JACC Vol. 30, No. 4
October 1997:1072–8

Role of Echocardiography in Evaluation of Patients With *Staphylococcus aureus* Bacteremia: Experience in 103 Patients

VANCE G. FOWLER, JR., MD, JENNIFER LI, MD, G. RALPH COREY, MD, JERRY BOLEY, MD, KIEREN A. MARR, MD, AJAY K. GOPAL, MD, LI KUO KONG, MD, GEOFFREY GOTTLIEB, MD, CAROLYN L. DONOVAN, MD, FACC, DANIEL J. SEXTON, MD, THOMAS RYAN, MD, FACC

Durham, North Carolina

Objectives. **The purpose of this prospective study was to examine the role of echocardiography in patients with *Staphylococcus aureus* bacteremia (SAB).**

Background. **The reported incidence of infective endocarditis (IE) among patients with SAB varies widely. Distinguishing patients with uncomplicated bacteremia from those with IE is therapeutically and prognostically important, but often difficult.**

Methods. **One hundred-three consecutive patients undergoing both transthoracic (TTE) echocardiography and transesophageal (TEE) echocardiography were prospectively evaluated. All patients presented with fever and ≥1 positive blood culture and were followed up for 12 weeks.**

Results. **Although predisposing heart disease was present in 42 patients (41%), clinical evidence of infective endocarditis (IE) was rare (7%). TTE revealed anatomic abnormalities in 33 patients, but vegetations in only 7 (7%), and was considered indeterminate in 19 (18%). TEE identified vegetations in 22 patients (aortic valve in 5, mitral valve in 9, tricuspid valve in 4, catheter in 2 and pacemaker in 2, abscesses in 2, valve perforation in 1 and new severe regurgitation in 1; 26 total [25%]). Using Duke criteria for the diagnosis of IE, definite IE was present in 26 patients (25%). Clinical findings and predisposing heart disease did not distinguish between patients with and without IE. The sensitivity of TTE for detecting IE was 32%, and the specificity was 100%. The addition of TEE increased the sensitivity to 100%, but resulted in one false positive result (specificity 99%). TEE detected evidence of IE in 19% of patients with a negative TTE and 21% of patients with an indeterminate TTE. At follow-up, cure of staphylococcal infection occurred in a similar percentage of patients with and without IE (77% and 75%, respectively). However, death due to sepsis was significantly more likely among patients with IE (4 of 26 [15%]) than among those without IE (2 of 77 [3%]) ($p = 0.03$).**

Conclusions. **Our results suggest that IE is common among patients admitted to the hospital with SAB and is associated with an increased risk of death due to sepsis. TEE is essential to establish the diagnosis and to detect associated complications. Therefore, the test should be considered part of the early evaluation of patients with SAB.**

(J Am Coll Cardiol 1997;30:1072–8)

Staphylococcus aureus bacteremia (SAB) is a serious, common condition often associated with infective endocarditis (IE). The reported incidence of IE in patients with SAB varies widely depending on the patient population and has been reported to be 5% to 64% (1–11). Distinguishing patients with uncomplicated SAB from those with IE is therapeutically and prognostically important, but often difficult. The clinical diagnosis of IE traditionally relies on typical Oslerian findings that are often absent, especially in the early stages of disease (12–14). The difficulty in diagnosing IE in patients with staphylococcemia has made the practice of short-course therapy (≤14 days) for the treatment of uncomplicated SAB controversial (15), primarily because of the potential for relapse in patients with inadequately treated IE. This concern underscores the importance of establishing an accurate diagnosis early in the course of therapy of patients with SAB.

Transthoracic echocardiography (TTE) is often used to evaluate patients with suspected IE; indeed, the latest diagnostic criteria for IE rely heavily on the echocardiogram (16). However, the sensitivity of TTE to detect vegetations, the most common echocardiographic manifestation of IE, is only 40% to 80% (17), and the clinical utility of the test will vary, depending on the prevalence of disease in the group being studied. Given the variable prevalence of IE and the modest sensitivity of TTE, it is not surprising that the clinical utility of echocardiography in patients with SAB has not been established.

Transesophageal echocardiography (TEE) has been shown to be superior to TTE for the diagnosis of IE (18–21), especially to identify small vegetations (22), prosthetic valve endocarditis (23) and paravalvular abscesses (24). We therefore hypothesized that TEE would be diagnostically and prognostically useful in patients with SAB. To test this hypothesis and to determine the relative diagnostic value of the two

From the Department of Medicine, Divisions of Infectious Diseases and Cardiology and Department of Pediatrics, Duke University Medical Center, Durham, North Carolina.

Manuscript received March 3, 1997; revised manuscript received June 3, 1997, accepted June 21, 1997.

Address for correspondence: Dr. Vance G. Fowler, Jr., P.O. Box 3824, Duke University Medical Center, Durham, North Carolina 27710. E-mail: fowle007@mc.duke.edu.

0735-1097/97/$17.00
PII S0735-1097(97)00250-7

Abbreviations and Acronyms

IE = infective endocarditis
SAB = *Staphylococcus aureus* bacteremia
TTE = transthoracic echocardiography
TEE = transesophageal echocardiography

echocardiographic modalities compared with clinical variables for detecting IE in patients with SAB, we prospectively evaluated a cohort of 103 consecutive patients with SAB who underwent both TTE and TEE.

Methods

Patient group. Between September 1, 1994 and January 1, 1996, 284 inpatients at Duke University Medical Center had one or more blood cultures positive for *S. aureus* and clinical evidence of infection. One hundred-nine patients were excluded for the following reasons: age <18 years (n = 26), polymicrobic infection (n = 30), neutropenia (white blood cell count $<1.0 \times 109$/liter) (n = 17), death before blood cultures turning positive (n = 16) or outpatient status (n = 20). The remaining 176 patients were eligible for the current study. Seventy-two of these patients did not undergo TEE because of refusal by either the patient or attending physician. One additional patient was excluded because TTE was not performed. Thus, 103 patients with one or more blood cultures positive for *S. aureus* underwent both TTE and TEE to find evidence of IE and are included in this analysis. Table 1 compares the demographic and clinical characteristics of the study group with those of patients who were screened and subsequently excluded from participation.

Each patient underwent a prospective clinical examination at the time of presentation by one of the investigators (V.G.F., K.A.M., A.K.G.) for signs suggestive of IE (new or changing heart murmur, peripheral stigmata or splenomegaly) and focus of infection. A lesion was considered the source (primary focus) of infection if its presence antedated the bacteremia; all other infections were considered secondary foci. An intravascular catheter was considered as the portal of entry if 1) there was evidence of inflammation at the catheter insertion site or 2) a catheter-tip culture was positive for *S. aureus*, or both, and 3) there was no evidence of an alternative source (25). *Staphylococcus aureus* bacteremia was defined as community acquired if positive blood cultures were obtained within 72 h of hospital admission and nosocomial if the first positive blood culture was obtained >72 h after hospital admission.

Definition of IE. Endocarditis was defined according to the Duke criteria (16), a sensitive (16,26–30) and specific (26,31) scheme relying on several criteria, designated major and minor, to establish the diagnosis of IE (Table 2). Major criteria include blood cultures persistently positive for typical endocardial pathogens and echocardiographic evidence of IE such as an intracardiac oscillating mass, abscess, new valvular regurgitation or new dehiscence of a prosthetic valve.

Patient outcome. All patients were followed up 12 weeks after the date of the first blood culture by telephone contact with the patient, a family member or the patient's primary care physician. Four categories of outcome were defined: 1) cure—patients in this category completed therapy for SAB and had no recurrent staphylococcal infection within the 12-week follow-up period; 2) relapse—patients in this category completed therapy for SAB and demonstrated clinical resolution of their infection but had culture-confirmed recurrent *S. aureus* infection with the same antibiogram as the initial isolate within the follow-up period; 3) death due to SAB—patient deaths were attributed to staphylococcal infection if the patient had persistent signs or symptoms of infection, positive blood cultures or a persistent focus of infection in the absence of

Table 1. Clinical and Demographic Characteristics of Patients With *Staphylococcus aureus* Bacteremia With and Without Infective Endocarditis

	Study Patients			
	All Pts (n = 103)	Pts With IE (n = 26)	Pts Without IE (n = 77)	Excluded Pts (n = 109)
Demographics				
Age (yr)	56 ± 15	60 ± 15	56 ± 16	54 ± 17
Gender (male)	57 (55%)	18 (69%)	39 (51%)	51 (47%)
Race				
White	49 (48%)	10 (38%)	39 (51%)	58 (56%)
Black	50 (48%)	15 (58%)	35 (45%)	45 (41%)
Source of infection				
No focus or unknown	6 (6%)	3 (12%)	3 (4%)	35 (32%)
Deep tissue infection	28 (27%)	7 (27%)	21 (27%)	35 (32%)
Catheter focus	69 (67%)	16 (61%)	53 (69%)	40 (37%)
Nosocomial	61 (59%)	17 (65%)	44 (57%)	68 (62%)
Community acquired	38 (37%)	8 (31%)	30 (39%)	36 (33%)
Acquired in nursing home	4 (4%)	1 (4%)	3 (4%)	4 (4%)

No comparison between patients with and without infective endocarditis reached statistical significance. Data are presented as mean value ± SD or number (%) of patients. IE = infective endocarditis; Pts = patients.

Table 2. Summary of Duke Criteria for Infective Endocarditis

I. Major criteria
  A. Positive blood cultures for IE
    1. Typical organisms from two or more separate blood cultures
      a. *Streptococcus viridans*,* *Streptococcus bovis*, HACEK group or
      b. Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, or
    2. Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from
      a. Blood cultures drawn >12 h apart or
      b. All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 h apart
  B. Evidence of endocardial involvement
    1. Echocardiogram positive for IE
      a. Oscillating intracardiac mass on valve or supporting structure, or in the path of regurgitant jets or on implanted material, in the absence of an alternative anatomic explanation or
      b. Abscess or
      c. New partial dehiscence of a prosthetic valve or
    2. New valvular regurgitation (increase or change in preexisting murmur not sufficient)
II. Minor criteria
  A. Predisposition: predisposing heart condition or intravenous drug use
  B. Fever ≥38°C
  C. Vascular phenomena
  D. Immunologic phenomena
  E. Microbiologic evidence: positive blood culture not meeting major criterion† or serologic evidence of active infection with appropriate organism
  F. Echocardiogram consistent with IE but not meeting major criterion
III. Definite IE defined using:
  A. Pathologic criteria
    1. Microorganism demonstrated by culture or histologic study in a vegetation, a vegetation that has embolized or in an intracardiac abscess or
    2. Pathologic lesions confirmed by histologic study showing active IE
  B. Clinical criteria (see above): two major or one major and three minor or five minor

*Including nutritional variant strains. †Excluding single positive cultures for organisms that do not cause infective echocarditis (IE). HACEK = *Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae.*

another explanation for death; and 4) death due to underlying disease—patients were placed in this category if deaths were from defined underlying disease other than staphylococcal bacteremia.

Echocardiography. TTE was performed using a 2.5- or 3.5-MHz phased-array transducer. Two-dimensional imaging from multiple tomographic planes and spectral Doppler and color flow imaging were used in all patients. TEE using a 5.0- or 6.2-MHz transducer was performed in fasting patients, using topical pharyngeal anesthesia and conscious sedation. Images were recorded on ½-in. superVHS videotape and in a digital full-screen cine loop display format (EchoNet, Heartlab, Inc.). All echocardiograms were performed within 9 days of study entry, and the results of all echocardiographic studies were made available to the referring physicians. Informed consent was obtained in all patients before TEE.

Echocardiograms were analyzed specifically for evidence of IE. Findings consistent with IE included vegetations, abscesses, paravalvular prosthetic valve regurgitation, new valvular regurgitation and otherwise unexplained valvular dysfunction (see later). Vegetations were defined as irregularly shaped echogenic masses adherent to valves, endothelial surfaces or intracardiac prosthetic devices (such as indwelling catheters or pacemaker leads). From the TEE recording, vegetations were categorized as either small (≤8 mm in greatest dimension) or large (>8 mm in dimension). Variables used to differentiate vegetations from noninfectious masses included oscillating motion (high frequency movement independent of the associated valvular motion), mobility (exceeding and independent of the associated valve structure) and shaggy or irregular surfaces. Because serial studies were not analyzed, a change in appearance or size over time was not a diagnostic criterion used in this study. Abscesses were defined as thickened areas or masses within the myocardium or annular region, characterized by an irregular nonhomogeneous echogenic or echolucent appearance. Blood flow within the space, as defined using color Doppler imaging, was an additional variable used to support the diagnosis of an abscess. Other unexplained valvular abnormalities believed to be consistent with IE included new valvular regurgitation (at least moderate in severity, not demonstrated on a previous echocardiogram) or valvular tissue destruction or perforation (detected with a combination of typical findings on two-dimensional echocardiographic and color flow imaging.)

Echocardiograms were also analyzed for the presence or absence of heart disease predisposing to IE. Factors thought to increase the risk of susceptibility included nonspecific abnormalities (such as leaflet thickening, prolapse, calcification or regurgitation), congenital heart disease (except uncomplicated secundum atrial septal defect) and the presence of intracardiac devices (including prosthetic valves, indwelling catheters or pacemaker leads).

TTE results were categorized as either diagnostic of IE, negative or indeterminate. A study was considered diagnostic of IE if any one of the echocardiographic criteria described previously was present. The TTE was considered negative if image quality was adequate to permit evaluation of all four valves and none of the diagnostic echocardiographic criteria listed above were fulfilled. An indeterminate result included 1) the presence of predisposing heart disease, not meeting diagnostic echocardiographic criteria for IE; 2) other structural or functional valvular abnormalities not meeting the previous criteria for a firm diagnosis of IE; or 3) inadequate image quality precluding complete evaluation.

TEE results were analyzed in a similar fashion, using identical criteria to establish the diagnosis of IE. Because TEE is often used as the final arbiter to judge the presence or absence of IE in patients with bacteremia, we attempted to categorize the TEE result as either positive or negative. Thus, an indeterminate result was not permitted in the interpretation of the TEE.

An attending echocardiographer did a clinical reading of all echocardiograms at the time of the procedure. In the majority

of cases, the TEE was performed after the TTE. Because of the potential bias created by sequential readings, all TEEs were later reinterpreted in a blinded manner by one of the investigators. To minimize the bias created by knowing that all patients in the series had SAB, 20 randomly selected TEEs were mixed into the case series being reviewed. This was designed to reduce the pretest likelihood of disease in the series of echocardiograms being interpreted in blinded manner. None of the 20 randomly selected TEEs were read as having IE. Agreement between the clinical and investigator interpretations was excellent (100 of 103 [97%]). In all three discordant results, the clinical reading was negative, whereas the blinded reading was positive for IE. The results of the clinical interpretation were used for all subsequent data analyses.

Statistics. For continuous variables, data are expressed as the mean value ± SD unless otherwise specified. Categoric variables are expressed as a percentage. For categoric variables, comparisons between groups were made using the chi-square test. Results were considered significant at $p < 0.05$.

Results

Demographics and clinical features. Between September 1, 1994 and January 27, 1996, 103 (59%) of 176 eligible patients with SAB were prospectively examined by TTE and TEE within 5.7 ± 3.4 days of the first positive blood culture. Of these 103 patients, 18 (17%) had one blood culture positive and 85 (83%) had more than one blood culture positive for SAB. All 26 patients with definite IE had more than one positive blood culture. The mean interval between TTE and TEE was 2.5 ± 4.0 days. The demographic and clinical features of the patients with and without IE are presented in Table 1. The mean age of the patients was 56 ± 15 years. Fifty patients (49%) were African-American, 49 (48%) were white, and 57 (55%) were men. Injection drug use was a predisposing factor in 12 patients (12%). An identifiable source of bacteremia was present in 97 patients (94%)—an intravascular device in 69 patients and a deep tissue infection in 28 patients. Six of the patients were injection drug users with no obvious focus of infection. Community- or nursing home–acquired SAB occurred in 42 patients, and nosocomial SAB occurred in the remaining 61 patients.

Clinical evidence of IE. Forty-two patients (41%) had either clinical or echocardiographic evidence, or both, of predisposing heart disease (Table 3). A prosthetic valve was present in 5 patients; 4 patients had pacemakers; and 33 had valvular abnormalities, including 16 patients with moderate or severe valvular regurgitation and 17 with thickened or calcified leaflets, or both.

Clinical evidence of IE was rare, occurring in only 7 (7%) of 103 patients. Of these seven patients, five had peripheral emboli and two developed new murmurs. Five (71%) of these seven patients met Duke criteria for definite IE. No patient demonstrated autoimmune phenomena or splenomegaly. A history of previous IE was present in four patients, all of whom were injection drug users. Two of these patients met Duke criteria for definite IE—one involving a native tricuspid valve and the other a prosthetic mitral valve. Thus, neither predisposing heart disease nor clinical findings at the time of presentation were useful variables to distinguish between patients with and without IE (Table 3).

Table 3. Predisposing Factors and Clinical Features in Patients With and Without Infective Endocarditis

	Pts With IE (n = 26)	Pts Without IE (n = 77)
Predisposing factors		
Intravenous drug use	5	7
Previous IE	2	3
Valvular abnormalities	12	21
Prosthetic valve	3	2
Pacemaker	2	2
Clinical features		
New murmur	2	0
Embolic event	3	2

None of the differences between the groups with and without IE reached statistical significance. IE = infective endocarditis; Pts = patients.

Echocardiographic findings. Echocardiographic findings are summarized in Table 3. TTE revealed predisposing anatomic abnormalities for IE, such as leaflet thickening or calcification, or both, in 33 (32%) of 103 patients. Transthoracic echocardiography was negative for IE in 77, indeterminate in 19 and positive for vegetations in 7 patients (Fig. 1). These vegetations involved the mitral valve (n = 2), aortic valve (n = 2) and tricuspid valve (n = 3). Other findings consistent with IE, such as abscess or leaflet perforation, were not detected with TTE. TEE was significantly more sensitive for detecting vegetations compared with TTE ($p = 0.004$) and identified vegetations in 22 patients (aortic valve in 5, mitral valve in 9, tricuspid valve in 4, indwelling catheter in 2 and pacemaker in 2), aortic root abscess in 2, valve perforation (anterior leaflet) in 1 and new severe valvular regurgitation in 1 patient. Vegetations were small (≤8 mm maximal dimension) in 15 patients (68%). Of the seven large vegetations (9- to 30-mm maximal dimension), four involved the tricuspid valve. No vegetation seen on TTE was missed by TEE and no single

Figure 1. A comparison of the results of TTE **(open bars)** and TEE **(solid bars)** in all 103 study patients. Although both tests identified the same number of patients as negative, TEE identified significantly more positive results ($p = 0.0005$). In 19 patients, the results of TTE were considered indeterminate for IE. By study design, TEE studies were not interpreted as indeterminate.

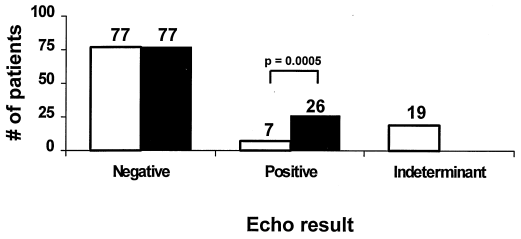

Table 4. Comparison of Findings Detected by Transthoracic and Transesophageal Echocardiography

	TTE	TEE
Vegetation	7	22*
Mitral	2	9
Aortic	2	5
Tricuspid	3	4
Other	0	4
Abscess	0	2
Perforation	0	1
New valvular regurgitation	0	1
Total	7	26†

*p = 0.004, †p = 0.0005 versus transthoracic echocardiography (TTE). TEE = transesophageal echocardiography.

category of findings accounted for the increased diagnostic yield provided by TEE (Table 4). Overall, TEE identified evidence of IE in 26 patients compared with 7 patients in whom TTE was used (p = 0.0005).

A comparison of the results of the two echocardiographic modalities is presented in Figure 2. Among 19 patients with an indeterminate TTE result, vegetations were detected by TEE in four patients, and the remaining 15 patients were reclassified as negative. Of the 77 patients with a negative TTE, 15 had vegetations on TEE. Thus, TEE detected evidence of IE in 4 (21%) of 19 patients with an indeterminate TTE and 15 (19%) of 77 patients with a negative TTE.

Diagnosis of IE. Twenty-six patients met Duke criteria for definite IE. In all patients, two major criteria (echocardiographic findings and persistently positive blood cultures) were present. The diagnosis was based on TTE findings in only seven patients. Thus, using Duke criteria, the sensitivity of TTE to detect definite IE in this group was 32%. Although there were no false positive TTE findings, the negative predictive value of the test was only 81%, in part due to the number of indeterminate TTE results (n = 19). In 19 patients (73%), the diagnosis was established on the basis of TEE findings alone. No patient met Duke criteria for definite IE in the absence of a positive TEE, resulting in a sensitivity of 100%.

Figure 2. TEE results are shown as a function of the TTE findings, demonstrating the incremental value of TEE. Among 77 patients with a negative TTE result, 15 had evidence of IE on TEE. Among 19 patients with an indeterminate TTE result, 15 were reclassified as negative and 4 as positive by TEE. All seven patients with a positive TTE also had a positive TEE.

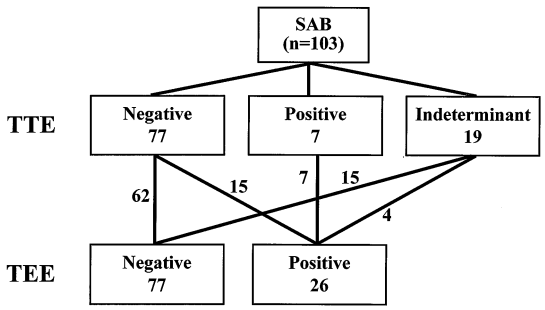

Table 5. Comparison of Clinical Outcome Among Patients With and Without Infective Endocarditis

	Pts With IE (n = 26)	Pts Without IE (n = 77)
Resolution of infection	20	58
Relapse	1	9
Death due to SAB	4	2*
Death due to other causes†	1	8

*p = 0.003 versus infective endocarditis. †Other causes include malignancy (n = 3), myocardial infarction (n = 2), infection with another organism, pulmonary embolus (n = 1) and toxic megacolon (n = 1). IE = infective endocarditis; SAB = *Staphylococcus aureus* bacteremia.

The incremental yield provided by TEE was predominantly due to its ability to detect small vegetations and intracardiac complications such as abscesses. One patient was diagnosed with IE despite the absence of vegetations on TEE, on the basis of new severe aortic regurgitation and persistently positive blood cultures. This patient, who was later found to have an aortic root dissection but no pathologic evidence of IE, was classified as having a false positive result, yielding a specificity of 99%.

Patient outcome. All patients were followed up for 12 weeks after the first positive blood culture. Clinical outcome at the time of follow-up is summarized in Table 5. Staphylococcal infection was cured with similar frequency in both groups (77% in patients with IE and 75% in patients without IE, p = NS). Death due to staphylococcal sepsis was significantly more likely in patients with IE (4 [15%] of 26) than in those without IE (2 [1.3%] of 77, p = 0.003). None of the 77 patients in whom the diagnosis of IE was excluded on the basis of the Duke criteria and a negative TEE subsequently developed IE, although 9 had a relapse due to deep tissue infections. Treatment failure occurred in 5 (19%) of 26 patients with IE and 11 (13%) of 77 patients without IE (p = NS).

Discussion

Comparison with previous studies. *Staphylococcus aureus* is the second most common cause of native valve endocarditis (32,33) and is associated with a high mortality (34–36). A continuing challenge has been the prospective identification of IE in patients with staphylococcemia. Both clinical and echocardiographic criteria have been suggested as means to establish a diagnosis. In their classic 1976 study, Nolan and Beaty (8), reporting on 105 retrospectively collected patients with SAB, found that *S. aureus* IE may be predicted by the clinical triad of 1) community acquisition; 2) absence of an obvious primary focus; and 3) evidence of metastatic foci. Our results contrast sharply with their observations. There are several possible explanations to account for this difference:

1. The majority of our patients with definite IE (65%) acquired endocarditis while in the hospital. This is in contrast to the only other large prospective series, in which IE was detected in only 2 of 114 consecutive episodes of SAB (6).

Unfortunately, in that series, a uniform method of screening for IE was not carried out and clinical variables were used to guide the evaluation. As a result, underestimation of the number of cases of IE is quite possible, as would have occurred in our study had only clinical variables been used. In support of this underdiagnosis was the high mortality (32%) of hospital-acquired SAB reported in that clinical study (15), despite the absence of apparent IE. Other evidence supporting the high incidence of unsuspected IE among patients with staphylococcemia comes from a Danish study of 118 patients with documented *S. aureus* IE (34). In a country where autopsies are compulsory, 65 of these patients (55%) had no clinical evidence of IE and were only diagnosed at autopsy.

2. A second difference between our results and that of Nolan and Beaty (8) is that most patients with IE in our series (88%) had a known focus of infection. There are several possible reasons for this difference. The prospective design of our registry mandated examination of each patient with SAB at the time of presentation. Thus, sources of infection were identified early in the course of therapy. The low number of injection drug users and the high percentage of hospitalized patients are additional features that distinguish the current study from that of Nolan and Beaty (8).

3. Metastatic foci of infection were much less common in our experience. This may be due to the brief interval between the onset of symptoms and the initiation of antibiotic therapy in our patients (mean interval 2.4 days), thus aborting subsequent metastatic complications (37).

Detecting IE among patients with SAB. Thus, the traditional clinical predictors of IE in patients with SAB were of minimal value in establishing a diagnosis. In addition, the clinical examination itself provided evidence of IE in <20% of patients. It is therefore apparent that other methods are needed to aid in the diagnosis of IE among patients with SAB. We postulated that echocardiography, because it is an integral element of the Duke criteria, would be useful for this purpose. This application of echocardiography has not been tested in any previous prospective series. We therefore elected to perform both TTE and TEE early in the course of therapy of patients with SAB. The consistent prospective implementation of TEE appears to be the most important factor in differentiating our study from previous ones. We found that TEE detected evidence of clinically unsuspected IE in a high percentage of patients with SAB and was more sensitive than either clinical findings or TTE for this purpose. Intracardiac complications such as abscess and valve perforation were only detected by TEE.

In an attempt to define a subset of patients in whom TEE would be most beneficial, we evaluated its incremental value in patients with indeterminate as well as normal transthoracic studies (Fig. 2). In contrast to previous reports in which the diagnostic yield of TEE among patients with a normal TTE is very low (38), our findings in patients with SAB suggest otherwise. In fact, TEE evidence of IE was equally likely among patients with negative compared with indeterminate TTE results (both ~20%). Performing TEE only in patients with an indeterminate TTE result would have led to a failure to diagnose IE in 15 patients with "normal" transthoracic studies. Thus, the incremental yield of TEE cannot be predicted on the basis of the TTE results. Indeed, from our results, it would appear impossible to define a subset of patients with SAB in which TEE should not be performed.

The increase in diagnostic yield provided by TEE compared with TTE is higher in the present study than in previously reported series of patients with IE (39). The most likely explanation for this finding relates to the study design, which promoted the use of echocardiography early in the course of bacteremia, often before IE was clinically suspected. As a result, most echocardiograms were obtained at an early stage of disease, when vegetations were smaller and complications less likely. These conditions would tend to maximize the diagnostic superiority of TEE. Support for this argument lies in our observation that most of the vegetations (11 of 16) detected only by TEE were small in size.

Study limitations. There are several limitations to our investigation. First, only 59% of eligible adult inpatients with SAB during the period of data collection underwent both TTE and TEE. Our study design was susceptible to sampling bias because physicians tended to refer patients who had a greater likelihood of IE for echocardiography. However, because over one-third of our study patients had "low risk" (6,40,41) catheter-related bacteremia and were undergoing echocardiography to support short-course antibiotic therapy, this sampling bias was minimized. Furthermore, even if all patients who did not undergo TEE had IE, 26 (15%) of the 174 total patients would still have definite IE.

Finally, the diagnosis of definite IE in our study was largely based on echocardiographic rather than pathologic features. According to the Duke criteria, the finding of a vegetation in a patient with persistent SAB would establish the diagnosis of IE by fulfilling two major criteria. In some cases, especially in the presence of a "small" vegetation, false positive results may occur. This would lead to overtreatment of some patients with uncomplicated bacteremia who are mislabelled as having IE. Alternatively, this group may represent a form of "early" IE that may be cured with short-course therapy. Although specificity is difficult to address in studies such as ours, previous investigators have confirmed the high specificity of the Duke criteria in other patient groups (31). The fact that 15% of all study patients with definite IE died from staphylococcemia, whereas <3% of the remaining patients died as a result of sepsis, suggests that the diagnosis of IE was correct in the majority of cases.

Conclusions. To our knowledge, this is the first prospective series to use TEE to evaluate patients with SAB and the first to compare TEE with TTE in patients with staphylococcemia. Our findings suggest that IE is common among patients with SAB and is associated with an increased risk of death from sepsis. Establishing the diagnosis of IE in these patients is often difficult. The results of the current study suggest that TEE is frequently needed to secure a diagnosis and to detect serious intracardiac complications. Therefore, the test should

be strongly considered in patients with SAB and may be of particular value early in the course of therapy. Further evaluation of patients with small vegetations seen only on TEE, as well as their response to short-course therapy, will help guide the use of this sensitive technology in the future.

We acknowledge Allen Hsieh, MD for assistance with statistical analysis.

References

1. Cooper G, Platt R. *Staphylococcus aureus* bacteremia in diabetic patients: endocarditis and mortality. Am J Med 1982;73:658–62.
2. Gransden WR, Eykyn SJ, Phillips I. *Staphylococcus aureus* bacteraemia: 400 episodes in St Thomas's Hospital. BMJ 1984;288:300–3.
3. Knudsen AM, Rosdahl VT, Espersen F, Frimodt-Moller N, Skinhoj P, Bentzon MW. Catheter-related *Staphylococcus aureus* infections. J Hosp Infect 1993;23:123–31.
4. Lautenschlager S, Herzog C, Zimmerli W. Course and outcome of bacteremia due to *Staphylococcus aureus*: evaluation of different clinical case definitions. Clin Infect Dis 1993;16:567–73.
5. Mirimanoff RO, Glauser MP. Endocarditis during *Staphylococcus aureus* septicemia in a population of non drug addicts. Arch Intern Med 1982;142: 1311–3.
6. Mylotte JM, McDermott C, Spooner JA. Prospective study of 114 consecutive episodes of *Staphylococcus aureus* bacteremia. Rev Infect Dis 1987;9: 891–907.
7. Mylotte JM, Beam TR, Allen JC. *Staphylococcus aureus* bacteremia: a prospective study. South Med J 1983;76:1131–5.
8. Nolan CM, Beaty HN. *Staphylococcus aureus* bacteremia: current clinical patterns. Am J Med 1976;60:495–500.
9. Raad II, Sabbagh MF. Optimal duration of therapy for catheter-related *Staphylococcus aureus* bacteremia: a study of 55 cases and review. Clin Infect Dis 1992;14:75–82.
10. Watanakunakorn C, Baird IM. *Staphylococcus aureus* bacteremia and endocarditis associated with a removable infected intravenous device. Am J Med 1977;63:253–6.
11. Wilson R, Hamburger M. Fifteen years experience with *Staphylococcus* septicemia in a large city hospital. Am J Med 1957;22:437–57.
12. Hedstrom SA, Christensson B. *Staphylococcus aureus* septicemia and endocarditis at the University Hospital in Lund 1976–1980. Scand J Infect Dis 1983;41:38–48.
13. Watanakunakorn C, Tan JS, Phair JP. Some salient features of *Staphylococcus aureus* endocarditis. Am J Med 1973;54:473–81.
14. Watanakunakorn C, Tan JS. Diagnostic difficulties of staphylococcal endocarditis in geriatric patients. Geriatrics 1973;28:168–73.
15. Jernigan JA, Farr BM. Short-course therapy of catheter-related *Staphylococcus aureus* bacteremia: a meta-analysis. Ann Intern Med 1993;119:304–11.
16. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings: Duke Endocarditis Service. Am J Med 1994;96:200–9.
17. Khandheria BK. Suspected bacterial endocarditis: to TEE or not to TEE. J Am Coll Cardiol 1993;21:222–4.
18. Daniel WG, Mugge A. Transesophageal echocardiography. N Engl J Med 1995;332:1268–79.
19. Erbel R, Rohmann S, Drexler M, et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach: a prospective study. Eur Heart J 1988;9:43–53.
20. Shapiro SM, Young E, De Guzman S, et al. Transesophageal echocardiography in diagnosis of infective endocarditis. Chest 1994;105:377–82.
21. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. J Am Coll Cardiol 1991;18:391–7.
22. Birmingham GD, Rahko PS, Ballantyne F. Improved detection of infective endocarditis with transesophageal echocardiography. Am Heart J 1992;123: 774–81.
23. Daniel WG, Mugge A, Grote J, et al. Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. Am J Cardiol 1993;71:210–5.
24. Daniel WG, Mugge A, Martin RP, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med 1991;324:795–800.
25. Libman H, Arbeit RD. Complications associated with *Staphylococcus aureus* bacteremia. Arch Intern Med 1984;144:541–5.
26. Bayer AS. Diagnostic criteria for identifying cases of endocarditis—revisiting the Duke criteria two years later [editorial]. Clin Infect Dis 1996;23:303–4.
27. Bayer AS. Revised diagnostic criteria for infective endocarditis. Cardiol Clin North Am 1996;14:345–50.
28. Bayer AS, Ward JI, Ginzton LE, Shapiro SM. Evaluation of new clinical criteria for the diagnosis of infective endocarditis. Am J Med 1994;96:211–9.
29. Del Pont JM, De Cicco LT, Vartalitis C, et al. Infective endocarditis in children: clinical analyses and evaluation of two diagnostic criteria. Pediatr Infect Dis J 1995;14:1079–86.
30. Hoen B, Selton-Suty C, Danchin N, et al. Evaluation of the Duke criteria versus the Beth Israel criteria for the diagnosis of infective endocarditis. Clin Infect Dis 1995;21:905–9.
31. Hoen B, Beguinot I, Rabaud C, et al. The Duke criteria for diagnosing infective endocarditis are specific: analysis of 100 patients with acute fever or fever of unknown origin. Clin Infect Dis 1996;23:298–302.
32. Sheagren JN. *Staphylococcus aureus*: the persistent pathogen (second of two parts). N Engl J Med 1984;310:1437–42.
33. Sheagren JN. *Staphylococcus aureus*: the persistent pathogen (first of two parts). N Engl J Med 1984;310:1368–73.
34. Espersen F, Frimodt-Moller N. *Staphylococcus aureus* endocarditis: a review of 119 cases. Arch Intern Med 1986;146:1118–21.
35. Sanabria TJ, Alpert JS, Goldberg R, Pape LA, Cheeseman SH. Increasing frequency of staphylococcal infective endocarditis. Arch Intern Med 1990; 150:1305–9.
36. Watanakunakorn C. *Staphylococcus aureus* endocarditis at a community teaching hospital, 1980 to 1991: an analysis of 106 cases. Arch Intern Med 1994;154:2330–5.
37. Chen SC, Dwyer DE, Sorrell TC. A comparison of hospital- and community-acquired infective endocarditis. Am J Cardiol 1992;70:1449–52.
38. Lindner JR, Case RA, Dent JM, Abbott RD, Scheld WM, Kaul S. Diagnostic value of echocardiography in suspected endocarditis: an evaluation based on the pretest probability of disease. Circulation 1996;93:730–6.
39. Mugge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: reassessment of the prognostic implications of vegetation size determined by the transthoracic and transesophageal approach. J Am Coll Cardiol 1989;14:631–8.
40. Ehni WF, Reller LB. Short-course therapy for catheter-associated *Staphylococcus aureus* bacteremia. Arch Intern Med 1989;149:533–6.
41. Malanoski GJ, Samore MH, Pefanis A, Karchmer AW. *Staphylococcus aureus* catheter-associated bacteremia: minimal effective therapy and unusual infectious complications associated with arterial sheath catheters. Arch Intern Med 1995;155:1161–6.