

Predicting Risk of Endocarditis Using a Clinical Tool (PREDICT): Scoring System to Guide Use of Echocardiography in the Management of *Staphylococcus aureus* Bacteremia

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(See the Editorial Commentary by Kaasch and Jung on pages 29–30.)

Background. Infective endocarditis (IE) is a serious complication of *Staphylococcus aureus* bacteremia (SAB). There is limited clinical evidence to guide use of echocardiography in the management of SAB cases.

Methods. Baseline and 12-week follow-up data of all adults hospitalized at our institution with SAB from 2006 to 2011 were reviewed. Clinical predictors of IE were identified using multivariable logistic regression analysis.

Results. Of the 757 patients screened, 678 individuals with SAB (24% community acquired, 56% healthcare associated, and 20% nosocomial) met study criteria. Eighty-five patients (13%) were diagnosed with definite IE within the 12 weeks of initial presentation based on modified Duke criteria. The proportion of patients with IE was 22% (36/166) in community-acquired SAB, 11% (40/378) in community-onset healthcare-associated SAB, and 7% (9/136) in nosocomial SAB. Community-acquired SAB, presence of cardiac device, and prolonged bacteremia (≥ 72 hours) were identified as independent predictors of IE in multivariable analysis. Two scoring systems, day 1 (SAB diagnosis day) and day 5 (when day 3 culture results are known), were derived based on the presence of these risk factors, weighted in magnitude by the corresponding regression coefficients. A score of ≥ 4 for day 1 model had a specificity of 96% and sensitivity of 21%, whereas a score of < 2 for day 5 model had a sensitivity of 98.8% and negative predictive value of 98.5%.

Conclusions. We propose 2 novel scoring systems to guide use of echocardiography in SAB cases. Larger prospective studies are needed to validate the classification performance of these scoring systems.

Keywords. *Staphylococcus aureus*; bacteremia; echocardiography; endocarditis; risk score.

Staphylococcus aureus is a highly virulent pathogen that has become a leading cause of bacteremia in both

community and healthcare settings, accounting for 20% of all healthcare-associated bacteremias [1, 2]. The mortality attributed to *S. aureus* bacteremia (SAB) and sepsis ranges from 20% to 30%. Mortality in *S. aureus* infective endocarditis (IE) is even higher and ranges from 19% to 65% [3–5]. In a large prospective study of SAB, 34% of cases developed 1 or more metastatic infections involving joints, kidneys, brain, bones, liver, spleen, or spine [6]. Therefore, timely diagnosis of IE in patients with SAB is critical as it has important implications regarding choice of antibiotic therapy, duration of treatment, and need for surgical intervention in patients with complicated IE.

Endocarditis may be either the primary source of SAB or a secondary metastatic complication resulting from hematogenous seeding of cardiac valves from an extracardiac

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infectious focus. Clinical manifestations of *S. aureus* IE are non-specific [7], and classic stigmata of IE are typically absent early in the course of infection. Transesophageal echocardiogram (TEE) is considered the imaging test of choice as it is superior to transthoracic echocardiogram (TTE) to evaluate for IE in adults, especially in the setting of prosthetic heart valves and implanted cardiac devices [8–13]. However, the evidence that TEE should be performed in every patient with SAB is limited [8, 14, 15]. TEE is an expensive and invasive test, is not readily available in all medical centers, and is performed in a fraction of patients with SAB in the usual course of patient care [16, 17].

The usefulness of TEE in SAB patients depends on the pretest probability of IE. The prevalence of IE among patients with SAB varies depending on the study population. While earlier investigations reported a wide range (5%–64%) of IE among SAB patients, more recent studies have reported 5%–17% prevalence [6, 18–22]. Therefore, while TEE is appropriate in patients with high likelihood of IE, it is probably not necessary for every patient with SAB. Recently, simple criteria to guide use of echocardiography were proposed [23–25]. However, a minority of patients in these studies underwent TEE. Our aim in this study was to develop a simple and easy-to-use clinical scoring system to guide use of TEE in the management of both community- and healthcare-associated SAB cases.

METHODS

Study Overview

All adults (age ≥ 18 years) hospitalized at our institution with SAB from July 2006 to June 2011 were included in the study. Cases of SAB were identified in the Department of Laboratory Medicine and Microbiology database. Demographic, microbiologic, echocardiographic, and follow-up (at least 12 weeks) data were collected. Patients who did not undergo TEE and for whom follow-up data at 12 weeks were unavailable were excluded from the analysis (Figure 1). Patients who did not undergo TEE but had 12-week follow-up were included. Patients who died or chose palliative care/hospice prior to diagnostic evaluation for IE were also excluded. Electronic medical records were reviewed to collect follow-up data for 12 weeks or longer. The Mayo Foundation Institutional Review Board approved the study.

Definitions

Cases of SAB were classified as nosocomial, healthcare associated, or community acquired, as defined by Friedman et al [26]. Nosocomial bacteremia was defined as positive blood culture result first obtained from patients who had been hospitalized for ≥ 48 hours. Healthcare-associated bacteremia was defined as a positive blood culture result obtained from a patient at the time of hospital admission or within 48 hours of admission if the patient (a) received intravenous therapy at home, received

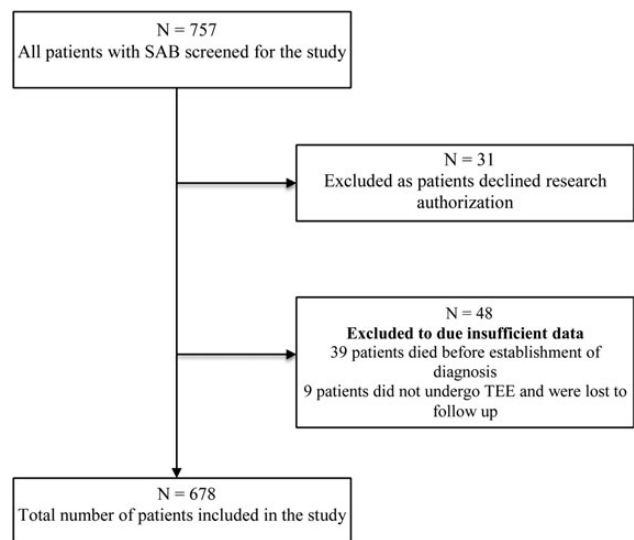


Figure 1. Study population. Figure shows total number of patients screened and those who were excluded from the study. Abbreviations: SAB, *Staphylococcus aureus* bacteremia; TEE, transesophageal echocardiogram.

wound care or specialized nursing care through a healthcare agency, or had intravenous medical therapy in the previous 30 days; patients whose only home therapy was oxygen use were excluded; (b) attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days; (c) was hospitalized in an acute care hospital for 2 days in the previous 90 days; or (d) resided in a nursing home or long-term care facility. Community-acquired bacteremia was defined as a positive blood culture result obtained at the time of hospital admission or within 48 hours after hospital admission. Prolonged bacteremia was defined as persistently positive blood cultures for ≥ 72 hours. IE was defined by modified Duke criteria [27]. Echocardiographic evidence of IE was defined as presence of an oscillating intracardiac mass, myocardial abscess, new valvular regurgitation, or new dehiscence of a prosthetic valve. Only patients who met the modified Duke criteria for definite endocarditis were included.

Statistical Methods

Model Derivation

Descriptive statistics on study variables are presented as median (range or interquartile range), mean (standard deviation [SD]), or frequency count (percentage), as appropriate. The associations between candidate risk factors and IE were measured using logistic regression and summarized with odds ratios and 95% confidence intervals. Each factor was screened for an association with IE via univariate logistic regression; those with an alpha level of 0.1 or less were carried forward in multivariable analyses. The multivariable logistic model was reduced to the most important risk factors using stepwise variable selection with backward elimination (alpha level of 0.05). Two-way

Table 1. Distribution of Candidate Variables for Overall *Staphylococcus aureus* Bacteremia Cohort and by Infective Endocarditis Status

Variable	Overall	IE	No IE	Univariate Association Odds Ratio (95% Confidence Interval) [P Value]
Baseline Variables	N = 678	N = 85	N = 593	
Age at baseline (yr)	64.8 ± 15.7	64.6 ± 17.9	64.9 ± 15.4	0.99 (.86, 1.14) [.879]
Male gender	442 (65%)	59 (69%)	383 (65%)	1.24 (.76, 2.03) [.383]
White ethnicity	648 (96%)	81 (95%)	567 (96%)	0.93 (.32, 2.73) [.893]
Onset of SAB				
Community	166 (24%)	36 (42%)	130 (22%)	2.34 (1.43, 3.83)
Healthcare	378 (56%)	40 (47%)	338 (57%)	1.0 (ref) [F test <i>P</i> < .001]
Nosocomial	134 (20%)	9 (11%)	125 (21%)	0.61 (.29, 1.29)
Duration of symptoms (d)				
0	292 (43%)	32 (38%)	260 (44%)	1.0 (ref) [F test <i>P</i> = .383]
1–3	210 (31%)	26 (31%)	184 (31%)	1.15 (.66, 1.99)
>3	176 (26%)	27 (32%)	149 (25%)	1.47 (.85, 2.55)
Hypotension at presentation	133 (20%)	22 (26%)	111 (19%)	1.52 (.89, 2.57) [.122]
Diabetes mellitus	250 (37%)	33 (39%)	217 (37%)	1.10 (.69, 1.75) [.690]
Hemodialysis dependent	80 (12%)	14 (16%)	66 (11%)	1.57 (.84, 2.95) [.156]
Central intravenous catheter prior to SAB	171 (25%)	16 (19%)	155 (26%)	0.66 (.37, 1.16) [.149]
Prosthetic joint	99 (15%)	17 (20%)	82 (14%)	1.56 (.87, 2.78) [.134]
Cardiac implantable electronic device				
Neither	594 (88%)	55 (65%)	539 (91%)	1.0 (ref) [F test <i>P</i> < .001]
Permanent pacemaker	49 (7%)	20 (24%)	29 (5%)	6.76 (3.59, 12.74)
Implantable cardioverter defibrillator	35 (5%)	10 (12%)	25 (4%)	3.92 (1.79, 8.59)
Prosthetic valve	43 (6%)	13 (15%)	30 (5%)	3.39 (1.69, 6.79) [<.001]
Prosthetic vascular graft	41 (6%)	5 (6%)	36 (6%)	0.97 (.37, 2.54) [.946]
Chronic Immunosuppressive therapy	158 (23%)	8 (9%)	150 (25%)	0.31 (.14, .65) [.002]
Intravenous drug use	15 (2%)	5 (6%)	10 (2%)	3.64 (1.21, 10.93) [.021]
Recent <i>Staphylococcus aureus</i> infections	34 (5%)	9 (11%)	25 (4%)	2.69 (1.21, 5.98) [.015]
Deep-seated abscesses	165 (24%)	12 (14%)	153 (26%)	0.47 (.25, .89) [.021]
Skin/skin structure infection	185 (27%)	13 (15%)	172 (29%)	0.44 (.24, .82) [.009]
Antibiotic duration (d) ^a	(N = 632)	28.0 (14.0, 42.0)	28.0 (14.0, 42.0)	42.0 (42.0, 42.0)
Underwent TEE within 12 wk	482 (71%)	83/85 (98%)	399 / 593 (67%)	
Time to first TEE (d) ^a	(N = 482)	4.0 (3.0, 6.0)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)
Cases that underwent TEE within first 5 d		351 (52%)	293 / 593 (49%)	58 / 85 (68%)
Timing of first TEE among those tested (d)	(N = 482)			
≤5		351 (73%)	293 / 399 (73%)	58 / 83 (70%)
>5		131 (27%)	106 / 399 (27%)	25 / 83 (30%)
Day 5 Variable	(N = 662)	N = 83	N = 579	
Prolonged bacteremia (≥72 h)	323 (49%)	68 (82%)	255 (44%)	5.76 (3.22, 10.32) [<.001]

Effects for all variables tested in univariable logistic regression models.

Abbreviations: IE, infective endocarditis; SAB, *Staphylococcus aureus* bacteremia; TEE, transesophageal echocardiogram.

^a Median (interquartile range).

interactions between candidate risk factors were also tested for importance. The day 1 scoring model was derived based on the modeling steps listed above using baseline risk factors available at the time of diagnosis. Excluding a small minority of patients who were lost to short-term follow-up, the algorithm was then repeated to derive a second scoring system, day 5, that incorporated “prolonged bacteremia.”

Model Validation

We internally validated the fit and performance of both final models using the bootstrap method with 400 resamples. In a given resample, a new set of patients is randomly sampled (with replacement) from the original set, on whom a new model is fit using the same stepwise criteria. The model derived on each bootstrap resample was then tested on the original set of

patients, as the difference in performance (eg, c-statistic) between this bootstrap and the test model provides a sense of overfitting in the original model selection. For both final models, we estimated the bias due to overfitting, or “optimism,” and recalculated the c-statistic correcting for this bias. A detailed description of this statistical methodology is provided in the [Supplementary Material](#).

Risk Stratification

From the final models, regression coefficients were used to derive the 2 separate risk scores for predicting IE. In particular, points were assigned for each risk factor in the model and weighted approximately by the respective regression coefficients. For optimal scoring, regression coefficients were rescaled by first dividing by the minimum absolute value among all coefficients and then multiplying each rescaled coefficient by a constant (such as 2 or 3, choosing the one producing the most optimal weighting scheme), and finally rounding the rescaled values to the nearest integer. Using these point values, a patient’s risk score was simply computed as the aggregate number of points from his or her risk factor profile.

RESULTS

Study Population

A total of 757 patients with SAB were hospitalized at Mayo Clinic Rochester from July 2006 to June 2011. Thirty-one patients were excluded as they had declined research authorization; 48 patients were excluded due to insufficient data (Figure 1); 39 patients died during the follow-up period before evidence of IE could be established; 9 patients did not undergo TEE and were lost to follow-up; and 678 individuals with SAB (24% community onset, 56% healthcare associated, and 20% nosocomial) who met the study criteria were included in the final analysis. Baseline characteristics are summarized in Table 1. The majority of patients were male (65%) and mean age (SD) was 64.8 (5.7) years. Twelve percent of the patients had a cardiovascular implantable electronic device (CIED). Of these, 7% were permanent pacemakers (PPMs) and 5% were implantable cardioverter defibrillators (ICDs). Only 6% of patients had a prosthetic heart valve. Thirty-nine percent of the *S. aureus* isolates were methicillin resistant.

Overall, 71% of the patients underwent TEE within 12 weeks of SAB diagnosis. In 68% of patients, TEE was performed

Table 2. Risk Factors for Infective Endocarditis and Development of Infective Endocarditis Risk Scores

Model/Variable	Multivariable Result Odds Ratio (95% Confidence Interval) [P Value]	β	β'	$c \times \beta'$	Points [^]
Day 1 Model				$c = 2$	
CIED					
ICD	4.58 (2.03, 10.35) [$<.001$]	1.52	1.00	2.00	2
PPM	7.94 (4.08, 15.44) [$<.001$]	2.07	1.36	2.72	3
Neither	1.0 (reference)	0
Onset of SAB					
Community	5.01 (2.22, 11.31) [$<.001$]	1.61	1.06	2.12	2
Healthcare	1.91 (.87, 4.19) [.104]	0.65	0.43	0.85	1
Nosocomial	1.0 (reference)	0
Model C Statistic	0.723				Score = \sum Points
Bias-Corrected C Statistic	0.693				Range, 0–5
Day 5 Model				$c = 2$	
CIED					
ICD	5.00 (2.09, 11.94) [$<.001$]	1.61	1.20	2.40	2
PPM	8.60 (4.18, 17.67) [$<.001$]	2.15	1.60	3.21	3
Neither	1.0 (reference)	0
Onset of SAB					
Community	3.83 (1.64, 8.96) [.002]	1.34	1.00	2.00	2
Healthcare	1.79 (.80, 4.03) [.159]	0.58	0.43	0.87	1
Nosocomial	1.0 (reference)	0
Prolonged bacteremia (≥ 72 h)	5.23 (2.85, 9.61) [$<.001$]	1.65	1.23	2.47	2
Model C Statistic	0.792				Score = \sum Points
Bias-Corrected C Statistic	0.761				Range, 0–7

Abbreviations: CIED, cardiovascular implantable electronic device; ICD, implantable cardioverter defibrillator; PPM, permanent pacemaker; SAB, *Staphylococcus aureus* bacteremia.

Table 3. Test Performance Characteristics of Two Independent Infective Endocarditis Risk Prediction Models

Risk Score	Sensitivity (%)	Specificity (%)	False-Positive Rate (%)	False-Negative Rate (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Day 1 Score \geq						
High Risk 5	9.4	99.5	0.5	90.6	72.7	88.5
↑ 4 ^a	21.2	95.6	4.4	78.8	40.9	89.4
3	35.3	92.4	7.6	64.7	40.0	90.9
2 ^b	64.7	70.2	29.8	35.3	23.7	93.3
↓ 1	95.3	18.4	81.6	4.7	14.3	96.5
Low Risk 0	100	0.0	100	0.0	12.5	...
Day 5 Score \geq						
High Risk 7	7.2	99.7	0.3	92.8	75.0	88.2
↑ 6	19.3	97.9	2.1	80.7	57.1	89.4
5	30.1	96.7	3.3	69.9	56.8	90.6
4	54.2	83.1	16.9	45.8	31.5	92.7
3 ^b	86.7	59.2	40.8	13.3	23.4	96.9
2 ^c	94.0	41.1	58.9	6.0	18.6	97.9
↓ 1	98.8	11.4	88.6	1.2	13.8	98.5
Low Risk 0	100	0.0	100	0.0	12.5	...

^a A stringent day 1 score ≥ 4 for screening would have resulted in 44 patients tested, in whom 18 (positive predictive value [PPV] 40.9%) had endocarditis (567 of the 634 not tested did not have endocarditis negative predictive value [NPV] 89.4%), leaving 67 endocarditis cases that would not have been tested.

^b Cutpoint from receiver-operating characteristic curve analysis that jointly optimizes sensitivity and specificity.

^c A conservative day 5 score ≥ 2 for screening would have resulted in 419 patients tested, in whom 78 (PPV 18.6%) had endocarditis (238 of the 243 not tested did not have endocarditis [NPV 97.7%]), leaving only 5 endocarditis cases that would have been missed.

within 14 days after first blood culture. A total of 85 patients (13%) fulfilled the modified Duke criteria for definite IE, of whom 56 (66%) had native valve endocarditis, 13 (15%) had prosthetic valve IE, and 25 (29%) had endocarditis related to a CIED. These included 8 (9%) patients with ICD-related IE and 17 (20%) with PPM-related IE. The proportion of patients with IE was 22% in community-acquired SAB, 11% in community-acquired healthcare-associated SAB, and 7% in nosocomial SAB. The proportion with IE was 18% in patients with hemodialysis, 30% in patients with prosthetic heart valves, 41% in patients with PPMs, 29% in patients with ICDs, and 21% in those with prolonged bacteremia lasting longer than 72 hours.

Model Derivation

Two scoring systems were derived for the clinical purpose of risk stratification at 2 time points: day 1 score (SAB diagnosis day) and day 5 score. Among the baseline factors identified from univariable screening and carried forward into multivariable modeling, the following were selected in the original model fit and corresponded to increased risk of IE: onset of SAB, CIED, prior intravenous drug abuse (IVDA), recent *S. aureus* infection, and absence of a skin or surgical site as a source of infection (Table 1). However, based on internal validation of the model fit via bootstrap resampling, only onset of SAB and CIED were deemed robust predictors of IE. To derive the day 5 model, the effect of prolonged bacteremia, along with baseline

variables, was assessed for 662 patients with SAB (7 patients who died within 5 days of an SAB diagnosis and 9 patients who lacked a negative culture were excluded). Prolonged bacteremia was found to be predictive of IE in the original sample and was internally validated as a predictor after being selected in 100% of the bootstrap models. The final day 5 model therefore included onset of SAB, presence of CIED, and prolonged bacteremia.

Risk Stratification

On the basis of final day 1 and day 5 models, regression coefficients were used to derive 2 risk scores for predicting IE in patients hospitalized for SAB. Points were assigned for each risk factor, weighted in magnitude by the corresponding regression coefficients, and summed together to define an individual's risk score (Table 2).

DISCUSSION

There is limited evidence regarding optimal use of TEE in patients with SAB to evaluate for underlying IE (Table 4). While some studies have suggested that TEE is dispensable in patients with uncomplicated SAB [23–25], these studies focused on nosocomial SAB and <30% of cohorts had TEE performed, increasing the risk of verification bias. Considering that patients with sustained bacteremia (>72 hours) in these studies received

Table 4. Key Studies Evaluating the Role of Transesophageal Echocardiography in Patients With *Staphylococcus aureus* Bacteremia

Study	Study Period	Study Design	No. of Patients	Study Findings/Conclusion	IE (%)	Comments
Joseph et al [25]	2006–2011	Retrospective study of all cases of SAB	306	Patients with underlying prosthetic intracardiac material were higher risk of IE; authors concluded the cardiac imaging should be prioritized to high-risk patients	10.1	Of 668 eligible patients with SAB, only 82 (12.7%) underwent TEE
Khatib and Sharma [24]	2002–2009	Included patients from 3 previous prospective observational studies (2002–2003, 2005–2006, 2008–2009)	379	Authors concluded that TEE is dispensable in patients with uncomplicated SAB	7.3	498 of 877 eligible patients (57%) did not undergo echocardiography (TTE or TEE) and were excluded; of 877 eligible patients with SAB, only 177 (20%) underwent TEE
Incani et al [7]	1998–2006	Retrospective study of all adult patients who were hospitalized with SAB and underwent TEE	144	46% of IE patients were not suspected to have IE based on clinical findings alone; authors concluded that TEE is indicated in all patients with SAB as clinical findings are not sensitive	29	83% of eligible patients underwent TEE and were included in the study
Rasmussen et al [28]	2009–2010	Prospective observational study of SAB patients	244	Noted high rates of IE; clinical symptoms and findings were noted to be insensitive and nonspecific; authors concluded that echocardiography should always be considered in early evaluation of patients with SAB	22	Limited by selection bias; 92 eligible patients (27%) did not undergo echocardiography (TTE or TEE) and were excluded; 62% of study patients underwent TEE
Kaasch et al [23]	1994–2009	Post hoc analysis of 2 prospective SAB cohorts (INSTINCT and SABG)	736 nosocomial	TEE may not be required in a subset of low-risk nosocomial SAB patients identified by using a simple criteria set	4.3 (INSTINCT) 9.3 (SABG)	Only 18.5% of INSTINCT and 27.6% of SABG cohorts underwent TEE; included only nosocomial SAB
Van Hal et al [29]	1996–2000	Retrospective study of patients who underwent both TTE and TEE	125	TEE may not be required in a subgroup of low-risk SAB patients if TTE is normal and there are no embolic signs	18	Of 808 eligible patients with SAB, 641 (79%) had no TEE and were excluded; limited by sampling bias; excluded patients with prosthetic valves, annuloplasty rings, implantable cardioverter defibrillator, or permanent pacemaker
Abraham et al [15]	1999–2002	Retrospective review of SAB cases who were referred for either TTE or TEE	104	Noted high rates of endocarditis; SAB patients should be aggressively evaluated for endocarditis	31.7	Limited by referral bias as only patients with high pretest clinical probability were likely referred for echocardiography
Fowler et al [8]	1994–1996	Prospective study of SAB patients who underwent both TTE and TEE	103	Only 7% of patients had clinical evidence of IE; sensitivity of TTE was only 32%; TEE had 100% sensitivity as none met Duke criteria for definite IE without positive TEE; authors concluded that TEE should be considered in early evaluation of patients with SAB	25.2	Only 59% of eligible patients with SAB underwent both TTE and TEE; limited by sampling bias as physicians tended to refer patients with higher likelihood of IE for TEE

Abbreviations: IE, infective endocarditis; INSTINCT, invasive *Staphylococcus aureus* infection cohort; SAB, *Staphylococcus aureus* bacteremia; SABG, *Staphylococcus aureus* bacteremia group; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

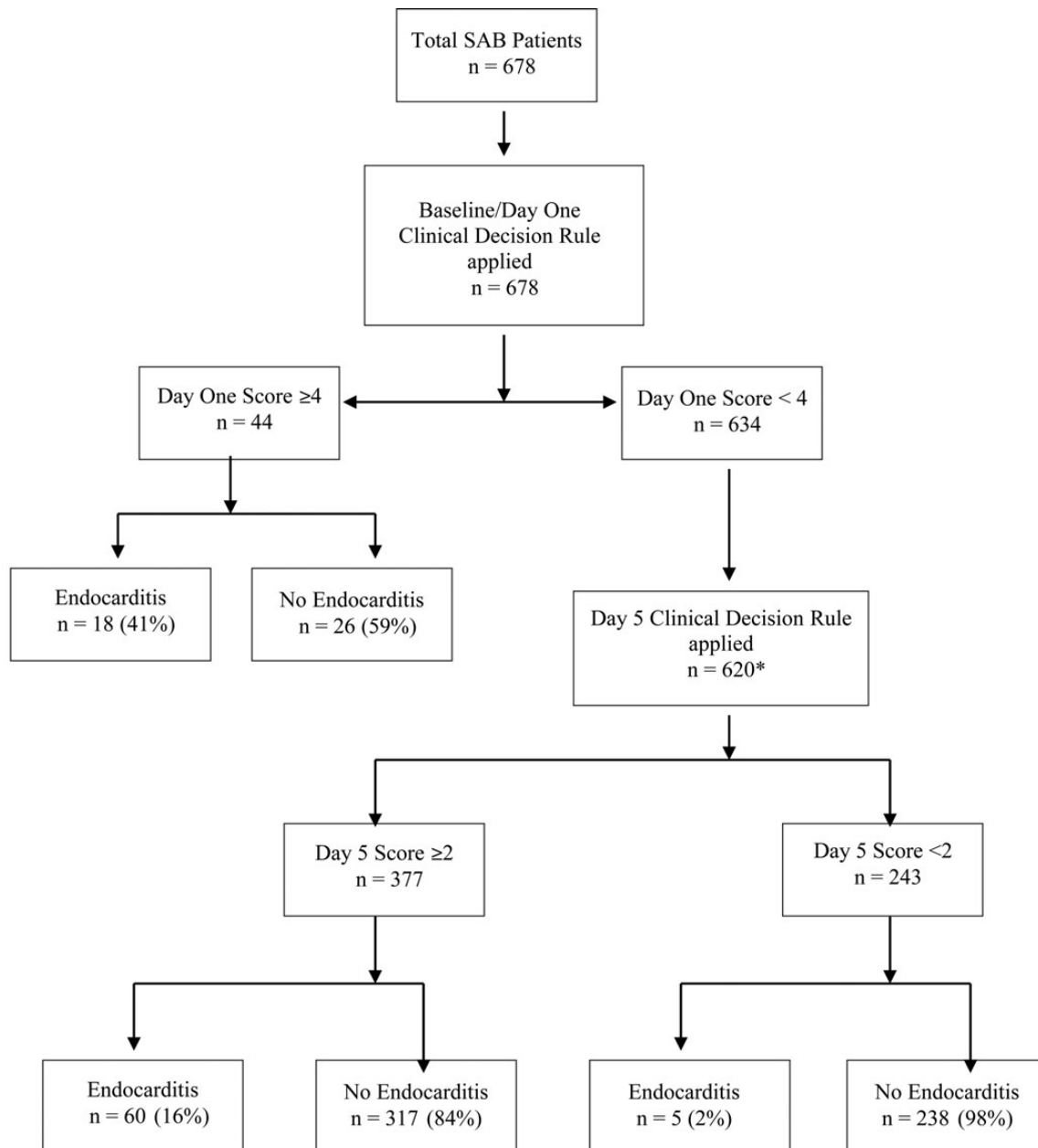


Figure 2. A hypothetical application of 2-stage screening strategy on our study cohort. *Day 5 score was applied only on 620 patients in this hypothetical scenario. Fourteen patients either died or did not have follow up blood cultures. Abbreviation: SAB, *Staphylococcus aureus* bacteremia.

prolonged (3–4 weeks) courses of antimicrobial therapy, it is conceivable that some patients with endocarditis were cured without an IE diagnosis being secured.

The current investigation is one of the largest studies to assess the role of TEE in patients with SAB in which the majority (68% underwent TEE within 14 days, 71% underwent TEE within 12 weeks) of patients underwent TEE, decreasing the risk of verification bias and therefore a low likelihood of missing IE. Based on the results of the multivariable analysis, we propose 2 scoring

systems to predict the risk of IE and, thus, the need for TEE on SAB diagnosis day (day 1) and when prolonged bacteremia is documented (day 5).

In the multivariable analysis, community-acquired SAB, presence of CIED or prosthetic heart valve, and prolonged bacteremia were independently associated with IE in patients with SAB. This is congruent with earlier publications aimed at identifying risk factors of complicated SAB [15, 19, 30–35]. For the day 1 risk score (range, 0–5), screening individuals with a score of 2 or

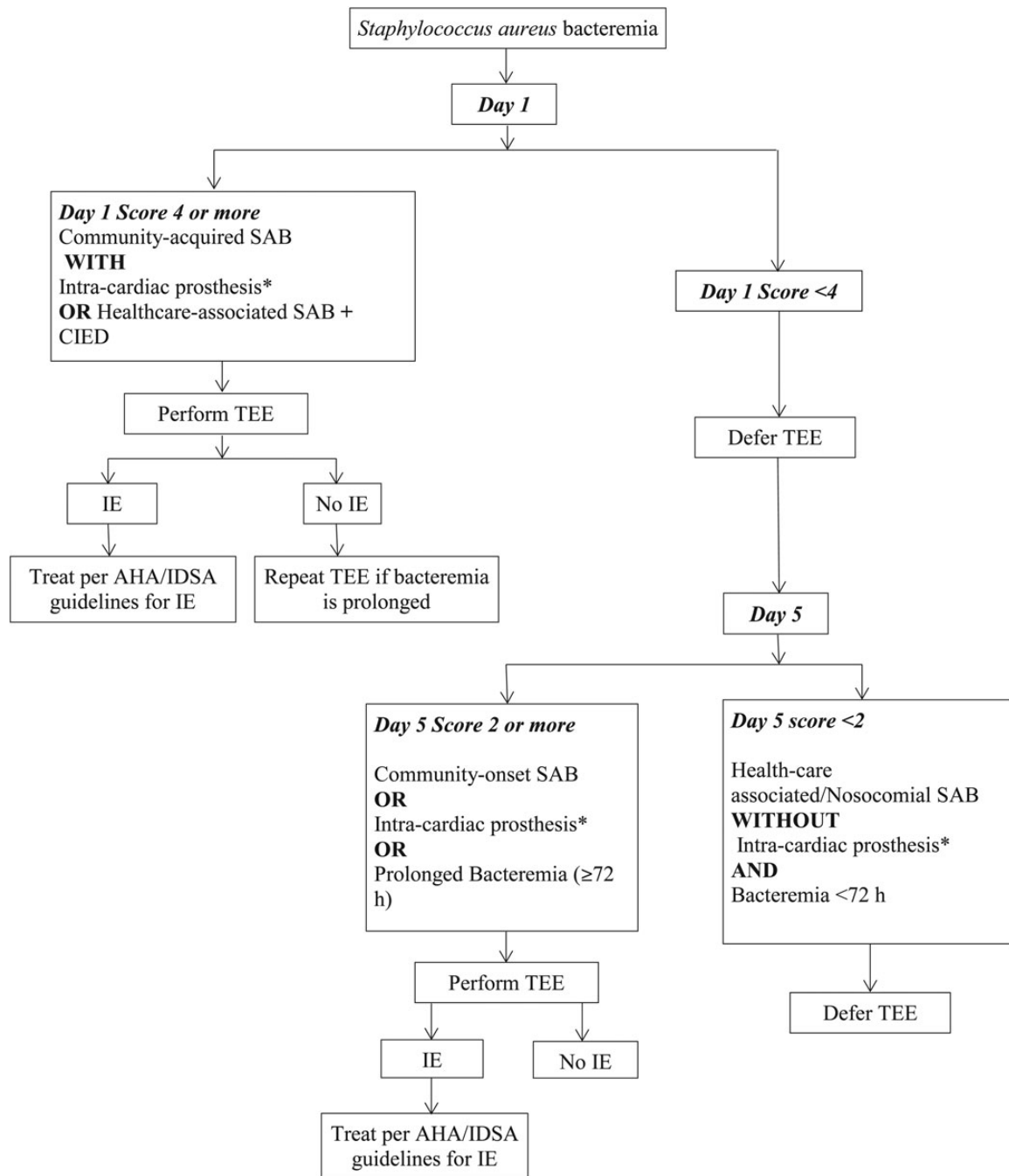


Figure 3. Proposed algorithm for optimal use of transesophageal echocardiogram (TEE) in patients with *Staphylococcus aureus* bacteremia (SAB). *Intracardiac prosthesis: Implantable cardioverter-defibrillator, permanent pacemaker, prosthetic heart valve. Abbreviations: AHA, American Heart Association; CIED, cardiovascular implantable electronic device; IE, infective endocarditis; IDSA, Infectious Diseases Society of America.

higher was the optimal threshold in terms of both sensitivity and specificity (65% and 70%, respectively). Choosing a higher cutoff value to target high-risk patients would improve specificity but at the expense of reduced sensitivity. For example, a screening cutoff of ≥ 4 would have selected 44 patients for TEE and correctly excluded a very high proportion of those without IE (specificity,

96%), while yielding only a small percentage of IE cases (sensitivity, 21%). Using the day 5 score (range 0–7) to inform an independent screening decision (assuming low-risk patients are not screened for IE based on the day 1 risk score), a cutpoint of ROC (receiver-operating characteristic curve) ≥ 3 had optimal diagnostic power based jointly on sensitivity and specificity (87%

Table 5. Clinical Characteristics of 5 Patients With Low Risk Score but Diagnosed With Infective Endocarditis

Patient Number	Age (yr)	Sex	Day 5 Risk Score	Onset of SAB	Intracardiac Prosthesis	Duration of SAB (d)	Comments
1	67	M	1	Community onset, healthcare associated	None	1	TEE showed right atrial mass/thrombus; treated as possible infected thrombus with 42 d of intravenous antibiotics
2	73	M	0	Nosocomial	Prosthetic valve, recent mitral valve replacement	2	Acute prosthetic valve endocarditis; patient had skin manifestations of IE (prosthetic valve is included as high-risk category in our revised algorithm)
3	88	M	1	Community onset, healthcare associated	None	2	Recent hip surgery with acute septic arthritis and secondary bacteremia; TEE was positive for vegetation
4	29	F	1	Community onset, healthcare associated	Prosthetic valve; recent tricuspid valve replacement	3	Acute prosthetic valve endocarditis; patient had skin manifestations of IE
5	61	M	1	Community onset, healthcare associated	None	1	Chemotherapy-induced neutropenia; patient had SAB recurrence on day 49 of follow-up; TEE revealed possible vegetation on aortic valve

Abbreviations: IE, infective endocarditis; SAB, *Staphylococcus aureus* bacteremia; TEE, transesophageal echocardiogram.

and 59%, respectively) with equal weight. Opting for a risk score more preferential to sensitivity, such as a score ≥ 2 , would ensure that a higher proportion of all IE cases (sensitivity, 94%) are identified, although with a trade-off cost of increased TEE screening (specificity, 41%).

We propose a 2-stage screening strategy that combines the predictive values of day 1 and day 5 risk scores. The first stage (day 1 risk score) should be used to identify patients at highest risk of IE. Patients who have a high risk score on day 1 screening, such as ≥ 4 , should undergo TEE soon after SAB is diagnosed as early detection of IE in high-risk patients may have therapeutic implications such as choice of antibiotic therapy (combination therapy if prosthetic valve IE is present) and need for surgical intervention (if indications for surgery, such as myocardial abscess, valve perforation, infected CIED, are present). This high-risk group includes patients with underlying implantable cardiac devices who develop community-onset SAB. If the initial TEE is negative for evidence of IE in this high-risk group, then they should be reevaluated with repeat TEE if bacteremia is prolonged. Repeat TEE was performed in 88 patients in our study cohort. In 5 patients whose initial TEE was negative, repeat TEE showed evidence of endocarditis. Patients with low risk score (eg, < 4) on day 1 should be reassessed on day 5. For day 5 risk score, we favor a cutoff with very high negative predictive value, given the high mortality rate associated with IE, and defer TEE only in those with a very low likelihood of IE. For day 5, we suggest a risk score cutoff of < 2 as it had a sensitivity of 98.8% and negative predictive value of 98.5%. Patients with either community-acquired SAB or prolonged bacteremia (≥ 72 hours) or those with underlying CIED will have day 5 scores ≥ 2 and should be evaluated with

TEE. Although a significant risk factor in the modeling, prosthetic heart valve did not meet the more stringent criteria for inclusion in the scoring tool; this is possibly due to the small number of patients with prosthetic heart valves in our study cohort (6%). However, 2 of the 5 IE cases deemed as low risk by the scoring system had a prosthetic valve in place. Therefore, we have added patients with prosthetic heart valves to the high-risk category in our proposed decision-making algorithm (Figure 3).

Strict application of the proposed scoring system to guide TEE use would have resulted in missing 5 IE cases in our SAB study cohort. Therefore, clinicians should not be discouraged from obtaining TEE if there is a strong clinical suspicion of IE in a given case, even if a patient does not meet scoring criteria. Table 5 includes the clinical characteristics of these 5 patients. As described above, 2 of the 5 patients had an underlying prosthetic heart valve, and we have added prosthetic valve to the high-risk category in our proposed algorithm. Moreover, all patients should have close clinical follow-up for at least 12 weeks to detect relapse or metastatic complications. In patients with recurrence or relapse of SAB, TEE should be done, regardless of initial clinical risk scoring and prior echocardiographic findings. Based on our classification scheme (Figures 2 and 3), more than one-third of SAB patients could be managed without performing TEE.

In our study, 131 patients underwent both TTE and TEE within 14 days after first positive blood culture, of whom 41 patients were diagnosed with IE. TEE was positive in 85% of IE (35/41) and TTE was positive in only 34% (14/41). These data are consistent with data from several earlier studies that suggest the sensitivity of TEE is much higher than that of TTE. TEE is the imaging modality of choice to evaluate for IE in patients with SAB.

Our study has several limitations, primarily due to its retrospective design. The decision to obtain TEE and its timing was at the discretion of the attending physician, and the median time to perform TEE was 4 days from the date of first positive blood culture. Therefore, it can be argued that some patients who underwent testing within 48 hours of SAB diagnosis but had prolonged bacteremia may have had a false-negative result for IE because testing at this stage may have missed evolving endocarditis. However, lack of relapse of SAB during the 12-week follow-up period suggests that these were likely true negative results. Because our cohort included few patients with IVDA as a risk factor for IE, our findings may not be applicable to this subset of higher-risk patients. The median duration of antibiotic therapy in those without IE was 28 days. The longer duration of antibiotics in non-IE patients is likely due to a higher complexity of cases in our tertiary referral center. It is possible that some patients with IE were undiagnosed but received longer antibiotic course. However, 71% of patients underwent TEE, hence the likelihood of unrecognized but treated IE is low. Also, due to variable duration of antimicrobial therapy in low-risk patients in our study cohort, it is unclear if a shorter course (2 weeks) of antimicrobial therapy is adequate, especially if an echocardiogram is deferred. Prospective studies are needed to further validate the scoring system and to address the question of antibiotic duration.

Overall, our study findings suggest that the risk of IE in individuals with SAB can be estimated using a simple scoring system that utilizes 2 elements of clinical history (onset of SAB and presence of CIED) and duration of bacteremia. We propose a 2-stage screening strategy to be applied on the day of SAB diagnosis (day 1) and when results of day 3 blood cultures are available (day 5) to help guide the optimal use of TEE.

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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