# Use of a Simple Criteria Set for Guiding Echocardiography in Nosocomial *Staphylococcus aureus* Bacteremia

**Achim J. Kaasch,**[1] **Vance G. Fowler Jr.,**[5] **Siegbert Rieg,**[4] **Gabriele Peyerl-Hoffmann,**[4] **Hanna Birkholz,**[2] **Martin Hellmich,**[3] **Winfried V. Kern,**[4] **and Harald Seifert**[1]

[1]Institute for Medical Microbiology, Immunology and Hygiene, [2]Clinical Trials Center, and [3]Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne, [4]Center for Infectious Diseases and Travel Medicine, Department of Medicine, University Hospital of Freiburg, Freiburg, Germany, [5]Department of Medicine, Duke University Durham, North Carolina

(See the editorial commentary by Soriano and Mensa, on pages 10–12.)

***Background.*** Infective endocarditis (IE) is a severe complication in patients with nosocomial *Staphylococcus aureus* bacteremia (SAB). We sought to develop and validate criteria to identify patients at low risk for the development of IE in whom transesophageal echocardiography (TEE) might be dispensable.

***Methods.*** Consecutive patients with nosocomial SAB from independent cohorts in Europe (Invasive *S. aureus* Infection Cohort [INSTINCT]) and North America (*S. aureus* Bacteremia Group [SABG]) were evaluated for the presence of clinical criteria predicting an increased risk for the development of IE (ie, prolonged bacteremia of >4 days' duration, presence of a permanent intracardiac device, hemodialysis dependency, spinal infection, and nonvertebral osteomyelitis). Patients were observed closely for clinical signs and symptoms of IE during hospitalization and a 3-month follow-up period.

***Results.*** IE was present in 13 (4.3%) of 304 patients in the INSTINCT cohort and in 40 (9.3%) of 432 patients in the SABG cohort. Within 14 days after the first positive blood culture result, echocardiography was performed in 39.8% and 57.4% of patients in the INSTINCT and  SABG cohorts, respectively. In patients with IE, the most common clinical prediction criteria present were prolonged bacteremia (69.2% vs 90% for INSTINCT vs SABG, respectively) and presence of a permanent intracardiac device (53.8% vs 32.5%). In total, 13 of 13 patients in the INSTINCT cohort and 39 of 40 patients in the SABG cohort with documented IE fulfilled at least 1 criterion (sensitivity, 100% vs. 97.5%; negative predictive value, 100% vs 99.2%).

***Conclusions.*** A simple criteria set for patients with nosocomial SAB can identify patients at low risk of IE. Patients who meet these criteria may not routinely require TEE.

*Staphylococcus aureus* is the second most common cause of nosocomial bloodstream infection (BSI) worldwide [1, 2]. It differs from other bacterial pathogens by its propensity to cause deep-seated infections as well as metastatic infections at distant sites. Identifying the focus of infection in *S. aureus* bacteremia (SAB) can be a considerable challenge. Even after an extensive diagnostic evaluation, a focus of infection is ascertained in only 60%–80% of cases [3–6]. However, recommendations on which diagnostic procedures (eg, echocardiography and other imaging techniques) are needed to identify the source of infection and when they should be performed is based on evidence from a few studies [7–9].

Infective endocarditis (IE) can be the source of bacteremia at admission or a secondary complication of SAB occurring either during hospitalization or within weeks or months after discharge. In recent studies, IE

occurred in 5%–17% of patients with SAB [5, 10–12]. Despite advances in imaging techniques, transthoracic echocardiography (TTE) is considered to be less sensitive than transesophageal echocardiography (TEE) for detection of vegetations on heart valves [13]. It has been suggested TEE should be performed routinely for all patients with SAB to exclude IE early in the course of the infection [8, 14–17].

In some clinical scenarios such as SAB with negative follow-up blood culture results, a removable focus of infection, and rapid clinical resolution ≤72 h after initiation of therapy in the absence of indwelling prosthetic devices (similar to simple SAB as defined in [18]), IE is unlikely to occur. To identify patients with nosocomial SAB who have a low risk for developing IE and for whom TEE may not be required, we propose simple clinical prediction criteria. Diagnostic accuracy of the criteria set was evaluated using data from a cohort of patients with SAB in Europe (Invasive *S. aureus* Infection Cohort [INSTINCT]) and North America (*S. aureus* Bacteremia Group [SABG]).

## METHODS

### Patients and Setting

Data was analyzed post hoc from 2 prospective cohort studies that were performed to investigate the epidemiology of SAB. Partial data from both studies have been published elsewhere [6, 12]. The INSTINCT study was conducted at 2 German tertiary care university hospitals in Cologne and Freiburg that have ~45,000 and ~59,000 annual admissions, respectively. The SABG study was conducted at Duke University (Durham, NC), a tertiary care hospital with 63,000 annual admissions. An infectious diseases (ID) consultation service was available throughout the study period in all centers.

Blood culture results were reviewed daily. Patients aged ≥18 years with nosocomial SAB who had ≥1 blood culture positive for *S. aureus* were included in the study.

### Ethical Considerations

The study was approved by the respective institutional review boards. We followed the ethical standards set by the Helsinki Declaration of 1975, as revised in 2004, and the research guidelines of Duke University, the University of Cologne, and the University of Freiburg.

### Data Acquisition

Patients with SAB were evaluated prospectively during their hospital stays for the source of infection, complicating factors (eg, the presence of prosthetic heart valves, vascular implants, or pacemakers), hemodialysis dependency, clinical signs of IE, early complications of SAB, duration of hospital stay, discharge date and status, and cause of death. Furthermore, the time and number of blood cultures obtained and the results of diagnostic

imaging studies were recorded. SAB was considered nosocomial if clinical symptoms developed ≥48 h after hospital admission [19]. The source of bacteremia was defined as the most likely source responsible for the first positive blood culture result on the basis of clinical signs, microbiological findings, and imaging results. Definite IE was assessed in accordance with modified Duke criteria [20]. TEE was encouraged by the ID consultation service and performed at the discretion of the attending physician by an experienced echocardiographer.

Follow-up data were obtained 3 months after the first positive blood culture result and used as reference standard for the possible development of IE after discharge. In particular, the presence of fever at any time during the observation period, antimicrobial therapy, signs and symptoms of late complications of SAB (eg, recurrent bacteremia, endocarditis, and osteomyelitis), and any new hospital admission were either determined by telephone interview with the patient and/or his primary care physician or when the patient was readmitted. If patients were admitted to another hospital, detailed information about their clinical course was obtained. All data were collected prospectively by a trained study nurse and validated by an ID physician. IE was excluded if there were no clinical (including stroke and heart failure), microbiological, and imaging data that suggested a diagnosis of IE.

### Criteria Set

The clinical prediction criteria included prolonged bacteremia, the presence of a permanent intracardiac device (eg, a prosthetic heart valve, pacemaker, or cardioverter-defibrillator), hemodialysis dependency, spinal infection (eg, vertebral osteomyelitis, epidural, subdural or intraspinal empyema, or abscess), and nonvertebral osteomyelitis. Irrespective of the timing and appropriateness of antimicrobial therapy, SAB was considered prolonged if >4 days elapsed between the first blood culture to yield *S. aureus* and the first negative follow-up blood culture result or if follow-up blood cultures were not performed. In this group, prolonged bacteremia was considered "documented" if follow-up blood cultures yielded *S. aureus* 2–4 days after the first positive blood culture result [12]. Cases in which no follow-up blood cultures were performed within 4 days were considered to represent "possible" prolonged bacteremia.

### Statistical Analysis

Descriptive statistics include counts and percentages for qualitative variables and quartiles (25th, 50th, and 75th percentile) for quantitative data. The 2-sided Fisher exact test was used to assess the association of qualitative variables. Estimates of conditional probability (eg, sensitivity and specificity) were accompanied by 95% confidence intervals (CIs; determined by the Wilson method). Because age data for the SABG cohort were provided in decades, quartiles were calculated using mid-class

values. The study is reported according to STARD (Statement for Reporting Diagnostic Accuracy Studies) [21].

## RESULTS

From 1 January 2006 to 30 June 2009, 572 consecutive patients with SAB were included in the INSTINCT study. Of these, SAB was considered nosocomial in 309 patients (54%). The SABG study recruited 1403 patients with SAB from 26 October 1994 to 30 December 2009; of these, 459 patients (32.7%) had nosocomial SAB. A total of 304 and 432 patients in the INSTINCT and SABG cohorts with complete data sets were included in additional analysis (Figures 1 and 2).

Age, source of infection, and 30-day and 90-day case-fatality rates were remarkably similar between the 2 cohorts (Table 1). Female sex was less prevalent in the INSTINCT cohort than in the SABG cohorts (33.9% vs 44.7%), and patients in the INSTINCT study were ethnically more homogenous (in the INSTINCT cohort, 97% of patients were white and 3% were ''other''; in the SABG cohort, 67% of patients were white, 28% were black, and 5% were ''other''). The rate of methicillin-resistant *S. aureus* (MRSA) was much higher in the US cohort, among both patients with IE (80% vs 7.7%) and patients without IE (64.3% vs 15.8 %).

Within 14 days after the first positive blood culture result, echocardiography (TTE or TEE) was performed in 121 patients (39.8%) in the INSTINCT cohort and in 248 patients (57.4%) in the SABG cohort. Although echocardiography was strongly encouraged for all patients with SAB, the remaining patients either were discharged, were transferred, or died before an echocardiogram could be performed or the attending physician refused to initiate echocardiography. Follow-up blood cultures were obtained ≤4 days after the first positive blood culture result in 171 patients (56.2%) in the INSTINCT cohort and 291 patients (67.4%) in the SABG cohort.

Infective endocarditis was found in 13 (4.3%) and 40 patients (9.3%) in the INSTINCT and SABG cohorts, respectively. In all patients with documented IE in the INSTINCT cohort, the diagnosis was established during hospitalization, and no additional patient developed IE during the follow-up period. All cases of IE were confirmed by echocardiography, which was performed a median of 6 days (range, 1–25 days) after the first positive blood culture result. The mitral (5 patients [38.5%]) and aortic valves (4 patients [30.8%]) were the most frequently affected sites; there was 1 case (7.7%) of tricuspid valve endocarditis, and 1 patient had 2 valves affected; there were 3 cases (23.1%) of pacemaker lead infections and 1 case (7.7%) of mural endocarditis. Four cases (30.8%) were prosthetic valve
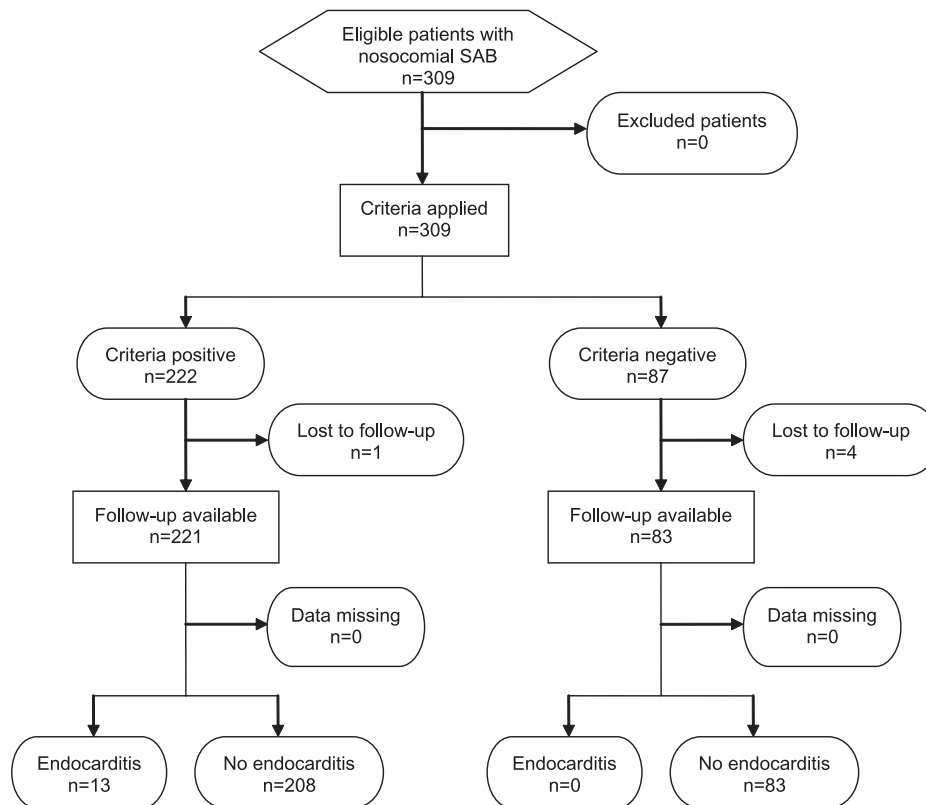


**Figure 1.** Flow diagram of patients recruited in the Invasive *S. aureus* Infection Cohort (INSTINCT) cohort.
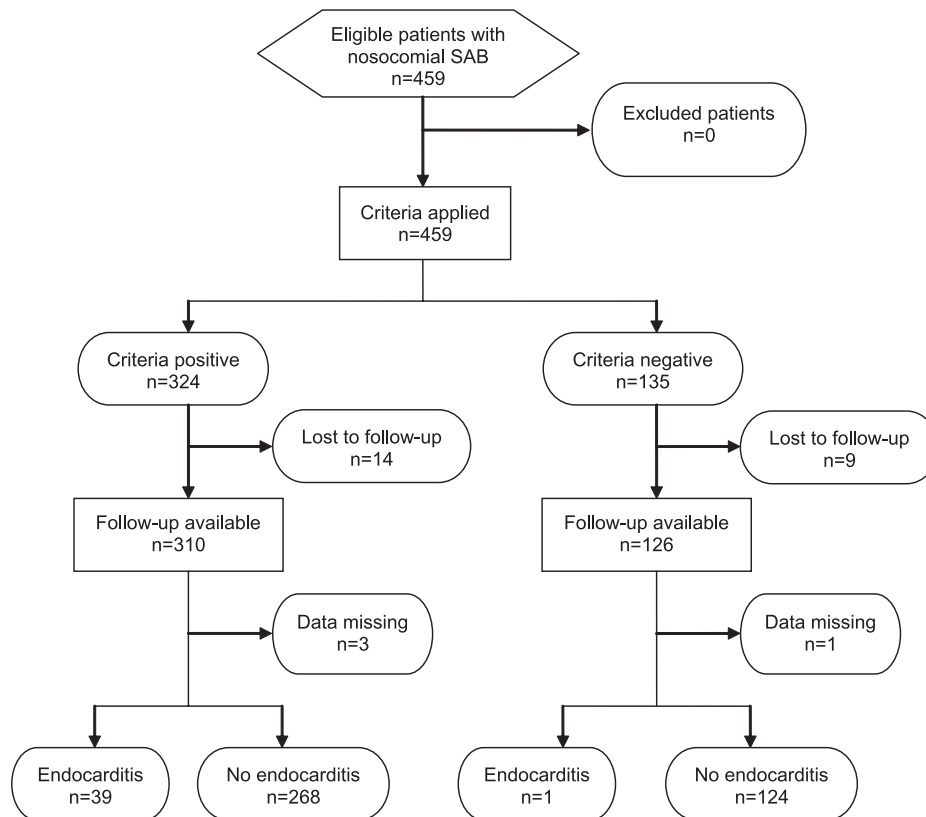
**Figure 2.** Flow diagram of patients recruited in the *S. aureus* Bacteremia Group (SABG) cohort.

infections. Seven patients (53.8%) with IE died within 90 days. No patient with IE developed late metastatic *S. aureus* infection or recurrent SAB.

In the SABG cohort, echocardiography was performed in 38 (95%) of 40 patients with IE a median of 5 days (range, 0–49 days) after the first positive blood culture result. In 17 patients (42.5%), the mitral valve was affected; in 11 patients (27.5%), the aortic valve was affected; and in 3 patients (7.5%), the tricuspid valve was affected. More than 1 valve was involved in 3 patients (7.5%). There were 4 cases (10%) of pacemaker lead infections and 3 cases (7.5%) of mural IE. Ten cases (25%) were prosthetic valve infections. In 5 patients (12.5%), no lesion was observed by echocardiography, and the diagnosis of IE was based on clinical Duke criteria alone. Within 90 days, 16 patients with IE (40%) died and 4 patients (10%) developed late metastatic infections or recurrent SAB.

Concerning the presence of the clinical prediction criteria defined above, both cohorts were remarkably similar. Most patients in both cohorts (INSTINCT vs. SABG, 57.2% vs 56%) fulfilled 1 criterion; 2 criteria were satisfied by 14.1% versus 14.1%, 3 criteria were fulfilled by 1.3% versus 0.9%, and no criteria were fulfilled by 27.3% versus 28.9% of patients.

In both cohorts, patients with IE were more likely to have documented prolonged bacteremia, a permanent intracardiac device, and spinal infections or nonvertebral osteomyelitis than patients without IE (Table 2). In the SABG cohort, each prediction criterion was present significantly more frequently in patients with IE, whereas in the INSTINCT cohort, this was the case only for the presence of a permanent intracardiac device. The frequency of hemodialysis dependency was similar in patients with and without IE in the INSTINCT cohort (7.7% vs 8.6%; $P > .99$), whereas in the SABG cohort, hemodialysis dependency was more common among patients with IE (15% vs 6.1%; $P = .05$). In both cohorts, with an increasing number of criteria fulfilled, the diagnosis of IE became more likely (Figure 3).

All patients in the INSTINCT study with a final diagnosis of *S. aureus* IE fulfilled at least 1 criterion for the identification of patients with increased risk of endocarditis (sensitivity, 100%; 95% CI, 77.2%–100%]) (Table 3). Among 83 patients who did not fulfill any of the prediction criteria, no cases with IE were found (negative predictive value, 100%; 95% CI, 95.6%–100%). Similar results were obtained in the SABG cohort. All but 1 patient with IE satisfied at least 1 criterion (sensitivity, 97.5% [95% CI, 87.1%–99.9%]; negative predictive value, 99.2% [95% CI, 95.6%–100%]).

In patients who did not satisfy any prediction criteria, IE may have gone undetected (Table 4). Seventeen patients died during

**Table 1. Characteristics of Patients With Nosocomial *Staphylococcus aureus* Bacteremia (SAB) in the Invasive *S. aureus* Infection Cohort (INSTINCT) and *S. aureus* Bacteremia Group (SABG) Cohorts**

| Characteristic | INSTINCT | | | SABG | | |
|---|---|---|---|---|---|---|
| | All patients (*n* = 304) | Patients without IE (*n* = 291) | Patients with IE (*n* = 13) | All patients (*n* = 432) | Patients without IE (*n* = 392) | Patients with IE (*n* = 40) |
| Age, years | | | | | | |
| Median (range) | 67 (21–91) | 67 (21–91) | 72 (47–86) | 65 (15–95) | 65 (25–95) | 65 (15–75) |
|   Interquartile range | 54–74 | 54–73 | 66–78 | 55–75 | 45–75 | 55–75 |
| Ratio of male to female patients | 103:201 | 99:192 | 4:9 | 193:239 | 171:221 | 22:18 |
| Percentage of female patients | 33.9 | 34 | 30.8 | 44.7 | 43.6 | 55 |
| Methicillin-resistant *S. aureus* | 47 (15.5) | 46 (15.8) | 1 (7.7) | 284 (65.7) | 252 (64.3) | 32 (80) |
| Long-term catheter present at onset | 29 (9.5) | 28 (9.6) | 1 (7.7) | 37 (8.6) | 32 (8.2) | 5 (12.5) |
| Source of bacteremia identified at onset | | | | | | |
| Short-term intravascular catheter | 117 (38.5) | 114 (39.2) | 3 (23.1) | 155 (35.9) | 149 (38.0) | 6 (15) |
| Long-term intravascular catheter | 23 (7.6) | 23 (7.9) | 0 | 37 (8.6) | 32 (8.2) | 5 (12.5) |
| Skin/soft tissue or wound | 33 (10.9) | 32 (11) | 1 (7.7) | 57 (13.2) | 51 (13) | 6 (15) |
| Respiratory tract | 11 (3.6) | 11 (3.8) | 0 | 57 (13.2) | 56 (14.3) | 1 (2.5) |
| Unknown | 92 (30.3) | 84 (28.9) | 8 (61.5) | 66 (15.3) | 57 (14.5) | 9 (22.5) |
| Other | 28 (9.2) | 27 (9.3) | 1 (7.7) | 60 (13.9) | 47 (12) | 13 (32.5) |
| Echocardiography within 14 days | 121 (39.8) | 111 (38.1) | 10 (76.9) | 248 (57.4) | 214 (54.6) | 34 (85) |
| TTE only | 65 (21.4) | 64 (22) | 1 (7.7) | 129 (29.9) | 117 (29.8) | 12 (30) |
| TEE only | 30 (9.9) | 29 (10) | 1 (7.7) | 41 (9.5) | 35 (8.9) | 6 (15) |
| TTE and TEE | 26 (8.6) | 18 (6.2) | 8 (61.5) | 78 (18.1) | 62 (15.8) | 16 (40) |
| Follow-up blood culture within 4 days | 171 (56.2) | 160 (55) | 11 (84.6) | 291 (67.4) | 260 (66.3) | 31 (77.5) |
| Duration of antimicrobial therapy, days | | | | | | |
| Median (range) | 14 (0–253) | 14 (0–253) | 22[a] (4–50) | 17 (0–176) | 17 (0–98) | 42 (0–176) |
|   Interquartile range | 9–19 | 9–18.5 | 13–33 | 12–33 | 11.8–30 | 15.5–54 |
| >14 days | 134 (44.1) | 125 (43) | 9 (69.2) | 267 (61.8) | 237 (60.5) | 30 (75) |
| >21 days | 59 (19.4) | 52 (17.9) | 7 (53.8) | 170 (39.4) | 141 (36) | 29 (72.5) |
| Late metastatic *S. aureus* infection or recurrent SAB | 9 (3) | 9 (3.1) | 0 | 27 (6.2) | 23 (5.9) | 4 (10) |
| 30-day case-fatality | 52 (17.1) | 48 (16.5) | 4 (30.8) | 93 (21.5) | 82 (20.9) | 11 (27.5) |
| 90-day case-fatality | 87 (28.6) | 80 (27.5) | 7 (53.8) | 125 (28.9) | 109 (27.8) | 16 (40) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a] Median duration of antimicrobial therapy in patients that survived >14 days, 31 (range, 13–50 days; interquartile range, 19–37.5).

the follow-up period without echocardiographic evaluation, and in 11 patients IE, may have been masked by >21 days of antimicrobial therapy.

## DISCUSSION

IE is a severe manifestation of SAB, and it has therefore been recommended to perform echocardiography, preferably TEE, in all patients with SAB [17, 22]. Although it is generally accepted standard to perform echocardiography in all patients with community-onset SAB and in those with nosocomial SAB associated with deep-seated infection, some clinicians are reluctant to perform TEE in patients who have uncomplicated SAB, show prompt clinical response to antimicrobial treatment, and have the focus of infection (eg, the intravascular catheter) promptly removed, as proposed previously [23, 24]. Even in a setting in which infectious diseases consultation is available, the

compliance with the recommendation to perform echocardiography ranges between 34% and 73% [18, 25–27].

By use of independent cohorts from 2 different continents, we evaluated simple clinical prediction criteria that can be used to identify patients with nosocomial SAB who are at very low risk for the development of IE and in whom TEE might therefore be dispensable. The criteria set is geared to evaluate patients 6–8 days after the first positive blood culture result and is based on data that is usually available at this time point.

The rationale for selecting the prediction criteria was (1) prolonged bacteremia has been shown to be the strongest predictor for complicated SAB and *S. aureus* IE [12, 28–30]; (2) permanent intracardiac devices, such as a prosthetic heart valve, a pacemaker, or an implantable cardioverter-defibrillator in patients with SAB have been found associated with a higher risk for endocarditis [7, 29, 31–34]; (3) patients with SAB who have end-stage renal disease and a history of hemodialysis are considered to be at risk to

**Table 2. Clinical Prediction Criteria Associated With Increased Risk of Infective Endocarditis (IE) in Patients With Nosocomial *Staphylococcus aureus* Bacteremia.**

| | No. (%) of Patients, by Study | | | | | | | |
| | INSTINCT | | | | SABG | | | |
| Clinical prediction criterion | All patients (*n* = 304) | Patients without IE (*n* = 291) | Patients with IE (*n* = 13) | *P*[a] | All patients (*n* = 432) | Patients without IE (*n* = 392) | Patients with IE (*n* = 40) | *P* |
|---|---|---|---|---|---|---|---|---|
| Prolonged bacteremia (>4 days) | 195 (64.1) | 186 (63.9) | 9 (69.2) | .78 | 272 (63) | 236 (60.2) | 36 (90) | <.01 |
| Documented prolonged bacteremia | 50 (16.4) | 47 (16.2) | 3 (23.1) | .46 | 111 (25.7) | 85 (21.7) | 26 (65) | <.01 |
| Possible prolonged bacteremia | 145 (47.7) | 139 (47.8) | 6 (46.2) | >.99 | 161 (37.3) | 151 (38.5) | 10 (25) | .12 |
| Permanent intracardiac device | 41 (13.5) | 34 (11.7) | 7 (53.8) | <.01 | 51 (11.8) | 38 (9.7) | 13 (32.5) | <.01 |
| Prosthetic heart valve | 18 (5.9) | 14 (4.8) | 4 (30.8) | <.01 | 25 (5.8) | 15 (3.8) | 10 (25.0) | <.01 |
| Pacemaker/cardioverter-defibrillator | 25 (8.2) | 22 (7.6) | 3 (23.1) | .08 | 29 (6.7) | 25 (6.4) | 4 (10.0) | .33 |
| Hemodialysis dependency | 26 (8.6) | 25 (8.6) | 1 (7.7) | >.99 | 30 (6.9) | 24 (6.1) | 6 (15) | .05 |
| Spinal infection or nonvertebral osteomyelitis | 8 (2.6) | 7 (2.4) | 1 (7.7) | .3 | 14 (3.2) | 9 (2.3) | 5 (12.5) | <.01 |
| No criteria fulfilled | 83 (27.3) | 83 (28.5) | 0 | | 125 (28.9) | 124 (31.6) | 1 (2.5) | |
| ≥1 criterion fulfilled | 221 (72.7) | 208 (71.5) | 13 (100) | | 307 (71.1) | 268 (68.4) | 39 (97.5) | |

**NOTE.** Data are shown for 304 patients in the Invasive *S. aureus* Infection Cohort (INSTINCT) and 432 patients in the *S. aureus* Bacteremia Group (SABG) with complete follow-up. More than 1 criterion may be present.

[a] Determined using the 2-sided Fisher exact test.

develop endocarditis [31, 35, 36]; (4) spinal infections and nonvertebral osteomyelitis due to *S. aureus* have been found to be associated with endocarditis [37–39].

Although long-term intravascular access devices (eg, tunneled or totally implantable catheters) have been shown to be associated with an increased risk of IE [40, 41], the presence of these catheters was not included in the criteria set. Prolonged bacteremia or hemodialysis dependency may represent independent risk factors for IE rather than the presence of these devices per se, particularly if long-term catheters are promptly removed.
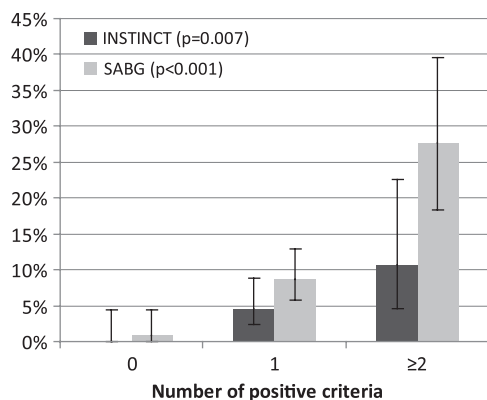


**Figure 3.** Relative frequency of infective endocarditis by number of positive criteria (error bars denote exact 95% confidence intervals) in the Invasive *S. aureus* Infection Cohort (INSTINCT; *n* = 304) and *S. aureus* Bacteremia Group (SABG; *n* = 432) cohorts. *P* values refer to intragroup (INSTINCT and SABG) comparisons of the relative frequency of infective endocarditis by the number of positive criteria (determined by the Fisher exact test).

In fact, only 1 of 29 patients in the INSTINCT cohort and 5 of 37 patients in the SABG cohort with a long-term intravascular access device present at onset developed IE.

The comparison between the European and North American cohorts showed strikingly similar results regarding patient characteristics and the source of SAB. Of note, MRSA was much more prevalent in the US cohort (65.7% vs 15.5%). Many studies, including a large meta-analysis, have shown that methicillin resistance is associated with a worse outcome in SAB [42]. However, the 30-day and 90-day case-fatality rates did not differ significantly between the 2 study sites, despite the prominent difference in MRSA prevalence.

Prolonged bacteremia was more common among patients with IE in the US cohort (90% vs 69.2%). It might be argued that this was due to the increased prevalence of MRSA in SABG cohort members and because empirical antimicrobial therapy is often not appropriate and definitive therapy less effective in patients with BSI caused by MRSA. However, our data do not

**Table 3. Sensitivity, Specificity, and Positive and Negative Predictive Values of the Clinical Prediction Criteria Set**

| | Percentage (95% CI) | |
| Variable | INSTINCT | SABG |
|---|---|---|
| Sensitivity | 100 (77.2–100) | 97.5 (87.1–99.9) |
| Specificity | 28.5 (23.6–34) | 31.6 (27.2–36.4) |
| Positive predictive value | 5.9 (3.5–9.8) | 12.7 (9.4–16.9) |
| Negative predictive value | 100 (95.6–100) | 99.2 (95.6–100) |

**NOTE.** Ninety-five percent confidence intervals (CIs) were determined on the basis of the Wilson method. INSTINCT, Invasive *Staphylococcus aureus* Infection Cohort; SABG, *S. aureus* Bacteremia Group

**Table 4. Characteristics of Patients Who Satisfied No Clinical Prediction Criteria**

| Characteristic | No. (%) of patients, by study | |
| --- | --- | --- |
| | INSTINCT (n = 83) | SABG (n = 125) |
| Death within 90 days | 15 (18.1) | 32 (25.6) |
| and no echocardiography performed[a] | 8 (9.6) | 9 (7.2) |
| Survived 90 days and no echocardiography performed | 26 (31.3) | 24 (19.2) |
| and >14 days of antimicrobial therapy | 13 (15.7) | 13 (10.4) |
| and >21 days of antimicrobial therapy | 5 (6) | 6 (4.8) |
| and >28 days antimicrobial therapy | 2 (2.4) | 4 (3.2) |

**NOTE.** INSTINCT, Invasive *Staphylococcus aureus* Infection Cohort; SABG, *S. aureus* Bacteremia Group

[a] Transthoracic echocardiography or transesophageal echocardiography within 90 days after onset of *S. aureus* bacteremia.

support this hypothesis because 20 (62.5%) of 32 SABG patients with IE caused by MRSA had documented prolonged bacteremia, compared with 6 (75%) of 8 patients with IE caused by MSSA (data not shown). It is tempting to speculate that the higher incidence of IE in the SABG cohort might be explained by the higher incidence of MRSA; however, our data do not prove this.

In both cohorts, the absence of any of the criteria had a high negative predictive value (100% and 99.2% in the INSTINCT and SABG cohorts, respectively) for the development of IE. Therefore, we propose that TEE to exclude IE may be dispensable in patients with nosocomial SAB who do not fulfill any of the clinical prediction criteria.

There are several limitations to the study. The reliable detection of IE is of critical importance. Neither of the 2 cohort studies was designed to measure the rate of IE at 3 months after the onset of SAB, and routine follow-up echocardiography data were not available. Also, a small number of patients were lost to follow-up or data were missing (INSTINCT, 1.6%; SABG, 5.9%). More importantly, only 39.5% (in INSTINCT) and 57.4% (in SABG) of patients underwent echocardiography ≤14 days after onset of SAB, despite considerable efforts of the investigators to include this diagnostic method into standard care. Thus, some cases of IE may have gone undetected. However, we reasoned that IE would become clinically apparent after discontinuation of antibiotic therapy; therefore, patients were observed closely for the development of clinical signs and symptoms suggestive of IE over a period of 3 months. One might argue that a considerable number of patients who did not fulfill any predictive criteria and in whom echocardiography was not performed died during follow-up, and in these patients undetected IE could have been present. However, a sudden death related to IE that goes undetected by the primary care physician and/or the hospital should occur only rarely. Furthermore, there was no case of IE observed among the surviving patients during the follow-up periods. One could also argue that

prolonged antimicrobial therapy could have adequately treated undetected early stage IE, and indeed, 11 patients for whom echocardiography was not performed were given >3 weeks of antimicrobial treatment.

The comparatively low specificity of the criteria set is largely due to the conservative definition of prolonged bacteremia, ie the absence of negative blood cultures obtained at day 1–4 after the first positive blood culture. Using this definition, 145 patients in INSTINCT and 161 patients in the SABG cohort with "possible" prolonged bacteremia were included in the prolonged bacteremia group, although most likely a considerable number of these patients could have been excluded if follow-up blood cultures had been obtained. If "documented" prolonged bacteremia (ie, the presence of a follow-up blood culture positive for *S. aureus* 2–4 days after the first positive blood culture result) was used as a criterion, the specificity of the test would be markedly increased (data not shown). However, we decided not to use this approach, because some patients with ongoing bacteremia could be missed if no follow-up blood samples are obtained for culture, leading to a lower negative predictive value.

In summary, we propose that in patients with at least 1 clinical prediction criterion, echocardiography to exclude IE is highly recommended. In the subset of patients with a low probability of IE (ie, those without any of the criteria), TEE evaluation may not be necessary. However, physicians should not be discouraged from performing echocardiography in criteria-negative patients when IE is clinically suspected during the course of the infection.

Furthermore, clinicians should be encouraged by ID physicians and clinical microbiologists to perform follow-up cultures for all patients with SAB 2–4 days after the first positive blood culture result. This approach can be used to exclude prolonged bacteremia and thus helps to identify patients in whom TEE might be dispensable, and it could lead to a more economical use of echocardiographic evaluations. Nevertheless, it is of critical importance to confirm the validity of the proposed prediction criteria prospectively in a controlled study, in which all patients with SAB would undergo echocardiography and follow-up blood cultures.

study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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