Importance of Transesophageal Echocardiography in the Evaluation of *Staphylococcus aureus* Bacteremia

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Background and aim of the study: **Staphylococcus *aureus* is a leading cause of bacteremia and is often associated with endocarditis. The diagnosis of endocarditis may be missed when relying on clinical risk prediction, and this has led others to recommend transesophageal echocardiography (TEE) for diagnosis in most cases of *S. aureus* bacteremia (SAB). The study aim was to determine the likelihood of finding vegetations on TEE in patients with SAB in a suburban teaching hospital setting, and to identify risk factors predictive of vegetation on TEE.**

Methods: **All cases of SAB at Walter Reed Army Medical Center between January 2000 and May 2003 were evaluated. The prevalence of vegetations was determined in those cases selected for TEE. Potential risk factors for endocarditis were analyzed by review of medical records.**

Results: **A total of 176 patients had documented SAB during the time frame of the study, and 64 of these had TEE performed. Among the latter patients, 14% had a previously unidentified vegetation discovered by TEE. Patients with vegetation on TEE were as likely as those without vegetation to have nosocomial bacteremia, an alternate source of infection, and lack of valvular disease by prior surface echocardiography. Patients with a vegetation were significantly older (mean age 68.4 ± 10.9 versus 54.6 ± 19.6 years; p = 0.04).**

Conclusion: **TEE identified a significant number of vegetations resulting from SAB. The clinical risk profile and transthoracic echocardiography did not reliably exclude vegetation. These findings support the liberal use of TEE for the diagnosis of SAB.**

The Journal of Heart Valve Disease 2005;14:23-28

Staphylococcus aureus bacteremia (SAB) now ranks as the second most common blood culture isolate in the United States (1). SAB alone is a poor prognostic finding as it may frequently be complicated by endocarditis, resulting in even higher morbidity and mortality. Accurate diagnosis of endocarditis in this setting is important not only for prognosis but also to guide the duration of antibiotic therapy. Controversy exists regarding the ability to exclude endocarditis based on clinical risk factors and standard transthoracic echocardiography (TTE) alone. One proposed diagnostic approach incorporating routine transesophageal echocardiography (TEE) found a high prevalence of unsuspected vegetations in patients with SAB at a large tertiary medical center (2). Since the applicability of this approach to other patient populations is not known, the present authors aimed to explore their TEE experience regarding the risk for unsuspected vegetations in SAB.

The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense

Presented as preliminary data at the Army American College of Physicians Meeting, November 8th 2003, San Antonio, Texas, USA

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Clinical material and methods

Patient population

All patients in this single-center study were from Walter Reed Army Medical Center, a suburban, university-affiliated, 150-bed military hospital serving active duty personnel and military retirees as well as their family members in the Washington DC area. The study was approved by the institution's Department of Clinical Investigation.

The written record log maintained by the microbiological laboratory of all blood cultures drawn between

January 2000 and May 2003 was reviewed in order to identify those patients having at least one blood culture positive for *S. aureus* (SA).

Subsequently, the TEE database was searched to determine which patients with SAB had undergone TEE during their index hospital admission. Further analysis was restricted to those SAB patients who had undergone TEE.

Data collection

The Clinical Information System (ClinComp, San Diego, CA, USA), an integrated electronic patient record system used at the present authors' institution, allowed full retrieval of each patient's admission record. Clinical factors studied included admission diagnosis, the presence of fever at admission (temperature ≥38°C), presence of persistent fever (fever lasting more than 48 h after the start of antibiotic therapy), length of hospital stay, presence of murmur, planned duration of antibiotic therapy, and final clinical diagnosis of definite endocarditis (based on standard clinical criteria (3)). A determination of community-acquired SAB was made based on positive blood cultures drawn less than 72 h after admission. The number of positive SA cultures, total number of cultures obtained, and methicillin-resistance status was recorded for each patient. Multiple positive blood cultures for SA were defined as greater than one positive culture, regardless of time between cultures. In a similar fashion, blood cultures positive for additional organisms was defined as any non-SA organisms grown in any blood culture during the index hospitalization.

An alternate source for bacteremia was defined as the presence of an indwelling central venous catheter, cellulitis (or other significant soft tissue infection), septic thrombophlebitis, osteomyelitis or septic joint, pneumonia, urosepsis, or suspected infected prosthetic material. Alternate sources of bacteremia did not require positive cultures for SA from the specific site (e.g. positive catheter tip culture from a central venous line). Maximal values for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) during the index hospital stay were noted for those select patients in whom these values were obtained.

Echocardiography variables

The following characteristics were recorded (if present) from each patient's TEE report: vegetation and/or abscess, size of vegetation, severity of valvular regurgitation, and type of prosthetic heart valve. Vegetation was defined as a mobile echo density on a valve or endocardial surface without alternate explanation. Similar variables were recorded if a TTE study was performed and was adequate for interpretation. Transthoracic ultrasound in most cases utilized harmonic imaging. TEE was performed by an experienced cardiologist, using a multiplane-imaging probe.

Outcomes

The sole outcome studied was the presence of vegetation on TEE during the index hospitalization for SAB.

Statistical analysis

Fisher's exact test was used in univariate analysis for significant differences between patients with and those without vegetation on TEE with regard to dichotomous variables. Comparisons involving continuous variables were performed with independent *t*-testing, except that the Mann-Whitney *U*-test was used for variables not normally distributed (i.e. CRP, ESR and antibiotic treatment duration). All statistical analyses were performed using SPSS software (version 10.05, SPSS Inc., Chicago, IL, USA). Values were reported as mean ± SD, except where indicated. A two-sided p-value ≤0.05 was considered to be statistically significant.

Results

A total of 176 cases of SAB was diagnosed between January 2000 and May 2003. Among these patients, 64 (36%) were referred for TEE. These 64 patients were predominantly males, with the majority (59%) admitted to the hospital for a febrile illness (Table I). Many of the patients referred for TEE were not at high risk for SAB endocarditis based on traditional clinical criteria (e.g. absence of primary focus of infection, community acquisition, underlying valvular heart disease, and metastatic foci). In particular, three out of every four of patients referred for TEE had an alternate source of bacteremia, with almost 40% having an indwelling central venous line. Almost half had nosocomial SAB. Only one patient had a prosthetic valve, and significant valvular heart disease (≥ moderate aortic or mitral valvular regurgitation) was present in just one patient among five, based on TEE findings (Table II).

TEE identified nine patients with valvular vegetations, which represents 14% of the patients with SAB referred for TEE. The mean vegetation size was 2.6 ± 1.5 mm, and the location was as follows: mitral valve (n = 5), aortic valve (n = 2), aortic and mitral valve (n = 1), and non-valvular (n = 1). None of these vegetations was previously identified with TTE, which had been successfully performed in 75% of all patients with SAB undergoing TEE. Two additional patients met other criteria for definite endocarditis without demonstrating vegetation on TEE; one of these patients had a vegetation seen only by TTE.

Table I: Characteristics of patients (n = 64) with S. aureus bacteremia referred for transesophageal echocardiography.

Characteristic	Result
Male gender (n)	45 (70.3)
Age (years)*	56.5 ± 19.1 (20-91)
Community-acquired infection (n)	35 (54.7)
Alternate source of bacteremia (n)	48 (75)
Central intravenous line (n)	25 (39.1)
Skin infection (n)	7 (10.9)
Deep tissue infection (n)	9 (14.1)
Pneumonia (n)	3 (4.7)
Prosthetic material infection (n)	4 (6.3)
Hospitalized for febrile illness (n)	38 (59.4)
Fever (n)	55 (85.9)
Persistent fever (n)	40 (62.5)
Murmur (anytime during hospitalization) (n)	29 (45.4)
Multiple +ve blood cultures for *S. aureus* (n)	33 (51.6)
Methicillin-resistant *S. aureus*	26 (40.6)
Blood cultures +ve for additional organisms (n)	27 (42.2)
Prosthetic heart valve (n)	1 (1.6)
TTE performed/interpretable (n)	48 (75)
Vegetation on TEE (n)	9 (14.1)
Perivalvular abscess on TEE (n)	2 (3.1)
Final diagnosis of bacterial endocarditis (n)	11 (17.2)
Death during hospitalization (n)	5 (7.8)

*Values are mean ± SD (range)
Values in parentheses are percentages.
TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography

Negative findings on TTE could not exclude any subsequent finding of vegetation by TEE. Patients with and without vegetation on TEE were both likely to have an interpretable transthoracic examination without significant valvular regurgitation (56% versus 60%).

Univariate analysis failed to show any significant differences between patients with and without vegetations (on TEE) in clinical risk factors for SAB-related endocarditis such as community-acquired infection, absence of alternate source of infection, or persistent fevers (Table III). The presence or absence of a central venous catheter had no effect on the likelihood of a vegetation on TEE. Peripheral physical findings of endocarditis were seen in only one patient with a vegetation on TEE (and in one patient without a vegetation). Neither prior endocarditis nor intravenous drug abuse were analyzed as risk factors since neither factor was present in any of the patients with vegetations.

Older age was the only clinical variable that had a significant association with the presence of valvular vegetation; the mean age of those with a vegetation was 68.4 ± 10.9 years, and those without a vegetation 54.6 ± 19.6 years ($p = 0.04$). No patients aged ≤40 years had a vegetation on TEE, despite this age group representing almost one-third of all patients in the study.

None of the laboratory results helped to find patients more likely to have a TEE-identified vegetation (Table

Table II: Transesophageal echocardiography results on patients (n = 64) referred for transesophageal echocardiography.

Condition present	Trace/Mild	Moderate	Severe	Total
Tricuspid regurgitation (n)	27 (42.1)	2 (3.1)	2 (3.1)	31 (48.4)
Mitral regurgitation (n)	31 (48.4)	10 (15.6)	3 (4.7)	44 (68.8)
Aortic regurgitation (n)	20* (31.2)	2 (3.1)	2 (3.1)	24 (37.5)
Vegetation (n)	-	-	-	9 (14.1)
Abscess (n)	-	-	-	2 (3.1)

Values in parentheses are percentages.
*Trace in 15 cases, mild in five cases.

III). In particular, multiple positive cultures for SA, presence of methicillin-resistance or polymicrobial bacteremia were all not significantly different. Positive cultures for SA on more than one day were similar in those patients with and without vegetation (33.3% versus 41.8%; p = 0.73). Uncomplicated SAB caused elevation of inflammatory markers to the same degree as SAB resulting in cardiac vegetation, specifically the levels of ESR (81.4 ± 35.2 versus 84.4 ± 34.0 mm/h; p = 0.834) and CRP (13.7 ± 17.0 versus 13.9 ± 11.3 mg/dl; p = 0.465) when measured.

Discussion

The major finding of the present investigation was the confirmation of at least a moderate prevalence of previously unidentified vegetations when TEE is requested for SAB of any cause. In addition, SAB-associated endocarditis could not be predicted on the basis of either clinical or TTE features alone in those patients referred for transesophageal imaging. These findings suggest the importance of TEE in less select patient settings than prior studies conducted in tertiary care centers.

SAB can result from underlying endocarditis or have endocarditis as a sequelae, and either way the endocarditis can frequently elude diagnosis. Currently, the importance of TEE is firmly established to evaluate for underlying endocarditis when the etiology of SAB is unclear, or if there are risk factors such as the presence of a prosthetic valve. The results of the present study support emerging evidence for the value of TEE in identifying occult endocarditis as well as endocarditis resulting from known sources of SAB, such as nosocomial line infections. Fowler et al. (2) demonstrated a 25% prevalence of endocarditis in a prospective study of 103 SAB patients who all underwent TEE. A large majority (68%) of these cases of endocarditis would not have been diagnosed if TEE had not been performed. In a recent multicenter evaluation of SAB, 10% of patients were found to have definite endocarditis, even when TEE was not rigorously utilized (4). Half of the cases of SAB-related endocarditis diagnosed postmortem were not suspected clinically (5).

Table III: Comparison of S. aureus bacteremia patients with and without vegetation on transesophageal echocardiography.

Characteristic	Positive for vegetation (n = 9)	Negative for vegetation (n = 55)	p-value
Male gender (n)	6 (66.7)	39 (70.9)	1.00
Age (years)*	68.4 ± 10.9	54.6 ± 19.6	0.04
Community-acquired infection (n)	5 (55.6)	30 (54.5)	1.00
Alternate source of bacteremia (n)	6 (66.7)	42 (76.3)	0.40
Central intravenous line (n)	4 (44.4)	21 (38.1)	1.00
Hospitalized for febrile illness (n)	6 (66.7)	32 (58.2)	0.73
Fever (n)	8 (88.9)	47 (87)	1.00
Persistent fever (n)	5 (55.6)	35 (67.3)	0.71
Murmur (anytime during hospitalization) (n)	5 (55.6)	24 (44.4)	0.47
Multiple +ve blood cultures for *S. aureus* (n)	3 (33.3)	30 (54.5)	0.29
Methicillin-resistant *S. aureus*	2 (22.2)	24 (44.4)	0.29
Blood cultures +ve for additional organisms (n)	2 (22.2)	25 (45.5)	0.28
ESR (mm/h)+	81.4 (56)	84.4 (24.4)	0.83
CRP (mg/dl)+	13.7 (27.1)	13.9 (16.3)	0.47
Vegetation suspected on TTE (n)†	0 (0)	2 (4.7)	1.00
≥Moderate valve regurgitation on TTE (n)†	0 (0)‡	10 (23.2)	0.57
≥Moderate MR/AR on TTE (n)†	0 (0)‡	9 (20.9)	0.54
Interpretable TTE with ≤mild AR/MR (n)	5 (55.6)	33 (60)	1.0
≥Moderate MR/AR on TEE (n)	4 (44.9)	10 (18.2)	0.10
Planned duration of antibiotics (weeks)	5.6 ± 0.9	3.4 ± 1.7	0.001
Death during hospitalization (n)	1 (11.1)	4 (7.3)	0.54

Values in parentheses are percentages.
*Values are mean ± SD (range).
+Values are mean (interquartile range).
†Percentage of TTE studies
‡Five patients with interpretable, performed TTE
AR: Aortic regurgitation; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MR: Mitral regurgitation; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography.

It is likely that several factors contribute to the significant number of vegetations seen only by transesophageal imaging. TEE is superior to TTE in detecting vegetations, in particular the small vegetations (≤4 mm) seen in the present study (6,7). The predictive ability of risk factors for SAB-related endocarditis (community-acquired source of infection, absence of alternate source of infection, underlying heart disease, and intravenous drug abuse) may have been overestimated, since past studies have not routinely used TEE (4,8-10). In the one published study which involved only patients with SAB undergoing TEE, none of these clinical factors could adequately differentiate between patients with and without endocarditis (2).

A predictive benefit of early clearance of bacteremia cannot be excluded, since early follow up blood cultures were not systematically drawn (4,12). Other study limitations include the retrospective nature of the investigation and a referral bias of patients selected to undergo TEE by their providers. The major concern was that this selected population was at higher risk than the overall population of SAB patients, and this might lead to an overestimation of the true prevalence of vegetations with SAB, and an underestimation of the predictive ability of clinical factors. However, the clinical characteristics of this selected population suggested that a significant proportion would not have been considered high risk by standard clinical risk prediction, in particular the modest prevalence of underlying significant valvular heart disease and a large percentage of nosocomial infection

Younger age was the only clinical factor predictive of a negative TEE in the present study. This finding contrasts with the classic teaching that SAB in a young patient favors endocarditis due to a lower likelihood for alternate causes of bacteremia (13). One possibility for this finding was the status of the present patient population, which notably included no intravenous drug abusers. However, Suryati and Watson also recently reported a very low prevalence (1.4%) of endocarditis related to SAB in the youngest population of children aged ≤15 years (14). In addition, the prognosis of SAB is better at a younger age (4,8,15). Regardless, the present findings must be viewed with significant caution based on the small number of patients enrolled who had endocarditis. The need to perform TEE for SAB diagnosis in the young (≤40 years old) requires further investigation, as current studies - including the present one - have a mean age well over this limit, and younger patients have a lower likelihood of underlying acquired heart disease and a higher likelihood of optimal TTE imaging.

The importance of using TEE to identify all vegetations is based on the premise that these cases of endocarditis require longer antibiotic treatment and carry a similar adverse prognosis to more clinically apparent cases of endocarditis. TEE-identified cases of endocarditis do appear to carry a worse prognosis than uncomplicated SAB, and failure to comply with a diagnostic/treatment strategy that includes routine TEE is associated with poorer outcomes (2,15,16). However, SA endocarditis confirmed only by TEE may not be as bad as other cases. Larger vegetations (≥10 mm) have a higher embolic risk than vegetations that are small, such as those identified by TEE in the present study (17). Fowler et al. (18) also recently reported a better prognosis with endocarditis when TEE was required to make the diagnosis as opposed to other cases.

This uncertainty with regard to the prognostic value of TEE-identified vegetations is inherent in some published diagnostic strategies which advocate that TEE may not be required in the absence of clinical risk factors or persistently positive blood cultures (12,19).

In addition, patients at lower predicted risk than in the present study may not derive any significant benefit from TEE compared to a high-quality transthoracic imaging study.

In conclusion, TEE identifies a significant number of vegetations that might not be recognized with the use of clinical risk prediction or TTE alone. Defining the duration of safe treatment required for clinically unapparent cases of endocarditis identified only by TEE will help to determine the true value of this modality.

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