Prioritizing echocardiography in Staphylococcus aureus bacteraemia

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Objectives: Infective endocarditis (IE) is a severe complication in Staphylococcus aureus bacteraemia (SAB) and recent guidelines from the BSAC recommend all patients undergo echocardiography. We assessed the use of echocardiography at a major tertiary referral centre and sought to identify those patients most likely to have positive findings.

Methods: We retrospectively evaluated all cases of SAB at Oxford University Hospitals NHS Trust between September 2006 and August 2011.

Results: Three-hundred-and-six out of 668 patients with SAB underwent cardiac imaging on average 9.8 ± 1.3 days from the first culture. Thirty-one patients (10.1%) had echocardiographic evidence of IE. Risk factors for observing evidence of IE on scanning included the presence of prosthetic heart valves (32% versus 4%, \( P < 0.001 \)) or cardiac rhythm management (CRM) devices (16% versus 3%, \( P < 0.004 \)). On excluding patients with prosthetic valves or CRM devices from the analysis, no patient with a line-related bacteraemia and only one patient (an intravenous drug user) with no/mild regurgitation on transthoracic echocardiography had echo evidence of IE.

Conclusions: We propose that the use of scarce echocardiography resources could be prioritized. Patients with prosthetic heart valves or a CRM device should receive early cardiological input and transoesophageal echocardiography. In patients with a clearly defined line-related bacteraemia who do not have a prosthetic valve or CRM device or clinical features of IE, response to treatment could be closely monitored and imaging deferred. Patients without a line-related infection or prosthetic valve/device could receive a transthoracic echocardiogram as a screening tool.

Keywords: endocarditis, MRSA, staphylococcal infections, algorithms

Introduction

Staphylococcus aureus bacteraemia (SAB) is associated with significant mortality due to its propensity to cause deep-seated and metastatic infections.1 Identifying the focus of infection in SAB is challenging and is only determined in 50%–85% of cases following extensive evaluation.2,3 Infective endocarditis (IE) can be the primary source of bacteraemia or a secondary complication and occurs in up to 14% of patients with SAB.4,5 Determining whether IE is complicating SAB is important, as it has implications for the duration of antibiotic therapy and for the monitoring of valvular regurgitation and abscesses, which may need surgical intervention.

Echocardiographic evidence forms a major criterion in the diagnosis of IE and the recently published BSAC guidelines6 recommend that all patients with SAB should undergo echocardiography, ideally within the first week of treatment or within 24 h if there is evidence to suggest IE. However, the imaging modality of choice in these circumstances is not specified and other international guidelines differ as to how soon imaging should be performed and whether transthoracic echocardiography (TTE)7,8 or transoesophageal echocardiography (TOE)9 should be performed first. Despite advances in imaging techniques, good quality TTE, with a diagnostic sensitivity of 82%–89%,10 remains less sensitive than TOE for the detection of vegetations.11

Despite these recommendations, echocardiography is a limited resource in the UK and TOE is costly, time consuming and carries a small risk to the patient. Some clinicians are reluctant to perform TOE in patients with SAB and no features of IE who show prompt clinical response to antimicrobial treatment and have the focus of infection (e.g. an intravenous, particularly...
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Patients and methods

We retrospectively evaluated the medical records of 668 consecutive patients with SAB presenting to Oxford University Hospitals NHS Trust during the period of September 2006 to August 2011. All patients with a positive blood culture for S. aureus were routinely entered on a microbiology database, including dates of blood culture and methicillin susceptibility [methicillin-susceptible S. aureus (MSSA)] or methicillin resistance [methicillin-resistant S. aureus (MRSA)]. The mode of acquisition of SAB was defined as hospital acquired if the first positive blood culture was obtained >48 h after admission.12 All other infections were defined as community acquired. A line-related infection was defined as SAB in the presence of a central venous catheter in the absence of an alternative source, and either (i) isolation of S. aureus with the same susceptibility profile from the catheter tip or insertion site, or (ii) temporal resolution of signs and symptoms following catheter removal. The clinical findings reported in this study were based on clinical examination by the treating physicians. Only clinical findings known to the patient or treating physician before echocardiography were registered.

Cases were cross-referenced with the echocardiography database and included in the study if they had SAB and had undergone either a TTE or TOE. As all imaging was performed as part of regular clinical care, ethical approval was not specifically sought for undertaking a retrospective audit, although informed consent for the procedure was obtained and research was conducted in accordance with the Declaration of Helsinki. Of the 668 patients with SAB, 306 patients (46%) underwent echocardiography. TOE was performed where TTE imaging was inadequate or if there was a high clinical suspicion of IE. Echocardiographic findings consistent with IE included the following: (i) an oscillating intracardiac mass or vegetation attached to a heart valve or other endocardial structures, including the endocardium, the ascending aorta or implanted intracardiac material; (ii) perivalvular involvement, including abscesses, pseudoaneurysms and fistulae; (iii) prosthetic valve dehiscence; and (iv) new valvular regurgitation due to perforation or destruction of the heart valve.7 Valvular regurgitation was graded according to combined American and European guidelines.13 The microbiology/infectious disease team was involved in the care and management of all cases of SAB and the cardiology team was involved in all cases where there was echocardiographic evidence of endocardial involvement.

Statistical analysis

Descriptive statistics are expressed as mean ± SEM. The statistical evaluation of two groups was performed using a two-tailed, unpaired t-test, as the data passed a normality test. ORs and 95% CIs were calculated to compare the risk factors for echocardiographic evidence of IE and univariate analysis was performed on binomial data using the χ² test. Statistical calculations were performed using SPSS version 20.0 (SPSS Inc., IL, USA) and significance accepted at P < 0.05.

Results

Prevalence of echocardiographic evidence of IE

Echocardiography was undertaken in 306 patients with a mean time from culture positivity to imaging of 9.8 ± 1.3 days. TTE was performed in 270 patients (88%) and 46 of these also underwent TOE. TOE was the only mode of imaging performed in the remaining 36 patients. Overall, 31 patients (10.1%) had echocardiographic findings suggestive of IE. Of these, 23 patients were assessed by both TOE and TTE, whilst 3 had TOE only and 5 had TTE alone. Twenty-three (74%) of the 31 cases with echocardiographic evidence of IE had a murmur documented in the notes prior to imaging. The difference in the 30 day mortality of patients with IE as compared with those without IE was not statistically significant (9.7% versus 8.7%, OR 1.12, 95% CI 0.25–4.28).

Risk factors for identifying echocardiographic evidence of IE

The clinical characteristics of SAB patients with and without echocardiographic evidence of IE were compared in order to identify the associated risk factors (see Table 1). The two groups were comparable with regard to gender, but those with echocardiographic evidence of IE were slightly younger. The strongest risk factors on univariate analysis for echocardiographic evidence of IE were a prosthetic heart valve, a cardiac rhythm management (CRM) device or community-acquired infection. Line-related infection was associated with a significantly lower likelihood of echocardiographic evidence of IE. Only three patients with a line-related bacteraemia had echocardiographic evidence of IE; of these, two had prosthetic heart valves and one had a CRM device.

Figure 1 stratifies all patients with SAB according to the presence of a prosthetic heart valve or CRM device and then as to whether they had echocardiographic evidence of IE.

Table 1. Characteristics of patients with SAB, with and without echocardiographic evidence of IE

<table>
<thead>
<tr>
<th>Patients</th>
<th>Echo evidence of IE, n=31</th>
<th>No echo evidence of IE, n=275</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, mean ± SEM (years)</td>
<td>50.7 ± 3.6</td>
<td>61.1 ± 1.1</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>male, n (%)</td>
<td>18 (58)</td>
<td>177 (64)</td>
<td>0.77 (0.4–1.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>Predisposing conditions, n (%)</td>
<td>10 (32)</td>
<td>10 (4)</td>
<td>12.6 (4.7–33.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>prosthesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>valve</td>
<td>5 (16)</td>
<td>9 (3)</td>
<td>5.7 (1.8–18.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>CRM device</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acquisition, n (%)</td>
<td>23 (74)</td>
<td>138 (50)</td>
<td>2.85 (1.2–6.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>community hospital</td>
<td>8 (26)</td>
<td>137 (50)</td>
<td>0.35 (0.2–0.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>line related</td>
<td>3 (10)</td>
<td>109 (40)</td>
<td>0.16 (0.1–0.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Microbial susceptibility, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>25 (81)</td>
<td>212 (77)</td>
<td>1.24 (0.5–3.2)</td>
<td>0.65</td>
</tr>
<tr>
<td>MRSA</td>
<td>6 (19)</td>
<td>63 (23)</td>
<td>0.81 (0.3–2.1)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
whether the infection was line related. Line-related infection was a useful criterion in those patients without a prosthetic valve or CRM device, but a poor discriminator otherwise (OR 0.88, 95% CI 0.16–4.71).

In the 270 patients who underwent TTE, normal valve function or mild valvular regurgitation was associated with a lower likelihood of identifying echocardiographic evidence of IE when compared with those with moderate–severe regurgitation (Table 2). Of the four patients in whom echocardiography suggested IE despite normal–mild valvular regurgitation, two had CRM devices in situ, one had a prosthetic valve and the remaining patient was an intravenous drug user and would be classified as high risk for IE regardless of imaging findings. Intravenous drug use is also associated with the seeding of right-sided heart valves, which are visualized less well using TTE.

Discussion

Our large, retrospective observational study of consecutive SAB patients assessed the utilization of echocardiography in the setting of a large UK tertiary referral centre. We demonstrated evidence of IE in 10.1% of patients with SAB who underwent echocardiography, with a 27% TOE rate (the percentage of imaged patients undergoing TOE). This is similar to that of the European Invasive Staphylococcus aureus Infection Cohort (INSTINCT) study (8.3% with a TOE rate of 46%), the North American Staphylococcus aureus Bacteremia Group (SABG) cohort (13.7% with a TOE rate of 48%)14 and an Australian study (6% with a TOE rate of 47%).15 Generally speaking, a higher prevalence of IE is observed in studies with higher TOE rates (e.g. 22% with a TOE rate of 62%)16 and in studies where only patients undergoing TOE were included in the analysis (e.g. 25%17 and 31.7%18).

We observed a similar 30 day mortality rate in those with and those without echocardiographic evidence of endocarditis, but it should be noted that the number of patients with evidence of endocarditis is small and the mortality rate at 30 days is high, highlighting the seriousness of SAB. The mortality rates we observed (9.7% versus 8.7%) are also generally lower than those of previous studies, which have shown a higher 30 day mortality in patients with evidence of endocarditis compared with those without (e.g. 20.8% versus 16.5% in the INSTINCT cohort, 27.5% versus 20.9% in the SABG cohort14 and 27% versus 15% in an Australian study).15 It seems logical that the early identification and management of endocarditis will improve outcomes, although our data do not consider that specifically. We speculate that the mortality for the endocarditis group might have been higher if they had not been correctly identified with echocardiography.

High-risk features

The likelihood of echocardiographic evidence of IE in SAB patients was greatest in patients with prosthetic intracardiac material (either a prosthetic valve or a CRM device) and those

Table 2. Severity of valvular regurgitation on TTE in patients with and without echocardiographic evidence of IE

<table>
<thead>
<tr>
<th>TTE regurgitation</th>
<th>Echo evidence of IE, n=28</th>
<th>No echo evidence of IE, n=242</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal–mild</td>
<td>4 (14%)</td>
<td>200 (83%)</td>
<td>0.04 (0.01–0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate–severe</td>
<td>24 (86%)</td>
<td>42 (17%)</td>
<td>28.57 (9.4–86.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 1. Stratification of all patients with SAB according to the presence of prosthetic heart valves or CRM device (CRMD) and whether infection was line related.
with community-acquired infections. This is consistent with previously published results that show up to a 5-fold increase in IE in patients with prosthetic valves and CRM devices.\textsuperscript{14,16,17} Patients with community-acquired SAB have also been reported as having up to a 3-fold higher risk of IE than patients with hospital-acquired SAB.\textsuperscript{15,16,18,19} Whilst one study reports MSSA bacteraemia as being a risk factor for IE (as compared with MRSA),\textsuperscript{18} we did not observe this relationship and neither have others.\textsuperscript{14} Another study reported that prolonged bacteraemia (>4 days) is a risk factor for developing IE.\textsuperscript{14} Very few of our patients had further blood cultures at this timepoint, so we were unable to evaluate this accurately.

Of note, no murmur was documented in the clinical record in 26% of cases with echocardiographic evidence of IE, despite every patient being reviewed by at least one consultant physician. Other studies report the absence of a murmur in 57%\textsuperscript{16} and 92%\textsuperscript{17} of patients with IE, making this an unreliable method for dependably excluding the need for imaging in patients with SAB.

**Low-risk features**

Where the bacteraemia was line related, we observed a low incidence of echocardiographic evidence of IE (3/112 cases). This is in keeping with previous studies demonstrating a low risk of IE when SAB occurs in the presence of an intravenous catheter without other identifiable sources.\textsuperscript{15,16} Interestingly, our data show that this does not apply in the presence of a prosthetic heart valve or CRM device—all three of the ‘line-related’ cases had these, and the proportion of echocardiograms positive for IE in patients with a valve/device and a line-related infection (43%) was similar to that in other high-risk groups. In contrast, no patient with a line-related bacteraemia and without a prosthetic heart valve or CRM device had echocardiographic evidence of IE, making these particularly useful discriminators in this subset of patients.

One study reported a higher prevalence of catheter-related IE (16/69, 23%)\textsuperscript{17} compared with our findings, although their definition of catheter-related infection was restricted to patients with ‘inflammation’ at the insertion site in the absence of an alternative source. It is also unclear how many patients with an intravascular catheter in this study also had a prosthetic heart valve or CRM device. Our definition required either (i) the isolation of \textit{S. aureus} with the same susceptibility profile from the catheter tip or insertion site, or (ii) the temporal resolution of signs and symptoms following catheter removal.

Several studies have evaluated subsets of patients in which both TTE and TOE have been performed in order to determine whether TTE can help exclude IE. The largest of these investigated 125 patients with SAB and concluded that, provided no

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**Figure 2.** Proposed algorithm for prioritization of echocardiography in the setting of SAB.

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**Definition of line-related bacteraemia**

- Bacteraemia due to \textit{S. aureus}, absence of another obvious source and any of the following:
  - Isolation of \textit{S. aureus} with the same susceptibility profile from:
    - Purulent exudate in catheter insertion site, or
    - The catheter tip without any other obvious source
  - Temporal resolution of signs and symptoms of infection after removing the catheter without active antibiotics (all cases will receive active antibiotics once bacteraemia is diagnosed)
embolic phenomena were present, a normal TTE conferred a probability of left-sided native-valve endocarditis of <2%. Conversely, in two other studies, 15/77 (19%)\(^1\) and 9/64 (14%)\(^2\) of patients with a ‘negative’ TTE had evidence of IE on TOE. However, the definitions of a ‘negative’ TTE study related to an absence of vegetations, abscesses, prosthetic paravalvular regurgitation, new valvular regurgitation and otherwise unexplained valvular dysfunction in a technically adequate study, rather than normal valvular function without vegetations or abscesses. It should be noted that the availability of harmonic imaging, digital processing and improved image resolution and quality have dramatically improved the sensitivity and specificity of TTE imaging in comparison with TOE over the last 10–15 years.\(^3\) As only 46 of our patients underwent both TTE and TOE, we are unable to comment on the clinical utility of one imaging modality over the other in this setting. However, when evaluating the 270 patients who underwent a TTE in our study, echocardiographic evidence of IE was found in only 2% of patients with normal–mild regurgitation and in all of these cases there were significant risk factors predisposing to IE (prosthetic heart valves, CRM device and intravenous drug use), which would have led to TOE if evidence of IE had not been obtained on TTE.

**Proposed treatment algorithm**

Given the limited echocardiography resources and increased cost, time and small risk of TOE, targeting imaging to those patients most likely to benefit is of importance, notwithstanding the BSAC guidelines suggesting echocardiography in all patients with SAB. Using the risk factors identified in this retrospective study and others published in the area, we propose an algorithm to help prioritize echocardiography (Figure 2). This should not be viewed to contradict published guidelines, but as a practical proposal of targeted implementation where resources are limited.

We emphasize that this treatment algorithm should operate only on the basis of the following: (i) continued input from a specialist infectious disease/microbiology team from the time of blood culture positivity; and (ii) early input of cardiology teams, especially in patients with haemodynamic instability, prosthetic heart valves, CRM device and intravenous drug use, which would have led to TOE if evidence of IE had not been obtained on TTE.

**Limitations**

Similar to other large observational studies, not every patient underwent echocardiography and not all who did had a TOE.\(^4\) It is therefore possible that cases of IE could have been missed both in the group undergoing TTE only and in those patients in whom imaging was not performed. Our study was not systematic and we have only included echocardiograms stored in our local database. We therefore may have underestimated the number and type of scans performed if images were not saved to the database and the results recorded directly in the clinical notes instead. This is more likely to have happened in critically ill patients whose scans were performed on an *ad hoc* emergency basis. Our data compare well with those of other large published studies; however, 46% of 668 SAB patients in our cohort underwent echocardiography, compared with 39.8% of 572 patients in the European INSTINCT cohort, 57.4% of 1403 patients in the US SABG cohort\(^5\) and 43.7% of 808 patients in an Australian study.\(^6\)

**Conclusions**

This study and others have demonstrated that SAB patients with underlying prosthetic intracardiac material are at higher risk of developing IE as evidenced by cardiac imaging, and we suggest that these patients should receive early cardiological input and TOE. In patients with a clearly defined line-related bacteraemia who do not have a prosthetic valve or CRM device or clinical features of IE, response to treatment could be closely monitored and imaging deferred. Patients without a line-related infection or prosthetic valve or CRM device could receive a TTE as a screening tool and the response to antimicrobial treatment could be monitored without more invasive imaging. These principles may be used to help prioritize echocardiography in cases of SAB, supported by the active and early input of both infectious disease and cardiology teams.

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**Transparency declarations**

None to declare.

**References**

Prioritizing echocardiography in S. aureus bacteraemia

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