshold of
268 2 is somewhat arbitrary but combines the assets of a high negative predictive value (>95%) and a small
269 number of undiagnosed IE cases (1.1%). The score can be applied as soon as SAB is diagnosed and

270 echocardiography indicated if the score is above 2. Otherwise, occurrence of complications and/or of a
271 positive T48h blood culture must lead to recalculation of the score and to indication for echocardiography
272 in those with a score which has risen to above 2.

273 In patients with a score ≥ 3 , echocardiography should be performed urgently using the most
274 sensitive method, *i.e.* TEE. According to the positive predictive value, more than one in 5 patients in this
275 group would be classified as definite IE. Of note, patients with one of the characteristics weighted ≥ 3 (*i.e.*
276 native valve disease or permanent intracardiac devices or previous IE or IVD use) exceed *per se* this cut-off.

277 In contrast, in patients with a score ≤ 2 , the probability of IE is very low and systematic urgent TEE
278 appears less justified. The use of this score in our cohort would have permitted the avoidance of urgent
279 TEE in 792 patients (39.4%). Of note, among the 9 patients with definite IE and a score ≤ 2 (false-negative),
280 none would have had an increased IE prediction score ≥ 3 if SAB complications that occurred later than 48
281 hours had been considered (data not shown).

282 **Limitations.** We acknowledge several limitations to our study. First, as with other large
283 observational prospective studies and despite recommendations to the contrary, a substantial proportion
284 of our patients' cohort did not undergo echocardiography in our cohort. This underlines the reluctance of
285 some physicians to perform echocardiography in all SAB patients, and supports the need for a scoring
286 system. To maintain the external validity of this prospective cohort, we chose to perform the main analysis
287 on the total population. However, we cannot exclude the possibility that cases of IE might have been
288 missed. Nevertheless, the systematic 12-week follow-up limited this possibility, and the "echo sensitivity
289 analysis" gives us confidence in the results. Second, patients were enrolled only in tertiary care centers.
290 This probably led to the recruitment of more severe patients with a higher prevalence of comorbidities.
291 However, we minimized the referral bias by excluding patients referred from other hospitals for the
292 management of IE. Third, despite the large sample size (*i.e.* 2,008 SAB patients), and use of a bootstrap
293 technique to validate our prediction model, it would have been of interest to add an external validity
294 measurement using another data set in addition to the internal validity assessment. Third, confirmation of

295 these findings with patients originating from different countries and/or infected by different
296 microbiological isolates is required.

297 **In conclusion**, our study is the largest multicenter prospective cohort of SAB patients reported to
298 date, with a high rate of echocardiography and a systematic 12-week follow-up; it proposes a simple scoring
299 system applicable in all subset of SAB patients within 48 hours and whatever the setting of acquisition (See
300 Table S2 in Supplementary Appendix). The sensitivity analyses reinforce the robustness of the model and
301 the validity of our results. We think that the early detection of IE in patients with SAB can be improved by
302 the use of the VIRSTA score. The high predictive performance of this score makes possible a reliable
303 assessment of the likelihood of IE. The routine use of this score may have important implications for
304 clinical practice, in particular with regard to indications for echocardiography for a given patient. Early TEE
305 should be performed urgently in patients with a score ≥ 3 , and repeated if initially negative, while in the
306 large subgroup of patients with a score ≤ 2 , urgent TEE is not needed at an early stage, although the
307 indications depend on the clinical context. The rationale behind early indications for echocardiography is
308 of particular importance when local resources are limited. Finally, this score is useful to selectively draw
309 the attention of clinicians to patients at high risk of IE, since recommendations for systematic
310 echocardiography are not currently applied.

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Table 1. Demographic and clinical variables present at the time of *Staphylococcus aureus* bacteremia diagnosis in the 2,008 enrolled patients, VIRSTA Study

	N or med	IQR or %	Non IE N=1,787	IE N=221	p-value
Background characteristics					
Age (Yr)	67	(65 ; 78)	67(5;78)	67 (3 ;79)	0.9
Gender (male)	1295	(64.5)	1151 (64.4)	144 (65.2)	0.8
Chronic hemodialysis	211	(10.5)	185 (10.4)	26 (11.8)	0.5
Mac Cabe score					
Ultimately fatal disease	751	(37.4)	674 (37.8)	77 (34.8)	0.4
Rapidly fatal disease	368	(18.3)	332 (18.6)	36 (16.3)	
Predisposing cardiac conditions					
Permanent intracardiac device or previous IE*	341	(17.0)	255 (14.3)	86 (38.9)	<0.0001
Pre-existing native valve disease	264	(13.1)	221 (12.4)	43 (19.5)	
None	1403	(69.9)	1311 (73.4)	92 (41.6)	
Initial SAB presentation					
Intravenous drug use	63	(3.1)	39 (2.2)	24 (10.9)	<0.0001
Known source of infection†	1602	(79.8)	1441 (80.6)	161 (72.9)	0.01
Presumed setting of acquisition					
Nosocomial	1075	(53.5)	1006 (56.3)	69 (31.2)	<0.0001
Community or non-nosocomial Health care associated	875	(43.6)	726 (40.6)	146 (67.4)	
Unknown setting of acquisition	58	(2.9)	55 (3.1)	3 (1.4)	
C-reactive protein at inclusion > 190 mg/L ‡					
No	952	(47.4)	880 (49.2)	72 (32.6)	<0.0001
Yes	929	(46.3)	788 (44.1)	141 (63.8)	
Missing value	127	(6.3)	119 (6.7)	8 (3.6)	
Methicillin resistance					
No	1627	(81.0)	1436 (80.3)	191 (86.4)	0.02
Yes	381	(19.0)	351 (19.7)	30 (13.6)	
Early extracardiac events (0-48 hours)					
Severe sepsis or septic shock	495	(24.7)	400 (22.4)	95 (43.0)	<0.0001
Cerebral or peripheral emboli	90	(4.5)	38 (2.1)	52 (23.5)	<0.0001
Meningitis	22	(1.1)	9 (0.5)	13 (5.9)	<0.0001
Vertebral osteomyelitis	28	(1.4)	20 (1.1)	8 (3.6)	<0.008
Persistent bacteremia	344	(17.1)	259 (14.5)	85 (38.5)	<0.0001

IE, infective endocarditis ; IQR, Interquartile range

* Prosthetic valve in 140 patients (7.0 %), pacemaker or ICD in 217 (10.8%) and previous IE in 34 (1.7%)

† venous or arterial line in 527 patients (26.2%), skin in 384 (19.1%), surgical wound in 303 (15.0%), lung in 122 (6.1%), urinary tract in 103 (5.1%) and other presumed source in 163 (8.1%)

‡ categorized according to the median of the distribution

Table 2. Distribution of the modified Duke criteria in the 2,008 *Staphylococcus aureus* bacteremia enrolled patients, VIRSTA Study

Modified Duke Classification	n	%	n	%	Modified Duke criteria	Total number of patients	Number of patients without echocardiography			
Definite	221	11.0	24	10.9	Histologically proven	24	0			
					Clinically proven	197	89.1	2 major criteria	139	3
								1 major criteria + ≥ 3 minor criteria	56‡	7
Possible	965	48.1			≥ 5 minor criteria	2‡	0			
					1 major criteria + 1 minor criteria	605	191†			
					1 major criteria + 2 minor criteria	267	49†			
Excluded	822	40.9			≥ 3 minor criteria	93	39†			
					0 minor criteria	179	59			
					1 minor criteria	261	115			
					2 minor criteria	374	196			
					3 minor criteria	8	1†			

* Patients with histologically proven IE who don't need to fulfill the clinical modified Duke criteria

† Patients removed from the echo sensitivity analysis

‡ Patients removed from the modified Duke criteria sensitivity analysis

Table 3. Final predictive model of infective endocarditis and median β Coefficients estimated by Multivariate Logistic Regression Model and Bootstrapping Procedure in the 2008 enrolled *Staphylococcus aureus* bacteremia patients, VIRSTA Study

	Multivariate analysis				.632 Bootstrap procedure	
	Odds Ratio	(95% CI)	p-value	β	β'	Weight
Cerebral or peripheral emboli	10.4	(6.0 ; 17.9)	<0.0001	2.33	2.37	<u>5</u>
Meningitis	9.6	(3.2 ; 29.2)	<0.0001	2.27	2.31	<u>5</u>
Permanent intracardiac device or previous IE	7.3	(4.9 ; 10.9)	<0.0001	1.99	2.02	<u>4</u>
Pre-existing native valve disease	3.6	(2.3 ; 5.7)		1.29	1.29	<u>3</u>
Intravenous drug use	5.8	(2.8 ; 11.7)	<0.0001	1.75	1.77	<u>4</u>
Persistent bacteremia	3.9	(2.8 ; 5.7)	<0.0001	1.38	1.40	<u>3</u>
Vertebral osteomyelitis	3.2	(1.2 ; 8.9)	0.03	1.17	1.15	<u>2</u>
Community or Non nosocomial Health care associated acquisition	2.6	(1.8 ; 3.7)	<0.0001	0.96	0.96	<u>2</u>
Severe sepsis or shock	2.0	(1.4 ; 2.9)	0.0001	0.71	0.72	<u>1</u>
C-reactive protein > 190 mg/L	1.9	(1.3 ; 2.7)	0.0006	0.64	0.65	<u>1</u>

CI, Confidence Interval

Table 4. Performance score for IE in 2,008 patients with *Staphylococcus aureus* bacteremia, VIRSTA Study

VIRSTA Score	Sensitivity (CI 95%)	Specificity (CI 95%)	Positive predictive value (CI 95%)	Negative predictive value (CI 95%)
0 versus ≥ 1	99.3 (99.2 ; 99.3)	18.5 (17.3 ; 19.6)	13.1 (12.1 ; 14.2)	99.5 (99.5 ; 99.6)
≤ 1 versus ≥ 2	97.2 (96.1 ; 98.7)	32.2 (30.8 ; 33.5)	15.1 (13.9 ; 16.2)	98.9 (98.4 ; 99.5)
≤ 2 versus ≥ 3	95.8 (94.3 ; 97.8)	44.2 (42.6 ; 45.6)	17.6 (16.2 ; 18.9)	98.8 (98.4 ; 99.4)
≤ 3 versus ≥ 4	85.5 (82.4 ; 88.6)	61.9 (60.5 ; 63.3)	21.8 (20.0 ; 23.5)	97.2 (96.5 ; 97.8)
≤ 4 versus ≥ 5	78.3 (74.8 ; 81.9)	74.4 (73.1 ; 75.7)	27.5 (25.3 ; 29.7)	96.5 (95.9 ; 97.1)
≤ 5 versus ≥ 6	70.1 (66.0 ; 74.1)	83.2 (82.1 ; 84.3)	34.0 (31.3 ; 36.7)	95.8 (95.1 ; 96.4)
≤ 6 versus ≥ 7	57.9 (53.9 ; 62.1)	91.1 (90.2 ; 92.0)	44.6 (40.9 ; 48.4)	94.6 (93.9 ; 95.3)
≤ 7 versus ≥ 8	45.7 (41.5 ; 49.7)	95.1 (94.5 ; 95.8)	53.7 (49.1 ; 58.6)	93.4 (92.7 ; 94.1)
≤ 8 versus ≥ 9	38.5 (34.6 ; 42.4)	97.3 (96.8 ; 97.8)	63.9 (58.4 ; 69.1)	92.8 (92.0 ; 93.5)
≤ 9 versus ≥ 10	26.7 (23.2 ; 30.2)	98.7 (98.5 ; 99.0)	71.9 (65.4 ; 78.4)	91.6 (90.8 ; 92.4)
≤ 10 versus ≥ 11	20.4 (17.0 ; 23.8)	99.4 (99.2 ; 99.7)	81.8 (75.0 ; 88.2)	91.0 (90.1 ; 91.8)

CI, Confidence Interval

Figure titles and legends

Figure 1. Timeline for collection of infective endocarditis's predictive factors, VIRSTA Study

SAB: *Staphylococcus aureus* bacteremia

D1 (T0) is considered as the day during which the first *S. aureus* positive blood sample is drawn (T0 blood sample collection). The culture result of this blood sample, available at a mean time of 24 hours is the day of SAB diagnosis which corresponds to D2 (T 24h=T0 blood sample result). The T48h blood sample is therefore drawn at D3 (T48h blood sample collection) and its results available at D4 (T 72h=T48h blood sample result).

Figure 2. Proposed score for optimal use of TEE in patients with SAB, VIRSTA Study

SAB: *Staphylococcus aureus* bacteremia

TEE : trans-esophageal echocardiography;

Figure 3. Association between VIRSTA score and IE probability in 2,008 patients with *Staphylococcus aureus* bacteremia, VIRSTA Study

Infective endocarditis rate increased significantly from 1.1% (score \leq 2) to 701.8% (score \geq 10). Rate of echocardiography performed rose from 54.2% (score \leq 2) to 89.9% (score \geq 10).

Figure 1

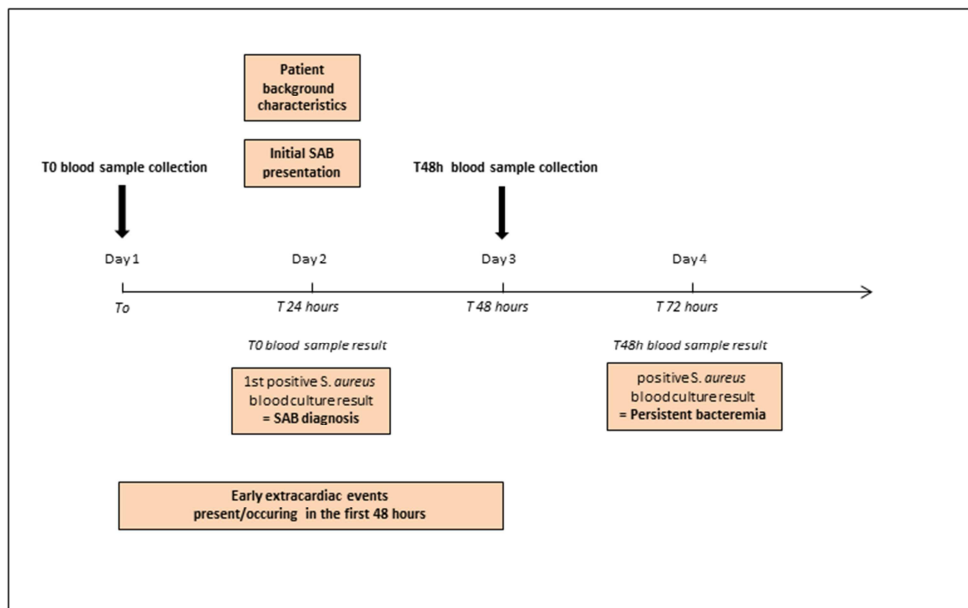


Figure 2

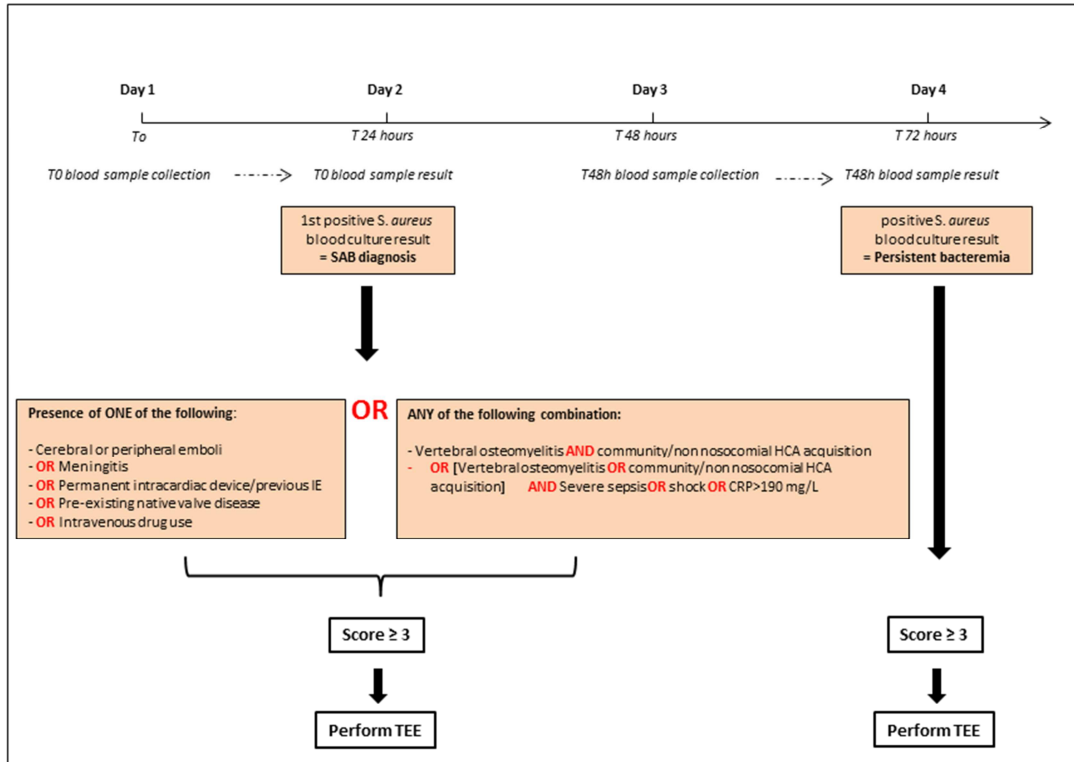


Figure 3

