GUIDANCE ON THE PROPHYLAXIS AND TREATMENT OF INFECTIVE ENDOCARDITIS IN ADULTS

Advisory Group of the British Cardiac Society Clinical Practice Committee and Royal College of Physicians Clinical Effectiveness and Evaluation Unit
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RECOMMENDATIONS

The grading A-D for each of the clinical recommendations has been applied according to the definitions used by the Scottish Intercollegiate Guidelines Network (see Appendix 1). (* = no supportive evidence, but good practice point)

GOOD PRACTICE AND AUDIT POINTS

DIAGNOSIS

1. In unwell patients with known cardiac disease or new cardiac murmurs, always suspect the diagnosis of infective endocarditis (IE). C

2. When the diagnosis is suspected, admit the patient to hospital for full and careful investigation, including blood cultures, recording of temperatures, haematological and biochemical investigation, ECG, chest X-ray and echocardiography. Three sets of blood cultures at intervals of >1 hour within the first 24 hours will suffice when clinical evidence suggests the diagnosis is highly likely in a sick patient. If the patient is not acutely sick or when the diagnosis is not obvious clinically, 6 sets of blood cultures should be taken within the first 24-48 hours. C

3. If the diagnosis is confirmed by blood culture – refer the patient to an experienced cardiologist. D

4. Involve microbiologist from the outset. *

5. Consider transoesophageal echocardiography (TOE) if transthoracic echocardiography is suboptimal, to obtain further information on the size, site or mobility of vegetations, abscess or fistula formation or valve perforation etc. TOE should be performed in all patients with prosthetic valve endocarditis (PVE). B

PROPHYLAXIS

6. Patients at moderate-risk or high-risk of endocarditis should be given antibiotic prophylaxis with appropriate antibiotics based upon the type of dental or surgical procedure being performed. C

7. Patients should be informed of their risk of IE and the need for antibiotic prophylaxis. They should be told to inform any doctor or dentist who is responsible for providing care and they should be given a card to carry reminding them of the importance of the risk and how to avoid IE. C
TREATMENT

8. Once the diagnosis is established, treatment should be commenced according to the Guidelines or with alternative antibiotics if microbiological tests suggest more appropriate agents are suitable. D

9. In a sick patient, antibiotic treatment should be commenced immediately after blood cultures have been collected and the regimen adjusted once the microbiological data is available. D

10. Generally, prolonged IV antibiotic therapy is necessary, administered via a large central vein. Only the most penicillin-sensitive streptococci should be considered for treatment with shorter courses of penicillin. D

11. The Guidelines for treatment should be followed unless the clinical state and microbiological data suggest alternative treatment is more appropriate. D

12. Culture-negative endocarditis requires close scrutiny for unusual and slow-growing microorganisms and fungi. Serological tests for *Coxiella burnetii*, *Bartonella* spp and *Chlamydia* spp should be performed if the diagnosis is still suspected and there is still no growth after 7 days. Microscopy and culture of any excised tissue is essential. Molecular assay for specific gene targets and universal loci for bacteria and fungi and subsequent sequencing may be applied to blood culture or excised material to help identify the causative organism. Treatment should involve antibiotics which are appropriate for the most likely organism for the particular clinical scenario but should generally cover Gram-positive and Gram-negative organisms. D

13. Be aware that the majority of native valve endocarditis and of late prosthetic valve endocarditis is caused by viridans streptococci (50-70%), *Staphylococcus aureus* (25%) and enterococci (10%). In early prosthetic valve endocarditis, *Staphylococcus epidermidis* and *Staphylococcus aureus* are the commonest organisms. D

14. Patients with a history of penicillin-allergy or who develop penicillin-allergy, should be treated with (or changed to) vancomycin or teicoplanin and gentamicin or other appropriate antibiotics. D

SURGERY

15. In haemodynamically-stable patients, early consultation with a cardiac surgeon is recommended in case surgery is suddenly required. D

16. Patients with life-threatening congestive heart failure, left heart failure or cardiogenic shock due to treatable valvular disease should undergo emergency cardiac surgery, if the patient has reasonable prospects of recovery and a satisfactory quality of life after surgery. D
17. Surgery is indicated in patients with annular or aortic abscess, in those with infections resistant to antibiotics and in those with fungal endocarditis. Large, mobile vegetations and recurrent emboli after appropriate antibiotic therapy are also indications for surgery. D

18. Patients with prosthetic valve endocarditis (PVE) will generally require further surgery. D

**Guidance development group**

These recommendations were developed by an advisory group nominated by the Clinical Practice Committee of the British Cardiac Society in collaboration with the Clinical Effectiveness Unit of the Royal College of Physicians (London). Contributors to the guidance document included representatives of the British Cardiac Society (BCS), the British Junior Cardiologist’s Association (BJCA), the Faculty of Dental Surgery of the Royal College of Surgeons, the Society of Cardiothoracic Surgeons (SCTS), the British Society of Echocardiography (BSE), the Royal College of Pathologists (Microbiology), the Royal College of Anaesthetists (RCA), the British Association for Nursing in Cardiac Care (BANCC) and the British Cardiac Patients’ Association (BCPA).

**Literature Search**

The recommendations reflect an extensive review of the literature and the personal knowledge and experience of the members of the working group. An electronic search of Medline using the keywords, “infective endocarditis”, revealed 12,697 publications between 1964 and 2002 - of which 8,844 were written in English. Only the latter were considered for review.

**Strength of evidence and grades of recommendation**

The strength of evidence and the recommendations drawn from it were classified according to the definitions used by the Scottish Intercollegiate Guidelines Network, derived from the US Agency for Health Care Policy and Research (see Appendix 1). The important clinical recommendations are accompanied by the SIGN gradings according to the level of evidence in the literature as judged by an independent group of SIGN reviewers.
Scope of the document

This review is intended to improve the care of patients with IE and those at risk of developing IE. It is directed at junior and senior cardiologists, cardiac surgeons and surgeons in other specialities, anaesthetists and intensivists, gynaecologists, physicians in all specialties, dental surgeons, microbiologists, general practitioners and nurses who are responsible for treating patients with cardiac disease and those patients at risk of developing IE. It is particularly important for those medical personnel who are likely to be involved in the first presentation of an illness to be aware that the diagnosis should always be considered in patients with a pyrexia, cardiac murmurs and any of the possible symptoms and signs associated with this potentially life-threatening condition.

The recommendations are aimed at aiding the establishment of the clinical diagnosis and recognition of the complications of IE, the use of blood cultures and other investigations for confirming the diagnosis, and the use of transthoracic and transoesophageal echocardiography for defining the extent of cardiac involvement and guiding clinical management. It is also concerned with the prophylactic treatment to prevent IE, in defining who is considered to be at significant risk of developing IE as well as the antibiotic regimens for the treatment of patients with confirmed or probable IE. The clinical scenarios that typically occur and the wide variety of responsible organisms responsible for IE are important issues that aid diagnosis and prompt appropriate management. The guidance aims to provide recommendations on the role of surgery in IE and in particular the management of patients with PVE.

The recommendations reflect the consensus of opinion of the working group, derived from the evidence in the literature, and is applicable to the majority of patients. Recommendations for investigations and treatments are made only where they can be justified on the basis of evidence of clinical benefit, do not preclude the use of alternative approaches in individual patients and should not be used to override clinical judgement. The document is consistent with recently published guidelines from the European Society of Cardiology

http://www.escardio.org/knowledge/guidelines/Guidelines_Infective_Endocarditis.htm

Given that the evidence base for recommendations is often based on case reports, small differences do exist between this and the ESC document. References are quoted
wherever possible to the sources of information from which the Advisory Group made its recommendations.

**Editorial independence and conflicts of interest**

This document has been developed without external funding. None of the members of the Advisory Group had any conflicts of interest.
INTRODUCTION

Infective endocarditis (IE) is uncommon. The yearly incidence reported in developed countries ranges between 1.8 and 6.2 per 100,000 of the population.\textsuperscript{1-5} Although it affects neonates, infants, children, young adults and the pregnant woman, the incidence increases after 30 years of age and exceeds 10 per 100,000 for people aged over 50 years.\textsuperscript{6-10} It is a life-threatening disease with a substantial morbidity and mortality (approximately 20%) despite improved diagnostic techniques, modern antibiotics and surgical therapies.\textsuperscript{11} Prosthetic valve endocarditis (PVE), although uncommon, carries an even higher mortality rate.\textsuperscript{12-14} Prevention of endocarditis is therefore extremely important.\textsuperscript{15}

IE predominantly affects individuals with underlying structural cardiac defects who develop bacteraemia with organisms likely to cause endocarditis.\textsuperscript{16} The incidence and risk of IE associated with various cardiac structural abnormalities and following cardiac surgical and interventional procedures has been reviewed in the literature.\textsuperscript{17,18} Experimental studies suggest that endothelial damage leads to platelet and fibrin deposition and thus a non-bacterial thrombotic endocardial lesion.\textsuperscript{19,20} If bacteraemia occurs as a result of a surgical or dental procedure or instrumentation involving mucosal surfaces contaminated by organisms, bacteria settle on damaged or abnormal heart valves or on the endocardium close to anatomic defects resulting in endocarditis or endarteritis. Valvular and congenital abnormalities, especially those that result in abnormal high-velocity jets, can damage the endothelial surface and predispose to the formation of a potential site for an infective endocardial lesion\textsuperscript{21,22} and the pathologic hallmark of IE – vegetations.\textsuperscript{23} Vegetations are composed of masses of organisms enmeshed with fibrin, platelets and variable inflammatory cell infiltrate.

Currently, patients with prosthetic cardiac valves, users of illicit IV drugs and patients with mitral valve prolapse or other non-rheumatic heart disease (eg: congenital heart disease, bicuspid aortic valves), rather than those with rheumatic heart disease account for the majority of cases of IE,\textsuperscript{16,24-28} although rheumatic heart disease is still responsible for approximately 40-50% of cases. Such patients are at increased risk when undergoing invasive procedures. Elderly patients, chronic alcoholics, patients with chronic inflammatory bowel disease, poor dental hygiene, chronic haemodialysis, those with diabetes mellitus and those on immunosuppressives are at increased risk of IE.\textsuperscript{5,29-40} Left-sided cardiac structures are most commonly affected (85% of cases) - isolated aortic lesions in 55-60%, isolated mitral lesions in 25-30% and mitral and aortic lesions in 15% of cases. Right-sided IE accounts for 10-15% of cases.

Although most cases of IE cannot be attributed to an invasive procedure, antibiotic prophylaxis forms a major role in attempting to minimize the frequency of this potentially lethal condition. Table 1 shows the causes of bacteraemia that are responsible for IE and the predominant pathogens.

SYMPTOMS AND CLINICAL FINDINGS

The clinical manifestations of IE will depend on factors such as the nature of any predisposing condition, the type and virulence of the responsible organism and the portal
of entry.\textsuperscript{41} Patients with acute IE typically present with an accelerated illness including high remitting pyrexia, rigors and prostration.\textsuperscript{42,43} It is usually caused by virulent pathogens such as \textit{S. aureus} and pre-existing valve disease can be minimal. In contrast, those with subacute IE present more insidiously with anorexia, weight loss, fever, chills, myalgia, arthralgia and fatigue.\textsuperscript{44,45}

It usually affects patients with major pre-existing heart valve defects and is caused by less virulent pathogens such as the viridans streptococci. Unique features occur in childhood.\textsuperscript{46} The clinical manifestations may be classified as cardiac and extracardiac, although specific features may be found in patients with right-sided IE, PVE, fungal IE and culture-negative IE.

**Cardiac manifestations** usually dominate the clinical presentation with the presence of new or worsening cardiac murmurs or the development of cardiac failure due to advanced valvular infection and destruction.\textsuperscript{44,47,48} Eighty per cent of patients present with a murmur whilst 15-20\% develop one in hospital.\textsuperscript{49,50} Pre-existing heart disease is found in 60-75\% of cases of left-sided endocarditis but is rarer in right-sided disease. The degree of valvular destruction depends on the organism responsible, the duration of infection and its anatomic site. It may consist of ulceration, tear and rupture of mitral or tricuspid chordae tendineae and perforation of the cusps themselves resulting in moderate or severe regurgitation.\textsuperscript{51}

Typically, vegetations occur on the atrial surface of the mitral valve, on the ventricular surface of the aortic valve, distal to a coarctation of the aorta, in the pulmonary artery in association with a patent ductus and on the right side of a ventricular septal defect. Occasionally all four valves are affected and mural endocarditis occurs.\textsuperscript{52} Eustachian valve endocarditis is well recognised.\textsuperscript{53-56}

Abscesses of the heart are observed in 20-40\% of cases, mainly in the aortic valve ring.\textsuperscript{57-61} They can spread to surrounding structures such as the aorta, the anterior mitral valve leaflet and the interventricular septum and can cause a fistula between the two ventricles, between the aorta and left atrium, between the left ventricle and the right atrium and even into the pericardial cavity causing tamponade.\textsuperscript{62-65} These complications are associated with a high mortality.\textsuperscript{66} Septal abscesses can lead to progressive conduction defects evidenced by prolongation of the PR interval and complete heart block.\textsuperscript{67} This is more often associated with prosthetic (PVE) than native valve endocarditis (NVE) and native aortic than mitral valve endocarditis. Aortic root abscesses may produce a sinus of Valsalva aneurysm or involve the coronary ostia and large vegetations can cause valvular obstruction.\textsuperscript{68,69} Subaortic aneurysm has been reported.\textsuperscript{70}

Occasionally, chest pain due to pleurisy, pericarditis or myocardial infarction resulting from coronary arterial emboli are presenting symptoms.\textsuperscript{71-74} An inflammatory or septic pericardial effusion mainly affects patients with aortic valve endocarditis but pericardial abscess may occur as a result of infection on the mitral valve.\textsuperscript{59} Primary involvement of the myocardium occurs with reduction in contractility and ST-T wave abnormalities and
ventricular arrhythmias may result. Free wall myocardial abscesses may rupture and cause sudden death.\textsuperscript{75,76}

**Extracardiac clinical manifestations** consist of embolic (13-40%) as well as vasculitic phenomena\textsuperscript{73,77,78} – the latter due to immune-complex deposition. Embolic events usually occur early - 50% within the first 20 days, and 80% within the first 32 days of initial presentation. Focal pain in the flanks or left upper quadrant may be due to embolic infarcts in the kidneys or spleen. Retinal and peripheral limb emboli may also occur. Splenomegaly is found in 30-50%.\textsuperscript{57,77,79} Splenic abscesses sometimes occur and splenic rupture can be fatal.\textsuperscript{80,81} Abdominal CT or MRI scans appear to be the best diagnostic tests for a splenic abscess and urgent splenectomy is indicated.

Neurological manifestations may be the presenting feature.\textsuperscript{5,82} These may be headache or any symptoms and signs associated with focal cerebral infarcts, cerebritis or abscess, haemorrhage or mycotic aneurysm, including stroke, confusion and seizures.\textsuperscript{83-86} Meningism/meningitis may occur and CSF cultures may be positive.\textsuperscript{87} These are particularly serious and life threatening features with a mortality rate of 40%.

Other vascular or immune-mediated phenomena may occur including petechiae (on extremities, above clavicles, buccal and palatal mucosa or on palpebral conjunctiva), splinter haemorrhages (5-15%), retinal haemorrhages, Roth spots (5-10%), painful Osler’s nodes (5-10%), painless red Janeway lesions on the palms and soles and finger clubbing – which occurs late in 10-20% of patients. Mycotic aneurysms, which occur in 2-15% of patients who have IE, involve mainly the sinuses of Valsalva, the cerebral and carotid arteries, the branches of the abdominal aorta (the mesenteric arteries, renal artery) and more rarely limb and coronary arteries.\textsuperscript{3,72,88-98} They occasionally rupture, causing subarachnoid or intraventricular haemorrhage or other vascular catastrophies.\textsuperscript{99-102} Intracranial mycotic aneurysms (1.2-5% of cases) have an overall mortality of 60% increasing to 80% if rupture should occur.\textsuperscript{72,100,103-105} Contrast-enhanced CT scanning and 3-D magnetic resonance imaging may provide adequate information but angiography remains the diagnostic imaging test of choice.\textsuperscript{103,106}

Deposits of immune complexes with complement along the renal glomerular basement membrane may cause a focal or diffuse glomerulonephritis and can be diagnosed by renal biopsy with appropriate glomeruli staining.\textsuperscript{107-109} Arthritis and Osler’s nodes have also been attributed to the local deposit of immune complexes.\textsuperscript{110-114} Besides immune complex glomerulonephritis and septic renal infarcts, haemodynamic instability, antibiotic drug and contrast medium toxicity can be responsible for acute renal failure which often indicates a poor prognosis.

Osteomyelitis is a rare complication.\textsuperscript{115}

Emboli are more likely to occur with enterococci, staphylococci, Gram-negative aerobic bacilli and fungi, with large mobile vegetations and especially when the mitral valve is affected. They tend to occur early before hospital admission and within the first two weeks of starting treatment. 50% of all emboli occur within 20 days and 80% within the
first month after initial symptoms of IE. After an embolic complication, recurrent episodes are likely to follow especially if vegetations persist on echocardiography. In >50% of cases, recurrence of a thromboembolic event occurs within 30 days after the first episode. It has been estimated that up to 65% of embolic events involve the central nervous system, that the majority lodge in the middle cerebral artery territory and that the associated mortality is high.\textsuperscript{116}

**In patients with right-sided endocarditis**, the tricuspid valve is most frequently involved (80%), pulmonary infarcts are often followed by lung abscesses and pleural effusions occur.\textsuperscript{117-120} Haemoptysis can be fatal.\textsuperscript{102} Peripheral emboli and immunologic vascular phenomena generally do not occur. The main cause is IV drug abuse but others include pacemaker infection, central IV lines, skin and gynaecological infections and bacteremia in patients who have congenital cardiac lesions.\textsuperscript{121-122} In IV drug abuse, the prognosis of right-sided IE is favorable (4-5% mortality). However, recurrences are frequent (30%).\textsuperscript{123,124} When IE is associated with infection of pacemakers, central IV or Hickman lines or other foreign bodies eg: septal occluder devices, tube grafts etc, the objects need to be removed in order to maximize the chance of successful treatment. Antimicrobial therapy is required for 4-6 weeks.\textsuperscript{125} *S. aureus* and *S. epidermidis* are responsible for 50% and 25% of pacemaker infections respectively. Special techniques have been reported for removal of infected material associated with large vegetations.\textsuperscript{126,127}

**When mechanical valves are affected** (5-15% of all cases in developed countries), abscesses are particularly frequent, extending beyond the prosthetic ring into the annulus and perianular tissue. Conduction system disturbance and even purulent pericarditis are serious complications. The diagnosis requires a high index of suspicion from the clinician.\textsuperscript{128} Ring or septal abscess, fistulous tracts and dehiscence of the prosthesis are frequent autopsy findings. Vegetations can interfere with disc function causing obstruction and/or regurgitation. In bioprosthetic valve IE, the anatomic lesions vary between limited leaflet infection and disseminated infection.\textsuperscript{129}

The microbiology of **early** PVE (<60 days) (0.4-1.2% of cases) and of those occurring within the first year of surgery is distinctive.\textsuperscript{130,131} *S. aureus* and *S. epidermidis* predominate (45-50%), followed by Gram-negative aerobic bacilli and fungi. Streptococci and enterococci are less common, accounting for <10% of cases. Contamination occurs intraoperatively via the wound or from the extracorporeal circulation or postoperatively from IV catheters, arterial lines, urethral catheters and endotracheal tubes. Of the staphylococci, coagulase-negative staphylococci predominate particularly *S. epidermidis* – an increasing number of which are methicillin-resistant. *S. aureus* PVE has a high mortality and surgery should be considered early.\textsuperscript{132} **In late** PVE (>60 days), the bacteriology more closely resembles that of community-acquired NVE\textsuperscript{5,133} although staphylococci are still important causative organisms. The incidence may be higher in tissue than mechanical valves.\textsuperscript{134}

**Fungal endocarditis** is frequently characterized by negative blood cultures and a paucity of physical signs.\textsuperscript{136-139} Candida or aspergillus infection are the commonest causes. Fever,
changing murmurs and the presence of peripheral emboli – commonly of large vessels, in the brain, gut, kidneys, coronary arteries and the limbs, are the most common signs. Although blood cultures are generally negative, 83-95% are positive in those with candida infection. Culture of a peripheral arterial embolus may provide the diagnosis and the specimen should be examined microscopically for hyphae. Routine serology has been useful in deep-seated cryptococcosis and histoplasmosis and although candida precipitins and aspergillus antigens and antibodies might provide supportive diagnostic evidence of fungal infection, their sensitivity and specificity are disappointing. Fungal vegetations are frequently large (10-30mm diameter), bulky and friable and valvular or endocardial in position.

Echocardiography and TOE in particular are most important in establishing an aetiological diagnosis, for defining the anatomical extent of the valvar disease and for guiding the surgical strategy. Emboli are frequently large and multiple, cause considerable functional and neurological damage and lead to the associated high mortality. Metastatic abscesses are another frequent complication – the heart and kidneys being involved most commonly. Medical treatment combined with early surgery is the mainstay of treatment. Surgery should be performed as soon as the bulky vegetations are identified in order to prevent the high rate (68%) of embolisation. Fungal endocarditis may complicate prolonged antibiotic treatment of PVE and prophylactic oral nystatin may be valuable.

**Blood culture-negative endocarditis** (CNE)(5-10%) is usually due to patients having been treated with antibiotics prior to the blood cultures being taken. Other causes include fungal infections, fastidious slow-growing organisms eg: *Brucella* spp, *Neisseria* spp, *Legionella* spp, *Nocardia* spp, *Mycoplasma* spp, cell-dependent organisms eg: *Bartonella* spp, *Chlamydia* spp, *Histoplasma* spp and *Coxiella burnetii* and “non-infective” endocarditis as seen in systemic lupus erythematosus and in terminal malignant disease (“marantic endocarditis”). However, systemic lupus erythematosus and IE can co-exist.

Some of the more unusual infections have clinical features which are suggestive. For example, Q-fever endocarditis often occurs in patients in contact with farm animals, frequently involving the aortic valve but also the mitral and prosthetic valves. Liver involvement, thrombocytopenia and purpura are common. Vegetations are usually small. Brucella endocarditis is also found in patients in contact with cattle and goats, usually farmers and veterinary surgeons. Again the aortic valve is more frequently affected. Aneurysms of the sinus of Valsalva with intramyocardial spread is common. PVE has been reported. Serological tests (antibodies, precipitins) may be helpful in these situations, particularly for rickettsia such as *Coxiella* and for *Chlamydia*. Although *Coxiella* (a strict intracellular Gram negative microorganism) may be found by Giemsa staining of the excised valve, endocarditis is best diagnosed by IgG (>1/800) and IgA (>1/100) titres to phase I antigen using the microimmunofluorescence (MIF) test. For *Brucella* spp (a facultative intracellular Gram-negative bacillus), high titres of specific IgG and IgM antibodies by tube agglutination are diagnostic. Bacterial polymerase chain reaction (PCR) analysis can be crucial in confirming the diagnosis in
CNE eg: *Tropherema whipelli* or *Bartonella* spp and such molecular analysis has been recently implemented into the newest revision of the Duke criteria. These additional tests may not only improve the sensitivity of the diagnosis, but may also improve the outcome by increasing the specificity of the antibiotic treatment.

In unwell patients with known cardiac disease or new cardiac murmurs, always suspect the diagnosis of infective endocarditis.

**Recommendation C**

**EVIDENCE LEVEL 3**

**INVESTIGATIONS**

Mild to moderate anaemia is commonly present with a normochromic, normocytic picture. Neutrophil leucocytosis is common and the ESR and CRP are elevated in 90% of patients and the latter have been proposed as additional minor criteria to the Duke classification of IE. Intraleucocyte bacteria can be seen in buffy coat preparations of blood in up to 50% of cases.

Microscopic haematuria and/or proteinuria occur in 50% of cases. In those developing immune complex glomerulonephritis, red blood cell casts and heavy proteinuria may be identified. Renal function should be repeatedly monitored to detect dysfunction early. A polyclonal increase in gammaglobulins is characteristic of active endocarditis and an elevated rheumatoid factor may be of diagnostic help.

Blood cultures remain the definitive procedure for diagnosing IE. At least three sets of blood cultures (aerobic and anaerobic) drawn >1 hour apart should be taken and if positive for the same organism (in the majority of the culture bottles), this confirms that an endovascular infection is likely.

An ECG and chest X-ray are useful for assessing the extent and severity of the infection, its effects on cardiac size and function and for determining whether surgery may need to be considered early or whether prophylactic temporary pacemaker implantation is indicated. The presence of significant conduction abnormalities demonstrated on the ECG especially if known to be new or progressive warrants urgent temporary pacing and this is classically seen in the presence of aortic root abscesses complicating aortic valve endocarditis due to *S. aureus* infection. Arrhythmias may be due to myocarditis or to ischaemia due to coronary emboli and should be treated in standard fashion.

A chest X-ray may show evidence of cardiomegaly and heart failure but in tricuspid valve endocarditis in intravenous drug abusers or in patients with serious permanent pacemaker infection may demonstrate infective pulmonary emboli and pulmonary abscesses.
Infection-related antiphospholipid antibodies may help in predicting risk of embolic events and the application of PCR technology to blood and tissue samples may be useful for identifying more unusual pathogens causing IE.\textsuperscript{178-182}

When valve replacement is undertaken, valvular tissue should be examined histologically and cultured for the presence of organisms which may allow postoperative antibiotics to be tailored accordingly. Bacterial DNA probe analysis of explanted tissue and amplification by PCR may be an alternative to or complement histology and culture.

The key tests, however, are blood cultures and echocardiography.\textbf{EVIDENCE LEVEL 3}

**OPTIMAL BLOOD CULTURE TECHNIQUE**

\textbf{Between 3 and 6 sets of blood cultures should be obtained at intervals >1 hour within the first 24 hours from all patients suspected of having IE before commencing antibiotic treatment.}

Three sets of blood cultures should be taken if the patient is extremely unwell and the clinical features suggest that IE is very likely and \textbf{six} sets if the patient is not acutely sick or when the diagnosis is not obvious clinically. Optimal aseptic technique is essential to avoid false positive cases due to contaminating organisms from the skin.\textsuperscript{183,184} Each set of blood cultures should be taken via a separate venepuncture (10mls of blood into each bottle).

The bacteraemia associated with IE is typically continuous, with 10-200 colony-forming units per ml of blood.\textsuperscript{185} However, this is not always the case and some patients may have intermittent bacteraemia or less than one microorganism per ml of blood. In such cases, the number of positive culture-results is directly related to the number of blood samples drawn and the volume of blood in each individual sample. Single samples should not be drawn because the most common contaminants, coagulase-negative staphylococci can be responsible for IE and a positive culture will be difficult to interpret.\textsuperscript{186} Ideally, cultures should be spaced at least 60 mins apart to prove that bacteraemia is continuous. Blood cultures should be stored in an incubator at 37\textdegree{}C and not in a refrigerator. The possibility of IE should be made clear on the request form.

Overall, about two-thirds of all samples drawn from patients with IE are positive. Those patients with untreated IE and continuous bacteraemia will generally have positive culture results in all samples.\textsuperscript{187} 90\% will be diagnosed by the first sample and 95\% after three cultures.\textsuperscript{186-188} Other patients will have a much lower incidence of positive cultures. These include patients who have already received antibiotic treatment, those with fungal endocarditis or with “difficult-to-culture” microorganisms and those with CNE.\textsuperscript{189} It has been estimated that blood cultures may be negative in as many as 25\% of patients who received recent outpatient antibiotic therapy and it may be prudent to delay treatment (dependent on clinical status of patient) in order to maximize the chance of obtaining positive blood cultures.\textsuperscript{190-193} Culturing arterial rather than venous blood and drawing
blood during spikes of temperature does not appear to be of any additional value.\textsuperscript{194} When blood cultures are negative because of previous antibiotic therapy, the period of time required for the blood cultures to become positive again varies from 24 hours to two weeks depending on the activity of the antibiotic against the organism and the duration of prior treatment. If treatment has been received for only 2-3 days, cultures will probably revert to positive quickly. It is important to indicate on the request form whether antibiotics have been received by the patient so that special culture methods for unusual microorganisms, lysis centrifugation techniques or serology may be considered. Identification should be to species level.

The yield of positive cultures of “slow-growing” organisms such as nutritionally variant streptococci (approximately 5% of streptococci in IE) and the fastidious Gram-negative aerobic bacilli such as \textit{Haemophilus} spp. or \textit{Bartonella} spp., may be improved by prolonged incubation (7-21 days) or by using optimized blood culture media.\textsuperscript{195-199} The microbiology laboratory should be informed when such organisms are suspected.

\textbf{When the diagnosis is suspected, admit the patient to hospital for full and careful investigation, including blood cultures, recording of temperatures, haematological and biochemical investigation, ECG, chest X-ray and echocardiography. Three sets of blood cultures at intervals of >1 hour within the first 24 hours will suffice when clinical evidence suggests the diagnosis is highly likely in a sick patient. If the patient is not acutely sick or when the diagnosis is not obvious clinically, 6 sets of blood cultures should be taken within the first 24-48 hours.}

\textbf{If the diagnosis is confirmed by blood culture – refer the patient to an experienced cardiologist. Involve microbiologist from the outset.}

\textbf{Recommendation C}

\textbf{EVIDENCE LEVEL 3}

\textbf{ECHOCARDIOGRAPHY}

Echocardiography is the most useful tool for confirming the anatomical diagnosis and for demonstrating vegetations on valves or other structures.\textsuperscript{200-207} It should be performed by appropriately trained echocardiographers.

Transthoracic M-mode echocardiography (TTE) has been used for the detection of vegetations associated with IE since 1973 and 2-D echocardiography since 1977. Reports suggest a specificity of 98% and a sensitivity of 60-75% and echocardiography should be performed early in all patients clinically suspected of having IE, including those with negative blood cultures.\textsuperscript{208-212}

Transoesophageal echocardiography (TOE) has proved most valuable in assessing patients with suspected IE – being more sensitive (95%) than transthoracic echo for detecting and sizing vegetations, abscesses, pseudoaneurysms and valvular perforations.\textsuperscript{202-217} The absolute sensitivity depends upon the site and the size of the abnormalities.\textsuperscript{205,218-220}
TOE using biplanar and multiplanar probes with colour flow, continuous and pulse-wave Doppler is more sensitive than TTE for detecting abscesses in patients with both NVE and PVE (87% vs 28%). \(^{221-223}\) TOE is the technique of choice in evaluating a patient with suspected PVE (since it is more likely to demonstrate a perivalvular abscess, dehiscence and fistulas), for those with NVE who have a prolonged course of infection, for those with endocarditis at unusual sites e.g. pacemaker leads, and for those who do not respond to adequate medical therapy. \(^{202,216,221-229}\) It is perhaps more useful in tissue PVE rather than mechanical PVE as it is often difficult to see detail on mechanical valves because of intense interfering echoes from the metal struts and valve ring. \(^{230}\)

Echocardiography may not only demonstrate vegetations and abscesses and predict embolic risk in IE but it also provides information on left ventricular function and an estimate of severity of regurgitant flow. \(^{231-233}\) For example, premature mitral valve closure in acute aortic regurgitation suggests the need for urgent surgical intervention. Moreover, repeat echocardiography is often useful for early detection of cardiac complications requiring surgical intervention.

For suspected NVE, a TTE should be the initial echo study. If the TTE is technically inadequate, then a TOE should be performed. If the TTE is clearly positive or clearly negative, no further echo is necessary. However, a TOE should be performed if the TTE is abnormal but non-diagnostic.

**Consider TOE if TTE is suboptimal, to obtain further information on the size, site or mobility of vegetations, abscess or fistula formation or valve perforation etc. TOE should be performed in all patients with PVE.**

**Recommendation B**

**EVIDENCE LEVEL 2+**

**CARDIAC CATHETERISATION IN INFECTIVE ENDOCARDITIS**

Doppler echocardiography allows accurate assessment of the haemodynamic and pathological consequences of infection in most cases. The use of invasive techniques is usually limited to coronary arteriography in those with a history of angina or risk factors for coronary artery disease and to the identification of fistulous connections between chambers if echocardiography is inconclusive. However, there is a risk of systemic embolisation if contact is made with loose or friable vegetations and crossing potentially infected aortic valves should be avoided. \(^{234}\)

**EVIDENCE LEVEL 4**

**CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS**

Criteria for the diagnosis of IE were proposed by Von Reyn and colleagues\(^ {235}\) depending upon the results of symptoms, clinical signs and blood cultures and subsequently refined by Durack et al.\(^ {177}\) They took into account information obtained by echocardiography and introduced the concept of major and minor diagnostic criteria (Table 2). The value and
limitations of the Duke criteria for the diagnosis of IE have been discussed in the literature and the quality of management of patients has also been appraised. 236-239

The individual value of each of the Duke criteria for the diagnosis of IE has been studied and modified but echo data, serology and culture of excised tissue appear to improve the specificity and sensitivity of the diagnostic criteria. 199,217,231-233,235-246 Comparison has been made between the Duke and other criteria (Beth Israel) for the diagnosis of IE and although the modified Duke criteria appear to be superior, confirmatory studies are few and small. 247,248 Larger studies are needed.

More recently, it has been proposed that PCR amplification of specific gene targets and universal loci for bacteria and fungi and subsequent sequencing to identify the possible causative organisms in blood culture and excised tissue should be considered as a major Duke criterion. 249 Such molecular methods have been validated in the diagnosis of CNE and recently included into the newest revision of the Duke criteria. 169,250

Diagnosis of “definite” IE requires the presence of 2 major or 1 major plus 3 minor criteria or 5 minor criteria and has a specificity of around 99% and sensitivity of >80%. 177,251

EVIDENCE LEVEL 3

PREVENTION AND TREATMENT

Despite medical treatment, IE continues to cause significant morbidity and mortality (20%). Prevention therefore is a priority as is early diagnosis and adequate treatment based on appropriate antibiotic therapy and in many cases cardiac surgery. Antimicrobial prophylaxis before selected procedures in patients at risk has become routine in most countries, despite the fact that no prospective study has been performed that proves that such therapy is definitely beneficial. 253-254 Animal experiments and some human studies have however suggested benefit from prophylactic antibiotics. 255 Even if prophylaxis is effective, it can only prevent a minority of cases of IE and it is not cost-effective as a general strategy. Nevertheless, current “best practice” continues to favour the use of antibiotic prophylaxis of selected patients at risk of IE who are undergoing procedures that can cause bacteraemia. Guidelines have been published by expert groups both in Europe 15,256 and USA 257 and the differences in recommendations are minor. However, the guidelines represent consensus recommendations based mainly on data from animal models, case-control studies and case series.

1. PROPHYLAXIS 256,258

Although doubts have been expressed about the value of antibiotic prophylaxis, the fact that clinical experience documents IE following bacteraemia, that bacteraemia occurs after various dental and instrumental procedures and that antibiotics are available that can kill potential causative organisms, means it is prudent to offer prophylactic antibiotic therapy to individuals who are at higher risk of IE than the general population. 259-271 It is particularly important for those in whom IE is associated with high morbidity and mortality and it is necessary to inform those at risk and provide them with written
instructions such as the British Heart Foundation “Endocarditis Dental Warning Card” (Figure 1). However, it would be more useful if the card indicated the type of cardiac lesion, the risk and how to avoid IE. Patients should be told to show the card to their doctor or dentist and there should be written communication between these professionals.272-274

PATIENTS AT RISK

Subgroups of patients with preexisting cardiac disorders may be classified at high, moderate or low risk of developing IE in the event of significant bacteraemia occurring following an interventional procedure. In these subgroups, the severity of the disease and the resulting morbidity is more severe.257 Table 3 stratifies these cardiac conditions into risk groups based on the outcome should IE develop and the increased susceptibility to IE compared to those in the general population275-293

Low risk patients are those patients with cardiac disease in whom the risk is no higher than in the general population and include some patients with grown-up congenital heart (GUCH) disease. Those with innocent heart murmurs and structurally normal hearts do not require antibiotic prophylaxis.

EVIDENCE LEVEL 3

PROCEDURES REQUIRING ANTIBIOTIC PROPHYLAXIS

Although bacteraemia commonly occurs during activities such as chewing and tooth brushing, significant bacteraemia causing IE seems to occur most often after certain invasive procedures.294-296 These mainly include dental procedures and instrumentation of the oral/respiratory tract, gastrointestinal or genitourinary tracts, although limited evidence exists for many other procedures.255,297-312

The risk of developing IE is probably directly related to the frequency and severity of bacteraemia that occurs with each individual procedure and its duration, and the procedure/portal of entry is a determinant of the organism involved and the type of prophylaxis regimen that should be appropriate.313,314 What constitutes a “significant” degree of bacteraemia has been a matter of much debate and research, and in the area of dentistry, such work has proved helpful in defining which procedures are associated with the greatest bacteraemia and hence especially worthy of antibiotic prophylaxis.315-317 For example, bleeding after dental treatment is not in itself associated with an increased frequency of bacteraemia and this has changed advice about antibiotic prophylaxis for certain dental procedures.

DENTAL AND ORAL PROCEDURES (Table 4)

Poor dental hygiene, periodontal or periapical infections may produce bacteraemia even in the absence of dental procedures and so those at risk of IE should establish and
maintain the best possible oral hygiene to minimize the risk. This can be aided by regular dental follow-up and daily techniques to minimize plaque build-up eg: toothbrushing, dental floss, plaque removal. However, even these simple procedures may not be without risk. Chlorhexidine mouthwash (0.2%), preferably non-alcoholic, may help patients who find a high standard of plaque control difficult. Although recent work has questioned its effectiveness, fifteen mls of chlorhexidine hydrochloride (0.2%) should be given as an oral rinse to all patients at risk 5 minutes prior to dental treatment to reduce the incidence and magnitude of odontogenic bacteraemia.

Antibiotic prophylaxis for at-risk patients is recommended for dental and oral procedures likely to cause bacteraemia. Prophylaxis against IE in orthodontics has been discussed in the literature. However, this is a specially difficult problem as some procedures cause significant bacteraemia (eg: tooth separation) but others such as banding and debanding cause only a small non-significant increase in bacteraemia. It is possible that the deterioration in gingival health as a consequence of the appliances placed in the mouth is a risk factor that needs to be considered more carefully. If patients are unable to maintain good oral hygiene when appliances are in the mouth, it may be helpful to use a chlorhexidine mouthwash for the period of the appliance therapy.

Antibiotics administered up to 1 hour before a dental procedure will effect a reduction in odontogenic bacteraemia and a most important clinical advance was the demonstration that oral administration of amoxicillin proved effective in significantly reducing dental bacteraemia. This has become the mainstay of outpatient dental care. Regimens for IV or IM administration have proved effective for adults and children.

Data from experimental animal models suggest that antimicrobial prophylaxis administered within 2 hours following the procedure will also provide protection. However, antibiotics given > 4 hours after the procedure probably have no prophylactic benefit. Intraligamental injections of local anaesthetic should be avoided if possible as severe bacteraemia occurs in a large proportion of patients.

For patients undergoing cardiac surgery, a careful preoperative dental evaluation is recommended so that necessary dental treatment can be completed before cardiac surgery in an attempt to reduce the incidence of late postoperative IE.

**EVIDENCE LEVEL 2-**

**OTHER PROCEDURES**

Antibiotic prophylaxis is recommended in patients at high or moderate risk of IE who are undergoing various gastrointestinal, genitourinary, respiratory or cardiac procedures and some subspecialty societies have published their own guidelines. Relevant procedures are listed in Table 5. The evidence for significant bacteraemia after many of these procedures has not been proven, but since cases of IE have been reported to follow them, prophylactic antibiotics are recommended. Some procedures do not require antibiotic prophylaxis.
Patients at moderate-risk or high-risk of IE should be given antibiotic prophylaxis with appropriate antibiotics based upon the type of dental or surgical procedure being performed.  

**Recommendation C**

Patients should be informed of their risk of IE and the need for antibiotic prophylaxis. They should be told to inform any doctor or dentist who is responsible for providing care and they should be given a card to carry reminding them of the cardiac lesion, the importance of the risk and how to avoid IE.

**Recommendation C**

**EVIDENCE LEVEL 4**

**ANTIBIOTIC PROPHYLAXIS REGIMENS**

Antibiotic prophylaxis varies according to the type of procedure being performed and the type of organism likely to cause infection. The regimens are shown in **Tables 6-7** and the relationships between procedure and likely causal organism are shown in **Table 1**. In patients with prosthetic valves, the antibiotics should be given 1 hour before and 6 hours after the procedure.  

Prior to (and after) permanent pacemaker implantation (**Table 8**) or cardiac surgery (**Table 9**), prophylactic antibiotics are given to prevent serious wound infection, mediastinitis and endocarditis due to staphylococci, streptococci and enterococci.  

Institution- or surgeon-specific selection of antibiotics is appropriate. Some examples of regimens can be found on the website. Data suggests that a 1-day course of IV antimicrobials is as efficacious as the traditional 48-hour (or longer) regimens. There are insufficient data to suggest that aminoglycosides add substantial benefit to the prophylactic regimen.

**EVIDENCE LEVEL 4**

2. **ANTIMICROBIAL THERAPY FOR INFECTIVE ENDOCARDITIS** (**Tables 8-14**)

**GENERAL MANAGEMENT**

An algorithm as a guide to the management of patients with IE is shown in **Figure 2**.

IE 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. Parenteral administration ensures complete bioavailability, high serum concentrations and good penetration into the vegetations. Treatment should begin immediately after blood cultures have been taken – especially in patients with severe sepsis, severe valvular dysfunction, conduction disturbance or embolic events and adjusted once the microorganism has been identified and the antibiotic sensitivities known.
The type and duration of antimicrobial treatment is based on the organism responsible, its sensitivity, a history of penicillin allergy and whether the valve involved is a native or a prosthetic valve. Advice from the microbiologist should be sought. Organisms exist at very high densities inside vegetations ($10^9$-$10^{10}$ per gram) protected from host defences, and cure requires sterilization of vegetations with bactericidal agents in high concentrations for long enough. Generally, bactericidal therapy requires a combination of antimicrobials with synergistic activity such as a cell-wall-active agent (B-lactams and glycopeptides) and an aminoglycoside. Antibiotics that may be used for the treatment of IE are presented in Appendix 2.

**PHARMACOKINETIC ISSUES**

For antimicrobials with time-dependent bactericidal activity (B-lactams and glycopeptides), it is necessary to attain concentrations persistently above the minimum inhibitory concentration (MIC) (see below), in both serum and vegetations. This justifies the use of high doses, despite their time-dependent activity, especially for teicoplanin in staphylococcal endocarditis, or ceftriaxone in endocarditis due to Gram-negative aerobic bacilli.

For antimicrobials with concentration-dependent bactericidal activity, high peak concentrations must be obtained. A post-antibiotic effect (PAE) observed in Gram-negative endocarditis allows an increased interval between doses, but this does not apply for Gram-positive and enterococcal endocarditis, for which no PAE has been shown in vivo.

**DOsing REGIMENS**

For B-lactams and glycopeptides with time-dependent activity and no PAE, serum levels must be maintained throughout the dosing interval to prevent regrowth of bacteria between doses. This interval is determined by the rate of drug elimination and the serum half-life. Benzylpenicillin and anti-staphylococcal penicillins should be administered every 3-4 hours. Ceftriaxone, which has a long serum half-life (8hrs) can be administered once a day in the case of highly susceptible organisms such as viridans streptococci. Vancomycin and teicoplanin are administered every 12 or 24 hours respectively after a loading dose for teicoplanin because of its long half-life. Aminoglycosides can be administered twice a day for Gram-negative bacilli endocarditis, but are needed three times daily for Gram-positive and enterococcal endocarditis.

**MAXIMISING EFFECTIVENESS OF ANTIMICROBIAL TREATMENT**

In evaluating the potential efficacy of an antibiotic, the MIC must be considered. The MIC is the minimum concentration that inhibits bacterial growth in vitro. With most streptococci or staphylococci, the MIC and minimum bactericidal concentration (MBC) of cell-wall active antibiotics (penicillins, cephalosporins and vancomycin) do not differ significantly. However, the MBC’s of these antibiotics are much higher than the MIC’s for a minority of strains of streptococci and staphylococci and for many strains of enterococci. When the difference is 10-fold or more, or when the MBC/MIC ratio is >32 - the strains are said to be tolerant which indicates a slower rate of kill. Tolerance can be overcome by addition of an aminoglycoside – resulting in a more rapid bactericidal activity.
In treatment of enterococcal endocarditis, an aminoglycoside must be added to amoxicillin or ampicillin to obtain adequate bactericidal effect and cure although this is probably not essential in tolerant streptococcal or staphylococcal infection. Serum drug level monitoring during aminoglycoside therapy is recommended. Gentamicin peak serum concentration (1 hour post IV dose) should be 6-10mg/L but the trough level should be < 2.0mg/L to avoid renal or ototoxic effects. Optimum vancomycin effects are achieved if serum concentrations are kept at least 2-4 times above the MIC of the causative organism. Trough levels should be 10-15mg/L.

The necessary frequency of dosing varies, depending on the organism and the antimicrobial(s) being used and whether or not a post-antibiotic effect exists. **Intravenous antibiotics should be commenced as soon as the diagnosis is made and after appropriate blood culture samples have been collected and sent to the microbiology laboratory.** Initially, IV benzylpenicillin and gentamicin in the same dosage as for treatment of IE caused by penicillin-sensitive viridans streptococci should be used. If there is a strong possibility of staphylococcal infection, eg: IV drug abuse, infected haemodialysis lines or pacemaker infection, IV flucloxacillin and/or vancomycin should be used instead of benzylpenicillin. Once the blood culture results are known, the treatment can be modified and a decision made about its duration. An exception to this might be in patients recently receiving antibiotics, when delaying treatment for a few days can increase the chance of isolating the responsible organism on subsequent blood cultures. Such delay is only reasonable in closely monitored patients with subacute illness who have no evidence of severe or progressive valve dysfunction, heart failure or embolic complications.

Isolation of the infecting organism is extremely important, so that an appropriate antimicrobial agent can be chosen and the antimicrobial susceptibility of the organism be established. Both MIC and MBC may both be useful although no data suggests that MBC is any better than the more simple and reproducible MIC test. **Therefore, routine determination of MBC or serum bactericidal level is not recommended.**

A peak serum bactericidal titre (the highest dilution of the patient’s serum whilst receiving antibiotics that kills a standard inoculum of the patient’s microorganism in vitro and measured by back-titration) of 1:8 or greater usually indicates an adequate therapeutic effect. A peak bactericidal titre of 1/64 and a trough of 1/32 has been reported to represent optimal therapy. **Determination of the titre is valuable only when response to treatment with the recommended regimens is suboptimal, when IE is due to an unusual microorganism or when an unconventional treatment regimen is used.** However, caution should be used when using titre data, in order to avoid false reassurance of microbiological efficacy despite the lack of evidence of clinical improvement.

*Once the diagnosis is established, treatment should be commenced according to the Guidelines or with alternative antibiotics if microbiological tests suggest more appropriate agents are suitable.*

**Recommendation D**
In a sick patient, antibiotic treatment should be commenced immediately after blood cultures have been collected and the regimen adjusted once the microbiological data is available. **Recommendation D**

Generally, prolonged IV antibiotic therapy is necessary, administered via a large central vein. Only the most penicillin-sensitive streptococci should be considered for treatment with shorter courses of penicillin. **Recommendation D**

The Guidelines for treatment should be followed unless the clinical state and microbiological data suggest alternative treatment is more appropriate. **Recommendation D**

**SPECIFIC TREATMENT REGIMENS**

**STREPTOCOCCI and STAPHYLOCOCCI**

The majority (80%) of NVE is caused by viridans streptococci (50-70%), *S. aureus* (25%) and enterococci (10%). Certain organisms are more frequently associated with particular clinical situations and procedures (Table 1). For example, *S. aureus* is the most frequent cause of endocarditis in IV drug abusers (60%), in insulin-dependent diabetes mellitus and in infection of the tricuspid valve. This microorganism is particularly destructive. *S. epidermidis* more often causes indolent infection on previously damaged valves. Regimens for treatment of streptococci are shown in Tables 10-11, for staphylococci in Tables 12-13 and for enterococci in Table 14.

Treatment of streptococcal endocarditis depends on the clinical complexity of the infection in the individual patient and on the antibiotic susceptibility of the organism. For example, in uncomplicated IE caused by fully penicillin-sensitive viridans streptococci or *Streptococcus bovis* (MIC <0.1mg/L) on a native valve, treatment for 2 weeks with IV benzylpenicillin + gentamicin is generally sufficient to cure the infection. Whereas, if there is any evidence of cardiac or embolic complications or if the organism is less sensitive to penicillin (MIC >0.1mg/L - <0.5mg/L), benzylpenicillin should be continued for 6 weeks with gentamicin for the first 2 weeks. For more resistant streptococci (MIC >0.5mg/L), treatment with gentamicin for longer may be necessary, although the risk of ototoxicity increases.

Frequent dosing of penicillin is necessary as the initial high peak concentration rapidly decreases due to glomerular filtration, tubular excretion in the kidney and inactivation of penicillin (half-life 20-30 minutes) in blood. Although prolonged courses of antibiotics probably produce more effective outcomes – on the whole, there is limited evidence that 4 weeks is better than 3, or that 6 weeks is better than 5 weeks. It is thought that combining penicillin or flucloxacillin with gentamicin results in a more rapid defervescence and clearance of bacteraemia. This is therefore recommended, although superiority over penicillin alone has not been demonstrated in a clinical trial. Teicoplanin is an alternative to penicillin in streptococcal endocarditis when the starting dose should
be at least 10mg/kg and the serum levels checked in order to ensure appropriate blood concentrations. Vancomycin is also an effective alternative to penicillin and the drug of choice in patients allergic to penicillin. Ceftriaxone has an excellent pharmacokinetic profile for treating streptococcal IE and may be useful in patients over 65 years or with renal or auditory nerve impairment.

**Staphylococcal IE** is a particularly severe and life-threatening infection responsible for about one third of all cases. Early treatment is the key to improving overall prognosis. Ninety per cent are due to *S. aureus* and 10% due to coagulase-negative staphylococci. *S. aureus* is the only common cause of acute endocarditis and can attack normal hearts in staphylococcal sepsis. The organism predominantly affects left-sided valves except in IV drug abusers. Less than 10% of *S. aureus* strains are susceptible to penicillin although community-acquired strains are frequently methicillin-sensitive. Methicillin-resistant *S. aureus* (MRSA) account for approximately 50% of cases of *S. aureus* endocarditis in drug abusers and endocarditis acquired in hospitals eg: IV access site infection or transvenous pacemaker infection. Methicillin-resistant *S. epidermidis* is responsible for most cases of *S. epidermidis* endocarditis on prosthetic valves but uncommonly cause NVE. When it does, it usually presents a subacute picture. Treatment of suspected methicillin-resistant staphylococcal endocarditis in these situations or of proven infection must include vancomycin. Rifampicin has been used as a supplement to therapy with a penicillin, cephalosporin or vancomycin with or without aminoglycosides in patients responding poorly to these agents. Rifampicin is actively taken up by granulocytes and becomes effective against intracellular staphylococci and staphylococci within abscesses. Other agents such as Linezolid and SynercidR may be alternative choices for infection with MRSA. The emergence of vancomycin-intermediate resistance *S. aureus* (VISA) among MRSA isolates is of great concern and many of these organisms are also resistant to teicoplanin as well and called glycopeptide-intermediate resistance *S. aureus* (GISA).

Although coagulase-negative staphylococci are the most common cause of PVE, they also affect patients with mitral valve prolapse. Here the course is typically indolent with a good response to medical or surgical treatment. However, *S. lugdunensis* is particularly virulent and causes high rates of perivalvular extension of infection and metastatic seeding to distant organs. Such patients require careful observation for the development of such complications.

**NUTRITIONALLY VARIANT STREPTOCOCCI**

These bacteria account for 5-6% of streptococcal endocarditis and an important cause of CNE. *Streptococcus adjacens* and *Streptococcus defecitivus* appear to be the predominant species. These organisms are residents of the oral cavity, genitourinary and intestinal mucosae. IE occurs in the setting of prior valvular disease and is characterized by a slow indolent course. Morbidity and mortality exceed those of other viridans...
streptococci and even enterococci. Bacteriological diagnosis may require special techniques. More than 30% of strains are relatively resistant to penicillin and either a penicillin/aminoglycoside combination or vancomycin regimen is usually necessary.

ENTEROCOCCI

E. faecalis account for 10% of cases of endocarditis and 90% of all enterococcal endocarditis. Other species that may be responsible include E. faecium and E. durans. E. faecalis endocarditis is most often found in elderly patients and usually associated with malignancy or manipulation of the gastrointestinal or genitourinary tract. It often produces a subacute rather than an acute endocarditis. These organisms are usually more resistant to penicillin than viridans streptococci and relatively resistant to aminoglycosides. Some enterococci are multiresistant to antibiotics including vancomycin (VRE). Regimens for treatment are shown in Table 14.

First-line treatment is with a synergistic bactericidal combination of IV amoxicillin + gentamicin. Gentamicin highly-resistant (MIC >500mg/L) enterococci may not respond to this combination but some strains may respond to high-dose amoxicillin for 6 weeks or to a combination of amoxicillin + streptomycin. Amoxicillin-resistant strains could be treated with a combination of vancomycin (or teicoplanin) and gentamicin. This regimen may be suitable for patients who are allergic to penicillin. For VRE, linezolid may be useful, while Synercid® may be used in vancomycin-resistant E. faecium.

GRAM-POSITIVE and GRAM-NEGATIVE BACILLI

Gram-positive (eg: Listeria monocytogenes and Propionibacterium acnes) and gram-negative bacilli (eg: E. coli, Klebsiella spp, Serratia spp, P. aeruginosa) are uncommon but serious causes of endocarditis. As susceptibility of these organisms is often unpredictable, treatment should be based on susceptibility testing.

Anaerobic Gram-negative bacilli (eg: Fusobacterium spp, Bacteroides spp) require specific treatment which includes high-dose IV penicillin, imipenem and the addition of metronidazole 500mg 8 hourly for 6-8 weeks.

HACEK GROUP

In recent years, the HACEK group of organisms (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella and Kingella species) have become important causes of IE, causing large vegetations (>1cm), large vessel emboli and congestive cardiac failure. This group of organisms will often require 7-21 days of incubation in 10% CO₂ to allow growth. The treatment is shown in Table 16.
Fungi, especially *Aspergillus* spp. and *Candida* spp., are also important causes (2-10%) of endocarditis particularly in patients with prosthetic valves, suppressed immunity or IV drug abuse. Patients receiving prolonged, intense antibiotic therapy and hyperalimentation, those with long-term IV catheters in-situ and those with bacterial endocarditis are also at increased risk of fungal endocarditis.

Fungal endocarditis demands intensive treatment with potentially toxic agents (Table 16). 75% are due to *Candida* species and they should be formally identified and sensitivity-tested. Patients require careful observation with frequent monitoring of their haematology and biochemistry. Surgery should be performed early after commencing treatment especially in patients with large vegetations, evidence of emboli, poor response to treatment, *Aspergillus* endocarditis and in those with prosthetic valves, since mortality is unacceptably high with treatment with antimycotic agents alone.

However, fungal valvar infection is aggressive and difficult to treat surgically. There is a high risk of embolisation and serious perioperative bleeding may occur when infected tissue is resected. Usually surgery is complicated by the need for radical debridement and aortic root reconstruction. Prosthetic valve fungal endocarditis is particularly serious – the first episode is usually a result of nosocomial candidaemia, and recurrent episodes are frequent. In this situation, urgent surgical intervention is recommended and antifungal drug treatment should be continued for life.

Amphotericin B has been the single most effective agent but it requires prolonged infusion periods and has unpleasant side-effects and adverse effects. Liposomal amphotericin B may be particularly effective in *Aspergillus* endocarditis. 5-fluorocytosine (5-FC) is less-well defined although most authors recommend a combination of the two agents. 5-FC is toxic to liver and bone marrow and frequent monitoring of blood and liver function tests are mandatory. Voriconazole is a new antifungal agent which may be useful for serious aspergillus infections.

**EVIDENCE LEVEL 3**

**BLOOD CULTURE-NEGATIVE ENDOCARDITIS**

Treatment should include antibiotics – appropriate for the most likely organism but should generally cover Gram-positive and Gram-negative organisms (Table 16). Early surgical intervention is often necessary. Patients with *Coxiella* and *Chlamydia* infection need valve replacement and prolonged treatment since reinfection commonly occurs.

For Q-fever endocarditis, treatment with doxycycline (1G/day) is indicated for at least 3 years (possibly for life) plus either cotrimoxazole (1.92G/day), rifampicin (300mg/day) or ciprofloxacin (1.5G/day) since the liver is usually chronically infected. Other agents eg: ofloxacin, hydroxychloroquine are being evaluated in combination therapy for Q-fever infection. During treatment, serological testing should be performed monthly for 6 months, and every 3 months thereafter. Antibody levels fall slowly. The IgM antibodies
disappear first, then the IgA but the IgG antibodies remain positive for years. It has been suggested that after 3 years, treatment can be stopped if the level of IgG against phase-I antigens is still below 400 and IgA against phase-I are no longer detectable.  

For *Brucella* endocarditis, consultation with a microbiologist is essential and culture bottles may need to be kept for up to 6 weeks. The combination of doxycycline (100mg twice daily) and IV gentamicin for 4 weeks followed by the combination of doxycycline and rifampicin (600mg twice daily) for 4-8 weeks is the most effective regimen.  

Most require valve replacement in combination with a prolonged period of antimicrobial agents.

In CNE, all material excised during cardiac surgery in patients with active IE should be cultured and examined.

*CNE requires close scrutiny for unusual and slow-growing microorganisms and fungi. Serological tests for Coxiella burnetii, Bartonella spp and Chlamydia spp should be performed if the diagnosis is still suspected and there is still no growth after 7 days.*

*Microscopy and culture of any excised tissue is essential.*

*Molecular assay for specific gene targets and universal loci for bacteria and fungi and subsequent sequencing may be applied to blood culture or excised material to help identify the causative organism.*

*Treatment should involve antibiotics which are appropriate for the most likely organism for the particular clinical scenario but should generally cover Gram-positive and Gram-negative organisms.*

**Recommendation D**

**EVIDENCE LEVEL 3**

**IV DRUG ABUSE**

IE is one of the most severe complications in IV drug abusers and IV drug addiction one of the most important causes of IE in some urban medical practices.

Methicillin-sensitive *S. aureus* is the causative organism in 60-70% of cases, streptococci and enterococci in 15-20%, *P. aeruginosa, Serratia marcesans* and other Gram-negative bacilli in <10%, *Candida* spp. in <2%, polymicrobial in 5% and culture-negative in 5-10% of cases. The tricuspid valve is most frequently affected (>70%), followed by left-sided valves. Pulmonary valve infection is rare (<1%). The type of antimicrobial therapy and mode of administration necessary is dependent on the organism(s) responsible which may be suggested by the type of drug and solvent used by the addict.

The prognosis of right-sided IE is favourable and in those with uncomplicated native valve IE caused by methicillin-sensitive *S. aureus*, 2 weeks treatment with IV flucloxacillin plus IV gentamicin may cure the infection. However, once the causative
organism has been isolated, therapy has to be adjusted. A standard 4-6 weeks treatment regimen should be used where there is a slow clinical or microbiological response to antibiotic therapy, right-sided endocarditis complicated by right heart failure, large (>20mm) valve vegetations, acute respiratory failure, septic metastatic foci outside the lungs or extracardiac complications such as acute renal failure, associated severe immunosuppression with or without AIDS and therapy with antibiotics other than penicillinase-resistant penicillins. It has been estimated that the prevalence of HIV-1 infection in IV drug abusers with IE ranges from 40-90% - an important consideration for nursing, medical, surgical and technical staff.

Surgery is necessary in <2% of cases and death occurs in <5%. The indications for surgery and the perioperative treatment is the same as in non-addicts but should be more conservative because of the higher incidence of recurrent IE due to continued IV drug abuse. The indication and type of surgery should be carefully considered to avoid PVE if drug abuse continues. The three main surgical indications are IE due to organisms that are difficult to eradicate eg: fungi, persisting bacteraemia (> 1 week) despite adequate antimicrobial therapy and large tricuspid valve vegetations (> 20mm) associated with recurrent pulmonary emboli with or without concomitant right heart failure.

EVIDENCE LEVEL 3

ENOCARDITIS in HIV-POSITIVE PATIENTS

Endocarditis in HIV-positive patients usually occurs as a result of IV drug abuse or long-term indwelling catheters. Estimates of IE occurrence vary from 6.3% - 34%. S. aureus is the most frequent causative organism and for drug-abusers, the tricuspid valve is most commonly affected and short courses of antibiotics have been reported to be successful. Fungal endocarditis is not uncommon and there is an increased risk of Salmonella infection. The outcome is worst in patients with AIDS and prolonged IV antibiotics are probably indicated.

EVIDENCE LEVEL 3

ENOCARDITIS IN PREGNANCY

Most of the first choice antibiotics are safe and effective in pregnancy. Penicillins do not appear to cause maternal or foetal complications. Aminoglycosides should be used only in special situations because of the potential for oto- and nephro-toxicity in the foetus. No teratogenic effects have so far been reported with imipenem or rifampicin. Quinolones are contraindicated in pregnancy. Amphotericin B does not appear to be associated with teratogenic effects unlike fluconazole where there appears to be a dose-dependent effect. For IE in pregnancy, advice of an expert microbiologist is strongly advised.

Cardiac surgery for IE in pregnancy is difficult. There is a risk of foetal distress, growth retardation and foetal death and wherever possible, surgical intervention should be postponed until the foetus is viable and heart surgery and caesarean section can be performed as a concomitant procedure. Close cooperation between cardiologist, cardiac
surgeon and obstetrician is essential. There is no absolute indication for pregnancy termination in active IE since in patients with heart failure due to valve insufficiency, haemodynamic improvement cannot be expected by termination of pregnancy alone.  

**EVIDENCE LEVEL 3**

**PROSTHETIC VALVE ENDOCARDITIS**

In early PVE, *S. epidermidis* and *S. aureus* are the most frequent organisms responsible. Vegetations are generally larger than those found in NVE and prosthetic material protects organisms against antimicrobial treatment – both making sterilization with antibiotics extremely difficult. Consequently, antibiotics have to be used in dosage which result in maximum but non-toxic serum concentrations in order to penetrate the vegetations and the duration of treatment must also be longer. Antibiotic sterilization of large vegetations is unlikely with organisms which have a high MIC. A minimum of 2 months IV therapy may cure some cases but most will require further valve surgery and another month’s IV treatment. Beyond 6 months, the organisms causing “late” PVE are not dissimilar to those responsible for NVE. When PVE is clinically apparent and blood cultures are not yet positive, empiric treatment should be initiated with IV vancomycin and gentamicin.

PVE has a poor prognosis and demands prompt and careful assessment of the need for early surgical intervention. TOE is essential in order to recognise the presence of vegetations on the prosthesis and for diagnosing periprosthetic abscess formation, fistulas and prosthetic valve dysfunction not seen on a transthoracic study. In patients with PVE due to aggressive organisms such as *S. aureus*, those who fail to respond immediately to antibiotics, those with large periprosthetic leaks or abscesses, fistula formation and false aneurysms, vegetations on the prosthesis, new-onset conduction disturbance, heart failure due to prosthetic valve dysfunction and fungal infection require surgery urgently. It is a forlorn hope that these situations will be cured by medical treatment alone as surgical mortality is probably related to the amount of anatomical destruction that has already occurred.

Although, superior results have been shown with surgery compared with antibiotics alone, occasionally medical treatment alone may be appropriate. Patients in whom the diagnosis is made early, those with streptococcal infection, a prompt antibiotic response, favourable TOE findings such as small or absent vegetations, no periprosthetic abscesses or prosthetic dysfunction may be managed conservatively. However, they require careful clinical monitoring and should be reconsidered for surgery if complications arise – as happens not infrequently Patients in whom surgery is contraindicated or who refuse to consent for surgery may also be managed medically, but mortality is significant (26-70%).

*The majority of NVE and of late PVE is caused by viridans streptococci (50-70%), S. aureus (25%) and enterococci (10%). In early PVE, S. epidermidis and S. aureus are the commonest organisms.*

**Recommendation D**

**EVIDENCE LEVEL 3**
3. PENICILLIN ALLERGY

Patients with a convincing history of immediate-type (IgE-mediated) hypersensitivity reaction to penicillin including urticarial rash or angioneurotic oedema should not receive penicillin, cephalosporin or other B-lactam antibiotics. Vancomycin or teicoplanin should be substituted and given with gentamicin, although the risk of nephrotoxicity increases and requires careful monitoring.

Patients with a history of penicillin-allergy or who develop penicillin-allergy, should be treated with (or changed to) vancomycin or teicoplanin and gentamicin or other appropriate antibiotics.

Recommendation D
EVIDENCE LEVEL 4

4. ANTICOAGULANT THERAPY

For patients on long-term oral anticoagulants (eg: for mechanical valve prosthesis), coumarin therapy should be discontinued and replaced by heparin immediately after the diagnosis of IE is confirmed.

5. MONITORING OF PLASMA DRUG LEVELS

Most treatment regimens require regular monitoring of plasma antimicrobial concentrations. Peak and trough levels should be checked twice weekly, but more frequently in the elderly and in those with renal or hepatic impairment. This will minimize the risk of toxicity (eg: with aminoglycosides or glycopeptides) and ensure that bactericidal concentrations are maintained. Monitoring of drug levels will generally require close liaison with the microbiologist. For vancomycin, trough levels generally between 10-15mg/L would be considered efficient. For teicoplanin (generally not recommended for treatment of IE due to S. aureus), a peak level > 20mg/L may be optimum in Gram-positive endocarditis and a trough level >20mg/L may be as effective as vancomycin in the treatment of S. aureus endocarditis. In those patients with impaired renal function, the starting dose of most antibiotics should be modified and thereafter serum levels should be monitored closely and the dose and/or frequency of administration adjusted accordingly. This applies to penicillin, ampicillin and amoxicillin as well as teicoplanin, gentamicin and vancomycin.

EVIDENCE LEVEL 4

6. RESPONSE TO TREATMENT

Patients should be monitored frequently to assess the response to treatment, to detect complications promptly and to reappraise the need for surgical intervention. Assessment should include clinical examination, measurement of body temperature, ECG, blood count, ESR and CRP, renal and liver function tests and repeat echocardiograms.
Most patients improve during the first week of effective antimicrobial therapy and the temperature should normalize within 5-10 days. CRP values usually decrease rapidly during the first or second week but may remain slightly elevated for 4-6 weeks. A persistently elevated CRP suggests inadequately controlled infection with cardiac or septic complications. ESR is less useful for reflecting the therapeutic response, since high values may persist over several weeks despite clinical improvement. Persistence or recurrence of fever may not only be due to inadequate therapy but to myocardial or metastatic abscesses, recurrent emboli, venous thrombosis extending from the site of venous cannulation, superinfection or febrile reaction to the antibiotics (commonly recurrence of fever). Persisting bacteraemia indicates persisting infection as does persisting leucocytosis.

If a rash develops, the antibiotics should be changed unless the antimicrobial therapy options are very limited.

Weight gain, improvement of appetite and a rise in haemoglobin may not occur for weeks after treatment and splenomegaly takes months to resolve. New or changing heart murmurs due to valvular destruction may occur during or after therapy and must be sought by regular physical examination during the period of treatment. Heart failure may develop and is the principal cause of death especially in aortic valve endocarditis. The natural history of vegetations during successful medical treatment of IE has been described by Vuille et al. Echocardiography should be performed at any time during the course of treatment if the symptoms or physical signs change and at the end of treatment. This will document the site and extent of valvular damage and be a baseline for long-term follow-up.

Mycotic aneurysms may regress on antimicrobial therapy or rupture weeks or years later. Central nervous system symptoms/physical signs suggest cerebral aneurysm formation with leakage or enlargement. These demand urgent investigation (by CT/MRI scanning) and treatment.

Renal insufficiency from glomerulonephritis usually improves with treatment but not always and a specialist opinion should be sought early. Other causes include haemodynamic instability, antibiotic drug toxicity, renal infarction and systemic embolisation, contrast media toxicity or be a postoperative phenomenon.

EVIDENCE LEVEL 3

7. RELAPSE/NEW EPISODES

If a primary focus responsible for IE is identified, it should be eliminated prior to an elective cardiac surgical procedure in an attempt to prevent relapse. Following medical or surgical treatment of IE, all patients require careful follow-up for signs of clinical relapse or haemodynamic deterioration. Most relapses occur within 2 months of stopping treatment and most within 4 weeks. The reported relapse rate is <2% for streptococcal IE in native valves, but is considerably higher for virulent organisms such as staphylococci and enterococci (8-20%) and for PVE (10-15%). Difficult-to-treat organisms such as Brucella, Chlamydia and Bartonella and polymicrobial IE seen in IV drug abusers are
associated with an increased relapse rate as are a suboptimal choice of antibiotic therapy or insufficient duration of treatment. Blood cultures 2-4 weeks after completion of treatment detect most relapses. Delayed relapses may occur with fungal and Q-fever endocarditis. When relapse occurs in patients with PVE after a course of medical therapy, a perivalvar infection is usually present and further surgery is usually required.

New episodes may occur in 6% of patients with NVE although IV drug abusers are more susceptible.275

EVIDENCE LEVEL 3

8. OUT-PATIENT TREATMENT

Because of the high morbidity and mortality associated with IE, the need for continued clinical observation and investigations to monitor progress and response to treatment, in-patient management is essential and only in exceptional circumstances would out-patient treatment be considered acceptable. This would only be after an initial period of hospitalization and stabilisation.511,512

EVIDENCE LEVEL 4

9. INDICATIONS FOR SURGERY IN PATIENTS WITH ACTIVE INFECTIVE ENDOCARDITIS, TIMING AND RESULTS (Table 17)

In many patients with IE, the infection can be cured with medical treatment alone.513 However, in 25-30% medical treatment alone is insufficient and must be combined with surgery. The purpose of surgery is to control infection by debridement and removal of necrotic tissue and restoration of cardiac morphology by surgical repair and/or valve replacement.

Surgery is indicated in patients with life-threatening congestive heart failure514 or cardiogenic shock due to surgically treatable valvular heart disease such as severe aortic or mitral regurgitation. This applies to cases with or without proven IE if the patient has reasonable prospects of recovery and a satisfactory quality of life after surgery. Development of cardiac failure carries a mortality of >50% in patients with IE managed with only medical treatment.513 Many studies have indicated that surgical intervention improves the prognosis of IE over medical therapy alone and a high early surgery rate is associated with good long-term results and no increase in-hospital mortality.193,515-520 However, randomized trials of medical versus surgical treatment do not exist and the conclusions that have emerged, although often well supported by case studies can only be rated D. Surgery should be postponed or avoided if serious complications make the prospect of recovery unlikely.

The indications for surgery for IE in patients with stable haemodynamics are less clear. They depend also whether native or prosthetic valves are involved. Early consultation with a cardiac surgeon is advisable in case surgery is suddenly required. Surgery is indicated in patients with annular or aortic abscesses, pseudoaneurysms, fistulous communications, those with fungal IE, those with PVE and those with infections resistant
to antibiotics. Indeed persisting fever often represents abscess of the valve ring and surrounding structures or widespread tissue destruction. It generally necessitates surgical intervention including radical debridement and extensive reconstruction if necessary. Periannular extension occurs in 10-40% of all native-valve IE and complicates aortic IE more commonly than mitral or tricuspid IE. It occurs in 56-100% of patients in PVE.

In haemodynamically-stable patients, early consultation with a cardiac surgeon is recommended in case surgery is suddenly required.

Patients with life-threatening congestive heart failure, left heart failure or cardiogenic shock due to treatable valvular disease should undergo emergency cardiac surgery, if the patient has reasonable prospects of recovery and a satisfactory quality of life after surgery.

Surgery is indicated in patients with annular or aortic abscess, in those with infections resistant to antibiotics and in those with fungal endocarditis. Large, mobile vegetations and recurrent emboli after appropriate antibiotic therapy are also indications for surgery.

Patients with PVE will generally require further surgery. Recommendation D EVIDENCE LEVEL 3

However, it should be remembered that penicillin hypersensitivity is a common cause of recurrent fever, with rash and eosinophilia being such indications. Neutropenia and impaired renal function may suggest toxic overdosing. In this case the fever usually promptly disappears after drug withdrawal. The emergence of antibiotic resistance in the infecting organism is seldom a cause. If the bacteria have been cultured and the patient given appropriate bactericidal antibiotics, then the temptation to change the treatment should be resisted.

Patients with a vegetation of diameter >10mm have a significantly higher incidence of embolisation than those with smaller vegetations and the risk is higher in mitral (25%) compared to aortic (10%) endocarditis and especially when the anterior leaflet of the mitral valve is involved. However, surgery on the basis of vegetation size alone is controversial. Valvular vegetations can be identified and sized by echocardiography and especially TOE. Early surgery should be considered for aortic/mitral kissing vegetations, markedly mobile vegetations and vegetations that appear to be rapidly increasing in size.

Prior systemic embolisation, recurrent emboli, persistent vegetation after a major systemic embolus and association with a perivalvar abscess are usually indications for surgery. This is especially in patients who have endocarditis caused by S. aureus, fungi or Haemophilus spp.
Many of the important issues concerning the surgical management of PVE have been the subject of discussions and review articles. Acute valvular regurgitation with pulmonary oedema, dehiscence of a prosthetic valve and abscess formation are absolute indications for surgery. Patients with PVE should have their warfarin replaced by heparin in case urgent surgery is necessary. Anticoagulant therapy is potentially hazardous in patients with IE.

Abdominal and splenic abscesses should be operated upon before cardiac surgery is performed.

In intravenous drug addicts with tricuspid valve endocarditis and tricuspid regurgitation, large vegetations can be treated by tricuspid valve repair, tricuspid valvectomy or vegetectomy.

Infection with certain organisms (eg: fungi, *Coxiella burnetii*) for which there is no synergistic bactericidal combination) rarely responds to medical treatment alone and usually requires surgery. Intraoperative TOE may provide useful information on the exact location and extent of the infection and in the planning of surgery.

**EVIDENCE LEVEL 3**

**TIMING OF SURGERY**

If there is an adequate indication for early surgery in the course of active IE such as severe aortic regurgitation and progressive pulmonary oedema, there is little evidence that there is anything to be gained by delaying surgery for prolonged periods of antibiotics. The frequency of early relapse and/or infection of the prosthesis after surgery is low. If heart failure regresses, the optimal timing remains controversial, although two weeks of antibiotic therapy is generally considered ideal.

Early surgery for PVE may reduce mortality even when the period of preoperative antibiotic treatment has been brief. Although 10 days of antibiotic therapy prior to surgery is desirable, surgery should not be delayed as post-operative endocarditis is surprisingly uncommon.

The optimal timing of surgery after a cerebral embolism is often unclear because heparinization during bypass may exacerbate the clinical course of a recent cerebral infarction. Ideally, 10 days should be allowed to elapse in patients who have sustained a cerebral infarct although surgical results are good within the first 72 hours. Such emergency surgery may be required if IE is complicated by severe prosthetic valve dysfunction, paravalvar leaks, persistent positive blood cultures, abscesses, large vegetations or conduction defects. At least 3 weeks should be allowed to elapse in those who have had an intracranial haemorrhage. CAT and MRI scanning should be performed prior to any possible surgery in order to exclude cerebral haemorrhage.

Contemporary approaches to the management of neurosurgical complications of IE have been recently presented in the literature.
The indications for surgery for NVE and PVE and the strength of evidence are shown in Table 15. Whether antibiotic-impregnation of heart valve sewing rings prevents IE or is useful in the surgical treatment of IE remains unclear at present.

EVIDENCE LEVEL 4

RESULTS OF SURGERY

Operative mortality varies from 4%-30%. The highest risk and poorest outcome appears to be in patients with *S. aureus* infection, heart failure, perivalvular abscess or aortic root abscess as well as those due to certain Gram-negative aerobic bacilli (*E. coli, Serratia* spp., *P. aeruginosa*), fungi and *S. epidermidis* which are resistant to penicillin and sometimes methicillin. Early surgical intervention is required in many cases but the mortality may still be >20%. Among patients who have NVE, survival ranges from 70%-80% at 5 years although it is less optimistic in those with PVE, where surgical treatment is generally better than medical therapy alone. A relapse rate of IE of 5%-10% occurs when surgery is performed in the acute phase of the disease and paravalvular regurgitation occurs in 5-15% of cases. Long-term results of surgical treatment of active infective aortic valve endocarditis with associated periannular abscess has been recently presented.

Surgical intervention for IE in infancy and childhood and in intravenous drug-abusers has been described in the literature.

Whether surgery using homograft or mechanical prostheses is best in the short or long-term remains debatable. Randomized trials would be necessary to settle this issue. A perforation in a valve cusp or leaflet can be repaired with a pericardial patch and kissing vegetations may be removed and the valve similarly repaired. Subannular, annular and supra-annular defects may be repaired by autologous pericardium but all abscesses must be drained and the cavity debrided. Allograft aortic root replacement is a valuable technique in the complex setting of PVE with involvement of the periannular region.

After surgery, antibiotics should be continued – the duration depends on the length of treatment preoperatively, the susceptibility of the microorganism to antibiotics, the presence of paravalvular lesions and the culture status of vegetations or valve removed. Generally, treatment should be continued for 2 weeks postoperatively.

EVIDENCE LEVEL 3

PROGNOSIS

The determinants of early and late survival in patients with IE have been identified. Several factors worsen the prognosis of IE and early surgical intervention may be necessary.
Clinical factors include old age, the presence of heart failure, renal failure, neurological symptoms, systemic emboli and delay in diagnosis. Persistent fever beyond the first week of treatment often indicates the development of complications such as progressive valve destruction, extension of infection to the valve’s annulus, development of perivalvular abscess or the presence of septic emboli.

Bacteriological factors include the causative organism with a worse prognosis with *S. aureus*, certain Gram-negative aerobic bacilli and fungi. These often present an acute IE and produce severe intracardiac destruction and major embolic complications. Early surgical intervention is frequently required and the mortality rate is >20%.43

Echocardiographic factors include aortic valve endocarditis, PVE and ring abscesses when persisting infection is more likely and surgery often inevitable.227 The presence of recent, large (>10mm), very mobile, pedunculated vegetations increase the risk of systemic embolisation which may significantly affect prognosis.

The cure rate for NVE is >90% for streptococci, 75-90% for enterococci and 60-75% for *S. aureus*.366,368,393,598 The usual causes of death are heart failure, emboli, rupture of mycotic aneurysms, post-op complications, renal failure and overwhelming infection. The prognosis is worse in PVE than in NVE, and on rare occasions only heart transplantation can resolve intractable infection on prosthetic valves.485 Late PVE has a better prognosis than early PVE with mortality rates of 19-50% and 41-80% respectively.482,486-489,599 Valvular dysfunction, dehiscence and intracardiac abscesses are commoner in early infection. The antibiotic-resistant microorganisms associated with early disease contribute to the higher mortality.

In 1995, Delahaye et al. reported on the long-term prognosis of IE.600 In their series (1970-1986), global survival was 75% at 6 months and 57% at 5 years with an annual instantaneous risk of death being 0.55 at 6 months, 0.18 at 1 year then 0.03. After 1 year, the only factor influencing prognosis was age. The risk of recurrence appears to be 0.3-2.5/100 patient/years.600,601 Castillo et al (1987-1997) reported a 5 year survival of 71%.519 In NVE, 5 year survival has been reported to be 88-96% in contrast to PVE where 5 year survival rate is between 60-82%.519,602,603 Late PVE may have 5 year survival rates of between 80-82%.

The long-term results of multivalvular surgery for IE have been recently reported.605
CONCLUSIONS

IE is a life-threatening disease with substantial morbidity and mortality (20% or more) despite improved techniques to aid diagnosis and modern antibiotics and surgical therapies.

In unwell patients with known cardiac disease or new cardiac murmurs, the diagnosis of IE should always be suspected. When the diagnosis is suspected, the patient should be admitted to hospital for full and careful investigation, including blood cultures, recording of temperatures, haematological and biochemical investigation, ECG, chest X-ray and echocardiography. Three sets of blood cultures should be collected at intervals of >1 hour within the first 24 hours when clinical evidence suggests the diagnosis is highly likely in a sick patient. If the patient is not acutely sick or if the diagnosis is not obvious clinically, 6 sets of blood cultures should be taken within the first 24-48 hours. If the diagnosis is confirmed by blood culture, the patient should be referred to an experienced cardiologist and the microbiologist should be involved from the outset.

If TTE is suboptimal, TOE should be considered to obtain further information on the size, site or mobility of vegetations, abscess or fistula formation or valve perforation. TOE should be performed in all patient with PVE.

The majority of NVE and of late PVE is caused by viridans streptococci (50-70%), S. aureus (25%) and enterococci (10%). In early PVE, S. epidermidis and S. aureus are the commonest organisms.

Once the diagnosis is established, treatment should be commenced according to the guidance or with alternative antibiotics if microbiological tests suggest more appropriate agents are suitable. In a sick patient, antibiotic treatment should be commenced immediately after blood cultures have been collected and the regimen adjusted once the microbiological data is available. Generally, prolonged IV antibiotic therapy is necessary, administered via a large central vein. Only the most penicillin-sensitive streptococci should be considered for treatment with shorter courses of penicillin.

CNE requires close scrutiny for unusual and slow-growing organisms and fungi. Serological tests for Coxiella burnetii, Bartonella spp and Chlamydia spp should be performed if the diagnosis is still suspected and there is still no growth after 7 days. Microscopy and culture of any excised tissue is essential. Molecular assay for specific gene targets and universal loci for bacteria and fungi and subsequent sequencing may be applied to blood culture or excised material to help identify the causative organism. Treatment should involve antibiotics which are appropriate for the most likely organism for the particular clinical scenario but should generally cover Gram-positive and Gram-negative organisms. Patients with a history of penicillin-allergy or who develop penicillin-allergy, should be treated with (or changed to) vancomycin, teicoplanin and gentamicin or other appropriate antibiotics.
With regard to prophylaxis, patients should be informed of their risk of IE and the need for antibiotic prophylaxis. They should be told to inform any doctor or dentist who is responsible for providing care and they should be given a card to carry reminding them of the importance of the risk and how to avoid IE. Patients at moderate-risk or high-risk of IE should be given antibiotic prophylaxis with appropriate antibiotics based upon the type of dental or surgical procedure being performed.

In haemodynamically-stable patients, early consultation with a cardiac surgeon is recommended in case surgery is suddenly required. Patients with life-threatening congestive heart failure, left heart failure or cardiogenic shock due to treatable valvular disease should undergo emergency cardiac surgery, if the patient has reasonable prospects of recovery and a satisfactory quality of life after surgery. Surgery is indicated in patients with annular or aortic abscess, in those with infections resistant to antibiotics and in those with fungal endocarditis. Large mobile vegetations and recurrent emboli after appropriate antibiotic therapy are also indications for surgery and patients with PVE will generally require repeat operative intervention.

The findings and recommendations are consistent with those of the Task Force on Infective Endocarditis of the European Society of Cardiology (ESC), except for the additional recommendations for antibiotic prophylaxis shown in Table 5.
<table>
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<tr>
<th>Cause</th>
<th>% of cases</th>
<th>Predominant pathogen</th>
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<tbody>
<tr>
<td>Dental procedures</td>
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<td>Penicillin-sensitive viridans streptococci</td>
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<td>Respiratory tract infection</td>
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<td>Oropharyngeal surgery</td>
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<td><strong>Haemophilus spp</strong></td>
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<td>Respiratory tract surgery</td>
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<td>Gastrointestinal infectious diseases</td>
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<td>Gastrointestinal tumours</td>
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<td>Gastrointestinal tract therapeutic</td>
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<td>Interventions</td>
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<td>Urologic interventions</td>
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<td>Gynaecological interventions</td>
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<td><em>S. aureus</em></td>
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<td><em>S. epidermidis</em></td>
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<td>Valvular heart surgery</td>
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<td><em>S. epidermidis</em></td>
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<td>- late</td>
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<tr>
<td>Ventriculo-atrial shunt</td>
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</table>

# for further references relevant to this section see website: www.bcs.com

* viridans streptococci (alpha hemolytic) comprises *S. bovis; S. mutans* (10%); *S. mitis* (25%) – includes *S. sanguis; S. anginosus* (5%) – formerly *S. milleri* group – includes *S. intermedus*

** *S. pneumoniae* is infrequent

*** IV lines in patients after valve replacement are important potential causes of IE

**** *S. aureus* (60%)

***** streptococci and enterococci (20%)

Gram-negative aerobic bacilli (10%)

Fungi (5%)
A wide variety of other microorganisms have been reported to cause IE including:

*Neisseria gonorrhoeae*<sup>659-661</sup>
*Neisseria meningitidis*<sup>662,663</sup>
HACEK Gram-negative bacilli<sup>664-669</sup>
*Pseudomonas aeruginosa*,<sup>670,671</sup> *mendocina*<sup>672</sup>
*Listeria*<sup>673-679</sup>
*Diptheroids*<sup>680</sup>
*Spirochaetes*<sup>681</sup>
*Brucella*<sup>153</sup>
*Mycoplasma pneumoniae*<sup>152,160</sup>
*Coxiella burnetii*<sup>159</sup>
*Chlamydiae*<sup>155,681-683</sup>
*Bartonella*<sup>684</sup>
*Salmonella*<sup>685-687</sup>
*Pasteurella*<sup>688,689</sup>
*Yersinia*<sup>690</sup>
*Nocardia*<sup>691</sup>
*Tropheryma whippellii*<sup>692-695</sup>
*Lactobacillus*<sup>696,697</sup>
*Clostridium*<sup>698,699</sup>
*Legionella*<sup>700-702</sup>
*Mycobacterium tuberculosis*<sup>703</sup>
*Rothia dentocariosa*<sup>704</sup>
*Erysipelothrix rhusiopathiae*<sup>705</sup>
*Gemella*<sup>706,707</sup>
*Histoplasma*<sup>708</sup>
*Serratia*<sup>709</sup>
*Moraxella*<sup>710</sup>
*Actinomyces*<sup>711</sup>
*Streptomyces*<sup>712</sup>
*Group B Streptococci*<sup>713</sup>
# TABLE 2. DUKE CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS AND TERMINOLOGY USED IN THE MODIFIED DIAGNOSTIC CRITERIA

## Definite infective endocarditis

**Pathological criteria**

Micro-organisms: demonstrated by culture or histology in a vegetation that has embolized, or in a intracardiac abscess, or pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

**Clinical criteria (use definitions in Table 3)**

- 2 major criteria, or
- 1 major and 3 minor criteria, or
- 5 minor criteria

## Possible infective endocarditis

Findings consistent with IE that fall short of “definite”, but not “rejected”

## Rejected

Firm alternate diagnosis for manifestations of endocarditis, or

Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, or

No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for 4 days or less

## DEFINITIONS

### Major criteria

1. **Positive blood culture for IE**
   
   Isolation of microorganism known to cause IE from 2 separate blood cultures eg: viridans streptococci, *S. bovis*, *S. aureus*, *S. epidermidis*, enterococci, *Haemophilus* spp, *Actinobacillus* spp. etc

   Persistently positive blood culture – defined as recovery of a micro-organism consistent with endocarditis from:
   
   (i) at least 2 blood cultures drawn more than 12 hrs apart, or
   
   (ii) all of three or a majority of 4 or more separate blood cultures, with first and last drawn at least 1 hr apart

2. **Evidence of endocardial involvement**
   
   Positive echo for IE:
   
   (i) mobile intracardiac mass on valve or supporting structures or in path of regurgitant jet, or on implanted material without any alternative anatomical explanation, or
   
   (ii) abscess, or
   
   (iii) new partial dehiscence of prosthetic valve, or new valve regurgitation

3. **Clinical evidence of new valvular regurgitation**

4. **Positive serology** for Q-fever or other causes of culture-negative endocarditis such as *Bartonella* spp and *Chlamydia psittaci*

5. **Positive identification of a microorganism** from blood culture or excised tissue using molecular biology methods
**Minor criteria**

Predisposition: predisposing heart condition or IV drug abuse

Fever: >38.0°C

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, Janeway lesions, newly diagnosed clubbing, splinter haemorrhages, splenomegaly*

Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth spots, +ve rheumatoid factor, high ESR (>1.5 times upper limit of normal), high C-reactive protein level (>100mg/l)*

Microbiologic evidence: positive blood culture, but not meeting major criteria as defined above

* additional modifications to the Duke criteria appear to improve diagnostic sensitivity whilst retaining specificity
<table>
<thead>
<tr>
<th>TABLE 3. ANTIBIOTIC PROPHYLAXIS FOR HIGH, MODERATE AND LOW RISK CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH RISK</strong></td>
</tr>
<tr>
<td>Previous infective endocarditis^275</td>
</tr>
<tr>
<td>Complex cyanotic congenital heart disease, transposition of</td>
</tr>
<tr>
<td>great arteries, Fallot’s tetralogy, Gerbode’s defect^276-278</td>
</tr>
<tr>
<td>Surgically constructed systemic pulmonary shunts or conduits</td>
</tr>
<tr>
<td>Mitral valve prolapse with mitral regurgitation or thickened</td>
</tr>
<tr>
<td>valve leaflets^1279-281</td>
</tr>
<tr>
<td>Prosthetic heart valves (5x more than those with native valves)</td>
</tr>
<tr>
<td><strong>MODERATE RISK</strong></td>
</tr>
<tr>
<td>Acquired valvular heart disease eg: rheumatic heart disease –</td>
</tr>
<tr>
<td>Aortic stenosis, aortic regurgitation, mitral regurgitation</td>
</tr>
<tr>
<td>Non-cyanotic congenital cardiac defects eg: bicuspid aortic</td>
</tr>
<tr>
<td>valve, primum atrial septal defect, patent ductus arterioso,</td>
</tr>
<tr>
<td>coarctation of aorta, atrial septal aneurysm/patent foramen</td>
</tr>
<tr>
<td>ovale, ventricular septal defect, Other structural cardiac</td>
</tr>
<tr>
<td>defects eg: aortic root replacement, hypertrophic obstructive</td>
</tr>
<tr>
<td>cardiomyopathy, subaortic membrane &amp;</td>
</tr>
<tr>
<td><strong>LOW RISK CASES NOT REQUIRING ANTIBIOTIC PROPHYLAXIS</strong></td>
</tr>
<tr>
<td>Isolated secundum atrial septal defect ~293 pulmonary stenosis</td>
</tr>
<tr>
<td>Surgically-repaired atrial septal defect, ventricular septal</td>
</tr>
<tr>
<td>defect or patent ductus arteriosus, post Fontan or Mustard</td>
</tr>
<tr>
<td>procedure without residual defect/murmur</td>
</tr>
<tr>
<td>Previous coronary artery bypass surgery</td>
</tr>
<tr>
<td>Mitral valve prolapse without regurgitation</td>
</tr>
<tr>
<td>Innocent heart murmurs^@</td>
</tr>
<tr>
<td>Cardiac pacemakers/defibrillators^$</td>
</tr>
<tr>
<td>Coronary artery stent implantation^*</td>
</tr>
<tr>
<td>Heart / Heart and Lung Transplant**</td>
</tr>
</tbody>
</table>

^ Mitral regurgitation should be obvious clinically or deemed to be more than physiological on Doppler echocardiography

~ Antibiotic prophylaxis is recommended for up to 12 months after ASD/PFO catheter-based closure procedures

@ Unless being performed in patients at moderate or high risk of endocarditis when antibiotic prophylaxis is advisable

$ Pre and post procedure antibiotics are generally used routinely for surgical prophylaxis

@ If unsure as to the exact nature of the murmur and the need for prophylaxis, an opinion should be sought from a cardiologist. In an emergency or when it is difficult to obtain specific advice then antibiotic prophylaxis should be given prior to dental or surgical treatment

**Within the first 6 months after heart/heart-lung transplantation, patients should receive antibiotic prophylaxis
<table>
<thead>
<tr>
<th>Examination Procedures</th>
<th>Investigative Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodontal probing(^{716})</td>
<td>Sialography(^{717})</td>
</tr>
<tr>
<td>Dental examination with mirror and probe(^{317})</td>
<td>Intra-oral radiographs</td>
</tr>
<tr>
<td>Extra-oral radiographs</td>
<td></td>
</tr>
</tbody>
</table>

**Preventive procedures**
- Nil
- Fissure Sealants
- Fluoride treatments

**Professional Cleaning Procedures**
- Polishing teeth with a Rubber Cup\(^{718,719}\)
- Oral irrigation with water jet\(^{720,721}\)
- Light scaling\(^{722,723}\)
- Deep scaling\(^{722,723}\)
- Scaling teeth with hand instrument\(^{719,724}\)
- Scaling with ultrasonic instrument\(^{724}\)

**Anaesthetic Procedures**
- Intraligamental local anaesthetic injections\(^{337}\)
- Infiltration local anaesthesia
- Nerve block local anaesthesia
- Oral airway for GA\(^{725,726}\)
- Nasal airway for GA\(^{725-727}\)
- Laryngeal mask airway for GA\(^{728,729}\)

**Comprehensive Dental Treatment under General Anaesthesia**\(^{730}\)
- Examinations and Fillings\(^{731-733}\)

**Conservative (Restorative) Procedures**\(^{\ast}\)
- Rubber dam placement\(^{734,735}\)
- Matrix band and wedge placement\(^{734,735}\)
- Gingival retraction cord placement\(^{735}\)

**Periodontal Procedures**
- Root planing (similar to scaling)
- Antibiotic fibres or strips placed subgingivally****
- Gingivectomy\(^{722}\)
- Periodontal Surgery\(^{726}\)

**Endodontic Procedures**\(^{\dagger}\)
- Root canal instrumentation beyond the apex\(^{722,737}\)
- Avulsed tooth reimplantation*****
- Non-vital pulpotomy of primary molar

**PROPHYLAXIS NOT REQUIRED**

<table>
<thead>
<tr>
<th>Examination procedures</th>
<th>Dental examination with mirror and probe(^{317})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigative Procedures</td>
<td>Intra-oral radiographs Extra-oral radiographs</td>
</tr>
<tr>
<td>Preventive procedures</td>
<td>Fissure Sealants Fluoride treatments</td>
</tr>
</tbody>
</table>

**Professional Cleaning Procedures**
- Air polishing\(^{765}\)

**Anaesthetic Procedures**
- Infiltration local anaesthetic injections\(^{337}\)
- Nerve block local anaesthesia
- Oral airway for GA\(^{725,726}\)
- Nasal airway for GA\(^{725-727}\)
- Laryngeal mask airway for GA\(^{728,729}\)

**Comprehensive Dental Treatment under General Anaesthesia**

**Conservative (Restorative) Procedures**
- Slow and fast drilling of teeth (without rubber dam)\(^{724,735}\)

**Periodontal Procedures**

**Endodontic Procedures**
- Root canal instrumentation within the root canal\(^{737}\)
- Vital Pulpotomy of primary molar\(^{738,739}\)
- Pulpotomy of permanent tooth****
Orthodontic Procedures
Tooth separation
Expose or expose and bond tooth/teeth

Surgical Procedures
Extraction of single tooth
Extraction of multiple teeth
Incision and drainage of an abscess with extraction
Mucoperiosteal flap to gain access to tooth or lesion
Dental implants (as for mucoperiosteal flap)

Post Surgical Procedures
Suture removal
Removal of surgical packs

Daily or physiological events
Exfoliation of primary teeth
Toothbrushing
Flossing
Use of interdental wooden points

* there is a paradox inherent in endocarditis prophylaxis in that many cleaning procedures like toothbrushing, dental flossing, interdental wooden points, oral irrigation all cause a significant bacteraemia. There is no justification for using antibiotic prophylaxis for these self-care procedures carried out at home on a daily or twice daily basis.

** it is common for a course of dental treatment to take several visits to the dentist. For patients at high or moderate risk of developing infective endocarditis, as much treatment as possible should be carried out at each visit. The antibiotic should be changed at alternate visits eg: Amoxycillin – Clindamycin – Amoxycillin etc. but no more than 2 doses of penicillin should be given within a month. For patients who are allergic to penicillin, then a period of 1 month must be allowed between visits.

*** no data but the procedure is very similar to gingival retraction cord placement

**** no data but the procedure is similar to pulpotomy of primary molar

***** the avulsed tooth can be quickly washed and reimplanted immediately and the antibiotic prophylaxis administered when the child attends the dental surgery provided this is within 2 hour of the reimplantation. This is because antibiotic prophylaxis is still successful if administered after the bacteraemic episode.

$ Dental treatment confined to the root canal does not require antibiotic prophylaxis. However, if a rubber dam is used, antibiotic prophylaxis should be used since significant bacteraemia often results in these circumstances.
### TABLE 5. OTHER PROCEDURES REQUIRING ENDOCARDITIS PROPHYLAXIS IN HIGH AND MODERATE AT-RISK CASES

#### PROPHYLAXIS REQUIRED

**Gastrointestinal tract**
- Oesophageal procedures\(^752,753\)
- Surgical operations on stomach, small or large bowel
- Endoscopic retrograde cholangiography/biliary obstruction\(^754\)
- Endoscopy with/without biopsy\(^338-340,755-759\)
- Endoscopic variceal sclerotherapy\(^622,759\)
- Percutaneous endoscopic gastrostomy\(^341\)
- Biliary tract surgery
- Lithotripsy of gall stones\(^761\)

**Genitourinary tract**
- Circumcision\(^762\)
- Prostatic surgery, transrectal biopsy\(^763\)
- Vasectomy\(^764,765\)
- Lithotripsy\(^766\)
- Cystoscopy
- Urethral catheterization in presence of bacteriuria
- Urethral dilatation
- Gynaecological operations eg: hysterectomy, caesarean section, vaginal delivery\(^767,768\)
  - Therapeutic abortion,\(^769-771\) uterine dilatation and curettage, sterilization procedures, insertion of intrauterine device\(^772\)
  - Removal of infected intrauterine devices\(^*\)
  - Smears\(^773\)

**Respiratory tract**
- Tonsillectomy/adenoidectomy
- Surgical procedures on respiratory tract
- Bronchoscopy – particularly rigid bronchoscopy\(^774,775\)
- Nasal packing\(^776\)

**Cardiac**
- Implantation of cardiac pacemakers/defibrillators\(^777-779\)
- Cardiac surgical operations
- Implantation of occlusive devices eg: ductal occluders,\(^780\) septal occluders\(^781,782\)
- Transoesophageal echocardiography\(^760\)
- Balloon valvuloplasty\(^783-787\)
- Balloon dilatation of coarctation of aorta\(^*710\)
- PTCA/PCI/Stent implantation\(^788-790\)

**Ophthalmological**
- Lacrimal duct probing\(^791\)

**Dermatological**
- Surgery\(^792,793\)

**Other**
- Thermal injury/burns\(^794,795\)
- Acupuncture\(^796,797\)
- Body piercing\(^799-800\)
- Tattooing\(^801\)

#### PROPHYLAXIS NOT REQUIRED

**Gastrointestinal tract** - Barium examinations

**Genitourinary tract** - Urethral catheterization – unless bacteriuria evident

**Respiratory tract** - Endotracheal intubation

**Cardiac** - Diagnostic cardiac catheterization
Although not considered “high-risk” procedures, bacteraemia and/or IE have been reported after these procedures and antibiotic prophylaxis should be considered for those patients considered at high or moderate risk of IE (Table 2). The ESC did not recognise these to be indications for antibiotic prophylaxis in their Task Force Report.802,803
**TABLE 6. PROPHYLACTIC ANTIBIOTIC REGIMENS FOR DENTAL, ORAL, RESPIRATORY TRACT OR OESOPHAEGAL PROCEDURES IN ADULTS**

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Drug</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk and moderate risk patients including patients with prosthetic heart valves*</td>
<td>Amoxicillin</td>
<td>3G oral 1hr preprocedure or 2G IV &lt;30min preprocedure^a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If allergic to penicillin^b</td>
<td>Clindamycin^804</td>
<td>600mg oral 1hr preprocedure or 300mg IV &lt;30min preprocedure^c</td>
</tr>
<tr>
<td></td>
<td>or Azithromycin^d</td>
<td>500mg oral 1hr preprocedure</td>
</tr>
<tr>
<td></td>
<td>or Vancomycin</td>
<td>1G IV over 2 hours, 1-2hrs preprocedure + gentamicin</td>
</tr>
<tr>
<td></td>
<td>+ gentamicin</td>
<td>1.5mg/kg IV &lt;30min preprocedure^a</td>
</tr>
<tr>
<td></td>
<td>or Teicoplanin</td>
<td>400mg IV &lt; 30 min preprocedure + gentamicin</td>
</tr>
<tr>
<td></td>
<td>+ gentamicin</td>
<td>1.5mg/kg &lt;30 min preprocedure^a</td>
</tr>
<tr>
<td>Patients with previous infective endocarditis^e</td>
<td>Amoxicillin</td>
<td>2G IV &lt;30min preprocedure + 1G IV or orally 6hrs post + gentamicin</td>
</tr>
<tr>
<td></td>
<td>+ gentamicin</td>
<td>1.5mg/kg IV &lt;30min preprocedure^a</td>
</tr>
<tr>
<td>If allergic to penicillin^b</td>
<td>Vancomycin</td>
<td>1G IV over 2 hrs, 1-2hrs preprocedure + gentamicin</td>
</tr>
<tr>
<td></td>
<td>+ gentamicin</td>
<td>1.5mg/kg IV &lt;30min preprocedure^a</td>
</tr>
<tr>
<td></td>
<td>or Clindamycin</td>
<td>300mg IV &lt;30min preprocedure^d then IV clindamycin 150mg 6 hours later</td>
</tr>
</tbody>
</table>

* Particular care should be taken to ensure that patients with prosthetic heart valves are protected by prophylactic antibiotics, since the consequences of IE are particularly serious. It is essential that they receive prophylactic antibiotics at least 1 hour before the procedure. If not, they should be given IV antibiotics immediately before the procedure or the procedure postponed.

^a for those undergoing GA, IV antibiotics should be given either on induction or within 30mins prior to starting the procedure; oral amoxicillin (3G) should be given 4 hrs before induction and again as soon as possible after the procedure.

Where oral antibiotics are not ideal and in whom IV access is difficult or impossible eg: IV drug abusers, IM clindamycin 600mg 1hr preop or IM teicoplanin (2mg/kg) 1hr preop may be alternative treatments.

^b or having received a penicillin within last 4 weeks

^c Clindamycin to be infused over 10-15 minutes

^d Azithromycin 500mg as an oral suspension, given 1 hour before the procedure may be an alternative if dysphagia is a problem

^e these patients are considered to be at particularly high risk of IE with the consequences being particularly serious for patients with prosthetic valve endocarditis
### TABLE 7. PROPHYLACTIC ANTIBIOTIC REGIMENS FOR GENITOURINARY OR GASTROINTESTINAL PROCEDURES IN ADULTS

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Drug</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk and moderate risk patients</td>
<td>Ampicillin or amoxicillin + gentamicin</td>
<td>2G IV – &lt;30min preprocedure and 1G IV or orally 6hr post</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If allergic to penicillin(^b)</td>
<td>Vancomycin + gentamicin</td>
<td>1G IV over 2hrs, 1-2hrs preprocedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) for those undergoing GA, IV antibiotics should be given either on induction or within 30mins prior to starting the procedure; oral amoxicillin (3G) should be given 4 hrs before induction and again as soon as possible after the procedure.

Where oral antibiotics are not ideal and in whom IV access is difficult or impossible eg: IV drug abusers, IM clindamycin 600mg 1hr preop or IM teicoplanin (2mg/kg) 1hr preop may be alternative treatments.

\(^b\) or having received a penicillin within last 4 weeks
### TABLE 8. PROPHYLACTIC ANTIBIOTIC REGIMENS FOR PERMANENT PACEMAKER IMPLANTATION*

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Drug</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk and moderate risk patients</td>
<td>Flucloxacillin**</td>
<td>1G IV &lt;30min preprocedure + 500mg orally qds for 2 days</td>
</tr>
<tr>
<td>If allergic to penicillin</td>
<td>Vancomycin</td>
<td>1G IV over 2hrs, 1-2 hrs preprocedure + erythromycin 500mg orally qds for 2 days</td>
</tr>
</tbody>
</table>

* Probably should be followed in high/moderate risk patients having defibrillator, stent or other intravascular device implantation

** Patients infected or colonized with MRSA should be given vancomycin rather than flucloxacillin
**TABLE 9. PROPHYLACTIC ANTIBIOTIC REGIMENS FOR CARDIAC SURGERY** *

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Drug</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG surgery</td>
<td>Flucloxacillin 1G IV + Gentamicin 1.5mg/kg IV</td>
<td>3 doses – first dose given on induction then 8 hourly 3 doses – first dose given on induction then 8 hourly</td>
</tr>
<tr>
<td>or Cefuroxime 1.5G IV</td>
<td></td>
<td>6 doses – first dose given on induction second after CPB then 8 hourly</td>
</tr>
<tr>
<td>Valvular or other cardiac surgery if any prosthetic device/ material is used</td>
<td>Flucloxacillin 1G IV + Gentamicin 1.5mg/kg IV</td>
<td>3 doses – first dose given on induction then 8 hourly 3 doses – first dose given on induction then 8 hourly</td>
</tr>
<tr>
<td>or Cefuroxime 1.5G IV + Vancomycin 1G IV (infused over 2 hrs)</td>
<td></td>
<td>3 doses – first dose given on induction then 8 hourly 3 doses – first dose given on induction then 8 hourly</td>
</tr>
<tr>
<td>If allergic to penicillin</td>
<td>Vancomycin 1G IV (infused over 2 hrs)</td>
<td>First dose 30-60min pre skin incision 2 further doses @ 12 and 24 hrs</td>
</tr>
</tbody>
</table>

* Prophylactic antibiotics at the time of cardiac surgery are given not only to prevent endocarditis and prosthetic infection but to prevent other serious infections such as mediastinitis and major wound infection.  
  The dose and type of antibiotics varies according to the sensitivity patterns of microorganisms in the cardiac surgical environment and in the individual patient. Some Cardiac Surgical Units use a combination of antibiotics, others use monotherapy.  
  The timing of antibiotics is important. They should be given prior to surgery and for at least 24-48 hours post-operatively.  
  In **MRSA** carriers or in units where there is a high prevalence of infection by **MRSA**, vancomycin should **always** replace flucloxacillin.
**TABLE 10. TREATMENT OF INFECTIVE ENDOCARDITIS DUE TO PENICILLIN-SENSITIVE VIRIDANS STREPTOCOCCI AND S. BOVIS (MIC <0.1mg/L) IN ADULTS**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>7.2G-12G IV daily in 4-6 divided doses</td>
<td>4-6 weeks**</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses (max 240mg)</td>
<td>2 weeks^</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>7.2G-12G IV daily in 4-6 divided doses</td>
<td>2 weeks#</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses (max 240mg)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Teicoplanin^@^</td>
<td>400mg IV bolus 12hrly for first 3 doses then 400mg IV daily~</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2G/day IV</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

For those patients allergic to penicillin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>30mg/kg IV in 24hrs in 2 divided doses^$ (infused over 2hrs)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses (max 240mg)</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

^ Loading dose and maintenance dose of gentamicin may be calculated on the basis of the patient’s age, weight and renal function using a nomogram, with appropriate adjustments in dose being made according to serum-gentamicin concentrations.

With renal impairment, dose may be reduced according to creatinine clearance using Mawer nomogram or to blood urea levels eg:

- 7-17mmol/l 80mg 12hrly
- 17-33 mmol/l 80mg daily
- >33mmol/l 80mg alternate days.

Serum gentamicin levels should be checked twice per week if serum creatinine normal and more often if elevated.

**Ideally:**

- Pre(Trough) level (taken just prior to dose) < 2mg/L
- If > 2mg/L – drug interval must be increased or dose reduced
- Peak level (taken 1 hour after IV dose) < 10mg/L Preferably 3-5mg/L
- If level exceeds this – reduce dose

^ 4 weeks of benzylpenicillin alone for sensitive streptococci may be a useful option for the elderly or those with existing hearing impairment of poor renal function

** Duration adjusted according to clinical response and advice from microbiologist

# Conditions to be met for a 2 week treatment regimen for viridans streptococci and S. bovis endocarditis:

- Penicillin-sensitive viridans streptococci including S. bovis (penicillin MIC <0.1mg/L)
- No cardiovascular risk factors eg: heart failure, aortic or mitral regurgitation, conduction abnormalities
- No evidence of thromboembolism
- Native valve infection
- No vegetations > 5mm diameter demonstrated on echocardiography
- Clinical response within 7 days including abolition of pyrexia

~ Serum teicoplanin levels should be checked to ensure appropriate blood concentrations

$ Serum trough level of vancomycin should be maintained between 10-15mg/L to ensure optimal efficacy
TABLE 11. TREATMENT OF INFECTIVE ENDOCARDITIS DUE TO PENICILLIN-RELATIVE RESISTANT VIRIDANS STREPTOCOCCI AND S. BOVIS (MIC >0.1mg/L) IN ADULTS

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>12G-14G IV daily in 4-6 divided doses</td>
<td>4-6 weeks**</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses (max 240mg)</td>
<td>2 weeks**</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teicoplanin~</td>
<td>400mg IV bolus 12hrly for 3 doses then 400mg IV daily</td>
<td>4 weeks**</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses (max 240mg)</td>
<td>2 weeks**</td>
</tr>
</tbody>
</table>

For those patients allergic to penicillin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin#</td>
<td>30mg/kg IV per 24hrs in 2 divided doses (infused over 2 hrs)</td>
<td>4 weeks**</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses (max 240mg)</td>
<td>2 weeks**</td>
</tr>
</tbody>
</table>

*See Table 10

# As a guide the dose may be adjusted to achieve 1 hour postinfusion serum concentrations of about 30mg/l and trough concentrations of 10-15mg/L although the correlation between peak and trough levels with toxicity and efficacy is not high.

*S. pneumoniae* – treat as penicillin-sensitive viridans streptococci but check sensitivity as penicillin resistant pneumococci are now being isolated.

*S. pyogenes* (Group A Strep.), Group B,C & G streptococci – treat as per penicillin-sensitive viridans streptococci.

*S. adjacens* and *S. defectives* (nutritionally variant streptococci) – treat with either benzylpenicillin/gentamicin combination or vancomycin and gentamicin regimen. Advice from microbiologist should be sought.

**Duration adjusted according to clinical response and advice from microbiologist

~ serum teicoplanin levels should be checked to ensure appropriate blood concentrations
### TABLE 12. TREATMENT OF ENDOCARDITIS DUE TO STAPHYLOCOCCI ON NATIVE VALVE

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillin-sensitive (non-B-lactamase producers)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzylpenicillin + Gentamicin*</td>
<td>12G-14G IV daily in 4-6 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>3-5 days</td>
</tr>
<tr>
<td><strong>Methicillin-sensitive staphylococci (B-lactamase producer)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin + Gentamicin*</td>
<td>8G-12G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>3-5 days</td>
</tr>
<tr>
<td><strong>For those patients allergic to penicillin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin + Gentamicin*</td>
<td>30mg/kg IV in 24 hours in 2 divided doses (infused over 2 hrs)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>3-5 days</td>
</tr>
<tr>
<td><strong>Methicillin-resistant staphylococci</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin + Gentamicin*</td>
<td>30mg/kg IV in 24 hours in 2 divided doses (infused over 2 hrs)</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

*Gentamicin blood levels must be checked 2-3 times in this week period. See Table 10. Peak levels 5-10mg/L.

Oral **Fusidic acid** may be considered as an alternative to gentamicin for combination treatment for fusidic acid-sensitive strains.

**Rifampicin** may be added to the penicillin, gentamicin or vancomycin regimens for poor responders.

In some patients with uncomplicated tricuspid valve endocarditis due to IV drug abuse – 2 weeks of IV flucloxacillin and gentamicin for methicillin-sensitive Staphylococcal infection is often effective (see text).

**Linezolid or Synercid** may be used in MRSA.

Vancomycin – 1 hour post infusion serum concentration of approximately 30mg/L and trough concentration of 10-15mg/L should ensure optimal efficacy although the correlation between peak and trough levels with toxicity and efficacy is not high.
**TABLE 13. TREATMENT OF ENDOCARDITIS DUE TO STAPHYLOCOCCI ON PROSTHETIC VALVE OR OTHER PROSTHETIC MATERIAL**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methicillin-sensitive staphylococci</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>8G-12G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+ Rifampicin*</td>
<td>300mg orally 8hrly</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+ Gentamicin**</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>Methicillin-resistant staphylococci</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>30mg/kg IV in 24hrs in 2 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(infused over 2 hrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Rifampicin*</td>
<td>300mg orally 8hrly</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+ Gentamicin**</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

* Resistance to rifampicin develops rapidly and therefore should never be given alone. Fluoroquinolones are an alternative to rifampicin if the microorganism is resistant to rifampicin.

** See Table 10. Peak levels 5-10mg/L.

***This regimen may be used if patient is allergic to penicillin
TABLE 14. TREATMENT OF INFECTIVE ENDOCARDITIS DUE TO ENTEROCOCCI IN ADULTS

<table>
<thead>
<tr>
<th>Gentamicin-sensitive or low-level resistant organism (MIC &lt;500mg/L)</th>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin or Ampicillin or Amoxicillin</td>
<td>10G-12G IV daily in 4-6 divided doses</td>
<td>4-6 weeks#</td>
<td></td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses (max 240mg/day)</td>
<td>4-6 weeks#</td>
<td></td>
</tr>
<tr>
<td>For those patients allergic to penicillin</td>
<td>Vancomycin**</td>
<td>30mg/kg IV per 24hrs in 2 divided doses (infused over 2 hrs)</td>
<td>4-6 weeks#</td>
</tr>
<tr>
<td>+ Gentamicin*</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>4-6 weeks#</td>
<td></td>
</tr>
</tbody>
</table>

# 6 weeks therapy recommended for patients with symptoms > 3 months

*Monitor drug serum levels and renal function

See Table 10

** Teicoplanin 10mg/kg IV bolus 12hrly for first 6 doses then 10mg/kg IV daily may be an alternative to vancomycin. Levels should be measured.

For Gentamicin-highly resistant strains (MIC >500mg/L), ampicillin or amoxicillin 12G IV per day in 6 divided doses or as a continuous infusion for 6 weeks is advisable. If the organism is sensitive to streptomycin this could also be added but dose monitoring is necessary to avoid ototoxicity. A microbiologist’s opinion should be sought and surgery considered early for antibiotic-treatment failure.

For Ampicillin-resistant strains, the vancomycin + gentamicin regimen may be effective.

Vancomycin-resistant enterococci (VRE) may respond to IV linezolid 600mg infused over 30-120min every 12 hrs.

Vancomycin-resistant *E. faecium* may respond to Synercid®.

For multiresistant strains, expert advice should be sought from the microbiologist.
<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Amoxicillin</td>
<td>12G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>+ gentamicin**</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Tazocin^R^</td>
<td>18G IV daily in 6 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>or ceftazidime</td>
<td>6G IV daily in 3 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>or Imipenem</td>
<td>2-4G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>or aztreonam</td>
<td>8G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>+ gentamicin**</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td></td>
<td>or tobramycin</td>
<td>8mg/kg IV daily in 4 divided doses</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td><em>Enterobacteraceae</em>**</td>
<td>Amoxicillin</td>
<td>12G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>or Cefotaxime</td>
<td>8G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>or Imipenem</td>
<td>2-4G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>or Aztreonam</td>
<td>8G IV daily in 4 divided doses</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>+ gentamicin**</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>4-6 weeks</td>
</tr>
</tbody>
</table>

* treatment is usually specific and based on results of antibacterial sensitivity testing

** See Table 10. Peak levels 5-10mg/L.

*** *E. coli/ Klebsiella/Enterobacter/Serratia/Proteus* – drug regimen often depends on individual organism, sensitivity testing and advice from microbiologist

^ Tazocin^R^ (piperacillin + beta-lactamase inhibitor, tazobactam) is probably better than piperacillin alone.
TABLE 16.  TREATMENT OF HACEK GROUP, FUNGAL AND CULTURE-NEGATIVE ENDOCARDITIS

**HACEK GROUP**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin or Amoxicillin$</td>
<td>12G IV daily in 4 divided doses</td>
<td>4-6 weeks*</td>
</tr>
<tr>
<td>+ Gentamicin**</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

$ If amoxicillin-resistant, a third generation cephalosporin such as IV ceftriaxone 2G/day in a single dose is given for 3-4 weeks in NVE and 6 weeks in PVE. It has a long half-life.

* 6 weeks for patients with PVE

** See Table 10. Peak levels 5-10mg/L.

Ofloxacin may be useful in *Actinobacillus* endocarditis$^{113}$

**FUNGI**$^5$

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B$^\wedge$</td>
<td>1mg/kg IV every 24hrs (total dose 2-2.5G)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+/- Flucytosine*</td>
<td>150-200mg/kg oral per day in 4 divided doses</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

$^\wedge$ Amphotericin B as a lipid complex or encapsulated in liposomes have been shown to have reduced toxicity enabling much higher doses to be given without substantial side effects.$^{114}$ Advice from microbiologist should be sought.

* marrow depression and hepatic necrosis are side effects; plasma concentrations for optimal response are 25-50mg/L and should not be allowed to exceed 80mg/L.

$^5$ current antifungal agents will not cure fungal endocarditis except in rare cases and combined medical treatment and surgical treatment should be employed

**CULTURE-NEGATIVE**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>15mg/kg IV every 12hrs</td>
<td>6 weeks</td>
</tr>
<tr>
<td>+ Gentamicin**</td>
<td>3-5mg/kg IV daily in 2-3 divided doses</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

* When serology for atypical organisms such as *Chlamydia*, *Coxiella* and *Bartonella* are negative

** See Table 10. Peak levels 5-10mg/L.
TABLE 17. INDICATIONS FOR SURGERY FOR NATIVE AND PROSTHETIC VALVE ENDOCARDITIS

**NATIVE**

- Acute AR or MR with heart failure\textsuperscript{490,491,514}
- Acute AR with tachycardia and early closure of the mitral valve
- Fungal endocarditis\textsuperscript{494,815-819}
- Annular or aortic abscess, true aneurysm of the sinus of valsalva, true or false aneurysm of the aorta\textsuperscript{490-493}
- Evidence of valvular dysfunction and persistent infection after a prolonged period (7-10 days) of appropriate antibiotics, as indicated by presence of fever, leukocytosis, bacteraemia\textsuperscript{490,491} - assuming that there are no non-cardiac causes for infection\textsuperscript{490,491}
- Recurrent emboli after appropriate antibiotic therapy\textsuperscript{490,491}
- Mobile vegetations >10mm diameter
- Early infection of the mitral valve – that can be repaired
- Persistent pyrexia and leukocytosis with negative blood cultures\textsuperscript{490,491}
- Relapse after an adequate course of antibiotics

**PROSTHETIC**

- Early prosthetic valve endocarditis (<2 months)\textsuperscript{490,491,495}
- Heart failure with prosthetic valve dysfunction
- Fungal endocarditis\textsuperscript{494,495}
- Staphylococcal endocarditis unresponsive to antibiotics\textsuperscript{490-493,495}
- Paravalvar leak, annular or aortic root abscess\textsuperscript{490-493}
- Infection with Gram-ve organisms or organisms with a poor response to antibiotics\textsuperscript{490,491,495}
- Sinus or aortic true/false aneurysm, fistula formation
- Persistent bacteraemia after 7-10 days of antibiotics
- Recurrent peripheral embolus
- Vegetation on prosthesis
- New-onset conduction disturbance
- Relapse after an adequate course of antibiotics
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APPENDIX

APPENDIX 1
SIGN Levels of Evidence and Grades of Recommendation
The strength of evidence and the recommendations from it were classified according to the definitions used by the Scottish Intercollegiate Guidelines Network derived from the US Agency for Health Care Policy and Research.820

Levels of evidence
1++ High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with very low risk of bias.
1+ Well conducted meta analyses, systematic reviews of RCTs or RCTs with a low risk of bias.
1- Meta analyses, systematic reviews of RCTs or RCTs with a high risk of bias.

2++ High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.
2+ Well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.

3 Non-analytic studies eg: case reports, case series.

4 Expert opinion

Grades of recommendations:
A At least one meta analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies as 1+, directly applicable to the target population and demonstrating overall consistency of results.

B A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++.

D Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
APPENDIX 2

ANTIBIOTICS

Benzylpenicillin remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases.

Penicillinase-resistant penicillins such as flucloxacillin are not inactivated by the enzyme and may be used in the treatment of penicillin-resistant staphylococci.

Broad-spectrum penicillins including ampicillin and amoxicillin are active against certain Gram-positive and Gram-negative organisms but are inactivated by penicillinases produced by Staph. aureus and by common Gram-negative bacilli such as Escherichia coli. Co-amoxiclav consists of amoxycillin with the beta-lactamase inhibitor clavulanic acid and can be of use in beta-lactamase producing bacteria that are resistant to amoxycillin.

Antipseudomonal penicillins include the carboxypenicillin ticarcillin and are principally indicated for infection with Pseudomonas aeruginosa and certain other Gram-negative bacilli including Proteus spp.. Ticarcillin is available in combination with clavulanic acid (TimentinR) which is active against beta-lactamase producing bacteria resistant to ticarcillin. The ureidopenicillin piperacillin is more active than ticarcillin against P.aeruginosa. TazocinR (piperacillin with the beta-lactamase inhibitor tazobactam) is active against bet-lactamase-producing bacteria resistant to the ureidopenicillins. Its spectrum of activity is comparable to the carbapenems, imipenem and meropenem. These agents should be given with an aminoglycoside since they have synergistic effects.

“Third-generation” cephalosporins such as cefotaxime, ceftazidime and ceftiraxone have greater activity than the “second generation” cefuroxime and cefamandole against certain Gram-negative bacteria but less active against Staph. aureus. Ceftazidime has good activity against P. aeruginosa and other Gram-negative bacteria and Ceftriaxone has a longer half-life and only needs once daily administration. Cefoxitin, a cephapemycin antibiotic, is active against Bacteroides fragilis.

Beta-lactam antibiotics include aztreonam, imipenem and meropenem.

Aztreanom is a monocyclic beta-lactam (monobactam) antibiotic active against Gram-negative aerobic bacteria including P. aeruginosa, Neisseria meningitides and Haemophilus influenzae. It is inactive against Gram-positive organisms. Imipenam, a carbapenem, has a broad spectrum of activity against many aerobic and anaerobic Gram-positive and Gram-negative bacteria. Since it is partially inactivated in the kidney by enzymatic activity, it is administered in combination with cilastin, a specific enzyme inhibitor which blocks its renal metabolism. Meropenem is similar to imipenem but is stable to the renal enzyme which inactivates imipenem and therefore can be used without cilastin.

Aminoglycosides include amikacin, gentamicin, streptomycin and tobramycin. All are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin and tobramycin are also active against P. aeruginosa. Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. In patients with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses but earlier and more frequent in those with renal impairment. Blood samples should be taken 1 hour after IV administration (peak) and just before the next dose (trough). Gentamicin
has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. It should be used in combination with another antibiotic such as penicillin. The dose is up to 5mg/kg daily in divided doses every 8 hours. Loading doses and maintenance may be calculated on the basis of the patient’s weight, using a nomogram. Adjustments are then made according to serum-gentamicin concentrations. In staphylococcal endocarditis, gentamicin is given in conventional doses to achieve a “peak” concentration of 5-10mg/L and a “trough” level of <2mg/L.

**Amikacin** is more stable than gentamicin to enzyme inactivation and may be used for serious infections caused by gentamicin-resistant Gram-negative bacilli. **Tobramycin** is similar to gentamicin but is slightly more active against *P. aeruginosa*.

**Macrolide** antibiotics include **erythromycin** and **clarithromycin**. **Erythromycin** has an antibacterial spectrum that is similar to penicillin and is an alternative in penicillin-allergic patients. **Azithromycin** is a macrolide with slightly less activity against Gram-positive bacteria but enhanced activity against some Gram-negative bacteria such as *H. influenzae*. It has a long tissue half-life and once daily dosage is recommended. **Clarithromycin** is an erythromycin derivative with greater activity than erythromycin. Tissue concentrations are higher than with erythromycin and is given twice daily.

**Clindamycin** is active against Gram-positive cocci, including penicillin-resistant staphylococci and also against many anaerobic bacteria especially *Bacteroides fragilis*.

**Fusidic acid** may be used for staphylococci, especially penicillin-resistant staphylococci, although a second antistaphylococcal antibiotic is required to prevent emergence of resistance.

The **glycopeptide antibiotics**, **vancomycin** and **teicoplanin** have bactericidal activity against aerobic and anaerobic Gram-positive bacteria. **Vancomycin** is used for treating Gram-positive cocci including multi-resistant staphylococci. There are increasing reports of vancomycin-resistant enterococci (VRE). It has a long duration of action and can be given 12 hourly. **Teicoplanin** is similar but has a longer duration of action and can be given once daily.

**Linezolid**, an oxazolidinone antibacterial, is active against Gram-positive bacteria including methicillin-resistant *Staph. aureus* (MRSA) and VRE. It should be reserved for treating organisms resistant to other antibacterials or when they are poorly tolerated. It is inactive against Gram-negative organisms.

**Synercid** R - a combination of the streptogramin antibiotics **quinupristin** and **dalfopristin** may be useful for Gram-positive bacterial endocarditis with MRSA or for patients who cannot be treated with other agents. It is not active against *Enterococcus faecalis*. 
### APPENDIX 3  
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired immuno-deficiency syndrome</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>AR</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>CNE</td>
<td>Culture negative endocarditis</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECHO</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>5-FC</td>
<td>5-flucytosine</td>
</tr>
<tr>
<td>G</td>
<td>gram</td>
</tr>
<tr>
<td>GA</td>
<td>General anaesthesia</td>
</tr>
<tr>
<td>GISA</td>
<td>Glycopeptide intermediate resistance <em>S. aureus</em></td>
</tr>
<tr>
<td>hr</td>
<td>hour</td>
</tr>
<tr>
<td>IE</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>MBC</td>
<td>Minimal bactericidal concentration</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimal inhibitory concentration</td>
</tr>
<tr>
<td>MIF</td>
<td>Microimmunofluorescence</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
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<td>mls</td>
<td>milliliters</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>MRSA</td>
<td>Meticillin-resistant <em>S. aureus</em></td>
</tr>
<tr>
<td>NVE</td>
<td>Native valve endocarditis</td>
</tr>
<tr>
<td>PAE</td>
<td>Post antibiotic effect</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PDA</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td>PVE</td>
<td>Prosthetic valve endocarditis</td>
</tr>
<tr>
<td>spp</td>
<td>species</td>
</tr>
<tr>
<td>TOE</td>
<td>Transoesophageal Echocardiography</td>
</tr>
<tr>
<td>TTE</td>
<td>Transthoracic Echocardiography</td>
</tr>
<tr>
<td>TV</td>
<td>Tricuspid valve</td>
</tr>
<tr>
<td>VISA</td>
<td>Vancomycin intermediate resistance <em>S. aureus</em></td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin Resistant Enterococci</td>
</tr>
</tbody>
</table>
FIGURE 1. British Heart Foundation “Endocarditis Dental Warning Cards” for patients requiring dental prophylaxis with antibiotics
**FIGURE 2. ALGORITHM FOR MANAGEMENT OF PATIENTS WITH INFECTIVE ENDOCARDITIS**

**CLINICALLY SUSPECTED INFECTIVE ENDOCARDITIS**

- Commence Antibiotics
  - Strong Likelihood
  - Weak Likelihood

**Await Blood Culture Results**

- BC+ve
- BC-ve

**Antibiotics according to:**
- Microorganism
- Clinical scenario
- Sensitivities
  (Table 1)

- STREP – Tables 10 & 11
- STAPH – Table 12 & 13
- ENTEROCOCCI – Tables 14
- G+ve/-ve Bacilli – Table 15
- HACEK – Table 16
- Fungi – Table 16

- Serology Atypical BC’s:
  - Consider other causes of BC-ve pyrexia
  - Consider withdrawing AB’s (if given) & observe with more BC’s.

**Symptoms/Signs of IE diminish**
- No indication for surgery

- *Complete antibiotic course & observe for evidence of:*
  - Control of infection
  - Cardiac/extracardiac complications

- Observe for one week after cessation of AB’s

- Discharge

**Symptoms/Signs of infection persist after one week**
- Features develop to indicate surgery (Table 17)

- Ensure good TEE/TOE obtained

- Refer to Cardiac Surgeons for Surgical Intervention

- *Observation should include:*
  - Clinical, ECG, Echo
  - Haematological & biochemical markers
  - Blood Cultures