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Your patient has a blood culture positive for *Staphylococcus aureus* – what do you do?

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ABSTRACT *Staphylococcus aureus* bacteraemia is an important clinical problem associated with a high mortality rate and a significant burden on healthcare resources. The severity, rate of complications, and prognosis of the infection depend on a multitude of factors including underlying patient factors, the virulence of the strain of *S. aureus*, and the timeliness of appropriate antibiotic therapy.

Detection of staphylococci in blood culture should trigger a chain of events beginning with assessment of the patient to determine signs of sepsis and the likely significance of the organism isolated. The level of risk of your patient having MRSA must be assessed. A deep-seated source, or metastatic complication, of the bacteraemia must be suspected and sought, with the most important complication being endocarditis. This assessment should not delay urgent treatment with IV antibiotic therapy in a patient with signs of sepsis. Treatment should be guided by local antibiotic policy alongside advice from microbiology and/or infectious diseases consultants.

This overview takes the form of a clinical case scenario with a step-wise approach to the management of a patient from first isolation of staphylococci in a blood culture to the management of MRSA endocarditis.

KEYWORDS bacteraemia, endocarditis, MRSA, *Staphylococcus aureus*

LIST OF ABBREVIATIONS Blood pressure (BP), British Society for Antimicrobial Chemotherapy (BSAC), C-reactive protein (CRP), coagulase-negative staphylococcus (CNS), computerised tomography (CT), confidence interval (CI), coronary artery bypass graft (CABG), infective endocarditis (IE), intravenous (IV), magnetic resonance imaging (MRI), mental status questionnaire (MSQ), methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), polymerase chain reaction (PCR), *Staphylococcus aureus* bacteraemia (SAB), transoesophageal echocardiogram (TOE), transthoracic echocardiogram (TTE), white blood cell count (WCC)

DECLARATION OF INTERESTS D Nathwani has a current personal interest with Pfizer Pharmaceuticals, Chiron Pharmaceuticals, and Wyeth Pharmaceuticals.

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CASE SCENARIO

You are the duty doctor covering Medical Ward X of St Elsewhere. You get a call from the duty microbiologist. Mr Smith on Ward X has grown staphylococci in both the blood culture bottles taken yesterday. The staphylococci are likely to be *Staphylococcus aureus* although the microbiologist cannot be sure until tomorrow.

WHAT SHOULD YOU DO?

Return to the patient and understand the reason for taking the blood culture.

Mr Smith, 68 years old, was admitted 23 days ago with an exacerbation of his congestive heart failure and renal dysfunction secondary to ischaemic heart disease and type II diabetes. He had received IV furosemide through a 'neck line' inserted during his acute medical emergency admission for monitoring his central venous pressure and fluid balance.

Yesterday he had 'spiked' a fever (38°C) with rigors. The resident had not found any localising signs of infection at the time but noted an intermittent low-grade fever over the past three days. At the time of the blood culture Mr Smith's pulse was 110 beats/minute, regular, and his BP was 110/62 mmHg. He was lucid with a MSQ of 9/10 and his respiratory rate was 22 breaths/minute. His WCC was 13 x 10^9/L and CRP was 245.

TABLE 1 Risk factors associated with MRSA colonisation.

- Recent hospitalisation.
- Recent (3–6months) antimicrobial use.
- Invasive lines or tube (IV, urinary catheters).
- Recent surgery.
- Nursing home resident.
- Advanced age.
- Underlying severe disease.
- Exposure to colonised or infected patient.
- Morbid obesity.
- Orthopaedic implant surgery.

WHAT IS THE LIKELY SIGNIFICANCE OF THIS CULTURE RESULT? COULD IT BE A CONTAMINANT?

In determining the significance of this isolate, a number of factors are likely to tell us whether this is a true bacteraemia as apposed to a contaminant:

1. The presence of local and/or systemic signs of infection and sepsis;
2. The detection of bacteria in both blood culture bottles;
3. The occurrence of early detection of bacteria in the laboratory (time to positivity of the blood culture <14 hours);
4. If the patient has a coagulase-negative staphylococcus (CNS) it is more likely to be a contaminant, although this is not always the case. Two positive blood cultures for CNS within five days, or one positive culture plus clinical signs of infection, are associated with clinical significance, i.e. infection rather than contamination; and
5. Previous colonisation with staphylococci or recent (within three months) isolation of staphylococci in blood cultures.

Your patient exhibited no obvious sign of local infection but had sepsis, as he exhibited symptoms of infection (fever, rigors) and a systemic inflammatory response to the infection (i.e. two out of four of temperature <36 or >38°C, tachycardia >90/min, tachypnoea >20/min, or WCC <4,000 or >12,000/mm^3). The staphylococci were isolated in both bottles within 24 hours of being taken by the resident. You note previous laboratory results of isolation of MRSA in a foot ulcer (right toe) during his previous admission three months ago as well as a positive MRSA screen on that occasion.

WHAT IS THE LIKELIHOOD THAT THIS STAPHYLOCOCCAL BACTERAEMIA IS MRSA?

The rate of nasal carriage of *S. aureus* varies from 10–40% in both community and hospital populations. There are many risk factors that promote colonisation with MRSA. These are outlined in Table 1. Most patients presenting to the acute receiving ward will have at least one of these risk factors. In addition, risk factors that appear to promote the development of nosocomial SAB are the presence of a central venous catheter, hyponatraemia, and anaemia. To advise prudent use of broad-spectrum antibiotics, the predicted likelihood of MRSA in a particular patient with SAB has recently been estimated and quantified in a clinical decision rule by Lodise *et al.*[7] (see Table 2). The presence of hospitalisation, recent long duration of hospital stay, recent course of antibiotics, and the presence of a decubitus ulcer, increase the likelihood of the infection being MRSA.

TABLE 2 Predicted likelihood of methicillin resistance in a patient with *Staphylococcus aureus* bacteraemia.[7]

Risk factors*	Community-onset		Hospital-onset	
	Prior antibiotic exposure		Prior antibiotic exposure	
	No	Yes	No	Yes
0	15%	62%	36%	84%
1	31%	81%	58%	94%
2	53%	91%	77%	97%

*History of hospitalisation or decubitus ulcer.

WHAT IS THE LIKELY SOURCE OF INFECTION AND WHAT SHOULD YOU DO?

The aetiology of SAB is as follows: primary bacteraemia, for which no source is identified (about 20% of cases), and secondary, which is the result of infection related to a distant site. In the hospital setting, wound infection and vascular line- or catheter-related infection (central > peripheral > urinary catheters) are the most common sources of bacteraemia (35%). Other sources include cellulitis or other skin and soft-tissue infection (17%), endocarditis (13%), bone infections (osteomyelitis), septic arthritis or prosthetic joint infections, and pneumonia.

Your patient had no evidence of obvious wound or 'venflon' site infection but you notice that the emergency central line had been *in situ* for 12 days before removal. It had been removed because of 'entry site infection'; treated with line removal and five days of oral flucloxacillin. He also has a right hip prosthesis inserted five years previously and a sternotomy scar from CABG three years ago. The hip was fine, with no pain or immobility, and the midline sternotomy scar was normal, although minimal tenderness was elicited on deep palpation. Auscultation of the heart revealed no definite abnormality but possibly a soft systolic murmur in the left sternal edge. Chest examination was normal.

WHAT IS YOUR WORKING DIAGNOSIS?

On the basis of the above findings, the patient most likely

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has an SAB secondary to a central-line infection. You are concerned that infection from the line has metastasised to another site causing a 'complicated bacteraemia'. Possible complications in this patient are endocarditis, although there are no clear stigmata of endocarditis, or a sub-acute right prosthetic hip infection, or sternal osteomyelitis. Fowler *et al.*[4] recently developed a prognostic model to aid estimation of the likelihood of complicated bacteraemia (see Table 3) to identify cases warranting aggressive investigation. The four identified risk factors (community acquisition, skin findings suggestive of acute infection, positive follow-up blood culture, and persistent fever) can be used to calculate the probability of complication, with positive follow-up culture being the most heavily weighted risk factor.

WHAT FURTHER INVESTIGATIONS WOULD YOU CONSIDER?

You should repeat the blood cultures from a peripheral site. In *S. aureus* endocarditis the first two blood cultures are positive in 90% of cases. If there is a central line, *in situ* simultaneous blood cultures should be taken from this. This is helpful in diagnosing central-line infection, indicated by negative peripheral cultures with positive line cultures. The volume of blood sampled is crucial in detecting the low levels of bacteraemia found in partially treated or relapsing infection. Simultaneous cultures, particularly, aid decision making if there is a clinical indication to retain the central venous access. The line should ideally be removed at the earliest opportunity.

You should then organise an echocardiogram as hospital-acquired *S. aureus* infections lead to endocarditis in 13% of cases. In some centres all patients with SAB undergo TOE, but others recommend that a normal TTE in a patient with low pre-test probability is sufficient. In one study, 31·7% of TOE examinations in patients with SAB had confirmed endocarditis but this group was highly selected by physician referral. The same study found that MRSA was less likely to be associated with endocarditis than sensitive strains.

If the echocardiogram is negative, other potential sources of ongoing bacteraemia must be considered. In this patient, sternal osteomyelitis may be suggested by the tenderness on deep palpation. *Staphylococcus aureus* is the causative organism in 50–70% of osteomyelitis. His previous sternotomy and the presence of surgical wires increase his risk of osteomyelitis. Plain X-ray changes can take several weeks to develop and more sensitive imaging, i.e. bone scan, CT, or MRI, should be carried out at this stage. Another potential site of infection in this patient is his prosthetic hip joint, i.e. septic arthritis, either as the source of bacteraemia or as a result of haematogenous spread from another site. This is not likely as the patient has no localising signs. The diagnosis of septic arthritis is confirmed by MRI scanning or examination of synovial fluid obtained by blind or CT-guided needle aspiration, or surgical washout demonstrating pus cells, with or without organisms, on microscopy or culture.

TABLE 3 Reduced prognostic model of complicated *Staphyloccocus aureus* bacteraemia.[4]

Variable	Odds ratio (95% CI)	P value
Community acquired	3·10 (1·96–4·87)	<0·001
Skin examination findings suggesting the presence of acute systemic infection	20·04 (1·30–3·18)	0·002
Positive follow-up blood culture result	5·58 (3·93–7·95)	<0·001
Persistent fever at 72 h	2·23 (1·55–3·12)	<0·001

SHOULD YOU START EMPIRIC TREATMENT AND WHY?

As the patient has features of sepsis you consider this is significant bacteraemia rather than a contaminant. You should therefore start anti-staphylococcal therapy immediately. There is some evidence that in an unwell patient or in a patient in the critical care, setting early appropriate therapy has a better clinical outcome compared with patients who receive inappropriate treatment at the onset.

The rationale behind the antibiotic choice here will be dependent on the likelihood of the organism being MRSA, the severity of the infection (i.e. the likely consequences if not optimally treated), the patient co-morbidity, and age. A risk assessment must be made, balancing the benefits against the risk that using a broader spectrum agent may foster future resistance.

The choice in this patient, on balance, is vancomycin, although some argue that high-dose flucloxacillin for 24 hours, before identification of the species and antimicrobial susceptibility, may also be a reasonable strategy. Antibiotic choice should ideally be in discussion with microbiology or infectious diseases and based on local policy or guidelines.

SHOULD I CONSIDER ADDING ANOTHER ANTIBIOTIC?

The rationale for combining either rifampicin or gentamicin with either flucloxacillin or vancomycin is based around bacterial synergy, excellent tissue and biofilm penetration in the case for rifampicin, and the potential for more rapid clearance of bacteraemia. Despite this, addition of either drug has never been shown to improve outcomes in MSSA or MRSA bacteraemia. However, they are often used or

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TABLE 4 Summary of treatment recommendations for staphylococcal endocarditis.[3]

Methicillin sensitive	Flucloxacillin (2 g, 4–6 hourly IV)
Methicillin resistant	Vancomycin (1 g, 12 hourly IV)* plus Rifampicin (300–600 mg, 12 hourly by mouth)† or Gentamicin (1 mg/kg body weight, 8 hourly)*† or Sodium fusidate (500 mg, 8 hourly by mouth)†
Endocarditis in presence of intracardiac prosthesis	Flucloxacillin (2 g, 4–6 hourly IV) or vancomycin (1 g, 12 hourly IV)* plus Rifampicin (300–600 mg, 12 hrly by mouth) † and/or Gentamicin (1 mg/kg body weight, 8 hourly)*† and/or Sodium fusidate (500 mg, 8 hourly by mouth)†

*Dose modified according to renal function.
†According to sensitivity.

recommended by infection specialists (see BSAC guidelines).

SHOULD I CONSIDER LINEZOLID HERE?

Linezolid is a novel synthetic antibiotic. It is the first oxazolidinone and has good oral bioavailability and activity against methicillin- and glycopeptide-resistant strains of *S. aureus*. It is currently only indicated for severe pneumonia and complicated skin and soft tissue infections under expert supervision. There has not been enough clinical experience to recommend linezolid as first-line therapy in the context of bacteraemia. Indications for considering linezolid include intolerance or allergy to glycopeptides, lack of IV access, renal impairment, and lack of response on first-line therapy or specific resistance patterns.

HOW LONG SHOULD I CONTINUE AND HOW SHOULD I MONITOR RESPONSE TO TREATMENT?

The blood culture the following day is confirmed as MRSA, susceptible to vancomycin, rifampicin and linezolid.

In uncomplicated MRSA bacteraemia, i.e. with no focus of deep-seated infection, IV vancomycin for a minimum of ten days is recommended. In your patient you suspect endocarditis so should augment the vancomycin therapy, as outlined below, while awaiting confirmatory imaging.

To monitor the response to treatment, the patient should be assessed frequently for clinical signs of sepsis with regular heart rate, respiratory rate, temperature, and blood pressure recordings. Clinical systems examination should be undertaken at least daily. Laboratory markers of inflammation, i.e. white cell count and CRP, are particularly useful in monitoring longer term response to treatment.

HOW SHALL I PROGRESS?

The TTE is negative but the TOE confirms tricuspid endocarditis.

Staphylococcus aureus *endocarditis*

Infective endocarditis was an invariably fatal infection before the availability of antimicrobials. Even after the introduction of antibiotic therapy and valve replacement, the reported early mortality rate of IE remains high (16–31%), and the mortality rate after five to ten years' follow-up ranges from 25–50%. Among cases of IE caused by the most frequent micro-organisms, IE caused by *S. aureus* carries the worst prognosis and has a high prevalence of embolic episodes and neurological involvement. Infection caused by MRSA is increasing. MRSA acts as a significant cause of IE internationally, accounting for almost 40% of the IE caused by *S. aureus* in certain regions. Endocarditis was associated with rheumatic heart disease but is now more commonly associated with IV drug use and vascular catheters. However, it is important to note that approximately 20% of patients with MRSA IE developed their infection in the absence of identifiable healthcare contact. It should be in the differential diagnosis of any hospital-acquired pyrexia and must be looked for in all cases of SAB.

The *S. aureus* organism carries particular adhesin molecules that attach to inflamed endothelial cells, which accounts for the development of vegetations on structurally normal heart valves. The bacteria can either internalise and persist locally, protected from antibiotic therapy and host defences, or lyse the endothelial cells, causing local tissue destruction and distant emboli. This helps explain the potential for *S. aureus* endocarditis to present either acutely or with a more indolent presentation.

Antimicrobial sensitivity of the organism is often only available 24 hours after the first positive culture. New techniques to detect bacteria, including the specific strain, using PCR are being developed. The proposed method would allow identification and typing of *S. aureus* from blood within 1·5 hours allowing more rapid initiation of appropriate therapy.

Patient assessment

The patient should be assessed for complications of endocarditis, particularly septic emboli and cardiac failure. In your patient, with tricuspid endocarditis, the development of cavitating pulmonary infection is the primary concern, and chest X-ray examination is

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mandatory. Fulminant cardiac failure (less likely in right-sided endocarditis) is an indication for early operative intervention despite the associated high mortality rate. All cases should be discussed with a cardiothoracic surgeon. Ongoing pyrexia, other signs of sepsis, and persistently raised inflammatory markers are indicative of treatment failure.

Antibiotic therapy

Traditionally, gentamicin is recommended in addition to flucloxacillin in MSSA endocarditis for the first 3–5 days. This is due to demonstrated synergistic effects in laboratory testing and some clinical evidence that it reduces the burden of vegetations when used early. However, the BSAC published guidelines for the management of endocarditis in 2004 that recommended against the use of gentamicin (see Table 4).

In your patient with MRSA endocarditis of a native valve, the recommended therapy is vancomycin (1 g IV every 12 hours) plus rifampicin (300–600 mg by mouth every 12 hours) or gentamicin (1 mg/kg every eight hours) or sodium fusidate (500 mg by mouth every eight hours). Exact choice of regime will depend on the sensitivity of the particular strain of MRSA so will be guided by microbiological and/or infectious diseases advice. Rifampicin is particularly useful in prosthetic valve infections due to its property of increased activity against bacteria attached to foreign material and against intracellular bacteria. It is therefore often recommended as an adjunct in *S. aureus* bone and joint infection, particularly involving a prosthesis.

Treatment is IV for an absolute minimum of four weeks for native valve endocarditis and six weeks for prosthetic valves. A shorter duration of therapy has been successful in several trials in right-sided endocarditis in IV drug users. Intravenous access is a problem in these patients but early switch to oral can only be advocated in the absence of complications. There is increasing availability of outpatient IV antibiotic services in the UK which allows flexibility of care once the patient is over the most acute phase of the illness. Attempts to shorten the duration of treatment often results in a relapse of infection and a poorer outcome, except in the specific case of right-sided endocarditis in IV drug users.

What infection control issues should I consider?

Your patient has previously had a positive screen for MRSA and now has invasive infection. A repeat set of screening swabs should be taken involving the nose, throat, perineum, and any wound, e.g. central-line site, in this patient. Universal Infection Control precaution should apply and eradication of colonisation should be attempted. This will not usually be achieved by systemic antibiotic therapy. A suitable eradication regime is topical nasal mupirocin three times daily for five days, and chlorhexidine or triclosan body wash for two weeks. Eradication is not guaranteed and repeat swabs are indicated. Advice can be obtained from your hospital infection control team.

WHAT IS THE EPIDEMIOLOGY OF HOSPITAL-ACQUIRED (NOSOCOMIAL) *STAPHYLOCOCCUS AUREUS* BACTERAEMIA?

Staphylococcus aureus is a leading cause of community- and healthcare-associated infection. Infection is considered to be community-acquired if it occurs within 48 hours of admission, and hospital-acquired from 48 hours post-admission. Rates of invasive infection, i.e. bacteraemia, have increased markedly in the last 20 years and, despite recent advances in antibiotic therapy, the mortality associated with bacteraemia remains high at 19–34%. Around 30% of healthy adults carry *S. aureus* in the anterior nares and they are three times more likely to have a nosocomial bacteraemia than non-carriers. However, the mortality of *S. aureus* infection is less in carriers. Risk factors for invasive infection include the presence of vascular or urinary catheters. There is a considerable burden on healthcare resources associated with *S. aureus* infection, with affected patients having a three times longer length of inpatient stay, a three times increase in cost of stay, and five times the mortality on average compared with other patients.

Infection with MRSA is associated with an attributable excess mortality compared with sensitive strains and is now responsible for approximately 40% of *S. aureus* bacteraemias. The rate of MRSA infection in hospitals has increased from 2·1% in 1975 to 35% (and up to 70% in some centres) by 1991. Although MRSA infection was considered to be exclusively hospital-acquired, increasing rates of community-acquired infections are being detected and studied to determine their true origin (hospital or community). A recent cohort study in Oxford found that 91% of admissions with MRSA bacteraemia and 77% of those with MSSA bacteraemia had previous recorded hospital contact.[8] There are, however, increasing isolates of community-acquired MRSA, particularly in the US, with different resistance patterns to hospital strains, that are predicted to increase in prevalence. Although community-acquired MRSA infections have emerged as a significant public health problem, it is difficult to determine what effect these infections will have on the incidence of MRSA infections among hospitalised patients.

KEYPOINTS

- *Staphylococcus aureus* bacteraemia is associated with significant mortality and economic healthcare burden.
- Underlying patient factors are important in determining the likelihood of complicated infection and/or infection with MRSA.
- Endocarditis is the most common and important

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complication of SAB.
- Appropriate antibiotic choice and duration of treatment improves outcomes.
- Antibiotic therapy is guided by culture results, national guidelines, local policy, and specialist advice.

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