Management of infective endocarditis

Infective endocarditis, in which infection or infective vegetations develop on heart valves or other endocardial surfaces, causes considerable morbidity and mortality. Prompt diagnosis and treatment can improve outcome and are therefore essential. Here, we discuss the management of infective endocarditis, concentrating on adult patients.

Background

The incidence of infective endocarditis in the USA and Europe is around 1.7–6.2 per 100,000 person-years.¹,² Predisposing cardiac conditions include mitral valve prolapse, the presence of prosthetic material (e.g., valves and patches), rheumatic heart disease, degenerative and bicuspid aortic valve disease, and many forms of congenital heart disease.³ Infective endocarditis may also involve previously normal heart valves and may be associated with infection in an intravascular device.¹,⁴ Other risk factors include poor dental hygiene, misuse of i.v. drugs, systemic sepsis, diabetes mellitus, long-term haemodialysis, immunosuppression and invasive procedures.²,⁵ In many instances, infective endocarditis cannot be clearly attributed to a prior procedure or bacteraemic event.⁵

Causative organisms

The commonest causative micro-organisms in native-valve infective endocarditis are the viridans group of streptococci (which cause around 50% of episodes), followed by Staphylococcus aureus (around 20%).³ In i.v. drug-users, S. aureus is commonest, causing 50–60% of episodes.³ In infective endocarditis occurring ‘early’ after prosthetic valve surgery (typically in the first 2 months, but up to 1 year after the operation) is thought to be due to peri-operative contamination and is mainly caused by staphylococci, particularly coagulase-negative staphylococci.²,³ In ‘late’ prosthetic-valve infections (presenting a year or more after surgery), viridans streptococci, S. aureus and coagulase-negative staphylococci are all common causes.²,³

Enterococcal endocarditis (mainly with Enterococcus faecalis or Enterococcus faecium) represents perhaps 10% of all infective endocarditis, and tends to occur in patients with disease of the genitourinary or lower gastrointestinal tracts and may follow an invasive procedure.³ A round 2–10% of episodes of infective endocarditis are caused by fungi (mainly Candida or Aspergillus spp.), for which particular risk factors include immunosuppression, i.v. drug use, cardiac surgery, prolonged exposure to antimicrobial drugs and i.v. feeding.³,⁷ Fungal endocarditis tends to cause bulky, friable vegetations which may embolise to large arteries, when embolectomy, with histology and culture, may be diagnostic.

In around 5% of patients with proven infective endocarditis, conventional blood cultures are negative.⁸ This may be due to infection with a slow-growing or difficult-to-culture (‘fastidious’) organism. Examples are Gram-negative bacilli of the so-called ‘HACEK’ group of oropharyngeal commensals, nutritionally variant streptococci and, rarely, Coxiella burnetii or Brucella spp.³,¹² More commonly, culture-negativity is due to recent exposure to antimicrobial drugs.

Clinical features

Clinical manifestations of infective endocarditis will depend on factors such as the nature of any predisposing condition and the virulence of the infecting organism. The disease may present insidiously with classical ‘subacute’ manifestations such as fever, systemic illness, clinical evidence of cardiac involvement and vascular and immunological phenomena (see below). In other patients, the clinical picture may be dominated by acute septicemia, or by persistent fever after seemingly appropriate antimicrobial therapy for a bloodstream infection. The patient’s age and immune status, concomitant chronic disease, and early development of a complication (such as a stroke), may confuse the presenting picture.

General manifestations

Most patients have fever, often accompanied by anorexia, malaise, weight loss and anaemia. Fever may be absent in patients with, for example, congestive heart failure, severe debility or chronic renal or liver disease, or after recent antimicrobial drug therapy.¹,¹² Clinically detectable splenomegaly
and finger clubbing, which are features of longstanding infection, are now relatively uncommon in UK practice.

Cardiac manifestations
Cardiac manifestations may result from direct damage by the infection, local spread of the infection and abscess formation, or haemodynamic complications. These may manifest as a new or changing murmur, development of conduction defects, or heart failure. In acute endocarditis, severe valve destruction may present with acute heart failure and severe dyspnoea. In i.v. drug-users, it is commonly the right heart valves (especially the tricuspid) that are affected, and right-sided heart failure is a complication.

Vascular complications
Embolism to major arteries is common and may be the presenting feature (e.g. stroke, renal or splenic infarction, lower limb embolism, or sudden loss of sight in one eye). Septic embolism may give rise to metastatic infection (e.g. cerebral abscess, septic arthritis). Right-sided endocarditis may present with septic pulmonary embolism, lung abscess or exudative pleural effusions. Yototic aneurysm (the result of septic embolism setting up infection in an arterial wall) is a rarer complication.

Neurological manifestations
Neurological complications develop in 20–40% of patients with infective endocarditis and are often a presenting feature. Manifestations include confusion and stupor (especially common in older patients), meningism (sometimes progressing to frank meningitis), seizures, stroke and cerebral abscess.

Mucocutaneous and immunological features
Petechiae (in the skin, conjunctivae and other mucous membranes) occur in up to two-thirds of patients. Splinter haemorrhages are a non-specific finding. Around 30–60% of patients develop microscopic haematuria, due to immune complex glomerulonephritis. O sel’s nodes (tender subcutaneous nodules, often in the pulp of the digits) occur in around 5% of patients. Roth’s spots (oval-shaped haemorrhages in the retina) and Janeway lesions (non-tender erythematous, haemorrhagic or purpuric lesions, often on the palms or soles) are manifestations of longstanding endocarditis and are rarely seen nowadays.

Prognosis
The risk of dying (chiefly from heart failure, central nervous system emboli or uncontrolled infection) varies with the infecting organism, from 4–16% with viridans streptococci, to 25–47% with S. aureus, and over 50% with fungal infections. Mortality is increased if endocarditis is complicated by congestive heart failure, abscess formation or a neurological event. Mortality from right-sided endocarditis in i.v. drug-users is around 10%.

Making the diagnosis
Diagnosis of infective endocarditis relies on a high level of suspicion in any patient with unexplained fever, bacteremia or systemic illness and/or with an apparently new murmur or other features of the illness. In general, patients with suspected infective endocarditis should be admitted to hospital. Routine investigations should include a full blood count, ESR and C-reactive protein, renal and liver function tests, urine examination, a chest X-ray and an ECG. The key diagnostic investigations, however, are blood culture and echocardiography.

Blood culture
In most patients with infective endocarditis, the causative organism can be identified within 2–3 days, using conventional blood culture (three separate samples, each preferably of at least 30mL, the first two within 1–2 hours of admission, and the third within 24 hours). When taking such cultures, it is important for clinicians to state the possibility of infective endocarditis on the accompanying request forms. A antibacterial treatment given within the previous 2 weeks reduces the rate of positive cultures by 35–40%. If the patient has not received an antibacterial and endocarditis is strongly suspected, failure to isolate an organism by 5–7 days may necessitate special culture methods for some less common organisms and/or serology for organisms such as Coxiella spp. and Brucella spp. Persistent failure to isolate an organism may suggest a non-infective cause of endocarditis (e.g. vasculitis or malignancy).

Echocardiography
Echocardiography is crucial in revealing features such as vegetations, abscesses and structural damage, and in assessing cardiac function. Repeated echocardiography is often necessary for early detection of cardiac complications requiring surgical intervention. Transthoracic echocardiography provides adequate imaging in most patients and has 98% specificity for detecting vegetations, but sensitivity below 65%, in most published studies. Transthoracic echocardiography is more invasive, requires sedation, and is less widely available. However, compared to transthoracic imaging, it provides better views of prosthetic valves and the aortic valve annulus, and has higher sensitivity for detecting vegetations on native or prosthetic valves (87–100%) and perivalvular abscesses (87% vs. 28% with transthoracic views). Transthoracic echocardiography is the imaging method of choice in patients with:

- negative or inconclusive findings on the transthoracic echocardiogram despite clinical suspicion of infective endocarditis
- suspected prosthetic-valve endocarditis
- any feature suggesting abscess or intracardiac spread of infection or a high risk of these developments (e.g. persistent fever despite appropriate antimicrobial treatment; new conduction defect; haemodynamic deterioration; or fulminant infection with a virulent organism, such as S. aureus).

The Duke diagnostic criteria
The Duke criteria, originally developed as research tools but now widely used clinically, enable stratification of patients with suspected infective endocarditis into ‘definite’, ‘possible’ or ‘rejected’ categories, based on the presence or...
absence of major and minor clinical and laboratory criteria. In brief, the major criteria comprise: positive blood cultures for organisms typical of, or consistent with, infective endocarditis; clear evidence of endocardial involvement (definite findings on echocardiography or clinical evidence of new valvular regurgitation); and positive serology for Coxiella burnetii. Minor criteria include the presence of any predisposing condition, fever, and vascular or immunological phenomena. Diagnosis of ‘definite’ infective endocarditis, requires, for example, the presence of two major, or one major plus three minor criteria, or five minor criteria, and has a specificity of around 99%, and sensitivity of more than 80%.

General management
Infective endocarditis requires prompt treatment with appropriate antimicrobial drugs, administered parenterally in doses sufficient to eradicate the organism from the blood, from vegetations, and from local or metastatic foci of infection. Empirical treatment should be started immediately once appropriate blood cultures have been taken, and adjusted when the antimicrobial susceptibility of the organism is known. The only exception might be in patients recently exposed to antibacterial drugs, in whom delaying antimicrobial treatment for a few days can increase the likelihood of isolating the causative organism on subsequent blood cultures. However, such delay is only reasonable in closely monitored patients with subacute illness who have no evidence of severe or progressive valvular dysfunction, heart failure or embolic complications.

All patients with suspected or proven infective endocarditis should be monitored frequently to assess the response to treatment and detect complications promptly. Assessment should include clinical examination, ECG, laboratory tests (full blood count, ESR and C-reactive protein, renal and hepatic function tests) and repeated echocardiography. In addition, many treatment regimens require regular monitoring of plasma antimicrobial concentrations (at least twice weekly, more frequently in older patients and those with renal impairment) to minimise the risk of toxicity (e.g. with aminoglycosides or glycopeptides) and to ensure that bactericidal concentrations are maintained.

Antimicrobial therapy
The British Society of Antimicrobial Chemotherapy and the American Heart Association have published detailed guidelines for the treatment of infective endocarditis. However, there have been few randomised clinical trials of antibacterial drug treatment, so the guidelines represent consensus recommendations based mainly on data from animal models, case-control studies and case-series. In practice, clinicians are likely to rely strongly on the advice of the local infectious diseases specialist.

Empirical treatment
Current UK guidelines recommend i.v. benzylpenicillin plus i.v. gentamicin as initial empirical treatment unless staphylococcal endocarditis is suspected, when vancomycin should be substituted for penicillin. In patients who are allergic to penicillin, empirical treatment should be with vancomycin plus gentamicin.

Streptococcal endocarditis
A nontuberculous treatment of streptococcal endocarditis depends on the clinical complexity of the infection in the individual patient and on the antibiotic susceptibility of the organism. In uncomplicated endocarditis caused by fully penicillin-sensitive viridans streptococci or S. bovis (minimum inhibitory concentration [MIC] <0.1mg/L) and involving a native valve, treatment for 2 weeks with i.v. benzylpenicillin (7.2g daily in six divided doses) plus i.v. gentamicin (usual adult dose 80mg 12-hourly) is generally sufficient to cure the infection.

The combination of penicillin and gentamicin is synergistic against streptococci in vitro and sterilises vegetations faster than penicillin alone in animal models of endocarditis. However, superiority over penicillin alone has not been demonstrated in a clinical trial. For fully penicillin-susceptible streptococci, the American guidelines recommend 4 weeks’ treatment with penicillin alone, or ceftriaxone alone (in preference to penicillin plus gentamicin), in patients aged over 65 years, or with renal or auditory nerve impairment.

In patients allergic to penicillin, vancomycin (1g twice daily by i.v. infusion) is an alternative. Experience with telithromycin in infective endocarditis is generally less than with vancomycin. Use of a glycopeptide concurrently with gentamicin increases the risk of nephrotoxicity from these antimicrobials and requires particularly careful monitoring.

Staphylococcal endocarditis
UK guidelines recommend i.v. vancomycin (30mg/kg/day; 0.5-1g 12-hourly) plus i.v. gentamicin (80–120mg three times daily) as initial empirical treatment for suspected staphylococcal endocarditis. This regime should be continued if culture reveals infection with a methicillin-resistant staphylococcus; for infection involving a native valve, vancomycin is usually given for 4 weeks and gentamicin for up to 1 week.

If a methicillin-sensitive staphylococcus is isolated, treatment can be changed to fluoroquinolones (12g daily i.v. in six divided doses, for 4 weeks) with gentamicin (80–120mg three times daily for up to 1 week). If the isolate is sensitive to penicillin (nowadays unusual), benzylpenicillin should be used instead of fluoroquinolones.
Longer treatment is needed for staphylococcal endocarditis involving a prosthetic valve. In these circumstances, many of our consultants follow the American guidelines, which recommend treatment for at least 6 weeks with nafcillin or oxacillin (equivalent to flucloxacillin) or with vancomycin (for methicillin-resistant staphylococci), plus gentamicin for the first 2 weeks. H owever, while the American guidelines recommend routine inclusion of oral rifampicin for 6 weeks in the treatment regimen, in the UK, the drug tends to be reserved for adjunctive treatment in difficult cases. R ifampicin should not be given alone as resistance may emerge rapidly.

In i.v. drug-users with uncomplicated right-sided native-valve endocarditis caused by methicillin-sensitive S. aureus, 2 weeks' treatment with i.v. flucloxacillin plus i.v. gentamicin will often cure the infection.

Enterococcal endocarditis
First-choice treatment of enterococcal endocarditis is with a synergistic bactericidal combination of amoxicillin (12g i.v. in six divided doses) plus gentamicin (80mg i.v. twice daily), for 4 weeks. H owever, around 25% of isolates from patients with enterococcal endocarditis are highly resistant to gentamicin (M IC >2mg/L ) and do not respond to the combination. S ome of these strains respond to amoxicillin plus streptomycin, but organisms with high-level resistance to both gentamicin and streptomycin are very difficult to treat; some (perhaps a half) respond to prolonged treatment (up to 12 weeks) with high-dose amoxicillin alone, but surgery to replace the infected valve is frequently necessary.

A synergistic combination of vancomycin (or teicoplanin) plus gentamicin is an alternative for patients allergic to penicillin or infected with an amoxicillin-resistant strain. H owever, this combination too is ineffective against enterococci with high-level resistance to gentamicin, or resistance to vancomycin.

Endocarditis caused by fungi
Standard chemotherapy for fungal infections is i.v. amphotericin B, with or without other antifungal drugs. H owever, medical treatment alone is rarely successful and early surgery is nearly always needed.

Medical plus surgical treatment
In many patients with infective endocarditis, the infection can be cured with medical treatment alone. W ith appropriate antimicrobial therapy, the incidence of systemic embolisation falls rapidly and fever usually resolves in a few days, accompanied by clinical improvement and a fall in the ESR and C-reactive protein titre. P ersistent fever requires urgent investigation: it may indicate local or metastatic spread of infection, intracardiac abscess, nosocomial infection (e.g. infection of an intravascular catheter) or drug hypersensitivity.

For some patients (perhaps 25–30%), medical treatment alone is insufficient and must be combined with surgery. U rgent surgical assessment should be undertaken in any patient who develops congestive heart failure or has persistent fever or recurrent embolisation despite maximal antimicrobial therapy, or in whom the echocardiogram reveals a large vegetation, persistent vegetation after a major systemic embolus, or evidence of an intracardiac abscess. M anagement of infective endocarditis involving a prosthetic valve should always be discussed early with a regional cardiac centre. A cute valvular regurgitation with pulmonary oedema, disappearance of a prosthetic valve, and abscess formation are absolute indications for surgery. D evelopment of cardiac failure carries a mortality of over 50% in patients with infective endocarditis managed with medical treatment alone; p rompt surgery, combined with medical therapy, substantially improves survival, while delay in referral is likely to lead to haemodynamic deterioration, which significantly increases the operative mortality.

I nfection with certain organisms (e.g. fungi, Coxiella burnetii, and enterococci for which there is no synergistic bactericidal combination) rarely responds to medical treatment alone and usually requires surgery.

Relapse
Following medical or surgical treatment of infective endocarditis, all patients require careful follow-up for signs of clinical relapse or haemodynamic deterioration. T he reported relapse rate is less than 2% for streptococcal endocarditis in native valves, but is considerably higher for virulent organisms such as staphylococci and enterococci and for prosthetic-valve endocarditis (10–15%). R elapse tends to present within a few weeks, and requires retreatment with antimicrobial drugs and, often, surgery.

Conclusion
Infective endocarditis causes substantial morbidity and mortality. E ffective management requires a high level of suspicion in any patient with unexplained fever and systemic illness, whether or not they are known to have a predisposing condition, to enable prompt diagnosis and treatment. I t is important that such patients are not treated blindly with antibacterial drugs, but are promptly referred to a specialist centre for diagnostic investigations, including blood cultures and echocardiography.

C urrent guidelines for antimicrobial therapy are hampered by a lack of high-quality evidence. C orrectly used, however, the recommended regimens will cure the infection in most patients with infective endocarditis. C lose liaison with microbiologists and infectious disease physicians is imperative to ensure that the patient receives the optimal combination of drugs in an adequate and safe dose. Involvement of cardiologists and cardiac surgeons is also essential in order that surgical intervention, which for some patients is urgent and life-saving, is not delayed.
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