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Infective endocarditis in the adult patient

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Abstract
Infective endocarditis (IE) is an uncommon disease with a high morbidity and mortality. The basic pathology involves adherence of microorganisms to areas of endothelial damage or associated implanted medical devices, such as prosthetic valves or pacemakers, resulting in localized infection and formation of vegetations. Complications include sepsis, valvular failure and embolization. Staphylococci and streptococci are the predominant causes of IE. Blood cultures and echocardiography are key diagnostic tests, but a diagnosis of IE can still be difficult to establish. Serological tests, particularly for fastidious microorganisms, can assist when blood cultures are negative. The Duke criteria can aid diagnosis but lack sensitivity, particularly when blood cultures are negative or transthoracic echocardiography images are non-diagnostic. Antibiotics are the mainstay of treatment, but surgical debridement and valvular surgery are frequently required. Recent changes in antibiotic prophylaxis for those considered to be at risk of IE have reduced the number of patients given antimicrobials by dental practitioners. This article summarizes how to diagnose IE and outlines current antibiotic treatment regimens.

Keywords
Antibiotics; cardiac; endocarditis; infection; prophylaxis; treatment

Key points
- Infective endocarditis remains a disease with a high morbidity and mortality
- The role of antibiotic prophylaxis continues to be debated
- New investigations, such as PET/CT and cardiac CT, have been incorporated into diagnostic guidelines, but blood cultures, taken correctly, remain the most important diagnostic test

- Empirical antibiotic therapy should be avoided if possible until blood cultures have been taken or (ideally) a microorganism identified
- Multidisciplinary teams, including cardiologists, infection specialists and cardiothoracic surgeons, are key to good management of cases
- The role of surgery continues to be refined, and surgery is recommended earlier in the course of the disease than previously

Infective endocarditis

Infective endocarditis (IE) is an uncommon condition with a recently reported incidence of 7.7 cases per 100,000 population per year in the USA. There is uncertainty over whether the incidence is increasing, some population-based analyses reporting a stable or falling incidence but others an increase. IE remains a serious problem with an in-hospital mortality of 20%. Infection can involve any part of the endocardium; native heart valves are most often affected, but implanted medical devices such as prosthetic heart valves, intravascular conduits and implantable cardiac electronic devices are increasingly involved.

The pathological hallmark of IE is a 'vegetation', composed of microorganisms, usually of one species, enmeshed in fibrin, platelets and other host-derived products. Vegetations usually form on heart valves, and infection can spread to adjacent structures. Vegetations are more common on the left side of the heart and on the free margins of incompetent valves, especially the atrial side in mitral regurgitation and the ventricular side in aortic regurgitation. Right-sided IE involving the tricuspid and pulmonary valves occurs more commonly in patients who are intravenous drug users, or have pacemakers or long-term indwelling vascular access devices, such as haemodialysis patients.

A clinical diagnosis of IE can be difficult to establish because of the non-specific symptoms or presentation with extracardiac complications. The modified Duke criteria, recently extended by the European Society of Cardiology (ESC),[1] provide a probabilistic approach to the diagnosis and an objective means of appraising clinical evidence to support a diagnosis, which still remains challenging. The criteria are, however, limited when blood cultures are negative or transthoracic echocardiography (TTE) is inconclusive.

Peripheral clinical manifestations of IE, such as Janeway lesions (haemorrhagic macular plaques, most often seen on the palms and soles), Osler's nodes and splinter haemorrhages, are less common than previously reported, occurring in <10% of cases.[2] Gram-positive bacteria, in particular streptococci and staphylococci, are the predominant causative microorganisms. Recent international registry data have suggested that staphylococci are now the leading cause of IE, accounting for 31% of all cases.[2]

Pathogenesis and prevention of infective endocarditis

To appreciate the rationale for measures aimed at preventing IE, it is necessary to understand its pathogenesis.

Approximately 50% of patients with a diagnosis of IE have an underlying cardiac predisposition.[2] Based on animal model work on native heart valve infection, it is thought that abnormal intracardiac blood flow resulting from structural heart disease or the presence of an intracardiac device causes endothelial damage and microthrombus formation. In the presence of bacteraemia or fungaemia, these microthrombi can become colonized with microorganisms, and vegetations can subsequently form. The vegetation enlarges because of recurrent fibrin deposition and microbial multiplication. IE related to an indwelling device or prosthetic valve can result from microbial contamination at the time of implantation as well as seeding via the bloodstream (in the same manner as native valve infection).

Many invasive medical and non-medical procedures, such as tooth extraction, urinary tract catheterization or body piercing, have the potential to cause the transient presence of microorganisms in the bloodstream that can subsequently seed a damaged endocardium. Historically, prophylactic antibiotics were given to patients at risk of IE undergoing procedures such as dental operations, which are associated with possible bacteraemia. There are multiple case reports of IE occurring after dental operations such as extractions, and it is well recognized that oral pathogens can cause IE and antibiotics can prevent IE in animal models. Consequently, over the last 50 years or so, antibiotic prophylaxis has been recommended by expert groups from around the world for many groups of patients at risk of IE undergoing dental procedures. Antibiotic prophylaxis has also been recommended for non-dental invasive procedures, especially involving the gastrointestinal, genitourinary or respiratory tract. In Europe and the USA, it is still recommended that antibiotic prophylaxis is given for dental and some other procedures in

patients perceived to be at high risk of complications from IE, for example with prosthetic valves, complex congenital heart disease or a history of IE.

However, it is now considered that bacteraemias resulting from daily activities are so frequent that they are more likely than an isolated procedure to be the cause of IE, although this does not exclude the possibility that procedures can cause a small proportion of cases. In the UK, the National Institute for Health and Care Excellence Clinical Guideline no. 64 on the prevention of IE recommended in 2008 that antibiotic prophylaxis should not be given to at-risk patients undergoing dental and non-dental procedures. The recommendation was slightly modified in 2016, stating that antibiotic prophylaxis should not be given routinely to at-risk patients, following a report of an increase in rates of IE above the baseline trend. The discrepancy in advice that exists worldwide reflects the fact that there has never been a randomized controlled clinical trial to settle the question of whether antibiotic prophylaxis is truly effective.

Healthcare-associated IE now comprises approximately 25% of all episodes.[2] This substantial group of potentially preventable infections should be a prime target for preventive measures. The emergence of these infections probably relates to an increasing prevalence of patients with either a cardiac device in situ or an indwelling vascular access device, for example haemodialysis or cancer patients, which increases the risk of bacteraemia and IE.

Traditional views about preventing IE through antimicrobial prophylaxis for dental procedures and invasive procedures are changing, as outlined above. Emphasis on prevention of IE has shifted towards a need for improved dental health in patients at risk of developing IE.[3] However, it should also probably include more attention to infection prevention practices. These include optimal antimicrobial prophylaxis when inserting cardiac devices and the use of enhanced aseptic procedures during the insertion and subsequent care of vascular access devices.

Establishing a diagnosis of infective endocarditis

The Duke criteria are used to aid in the diagnosis of IE (Table 1). They have recently been modified by the ESC to take account of new imaging techniques.[1] The clinical diagnosis of IE continues to be difficult to establish because the symptoms are often non-specific or non-cardiac. The most common presenting symptoms are loss of appetite, night sweats and fatigue. There should be a low threshold for considering IE in patients with any of the following sets of clinical findings:

- febrile illness and a new cardiac murmur of valvular regurgitation
- febrile illness, a pre-existing at-risk cardiac lesion and no clinically obvious site of infection
- febrile illness associated with any of the following vascular or immunological phenomena: embolic event, stroke, splinter haemorrhages, Janeway lesions, Roth's spots, Osler's nodes or peripheral abscesses of unknown cause
- prolonged history of sweats, weight loss, anorexia or malaise.

Blood cultures are a key means of establishing a diagnosis of IE. Multiple positive blood cultures remain the most important diagnostic indicator and are a major Duke criterion.[4] The subsequent choice and duration of antimicrobial treatment are based on several factors, including the causative microorganism and its susceptibility to antimicrobial agents.

The most common cause of culture-negative blood cultures in IE is prior antibiotic use. Therefore, empirical treatment should be avoided if possible until blood cultures have been obtained, even if the patient is clinically unwell.[4] In a patient with severe sepsis and suspected IE, two sets of blood cultures from different veins should be taken before starting empirical therapy within an hour. In haemodynamically stable patients, three sets of optimally collected blood cultures should ideally be taken at different times over a 24-hour period before initiating treatment.[4] The maximum allowable volume of blood for the system being used should be inoculated into each blood culture bottle to optimize sensitivity, as low numbers of bacteria are often present in the blood in IE. Intermittently positive blood cultures are unusual as, unlike most other sources of sepsis, bacteraemia is constant. Blood culture systems now enable the vast majority of pathogens to be isolated. Blood cultures from patients with IE caused by fungi are often sterile.

Other approaches to identify the causative microorganism, particularly in culture-negative endocarditis include serology for pathogens such as Legionella and Coxiella burnetii. In cardiac surgery patients, polymerase chain reaction-based tests can be applied to the explanted heart valves and used to identify some causative pathogens. Patients with unexplained persistently positive blood cultures or intravascular catheter-related bloodstream infection with persistently positive blood cultures 72 hours after catheter removal should be actively investigated for IE.[4]

Echocardiography is a crucial tool, both to diagnose IE and to influence management decisions by outlining the anatomy and function of the diseased heart. Positive echocardiographic findings are a major criterion in the diagnosis of IE and can include the presence of a vegetation, cardiac abscess, new dehiscence of a prosthetic valve and new valvular regurgitation. TTE is the first-line investigation. However, transoesophageal echocardiography (TOE) is usually required, owing to its superior sensitivity and more detailed images. The sensitivity of TTE ranges from 40% to 63% and that of TOE from 90% to 100%.[4] Current guidelines advise routine echocardiography for patients with Staphylococcus aureus bacteraemia or candidaemia, because of the frequency of IE in this setting, the virulence of these microorganisms, the serious consequences once intracardiac infection is established and the frequent need for surgery.[4]

The latest ESC guidelines, published in 2015, also discuss other imaging techniques. Gated, multislice computed tomography (CT) scanning can be superior to TOE in imaging the aortic root to determine the extent and consequences of infection; it can also be used to determine coronary anatomy in those requiring surgery, sometimes obviating the need for invasive coronary angiography.[1]

Positron emission tomography (PET), particularly when combined with CT (PET/CT), can be helpful in categorizing cases of probable IE, as can single photon emission CT (SPECT). This can determine whether certain areas are infected, and is of value in imaging prosthetic valves and pacemakers when the diagnosis remains uncertain.

Antibiotic treatment of IE

The treatment of IE involves prolonged courses of intravenous antibiotics and must often be combined with surgery to achieve a cure.

When a diagnosis of IE has been established, treatment comprises antimicrobial therapy, often in combination with cardiac surgery or associated device removal. Empirical treatment is the initiation of antibiotics before identifying the infecting microorganism and its antibiotic susceptibility. This represents the time between the diagnosis being considered and confirmation of a causative microorganism (e.g. isolation from a blood culture or positive serology). In the absence of prior antibiotic use, most non-fastidious microorganisms are identified within 48 hours using automated blood culture systems. In general, bactericidal antibiotics should be used as historical trials have shown poor outcomes in patients treated with bacteriostatic antibiotics (e.g. clindamycin).

Empirical treatment recommendations are summarized in Table 2. Currently recommended regimens include vancomycin for acute severe illness,[4] which reflects the increasing incidence of staphylococci as a cause of IE and the difficulties of predicting meticillin (flucloxacillin) resistance. However, the prevalence of meticillin-resistant Staphylococcus aureus is currently declining in the UK, and these recommendations may need revision. Staphylococcus aureus is known to cause an aggressive form of IE with more acute onset and rapid progression. This contrasts with what was previously referred to as ‘subacute’ IE, commonly caused by streptococci found in the oral cavity, which tends to present with a more indolent clinical course.

In the presence of intracardiac prosthetic material, such as prosthetic heart valves, vancomycin should be used in addition to gentamicin and rifampicin, as this regimen is more effective against bacteria growing in ‘biofilms’ on the prosthetic material. Therapy should always be reviewed when the causative microorganism is identified or if a patient fails to respond to treatment.

Recommended therapy for the common IE-causing microorganisms is summarized in Table 3. Treatment at home can be considered for some patients, usually after an initial 2-week period of treatment in hospital and in patients without indications for surgery. This requires appropriate outpatient or home drug administration methods, and the ability to evaluate the response to therapy to allow readmission or investigation if treatment failure is suspected.

Duration of antibiotic treatment

Treatment should generally be continued for at least 4 weeks, and should usually be extended to 6 weeks for patients with intracardiac prostheses in situ. Aminoglycosides are usually administered for the first 2 weeks and then stopped to minimize the risk of adverse effects, but there are exceptions. For the most sensitive streptococci, a short course (2 weeks) of treatment including an aminoglycoside has been shown to be equivalent to more prolonged therapy. This short therapeutic course can only be applied in the absence of significant valvular regurgitation, emboli or heart failure, and with a vegetation size <10 mm.

Surgery for IE

Approximately 50% of patients in whom IE is diagnosed require cardiac surgery (Figure 1 shows an bileaflet prosthetic valve and prosthetic aortic root explanted because of IE). Individual patients should be reviewed with a cardiac surgeon as early as possible, with appropriate involvement of an associated multidisciplinary team. Indications for and timing of surgery are shown in Table 4. In general, there is now a move towards earlier surgery, which has been shown to improve outcomes.[5]

The Duke criteria and ESC modification[1]

Major criteria

1. **Blood cultures positive for IE**
    a. Typical microorganisms consistent with IE from 2 separate blood cultures:
        i. Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus; or
        ii. Community-acquired enterococci, in the absence of a primary focus; or
    b. Microorganisms consistent with IE from persistently positive blood cultures:
        i. ≥2 positive blood cultures of blood samples drawn >12 h apart; or
        ii. All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or
    c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800
2. **Imaging positive for IE**
    a. Echocardiogram positive for IE:
        i. Vegetation;
        ii. Abscess, pseudoaneurysm, intracardiac fistula;
        iii. Valvular perforation or aneurysm;
        iv. New partial dehiscence of prosthetic valve.
    b. Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.
    c. Definite paravalvular lesions by cardiac CT.

Minor criteria

1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature >38℃.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with microorganism consistent with IE.

Definite diagnosis

1. 2 major criteria; or
2. 1 major criterion and 3 minor criteria; or
3. 5 minor criteria

Possible diagnosis

1. 1 major and 1–2 minor criteria; or
2. 3–4 minor criteria

Rejected IE

1. Firm alternate diagnosis; or
2. Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or
3. No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
4. Does not meet criteria for possible IE, as above

Note that the diagnosis can also be made from pathological specimens obtained at surgery or post-mortem.

IE, infective endocarditis.

Table 1.

Empirical antimicrobial treatment regimens for infective endocarditis

Clinical situation	Empirical treatment
Acute presentation	Vancomycin or daptomycin i.v. (for Gram-positive cover) plus gentamicin i.v. or ciprofloxacin i.v. or meropenem i.v. (for Gram-negative cover)
Indolent presentation	Amoxicillin i.v. plus optional gentamicin i.v.
Intracardiac prosthesis	Vancomycin i.v. plus rifampicin orally plus gentamicin i.v.

i.v., intravenous.
Refer to the current British Society for Antimicrobial Chemotherapy guidelines[4] and British National Formulary for up-to-date dosing regimens and drug interactions/cautions.

Table 2.

Recommendations for treatment of native-valve infective endocarditis caused by fully antimicrobial-sensitive microorganisms

Causative microorganism	Recommended treatment
Meticillin-sensitive Staphylococcus aureus	Flucloxacillin i.v.
Oral streptococci or Streptococcus bovis	Benzylpenicillin i.v.
Enterococcus spp.	Ampicillin i.v. plus gentamicin i.v.

Note: regimens can vary according to patient factors, such as allergies or kidney dysfunction.
i.v., intravenous.

Table 3.

Indications for surgery	Timing[a]
Heart failure	
Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock	Emergency
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance	Urgent
Uncontrolled infection	
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent
Infection caused by fungi or multiresistant organisms	Urgent/elective
Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	Urgent
PVE caused by staphylococci or non-HACEK Gram-negative bacteria	Urgent/elective
Prevention of embolism	
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after ≥1 embolic episode despite appropriate antibiotic therapy	Urgent
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	Urgent
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery	Urgent
HF, heart failure; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis. HACEK: Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus, Haemophilus influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, Kingella denitrificans.	
[a]Emergency surgery: performed within 24 hours; urgent surgery: within a few days; elective surgery: after at least 1–2 weeks of antibiotic therapy. Source: Derived from ESC guidelines (2015)[1]	

Table 4. Indications and timing for surgery

Figure 1. An explanted bileaflet prosthetic valve and prosthetic aortic root. This patient had prosthetic valve endocarditis caused by a Haemophilus species. Transoesophageal echocardiography had confirmed an abscess in the intraventricular septum and worsening aortic regurgitation with a right atrial fistula connecting to the left ventricular outflow tract.

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