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MAJOR ARTICLE

Timing of Patient Management Decisions Relative to Echocardiography in *Staphylococcus aureus* Bacteremia: A Single-Center Retrospective Analysis

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Background. In patients with *Staphylococcus aureus* bacteremia (SAB), endocarditis evaluation includes transthoracic echocardiography (TTE) and, in patients at increased risk of endocarditis, subsequent transesophageal echocardiography (TEE). Whether performing TTE before TEE influences clinicians' decision making has not been well studied in patients deemed to warrant TEE.

Methods. In this retrospective case series, we studied clinician behavior at a large Veterans Affairs medical center regarding the care of adult patients diagnosed with SAB who completed both TTE and TEE ($n = 206$ episodes of SAB). The timing of key patient management decisions was compared to the timing of the patient's TTE and TEE. It was inferred whether each management decision could have been informed by TTE alone versus TTE plus subsequent TEE. Management decisions included the following: documentation of antibiotic treatment duration, initiation of synergistic antibiotics, consultation of relevant specialists, ordering of relevant imaging studies, and performance of valve surgery or cardiac device explanation.

Results. The primary outcome (any of the above 5 management decisions taking place) occurred after completion of TTE but before TEE in 13 SAB episodes (6.3%). The primary outcome occurred after completion of both TTE and TEE in 178 SAB episodes (86.4%). Documentation of antibiotic treatment duration accounted for the large majority of observed management decisions.

Conclusions. Among patients with SAB who are deemed to warrant TEE for endocarditis evaluation, TTE results alone rarely prompt clinical management decisions.

Keywords. endocarditis; *Staphylococcus aureus* bacteremia; transesophageal echocardiography; transthoracic echocardiography.

An episode of *Staphylococcus aureus* bacteremia (SAB) is associated with infective endocarditis in 6% to 22% of cases [1–5]. An individual's risk is heavily influenced by additional risk factors for endocarditis such as the presence of prosthetic heart valves or cardiac implantable electronic devices (CIEDs) [1–4, 6, 7]. A diagnosis of *S aureus* endocarditis carries a 6-month mortality of 26%, compared to 15% for SAB without endocarditis [5].

National and international guidelines recommend that all patients with SAB undergo echocardiography to evaluate for endocarditis [8–10]. Transthoracic echocardiography (TTE) is a noninvasive and widely available imaging modality for valvular assessment. Transthoracic echocardiography can be used to rule-in endocarditis if a valvular vegetation is identified, and, in select patients with a low pretest probability of endocarditis, TTE can also be used to rule-out endocarditis. Transesophageal echocardiography (TEE) is more costly and is semi-invasive, but offers increased diagnostic sensitivity for identification of vegetations [11, 12], especially vegetations on prosthetic heart valves [13] and CIED leads [6]. Transesophageal echocardiography also has been shown to offer superior sensitivity for detecting complications of infective endocarditis including perivalvular abscesses [14] and valve leaflet perforations [11]. Due to a lack of prospective clinical trial data, current guidelines regarding which SAB patients warrant TEE are categorized only as weak to moderate strength recommendations [10]. Numerous studies have identified endocarditis risk factors and designed scoring systems for patients with SAB that identify high-risk patients who should undergo TEE [3–5, 15–17].

An area of uncertainty is whether patients who are deemed to warrant TEE before they have completed a TTE should still undergo TTE first. From the current literature, it is not known whether TTE before TEE provides useful or actionable clinical information. It also is unknown whether performing TTE

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before TEE impacts the time to key management decisions. This retrospective chart review studied patients with an episode of SAB who underwent both TTE and TEE and measured the timing of key patient management decisions. Our aim was to explore how often management decisions were made after TTE but before TEE. By offering insight into real-world clinician behaviors, we hope to analyze the utility of current endocarditis testing to improve resource utilization and expedite effective endocarditis workup and management.

METHODS

Study Overview and Subjects

We performed a retrospective case series of patients diagnosed with SAB at the Minneapolis Veterans Affairs Medical Center (MVAMC); a 200-bed academically affiliated tertiary care hospital. Patients were identified using microbiology laboratory logs. Adult patients (≥18 years old) who had an episode of SAB (≥1 blood culture positive for growth of *S aureus*) between April 2012 and December 2019 were screened for inclusion. Patients who underwent sequential TTE and TEE were eligible for inclusion. Exclusion criteria were (1) not completing both TTE and TEE at the MVAMC within 6 weeks from the time of the initial positive *S aureus* blood culture, (2) completing TEE before TTE, and (3) having a prior history of incompletely treated endocarditis. A single patient with multiple episodes of SAB could be included more than once in the study if >21 days elapsed between initial blood culture clearance and newly re-positive blood cultures. It was thought that after 21 days, return of SAB would universally warrant repeating endocarditis workup.

Patient Consent Statement/Compliance With Ethics Guidelines

This study was reviewed by the MVAMC Institutional Review Board and determined to be exempt from review.

Outcomes

The outcomes of this study were meant to analyze real-world clinician behavior as opposed to more traditional patient-health outcomes. Among SAB patients who met inclusion criteria, we recorded the occurrence and timing of 5 key management decisions that were considered to be potentially influenced by echocardiography results:

1. Documentation of antibiotic treatment duration - Defined as the formal recommendation of an antibiotic treatment course duration in a note signed by an Infectious Diseases (ID) physician. (Of note, institutional protocol at the MVAMC requires automatic ID consultation for all patients with SAB. One hundred percent of included patients had an ID consult).
2. Ordering of synergistic antibiotics - Defined as the addition of ceftaroline, daptomycin, gentamicin, or rifampin to a primary antistaphylococcal antibiotic.
3. Ordering of relevant consultation(s) - Consults to Cardiology and Cardiac Surgery were considered "relevant" in all patients. Consults to Cardiology-Electrophysiology were considered relevant only in patients with a CIED (implantable cardioverter-defibrillator [ICD] and/or pacemaker).
4. Ordering of relevant imaging - Defined as any computed tomography or magnetic resonance study that was requested to evaluate for any of the following: "septic emboli," "infectious emboli," "metastatic infection," and/or "seeding."
5. Performance of cardiac procedure(s) - Defined as the performance of valve replacement, valve repair, myocardial abscess drainage, and/or explanation of a CIED. The time of the procedure reflects the time of the preoperative time-out.

The time of each management decision was compared to the time that a patient completed TTE and TEE to infer which of the echocardiograms "could" have influenced each management decision. If the preceding echocardiogram was positive or equivocal for signs of endocarditis, then all 5 management decisions were deemed to be potentially related to the result. However, if the proceeding echocardiogram was entirely negative for any signs of endocarditis, then only documentation of antibiotic duration was deemed to be potentially related (Figure 1). Because documentation of antibiotic duration can be guided by positive or negative echocardiography results, this was always classified as being potentially related to echocardiography. To be considered negative for endocarditis, echocardiography had to reveal no evidence of a valvular vegetation, CIED lead vegetation, valvular thickening, nonspecific valvular lesion, perivalvular myocardial abnormality, or previously unrecognized valvular dysfunction.

For all SAB episodes, it was noted whether the patient was ultimately diagnosed with definite endocarditis per modified Duke criteria [18]. The term "endocarditis" in this manuscript also includes CIED lead vegetations.

The primary outcome was a composite of any of the management decisions (above) occurring during a SAB episode. Each of the 5 management decisions was an individual secondary outcome. Primary and secondary outcomes were analyzed for the total study population and for the subgroup of patients diagnosed with endocarditis.

Additional outcomes analyzed included rate of serious TEE complications (GI perforation, significant bleeding, hemodynamically significant arrhythmias, severe persistent pain, laryngeal injury, or death) and the relative timing of TTE and TEE order placement and study completion.

At our institution, TTE studies are performed 7 days a week, with some limited availability on weekends. Transesophageal echocardiography studies for endocarditis workup are typically

Secondary Outcomes:	After TTE, Prior to TEE		After TTE and TEE	
	TTE negative:	TTE positive or equivocal:	TEE negative:	TEE positive or equivocal:
Documentation of Antibiotic Treatment Duration				
Ordering of Synergistic Antibiotics	Unrelated		Unrelated	
Ordering of Relevant Consult(s)	Unrelated		Unrelated	
Ordering of Relevant Imaging	Unrelated		Unrelated	
Performance of Cardiac Procedure(s)	Unrelated		Unrelated	

Figure 1. Removal of outcomes deemed to be unrelated to echocardiography. TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

performed only on weekdays. All TTE and TEE studies were interpreted by board-certified cardiologists specializing in echocardiographic imaging. Study quality was considered adequate or better when the aortic, mitral, and tricuspid valve anatomy and perivalvular tissues were seen well in multiple views.

Statistical Analysis

Our data analysis involved only the use of basic descriptive statistics.

RESULTS

Study Population

There were 426 episodes of SAB identified between April 2012 and December 2019. Of these, 206 episodes, involving 190 unique patients, met all criteria for inclusion in our analysis (Figure 2, Supplementary Tables 1 and 2). Of the included patients, the median age was 67.5 years old. A total of 98.5% of our Veteran population was male. In 26 episodes (12.6%), the patient had a CIED. In 8 episodes (3.9%), the patient had a prosthetic heart valve. In 3 episodes (1.5%), the patient had a history of infective endocarditis. No patients had a known history of congenital heart disease or rheumatic valvular disease. *Staphylococcus aureus* bacteremia was due to methicillin-resistant *S aureus* (MRSA) in 27.2% of episodes. Median duration of bacteremia was 2 days (range, 1–19 days), with a median duration of 1 day for methicillin-sensitive *S aureus* isolates and 3 days for MRSA isolates. The most common infection source was skin/soft tissue infections (with or without underlying osteomyelitis), which accounted for 76 episodes (36.7%). Twenty-eight episodes (13.5%) were attributed to an indwelling

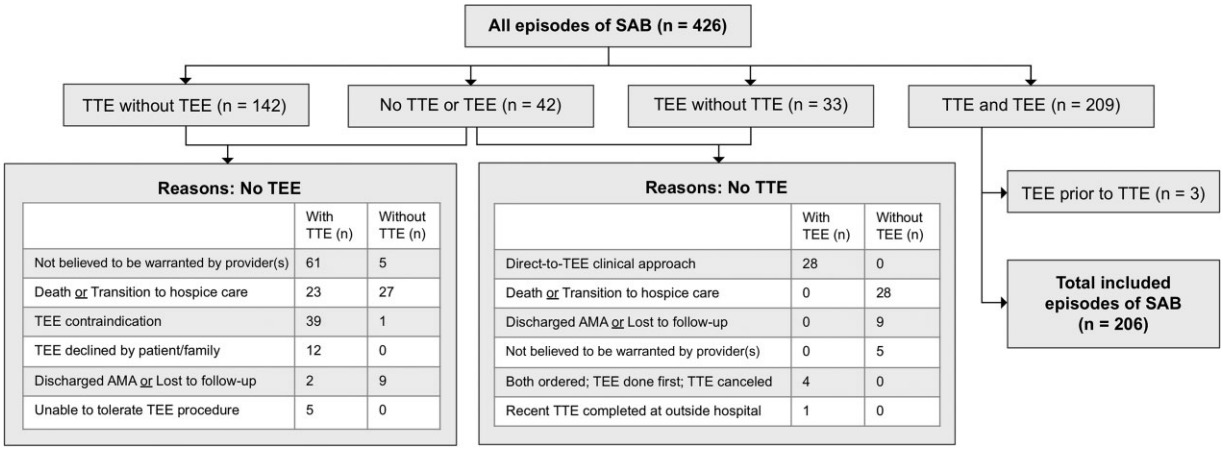

Figure 2. Flow diagram of all patients with an episode of *Staphylococcus aureus* bacteremia. AMA, against medical advice; SAB, *Staphylococcus aureus* bacteremia; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Table 1. Baseline Patient Demographic Characteristics and Bacteremia Characteristics

Patient Demographics and Background	
Age, median (years)	67.5
Age (years)	
18–34	2 (1.0%)
35–49	6 (2.9%)
50–64	70 (34.0%)
65–79	104 (50.5%)
80+	24 (11.7%)
Sex, female	3 (1.5%)
Sex, male	203 (98.5%)
Relevant Cardiac History	
Presence of CIED	26 (12.6%)
Presence of prosthetic heart valve(s) (mechanical or bioprosthetic)	8 (3.9%)
History of endocarditis	3 (1.5%)
Bacteremia Characteristics	
MSSA	150 (72.8%)
MRSA	55 (26.7%)
MSSA and MRSA	1 (0.5%)
Bacteremia duration, average (days)	3.07
Bacteremia duration, median (whole days)	2
Bacteremia duration (MSSA), median (whole days)	1
Bacteremia duration (MRSA), median (whole days)	3
Bacteremia Duration (Days)	
≤1 day	97 (47.1%)
2–3 days	42 (20.4%)
4–5 days	36 (17.5%)
6–9 days	21 (10.2%)
10+ days	10 (4.9%)
Diagnosis of endocarditis	35 (17.0%)
Initial Bacteremia Source	
Skin and soft tissue (with or without underlying osteomyelitis)	76 (36.7%)
Central line/venous access port/arteriovenous graft	32 (15.5%)
Genitourinary	15 (7.2%)
Primary septic arthritis (with or without orthopedic hardware)	14 (6.8%)
Other identified sources	18 (8.7%)
Unclear/unidentified	52 (25.1%)
Bacteremia associated with intravenous drug use	3 (1.4%)

Abbreviations: CIED, cardiac implantable electronic device; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S aureus*.

central catheter as the source. Fifty-two episodes were of unclear source (25.1%). Intravenous drug use was known to be present in 3 episodes (1.5%). In 35 episodes (17.0%), the patient was ultimately diagnosed with *S aureus* endocarditis by the modified Duke criteria (Table 1).

Transthoracic Echocardiography Quality

Transthoracic echocardiography quality was listed as "nondiagnostic," "poor," "suboptimal," or "less than ideal" in 15 episodes (7.3%), "fair" in 28 episodes (13.6%), "adequate" or "good" or in 155 episodes (75.2%), and was not documented in 8 episodes (3.9%).

Table 2. Observed Echocardiography Timing

Timing Between Echocardiography Order and Completion	
Median time between TTE order and TTE completion	0d 10h 38m
Median time between TEE order and TEE completion	1d 1h 17m
Relative Timing of TTE and TEE Completion	
Median time between TTE completion and TEE completion	2d 3h 26m
Time between TTE completion and TEE completion	
<24 hours	49 (23.8%)
24–48 hours	41 (19.9%)
48–72 hours	35 (17.0%)
72–96 hours	28 (13.6%)
96–120 hours	24 (11.7%)
>120 hours	29 (14.1%)
Relative Timing of TTE and TEE Orders	
Median time between TTE order and TEE order	1d 2h 50m
Time between TTE order and TEE order	
TEE ordered at same time as TTE (within 1 hour)	28 (13.6%)
TEE ordered 1–24 hours after TTE ordered	89 (43.2%)
TEE ordered >24 hours after TTE ordered	117 (56.8%)
TEE order placed after TTE was completed	164 (79.6%)

Abbreviations: d, days; h, hours; m, minutes; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Timing of Transthoracic Echocardiography and Transesophageal Echocardiography

The relative timing of echocardiography orders and completion are outlined in Table 2. The median time between TTE order and TTE completion was 10.6 hours. The median time between TEE order and TEE completion was 25.3 hours. The median interval between TTE completion and TEE completion was 51.4 hours.

We observed that TEE was ordered simultaneously with TTE in 28 (13.6%) episodes. Transesophageal echocardiography order was placed after TTE had already been completed in 164 (79.6%) episodes.

Primary and Secondary Outcomes

Primary and secondary outcomes are outlined in Table 3. The primary outcome occurred after completion of TTE but before completion of TEE in 13 episodes (6.3%). The primary outcome occurred after completion of both TTE and TEE in 178 episodes (86.4%).

Antibiotic treatment duration was documented after TTE but before TEE in 8 episodes (3.9%) and after both TTE and TEE in 176 episodes (85.4%). Synergistic antibiotic(s) were ordered after TTE but before TEE in 1 episode (0.5%) and after both TTE and TEE in 8 episodes (3.9%). Relevant consult(s) were ordered after TTE but before TEE in 3 episodes (1.5%) and after both TTE and TEE in 10 episodes (4.9%). Relevant imaging was ordered after TTE but before TEE in 1 episode (0.5%) and after both TTE and TEE in 3 episodes (1.5%). Cardiac procedures such as valve surgery, ICD explantation, and/or pacemaker explantation always took place after both TTE and TEE and occurred in 5 patients (2.4%).

Table 3. Primary and Secondary Outcomes

	SAB Episodes	SAB Episodes With Endocarditis Diagnosis
Primary Outcome: (Occurrence of Any of the 5 Secondary Outcomes)		
After TTE, before TEE	13 (6.4%)	2 (5.7%)
After TTE and TEE	178 (86.4%)	34 (97.1%)
Individual Secondary Outcomes		
1. Antibiotic Treatment Duration Documented		
After TTE, before TEE	8 (3.9%)	0 (0.0%)
After TTE and TEE	176 (85.4%)	32 (91.4%)
2. Synergistic Antibiotics Ordered		
After TTE, before TEE	1 (0.5%)	0 (0.0%)
After TTE and TEE	8 (3.9%)	7 (20.0%)
3. Relevant Consultation(s) Ordered		
After TTE, before TEE	3 (1.5%)	2 (5.7%)
After TTE and TEE	10 (4.9%)	10 (28.6%)
4. Relevant Imaging Ordered		
After TTE, before TEE	1 (0.5%)	0 (0.0%)
After TTE and TEE	3 (1.5%)	3 (8.6%)
5. Cardiac Procedure(s) Performed		
After TTE, before TEE	0 (0.0%)	0 (0.0%)
After TTE and TEE	5 (2.4%)	5 (14.3%)

Abbreviations: SAB, *Staphylococcus aureus* bacteremia; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

There were a total of 219 management decisions among the 206 episodes of SAB. Documentation of antibiotic duration accounted for a large majority of all management decisions. Of the 219 total management decisions, 14 (6.4%) took place after TTE but before TEE, and 205 (93.6%) took place after both TTE and TEE had been completed. (Additional data for each secondary outcome can be found in Supplementary Tables 3 and 4.)

When the primary outcome was limited to the subset of SAB episodes in which the patient was ultimately diagnosed with endocarditis ($n = 35$ episodes), the primary outcome occurred after TTE but before TEE in 2 episodes (5.7%) and occurred after completion of both TTE and TEE in 34 episodes (97.1%).

Serious TEE complications occurred in 0 patients. Among 5 patients excluded from this study due to their inability to tolerate TEE, none experienced significant TEE complications.

DISCUSSION

This retrospective case series analyzed provider behaviors in patients with SAB who underwent both TTE and TEE as part of their endocarditis workup. We observed that clinical management decision(s) took place after completion of TTE but before TEE in 6.4% of SAB episodes and took place after both TTE and TEE in 86.4% of episodes. Within the subpopulation of patients who were ultimately diagnosed with endocarditis by modified Duke criteria, 5.7% of episodes had management decision(s) made after TTE but before TEE, compared with 97.1% after both TTE and TEE.

Our results demonstrate that in this single-center observational study, among patients with SAB who underwent both TTE and TEE, few clinical management decisions were made before the completion of TEE. This finding held true for patients with endocarditis. We also observed a behavior at this institution that TTE and TEE are typically ordered in series, not in parallel, with TEE orders being placed after TTE had already been completed in 79.6% of cases.

Transthoracic echocardiography quality was listed as fair, adequate, or good in 89% of cases, so we believe that the majority of patients who underwent TEE did not do so because they had a low-quality or inadequate TTE. Rather, we suspect TEE was prompted by patients' endocarditis risk factors. Many patients had identifiable risk factors for endocarditis at the time of SAB diagnosis, which would qualify them for TEE per published endocarditis risk scores [3–5, 15–17]. Although some risk factors such as persistence of bacteremia cannot be known at the time of a patient's initial SAB diagnosis, several other key risk factors are typically immediately evident; for example, the presence of a prosthetic heart valve or CIED, history of endocarditis, underlying valvular heart disease, community-acquired bacteremia, intravenous drug usage, and short blood culture time to positivity. Physical manifestations of endocarditis including embolic phenomenon, secondary foci of infection, or cardiac conduction abnormalities can also be present at the time SAB is initially recognized. Separately, some patients can be immediately identified as being poor TTE candidates, including those with morbid obesity, chest wall deformities, or advanced chronic obstructive pulmonary disease [19, 20]. In many patients, it is evident at the time of SAB diagnosis that TEE will be warranted regardless of TTE results.

Our data suggest that in real-world practice, performing TTE before TEE rarely informs clinical management and may delay TEE. Among patients who qualify for TEE based on validated SAB endocarditis risk scores, delaying requests for TEE until after TTE may increase hospital length of stay, raise hospitalization costs, delay endocarditis diagnoses, and worsen patient outcomes. In patients diagnosed with endocarditis who warrant surgical valve replacement, prompt surgical intervention has been shown to reduce embolic events [21] and improve patient mortality [22], emphasizing the importance of prompt endocarditis diagnosis and management.

A notable limitation of our study is that our conclusions rely on the presumption that clinicians at our institution rationally responded to the information provided by TTE and applied knowledge of practice guidelines and endocarditis risk factor scores when deciding to pursue TEE. Infectious Diseases consultation was present in 100% of SAB episodes, and we therefore think this is a reasonable presumption to make, although patient cases were not independently evaluated to confirm that an indication for TEE was present. Such an analysis was not attempted because determining which intermediate-risk and low-risk SAB patients warrant TEE remains a topic of ongoing debate. Moreover, multiple SAB endocarditis risk scores

were published during our study time frame so attempting to retrospectively determine whether past clinician decision making was appropriate in the context of the medical literature at that specific point in time was not thought to be feasible.

There are additional limitations to this study. All relationships between echocardiography findings and patient management decisions were inferred based on the timing of management events relative to echocardiography results. In addition, it is possible that there are management decisions other than the 5 that we measured that are influenced by echocardiography. The single-center design of our study limits generalizability of our results, as does our Veteran population's strong male-predominance, older age, and high proportion of SAB related to skin and soft tissue infections and our low number of included persons who inject drugs. The secondary endpoint "documentation of antibiotic duration" was observed far more frequently than the other secondary endpoints and therefore heavily influenced the primary outcome. Although we believe this reflects real-world practice at our institution, the rarity of cardiac procedures and other secondary outcomes does suggest that our population may have been less ill than other SAB populations. This is also reflected in the relatively short observed median duration of bacteremia (2 days).

Our study did not investigate potential benefits of TTE before TEE outside of endocarditis evaluation, such as the assessment of cardiovascular hemodynamics and myocardial function. American Heart Association (AHA) guidelines on endocarditis have proposed, based on expert opinion, that TTE may be superior to TEE for quantifying hemodynamic dysfunction resulting from valvular regurgitation [8].

This study was performed in a high-resource medical setting, and the above discussion is focused on clinical care in high-income countries. TTE and especially TEE availability may be significantly limited in low- and middle-income countries. In such settings, different clinical approaches are needed to optimize SAB patient care and endocarditis evaluation.

Further prospective study of this topic is needed. In an ideal setting, randomized trials of SAB patients with risk factors for endocarditis would compare direct-to-TEE management versus a sequential TTE plus TEE approach and measure outcomes including time to endocarditis diagnosis, hospital length of stay, and clinical outcomes such as rate of septic embolic phenomenon. Updated cost efficiency analyses of different echocardiography approaches are also needed.

CONCLUSIONS

In patients with SAB who underwent both TTE and TEE for endocarditis evaluation, we observed that clinicians typically ordered these studies in series, but clinical management was rarely prompted by TTE results alone.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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