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# How to investigate and manage a patient with a *Staphylococcus aureus* bacteraemia

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## Abstract

*Staphylococcus aureus* bacteraemia is common, and associated with significant morbidity and mortality as a result of its high relapse rate and the risk of complicated infection. A positive blood culture for *S. aureus* should prompt a thorough patient assessment to identify a potential focus of infection, and the risk factors for the development or presence of complicated infection. Clinical management depends on the patient's characteristics and presenting features. This article gives a systematic approach to the patient with *S. aureus* bacteraemia, including points to look for on history and examination, the markers of complicated infection, and when to request transoesophageal echocardiography and further imaging. Treatment principles outlined include the rationale for choice of antibiotic treatment and need to involve infection specialists.

Key words: Blood culture; Infectious diseases; Microbiology

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## Introduction

*Staphylococcus aureus* is a common cause of bacteraemia associated with high morbidity and mortality, and is one of the most commonly isolated organisms in blood cultures (Naber, 2009). This article outlines a strategy for approaching a patient with a positive blood culture for *S. aureus*.

## Pathogenesis

*S. aureus* is a Gram-positive coccus, which forms clumps visible on microscopy. It is a normal skin commensal in approximately 20–30% of the population, but only typically colonises some areas of the skin, such as the nostrils and perineum (Wertheim et al, 2005). It is therefore rarely a skin contaminant. *S. aureus* is categorised as meticillin-sensitive (MSSA) or meticillin-resistant (MRSA). There has been a sustained reduction in rates of MRSA in UK hospitals since they peaked in 2007–8 (Public Health England, 2020).

Potential sources of *S. aureus* bacteraemia include acute bacterial skin and skin structure infections, abscesses, infective endocarditis, intravascular catheters and prosthetic devices (Naber, 2009; Thwaites et al, 2011).

Other risk factors for *S. aureus* bacteraemia include previous MRSA infection or colonisation, intravenous drug use, immunosuppressive conditions, haemodialysis dependence, liver disease and use of corticosteroids (Naber, 2009).

*S. aureus* infection may be complicated by metastatic seeding to organs. Examples of complicated infections include infective endocarditis, septic arthritis, deep tissue, psoas or epidural abscesses, vertebral osteomyelitis and septic thrombophlebitis (Fowler et al, 2003).

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## Prognosis

*S. aureus* bacteraemia is associated with high morbidity and mortality: 30-day and 90-day mortality have been quoted as up to one in four and one in three patients respectively (Kuehl et al, 2020). However, high mortality is not solely attributable to bacteraemia, as some risk factors for *S. aureus* bacteraemia, such as haemodialysis and MRSA colonisation, infer previous hospital exposure and presence of complex chronic conditions (Naber, 2009), both of which contribute to the observed mortality.

**Table 1. Independent predictors of complicated *Staphylococcus aureus* bacteraemia**

| Predictor | Score |
|---|---|
| Community acquired | 1 |
| Skin examination findings suggesting the presence of acute systemic infection | 1 |
| Persistent fever at 72 hours | 1 |
| Positive follow-up blood culture result | 2 |

*From Fowler et al (2003)*

Morbidity arises from complicated infections and relapse. It is difficult to identify complicated infections at the time of initial positive blood culture, so treatment should be refined depending on clinical response (Corey, 2009). Use of a risk stratification score is recommended. Fowler et al (2003) identified four independent predictors of complicated *S. aureus* bacteraemia: community-acquired infection, skin lesions suggestive of acute systemic infection, persistent fever at 72 hours, and positive follow-up blood culture result (Table 1). Each is given a score and the risk of complicated infection increases with the total score: from 16% with a score of 0 to 90% with a score of 5.

Risk factors for relapse include insufficient duration of anti-staphylococcal therapy, lack of infectious disease bedside consultation, presence of MRSA (Rieg et al, 2009), infective endocarditis, and inappropriate (Chang et al, 2003) or delayed antibiotic therapy.

## Clinical approach

A positive *S. aureus* blood culture should be assumed to represent bacteraemia, and not be dismissed as a skin contaminant (Mitchell and Howden, 2005). If an infectious diseases service is available, they should be consulted as soon as possible. This reduces mortality, frequency of readmissions and frequency of relapsing bacteraemia (Rieg et al, 2009).

This article presents a six-stage approach of how to work up a patient with *S. aureus* bacteraemia (Figure 1). In general, if risk factors for complicated infection are present, more invasive diagnostic tests should be considered and longer treatment courses given (Fowler et al, 2003).

## Step 1: history

A comprehensive history should be taken as with any patient, but direct questioning on the following areas is helpful in the context of *S. aureus* bacteraemia:

- Ascertain if the patient has recently been hospitalised, used another healthcare facility (such as a haemodialysis centre), or has developed the infection at home (community-acquired)
- Enquire about systemic symptoms, such as fever, lethargy, anorexia, weight loss and night sweats, as these may suggest a deep focus of infection
- Pain in the site of the infection may be reported. For example, back pain is commonly seen in patients with vertebral osteomyelitis, discitis or epidural abscesses, along with difficulty in walking. Abdominal pain may suggest the presence of embolic disease in the kidney or spleen
- Explore risk factors for infection, such as intravenous drug use, recent surgery or trauma. Ask about the presence of intravascular devices such as tunnelled lines, and of cardiac or orthopaedic prostheses.

## Step 2: examination

Inspect the hands for the peripheral stigmata of endocarditis including splinter haemorrhages, Janeway lesions and Osler nodes. Look for other signs of infective endocarditis: a collapsing pulse (indicative of aortic regurgitation), Roth spots on fundoscopy, or a regurgitant murmur on auscultation.

| **Steps** | **Features that increase the likelihood of or indicate a complicated *Staphylococcus aureus* bacteraemia** |
|---|---|
| Step 1<br>History | ■ Community-acquired infection<br>■ Intravenous drug user or haemodialysis-dependent<br>■ Complex cardiac condition<br>■ Localising bone or joint pain |
| Step 2<br>Examination | ■ Persistent fever at 72 hours<br>■ Evidence of acute systemic infection on skin<br>■ Signs of infective endocarditis<br>■ Localising bone or joint tenderness |
| Step 3<br>Simple investigations | ■ Positive follow-up blood culture<br>■ Positive urine culture |
| Step 4<br>Echocardiography | Vegetations or other evidence of infective endocarditis |
| Step 5<br>Imaging | Evidence of bone and joint disease, abscesses or solid organ involvement |
| Step 6<br>Additional investigations | |

**Figure 1.** Strategy for treating a patient with *Staphylococcus aureus* bacteraemia.

A full examination of the skin should take place to identify wounds, ulcers, cellulitis, evidence of intravenous drug use or 'skin-popping', presence of lines and any inflammation or tenderness at line sites (Horino and Hori, 2020). Look for evidence of acute systemic infection on the skin, for example, petechiae, infarcts, ecchymoses or pustules (Fowler et al, 2003).

Examine joints to exclude septic arthritis. Include hip examination, as a psoas abscess may cause pain on hyperextension (Mallick et al, 2004). Finally, palpate down the spine to elicit tenderness suggestive of osteomyelitis, and perform a neurological examination of the limbs in case of occult epidural abscess.

It must be remembered that in a proportion of complicated infections (up to 41%, according to Vos et al (2012)) there may be no localising symptoms or signs at presentation, and thus all negative history and examination findings should be interpreted with a degree of caution.

## Step 3: simple investigations

Basic investigations should include those for any patient with an infection: blood glucose, venous blood gas, blood tests for full blood count, renal function, electrolytes, liver function tests and C-reactive protein levels.

Urine sample for dipstick and microscopy, sensitivity and culture should be taken. Blood and protein on dipstick may indicate endocarditis, and *S. aureus* bacteriuria may indicate the presence of bacteraemia or complicated infection, and should be taken seriously (Stokes et al, 2019).

For patients with indwelling vascular access catheters, blood cultures should be taken peripherally and from each port of the line. Repeat blood cultures should then be taken to detect 'persistent bacteraemia', definitions of which vary. Kuehl et al (2020) found a significant increase in 90-day mortality and development of complicated infection at 2 days or more of bacteraemia, despite antibiotic therapy. They propose that persistent bacteraemia should be defined as positive cultures 48 hours after commencing appropriate antibiotic treatment, and hence repeat blood cultures should be taken then. A pragmatic approach is to take a set of repeat blood cultures as soon as the laboratory informs the clinical team that a set of blood cultures is positive, and continue taking daily cultures until these are negative.

## Step 4: echocardiography

All patients should undergo transthoracic echocardiography to look for endocarditis, which is seen in about 15% in this population (Kaasch et al, 2011), but can reach 43% in patients with prosthetic valves (Fang et al, 1993). Transoesophageal echocardiography is superior to transthoracic echocardiography at detecting infective endocarditis (Kaasch et al, 2011), except in cases of right-sided infective endocarditis when they both have a similar diagnostic yield (San Román et al, 2012). Thus, for patients who use intravenous drugs in whom right-sided infective endocarditis is more common, transthoracic echocardiography may be sufficient. Obtaining a transoesophageal echocardiography for every patient with *S. aureus* bacteraemia is impractical. However, one should be undertaken if there is high clinical suspicion of endocarditis, and transthoracic echocardiography is negative.

Kaasch et al (2011) and Showler et al (2015) defined high-risk criteria for endocarditis for which a transoesophageal echocardiography should be sought, outlined in Table 2. One of these is positive blood cultures at 72 hours; however, given the evidence by Kuehl et al (2020) that positive blood culture at 48 hours carries greatest risk, the authors have revised it to reflect this.

It is recommended to re-evaluate the patient at day three (48 hours after initial positive blood cultures), to determine whether they satisfy the criteria in Table 2 and hence require transoesophageal echocardiography.

Transoesophageal echocardiography should also always be sought if the transthoracic echocardiography has suboptimal image quality, or is positive for endocarditis (Habib et al, 2015), to help determine the need for and timing of potential valve surgery. Once infective endocarditis is diagnosed, outcomes are improved by the involvement of an endocarditis multidisciplinary team, if feasible (Kaura et al, 2017).

**Table 2. Indications for transoesophageal echocardiography in a patient with *Staphylococcus aureus* bacteraemia**

| | |
|---|---|
| Prolonged bacteraemia with either | Community-acquired transmission or |
| | Positive blood culture at 48 hours despite antibiotic therapy |
| High-risk cardiac condition, such as | Prosthetic heart valve, or prosthetic material used in valve operation |
| | Congenital heart disease |
| | Cardiac transplantation with valvopathy |
| | Pacemaker or implantable cardioverter defibrillator |
| | History of endocarditis |
| Clinical suspicion of endocarditis on examination | |
| Intravenous drug user | |
| Dependent on haemodialysis | |
| Evidence of other complicated infection, such as discitis or osteomyelitis | |

## Step 5: imaging

Cross-sectional imaging can help identify complicated infection. It is used based on specific symptoms or signs, or in patients with persistent bacteraemia or raised levels of inflammatory markers. Computed tomography is the investigation of choice for abscesses or organ involvement (Mallick et al, 2004), while magnetic resonance imaging is more sensitive for detecting osteomyelitis (Horino and Hori, 2020).

The most sensitive form of imaging in the case of complicated infection is a 18F-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG-PET) scan, as it can detect metastatic foci when other imaging modalities have not, and thus may be required in challenging cases (Vos et al, 2012). For example, $^{18}$F-FDG-PET can be used to aid the diagnosis of suspected prosthetic valve and intra-cardiac device-related infective endocarditis that was not picked up on echocardiography (Harding et al, 2018).

## Step 6: additional investigations

Joint aspiration for microscopy, sensitivity and culture should be performed in suspected septic arthritis (Horino and Hori, 2020). Diagnostic aspiration of any collection or abscess should also be considered.

## Treatment

Treatment of *S. aureus* bacteraemia will be based on local guidance, with reference to the antibiotic sensitivities of the isolate and the individual patient characteristics (for example, drug allergies, renal impairment, liver disease). Therefore, the authors recommend consulting the microbiology or infectious diseases team to advise on appropriate treatment. However, some principles for treatment of *S. aureus* bacteraemia are outlined below:

Initial treatment should include removing the source of infection where possible, such as removing infected vascular access devices or drainage of an abscess (Thwaites et al, 2011).

In the UK, treat the patient empirically for MSSA, as rates of MRSA in the UK are relatively low (Public Health England, 2020), unless the patient is known or suspected to be colonised with MRSA. The beta-lactam antibiotic flucloxacillin, administered intravenously, is the gold-standard first line treatment (Corey, 2009). In a patient with penicillin allergy, the nature of the reaction should be ascertained. If it involves an anaphylactic or unascertainable reaction, glycopeptides such as vancomycin may be used (although outcomes are inferior) (Chang et al, 2003). Vancomycin is also often first line for MRSA bacteraemia, as levels can be measured to ensure dosing is therapeutic, although newer agents such as daptomycin may be used. Daptomycin is preferable in patients with right-sided endocarditis or complex acute bacterial skin and skin structure infection (Fowler et al, 2006). Switching from vancomycin to daptomycin within 3 days of commencing therapy reduces mortality in patients with MRSA bacteraemia (Schweizer et al, 2021).

The duration of treatment depends on whether MSSA or MRSA is isolated and the presence or absence of complicated infection, such as osteomyelitis or endocarditis. A minimum duration of 2 weeks treatment is usually required in patients with uncomplicated *S. aureus* bacteraemia, although there is emerging evidence that shorter durations may be sufficient (Thwaites et al, 2011).

If available, outpatient parenteral antibiotic therapy is recommended for stable patients completing prolonged treatment courses. Outpatient parenteral antibiotic therapy can improve compliance and shorten inpatient stay with similar clinical success to inpatient treatment (Rehm et al, 2009).

*S. aureus* bacteraemia is traditionally treated with intravenous antibiotics, but trials support the safety of an early oral switch in highly selected patient groups (Bupha-Intr et al, 2020). However, the authors do not recommend oral treatment of *S. aureus* bacteraemia except where endorsed by local infection specialists.

*S. aureus* bacteraemia is often managed by a multidisciplinary team, with cases discussed to ensure consensus on the treatment plan. Treatment should always be overseen by local infection teams to help tailor treatment to prevent relapse. Specialist pharmacists are often involved to help identify possible interactions between the antibiotics and the patient's

## Key points

- A positive blood culture for *Staphylococcus aureus* should trigger a thorough assessment looking for foci of infection and evidence of complicated infection.
- Repeat blood culture 48 hours after initiation of antibiotic therapy will help risk stratify patients with *S. aureus* bacteraemia.
- All patients should have echocardiography, with transoesophageal echocardiography required when there is a high risk for infective endocarditis.
- Management and treatment of patients with *S. aureus* bacteraemia is best managed with input from infectious diseases or microbiology teams, and in a multidisciplinary fashion.

other medications, and to monitor for adverse effects. Patients with complicated infections requiring protracted courses of treatment will require follow up in secondary care, which should be communicated to the patient and their GP.

## Conclusions

*S. aureus* bacteraemia is a common problem that may present unexpectedly. However, through a systematic approach towards history, examination and investigations, with early infection specialist input and prompt effective antimicrobial therapy, the source of the infection can be identified and the patient appropriately treated to minimise the associated morbidity and mortality.


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#### Conflicts of interest

The authors declare that they have no conflicts of interest.


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## Curriculum checklist

This article covers the following areas from the general internal medicine curriculum:

- Managing an acute unselected take
- Providing continuity of care to medical inpatients, including management of comorbidities and cognitive impairment
- Managing medical problems in patients in other specialties and special cases.

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