

Infective endocarditis: A contemporary update

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ABSTRACT

Infective endocarditis (IE) remains a rare condition but one with high associated morbidity and mortality. With an ageing population and increasing use of implantable cardiac devices and heart valves, the epidemiology of IE has changed. Early clinical suspicion and a rapid diagnosis are essential to enable the correct treatment pathways to be accessed and to reduce complication and mortality rates. In the current review, we detail the latest guidelines for the evaluation and management of patients with endocarditis and its prevention.

Introduction

Infective endocarditis (IE) is an infection of the endothelium of the heart. It has an annual incidence of 3–10/100,000 of the population with a mortality of up to 30% at 30 days.^{1,2} The epidemiology of IE has gradually changed over the years with healthcare-associated IE now accounting for 25–30% of contemporary cohorts as a result of a greater use of intravenous lines and intracardiac devices.³ *Staphylococcus aureus* is now the most prevalent cause of IE in most studies at ~26.6% of all cases, followed by viridans group streptococci at 18.7%, other streptococci at 17.5% and enterococci at 10.5%.⁴ These organisms together account for 80–90% of all cases of endocarditis.

Clinical suspicion

The clinical presentation of IE is highly variable and may present as an acute, subacute or chronic condition reflecting the variable causative microorganisms, underlying cardiac conditions and pre-existing comorbidities. Up to 90% of patients present with fevers, night sweats, fatigue, and weight and appetite loss, with approximately 25% having evidence of embolic phenomena at presentation.^{2,4} A diagnosis of IE should be carefully considered in those patients who present with predisposing risk factors, heart murmurs, vasculitic and embolic phenomena associated with IE (Box 1).^{5,6} Antimicrobial therapy should generally not be commenced until three sets of blood cultures have been taken; this will detect bacteraemia successfully in up to 98% of cases.^{5,7} Conversely, prior administration of antibiotic therapy is the singular most prevalent reason for culture negative endocarditis and results in untargeted antimicrobial therapy, diagnostic uncertainty and frequently longer and more toxic treatment regimens.

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Diagnosis

The modified Duke criteria can be used to help diagnose IE (Box 2).⁵ These have an overall sensitivity of 80% but this is significantly lower in cases of prosthetic valve endocarditis or implantable electronic device infections.^{8–10} Here, clinical suspicion, microbiological correlation and additional imaging may be required with whole body computed tomography (CT), cerebral magnetic resonance imaging (MRI) or increasingly ¹⁸F-labelled fluoro-2-deoxyglucose positron emission tomography (¹⁸F-FDG-PET) / CT.¹¹

Key points

Infective endocarditis has an annual incidence of up to 10/100,000 of the general population and carries a mortality of up to 30% at 30 days.

Healthcare related infections now account for 25–30% of newly reported cases of endocarditis.

The modified Duke criteria are used to help establish a diagnosis of endocarditis. This introduces the use of molecular imaging techniques for implanted heart valves where conventional echocardiography has reduced sensitivity.

Complicated cases of endocarditis that are accompanied by heart failure, valvular incompetence, structural destruction (abscess, perforation, fistula formation) should be managed at a reference centre by a dedicated endocarditis team.

Antibiotic management of endocarditis, especially in culture negative cases, is complex; choice of regimens and ongoing input should be provided by an infection specialist.

Antibiotic prophylaxis is recommended for those individuals at high risk of developing endocarditis (prosthetic heart valves or valve repair, prior endocarditis and unrepaired cyanotic congenital heart disease or an unrepaired shunt) who are scheduled for dental extractions, subgingival scaling or manipulation of the gingival tissue, teeth or oral mucosa.

KEYWORDS: Infective endocarditis, endocarditis team, diagnosis, surgical indications, antibiotic prophylaxis ■

Box 1. Predisposing risk factors for endocarditis**Cardiac conditions:**

- > bicuspid aortic valve
- > mitral valve prolapse
- > rheumatic valve disease
- > congenital heart disease
- > prior infective endocarditis
- > patients with implanted cardiac devices (permanent pacemakers / implantable cardioverter-defibrillator)
- > prosthetic heart valves.

Comorbidities:

- > intravenous drug use
- > chronic kidney disease (particularly dialysis patients)
- > chronic liver disease
- > malignancy
- > advanced age
- > corticosteroid use
- > poorly controlled diabetes
- > indwelling line for venous access
- > immunocompromised state (including HIV infection).

Microbiological diagnosis

Positive blood cultures are vital in establishing a diagnosis of IE and provide organisms for identification and susceptibility testing. The correct technique for obtaining specimens is to obtain three blood samples (10 mL each in aerobic and anaerobic bottles) at least 1 hour apart from separate access sites using aseptic non-touch technique. Isolated positive blood cultures are inconclusive for IE, however, persistent bacteraemia in multiple culture bottles of a typical organism is highly suggestive.

If blood cultures demonstrate no growth and the clinical suspicion of IE remains high, especially if there has been no prior antibiotic exposure, prolongation of blood culture bottle incubation and serological testing should be undertaken following consultation with an infection specialist. Causes of culture negative endocarditis such as *Bartonella* spp, *Coxiella burnetii*, *Tropheryma whippelii* and some fungi (especially *Aspergillus* spp) need to be considered. If patients undergo valve surgery for endocarditis, polymerase chain reaction (PCR) analysis of valve tissue will identify the infecting organism in most cases. Broad range PCR of whole blood is not recommended due to the very low sensitivity. In the event of all microbiological testing being negative, non-bacterial thrombotic (marantic) endocarditis related to malignancy, hypercoagulable states, systemic lupus erythematosus (Libman–Sacks endocarditis) and trauma should be excluded by appropriate investigation and testing.

Cardiac imaging

Transthoracic echocardiography (TTE) should only be requested if there is a strong clinical suspicion of IE and ideally once the results of blood cultures are available. Small mobile echogenic masses upon the cardiac surfaces are not uncommon and may reflect small areas of valvular degeneration in the absence of infection. Echocardiographic vegetations are septic thrombi and

require microbiological confirmation. They are normally located on the upstream surfaces of the cardiac valves and may lead to local or systemic complications. Valvular regurgitation is often the principal sign of leaflet destruction/perforation, while first degree and progressive heart block can signal the presence of an aortic root abscess and prompt the need for additional cardiac imaging. Systemic embolic complications are related to the size and mobility of the vegetation. A threshold of 4 mm for a vegetation has been shown to be associated with clinically silent neurological emboli, while 10 mm is taken as a threshold in the European guidelines for early intervention in the setting of one established systemic embolic event while on appropriate antibiotic therapy.^{12,13} A linear relationship exists between the size of the vegetation and neurological complications. Up to 60% of patients experience neurological complications in the presence of vegetations >30 mm.¹⁴

The sensitivity of TTE in detecting vegetations upon native valves is about 70%.⁵ This is reduced to 50% in patients with prosthetic valves and is lower in patients with implanted electronic devices.^{5,15} Where TTE is non-confirmatory and the microbiology is clinically suggestive of IE, a repeat TTE may be appropriate at an interval of 5–7 days.¹⁶ Transoesophageal echocardiography (TOE) has a sensitivity and specificity exceeding 90% for vegetations.¹⁷ TOE is performed to confirm the diagnosis of IE in the context of a non-diagnostic TTE and a high clinical suspicion of endocarditis; when prosthetic or device-related endocarditis is suspected; in the presence of *S aureus* bacteraemia; and when IE related complications have occurred (heart block, new murmur, persistent fever, embolism and intracardiac abscess).⁵ Repeat imaging is generally not required during the treatment course of IE unless there is clinical deterioration or complications are suspected. At the end of antimicrobial treatment, a TTE should be performed to serve as a post-treatment baseline for future comparison.

Additional imaging

For patients with suspected prosthetic heart valve endocarditis (PVE) or cardiac implantable electronic device (CIED) endocarditis, TTE and TOE may prove to be indeterminate owing to the presence of an artefact. In these cases, ¹⁸F-FDG-PET/CT or radiolabelled leucocyte single-photon emission computed tomography–CT (SPECT-CT) may be considered as adjunctive investigations to determine whether there is inflammation or infection of the prosthetic heart valve that would substantiate a diagnosis of IE. A recent study showed that ¹⁸F-FDG-PET/CT had a sensitivity of 93% in prosthetic valve endocarditis, but only 22% in native valve infection.¹⁸ CT is of value in determining the presence of perivalvular pathology (abscess, aneurysm or pseudoaneurysm formation) particularly when aortic valve endocarditis or root abscess is suspected. It also provides additional value in preoperative planning and the evaluation of coronary anatomy and prosthetic valve function. There should be a low threshold for cerebral MRI to investigate for neurological complications given the high rates of recognised neurological involvement (up to 80%) with most lesions being ischaemic in origin.

Management and treatment**The ‘endocarditis team’**

The management of IE should be coordinated by a dedicated team which resides at a reference centre. This should comprise

Box 2. Modified Duke criteria for endocarditis. Definite infective endocarditis = two major, or one major and three minor, or five minor; possible infective endocarditis = one major and one minor, or three minor.

Major criteria:

- > blood cultures:
 - > typical microorganisms consistent with IE from two separate blood cultures:
 - > viridans group streptococci, *Streptococcus bovis* group, HACEK group, *Staphylococcus aureus*; or
 - > community-acquired enterococci with absence of a primary focus; or
 - > microorganisms consistent with IE from persistently positive blood cultures:
 - > ≥ 2 positive blood cultures drawn > 12 hours apart; or
 - > all of three or a majority of ≥ 4 separate blood cultures (first and last samples ≥ 1 hour apart); or
 - > single positive blood culture for *Coxiella burnetii* or phase IgG antibody titre $> 1:800$
- > imaging:
 - > echocardiogram positive for IE:
 - > vegetation
 - > abscess, pseudoaneurysm or intracardiac fistula
 - > valvular perforation or aneurysm
 - > new partial dehiscence of prosthetic valve
 - > abnormal activity around the site of a prosthetic valve detected by PET/CT assuming > 3 months after surgery or radiolabelled leucocyte-SPECT/CT
 - > definite paravalvular lesions by cardiac CT.

Minor criteria:

- > predisposing heart condition or intravenous drug use
- > fever $> 38^{\circ}\text{C}$
- > vascular phenomena (including those detected by imaging alone): arterial emboli, splenic infarction, mycotic aneurysms, intracranial haemorrhage and Janeway lesions
- > immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots and rheumatoid factor
- > microbiological evidence: positive blood cultures not meeting major criteria above or serological evidence of infection with organism consistent with IE.

CT = computed tomography; HACEK = *Haemophilus* spp, *Aggregatibacter* spp, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp; IE = infective endocarditis; IgG = immunoglobulin G; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

cardiologists with a specialist interest in valvular heart disease / cardiac imaging, infectious diseases specialists and/or microbiologists, cardiac surgeons, and cardiac devices specialists. There should be access to neurology and neurosurgical expertise, since up to 30% of patients will experience symptomatic neurological events, and congenital heart disease specialists under specific circumstances. This IE team approach enables early guideline directed referral to surgery, appropriate antibiotic medication regimens, access to advanced imaging, close monitoring for complications and follow-up once treatment is complete. In this setting, 1-year mortality can be expected to be approximately halved.⁵

Uncomplicated IE can normally be managed locally with regular communication with the IE team at the reference centre. Complicated IE with heart failure, severe valve incompetence, structural destruction (abscess, perforation or fistula formation) and embolic or neurological complications should be managed by a dedicated IE team. At the reference centre, all IE cases should be discussed on a regular basis to determine the optimal antimicrobial therapy and its duration, the requirement and timing or surgical intervention, and the type of follow-up required.

Antibiotic treatment

Infective endocarditis was universally fatal prior to the advent of antibiotics. Selecting an appropriate bactericidal regimen which is administered for the correct duration is essential to achieving cure in this disease. Based largely on experience and cohort studies, rather than controlled trials, recommended regimens for common organisms vary minimally in published guidelines (Table 1). Gentamicin has been dropped from most guidelines for treating methicillin sensitive *S. aureus* due to lack of evidence of clinical benefit. In addition, there is increasing experience with using ceftriaxone as a synergistic agent in enterococcal endocarditis; consequently, amoxicillin plus ceftriaxone is recommended in the European guidelines and is especially useful in patients with renal impairment.⁵ Partially oral treatment of endocarditis is gaining increasing attention and a recent randomised controlled trial has suggested this approach may be acceptable in a highly selected patients.¹⁹ Choosing an appropriate regimen in patients presenting acutely ill or with negative blood cultures is best undertaken after consultation with an infection specialist. Where possible, the siting of a peripherally inserted central line is advised owing to the long duration of antibiotic therapy.

Table 1. Recommended treatment regimens for common causes of endocarditis

Organism	Native valve	Prosthetic valve
<i>Staphylococcus aureus</i> (methicillin sensitive)	Flucloxacillin 2 g, 4–6 hourly	Flucloxacillin 2 g, 4–6 hourly, and rifampicin 450–600 mg, bd, and gentamicin 1 mg/kg, bd (latter for 2–6 weeks)
<i>Staphylococcus aureus</i> (methicillin resistant)	Vancomycin (dose weight-based)	Vancomycin (dose weight-based), and rifampicin 450–600 mg, bd, and gentamicin 1 mg/kg, bd (latter for 2–6 weeks)
Viridans group streptococci and <i>Streptococcus bovis</i> group	Benzyl penicillin 1.2 g, 4 hourly; or ceftriaxone 2 g, once a day (od); or benzyl penicillin 1.2 g, 4 hourly and gentamicin 1 mg/kg, twice a day (bd; both for two weeks)	Benzyl penicillin 1.2 g, 4 hourly; or ceftriaxone 2 g, od
<i>Enterococcus faecalis</i>	Amoxicillin 2 g, 4 hourly, and gentamicin 1 mg/kg, bd or ceftriaxone 2 g, bd	Amoxicillin 2 g, 4 hourly, and gentamicin 1 mg/kg, bd or ceftriaxone 2 g, bd

Treatment regimens all assume normal renal function and are administered intravenously (Table 1).^{5,20} Native valve and prosthetic valve endocarditis are treated for 4 and 6 weeks, respectively, unless otherwise stated.

Outpatient parenteral antibiotic therapy

In patients with a microorganism that is highly responsive to antibiotic therapy who demonstrate an uncomplicated clinical course following treatment, consideration is given to outpatient parenteral antibiotic therapy (OPAT). Inpatient treatment is usually advised for the first 2 weeks when the complication rates are the highest. OPAT via a long line can be considered before this if patients are stable and a viridans group streptococcus or *Streptococcus bovis* group organism is the culprit organism on a native valve. OPAT should only occur however with the appropriate patient education, regular post-discharge follow-up clinics and ongoing clinician input.

Prognosis

The in-hospital mortality for IE can be up to 30%. High-risk patients can be identified as those with specific patient characteristics (age, PVE or comorbidities), the presence of IE complications (heart failure, renal failure, septic shock or brain haemorrhage), echocardiographic findings (abscess, significant valve destruction or pseudoaneurysm) and the culprit organism (*S aureus*, fungi and non-*Haemophilus* spp, *Actinobacillus* spp, *Cardiobacterium hominis*, *Eikenella corrodens* or *Kingella* spp (non-HACEK) Gram-negative bacilli).⁵ These prognostic variables should be taken into consideration when determining the timing of surgical intervention. Plans for surgery should be reviewed weekly and be classified as being emergency (<24 hours), urgent (within 7 days) or elective in timing.

Complications of endocarditis and indications for surgery

Up to 50% of patients will require surgery for IE. The principal indications for this are:

- heart failure
 - cardiogenic shock as a result of progressive native or prosthetic valve obstruction/regurgitation or fistula formation – emergency surgery (<24 hours)

- severe valve disease and symptoms of heart failure and a poor haemodynamic response – urgent surgery (<7 days)
- failure to control infection – urgent surgery
 - local ongoing infection: aortic root abscess, aneurysm or fistula formation, expanding vegetation size
 - infection with a difficult to treat organism (fungi or multiresistant organism, staphylococci or non-HACEK Gram-negative bacilli on a prosthetic valve)
 - persistence of positive blood cultures despite appropriate antibiotics or inadequate control of metastatic septic foci
- prevention of septic emboli – urgent surgery
 - vegetation >10 mm with an embolic event while on appropriate antibiotic therapy
 - vegetation >30 mm
 - vegetation >10 mm and severe native or prosthetic valve disease and patient is at a low operative risk.

Box 3. Endocarditis prophylaxis for high-risk patients and dental procedures

Amoxicillin 3 g (child 50 mg/kg), or clindamycin 600 mg (child 20 mg/kg) with a penicillin allergy.

Dental procedures to consider antibiotic prophylaxis:

dental extractions
subgingival scaling
manipulation of the gingival tissue, periapical region of teeth or the oral mucosa.

High-risk patients:

prosthetic heart valve / valve repair
prior endocarditis
unrepaired cyanotic congenital heart disease or residual shunt.

Moderate-risk procedures:

unoperated heart valve disease
hypertrophic cardiomyopathy.

Follow-up

Most post-endocarditis treatment complications occur within the first 12 months. Vigilant follow-up should be conducted by an IE team member and ideally at 1, 3, 6 and 12 months based upon the clinical situation. The risk of IE recurrence is estimated to be 2–6% while up to 30% of patients may require surgery within the first year. Patient education on good dental hygiene, avoidance of intravenous drug use and body piercings/tattoos should be given and prophylactic measures advised (Box 3).^{21–23}

Conclusions

Infective endocarditis is associated with significant morbidity and mortality despite improvements in diagnostics and microbiological techniques. Establishing an early diagnosis with early involvement of a dedicated IE team and prompt surgical intervention where indicated are established measures that improve patient outcomes. Further patient pathway development is required to ensure equitable IE care across different clinical networks. ■

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