Murmur and weight loss

Is it subacute bacterial endocarditis?

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Articles in this section use cases to illustrate the emergency management of patients presenting in general practice with cardiac problems. They are inspired by, but not based on, real patient situations.

A 65-year-old retired statistician, Mr PG, is reporting six weeks of lethargy and mild weight loss. He has been married for 39 years, is a lifelong nonsmoker and has no significant past medical history. He usually plays tennis three times a week but is now playing only once a week because of his increased fatigue. There is no dyspnoea or chest pain associated with this fatigue. In spite of the decrease in physical activity, his weight has dropped by 6 kg from 77 kg to 71 kg. He has had no rigors or night sweats, has no personal or family history of cancer, nor any additional symptoms that may suggest a malignancy, and his National Screening faecal occult blood test was negative this year. You ask briefly about his mood and marriage, which he insists are fine. 'Just tell me what's wrong, doc', he says.

What do you look for on clinical examination?

On examination, Mr PG has a temperature of 37.5°C, his pulse rate is 70 beats per minute and regular, and his blood pressure is 135/85 mmHg. There is no conjunctival pallor and no thyroid mass. You examine his mouth, at which time he volunteers that he had a tooth extraction nine weeks ago. Chest auscultation reveals normal vesicular breath sounds and dual heart sounds with a non-radiating pansystolic murmur at the apex. The abdomen is soft with no organomegaly. You check his hands and feet for peripheral signs of infective endocarditis, but they are normal.

You perform an ECG, which reveals sinus rhythm, no heart block and no ischaemic changes. It is not lost on you that the heart murmur is possibly new, but as Mr PG is not tachycardic or in cardiac failure, rather than send him to hospital you organise some tests and ask to see him the next morning.

Mr PG returns the following day, and when asked how he feels, replies that nothing has changed. You give him the results of the initial tests, which are mostly normal: haemoglobin is 142 g/L, white cell count is 6.8 x 10^9/L, creatinine is 60 µmol/L and thyroid stimulating hormone is 1.3 mIU/L. C-reactive protein is mildly elevated at 45 mg/L. Chest x-ray reveals clear lung fields without cardiomegaly or pulmonary congestion (Figures 1a and b). Another examination shows no new findings.

What is the next step?

The next step is to organise a transthoracic echocardiogram, which can happen this afternoon if you phone ahead.

The transthoracic echocardiogram report shows the left ventricular size and systolic function to be normal. There is a sub-centimetre mobile mass on the anterior leaflet of the mitral valve (Figure 2a) with

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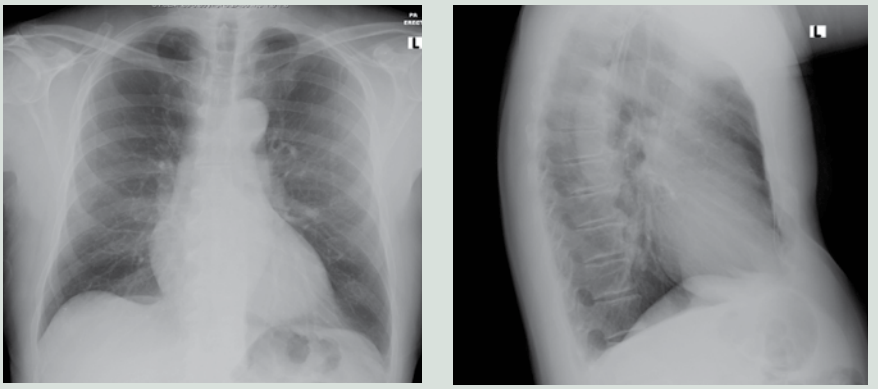
mild regurgitation on colour Doppler mapping. There are no mitral inflow changes to suggest chronicity. There is no other valvular disease and right ventricular size and systolic function are normal.

You receive a phone call from the cardiologist, who suspects native valve endocarditis. Given the absence of autoimmune disease and the history of tooth extraction, she suspects an infective cause. Admission arrangements are made via the emergency department, where blood cultures are taken before empiric antibiotics are commenced. As an inpatient, Mr PG undergoes transoesophageal echocardiography (Figure 2b) to examine closely all heart valves and to rule out complications such as severe regurgitation, chordae rupture or a root abscess.



Figures 1a and b. Mr PG's chest x-rays, posterioanterior (a, left) and lateral (b, right) views, showing clear lung fields without cardiomegaly or pulmonary congestion.

How is infective endocarditis diagnosed?

The causes of native valve endocarditis are divided into infective and noninfective and the presentations into acute and subacute. There are many other types of endocarditis but these are not discussed here other than to say they include infections of prosthetic valves, permanent pacemakers, cardioverter–defibrillators and ventricular assist devices and that if a device is involved, often the endocarditis will necessitate its removal.

The modern accepted criteria for diagnosing infective endocarditis were created in 1994 and revised in 2000, and are known as the modified Duke criteria (Box).[1] The Duke schema contains major and minor criteria, and infective endocarditis is diagnosed by the presence of two major criteria, one major and any three minor criteria, or five minor criteria. Cases can be classified as definite, possible or rejected by the modified Duke criteria. It is important to remember that failure to meet possible or definite endocarditis has a negative predictive value for infective endocarditis of 92%.

What organisms cause infective endocarditis?

Various bacteria and fungi can cause endocarditis, some of which may not be evident on blood culture (culture-negative endocarditis).

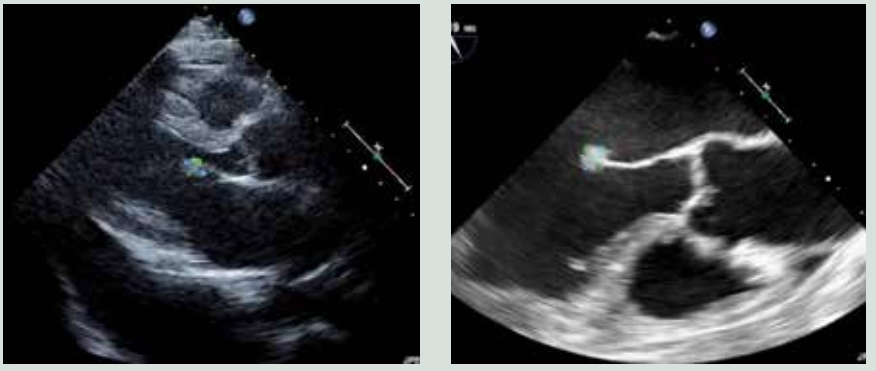
- *Staphylococcus aureus* can be highly pathogenic, and it is now the leading cause of native valve endocarditis. Due to the aggressive nature of this bacterium, patients with *S. aureus* bacteraemia often present acutely unwell to emergency departments. As Mr PG is not acutely unwell, *S. aureus* is not likely to be the causative organism in this case.
- Viridans streptococci are the second most common cause of infective endocarditis. These α-haemolytic streptococci that frequently colonise the oral cavity are particularly important in community-acquired infective endocarditis, which may present in a subacute manner.
- Beta-haemolytic streptococci are a less frequent cause of infective endocarditis but patients infected with these bacteria also tend to present acutely. One species deserves particular mention: a finding on blood culture of *Streptococcus gallolyticus* (formerly *Strep. bovis*) should prompt investigation of the gastrointestinal tract for a potential source such as colon cancer.

How are patients with infective endocarditis managed?

All patients with infective endocarditis will initially be managed as an inpatient and should be seen by the cardiology and infectious diseases teams. If required, a cardiothoracic surgical team should also be involved.

The diagnosis and management of infective endocarditis may be challenging for even the most experienced health practitioner as it is a heterogeneous syndrome in both presentation and therapeutic response. Furthermore, due to this diverse nature of the disease, large and multicentre trial data are lacking compared with other fields in cardiology.

Intravenous antibiotics form the standard of care, with the antibiotic choice being ideally targeted to the specific organism and its sensitivities. Antibiotics are normally commenced before blood culture results are available as it is critical to commence therapy as soon as possible. Therapy is chosen based on the individual patient's risk factors for causative organisms and microbial drug resistance as well as consideration of any pertinent drug contraindications, precautions or interactions. The current Australian antibiotic guidelines (*Therapeutic Guidelines: Antibiotic, Version 15, 2014*) suggest the following initial antibiotic combination for treatment of native valve endocarditis:[2]



Figures 2a and b. Mr PG's transthoracic (a, left) and transoesophageal (b, right) echocardiograms showing a 0.7 x 0.5 cm mobile mass on the anterior leaflet of the mitral valve.

Modified Duke criteria for infective endocarditis[1]

Major criteria

- **Positive blood cultures for infective endocarditis**
  - Typical micro-organisms for infective endocarditis from two separate blood cultures:
    - viridans streptococci
    - *Streptococcus gallolyticus* (formerly *Strep. bovis*), including nutritional variant strains (*Granulicatella* spp and *Abiotrophia defectiva*)
    - HACEK group: *Haemophilus* spp, *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis, Eikenella* spp and *Kingella kingae*
    - *Staphylococcus aureus*
    - community-acquired enterococci, in the absence of a primary focus, **OR**
  - Persistently positive blood culture, defined as recovery of a micro-organism consistent with infective endocarditis from:
    - blood cultures drawn more than 12 hours apart **OR**
    - all of three or a majority of four or more separate blood cultures, with first and last drawn at least one hour apart, **OR**
  - Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titre >1:800
- **Evidence of endocardial involvement**
  - Positive echocardiogram for infective endocarditis – transoesophageal echocardiogram recommended in patients with prosthetic valves, rated at least 'possible infective endocarditis' by clinical criteria or complicated infective endocarditis (paravalvular abscess); transthoracic echocardiogram as first test in other patients. Positive echocardiogram defined as:
    - vegetation (oscillating intracardiac mass on valve or supporting structures, or in path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation) **OR**
    - abscess **OR**
    - new partial dehiscence of prosthetic valve, **OR**
  - New valvular regurgitation (increase or change in pre-existing murmur not sufficient)

Minor criteria*

- **Predisposition:** predisposing heart condition or intravenous drug use
- **Fever:** >38.0°C
- **Vascular phenomena:** major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, Janeway lesions
- **Immunological phenomena:** glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
- **Microbiological evidence:** positive blood culture but not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) **OR** serological evidence of active infection with organism consistent with infective endocarditis

Diagnosis of infective endocarditis

Definite infective endocarditis:

- *Direct evidence of endocarditis based on histological findings*
- *Positive Gram stain results or cultures of specimen obtained from surgery or autopsy*
- *The two major clinical criteria*
- *One major and any three of the five minor clinical criteria*
- *The five minor clinical criteria alone*

Possible infective endocarditis

- *One major and one or two minor clinical criteria*
- *Three minor clinical criteria*

Rejected infective endocarditis

- *A firm alternative diagnosis made*
- *Resolution of clinical manifestations within four days of antibiotic therapy*
- *No pathological evidence of infective endocarditis found at surgery or autopsy after antibiotic therapy of four days or less*
- *Clinical criteria for possible or definite endocarditis not met (Note: this has a negative predictive value of 92%)*

* The minor criterion of 'Echocardiographic findings consistent with endocarditis but not meeting major criteria' was eliminated in the revision of the Duke criteria to the modified Duke criteria.

Adapted from: Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30: 633-638.[1]

- gentamicin IV once-daily *plus*
- benzylpenicillin 1.8 g IV four-hourly *plus*
- flucloxacillin 2 g IV four-hourly.

Vancomycin must be used in place of benzylpenicillin for patients at risk of having methicillin-resistant *S. aureus* infection.

In patients with subacute infective endocarditis, antibiotic therapy is often delayed as the need for diagnostic confirmation and organism identification may outweigh the need for empiric therapy in these more stable patients. Where possible, two sets of blood cultures should be performed before starting antibiotics.

The duration of total antibiotic therapy is an evolving topic. Most patients will require at least two weeks of IV therapy, with many requiring up to six weeks and some even longer.

Patient outcome

Pre-antibiotic blood cultures from Mr PG grew* Streptococcus sanguinis *(a member of the viridans group). Surveillance cultures were negative. As expected and consistent with species in the viridans subgroup of α-haemolytic streptococci, the infective strain was highly sensitive to the benzylpenicillin used in the initial regimen to treat Mr PG and he was discharged from hospital with intravenous benzylpenicillin supplied by the ambulatory care service. After two weeks, his inflammatory markers had normalised. He underwent transthoracic echocardiography four weeks after discharge, which showed persistence of mild mitral regurgitation but no valvular masses. His wife and tennis friends are grateful to have him back to normal.

You make a note for future reference that, according to the Australian antibiotic guidelines (*Therapeutic Guidelines: Antibiotic, Version 15*), as Mr PG has had previous infective endocarditis he is to receive antibiotic prophylaxis when undergoing invasive dental and other procedures at high risk for causing bacteraemia.[2] **CT**

References

1. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30: 633-638.
2. Antibiotic Expert Groups. Therapeutic guidelines: antibiotic. Version 15. Melbourne: Therapeutic Guidelines Ltd; 2014.

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