Staphylococcus aureus bacteremia: evaluation of the role of transesophageal echocardiography in identifying clinically unsuspected endocarditis.

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Abstract

Background

Staphylococcus aureus bacteremia (SAB) is an important cause of community and nosocomial sepsis with a significant mortality rate. Infective endocarditis (IE) is a serious complication occurring in up to 25% cases. Transesophageal echocardiography (TOE) significantly improves sensitivity of diagnosis. We compared the sensitivity and specificity of clinical evaluation alone in diagnosing IE.

Methods

We evaluated all adult patients with SAB at our centre from 1998-2006 to determine what proportion of clinically unsuspected cases were diagnosed with IE on TOE. IE was defined according to modified Duke criteria.

Results

The median age was 68 years, 77% were male and the majority of cases did not have a known pre-existing condition. 21% were MRSA. Intravascular devices was the most common cause of bacteraemia. TOE was performed in 144 (100%) of cases. IE was suspected clinically in 15% of cases, the overall prevalence of IE possible or definite on TOE inclusive Duke criteria was 29% (n=41). Following TOE, 22 (15%) cases were reclassified as either possible or definite endocarditis. TOE detected a vegetation in 37 (90%) of the 41 cases of IE. 19 (46%) were not suspected clinically by Duke criteria. Sensitivity improved in the presence of pre-existing valve lesion or community acquisition. Overall in-hospital mortality was 10%.

Conclusion

There is a high incidence of endocarditis in SAB and a large percentage of cases are not evident on clinical grounds. TOE evaluation is indicated for all medically suitable adult patients with SAB to improve detection of endocarditis.

Key words

Infective endocarditis; Staphylococcus aureus bacteremia; transesophageal echocardiography.

Running title

S. aureus bacteremia transesophageal echocardiography

Introduction

Staphylococcus aureus bacteremia (SAB) is an important cause of community and health care associated sepsis with a significant mortality rate^{1,2,3}. Infective endocarditis (IE) is a serious complication occurring in up to 25% cases^{4,5,6,7}. Important risk groups include injecting drug users, the elderly, those with intravascular prostheses and hemodialysis patients^{8,9}. An early diagnosis is essential for the appropriate duration of antimicrobial therapy and is often extended to 6 weeks. The mortality of Staphylococcus aureus IE can be as high as 50%^{4,5}. Transesophageal echocardiography (TOE) significantly improves the sensitivity of diagnosis but may not be readily available in many centres^{6,7,19,11}. Some investigators advocate routine transthoracic echocardiography alone in cases of uncomplicated SAB with a clearly defined source^{8,12}. We reviewed our experience at a referral centre where TOE is performed routinely in all adult patients with SAB. We compared the sensitivity and specificity of clinical evaluation including transthoracic echocardiography alone in diagnosing IE.

Methods and Definitions

All cases of SAB were identified from the microbiology laboratory of Barwon Health during the study period. Patients were excluded if younger than 18 years of age, managed at another centre or had refused TOE. We prospectively enrolled all adult patients with SAB at our centre from 1998 to 2006 to assess sensitivity, and specificity of clinical versus TOE inclusive criteria to determine what proportion of clinically unsuspected cases were only diagnosed on TOE. The Barwon Health Research and Ethics committee approved this project and all patients provided written informed consent for TOE. Using a two by two table analysis the sensitivity, specificity, negative and positive predictive values and likelihood ratios of clinical evaluation alone was estimated.

Patient characteristics, known risk factors and in hospital outcomes were also analysed. Predisposing factors included injecting drug use or valvular condition (ie prosthetic valve

or a valve lesion with significant regurgitation or turbulence of blood flow) presence of diabetes mellitus, immunosuppression or hemodialysis. Health care associated SAB was defined as a new positive blood culture greater than 48 hours after admission to hospital. SAB occurring at less than 48 hours of admission was considered community associated. Clinically suspected infective endocarditis (IE) was defined according to modified Duke Criteria as per Li et al ¹³, including possible, definite and excluded, in the absence of TOE findings. See Table 1.

The presence of predisposing cardiac valve lesions was not always apparent at admission. In addition at our centre all cases of SAB are referred to the Infectious Diseases service promptly and undergo a thorough clinical assessment by senior clinicians. Briefly key clinical findings suggesting possible IE included presence of a new regurgitant cardiac murmur, cardiac failure, evidence of metastatic infection or any vascular embolic phenomena and all patients underwent in hospital trans-thoracic echocardiography.

We evaluated several in hospital outcomes including need for cardiac surgery, 30-day mortality, any metastatic complications, clinical cure or resolution of infection. Metastatic complications included: embolic stroke, bone or joint infection, septic pulmonary emboli. Clinical cure was defined as complete recovery at 3 months follow up with normal inflammatory markers. Resolution of infection during in hospital admission was defined as resolution of fever, clearance of blood cultures and improving inflammatory markers. Relapsed infection was defined as increased inflammatory markers and or positive cultures despite appropriate initial therapy. All patients were followed out to at least 3 months by the Infectious Diseases service.

Results

Demographic and pre-existing lesions

During the study period 1998 to 2006 we identified a total of 230 episodes of SAB from our microbiology laboratory managed at our centre. Following exclusion for age less than 18 years (55), or patients who had refused TOE (31), we included a total of 144 (83%) adult cases for this study. TOE was performed between 3 and 7 days in all cases.

The median age of the cohort was 68, and male patients represented 77% of the study population. In terms of known risk factors for IE, the majority of cases did not have a known pre-existing condition (n=81, 57%). Diabetes mellitus comprised 19% of cases followed by hemodialysis patients (12.5%) and immunosuppressed patients (combined corticosteroids and other immunosuppression use, 8.3%). 80% of patients did not have a pre-existing valvular heart condition and only 9 patients had a prosthetic valve. Methicillin susceptible *Staphylococcus aureus* (MSSA) was present in 79% of cases, and methicillin resistance (MRSA) in 21%. There was a single case of community acquired MRSA (CA-MRSA). Health care associated bacteremia was more common than community acquired bacteremia (56% v 44%), and of these MRSA represented 31% of cases. MRSA was more commonly acquired in the hospital setting than in the community (31% versus 7.8% respectively, p=0.001). Of the patients with IE 58%

(24/41) had no clinical risk factors and the frequency of diabetes mellitus, immunosuppression and hemodialysis was 7.3%, 7.3% and 2.4% respectively. See table 2.

Source of infection

Intravascular catheter devices were the most common cause of bacteraemia. Central and peripheral intravascular catheters were the primary clinical source of infection in 37% of cases (n=54). This was followed by skin infection (cellulitis, wound or ulcer) contributing a further 27% of cases. See table 3.

Results of TOE

TOE was successfully completed in 144 100% of cases. IE was suspected clinically in 15% of cases (n=22), however the overall prevalence of IE as defined by the gold standard of either possible or definite on TOE inclusive Duke criteria was 29% (n=41).

Of the total 144 patients, 122 cases were thought not to have IE prior to TOE. Following TOE 22 (15%) cases were reclassified as either possible IE (n=6) where irregularities less than 2mm or valve thickening was noted on TOE but not specific vegetations, and as definite IE (n=16) on the basis of significant mobile vegetations larger than 1-2 mms detected that had not been identified on transthoracic echocardiography. The diagnosis of IE was rejected in 100 cases (72%).

TOE detected a vegetation in 37 (90%) of the 41 cases of IE and 19 of the 41 (46%) cases were not suspected clinically by Duke criteria. The sensitivity and specificity of clinical evaluation is shown in Table 4. Sensitivity improved in the presence of known risk factors such as pre-existing valve lesion or community acquisition.

At TOE, there were a total of 40 vegetations in 37 cases (26%). Of these, 14 (38%) involved the mitral valve, 12 (32%) the aortic valve, 5 (14%) were right sided vegetations and 6 (16%) were mixed valvular or device related infection. See Table 5.

Complications and outcome

The in hospital clinical outcomes of all the cases of SAB were evaluated. Cardiac surgery was performed in 2 cases for IE and overall in hospital mortality < 30 days was 10% (14 cases). The important complications and outcomes are described in table 6.

Discussion

We found that just over half the cases of infective endocarditis were clinically unsuspected. Over a quarter of the patients had IE of which only a half had suggestive signs. Although the sensitivity of a more general clinical rule (clinical suspicion, or pre-existing valve lesion, or community-onset) was higher, a significant minority of patients with none of these features had IE.

Our other findings are consistent with other reported case series of endocarditis^{6,7}. In this single center study of an 8 year cohort of adult patients with SAB we found that the epidemiology reflects that reported in the literature with increased age and male predominance^{1,4,5}. Most cases did not have known underlying risk factors such as pre-existing cardiac lesions, however diabetes mellitus, hemodialysis and immunosuppression were common and have been noted in other SAB studies^{1,3,8,10}.

A significant number 56% of cases were health care associated and 21% were MRSA. Most of the health care associated cases were related to an intravascular device source and this association been well reported in the literature and reflects the changing epidemiology of SAB and IE^{1,3,4,8,13}. This finding underlines the importance of prevention through meticulous line care and early intravascular device removal.

We identified that a significant proportion of patients had IE with an overall incidence of 29% (41 of 144). This has been reported in the literature but importantly (19 of 41) in our study 46% of cases, were not suspected on clinical grounds^{4,5,6,7}. Kaasch report an incidence rate of up to 9.3% in their cohort study but TOE was not performed in 43% of cases¹². TOE was safe and well tolerated and there were no adverse events reported in our cohort.

The sensitivity of clinical assessment alone improved in the presence of a pre-existing valvular heart lesion or a history of community acquisition from 46% to 73% respectively, but overall remained low. This provides some simple epidemiologic clues in ascertaining risk of IE for patients with SAB. This contrasts with the findings of Kaasch et al who reported a very high negative predictive value in health care associated SAB using criteria such as persistent bacteremia (>4 days), presence of an intra-cardiac device among other clinical findings. However significantly this cohort study had low utilization of TOE only 43-60% and in up to 50% of cases of persistent bacteremia was not adequately defined¹².

There remains significant debate in the scientific community regarding the need for detailed evaluation of all cases of SAB particularly those which appear uncomplicated. For patients experiencing a short duration bacteremia, a known removable source and no underlying cardiac lesions a high quality trans-thoracic echocardiography may be appropriate in limited settings. Increasingly patients with SAB in modern health care rarely fulfill these criteria and will require a more detailed evaluation and careful monitoring^{8,9,14}.

Outcomes in our cohort of SAB were similar to that reported in the literature with an overall in-hospital mortality rate of 10%^{2,3}. Interestingly we found a relatively low rate of cardiac surgery in those cases confirmed with IE. Cardiac surgery has been reported in up to 40% of cases with left heart involvement in some series⁸. The relatively low rate of surgery may reflect earlier diagnosis and treatment or perhaps less severe disease in our patients⁸ but this requires further analysis.

Some important limitations of this study include a single centre experience with ready access to TOE. The diagnostic process including TOE was performed prospectively as standard of care; however patient outcome data were analysed subsequent to the hospital admission and the medical decision making was obtained from the patient records. Given the well reported reduced sensitivity we chose not to make a direct comparison of the role of trans-thoracic echocardiography alone in patients with SAB^{11,15}. Although the objective of this study was to better define the role of TOE in diagnosing or excluding IE in patients with SAB there is often a clinical indication for repeat studies particularly if there is a poor clinical response or persistent bacteremia¹⁴. We recommend that any implementation of this policy in different clinical contexts requires further evaluation.

Conclusion

There is a high incidence of infective endocarditis in SAB (29%) and a large percentage of cases are not evident on clinical grounds. Following TOE, 22 (15%) cases were reclassified as either possible (n=6) or definite endocarditis (n=16). TOE evaluation is indicated for all adult patients with SAB to improve detection of endocarditis.

Disclosure statement

No funding was received for this work and the authors declare that they have no conflict of interest.

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Table 1. Adapted from Li JS, Sexton DJ, Mick N et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *CID* 2000;30(4):633-8.

Duke criteria on clinical grounds:
<u>Definite endocarditis:</u> any one of the following: <ul style="list-style-type: none"> • 2 major criteria, OR • 1 major PLUS 3 minor criteria, OR • 5 minor criteria
<u>Possible endocarditis:</u> any one of the following: <ul style="list-style-type: none"> • 1 major PLUS 1 minor criteria, OR • 3 minor criteria
<u>Major clinical criteria:</u> <ul style="list-style-type: none"> • Typical organism on blood cultures (Strep viridans, Strep bovis, HACEK group, Staph aureus, Enterococci) • Typical echo findings, such as vegetations • Evidence of endocardial damage, such as new regurgitant murmur • Serological or culture evidence of Coxiella burnetii (Q fever)
<u>Minor clinical criteria:</u> <ul style="list-style-type: none"> • Fever • Predisposition : IV drug abuse or predisposing valvular condition (ie prosthetic valve or a valve lesion with significant regurgitation or turbulence of blood flow) • Vascular phenomenon : emboli, conjunctival haemorrhages, mycotic aneurysm, Janeway lesions • Immunologic phenomenon : glomerulonephritis, rheumatoid factor, Roth's spots, Osler's nodes • Positive blood cultures that do not meet the strict definitions of a major criterion, OR serologic evidence of active infection with typical organism

Table 2. Characteristics of 144 patients and *Staphylococcus aureus* bacteremia (SAB) isolates

Demographics	Frequency
Median age years	68 (IQR 53-76)
Sex male	111 (77%)
Risk factors	
Diabetes mellitus	20 (14%)
Hemodialysis	18 (12.5%)
Immunosuppression	7 (5%)
Injecting drug use	3 (2%)
None	116 (81%)
Pre-existing valve lesion or Cardiac device	
Mitral valve prolapse with regurgitation	6 (4.2%)
Mitral regurgitation and Aortic stenosis	2 (1.4%)
Aortic stenosis	3 (2.1%)
Prosthetic valve	9 (6.3%)
Repaired Atrial septal defect	2 (1.4%)
Cardiac device: pacemaker/implantable cardioverter defibrillator.	7 (5%)
None	116 (81%)
SAB isolates	
Methicillin sensitive	114 (79%)
Methicillin resistant	29 (20%)
Community associated methicillin resistant	1 (1%)
Acquisition	
Community associated	64 (44%)
Health care associated	80 (56%)
Total	144 (100%)

Table 3. Clinical source of *Staphylococcus aureus* bacteremia (SAB)

Source	Frequency
Central line	29 (20%)
Peripheral catheter	25 (17%)
Arterio-venous fistula	9 (6%)
Subtotal intravascular	63 (43%)
Cellulitis/Wound/ulcer	38 (27%)
Bone/Joint	13 (9%)
Injecting drug use	3 (2%)
Vascular graft	3 (2%)
Other	10 (7%)
Unknown	14 (10%)
Total	144 (100%)

Table 4a and b. Two by two table for calculating sensitivity and specificity of clinical criteria alone for Infective Endocarditis (IE).

	Possible/Definite IE following TOE	Rejected IE following TOE	Total
Clinically suspected by Duke criteria 1 Major 1 or 2 Minor	19	3	22
Non-suspected by Duke criteria 1 Major 1 or no Minor	22	100	122
Total	41	103	144

Clinical suspicion only	Sensitivity Specificity PPV NPV LR+ LR-	46% (31-63%) 97% (92-99%) 86% (65-97%) 82% (74-88%) 15.9 0.55
Clinical suspicion and/or any pre-existing valve lesion	Sensitivity Specificity PPV NPV LR+ LR-	53% (37-69%) 87% (79-93%) 63% (44-79%) 83% (74-89%) 4.3 0.53
Clinical suspicion, pre-existing valve lesion and/or community-acquisition	Sensitivity Specificity PPV NPV LR+ LR-	73% (57-85%) 52% (42-62%) 38% (27-50%) 84% (72-92%) 1.54 0.51

** PPV positive predictive value, NPV negative predictive value, LR+, LR- positive and negative likelihood ratios.

Table 5. Transesophageal echocardiography (TOE) findings

Echo features	No.
Normal	107 (74%)
Mitral vegetations	14 (10%)
Aortic vegetations	12 (8%)
Mixed Mitral/Aortic	5 (3.5%)
Tricuspid vegetations	5 (3.5%)
Cardiac device vegetation	1 (1%)
Total	144 (100%)

Table 6. In hospital complications and outcomes for 144 cases of *Staphylococcus aureus* bacteremia (SAB)

Outcome	No.
Cardiac surgery for Infective endocarditis	2 (1.4%)
Osteomyelitis /septic arthritis	8 (6%)
Spine infection	5 (3.5%)
Stroke	3 (2%)
Septic pulmonary emboli	2 (1.4%)
Relapsed infection	2 (1.4%)
Complete cure/resolution	120 (83%)
Suppression of infection	2 (1.4%)
In hospital mortality all cases	14 (10%)
In hospital mortality for IE cases	8 (20%)
Unknown	6 (4.2%)