JACC: CARDIOVASCULAR IMAGING
VOL. 8, NO. 8, 2015

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2015.02.027

Use of Transthoracic Echocardiography in the Management of Low-Risk *Staphylococcus aureus* Bacteremia

Results From a Retrospective Multicenter Cohort Study

Adrienne Showler, MD,*† Lisa Burry, PharmD,‡§ Anthony D. Bai, BHSc,‖ Marilyn Steinberg, RN,‡ Daniel R. Ricciuto, MD,†¶ Tania Fernandes, PharmD,# Anna Chiu, BScPhm,# Sumit Raybardhan, BScPhm, MPH,** Michelle Science, MD, MSc,†† Eshan Fernando, MD,* Chaim M. Bell, MD, PhD,*‡ ‡‡ Andrew M. Morris, MD, SM*†‡

ABSTRACT

OBJECTIVES The aim of this study was to develop a prediction model to identify patients with low-risk *Staphylococcus aureus* bacteremia (SAB), in whom infective endocarditis (IE) can be ruled out based on transthoracic echocardiogram (TTE).

BACKGROUND *S. aureus* is a major cause of bacteremia and often leads to IE. Current guidelines recommend performing transesophageal echocardiography on all patients or treating all patients empirically with prolonged intravenous antibiotics; however, this approach is resource intensive, many physicians do not adhere to guidelines, and recent studies suggest that low-risk patients may not require transesophageal echocardiography.

METHODS We conducted a retrospective cohort study of 833 consecutive hospitalized patients with SAB from 7 academic and community hospitals in Toronto, Canada, over a 3-year period (2007 to 2010). Patients who received a TTE within 28 days of bacteremia ($n = 536$) were randomly divided into derivation and validation cohorts. Multivariable logistic regression analysis was used to determine high-risk criteria for IE in the derivation cohort, and criteria were then applied to the validation cohort to determine diagnostic properties.

RESULTS Four high-risk criteria predicted IE: indeterminate or positive TTE ($p < 0.001$), community-acquired bacteremia ($p = 0.034$), intravenous drug use ($p < 0.001$), and high-risk cardiac condition ($p < 0.004$). In the validation cohort, the presence of any 1 of the high-risk criteria had 97% sensitivity (95% confidence interval [CI]: 87% to 100%) and 99% negative predictive value (95% CI: 96% to 100%) for IE. The negative likelihood ratio was 0.05 (95% CI: 0.007 to 0.35).

CONCLUSIONS A normal TTE ruled out IE in patients without community-acquired SAB, high-risk cardiac conditions, and intravenous drug use. This study provides evidence that clinical risk stratification combined with a normal TTE may be adequate to rule out IE in most patients with SAB. (J Am Coll Cardiol Img 2015;8:924–31) © 2015 by the American College of Cardiology Foundation.

From the *Department of Medicine, University of Toronto, Toronto, Ontario, Canada; †Division of Infectious Diseases, University of Toronto, Toronto, Ontario, Canada; ‡Mount Sinai Hospital, Toronto, Ontario, Canada; §Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; ‖Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; ¶Lakeridge Health, Oshawa, Ontario, Canada; #Trillium Health Partners, Mississauga, Ontario, Canada; **North York General Hospital, Toronto, Ontario, Canada; ††Hospital for Sick Children, Toronto, Ontario, Canada; and the ‡‡Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada. The Mount Sinai Hospital-University Health Network Antimicrobial Stewardship Program was supported by an unrestricted educational grant from Pfizer Canada Inc. from 2010 to 2012. These funds were not used for the program's clinical work. Part of the Research Coordinator's (M. Steinberg) salary was supported by this grant at the time of this study. Pfizer Canada had no role in the topic, design, conduct, interpretation, or manuscript preparation of this study. Mr. Raybardhan serves on the advisory board of Cubist Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 1, 2014; revised manuscript received February 1, 2015, accepted February 5, 2015.

Staphylococcus aureus is a major cause of bacteremia and commonly leads to severe complications (1-3). Infective endocarditis (IE) occurs in up to 25% of cases and is associated with lengthy hospitalization, relapsing bacteremia, and high mortality (3-9). Identification of IE is crucial because patients require a more complex approach to management, which includes prolonged use of intravenous antibiotic therapy (10,11). The majority of patients with IE do not have clinically evident disease at the time of bacteremia, which makes early diagnosis challenging (4,8,12).

Current guidelines for management of *S. aureus* bacteremia (SAB) assume IE, requiring at least 4 weeks of intravenous antibiotic therapy unless a transesophageal echocardiogram (TEE) is negative (13). This is based on historical studies demonstrating that transthoracic echocardiography (TTE) may not be sufficiently sensitive to rule out IE (4). However, performing a TEE on all patients is resource intensive, and clinicians frequently deviate from current guidelines according to TEE availability, patient refusal, and comorbid critical illness (8,14,15).

SEE PAGE 932

Modern echocardiographic techniques and equipment have improved TTE sensitivity in SAB, particularly in low-risk patients (16-18). TTE might therefore exclude IE in many patients and eliminate the need for more invasive testing with TEE (19). Thus, we sought to describe the current use of echocardiography in a multicenter SAB cohort in Toronto, Canada. We then tested the potential of a multivariable model to identify low-risk patients, in whom IE can be ruled out based on TTE alone.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

IE = infective endocarditis

IQR = interquartile range

MRSA = methicillin-resistant *Staphylococcus aureus*

SAB = *Staphylococcus aureus* bacteremia

TEE = transesophageal echocardiogram

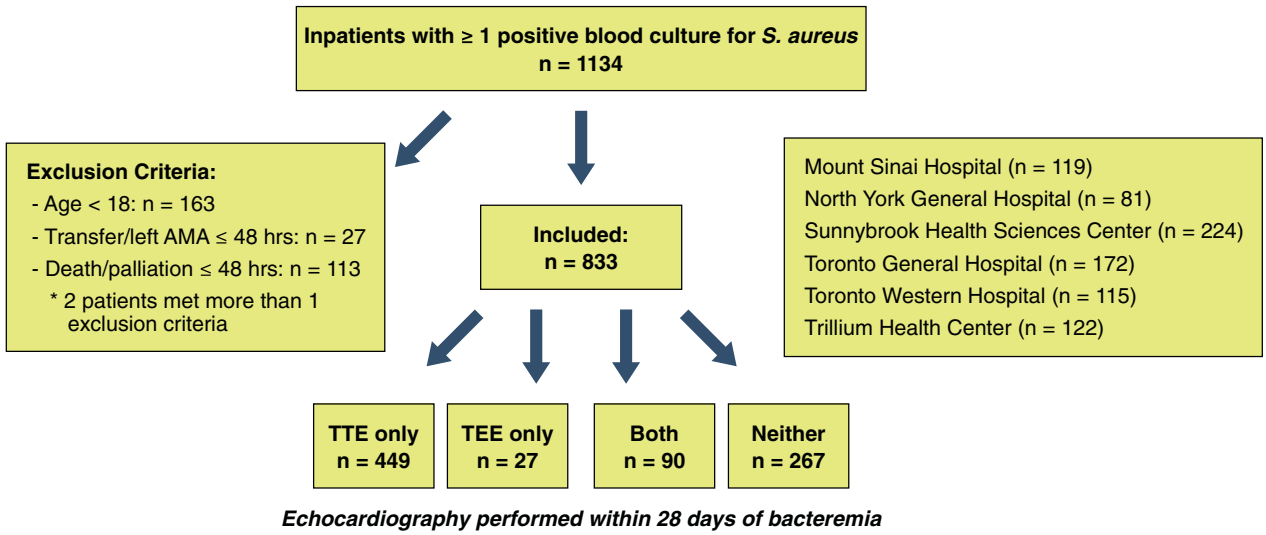
TTE = transthoracic echocardiography

METHODS

PATIENTS AND SETTING. We conducted our study at 7 university-affiliated and community hospitals in the Greater Toronto area. The 7 sites accounted for a total of 3,338 acute care beds and approximately 160,000 annual patient admissions. We obtained approval from the research ethics boards at all sites. We retrospectively identified all inpatients with at least 1 positive blood culture for *S. aureus* from each hospital's microbiology laboratory information system during a 3-year period from April 1, 2007, through March 31, 2010. Five microbiology laboratories provided results for the 7 study sites. All sites used standard methods that conformed to Clinical and Laboratory Standards Institute guidelines for *S. aureus* identification and antimicrobial susceptibilities (20).

We included only adult inpatients (age ≥18 years) with a first SAB episode and excluded patients who died, were deemed suitable for palliative care only, were transferred to another facility, or left against medical advice within 48 h of bacteremia. We entered each patient in the study only once, using the first positive blood culture as the index isolate. Request

FIGURE 1 Flow Diagram of Patients With *Staphylococcus aureus* Bacteremia, Including Type of Echocardiography Performed



AMA = against medical advice; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram.

TABLE 1 Characteristics of Patients With SAB, by Type of Echocardiogram

	Echocardiogram Status			
	No Echocardiogram (n = 267)	TTE Only (n = 449)	TEE Only (n = 27)	TTE and TEE (n = 90)
Age, yrs	64 (52–79)	66 (52–79)	53 (45–64)	60.5 (49–71)
Female	90 (34)	169 (38)	10 (37)	30 (33)
Admitting service				
Medical	140 (52)	303 (67)	11 (41)	54 (60)
Surgical	77 (29)	88 (20)	9 (33)	17 (19)
ICU	50 (19)	58 (13)	7 (26)	19 (21)
Location of acquisition*				
Community-acquired	47 (18)	135 (31)	7 (26)	41 (46)
Health care-associated	102 (38)	172 (38)	6 (22)	27 (30)
Nosocomial	112 (43)	134 (30)	14 (52)	21 (24)
Risk factors for complicated SAB				
High-risk cardiac condition	15 (5.6)	35 (7.8)	6 (22)	14 (16)
Intravenous drug use	5 (1.9)	27 (6.0)	2 (7.4)	7 (7.8)
Hemodialysis	21 (7.9)	52 (12)	2 (7.4)	14 (16)
MRSA	50 (19)	71 (16)	7 (26)	14 (16)
Early infectious foci†				
Intravascular catheter	48 (18)	77 (17)	6 (22)	15 (17)
Skin/soft tissue	61 (23)	92 (20)	3 (11)	18 (20)
Bone or joint	27 (10)	80 (18)	3 (11)	21 (23)
Respiratory	47 (18)	75 (17)	6 (22)	20 (22)
Endovascular	7 (2.6)	23 (5.1)	3 (11)	5 (5.6)
Unknown	67 (25)	107 (24)	8 (30)	23 (26)
Other	49 (18)	97 (22)	4 (15)	28 (31)
Febrile at 72 h	42 (16)	47 (10)	6 (22)	20 (22)
Repeat blood cultures 2 to 4 days after initial positive culture‡				
Positive	15 (5.6)	52 (12)	1 (3.7)	22 (24)
Negative	55 (21)	122 (27)	6 (22)	30 (33)
Not performed	183 (69)	258 (57)	17 (63)	33 (37)
ID consultation within 7 days	125 (47)	292 (65)	22 (81)	59 (66)
Antibiotic duration, days§	14 (6–27)	19 (14–32)	17 (9–35)	29.50 (16–45)
IE within 90 days	4 (2)	40 (9)	7 (26)	25 (28)
Mortality within 90 days	76 (28)	91 (20)	5 (19)	23 (26)
Follow-up, days	15 (7–32)	23 (11–43)	26 (17–37)	29 (16–54)

Values are median (interquartile range) or n (%). *Location of acquisition was not available for 15 patients (1.8%). †Documented infectious foci within 10 days of SAB, excluding IE. Some patients had >1 infectious focus. Data were not available for 16 patients (1.9%). ‡Data were not available for 39 patients (4.7%). §Data were not available for 40 patients (4.8%).

ICU = intensive care unit; ID = infectious disease; IE = infective endocarditis; MRSA = methicillin-resistant *Staphylococcus aureus*; SAB = *Staphylococcus aureus* bacteremia; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram.

for echocardiography was at the discretion of the primary responsible physician. All echocardiograms were reported by cardiologists, except at 1 site where intraoperative TEEs were read by National Board of Echocardiography-certified anesthesiologists. A variety of different echocardiography machines were used at the 7 sites.

Infectious disease services consultation was available at all hospital sites. At 3 hospitals, the microbiology laboratory notified the infectious diseases service when inpatient blood cultures were positive for *S. aureus*. Departmental policy at these hospitals included the offering of a consultation for patients admitted to general internal medicine or the medical-surgical intensive care unit and automatic performance of a consultation for patients admitted to all other services.

DATA COLLECTION AND VERIFICATION. We abstracted data from electronic and paper medical records using a standardized electronic case report form designed by a multidisciplinary team. The recorded data included patient demographics, comorbidities, microbiological data, and inpatient antibiotic treatment and investigations, as well as clinical outcomes that occurred within 90 days of initial bacteremia. We independently conducted source data verification by assessing a random sample of 10% of data entry points for accuracy, and we performed range edits and value checks to reduce the potential for data entry errors. We referred data gaps and suspected anomalies back to hospital sites for verification. Data were deemed high quality and near complete.

DEFINITIONS. We classified bacteremia as nosocomial, health care-associated, or community-acquired according to standard definitions (20,21). Patients had prolonged bacteremia when repeat blood cultures performed 2 to 4 days after initial bacteremia were positive for *S. aureus*. High-risk cardiac conditions were defined as prosthetic heart valve or prosthetic material used for cardiac valve repair, congenital heart disease, cardiac transplantation with valvulopathy, history of prior endocarditis, and presence of a pacemaker or automatic implantable cardioverter-defibrillator (22). We defined IE according to the modified Duke criteria (22).

Echocardiographic findings that fulfilled major Duke criteria included the presence of an oscillating intracardiac mass, perivalvular leak, or abscess (4). We classified TTE as indeterminate when documented abnormalities that did not fulfill the above criteria were present, including new or significantly worsening valvular regurgitation, abnormal valvular thickening, abnormal nonoscillatory echogenic focus, or any abnormality for which TEE was specifically recommended for further evaluation. We also classified as indeterminate any echocardiogram that demonstrated suboptimal views because of technical difficulties, was noted to be of poor quality, or was characterized as a limited study for an alternate indication. Normal TTEs had no documented major Duke criteria features or indeterminate features. In patients who received multiple TTEs, we categorized patients in the multivariable model according to the first TTE performed within 28 days of bacteremia.

OUTCOMES. The primary outcome was diagnosis of IE within 90 days of SAB. The secondary outcome was SAB relapse with an identical antimicrobial susceptibility pattern that occurred >14 days after initial positive blood culture.

STATISTICAL ANALYSIS. Descriptive analysis included median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. We compared continuous variables using the Student *t* test or Wilcoxon rank-sum test. We used the chi-square or Fisher exact test to compare categorical variables.

Patients who received a TTE within 28 days of bacteremia were randomized in a 1:1 ratio into a derivation or validation cohort. In the derivation cohort, we used a multivariable logistic regression model to identify predictors of endocarditis along with initial TTE result. In the logistic model, endocarditis was the dependent variable. Initial TTE result was an independent variable along with other potential predictors, including community-acquired infection, high-risk cardiac condition, hemodialysis, intravenous drug use, methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, intravenous catheter infection, fever, and prolonged bacteremia. We used several methods to confirm the final multivariable logistic regression model of significant predictors, including univariate selection based on p value, full model with all predictors, and both forward and backward stepwise regression based on Akaike information criterion and likelihood ratio test.

In the validation cohort, we used significant predictors in the final multivariable regression model as a clinical prediction rule for endocarditis. In determining diagnostic properties, we used our clinical prediction rule as the test and endocarditis as the criterion standard. We calculated sensitivity, specificity, and predictive values with 95% confidence intervals (CIs) using the Wilson method. For likelihood ratios, we calculated the 95% CI according to the method described by Simel et al. (23).

All reported CIs were 2-sided 95% intervals, and all tests were 2-sided with a $p < 0.05$ significance level. All analyses were performed with R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identified 1,134 consecutive inpatients with first-episode SAB; 833 met inclusion criteria (Figure 1). Bacteremia was community acquired in 230 patients (27.6%), health care-associated in 307 patients (36.9%), and nosocomial in 281 patients (33.7%). *S. aureus* was methicillin resistant (MRSA) in 142 patients (17.0%). Seventy patients (8.4%) had a high-risk cardiac condition.

Within 28 days of the first positive blood culture for *S. aureus*, 449 patients (53.9%) received a TTE

TABLE 2 Baseline Characteristics of Derivation and Validation Cohorts

	Derivation Cohort (n = 268)	Validation Cohort (n = 268)	p Value
Age, yrs	64 (49–77)	66 (52–78)	0.21
Female	100 (37)	98 (37)	0.93
Admitting service			
Medical	174 (65)	181 (68)	
Surgical	51 (19)	53 (20)	0.54
ICU	43 (16)	34 (13)	
Location of acquisition*			
Community-acquired	90 (34)	84 (31)	
Health care-associated	97 (37)	102 (39)	0.85
Nosocomial	77 (29)	77 (29)	
Risk factors for complicated SAB			
High-risk cardiac condition	18 (6.7)	30 (11)	0.10
Intravenous drug use	17 (6.3)	17 (6.3)	>0.99
Hemodialysis	38 (14)	27 (10)	0.19
MSSA	222 (83)	229 (85)	0.48
MRSA	46 (17)	39 (15)	
Early infectious foci†			
Intravascular catheter	44 (16)	48 (18)	0.70
Skin/soft tissue	53 (20)	57 (21)	0.68
Bone or joint	54 (20)	45 (17)	0.41
Respiratory	54 (20)	40 (15)	0.12
Endovascular	16 (6.0)	12 (4.5)	0.56
Unknown	63 (24)	67 (25)	0.76
Other	66 (25)	57 (21)	0.36
Early clinical course			
Febrile at 72 h	35 (13)	31 (12)	0.59
Repeat blood cultures 2–4 days after initial positive culture‡			
Positive	33 (12)	39 (15)	
Negative	81 (30)	71 (26)	0.53
Not performed	142 (53)	148 (55)	
ID consultation within 7 days	181 (68)	169 (63)	0.32
Echocardiogram			
TTE and TEE	45 (17)	44 (16)	>0.99
TTE result			
Normal	187 (70)	181 (68)	
Indeterminate	57 (21)	61 (23)	0.86
Positive	24 (9.0)	26 (9.7)	
Antibiotic duration, days§	21 (14–38)	20 (13–32)	0.21
IE within 90 days	26 (9.7)	38 (14)	0.14
Mortality within 90 days	56 (21)	55 (21)	>0.99
Follow-up, days	25 (13–45)	25 (12–44)	0.83

Values are median (interquartile range) or n (%). *Location of acquisition was not available for 9 patients (1.7%). †Documented infectious foci within 10 days of SAB, excluding IE. Some patients had >1 infectious focus. Data were not available for 7 patients (1.3%). ‡Data were not available for 22 patients (4.1%). §Data were not available for 10 patients (1.9%).

MSSA = methicillin-sensitive *Staphylococcus aureus*; other abbreviations as in Table 1.

alone, performed a median of 4 days (IQR: 2 to 6 days) after the initial positive blood culture. An additional 90 patients (10.8%) received both TTE and TEE, performed a median of 2 days (IQR: 2 to 4 days) and 8 days (IQR: 5 to 11 days) after initial positive culture, respectively. Only 27 patients (3.2%) received a TEE alone, a median of 6 days (IQR: 4 to 12.5 days) after initial positive culture (Table 1). Echocardiography was more likely to be performed in patients with community-acquired bacteremia ($p < 0.001$) or prolonged bacteremia ($p = 0.007$) and in those who received an infectious disease consultation ($p < 0.001$). Patients admitted to a medical service received echocardiography more often than those admitted to a surgical service ($p = 0.002$).

Of 536 patients with a reported TTE within 28 days of SAB, 368 (68.7%) had a normal echocardiogram. Fifty patients (9.3%) had a TTE that fulfilled major echocardiographic Duke criteria, and 118 patients (22.0%) had an indeterminate TTE. IE was diagnosed in 76 patients (9.1%) in the entire cohort and in 64 patients (11.9%) in the group receiving TTE. Median duration of documented follow-up in patients receiving TTE was 29 days (IQR: 13 to 50 days), excluding patients who died within 30 days of bacteremia.

There were 268 patients in each of the derivation and validation cohorts. The cohorts had similar baseline characteristics (Table 2). Indeterminate or positive TTE, high-risk cardiac conditions, intravenous drug use, and community-acquired bacteremia were statistically significant predictors of IE in univariate analysis and were therefore used in developing the final multivariable model (Table 3). Hemodialysis ($p = 0.49$), MRSA ($p = 0.38$), non-intravenous catheter focus ($p = 0.40$), fever at 72 h ($p = 0.20$), and prolonged bacteremia ($p = 0.73$) were not significant IE predictors. Patients who met any prediction criteria were considered at high risk for IE, and all others were at low risk.

TABLE 3 Final Multivariable Model Predictive for Infective Endocarditis (Derivation Cohort, n = 268)

	OR (95% CI)	OR p Value	Likelihood Ratio p Value
Indeterminate or positive TTE	20.56 (6.61–84.64)	<0.001	<0.001
Intravenous drug use	14.31 (3.32–70.15)	<0.001	<0.001
High-risk cardiac condition	8.73 (2.10–36.02)	0.002	0.004
Community-acquired*	3.15 (1.09–9.45)	0.035	0.034

*Bacteremia was considered to not be community-acquired in 4 patients in whom the location of acquisition could not be confirmed.

CI = confidence interval; OR = odds ratio; TTE = transthoracic echocardiogram.

On the basis of the multivariable model criteria, 147 patients (55%) were at high risk for IE and 121 (45%) were at low risk in the validation cohort. Multivariable model criteria had a sensitivity of 97% for IE and a specificity of 52%. The negative predictive value for IE was 99%, and the positive predictive value was 25% (Table 4). Only 1 patient with IE was considered at low risk. The negative likelihood ratio was 0.05 (95% CI: 0.007 to 0.35). The prevalence of IE in the validation cohort was 14.2%. Patients who met more than 1 multivariable model criterion were at higher risk for IE (Figure 2). Almost all patients with IE were diagnosed within 10 days of initial positive blood culture (Figure 3).

SAB relapse with MRSA occurred in 3 patients who met low-risk criteria, all in the derivation cohort. Two of 3 patients were already receiving antibiotic therapy at the time of relapse, and 1 patient relapsed after completing more than 5 weeks of treatment. All had noncardiac deep-space or persistent infectious foci. Endocarditis was ruled out on TEE in 1 patient, whereas the other 2 had normal serial TTEs without confirmatory TEE. No patient in the validation cohort experienced SAB relapse.

DISCUSSION

We evaluated 833 consecutive inpatients with SAB who received echocardiography at 7 community and academic hospitals. Using a split derivation and validation cohort, we found that a normal TTE ruled out IE in patients without community-acquired SAB, high-risk cardiac conditions, and intravenous drug use. Our criteria were 97% sensitive for IE, with a negative predictive value of 99% in a population with

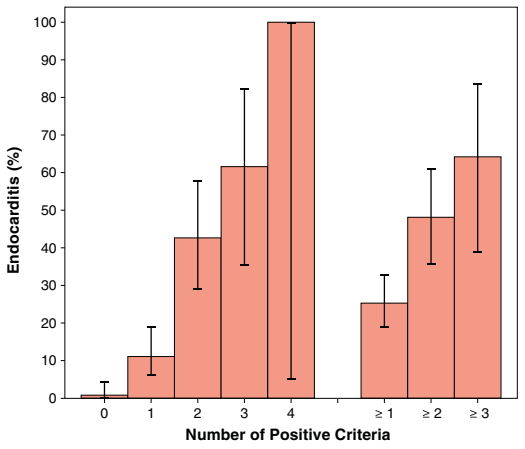
TABLE 4 Diagnostic Properties of Multivariable Model in the Validation Cohort (n = 268)

True positive	37
False positive	110
True negative	120
False negative	1
Sensitivity, %	97 (87–100)
Specificity, %	52 (46–59)
Positive predictive value, %	25 (19–33)
Negative predictive value, %	99 (96–100)
Positive likelihood ratio	2 (1.8–2.4)
Negative likelihood ratio	0.05 (0.007–0.35)

Values are n or % (95% confidence interval). Prevalence of infective endocarditis in the validation cohort was 14.2%.

False negative = low-risk patient with infective endocarditis; False positive = high-risk patient without infective endocarditis; True negative = low-risk patient without infective endocarditis; True positive = high-risk patient with infective endocarditis.

FIGURE 2 Frequency of Infective Endocarditis by Number of Positive Criteria in the Validation Cohort (n = 268)



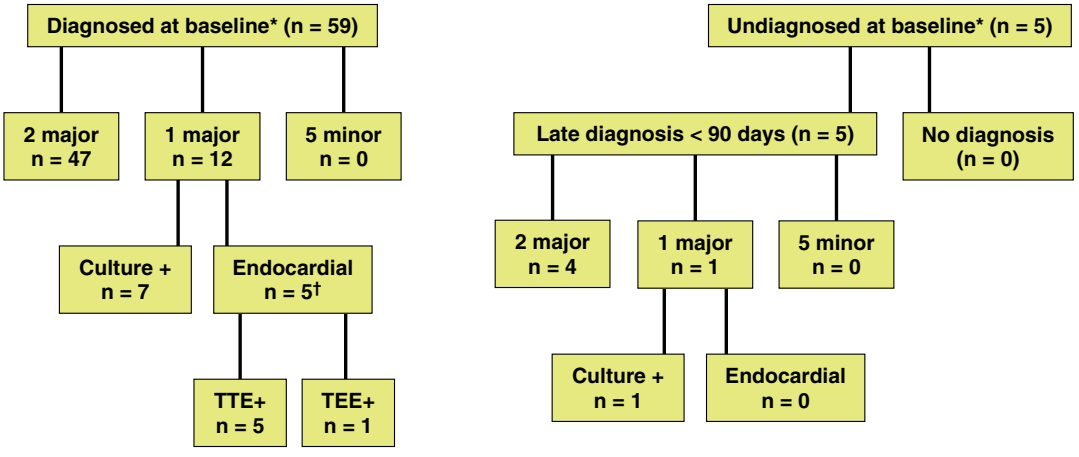
The 4 criteria include: 1) indeterminate or positive transthoracic echocardiogram; 2) intravenous drug use; 3) high-risk cardiac condition; and 4) community-acquired bacteremia. Error bars indicate 95% confidence intervals.

14.2% IE prevalence. Specificity was lower (52%), possibly because of the stringent requirements for a normal TTE. On the basis of our findings, we propose that our combined clinical and TTE criteria are sufficient to rule out IE in a sizeable proportion of patients with SAB. The use of this approach eliminated the need for a TEE in almost one-half of these patients (45%), while missing IE in only 0.4% of those screened.

Few studies using modern echocardiography have examined a model with clinical and TTE criteria (19). All were small or single-center studies, and none used separate derivation and validation cohorts (17,18,24). In a 2009 to 2010 study, Rasmussen et al. (17) concluded that TTE may be an adequate screening tool in patients at low risk for IE; however, criteria were complex and based on many variables, which introduces model instability. In another small study from 2006 to 2011, IE was rare in patients without prosthetic cardiac devices who had no valvular regurgitation on echocardiogram (24). In an older single-center study, patients without prosthetic cardiac material, TTE evidence of regurgitation, and clinical embolic phenomena had a <2% post-test probability of IE (18). Our study supports the role of TTE in risk stratification, although our clinical predictors and definition of normal TTE differed (18,19,24).

In contrast to other recent studies of nosocomial SAB, we demonstrate that TTE combined with simple clinical risk criteria is useful to rule out IE in SAB acquired from any location. Although 5 high-risk criteria had >97% sensitivity and >99% negative predictive value for IE in nosocomial SAB (14), diagnostic properties were less robust when these criteria were applied to a prospective cohort that also included community-acquired and health care–associated SAB (15). Khatib and Sharma (15) found evidence of IE in only 0.4% of patients with uncomplicated SAB,

FIGURE 3 Duke Criteria Fulfilled for Cases of Infective Endocarditis in the Derivation and Validation Cohorts



*Baseline diagnosis of infective endocarditis occurred within 10 days of initial positive blood culture. †One patient had both a positive transthoracic echocardiogram (TTE) and a positive transesophageal echocardiogram (TEE).

defined on the basis of clinical criteria; however, the majority did not receive any form of cardiac imaging (14,15), and other studies with higher rates of echocardiography utilization do not support the use of clinical predictors alone to rule out IE (8,12,19).

Our study has several strengths. We examined a large SAB cohort from 7 diverse hospital sites, whereas most studies are limited to single hospital centers (15,18,24). Furthermore, all patients included in our multivariable model received at least 1 echocardiogram, in contrast to other large cohorts in which the majority did not receive cardiac imaging (9,14). Patient charts were reviewed for 90 days after the initial bacteremia episode, and follow-up was documented for a median of 29 days. Finally, our cohort included patients who acquired SAB from different locations, including community-acquired, health care–associated, and nosocomial settings.

STUDY LIMITATIONS. Our study has limitations that merit mention. We obtained patient information by reviewing hospital charts retrospectively, which has inherent limitations. Our derivation and validation cohorts excluded the 267 patients who did not receive cardiac imaging. This represents potential selection bias, because we observed differences in patients who received echocardiography compared with the group who did not: patients who did not receive echocardiography had lower rates of community-acquired bacteremia, intravenous drug use, prolonged bacteremia, and infectious disease consultation and were more likely to be admitted to surgical services. Only a minority of patients undergoing TTE also received a TEE (16.7% in 28 days). Eighty patients (15%) received serial TTEs, at a median of 18.5 days (IQR: 9 to 34 days) after initial TTE, which may have increased detection of IE cases through follow-up of patients over time. Although no patient who satisfied all negative prediction criteria was readmitted to the hospital with IE, we cannot exclude the possibility that patients sought medical attention at a health care facility other than the original admitting hospital; however, 3 hospital sites share a single microbiology laboratory, and previous work has demonstrated that most patients in Toronto who are readmitted soon after discharge return to the same hospital (25). Moreover, the prevalence of IE in our population was similar to that of other large unselected SAB cohorts, which suggests that we did not miss significant numbers of patients with IE (6,9,14,24,26).

CONCLUSIONS

In our multicenter SAB cohort, a normal TTE ruled out IE in patients without community-acquired SAB, intravenous drug use, and high-risk cardiac conditions. Our criteria provide evidence that in low-risk patients with SAB, a TTE is adequate to exclude IE, which could decrease the use of invasive tests and provide more efficient patient care.

ACKNOWLEDGMENTS This project was performed in collaboration with the Toronto Antimicrobial Stewardship Corridor (TASC). The authors are indebted to Pamilla Cheema, Bin Chen, Karol Sitarski, Bruce Tugwood, Bonnie Chi Thieu, Mei Shi, and Rochelle Liem for their assistance with data collection and verification.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Andrew Morris, Mount Sinai Hospital, 600 University Avenue, Room 415, Toronto, Ontario M5G 1X5, Canada. E-mail: amorris@mtsinai.on.ca.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: All patients with SAB should be evaluated for IE. Significant predictors of IE include intravenous drug use, high-risk cardiac conditions, and community-acquired bacteremia. In patients without these risk factors, a normal transthoracic echocardiogram has a high negative predictive value for endocarditis.

TRANSLATIONAL OUTLOOK: Adherence to published SAB guidelines is poor. The implementation of an endocarditis risk-stratification model as part of a broader SAB policy initiative should be evaluated in prospective studies.

REFERENCES

1. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 1999;29:239–44.

2. Uslan DZ, Crane SJ, Steckelberg JM, et al. Age- and sex-associated trends in bloodstream infection: a population-based study in Olmsted County, Minnesota. Arch Intern Med 2007;167:834–9.

3. Chang F-Y, MacDonald BB, Peacock JE, et al. A prospective multicenter study of staphylococcus aureus bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) 2003;82:322–32.

4. Fowler VG Jr., Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with Staphylococcus aureus bacteremia: experience in 103 patients. J Am Coll Cardiol 1997;30:1072–8.

5. Fowler VG Jr., Justice A, Moore C, et al. Risk factors for hematogenous complications of intravascular catheter-associated *Staphylococcus aureus* bacteremia. Clin Infect Dis 2005;40:695–703.

6. Hill EE, Vanderschueren S, Verhaegen J, et al. Risk factors for infective endocarditis and outcome of patients with *Staphylococcus aureus* bacteremia. Mayo Clinic Proc 2007;82:1165–9.

7. Turnidge JD, Kotsanas D, Munckhof W, et al., on behalf of the Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust 2009;191:368–73.

8. Holden E, Bashir A, Das I, et al. *Staphylococcus aureus* bacteraemia in a UK tertiary referral centre: a "transoesophageal echocardiogram for all" policy. J Antimicrob Chemother 2014;69:1960–5.

9. Kaasch AJ, Barlow G, Edgeworth JD, et al., on behalf of ISAC, INSTINCT, SABG, UKCIRG, and Colleagues. *Staphylococcus aureus* bloodstream infection: a pooled analysis of five prospective, observational studies [published correction appears in J Infect 2014;69:306–7]. J Infect 2014;68:242–51.

10. Vos FJ, Kullberg BJ, Sturm PD, et al. Metastatic infectious disease and clinical outcome in *Staphylococcus aureus* and Streptococcus species bacteremia. Medicine (Baltimore) 2012;91:86–94.

11. Hubert S, Thuny F, Resseguier N, et al. Prediction of symptomatic embolism in infective endocarditis: construction and validation of a risk calculator in a multicenter cohort. J Am Coll Cardiol 2013;62:1384–92.

12. Incani A, Hair C, Purnell P, et al. *Staphylococcus aureus* bacteraemia: evaluation of the role of transoesophageal echocardiography in identifying clinically unsuspected endocarditis. Eur J Clin Microb Infect Dis 2013;32:1003–8.

13. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America [published corrections appear in Clin Infect Dis 2010;50:1079 and Clin Infect Dis 2010;50:457]. Clin Infect Dis 2009;49:1–45.

14. Kaasch AJ, Fowler VG Jr., Rieg S, et al. Use of a simple criteria set for guiding echocardiography in nosocomial *Staphylococcus aureus* bacteremia. Clin Infect Dis 2011;53:1–9.

15. Khatib R, Sharma M. Echocardiography is dispensable in uncomplicated *Staphylococcus aureus* bacteremia. Medicine (Baltimore) 2013;92:182–8.

16. Casella F, Rana B, Casazza G, et al. The potential impact of contemporary transthoracic echocardiography on the management of patients with native valve endocarditis: a comparison with transesophageal echocardiography. Echocardiography 2009;26:900–6.

17. Rasmussen RV, Høst U, Arpi M, et al. Prevalence of infective endocarditis in patients with *Staphylococcus aureus* bacteraemia: the value of screening with echocardiography. Eur J Echocardiogr 2011;12:414–20.

18. Van Hal SJ, Mathur G, Kelly J, Aronis C, Cranney GB, Jones PD. The role of transthoracic echocardiography in excluding left sided infective endocarditis in *Staphylococcus aureus* bacteraemia. J Infect 2005;51:218–21.

19. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: a review. JAMA 2014;312:1330–41.

20. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. CLSI Approved Standard M100-S23. Wayne, PA: Clinical and Laboratory Standards Institute, 2013.

21. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791–7.

22. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–8.

23. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol 1991;44:763–70.

24. Joseph JP, Meddows TR, Webster DP, et al. Prioritizing echocardiography in *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2013;68:444–9.

25. Gruneir A, Dhalla IA, van Walraven C, et al. Unplanned readmissions after hospital discharge among patients identified as being at high risk for readmission using a validated predictive algorithm. Open Med 2011;5:e104–11.

26. Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000–2006. J Infect Dis 2008;198:336–43.

KEY WORDS bacteremia, echocardiogram, endocarditis, *Staphylococcus aureus*