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
2004

Lead author: **David R Ramsdale**

Advisory Group:
David R Ramsdale (Cardiology)
Tom SJ Elliott (Microbiology)
Paul Wright (Microbiology)
Graham J Roberts (Dentistry)
Peter Wallace (Cardiac Anaesthesia)
Brian Fabri (Cardiac Surgery)
Nicholas Palmer (Cardiology)
Petros Nihoyannopoulos (Echocardiography)
Michael Pearson (Clinical Effectiveness & Evaluation Unit)
Chris Mutton (Cardiac Nursing)
Douglas Broadbent (Cardiac Patients Association)

SIGN Reviewers:
Peter M Schofield (Cardiology)
David H Roberts (Cardiology)
Godfrey Smith (Microbiology)
Mark D Pullen (Cardiac Surgery)

CONTENTS

GUIDANCE ON THE PROPHYLAXIS AND TREATMENT OF INFECTIVE ENDOCARDITIS IN ADULTS

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 tha 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.[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.[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.[11] Prosthetic valve endocarditis (PVE), although uncommon, carries an even higher mortality rate.[12-14] Prevention of endocarditis is therefore extremely important.[15]

IE predominantly affects individuals with underlying structural cardiac defects who develop bacteraemia with organisms likely to cause endocarditis.[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.[17,18] Experimental studies suggest that endothelial damage leads to platelet and fibrin deposition and thus a non-bacterial thrombotic endocardial lesion.[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[21,22] and the pathologic hallmark of IE – vegetations.[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,[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.[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.[41] Patients with acute IE typically present with an accelerated illness including high remitting pyrexia, rigors and prostration,[42,43] It is usually caused by virulent pathogens such as *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.[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.[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.[44,47,48] Eighty per cent of patients present with a murmur whilst 15-20% develop one in hospital.[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.[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.[52] Eustachian valve endocarditis is well recognised.[53-56]

Abscesses of the heart are observed in 20-40% of cases, mainly in the aortic valve ring.[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.[62-65] These complications are associated with a high mortality.[66] Septal abscesses can lead to progressive conduction defects evidenced by prolongation of the PR interval and complete heart block.[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.[68,69] Subaortic aneurysm has been reported.[70]

Occasionally, chest pain due to pleurisy, pericarditis or myocardial infarction resulting from coronary arterial emboli are presenting symptoms.[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.[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.[75,76]

Extracardiac clinical manifestations consist of embolic (13-40%) as well as vasculitic phenomena[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%.[57,77,79] Splenic abscesses sometimes occur and splenic rupture can be fatal.[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.[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.[83-86] Meningism/meningitis may occur and CSF cultures may be positive.[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.[3,72,88-98] They occasionally rupture, causing subarachnoid or intraventricular haemorrhage or other vascular catastrophies.[99-102] Intracranial mycotic aneurysms (1.2-5% of cases) have an overall mortality of 60% increasing to 80% if rupture should occur.[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.[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.[107-109] Arthritis and Osler's nodes have also been attributed to the local deposit of immune complexes.[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.[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 30days 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.[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.[117-120] Haemoptysis can be fatal.[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 bacteraemia in patients who have congenital cardiac lesions.[121-122] In IV drug abuse, the prognosis of right-sided IE is favorable (4-5% mortality). However, recurrences are frequent (30%).[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.[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.[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 periannular tissue. Conduction system disturbance and even purulent pericarditis are serious complications. The diagnosis requires a high index of suspicion from the clinician.[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.[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.[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 extracorpoeal 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.[132] **In late** PVE (>60 days), the bacteriology more closely resembles that of community-acquired NVE[5,133] although staphylococci are still important causative organisms. The incidence may be higher in tissue than mechanical valves.[134]

Fungal endocarditis is frequently characterized by negative blood cultures and a paucity of physical signs.[135-139]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. [140-143] Fungal vegetations are frequently large (10-30mm diameter), bulky and friable and valvular or endocardial in position.[144]

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.[145] Emboli are frequently large and multiple, cause considerable functional and neurological damage and lead to the associated high mortality.[139] Metastatic abscesses are another frequent complication – the heart and kidneys being involved most commonly.[146,147] 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.[148]

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").[149-160] However, systemic lupus erythematosus and IE can co-exist.[161]

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, thrombocytopaenia and purpura are common.[162,163] 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.[164] Serological tests (antibodies, precipitins) may be helpful in these situations, particularly for rickettsia such as *Coxiella* and for *Chlamydia*.[165] 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.[165-167] 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.[168,169] 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.[170-173] Intraleucocyte bacteria can be seen in buffy coat preparations of blood in up to 50% of cases.[174]

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.[175,176]

Blood cultures remain the definitive procedure for diagnosing IE.[177] 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.[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.

EVIDENCE LEVEL 3

OPTIMAL BLOOD CULTURE TECHNIQUE

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 **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.[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.[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.[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 37^0C 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.[187] 90% will be diagnosed by the first sample and 95% after three cultures.[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.[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.[190-193] Culturing arterial rather than venous blood and drawing

blood during spikes of temperature does not appear to be of any additional value.[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 *Haemophilus* spp. or *Bartonella* spp., may be improved by prolonged incubation (7-21 days) or by using optimized blood culture media.[195-199] The microbiology laboratory should be informed when such organisms are suspected.

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.

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

Recommendation C
EVIDENCE LEVEL 3

ECHOCARDIOGRAPHY

Echocardiography is the most useful tool for confirming the anatomical diagnosis and for demonstrating vegetations on valves or other structures.[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.[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.[202-217] The absolute sensitivity depends upon the site and the size of the abnormalities.[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 eg. 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.[252-254] 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 concensus 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 population[275-293]

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.[299,318,319] This can be aided by regular dental follow-up and daily techniques to minimize plaque build-up eg: toothbrushing, dental floss, plaque removal.[320] However, even these simple procedures may not be without risk.[321] 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.[318,322-324]

Antibiotic prophylaxis for at-risk patients is recommended for dental and oral procedures likely to cause bacteraemia.[299,300,325,326] Prophylaxis against IE in orthodontics has been discussed in the literature.[315,327,328] 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.[326,329,330] 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.[331,332]

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.[333] This has become the mainstay of outpatient dental care. Regimens for IVor IM administration have proved effective for adults and children.[334,335]

Data from experimental animal models suggest that antimicrobial prophylaxis administered within 2 hours following the procedure will also provide protection.[336] 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.[337]

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.[338-341] 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.[342,343]

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.[344,345] Institution- or surgeon-specific selection of antibiotics is appropriate[346,347] 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.[348-352] There are insufficient data to suggest that aminoglycosides add substantial benefit to the prophylactic regimen.[346] **EVIDENCE LEVEL 4**

2. ANTIMICROBIAL THERAPY FOR INFECTIVE ENDOCARDITIS (Tables 8-14)[353,354]

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.[355,356] 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.[357,358] 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.[359] 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.[360] 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.[361] Tolerance can be overcome by addition of an aminoglycoside – resulting in a more rapid bactericidal activity.[362-364]

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.[365-368] 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 sould 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.**[369]

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.[370] **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.**[366] 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***

EVIDENCE LEVEL 3

SPECIFIC TREATMENT REGIMENS

STREPTOCOCCI and STAPHYLOCOCCI

The majority (80%) of NVE is caused by viridans streptococci (50-70%), *S. aureus* (25%) and enterococci (10%).[16,43,44,371-375] 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.[43,375] *S. epidermidis* more often causes indolent infection on previously damaged valves.[373,376] Regimens for treatment of streptococci are shown in **Tables 10-11**, for staphylococci in **Tables 12-13** and for enterococci in **Table 14.**[366,373,377-380]

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 maybe 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.[355,381] 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.[382-388]

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 septicaemia. 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.[389,390] Methicillin-resistant *S.epidermidis* is responsible for most cases of *S. epidermidis* endocarditis on prosthetic valves but uncommonly cause NVE.[390-392] 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.[393,394] Rifampicin is actively taken up by granulocytes and becomes effective against intracellular staphylococci and staphylococci within abscesses. Other agents such as Linezolid and Synercid^{R} 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).[395]

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.[395-398] Such patients require careful observation for the development of such complications.

The routine use of back titrations of the patient's serum against the organism is not recommended for monitoring antibiotic treatment.

EVIDENCE LEVEL 3

NUTRITIONALLY VARIANT STREPTOCOCCI

These bacteria account for 5-6% of streptococcal endocarditis and an important cause of CNE.[399] *Streptococcus adjacens* and *Streptococcus defectivus* 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.[399,400] Morbidity and mortality exceed those of other viridans

streptococci and even enterococci.[400] Bacteriological diagnosis may require special techniques.[401] More than 30% of strains are relatively resistant to penicillin and either a penicillin/aminoglycoside combination or vancomycin regimen is usually necessary.[401]

ENTEROCOCCI[402]

E. faecalis account for 10% of cases of endocarditis and 90% of all enterococcal endocarditis.[403] 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.[404-407] Some enterococci are multiresistant to antibiotics including vancomycin (VRE).[408,409] Regimens for treatment are shown in **Table 14**.[366-368,410-411]

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^{R} may be used in vancomycin-resistant *E. faecium*.

EVIDENCE LEVEL 3

GRAM-POSITIVE and GRAM-NEGATIVE BACILLI

Gram-positive (eg: *Listeria monocytogenes* and *Proprionibacterium acnes*) and gram-negative bacilli (eg: *E. coli*, *Klebsiella* spp, *Serratia* spp, *P. aeruginosa*) are uncommon but serious causes of endocarditis.[412-420] Regimens for treatment are shown in **Table 15**.[421-433] 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.[434,435]

EVIDENCE LEVEL 3

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.[436-445] This group of organisms will often require 7-21 days of incubation in 10% CO_2 to allow growth. The treatment is shown in **Table 16.**[445-450]

EVIDENCE LEVEL 3

FUNGI

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.[139,144,451,452] 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.[135,453,454]

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.[455] 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.[454,456,457] 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 amphoteracin 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.[458,459] 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.[460] 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.[461]

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.[462] 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.[463]

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.[464,465]

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.[466-468]

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.[469] 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

ENDOCARDITIS in HIV-POSITIVE PATIENTS

Endocarditis in HIV-positive patients usually occurs as a result of IV drug abuse or long-term indwelling catheters.[470] Estimates of IE occurrence vary from 6.3% - 34%.[471] *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.[472] Fungal endocarditis is not uncommon and there is an increased risk of *Salmonella* infection.[473] The outcome is worst in patients with AIDS and prolonged IV antibiotics are probably indicated.[474-476]

EVIDENCE LEVEL 3

ENDOCARDITIS IN PREGNANCY

Most of the first choice antibiotics are safe and effective in pregnancy. Penicillins do not appear to cause maternal or foetal complications.[477] Aminoglycosides should be used only in special situations because of the potential for oto- and nephro-toxicity in the foetus.[478] No teratogenic effects have so far been reported with imipenem or rifampicin. Quinolones are contraindicated in pregnancy.[478] Amphotericin B does not appear to be associated with teratogenic effects unlike fluconazole where there appears to be a dose-dependent effect.[479] 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 noabsolute 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.[480,481] 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.[482] 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.[482-489] 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.[490-495] 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.[484,496-502] 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[484,500] Patients in whom surgery is contraindicated or who refuse to consent for surgery may also be managed medically, but mortality is significant (26-70%).[503,504]

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.[355,505] Monitoring of drug levels will generally require close liason 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.[506,507] 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).[508] 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.[509] 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[510]

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 onle 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 failure[514] 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.[521-523] Periannular extension occurs in 10-40% of all native-valve IE and complicates aortic IE more commonly than mitral or tricuspid IE.[524-526] It occurs in 56-100% of patients in PVE.[527]

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[528] 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.[529-537] 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.[538]

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.[539-542]

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[543]

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.[544,545] The frequency of early relapse and/or infection of the prosthesis after surgery is low.[546,547] If heart failure regresses, the optimal timing remains controversial, although two weeks of antibiotic therapy is generally considered ideal.[548]

Early surgery for PVE may reduce mortalityeven when the period of preoperative antibiotic treatment has been brief.[549,550] Although 10 days of antibiotic therapy prior to surgery is desirable, surgery should not be delayed as post-operative endocarditis is surprisingly uncommon.[551,552]

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.[553,554] 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.[555-558] 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.[559,560] Contemporary approaches to the management of neurosurgical complications of IE have been recently presented in the literature.[561-563]

The indications for surgery for NVE and PVE and the strength of evidence are shown in **Table 15**.[564-568] Whether antibiotic-impregnation of heart valve sewing rings prevents IE or is useful in the surgical treatment of IE remains unclear at present.[569]

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.[570,571] Early surgical intervention is required in many cases but the mortality may still be >20%.[572] 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.[573] 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.[574,575]

Surgical intervention for IE in infancy and childhoodand in intravenous drug-abusers has been described in the literature.[576,577]

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.[500,578-595] 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.[584,593]

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.[596] Several factors worsen the prognosis of IE and early surgical intervention may be necessary.[597]

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%.[519,604.]

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

EVIDENCE LEVEL 3

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 1. CAUSES OF BACTERAEMIA RESPONSIBLE FOR INFECTIVE ENDOCARDITIS[606]

Cause	% of cases	Predominant pathogen
Dental procedures	20	Penicillin-sensitive viridans streptococci*[607-610]
Respiratory tract infection Oropharyngeal surgery Respiratory tract surgery	<5	*S. pneumoniae***[611-615] *Haemophilus* spp
Gastrointestinal infectious diseases Gastrointestinal tumours[616] Gastrointestinal tract therapeutic Interventions[621-622] Gall bladder disease[623] Inflammatory bowel disease[624-627]	10-15	enterococci *S. bovis*[617-620] Gram-negative aerobic bacilli staphylococci
Urosepsis[628]	5-10	enterococci[366,629-631] *S. bovis*[632-635]
Urologic interventions		Gram-negative aerobic bacilli *S. aureus*
Gynaecological infections Gynaecological interventions	1-5	streptococci enterococci
Pacemaker implantation/infection[636,637] (TV)		*S. epidermidis/S. aureus*
Valvular heart surgery		
- early		*S. aureus* *S. epidermidis*
- late		*S. aureus, S.epidermidis* viridans streptococci Any organism
Other		
Dermatological conditions[638-641]		
Wound infections Skin injuries/burns[642,643] Osteomyelitis[644,645] Intravascular catheters***[646-648] Chronic haemodialysis Portosystemic stent shunt[649] IV drug abuse****[650-652]	10-15	*S. aureus* *S. epidermidis* Gram-negative aerobic bacilli Fungi[135,139]
Cardiac surgery Ventriculo-atrial shunt[653]	10	

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. intermedius*)[654-656]
** *S. pneumoniae* is infrequent[657,658]
*** 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,[659-661]
Neisseria meningitidis[662,663]
HACEK Gram-negative bacilli [664-669]
Pseudomonas aeruginosa,[670,671] *mendocina*[672]
Listeria [673-679]
Diptheroids [432]
Spirochaetes [680]
Brucella [153]
Mycoplasma pneumoniae [152,160]
Coxiella burnetii [159]
Chlamydiae [155,681-683]
Bartonella[684]
Salmonella[685-687]
Pasteurella[688,689]
Yersinia[690]
Nocardia[691]
Tropheryma whippelii[692-695]
Lactobacillus[696,697]
Clostridium[698,699]
Legionella[700-702]
Mycobacterium tuberculosis[703]
Rothia dentocariosa[704]
Erysipelothrix rhusiopathiae [705]
Gemella[706,707]
Histoplasma[708]
Serratia[709]
Moraxella[710]
Actinomycosis[711]
Streptomyces[712]
Group B Streptococci[713]

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^{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 (>1.5times 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 3. ANTIBIOTIC PROPHYLAXIS FOR HIGH, MODERATE AND LOW RISK CASES

HIGH RISK

Previous infective endocarditis[275]
Complex cyanotic congenital heart disease, transposition of great arteries, Fallot's tetralogy, Gerbode's defect[276-278]
Surgically constructed systemic pulmonary shunts or conduits
Mitral valve prolapse with mitral regurgitation or thickened valve leaflets] [279-281]
Prosthetic heart valves (5x more than those with native valves)[282,283]

MODERATE RISK

Acquired valvular heart disease eg: rheumatic heart disease – Aortic stenosis, aortic regurgitation, mitral regurgitation
Non-cyanotic congenital cardiac defects eg: bicuspid aortic valve, primum atrial septal defect, patent ductus arteriosus,[284] coarctation of aorta,[286] atrial septal aneurysm/patent foramen ovale,[287] ventricular septal defect,[288]
Other structural cardiac defects eg: aortic root replacement,[285] hypertrophic obstructive cardiomyopathy,[289-291] subaortic membrane[292]

LOW RISK CASES NOT REQUIRING ANTIBIOTIC PROPHYLAXIS

Isolated secundum atrial septal defect ~,[293] pulmonary stenosis
Surgically-repaired atrial septal defect, ventricular septal defect or patent ductus arteriosus, post Fontan or Mustard procedure without residual defect/murmur
Previous coronary artery bypass surgery
Mitral valve prolapse without regurgitation
Innocent heart murmurs@
Cardiac pacemakers/defibrillators*$
Coronary artery stent implantation*
Heart / Heart and Lung Transplant**

] 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 4. DENTAL PROCEDURES AND ENDOCARDITIS ANTIBIOTIC PROPHYLAXIS FOR HIGH AND MODERATE AT-RISK CASES[714,715]

PROPHYLAXIS REQUIRED	PROPHYLAXIS NOT REQUIRED
Examination Procedures	**Examination procedures**
Periodontal probing[716]	Dental examination with mirror and probe[317]
Investigative Procedures	**Investigative Procedures**
Sialography[717]	Intra-oral radiographs
	Extra-oral radiographs
Preventive procedures	**Preventive procedures**
Nil	Fissure Sealants
	Fluoride treatments
Professional Cleaning Procedures*	**Professional Cleaning Procedures**
Polishing teeth with a Rubber Cup[718,719]	Air polishing[765]
Oral irrigation with water jet[296,721]	
Light scaling[722,723]	
Deep scaling[722,723]	
Scaling teeth with hand instrument[719,724]	
Scaling with ultrasonic instrument[724]	
Anaesthetic Procedures	**Anaesthetic Procedures**
Intraligamental local anaesthetic	Infiltration local anaesthetic injections[337]
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[730]	**Comprehensive Dental Treatment under General Anaesthesia**
Extractions and Fillings[731-733]	
Conservative (Restorative) Procedures**	**Conservative (Restorative) Procedures**
Rubber dam placement[734,735]	Slow and fast drilling of teeth (without rubber dam)[734,735]
Matrix band and wedge placement[734,735]	
Gingival retraction cord placement[735]	
Periodontal Procedures	**Periodontal Procedures**
Root planing (similar to scaling)	
Antibiotic fibres or strips placed subgingivally***	
Gingivectomy[722]	
Periodontal Surgery[736]	
Endodontic Procedures$	**Endodontic Procedures**
Root canal instrumentation beyond the apex[722,737]	Root canal instrumentation within the root canal[737]
Avulsed tooth reimplantation*****	Vital Pulpotomy of primary molar[738,739]
Non-vital pulpotomy of primary molar	Pulpotomy of permanent tooth****

Orthodontic Procedures[740]	**Orthodontic Procedures**[740,741]
Tooth separation[315]	Alginate impressions[315]
Expose or expose and bond tooth/teeth[741]	Placement of removable appliances
	Band placement and cementation[315,329,742]
	Band removal[330]
	Adjustment of fixed appliances[315,743]
Surgical Procedures	**Surgical Procedures**
Extraction of single tooth[722,730,741,744,745]	Incision and drainage of an abscess without extraction[746]
Extraction of multiple teeth[722,741,744,747]	Dental implants – transmucosal fixture
Incision and drainage of an abscess with extraction	
Mucoperiosteal flap to gain access to tooth or lesion[741,748]	
Dental implants (as for mucoperiosteal flap)	
Post Surgical Procedures	**Post Surgical Procedures**
	Suture removal[749-751]
	Removal of surgical packs
Daily or physiological events	**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 ie: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.[336]

$ 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]

Opthalmological

- Lacrimal duct probing*[791]

Dermatological

- Surgery*[792,793]

Other

- Thermal injury/burns*[794,795]
- Acupuncture*[796,797]
- Body piercing*[798-800]
- 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 OESOPHAGEAL PROCEDURES IN ADULTS

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

***** 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

Clinical situation	Drug	Regimen
High-risk and moderate risk patients	Ampicillin or amoxicillin	2G IV – <30min preprocedure[a] and 1G IV or orally 6hr post
	+ gentamicin	1.5mg/kg IV <30min preprocedure[a]
If allergic to penicillin[b]	Vancomycin	1G IV over 2hrs, 1-2hrs preprocedure
	+ gentamicin	1.5mg/kg IV <30min preprocedure[a]

[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*

Clinical situation	Drug	Regimen
High-risk and moderate risk patients	Flucloxacillin**	1G IV <30min preprocedure + 500mg orally qds for 2 days
If allergic to penicillin	Vancomycin	1G IV over 2hrs, 1-2 hrs preprocedure + erythromycin 500mg orally qds for 2 days

* 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 *

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

***** 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.[805]

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

Antibiotic	Dose/route	Duration
Benzylpenicillin	7.2G-12G IV daily in 4-6 divided doses	4-6weeks**
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses (max 240mg)	2 weeks^
Benzylpenicillin	7.2G-12G IV daily in 4-6 divided doses	2 weeks[#]
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses (max 240mg)	2 weeks
Teicoplanin[806]	400mg IV bolus 12hrly for first 3 doses then 400mg IV daily~	4 weeks
Ceftriaxone	2G/day IV	4 weeks
For those patients allergic to penicillin		
Vancomycin	30mg/kg IV in 24hrs in 2 divided doses[$] (infused over 2hrs)	4 weeks
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses (max 240mg)	2 weeks

*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

Antibiotic	Dose/route	Duration
Benzylpenicillin	12G-14G IV daily in 4-6 divided doses	4-6 weeks**
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses (max 240mg)	2 weeks**
or		
Teicoplanin~	400mg IV bolus 12hrly for 3 doses then 400mg IV daily	4 weeks**
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses (max 240mg)	2 weeks**
For those patients allergic to penicillin		
Vancomycin#	30mg/kg IV per 24hrs in 2 divided doses (infused over 2 hrs)	4 weeks**
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses (max 240mg)	2 weeks**

***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.[807]
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

Antibiotic	Dose/route	Duration
Penicillin-sensitive (non-B-lactamase producers)		
Benzylpenicillin	12G-14G IV daily in 4-6 divided doses	6 weeks
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses	3-5 days
Methicillin-sensitive staphylococci (B-lactamase producer)		
Flucloxacillin	8G-12G IV daily in 4 divided doses	6 weeks
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses	3-5 days
For those patients allergic to penicillin		
Vancomycin	30mg/kg IV in 24 hours in 2 divided doses (infused over 2 hrs)	6 weeks
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses	3-5 days
Methicillin-resistant staphylococci**		
Vancomycin	30mg/kg IV in 24 hours in 2 divided doses (infused over 2 hrs)	6 weeks
+ Gentamicin*[808]	3-5mg/kg IV daily in 2-3 divided doses	3-5 days

***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[809-811]

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^{R} 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

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

* 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

Gentamicin-sensitive or low-level resistant organism (MIC <500mg/L)

Antibiotic	Dose/route	Duration
Benzylpenicillin	10G-12G IV daily in 4-6 divided doses	4-6 weeks#
or Ampicillin or Amoxicillin	12G IV daily in 4 divided doses	4-6 weeks#
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses (max 240mg/day)	4-6 weeks#
For those patients allergic to penicillin		
Vancomycin**	30mg/kg IV per 24hrs in 2 divided doses (infused over 2 hrs)	4-6 weeks#
+ Gentamicin*	3-5mg/kg IV daily in 2-3 divided doses	4-6 weeks#

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^{R}.

For multiresistant strains, expert advice should be sought from the microbiologist.

TABLE 15. TREATMENT OF ENDOCARDITIS DUE TO GRAM-POSITIVE AND GRAM-NEGATIVE BACILLI*

Organism	Antibiotic	Dose/route	Duration
Listeria	Amoxicillin	12G IV daily in 4 divided doses	6 weeks
*monocytogenes**	+ gentamicin**	3-5mg/kg IV daily in 2-3 divided doses	4-6 weeks
*P. aeruginosa**	Tazocin^{R}^	18G IV daily in 6 divided doses	6 weeks
	or ceftazidime	6G IV daily in 3 divided doses	6 weeks
	or Imipenem	2-4G IV daily in 4 divided doses	6 weeks
	or aztreonam	8GIV daily in 4 divided doses	6 weeks
	+ gentamicin**	3-5mg/kg IV daily in 2-3 divided doses	4-6 weeks
	or tobramycin	8mg/kg IV daily in 4 divided doses	4-6 weeks
*Enterobacteraceae****	Amoxicillin	12G IV daily in 4 divided doses	6 weeks
	or Cefotaxime	8G IV daily in 4 divided doses	6 weeks
	or Imipenem	2-4G IV daily in 4 divided doses	6 weeks
	or Aztreonam	8G IV daily in 4 divided doses	6 weeks
	+ gentamicin**	3-5mg/kg IV daily in 2-3 divided doses	4-6 weeks

* treatment is usually specific and based on results of antibacterial sensitivity testing[812]

** **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

Antibiotic	Dose/route	Duration
Ampicillin or Amoxicillin[$]	12G IV daily in 4 divided doses	4-6 weeks*
+ Gentamicin**	3-5mg/kg IV daily in 2-3 divided doses	2 weeks

$ 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[813]

FUNGI[$]

Antifungal	Dose/route	Duration
Amphotericin B^	1mg/kg IV every 24hrs (total dose 2-2.5G)	6 weeks
+/- Flucytosine*	150-200mg/kg oral per day in 4 divided doses	6 weeks

^ 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.[814] 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.

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

CULTURE-NEGATIVE*

Antibiotic	Dose/route	Duration
Vancomycin	15mg/kg IV every 12hrs	6 weeks
+ Gentamicin**	3-5mg/kg IV daily in 2-3 divided doses	2 weeks

* 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[490,491,514]

Acute AR with tachycardia and early closure of the mitral valve

Fungal endocarditis[494,815-819]

Annular or aortic abscess, true aneurysm of the sinus of valsalva, true or false aneurysm of the aorta[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** -assuming that there are no non-cardiac causes for infection[490,491]

Recurrent emboli after appropriate antibiotic therapy[490,491]

Mobile vegetations >10mm diameter

Early infection of the mitral valve – that can be repaired

Persistent pyrexia and leukocytosis with negative blood cultures[490,491]

Relapse after an adequate course of antibiotics

PROSTHETIC

Early prosthetic valve endocarditis (<2 months)[490,491,495]

Heart failure with prosthetic valve dysfunction

Fungal endocarditis[494,495]

Staphylococcal endocarditis unresponsive to antibiotics[490-493,495]

Paravalvar leak, annular or aortic root abscess[490-493]

Infection with Gram-ve organisms or organisms with a poor response to antibiotics[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

REFERENCES

1. van der Meer JT, Thompson J, Valkenburg HA and Michel MF. Epidemiology of bacterial endocarditis in the Netherlands. 1. Patient Characteristics. Arch Intern Med 1992;152:1863-8.

2. Delahaye F, Goulet V, Lacassin F et al. Epidemiology of infective endocarditis in France in 1991. Arch Mal Coeur 1993;86(Suppl 12):180-6.

3. Horstkotte D, Piper C. Endocarditis. In: Acar J, Bodnar E, eds. Textbook of acquired heart valve disease, vol II. London: ICR Publishers;1995:596-677.

4. Karchmer AW. Infective endocarditis. Braunwald's Heart Disease, 5th ed, vol 2. Philadelphia: WB Saunders;1997:1077-104.

5. Mylonakis E and Calderwood SB. Infective endocarditis in adults. N Engl J Med 2001;345:1318-30.

6. O'Callaghan C and McDougall P. Infective endocarditis in neonates. Arch Dis Child 1988;63:53-7.

7. Lorber A, Luder AS and Dembo L. Acute bacterial endocarditis in early infancy. Int J Cardiol 1987;17:343-5.

8. Fukushige J, Igarashi H and Ueda K. Spectrum of infective endocarditis during infancy and childhood: 20 year review. Pediatr Cardiol 1994;15:127-31.

9. Dommisse J. Infective endocarditis in pregnancy. A report of 3 cases. S Afr Med J 1988;73:186-7.

10. Selton-Suty C, Hoen B, Grentzinger A et al. Clinical and bacteriological characteristics of infective endocarditis in the elderly. Heart 1997;77:260-3.

11. Bouza E, Menasalvas A, Munoz P et al. Infective endocarditis – a prospective study at the end of the twentieth century: new predisposing conditions, new etiologic agents and still a high mortality. Medicine 2001;80:298-307.

12. Schulz R, Werner J, Fuchs B et al. Clinical outcome and echocardiographic findings of native and prosthetic valve endocarditis in the 1990s. Eur Heart J 1996;17:281-8.

13. Netzer ROM, Zollinger E, Seiler C et al. Infective endocarditis: clinical spectrum, presentation and outcome. An analysis of 212 cases 1980-1995. Heart 2000;84:25-30.

14. Piper C, Korfer R and Horstkotte D. Prosthetic valve endocarditis. Heart 2001;85:590-3.

15. Leport C, Horstkotte D, Burckhardt D and the Group of Experts of the International Society for Chemotherapy. Antibiotic prophylaxis for infective endocarditis from an international group of experts towards a European consensus. Eur Heart J 1995;16(Suppl B):126-31.

16. McKinsey DS, Ratts TE and Bisno AL. Underlying cardiac lesions in adults with infective endocarditis: The changing spectrum. Am J Med 1987;82:681-8.

17. Michel PL and Acar J. Native cardiac disease predisposing to infective endocarditis. Eur Heart J 1995;16(Suppl B):2-6.

18. de Gevigney G, Pop C, Delahaye JP. The risk of infective endocarditis after cardiac surgical and interventional procedures. Eur Heart J 1995;16:(Suppl B):7-14.

19. Ferguson DJ, McColm AA, Savage TJ et al. A morphological study of experimental rabbit staphylococcal endocarditis and aortitis. I.Formation and effect of infected and

uninfected vegetations on the aorta. Br J Exp Pathol 1986;67:667-78.

20. Ferguson DJP, McColm AA, Ryan DM and Acred P. A morphological study of experimental staphylococcal endocarditis and aortitis. II. Inter-relationship of bacteria, vegetation and cardiovasculature in established infections. Br J Exp Pathol 1986;67:679 -86.

21. Lopez JA, Ross RS, Fishbein MC and Siegel RJ. Non bacterial thrombotic endocarditis. A review. Am Heart J 1987;113:773-84.

22. Rodbard S. Blood velocity and endocarditis. Circulation 1963; 27:18-25.

23. Livornese IL Jr. and Korzeniowski O. Pathogenesis of infective endocarditis. In Kaye D ed. Infective endocarditis. Second edition. New York: Raven Press. 1992, pp 19-35.

24. Reisberg BE. Infective endocarditis in the narcotic addict. Prog Cardiovasc Dis 1979;22:193-204.

25. Korzeniowski OM and Kaye D. Infective endocarditis. In: Heart Disease – A Textbook of Cardiovascular Medicine, 4th Edition. 1992. Braunwald E.(ed). W.B.Saunders Co., PA,USA. Chapter 35, pp 1078-1105.

26. Bayliss R, Clarke C, Oakley CM, Somerville W, Whitfield AG and Young SE. The microbiology and pathogenesis of infective endocarditis. Br Heart J 1983;50:513-9.

27. Piper C, Horstkotte D, Schulte HD and Schultheib HP. Mitral valve prolapse and infection: a prospective study for risk calculation. Eur Heart J 1996;17:210.

28. Bansal RC et al. Infective endocarditis. Med Clin North Am 1995;79:1205-40.

29. Kaye D. Changing pattern of infective endocarditis. Am J Med 1985;78(Suppl 6B):157-62.

30. Buchbinder NA and Roberts WC. Alcoholism: an important but unemphasised factor predisposing to infective endocarditis. Arch Intern Med 1973;132:689-92.

31. Beales IL and Ledson M. Endocarditis in chronic liver disease. Am J Gastroenterol 1994;89:2279.

32. Kreuzpaintner G, Horstkotte D, Heyll A et al. Increased risk of bacterial endocarditis in inflammatory bowel disease. Am J Med 1992;92:391-5.

33. Cross AS and Steigbigel RJ. Infective endocarditis and access site infections in patients on hemodialysis. Medicine 1976;55:453-66.

34. Dobkin JF, Miller MH and Steigbigel NH. Septicaemia in patients on chronic haemodialysis. Ann Intern Med 1978;88:28-33.

35. Rayfield EJ, Ault MJ, Keusch GT et al. Infection and diabetes: The case for glucose control. Am J Med 1982;72:439-50.

36. Gallagher PG and Watanakunakorn C. Group B streptococcal endocarditis: Report of seven cases and review of the literature, 1962-1985. Rev Infect Dis 1986;8:175-88.

37. Wilkinson NM. Fatal bacterial endocarditis following aortic valve replacement in a patient being treated with methotrexate. J Heart Valve Dis 1999;8:591-2.

38. Hearn CJ and Smedira NG. Pulmonic valve endocarditis after orthotopic liver transplantation. Liver Transpl Surg 1999;5:456-7.

39. Strom BL, Abrutyn E, Berlin JA et al. Risk factors for infective endocarditis: oral hygiene and non-dental exposure. Circulation 2000;102:2842-8.

40. Steckelberg JM and Wilson WR. Risk factors for infective endocarditis. Infect Dis Clin North Am 1993;7:9-19.

41. Bayer AS, Bolger AF, Taubert KA et al. Diagnosis and management of infective endocarditis and its complications. Circulation 1998;98:2936-48.

42. Chambers HF, Korzeniowski OM and Sande MA. Staphylococcus aureus endocarditis: clinical manifestations in addicts and non-addicts. Medicine 1983;62:170-7.

43. Espersen F and Frimodt-Moller N. Staphylococcus aureus endocarditis. A review of 119 cases. Arch Intern Med 1986;146:1118-21.

44. Terpenning MS, Buggy BP and Kauffman CA. Infective endocarditis: clinical features in young and elderly patients. Am J Med 1987;83:626-34.

45. Durack DT. Infective and non-infective endocarditis. In Hurst JW ed. The heart, arteries and veins. 7th edn. New York: McGraw-Hill 1990, pp 1230-55.

46. Ferrieri P, Gewitz MH, Gerber MA et al. Unique features of infective endocarditis in childhood. AHA Scientific Statement. Circulation 2002;105:2115-27.

47. Varma MP, McCluskey DR, Khan MM et al. Heart failure associated with infective endocarditis. A review of 40 cases. Br Heart J 1986;55:191-7.

48. Mills J, Utley J and Abbott J. Heart failure in infective endocarditis: predisposing factors, course and treatment. Chest 1974;66:151-7.

49. Smith RH, Radford DJ, Clark RA and Julian DG. Infectious endocarditis: A survey of cases in the South East region of Scotland between 1969 and 1972. Thorax 1976;31:373-9.

50. Lerner PI and Weinstein L. Infective endocarditis in the antibiotic era. N Engl J Med 1966;274:199-206; 259-66; 388-93.

51. Weinstein L. Life-threatening complications of infective endocarditis and their management. Arch Intern Med 1986;146:953-7.

52. Lam D, Emilson B and Rapaport E. Four-valve endocarditis with associated right ventricular mural vegetations. Am Heart J 1988;115:189-92.

53. James PR, Dawson D and Hardman SM. Eustachian valve endocarditis diagnosed by transoesophageal echocardiography. Heart 1999;81:91.

54. Palakodeti V, Keen WD Jr., Rickman LS and Blanchard DG. Eustachian valve endocarditis: detection with multiplanar transesophageal echocardiography. Clin Cardiol 1997;20:579-80.

55. San Roman JA, Vilacosta I, Sarria C et al. Eustachian valve endocarditis: Is it worth searching for? Am Heart J 2001;142:1037-40.

56. Sawhney N, Palakodeti V, Raisinghani A et al. Eustachian valve endocarditis: a case series and analysis of the literature. J Am Soc Echocardiogr 2001;14:1139-42.

57. Thomas D, Desruennes M, Jault F, Isnard R, Gandjbakhch I. Cardiac and extracardiac abscesses in infective endocarditis. Arch Mal Coeur 1993;86(Suppl 12):1825-37.

58. Arnett EN and Roberts WC. Valve ring abscess in active endocarditis. Frequency, location and clues to clinical diagnosis from the study of 95 necropsy patients. Circulation 1976;54:140-5.

59. Sandler MA, Kotler MN, Bloom RD and Jacobson L. Pericardial abscess extending from mitral vegetation:an unusual complication of infective endocarditis. Am Heart J 1989;118:857-9.

60. Oakley CM. Perivalvular abscesses in infective endocarditis. Eur Heart J 1999;20:170-1.

61. Hwang SW, Yucel EK and Bernard S. Aortic root abscess with fistula formation. Chest 1997;111:1436-8.

62. Piper C, Hetzer R, Korfer F et al. The importance of secondary mitral valve involvement in primary aortic valve endocarditis: The mitral kissing vegetation. Eur Heart J 2002;23:79-86.

63. Vaghjimal A, Lutwick LI, Chapnick EK and Greengart A. Interventricular septal endocarditis. South Med J 1998;91:43-4.

64. Behnam R. Aortico-left atrial fistula in aortic valve endocarditis. Chest 1992;102:1271-3.

65. Anguera I, Quaglio G, Miro JM et al. Aortocardiac fistulas complicating infective endocarditis. Am J Cardiol 2001;87:652-4.

66. Bussani R, Sinagra G, Poletti A et al. Cardiac tamponade: an unusual, fatal complication of infective endocarditis. G Ital Cardiol 1999;29:1512-6.

67. DiNubile MJ, Calderwood SB, Steinhaus DM and Karchmer AW. Cardiac conduction abnormalities complicating native valve active infective endocarditis. Am J Cardiol 1986;58:1213-7.

68. Brogdon BG. Sinus of Valsalva aneurysm secondary to aortic valve endocarditis. Invest Radiol 1988;23:222-3.

69. Charney R, Keltz TN, Attai L et al. Acute valvular obstruction from streptococcal endocarditis. Am Heart J 1993;125:544-7.

70. Bhagwat AR, Patil RB, Loya YS and Sharma S. Subaortic aneurysm in infective endocarditis. Am Heart J 1991;122:588-9.

71. McDonald CL, Crafton EM, Covin FA et al. Pericarditis: a probable complication of endocarditis due to Haemophilus influenzae. Clin Infect Dis 1994;18:648-9.

72. Wilson WR, Giuliani ER, Danielson GK and Geraci JE. Management of complications of infective endocarditis. Mayo Clinic Proc 1982;57:162-70.

73. Perera R, Noack S and Dong W. Acute myocardial infarction due to septic coronary embolism. N Engl J Med 2000;342:977-8.

74. Jeremias A, Casserly I, Estess JM et al. Acute myocardial infarction after aortic valve endocarditis. Am J Med 2001;110:417-8.

75. Anguera I, Quaglio G, Ferrer B et al. Sudden death in Staphylococcus aureus-associated infective endocarditis due to perforation of a free-wall myocardial abscess. Scand J Infect Dis 2001;33:622-5.

76. Shackcloth MJ and Dihmis WC. Contained rupture of a myocardial abscess in the free wall of the left ventricle. Ann Thorac Surg 2001;72:617-9.

77. Ting W, Silverman NA, Arzouman DA and Levitsky S. Splenic septic emboli in endocarditis. Circulation 1990;82(Suppl IV):105-9.

78. Millaire A, Leroy O, Gaday V et al. Incidence and prognosis of embolic events and metastatic infections in infective endocarditis. Eur Heart J 1997;18:677-84.

79. Weinstein L and Rubin RH. Infective endocarditis - 1973. Prog Cardiovasc Dis 1973;16:239-74.

80. Lutwick LI, Gradon JD, Chapnick EK et al. Haemophilus parainfluenzae endocarditis treated with vegetectomy and complicated by late, fatal splenic rupture. Pediatr Infect Dis J 1991;10:778-81.

81. Pringle SD, McCartney AC and Cobbe SM. Spontaneous splenic rupture as complication of infective endocarditis. Int J Cardiol 1988;19:384-6.

82. Heiro M, Nikoskelainen J, Engblom E et al. Neurological manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med 2000;160:2781-7.

83. Salgado AV, Furlan AJ, Keys TF et al. Neurologic complications of endocarditis: a 12 year experience. Neurology 1989;39:173-8.

84. Delahaye JP, Poncet P, Malquarti V et al. Cerebrovascular accidents in infective endocarditis: role of anticoagulation. Eur Heart J 1990;11:1074-8.

85. Weeks SG, Silva C, Auer RN et al. Encephalopathy with staphylococcal endocarditis: multiple neuropathological findings. Can J Neurol Sci 2001;28:260-4.

86. Cabell CH, Pond KK, Peterson GE et al. The risk of stroke and death in patients with aortic and mitral valve endocarditis. Am Heart J 20901;142:75-80.

87. Kelly J and Barnass S. Staphylococcus aureus endocarditis presenting as meningitis and mimicking meningococcal sepsis. Int J Clin Pract 1999;53:306-7.

88. Hubautt JJ, Albat B, Frapier JM and Chaptal PA. Mycotic aneurysm of the extracranial carotid artery: an uncommon complication of bacterial endocarditis. Ann Vasc Surg 1997;11:634-6.

89. Silver SG. Ruptured mycotic aneurysm of the superior mesenteric artery that was due to Cardiobacterium endocarditis. Clin Infect Dis 1999;29:1573-4.

90. Ohebshalom MM, Tash JA, Coll D et al. Massive hematuria due to right renal artery mycotic pseudoaneurysm in a patient with subacute bacterial endocarditis. Urology 2001;58:607.

91. Cakalagaoglu C, Keser N and Alhan C. Brucella-mediated prosthetic valve endocarditis with brachial artery mycotic aneurysm. J Heart Valve Dis 1999;8:586-90.

92. McKee MA and Ballard JC. Mycotic aneurysm of the tibio-peroneal arteries. Ann Vasc Surg 1999;13:188-90.

93. Mann CF and Barker SG. Occluded mycotic popliteal aneurysm secondary to infective endocarditis. Eur J Vasc Endovasc Surg 1999;18:169-70.

94. Safar HA and Cina CS. Ruptured mycotic aneurysm of the popliteal artery. A case report and review of the literature. J Cardiovasc Surg 2001;42:237-40.

95. Jhirad R and Kalman PG. Mycotic axillary artery aneurysm. J Vasc Surg 1998;28:708-9.

96. WilsonWR, Lie JT, Houser OW et al. The management of patients with mycotic aneurysms. Curr Clin Top Infect Dis 1981;2:151.

97. Mansur AJ, Grinberg M, Leao PP et al. Extracranial mycotic aneurysms in infective endocarditis. Clin Cardiol 1986;9:65-72.

98. Reece IJ, al Tareif H, Tolia J and Saeed FA. Mycotic aneurysm of the left anterior descending coronary artery after aortic endocarditis. A case report and brief review of the literature. Tex Heart Inst J 1994;21:231-5.

99. Krapf H, Skalej M and Voight K. Subarachnoid hemorrhage due to septic embolic infarction in infective endocarditis. Cerebrovasc Dis 1999;9:182-4.

100. Bohmfalk GL, Story JL, Wissinger JP and Brown WE Jr. Bacterial intracranial aneurysm. J Neurosurg 1978;48:369-82.

101. Roach MR and Drake CG. Ruptured cerebral aneurysms caused by microorganisms. N Engl J Med 1965;273:240-4.

102. Cosmo LY, Risi G, Nelson S et al. Fatal hemoptysis in acute bacterial endocarditis. Am Rev Respir Dis 1988;137:1223-6.

103. Camarata PJ, Latchaw RE, Rufenacht DA and Heros RC. Intracranial aneurysms. Invest Radiol 1993;28:373-82.

104. Lerner P. Neurologic complications of infective endocarditis. Med Clin North Am 1985;69:385-98.

105. Clare CE and Barrow DL. Infectious intracranial aneurysms. Neurosurg Clin N Am 1992;3:551-566.

106. Huston J III, Nichols DA, Luetmer PH et al. Blinded prospective evaluation of sensitivity of MR angiography to known intracranial aneurysms: importance of aneurysm size. Am J Neuroradiol 1994;15:1607-14.

107. McKinsey DS, McMurray TI and Flynn JM. Immune complex glomerulonephritis associated with Staphylococcus aureus bacteremia: response to corticosteroid therapy. Rev Infect Dis 1990;12:125-7.

108. Eknoyan G, Lister BJ, Kim HS and Greenberg SD. Renal complications of bacterial endocarditis. Am J Nephrol 1985;5:457-69.

109. Weinstein L and Schlesinger JJ. Pathoanatomic, pathophysiologic and clinical correlations in endocarditis. N Engl J Med 1974;291:832-7.

110. Roberts-Thomson PJ, Rischmueller M, Kwiatek RA et al. Rheumatic manifestations of infective endocarditis. Rheumatol Int 1992;12:61-3.

111. Churchill MA Jr., Geraci JE and Hunder GG. Musculoskeletal manifestations of bacterial endocarditis. Ann Intern Med 1977;87:754-9.

112. Yee J and McAllister CK. The utility of Osler's nodes in the diagnosis of infective endocarditis. Chest 1987;92:751-2.

113. Watanakunakorn C. Osler's nodes on the dorsum of the foot. Chest 1988;94:1088-90.

114. Alpert JS, Krous HF, Dalen JE et al. Pathogenesis of Osler's nodes. Ann Intern Med 1976;85:471-3.

115. Barham NJ, Flint EJ and Mifsud RP. Osteomyelitis complicating Streptococcus milleri endocarditis. Postgrad Med J 1990;66:314-5.

116. Pruitt AA, Rubin RH, Karchmer AW and Duncan GW.Neurologic complications of bacterial endocarditis. Medicine 1978;57:329-43.

117. Robbins MJ, Soeiro R, Frishman WH and Strom JA. Right-sided valvular endocarditis: etiology, diagnosis and an approach to therapy. Am Heart J 1986;111:128-35.

118. Cassling RS, Rogler WC and McManus BM. Isolated pulmonic valve infective endocarditis: a diagnostically elusive entity. Am Heart J 1985;109:558-67.

119. Dressler FA and Roberts WC. Infective endocarditis in opiate addicts: analysis of 80 cases studied at necropsy. Am J Cardiol 1989;63:1240-57.

120. Sexauer WP, Quezado Z, Lippmann ML and Goldberg SK. Pleural effusions in right-sided endocarditis: characteristics and pathophysiology. South Med J 1992;85:1176-80.

121. Federmann M, Dirsch OR and Jenni R. Pacemaker endocarditis. Heart 1996;75:446.

122. Tang DC and Huang TP. Internal jugular vein haemodialysis catheter-induced right atrial endocarditis – case report and review of literature. Scand J Urol Nephrol 1998;32:411-4.

123. Hecht SR and Berger M. Right sided endocarditis in intravenous drug users. Ann Intern Med 1992;117:560-6.

124. Chambers HF, Morris DL, Tauber MG and Modin G. Cocaine use and the risk for endocarditis in intravenous drug users. Ann Intern Med 1987;106:833-6.

125. Cacoub P, Leprince P, Nataf P et al. Pacemaker infective endocarditis. Am J Cardiol 1998;82:480-4.

126. Miralles A, Moncada V, Chevez H et al. Pacemaker endocarditis: approach for lead extraction in endocarditis with large vegetations. Ann Thorac Surg 2001;72:2130-2.

127. Chu JJ, Lin PT, Chang CH et al. Video-assisted endoscopic removal of infected pacemaker lead with large floating vegetations. Pacing Clin Electrophysiol 1999;22:1700-3.

128. Arvay A and Lengyel M. Incidence and risk factors of prosthetic valve endocarditis. Eur J Cardiothoracic Surg 1988;2:340-6.

129. Bortolotti U, Thiene G, Milano A et al. Pathological study of infective endocarditis on Hancock porcine bioprostheses. J Thorac Cardiovasc Surg 1981;81:934-42.

130. Horstkotte D, Korfer R, Loogen F et al. Prosthetic valve endocarditis: clinical findings and management. Eur Heart J 1984;5(Suppl C):117-22.

131. Chastre J and Trouillet JL. Early infective endocarditis in prosthetic valves. Eur Heart J 1995;16(Suppl B):32-8.

132. John MD, Hibberd PL, Marchmer AS et al. Staphylococcus aureus prosthetic valve endocarditis: optimal management and risk factors for death. Clin Infect Dis 1998;26:1302-9.

133. Braunwald E. Infective endocarditis, Chapter 35. In “Heart Disease. A textbook of cardiovascular medicine, 4th edition. WB Saunders Co, 1992. pp 1082.

134. Horstkotte D, Piper C, Niehues R et al. Late prosthetic valve endocarditis. Eur Heart J 1995;16(Suppl B):39-47.

135. Rubinstein E and Lang R. Fungal endocarditis. Eur Heart J 1995;16(Suppl B):84-9.

136. Moyer DV, Edwards Jr. JE. Fungal endocarditis. In:Kaye D. ed. Infective endocarditis, 2nd edn. New York: Raven Press, 1992:299-312.

137. Kammer RB, Utz JP. Aspergillus species endocarditis: the face of a not so rare disease. Am J Med 1974;56:506-21.

138. Seelig MS, Speth CP, Kozinn PJ et al. Patterns of Candida endocarditis following cardiac surgery: importance of early diagnosis and therapy (an analysis of 91 cases). Prog Cardiovasc Dis 1974;17:125-60.

139. Rubinstein E, Noriega ER, Simberkoff MS, Holzman R, Rahal Jr. JJ. Fungal endocarditis: analysis of 24 cases and review of the literature. Medicine 1975;54:331-44.

140. Microbiology Resource Committee, College of American Pathologists. Memorandum to CAP Mycology Survey participants re 1987 Survey set F-B. Traverse City, Michigan 1987.

141. Paya CV, Roberts GD, Cockerill RF. Laboratory methods for the diagnosis of disseminated histoplasmosis. Mayo Clinic Proc 1987;62:480-5.

142. Bisbe J, Miro JM, Torres JM et al. Diagnostic value of serum antibody and antigen detection in heroin addicts with systemic candidiasis. Rev Inf Dis 1989;11:310-5.

143. Weiner MH. Antigenaemia detected by radioimmunoassay in systemic aspergillosis. Ann Int Med 1980;92:793-6.

144. Donal E, Abgueguen P, Coisne D et al. Echocardiographic features of Candida species endocarditis: 12 cases and a review of published reports. Heart 2001;86:179-82.

145. Lengyel M. The impact of transesophageal echocardiography on the management of prosthetic valve endocarditis: experience of 31 cases and review of the literature. J Heart Valve Dis 1997;6:204-11.

146. Walsh TJ, Hutchins GM, Bulkley BH et al. Fungal infections of the heart: analysis of 51 autopsy cases. Am J Cardiol 1980;45:357-66.

147. Andriole VT, Kravetz HM, Roberts WC et al. Candida endocarditis. Am J Med 1962;32:251-85.

148. Gregg CR, McGee ZA, Bodner SJ et al. Fungal endocarditis complicating treatment of prosthetic valve bacterial endocarditis:value of prophylactic oral nystatin. South Med J 1987;80:1407-9.

149. Oakley CM. The medical treatment of culture-negative infective endocarditis. Eur Heart J 1995;16(Suppl B):90-3.

150. Brouqui P and Raoult D. Endocarditis due to rare and fastidious bacteria. Clin Microbiol Rev 2001;14:177-207.

151. Rolain JM, Maurin M and Raoult D. Bactericidal effect of antibiotics on Bartonella and Brucella spp.: clinical complications. J Antimicrob Chemother 2000;46:811-4.

152. Popat K, Barnardo D and Webb-Peploe M. Mycoplasma pneumoniae endocarditis. Br Heart J 1980;44:111-2.

153. Al-Kasab S, al-Fagih MR, al-Yousef S et al. Brucella infective endocarditis. Successful combined medical and surgical therapy. J Thorac Cardiovasc Surg 1988;95:862-7.

154. Shafer RW and Braverman ER. Q-fever endocarditis: delay in diagnosis due to an apparent clinical response to corticosteroids. Am J Med 1989;86:729.

155. Jones RB, Priest JB and Kuo C. Subacute chlamydial endocarditis. JAMA 1982;247:655-8.

156. Fernandez-Guerrero ML, Muelas JM, Aguado JM et al. Q-fever endocarditis on porcine bioprosthetic valves. Clinicopathologic features and microbiologic findings in three patients with doxycycline, cotrimoxazole and valve replacement. Ann Intern Med 1988;108;209-13.

157. Brearley BF and Hutchinson DN. Endocarditis associated with Chlamydia trachomatis infection. Br Heart J 1981;46:220-1.

158. Noseda A, Liesnard C, Goffin Y and Thys JP. Q-fever endocarditis: relapse 5 years after successful valve replacement for a first unrecognized episode. J Cardiovasc Surg 1988;29:360-3.

159. Stein A and Raoult D. Q fever endocarditis. Eur Heart J 1985;16(Suppl B):19-23.

160. Cohen JI, Sloss LJ, Kundsin R and Golightly L. Prosthetic valve endocarditis caused by Mycoplasma hominis. Am J Med 1989;86:819-21.

161. Demiricin M, Dogan R, Peker O et al. Aortic insufficiency and enterococcal endocarditis complicating systemic lupus erythematosus. Thorac Cardiovasc Surg 1995;43:302-4.

162. Houpikian P, Habib G, Mesana T and Raoult D. Changing clinical presentation of Q fever endocarditis.Clin Infect Dis 2000;34:E 28-31.

163. Musso D and Raoult D. Coxiella burnetii blood cultures from acute and chronic Q-fever patients. J Clin Microbiol 1995;33:3129-32.

164. Akinci E, Gol MK and Balbay Y. A case of prosthetic mitral valve endocarditis caused by Brucella abortus. Scand Infect Dis 2001;33:71-2.

165. Raoult D, Urvolgyi J, Etienne J et al. Diagnosis of endocarditis in acute Q-fever by immunofluorescence serology. Acta Virol 1988;32:70-4.

166. Muhlemann K, Matter L, Meyer B et al. Isolation of Coxiella burnetti from heart valves of patients treated for Q-fever endocarditis. J Clin Microbiol 1995;33:428-31.

167. Siegman-Igra Y, Kaufman O, Kaysary A et al. Q-fever endocarditis in Israel and a worldwide review. Scand J Infect Dis 1997;29:41-9.

168. Nikkari S, Gotoff R, Bourbeau PP et al. Identification of Cardiobacterium hominis by broad-range bacterial polymerase chain reaction analysis in a case of culture-negative endocarditis. Arch Intern Med 2002;162:477-9.

169. Lisby G, Gutschik E, Durack DT. Molecular methods for diagnosis of infective endocarditis. Infect Dis Clin North Am 2002;16:393-412.

170. McCartney AC, Orange GV, Pringle SD et al. Serum C reactive protein in infective endocarditis. J Clin Pathol 1988;41:44-8.

171. Hogevik H, Olaison L, Andersson R and Alestig K. C-reactive protein is more sensitive than erythrocyte sedimentation rate for diagnosis of infective endocarditis. Infection 1997;25:82-5.

172. Olaison L, Hogevik H and Alestig K. Fever, C-reactive protein, and other acute-phase reactants during treatment of infective endocarditis. Arch Intern Med 1997;157:885-92.

173. Lamas CC and Eykyn SJ. Suggested modifications to the Duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. Clin Inf Dis 1997;25:713-9.

174. Powers DL and Mandell GL. Intraleukocytic bacteria in endocarditis patients. JAMA 1974;227:312-3.

175. Williams RC. Rheumatoid factors in subacute bacterial endocarditis and other infectious diseases. Scand J Rheumatol Suppl 1988;75:300-8.

176. Asherson RA, Tikly M, Staub H et al. Infective endocarditis, rheumatoid factor and cardiolipin antibodies. Ann Rheum Dis 1990;49:107-8.

177. Durack D, Lukes A, Bright D. The Duke Endocarditis Service. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 1994;96:200-9.

178. Roggenkamp A, Leitritz L, Baus K, Falsen E and Heesemann J. PCR for detection and identification of Abiotrophia spp. J Clin Microbiol 1998;36:2844-6.

179. Goldenberger D, Kunzli A, Vogt P, Zbinden R and Altwegg M. Molecular diagnosis of bacterial endocarditis by broad-range PCR amplification and direct sequencing. J Clin Microbiol 1997;35:2733-9.

180. Qin X and Urdahl KB. PCR and sequencing of independent genetic targets for the diagnosis of culture negative bacterial endocarditis. Diagn Miucrobiol Infect Dis 2001;40:145-9.

181. Wilck MB, Wu Y, Howe JG et al. Endocarditis caused by culture-negative organisms visible by Brown and Brenn staining: utility of PCR and DNA sequencing for diagnosis. J Clin Microbiol 2001;39:2025-7.

182. Watkin RW, Lang S, Lambert PA, Littler WA and Elliott TSJ. The microbial diagnosis of infective endocarditis. J Infect 2003;(in press)

183. Washington JA II. The role of the microbiology laboratory in the diagnosis and antimicrobial treatment of infective endocarditis. Mayo Clin Proc 1982;57:22-32.

184. Washington JA II. The microbiological diagnosis of infective endocarditis. J Antimicrob Chemother 1987;20:29-39.

185. Werner AS, Cobbs CG, Kaye D and Hook EW. Studies on the bacteremia of bacterial endocarditis. JAMA 1967;202:199-203.

186. Weinstein M, Reller L, Murphy J, Lichenstein K. Clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteraemia and fungemia in adults. I. Laboratory and epidemiologic observations. Rev Infect Dis 1983;5:35-53.

187. Belli J and Waisbren BA. The number of blood cultures necessary to diagnose most cases of bacterial endocarditis. Am J Med Sci 1956;232:284-8.

188. Weinstein M, Reller L, Murphy J, Lichenstein K. Clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteraemia and fungemia in adults. I. Clinical observations, with special reference to factors influencing prognosis. Rev Infect Dis 1983;5:54-70.

189. Barnes PD and Crook DWM. Culture negative endocarditis. J Infect 1997;35:209-13.

190. Pesanti EL and Smith IM. Infective endocarditis with negative blood cultures. An analysis of 52 cases. Am J Med 1979;66:43-50.

191. Van Scoy RE. Culture-negative endocarditis. Mayo Clin Proc 1982;57:149-54.

192. Pazin GJ, Saul S and Thompson ME. Blood culture positivity: Suppression by outpatient antibiotic therapy in patients with bacterial endocarditis. Arch Intern Med 1982;142;263-8.

193. Hoen B, Selton-Suty C, Lacassin F et al. Infective endocarditis in patients with negative blood cultures:analysis of 88 cases from a one-year nationwide survey in France. Clin Infect Dis 1995;20:501-6.

194. Mallen MS, Hube EL and Brenes M. Comparative study of blood cultures made from artery, vein and bone marrowin patients with subacute bacterial endocarditis. Am Heart J 1946; :692-5.

195. Geraci JE and Wilson WR. Endocarditis due to gram-negative bacteria: report of 56 cases. Mayo Clin Proc 1982;57:145-8.

196. Chen YC, Chang SC, Luh KT and Hsieh WC. Actinobacillus actinomycetemcomitans endocarditis: a report of four cases and review of literature. Q J Med 1992;81:871-8.

197. Drancourt M, Birtles R, Chaumentin G et al. New serotype of Bartonella henselae in endocarditis and cat-scratch disease. Lancet 1996;347:441-3.

198. Doern GV, Davaro R, George M and Campognone G et al. Lack of requirement for prolonged incubation of Septi-Chek blood culture bottles in patients with bacteremia due to fastidious bacteria. Diagn Microbiol Infect Dis 1996;24:141-3.

199. Raoult D, Fournier PE, Drancourt M et al. Diagnosis of 22 new cases of Bartonella endocarditis. Ann Intern Med 1996;125:646-52.

200. Editorial. Vegetations, valves and echocardiography. Lancet 1988;2:1118-9.

201. Buda AJ, Zotz RJ, Le Mire MS and Bach DS. Prognostic significance of vegetations detected by two-dimensional echocardiography in infective endocarditis. Am Heart J 1986;112;1291-6.

202. Erbel R, Rohmann S, Drexler M et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach. A prospective study. Eur Heart J 1988;9:43-53.

203. Mugge A, Daniel WG, Franck G and Lichtlen PR. Echocardiography in infective endocarditis: Reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol 1989;14:631-8.

204. Schwinger ME, Tunick PA, Freedberg RS and Kronzon I. Vegetations on endocardial surfaces struck by regurgitant jets: Diagnosis by transesophageal echocardiography. Am Heart J 1990;119:1212-5.

205. Taams MA, Gussenhoven EJ, Bos E et al. Enhanced morphological diagnosis in infective endocarditis by transoesophageal echocardiography. Br Heart J 1990;63:109-13.

206. Steckelberg JM, Murphy JG, Ballard D et al. Emboli in infective endocarditis: The prognostic value of echocardiography. Ann Intern Med 1991;114:635-40.

207. Birmingham GD, Rahko PS and Ballantyne F 3rd et al. Improved detection of infective endocarditis with transesophageal echocardiography. Am Heart J 1992;123:774-81.

208. Gilbert BW, Haney RS, Crawford F et al. Two-dimensional echocardiographic assessment of vegetative endocarditis. Circulation 1977;55:346-53.

209. Plehn JF. The evolving role of echocardiography in management of bacterial endocarditis. Chest 1988;94:904-6.

210. Stewart JA, Silimperi D, Harris P et al. Echocardiographic documentation of vegetative lesions in infective endocarditis: clinical implications. Circulation 1980;61:374-80.

211. Irani WN, Grayburn PA and Alfredi I. A negative transthoracic echocardiogram obviates the need for transesophageal echocardiography in patients with suspected native valve active infective endocarditis. Am J Cardiol 1996;78:101-3.

212. Nihoyannopoulos P, Oakley CM, Exadactylos N, Ribeiro P, Westaby and Foale RA. Duration of symptoms and the effects of a more aggressive surgical policy: two factors affecting prognosis of infective endocarditis. Eur Heart J 1985;6:380-90.

213. Kupferwasser LI, Darius H, Muller AM et al. Diagnosis of culture-negative endocarditis: the role of the Duke criteria and the inpact of Transesophageal echocardiography. Am Heart J 2001;142:146-52.

214. Tingleff J, Egeblad H, Gotzsche CO et al. Perivalvular cavities in endocarditis: abscesses versus pseudoaneurysms? A transesophageal Doppler echocardiographic study in 118 patients with endocarditis. Am Heart J 1995;130:93-100.

215. Tunick PA, Freedberg RS, Schrem SS and Kronzon I. Unusual mitral annular vegetation diagnosed by transesophageal echocardiography. Am Heart J 1990;120:444-6.

216. Jaffe WM, Morgan DE, Pearlman AS and Otto CM. Infective endocarditis. 1983-1988: echocardiographic findings and factors influencing morbidity and mortality. J Am Coll Cardiol 1990;15:1227-33.

217. Martin RP. The diagnostic and prognostic role of cardiovascular ultrasound in endocarditis: bigger is not better. J Am Coll Cardiol 1990;15:1234-7.

218. Rohmann S, Erbel R, Gorge G et al. Clinical relevance of vegetation localization by transoesophageal echocardiography in infective endocarditis. Eur Heart J 1992;12:446-52.

219. Shapiro SM and Bayer AS. Transesophageal and Doppler echocardiography in the diagnosis and management of infective endocarditis. Chest 1991;100:1125-30.

220. Pedersen WR, Walker M, Olson JD et al. Value of transesophageal echocardiography as an adjunct to transthoracic echocardiography in evaluation of native and prosthetic valve endocarditis. Chest 1991;100:351-6.

221. Daniel W, Mugge A, Martin R, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med 1991;324:795-800.

222. Job FP, Gronke S, Lethen H et al. Incremental value of biplane and multiplane transesophageal echocardiography for the assessment of active infective endocarditis. Am J Cardiol 1995;75:1033-37.

223. Lowry RW, Zoghbi WA, Baker WB et al. Clinical impact of transesophageal echocardiography in the diagnosis and management of infective endocarditis. Am J Cardiol 1994;73:1089-91.

224. Culver DL, Cacchione J, Stern D et al. Diagnosis of infective endocarditis on a Starr-Edwards prosthesis by transesophageal echocardiography. Am Heart J 1990;119:972-3.

225. Shapiro S, Young E, De Guzman S et al. Transesophageal echocardiography in diagnosis of infective endocarditis Chest 1994;105:377-82.

226. Leung D, Cranney G, Hopkins A, Walsh W. Role of transesophageal echocardiography in the diagnosis and management of aortic root abscess. Br Heart J 1994;72:175-81.

227. Rohmann S, Erbel R, Mohr-Kahaly S and Meyer J. Use of transoesophageal echocardiography in the diagnosis of abscess in infective endocarditis. Eur Heart J 1995;16(Suppl B):54-62.

228. Vered Z, Mossinson D, Peleg E et al. Echocardiographic Assessment of prosthetic valve endocarditis. Eur Heart J 1995;16(Suppl B):63-7.

229. Mukhtari O, Horton CJ Jr., Nanda NC et al. Transesophageal color Doppler three-dimensional echocardiographic detection of prosthetic aortic valve dehiscence: correlation with surgical findings. Echocardiography 2001;18:393-7.

230. Martin RP, French JW and Popp RL. Clinical utility of two-dimensional echocardiography in patients with bioprosthetic valves. Adv Cardiol 1980;27:294-304.

231. Shapiro S and Kupferwasser LI. Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol 2001;37:1077-9.

232. Di Salvo G, Habib G, Pergola V et al. Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol 2001;37:1069-76.

233. Heinle S, Wilderman N, Harrison JK et al. Value of transthoracic echocardiography in predicting embolic events in active endocarditis. Duke Endocarditis Service. Am J Cardiol 1994;74:799-801.

234. Ward C. Cardiac Catheterisation in patients with infective endocarditis. J R Coll Physicians Lond 1997;31:341-2.

235. von Reyn C, Levy B, Arbeit R, Friedland G, Crumpacker C. Infective endocarditis: an analysis based on strict case definitions. Ann Intern Med 1981;94:505-18.

236. Heiro M, Nikoskelainen J, Hartiala JJ et al. Diagnosis of infective endocarditis. Sensitivity of the Duke vs von Reyn criteria. Arch Intern Med 1998;158:18-24.

237. Habib G, Derumeaux G, Avierinos JF et al. Value and limitations of the Duke criteria for the diagnosis of infective endocarditis. J Am Coll Cardiol 1999;33:2023-9.

238. Muhlestein JB. Infective endocarditis: how well are we managing our patients? J Am Coll Cardiol 1999;33:794-5.

239. Delahaye F, Rial MO, de Gevigney G et al. A critical appraisal of the quality of the management of infective endocarditis. J Am Coll Cardiol 1999;33:788-93.

240. Hoen B, Beguinot I, Raboud C et al. The Duke criteria for diagnosing infective endocarditis are specific: analysis of 100 patients with acute fever or fever of unknown origin. Clin Infect Dis 1996;23:298-302.

241. Cecchi E, Parrini I, Chinaglia A et al. New diagnostic criteria for infective endocarditis. A study of sensitivity and specificity. Eur Heart J 1997;18:1149-56.

242. Olaison L and Hogevik H. Comparison of the von Reyn and Duke criteria for the diagnosis of infective endocarditis: a critical analysis of 161 episodes. Scand J Infect Dis 1996;28:399-406.

243. Dodds GA, Sexton DJ, Durack DT et al. Negative predictive value of the Duke criteria for infective endocarditis. Am J Cardiol 1996;77:403-7.

244. Rognon R and Kehtari R. Individual value of each of the Duke criteria for the diagnosis of infective endocarditis. Clin Microbiol Infect 1999;5:396-403.

245. Fournier PE, Casalta JP, Habib G et al. Modification of the diagnostic criteria proposed by the Duke Endocarditis Service to permit improved diagnosis of Q fever endocarditis. Am J Med 1996;100:629-33.

246. Lamas CC and Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. Heart 2003;89:258-62.

247. Hoen B, Selton-Suty C, Danchin N et al. Evaluation of the Duke criteria versus the Beth Israel criteria for the diagnosis of infective endocarditis. Clin Infect Dis 1995;21:905-9.

248. Naber CK, Bartel T, Eggebrecht H et al. Diagnosis of endocarditis today: Duke criteria or clinical judgement? Herz 2001;26:379-90.

249. Millar BC, Moore JE, Mallon P et al. Molecular diagnosis of infective endocarditis – a new Duke's criterion. Scand J Infect Dis 2001;33:673-80.

250. Grijalva M, Horvath R, Dendis M et al. Molecular diagnosis of culture-negative infective endocarditis: clinical validation in a group of surgically treated patients. Heart 2003;89:263-8.

251. Li JS, Sexton DJ, Mick N et al. Proposed modifications to the Duke's criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.

252. Horstkotte D, Rosin H, Friedrichs W and Loogen F. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J 1987;8(Suppl J):379-81.

253. Imperpale T, Horwitz T. Does prophylaxis prevent post-dental infective endocarditis? A controlled evaluation of predictive efficacy. Am J Med 1990;88:131-6.

254. van de Meer J, van Wijk W, Thompson J et al. Efficacy of antibiotic prophylaxis for prevention of native valve endocarditis. Lancet 1992;339:135-9.

255. Durack D. Prevention of infective endocarditis. N Engl J Med 1995;332:38-44.

256. Simmons NA. Recommendations for endocarditis prophylaxis. The Endocarditis Working Party for Antimicrobial Chemotherapy. J Antimicrob Chemother 1993;31:437-8.

257. Dajani A, Taubert K, Wilson W et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. Circulation 1997;96:358-66.

258. Simmons NA, Ball AP, Cawson RA et al. Antibiotic prophylaxis and infective endocarditis. Lancet 1992;339:1292-3.

259. Editorial. Chemoprophylaxis for infective endocarditis: faith, hope and charity challenged. Lancet 1992;339:525-6.

260. Taran LM. Rheumatic fever in its relation to dental disease. NYJ Dent 1944;14:107-113.

261. Blatter M and Franciolo P. Endocarditis prophylaxis:from experimental models to human recommendation. Eur Heart J 1995;16(Suppl B):107-9.

262. Durack DT and Petersdorf RG. Chemotherapy of experimental streptococcal endocarditis I: Comparison of commonly recommended prophylactic regimens. J Clin Invest 1973;52:592-8.

263. Glauser PM, Bernard JP, Morcillon P and Franciolo P. Successful single dose amoxycillin prophylaxis against experimental streptococcal endocarditis: evidence of two mechanisms of protection. J Infect Dis 1983;147:568-75.

264. Malinverni R, Overholsen CD, Bille J and Glauser MP. Antibiotic prophylaxis of experimental endocarditis after dental extraction. Circulation 1988;77:182-7.

265. Strom BL, Abrutyn E, Berlin JA et al. Dental and cardiac risk factors for infective endocarditis. Ann Intern Med 1998;129:761-9.

266. Seymour RA, Lowry R, Whitworth JM et al. Infective endocarditis, dentistry and antibiotic prophylaxis; time for a rethink? Br Dent J 2000;189:610-6.

267. Durack DT, Kaplan EL and Bisno AL. Apparent failures of endocarditis prophylaxis. Analysis of 52 cases submitted to a national registry. J Am Med Assoc 1983;250:2318-22.

268. Roberts GJ. Dentists are innocent! Everyday bacteraemia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. Pediatr Cardiol 1999;20:317-25.

269. Fleming P, Feigal RJ, Kaplan EL et al. The development of penicillin-resistant oral streptococci after repeated penicillin prophylaxis. Oral Surgery 1990;70:440-4.

270. Leviner E, Tzukert A, Benoliel R et al. Development of resistant oral viridans streptococci after administration of prophylactic antibiotics:time management in the dental treatment of patients susceptible to infective endocarditis. Oral Surgery, Oral Medicine and Oral Pathology 1987;64:417-420.

271. Longman LP, Pearce PK, McGowan P et al. Antibiotic resistant oral streptococci in dental patients susceptible to infective endocarditis. J Med Microbiol 1991;34:33-7.

272. Delahaye F and De Gevigney G. Should we give antibiotic prophylaxis against infective endocarditis in all cardiac patients, whatever the type of dental treatment? Heart 2001;85:9-10.

273. Cetta F and Warnes CA. Adults with congenital heart disease: patient knowledge of endocarditis prophylaxis. Mayo Clin Proc 1995; 70:50-4.

274. Buckingham JK, Gould IM, Tervitt G and Williams S. Prevention of endocarditis: communication between doctors and dentists. Br Dent J 1992;172:414-5.

275. Lossos IS and Oren R. Recurrent infective endocarditis. Postgrad Med J 1993;69:816-8.

276. Noreuil TO, Katholi RE and Graham DR. Recurrent bacterial endocarditis in a man with tetralogy of Fallot: earliest recurrence on record. South Med J 1990;83:455-7.

277. Li W and Somerville J. Infective endocarditis in the grown-up congenital heart (GUCH) population. Eur Heart J 1998;19:166-73.

278. Michel C, Rabinovitch MA and Huynh T. Gerbode's defect associated with acute sinus node dysfunction as a complication of infective endocarditis. Heart 1996;76:379.

279. Bisno AL. Mitral valve prolapse and infective endocarditis. Arch Intern Med 1993;153;1506.

280. Carabello BA. Mitral valve disease. Curr Probl Cardiol 1993;7:423-78.

281. Cheng TO. Should antibiotic prophylaxis be recommended for all patients with mitral valve prolapse? Am J Cardiol 1991;68:564.

282. Calderwood SB, Swinski LA, Watermaux CM et al. Risk factors for the development of prosthetic valve endocarditis. Circulation 1985;72:31-7.

283. Leport C, Vilde JL, Bricaire F et al. 50 cases of late prosthetic valve endocarditis: improvement in prognosis over a 15 year period. Br Heart J 1987;53:66-71.

284. Mandel KE and Ginsburg CM. Staphylococcal endocarditis complicating a patent ductus arteriosus. Pediatr Infect Dis J 1994;13:833-4.

285. Ralph-Edwards A, David TE and Bos J. Infective endocarditis in patients who had replacement of the aortic root. Ann Thorac Surg 1994;58:429-32.

286. D'Costa DF and Davidson AR. Coarctation of the aorta associated with a sinus venosus atrial septal defect presenting with endocarditis in middle age. Postgrad Med J 1990;66:951-2.

287. Sommer R, Dussoix P, Anwar A and Garbino J. Unusual association: Streptococcus bovis tricuspid endocarditis with atrial septal aneurysm and patent foramen ovale. Schweiz Med Wochenschr 2000;130:395-7.

288. Villa E, Mohammedi I, Dupperret S et al. Community-acquired methicillin-resistant Staphylococcus aureus right-sided infective endocarditis in a non-addict patient with ventricular septal defect. Intensive Care Med 1999;25:236-7.

289. Spirito P, Rapezzi C, Bellone P et al. Infective endocarditis in hypertrophic cardiomyopathy: prevalence, incidence and indications for antibiotic prophylaxis. Circulation 1999;99:2132-7.

290. Stulz P, Zimmerli W, Mihatsch J and Gradel E. Recurrent infective endocarditis in idiopathic hypertrophic subaortic stenosis. Thorac Cardiovasc Surg 1989;37:99-102.

291. Alessandri N, Pannarale G, del Monte F et al. Hypertrophic obstructive cardiomyopathy and infective endocarditis: a report of seven cases and a review of the literature. Eur Heart J 1990;11:1041-8.

292. Pentousis D, Cooper JP and Rae AP. Bacterial endocarditis involving a subaortic membrane. Heart 1996;76:370-1.

293. Rahman A, Burma O, Felek S and Yekeler H. Atrial septal defect presenting with Brucella endocarditis. Scand J Infect Dis 2001;33:776-7.

294. Everett ED and Hirschmann JV. Transient bacteremia and endocarditis prophylaxis. A review. Medicine 1977;56:61-77.

295. Cobe HM. Transitory bacteraemia. Oral Surg 1954;7:609-15.

296. Berger SA, Weitzman S and Edberg SC. Bacteraemia after using an oral irrigation device. Ann Intern Med 1974;80:510-1.

297. Meneely JK. Bacterial endocarditis following urethral manipulation. N Engl J Med 1948;239:708-9.

298. Brenman HS and Randall E. Local degerming with povidone-iodine. J Periodontol 1974;45:870-2.

299. Gunteroth WG. How important are dental procedures as a cause of infective endocarditis? Am J Cardiol 1984;130:715-8.

300. Delaye J, Etienne J, Feruglio GA et al. Prophylaxis of infective endocarditis for dental procedures. Report of a working party of the European Society of Cardiology. Eur Heart J 1985;6:826-8.

301. Slade N. Bacteraemia and septicaemia after urological operations. Proc Roy Soc Med 1958;51:331-4.

302. Sullivan NM, Sutter VL, Mims MM et al. Clinical aspects of bacteremia after manipulation of the genitourinary tract. J Infect Dis 1973;127;49-55.

303. Camara DS, Gruber M, Barde CJ et al. Transient bacteremia following endoscopic injection sclerotherapy of esophageal varices. Arch Intern Med 1983;143:1350-2.

304. Shorvon PJ, Eykyn SJ and Cotton PB. Gastrointestinal instrumentation, bacteraemia and endocarditis. Gut 1983;24:1078-93.

305. Edson RS, van Scoy RE and Leary FJ. Gram-negative bacteremia after transrectal needle biopsy of the prostate. Mayo Clin Proc 1980;55:489-91.

306. Livengood CH III, Land MR and Addison WA. Endometrial biopsy, bacteremia and endocarditis risk. Obstet Gynecol 1985;65:678-81.

307. Mellow MH and Lewis RJ. Endoscopy-related bacteremia. Incidence of positive blood cultures after endoscopy of upper gastrointestinal tract. Arch Intern Med 1976;136:667-9.

308. Yin TP and Dellipiani AW. Bacterial endocarditis after Hurst bougienage in a patient with a benign oesophageal stricture. Endoscopy 1983;15:27-8.

309. Giglio JA, Rowland RW, Dalton HP and Laskin DM. Suture removal-induced bacteremia: a possible endocarditis risk. J Am Dent Assoc 1992;123:65-70.

310. Ho H, Zuckerman MJ and Wassem C. A prospective controlled study of the risk of bacteremia in emergency sclerotherapy of esophageal varices. Gastroenterology 1991;101:1642-8.

311. Low DE, Shoenut JP, Kennedy JK et al. Prospective assessment of risk of bacteremia with colonoscopy and polypectomy. Dig Dis Sci 1987;32:1239-43.

312. Biorn CL, Browning WH and Thompson L. Transient bacteremia immediately following transurethral prostatic resection. J Urol 1950;63:155-61.

313. Levison ME and Abrutyn E. Infective endocarditis: current guidelines on prophylaxis. Curr Infect Dis Rep 1999;1:119-25.

314. Lockhart PB. The risk for endocarditis in dental practice. Periodontol 2000;23:127-35.

315. Lucas VS, Omar J, Vieira A and Roberts GJ. The relationship between odontogenic bacteraemia and orthodontic treatment procedures. Eur J Orthod 2002;24:293-301.

316. Roberts GJ, Gardner P and Simmons NA. Optimum sampling time for detection of odontogenic bacteraemia in children. Int J Cardiol 1992;35:311-5.

317. Roberts GJ, Holzel H, Sury MRJ et al. Dental bacteraemia in children. Pediatric Cardiol 1997;18:24-7.

318. Okell CC and Elliot SD. Bacteraemia and oral sepsis with special reference to the etiology of subacute endocarditis. Lancet 1935;2:869-74.

319. Elliot SD. Bacteraemia and oral sepsis. Proc R Soc Med 1939;32:747-54.

320. Donley TG and Donley KB. Systemic bacteremia following toothbrushing: a protocol for the management of patients susceptible to infective endocarditis. Gen Dent 1988;36:482-4.

321. Jenney AW, Cherry CL, Davis B and Wesselingh SL. “Floss and (nearly) die”: dental floss and endocarditis. Med J Aust 2001;174:107-8.

322. Pallasch TJ. A critical appraisal of antibiotic prophylaxis. Int Dent J 1989;39:183-96.

323. Bender IB, Naidorf IJ and Garvey GJ. Bacterial endocarditis: A consideration for physician and dentist. J Am Dent Assoc 1984;109:415-20.

324. Lockhart PB. An analysis of bacteremias during dental extractions. Arch Int Med 1996;156:513-20.

325. Morris AM and Webb GD. Antibiotics before dental procedures for endocarditis prophylaxis: back to the future. Heart 2001;86:3-4.

326. Durack DT. Antibiotics for prevention of endocarditis during dentistry: time to scale back? Ann Intern Med 1998;129:829-31.

327. Samaranayake LP. Orthodontics and infective endocarditis prophylaxis. Br Dent J 1995;179:48.

328. Roberts GJ, Lucas VS and Omar J. Bacterial endocarditis and orthodontics. J Royal Coll Surg Edin 2000;45:141-5.

329. Erverdi N, Kadir T, Ozkan H and Acar A. Investigation of bacteraemia after orthodontic banding. Am J Orthod Dentofacial Orthop 1999;116:687-90.

330. Erverdi N, Biren S, Kadir T and Acar A. Investigation of bacteraemia following orthodontic debanding. Angle Orthod 2000;70:11-4.

331. Macfarlane TW, Ferguson MM and Mulgrew CJ. Post-extraction bacteraemia:role of antiseptics and antibiotics. Br Dent J 1984;156:179-81.

332. Stirrups DR, Laws E and Honigan JL. The effect of chlorhexidine gluconate mouthrinse on oral health during fixed appliance orthodontic treatment. Br Dent J 1995;151:84-6.

333. Shanson DC, Ashford RFU and Singh J. High dose oral amoxicillin for preventing endocarditis. Br Med J 1980;280:446-8.

334. Shanson DC, Shehata A, Tadayon M and Harris M. Comparison of intravenous teicoplanin with intramuscular amoxycillin for the prophylaxis of streptococcal bacteraemia in dental patients. J Antimicrob Chemotherapy 1987;20:85-93.

335. Roberts GJ and Holzel H. The efficacy of intravenous antibiotics in reducing bacteraemia following extractions and restorations in children with severe congenital heart disease. Br Dental J 2002;in press.

336. Berney P and Francioli P. Successful prophylaxis of experimental streptococcal endocarditis with single dose amoxicillin administered after bacterial challenge. J Infect Dis 1990;161:281-5.

337. Roberts GJ, Simmons NB, Longhurst PB and Hewitt PB. Bacteraemia following local anaesthetic injections in children. Br Dental J 1998;185:295-8.

338. Mani V, Cartwright K, Dooley J et al. Antibiotic prophylaxis in gastrointestinal endoscopy: a report by a Working Party for the British Society of Gastroenterology Endoscopy Commmittee. Endoscopy 1997;29:114-9.

339. American Society for Gastrointestinal Endoscopy. Antibiotic prophylaxis for gastrointestinal endoscopy. Gastrointest Endosc 1995;42:630-5.

340. The American Society of Colon and Rectal Surgeons. Practice parameters for antibiotic prophylaxis to prevent infective endocarditis or infected prosthesis during colon and rectal endoscopy. Dis Colon Rectum 1992;35:277.

341. Rey JR, Axon A, Budzynska A et al. European Society of Gastrointestinal Endoscopy. Guidelines of the European Societey of Gastrointestinal Endoscopy (E.S.G.E) antibiotic prophylaxis for gastrointestinal endoscopy. Endoscopy 1998;30:318-24.

342. Hyde JA, Darouiche RO and Costerton JW. Strategies for prophylaxis against prosthetic valve endocarditis:a review article. J Heart Valve Dis 1998;7:316-26.

343. Horstkotte D, Weist K and Ruden H. Better understanding of the pathogenesis of prosthetic valve endocarditis – recent perspectives for prevention strategies. J Heart Valve Dis 1998;7:313-5.

344. Kreter B and Woods M. Antibiotic prophylaxis for cardiothoracic operations: meta-analysis of thirty years of clinical trials. J Thorac Cardiovasc Surg 1992;104:590-9.

345. Townsend TR, Reitz BA, Bilker WB and Bartlett JG. Clinical trial of cefamandole, cefazolin and cefuroxime for antibiotic prophylaxis in cardiac operations. J Thorac Cardiovasc Surg 1993;106:664-70.

346. Eagle KA and Guyton RA et al. ACC/AHA Guidelines for Coronary Artery Bypass Graft surgery. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 1999;34:1262-347.

347. Ariano RE and Zhanel GG. Antimicrobial prophylaxis in coronary bypass surgery: a critical appraisal. DICP 1999;25:478-84.

348. Vuorisalo S, Pokela R and Syrjala H. Is single-dose antibiotic prophylaxis sufficient for coronary artery bypass surgery? An analysis of peri- and postoperative serum cefuroxime and vancomycin levels. J Hosp Infect 1997;37:237-47.

349. Kriaras I, Michalopoulos A, Michalis A et al. Antibiotic prophylaxis in cardiac surgery. J Cardiovasc Surg 1997;38:605-10.

350. Kaiser AB, Petracek MR, Lea JW IV et al. Efficacy of cefazolin, cefamandole and gentamicin as prophylactic agents in cardiac surgery: results of a prospective, randomized, double-blind trial in 1,030 patients. Ann Surg 1987;206:791-7.

351. Niederhauser U, Vogt M, Genoni M et al. Cardiac surgery in a high risk group of patients: is prolonged postoperative antibiotic prophylaxis effective? J Thorac Cardiovasc Surg 1997;114:162-8.

352. Wellens F, Pirlet M, Larbuisson R et al. Prophylaxis in cardiac surgery: a controlled randomized comparison between cefazolin and cefuroxime. Eur J Cardiothorac Surg 1995;9:325-9.

353. Shanson DC. New guidelines for the antibiotic treatment of streptococcal, enterococcal and staphylococcal endocarditis. J Antimicrob Chemother 1998;42:292-6.

354. Working Party of the British Society for Antimicrobial Chemotherapy. Antibiotic treatment of Streptococcal, Enterococcal and Staphylococcal endocarditis. Guidelines. Heart 1998;79:207-210.

355. Wilson W, Karchmer A, Dajani A et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci and HACEK microorganisms. JAMA 1995;274:1706-13.

356. Besnier JM and Choutet P. Medical treatment of infective endocarditis: general principles. Eur Heart J 1995;16(Suppl B):72-4.

357. Scheld WM. Pathogenesis and pathophysiology of infective endocarditis. In: Sande MA, Kaye D and Root RK (eds): Endocarditis. New York, Churchill Livingstone, 1984, pp. 1-32.

358. Durack DT and Beeson PB. Experimental bacterial endocarditis. II. Survival of bacteria in endocardial vegetations. Br J Exp Pathol 1972;53:50-3.

359. Washington JA. In vitro testing of antimicrobial agents. Infect Dis Clin North Am 1989;3:375-87.

360. Mulligan MJ and Cobbs CG. Bacteriostatic versus bactericidal activity. Infect Dis Clin North Am 1989;3:389-98.

361. Holloway Y, Dankert J and Hess J. Penicillin tolerance and bacterial endocarditis. Lancet 1980;1:589.

362. Eliopoulos GM. Synergism and antagonism.Infect Dis Clin North Am 1989;3:399-406.

363. Watanakunakorn C and Glotzbecker C. Synergism with aminoglycosides of penicillin, ampicillin and vancomycin against non-enterococcal group-D streptococci and Viridans streptococci. J Med Microbiol 1976;10:133-8.

364. Sande MA and Irvin RG. Penicillin-aminoglycoside synergy in experimental Streptococcus viridans endocarditis. J Infect Dis 1974;129:572-6.

365. Mandell GL, Kaye D, Levison ME and Hook EW. Enterococcal endocarditis: an analysis of 38 patients observed at the New York Hospital-Cornell Medical Center. Arch Intern Med 1970;125:258-64.

366. Bisno AL, Dismukes WE, Durack DT et al. Antimicrobial treatment of infective endocarditis due to viridans streptococci, enterococci and staphylococci. JAMA 1989;261:1471-7.

367. Moellering RC. Treatment of enterococcal endocarditis. In: Sande MA, Kaye D and Root RK (eds). Endocarditis. New York, Churchill Livingstone, 1984, pp. 113-133.

368. Wilson WR and Geraci JE. Treatment of streptococcal infective endocarditis. Am J Med 1985;78(Suppl 6B):128-37.

369. Gutschik E and the Endocarditis Working Group of the International Society of Chemotherapy. Microbiological recommendations for the diagnosis and follow-up of infective endocarditis. Clin Microbiol Infect 1998;4(Suppl 3):S10-16.

370. Weinstein MP, Stratton CW, Ackley A et al. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. Am J Med 1985;78:262-9.

371. MacMahon SW, Roberts JK, Kramer-Fox R et al. Mitral valve prolapse and infective endocarditis. Am Heart J 1987;113:1291-8.

372. Facklam RR and Carey RB. Streptococci and aerococci. In Lennete EH, Balows A, Hausler WJ Jr. et al. (eds). Manual of Clinical Microbiology. 4th ed. Washington, DC, American Society of Microbiology, 1985, pp. 154-175.

373. Karchmer AW. Staphylococcal endocarditis. Laboratory and clinical basis for antibiotic therapy. Am J Med 1985;78:(Suppl 6B)116-27.

374. Eykyn SJ. Staphylococcal sepsis. The changing pattern of disease and therapy. Lancet 1988;1:100-4.

375. Chambers HF, Korzeniowski OM and Sande MA. Staphylococcus aureus endocarditis: clinical manifestations in addicts and non-addicts. Medicine 1983;62:170-7.

376. Caputo GM, Archer GL, Calderwood SB et al. Native valve endocarditis due to coagulase-negative staphylococci. Clinical and microbiologic features. Am J Med 1987;83:619-25.

377. Francioli P. Antibiotic treatment of streptococcal and enterococcal endocarditis: an overview. Eur Heart J 1995;16(Suppl B):75-9.

378. Bille J. Medical treatment of staphylococcal infective endocarditis. Eur Heart J 1995;16(Suppl B):80-3.

379. Korzeniowski O and Sande MA. Combination antimicrobial therapy for Staphylococcus aureus endocarditis in patients addicted to parenteral drugs and in non-addicts. A prospective study. Ann Intern Med 1982;97:496-503.

380. Bille J. Medical treatment of staphylococcal infective endocarditis. Eur Heart J 1995;16(Suppl B):75-9.

381. Besnier JM, Leport C, Bure A and Vilde JL. Vancomycin-aminoglycoside combinations in therapy of endocarditis caused by Enterococcus species and Streptococcus bovis. Eur J Clin Microbiol Infect Dis 1990;9:130-3.

382. Pollock AA, Tee PE, Patel IH et al. Pharmacokinetic characteristics of IV ceftriaxone in normal adults. Antimicrobial Agents. Chemother 1981;22:816-23.

383. Francioli P, Etienne J, Hoigne R et al. Treatment of streptococcal endocarditis with a single daily dose of devtriaxone sodium for 4 weeks. Efficacy and out-patient treatment feasibility. JAMA 1992;267:264-7.

384. Johnson AP, Warner M, Broughton K et al. Antibiotic susceptibility of streptococci and related genera causing endocarditis: analysis of UK reference laboratory referrals, January 1996-March 2000. BMJ 2001;322:395-6.

385. Sexton DJ, Tenenbaum MJ, Wilson WR et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. Clin Infect Dis 1998;27:1470-4.

386. Wilson WR. Ceftriaxone sodium therapy of penicillin G-susceptible streptococcal endocarditis. JAMA 1992;267:279-80.

387. Garcia Rodriguez JF, Mesias Prego JA and Dominguez Gomez D. Treatment of endocarditis due to penicillin-susceptible streptococci with a two-week course of ceftriaxone followed by oral amoxicillin. Eur J Clin Microbioil Infect Dis. 1992;11:952-3.

388. Francioli P, Ruch W and Stamboulian D. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone and netilmicin for 14 days: a prospective multicenter study. Clin Infect Dis 1995;21:1406-10.

389. Myers JP and Linnemann CC Jr. Bacteremia due to methicillin-resistant Staphylococcus aureus. J Infect Dis 1982; 145:532-6.

390. Archer AW. Antibiotic therapy of nonenterococcal streptococcal and staphylococcal endocarditis: current regimens and some future considerations. J Antimicrob Chemother 1988;21(Suppl C):91-106.

391. Karchmer AW, Archer GL and Dismukes WE. Staphylococcus epidermidis causing prosthetic valve endocarditis: microbiolgic and clinical observations as guides to therapy. Ann Intern Med 1983;98:447-55.

392 Heimberger TS and Duma RJ. Infection of prosthetic heart valves and cardiac pacemakers. Infect Dis Clin North Am 1989;3:221-45.

393. Faville RJ Jr., Zaske DE, Kaplan EL et al. Staphylococcus aureus endocarditis: Combined therapy with vancomycin and rifampicin. JAMA 1978;240:1963-5.

394. Acar JF, Goldstein FW and Duval J. Use of rifampicin for the treatment of serious staphylococcal and gram-negative bacillary infections. Rev Infect Dis 1983;5:(Suppl 3)502-6.

395. Linares J. Clin Microbiol Infect 2001;7(Suppl 4):8-15.

396. Dehondt G, Leven M, Vandermersch C and Colaert J. Destructive endocarditis caused by Staphylococcus lugdunensis: case report and review of the literature. Acta Clinica Belgica 1997;52:27-30.

397. Vandenesch F, Etienne J, Reverdy ME and Eykyn SJ. Endocarditis due to Staphylococcus lugdunensis: report of 11 cases and review. Clin Infect Dis 1993;17:871-6.

398. Lessing MP, Crook DW, Bowler IC and Gribbin B. Native valve endocarditis caused by Staphylococcus lugdunensis. QJM 1996;89:855-8.

399. Roberts RB, Kriger AG, Schiller NL and Gross KC. Viridans streptococcal endocarditis: role of various species , including pyridoxal-dependent streptococci. Ren Infect Dis 1979;1:955-65.

400. Stein DS and Nelson KE. Endocarditis due to nutritionally deficient streptococci:therapeutic dilemma. Rev Infect Dis 1987;9:908-16.

401. Bouvet A. Human endocarditis due to nutritionally variant streptococci: *Streptococcus adjacens* and *Streptococcus defectivus*. Eur Heart J 1995;16(Supplement B):24-7.

402. Francioli P. Antibiotic treatment of streptococcal and enterococcal endocarditis: general principles. Eur Heart J 1995;16(Suppl B):72-4.

403. Hricak V Jr., Kovacik J, Marx P et al. Endocarditis due to enterococcus faecalis: risk factors and outcome in 21 cases from a 5 year National Survey. Scand J Infect Dis 1998;30:540-1.

404. Johnson AP, Warner M, Woodford N et al. Antibiotic resistance among enterococci causing endocarditis in the UK: analysis of isolates referred to a reference laboratory. BMJ 1998;317:629-30.

405. Landman D and Quale JM. Management of infections due to resistant enterococci: a review of therapeutic options. J Antimicrob Chemother 1997;40:161-70.

406. Antony SJ, Ladner J, Stratton CW et al. High-level aminoglycoside-resistant enterococcus causing endocarditis successfully treated with a combination of ampicillin, imipenem and vancomycin. Scand J Infect Dis 1997;29:628-30.

407. Lee PY and Das SS. Endocarditis due to high-level gentamicin-resistant Enterococcus faecalis. Postgrad Med J 1995;71:117-9.

408. Matsumura S and Simor AE. Treatment of endocarditis due to vancomycin-resistant Enterococcus faecium with quinupristin/dalfopristin, doxycycline, and rifampicin: a synergistic drug combination. Clin Infect Dis 1998;27:1554-6.

409. Brisk AJ, van der Ende J et al. A case of Vancomycin-resistant enterococcal endocarditis. S Afr Med J 2000;90:1113-5.

410. Zervos MJ, Terpenning MS, Schaberg DR et al. High-level aminoglycoside-resistant enterococci. Colonization of nursing home and acute care hospital patients. Arch Intern Med 1987;147:1591-4.

411. Wilson WR, Wilkowske CJ, Wright AJ et al. Treatment of streptomycin-susceptible and streptomycin-resistant enterococcal endocarditis. Ann Intern Med 1984;100:816-23.

412. Hood S and Baxter RH. Listeria endocarditis causing aortic root abscess and fistula to the left atrium. Scott Med J 1999;44:117-8.

413. Moreira AL, Haslett PA and Symmons WF. Proprionibacterium acnes as the cause of endocarditis in a liver transplant recipient. Clin Infect Dis 2000;30:224-6.

414. Mitchell AR and Hayak LJ. Lactobacillus endocarditis. J Infect 1999;38:200-1.

415. Huynh TT, Walling AD, Miller MA et al. Proprionibacterium acnes endocarditis. Can J Cardiol 1995;11:785-7.

416. Morrison DJ, Sperling LS, Schwartz DA and Felmer JM. Escherichia coli endocarditis of a native aortic valve. Arch Pathol Lab Med 1997;121:1292-5.

417. Anderson MJ and Janoff EN. Klebsiella endocarditis: report of two cases and review. Clin Infect Dis 1998;26:468-74.

418. Ananthasubramanian K and Karthikeyan V. Aortic ring abscess and aortoatrial fistula complicating fulminant prosthetic valve endocarditis due to proteus mirabilis. J Ultrasound Med 2000;19:63-6.

419. Raymond NJ, Robertson MD and Lang SD. Aortic valve endocarditis due to Escherichia coli. Clin Infect Dis 1992;15:749-50.

420. Thomas MG, Rowland-Jones S and Smyth E. Klebsiella pneumoniae endocarditis. J R Soc Med 1989;82:114-5.

421. Donowitz GR and Mandell GL. Beta-lactam antibiotics. N Engl J Med 1988;318:419-26.

422. Donowitz GR. Third generation cephalosporins. Infect Dis Clin North Am 1989;3:595-612.

423. Sobel JD. Imipenem and aztreonam. Infect Dis Clin North Am 1989;3:613-24.

424. Lipman B and Neu HC. Imipenam: A new carbapenam antibiotic. Update on antibiotics II. Med Clin North Am 1988;72:567-79.

425. Dickinson G, Rodriguez K, Arcey S et al. Efficacy of imipenem/cilastatin in endocarditis. Am J Med 1985;78:(6A)117-21.

426. Neu HC. Aztreonam: The first monobactam. Med Clin North Am 1988;72:555-66.

427. Bush LM, Calmon J and Johnson CC. Newer penicillins and beta-lactamase inhibitors. Infect Dis Clin North Am 1989;3:571-94.

428. Reyes MP and Lerner AM. Current problems in the treatment of infective endocarditis due to Pseudomonas aeruginosa. Rev Infect Dis 1983;5:314-21.

429. Cohen PS, Maguire JH and Weinstein L. Infective endocarditis caused by gram-negative bacteria: a review of the literature. Prog Cardiovasc Dis 1980;22:205-42.

430. Komshian SV, Tablan OC, Palutke W and Reyes MP. Characteristics of left-sided endocarditis due to Pseudomonas aeruginosa in the Detroit Medical Center.Rev Infect Dis 1990;12:693-702.

431. Carvajal A and Frederiksen W. Fatal endocarditis due to Listeria monocytogenes. Rev Infect Dis 1988;10:616-23.

432. Lindner PS, Hardy DJ and Murphy TF. Endocarditis due to Corynebacterium pseudodiphtheriticum. N Y State J Med 1986;86:102-4.

433. Nord CE. Anaerobic bacteria in septicaemia and endocarditis. Scand J Infect Dis 1982;31(Suppl):95-104.

434. Weber G, Borer A, Riesenberg K and Schlaeffer F. Infective endocarditis due to Fusobacterium nucleatum in an intravenous drug abuser. Eur J Clin Microbiol Infect Dis 1999;18:655-7.

435. Shammas NW, Murphy GW, Eichelberger J et al. Infective endocarditis due to Fusobacterium nucleatum: case report and review of the literature. Clin Cardiol 1993;16:72-5.

436. Tornos MP, Almirante B, Pahissa A et al. Prosthetic valve endocarditis caused by gram-negative bacilli of the HACEK group. Am J Med 1990;88(Suppl N):64N.

437. Das M, Badley AD, Cockerill FR et al. Infective endocarditis caused by HACEK microorganisms. Annu Rev Med 1997;48:25-33.

438. Lesage V, Van Pee D, Luyx C et al. Septic arthritis caused by Haemophilus influenzae associated with endocarditis. Clin Rheumatol 1998;17:340-2.

439. Darras-Joly C, Lortholary O, Mainardi JL et al. Haemophilus endocarditis:report of 42 cases in adults and review. Haemophilus Endocarditis Study Group. Clin Infect Dis 1997;24:1087-94.

440. Lin BH and Vieco PT. Intracranial mycotic aneurysm in a patient with endocarditis caused by Cardiobacterium hominis. Can Assoc Radiol J 1995;46:40-2.

441. Le Quellec A, Bessis D, Perez C and Ciurana AJ. Endocarditis due to beta-lactamase-producing Cardiobacterium hominis. Clin Infect Dis 1994;19:994-5.

442. Pritchard TM, Foust RT, Cantely JR and Leman RB. Prosthetic valve endocarditis due to Cardiobacterium hominis occurring after gastrointestinal endoscopy. Am J Med 1991;90:516-8.

443. Olopoenia LA, Mody V and Reynolds M. Eikenella corrodens endocarditis in an intravenous drug user: case report and literature review. J Natl Med Assoc 1994;86:313-5.

444. Chakraborty RN, Meigh RE and Kaye GC. Kingella Kingae prosthetic valve endocarditis. Indian Heart J 1999;51:438-9.

445. Hassan IJ and Hayek L. Endocarditis caused by Kingella denitrificans. J Infect 1993;27:291-5.

446. Lynn DJ, Kane JG and Parker RH. Haemophilus parainfluenzae and influenzae endocarditis: a review of 40 cases. Medicine 1977;56:115-28.

447. Ellner JJ, Rosenthal MS, Lerner PI and McHenry MC. Infective endocarditis caused by slow-growing, fastidious, gram-negative bacteria. Medicine 1979;58:145-58.

448. Schack SH, Smith PW, Penn RG and Rapoport JM. Endocarditis caused by Actinobacillus actinomycetemcomitans. J Clin Microbiol 1984; 20:579-81.

449. Decker MD, Graham BS, Hunter EB and Liebowitz SM. Endocarditis and infections of intravascular devices due to Eikenella corrodens. Am J Med Sci 1986;292:209-12.

450. Jenny DB, Letendre PW and Iverson G. Endocarditis due to Kingella species. Rev Infect Dis 1988;10:1065-6.

451. Woods GL, Wood RP and Shaw BW Jr. Aspergillus endocarditis in patients without prior cardiovascular surgery: report of a case in a liver transplant recipient and review. Rev Infect Dis 1989;11:263-72.

452. Johnston PG, Lee J, Domanski M et al. Late recurrent Candida endocarditis. Chest 1991;99:1531-3.

453. Ellis M. Fungal endocarditis. J Infect 1997;35:99-103.

454. Muehrcke DD, Lytle BW and Cosgrove DM. Surgical and long-term antifungal therapy for fungal prosthetic valve endocarditis. Ann Thorac Surg 1995;60:538-43.

455. Remsey ES and Lytle BW. Repair of fungal aortic prosthetic valve endocarditis associated with periannular abscess. J Heart Valve Dis 1998;7:235-9.

456. Zedtwitz-Liebenstein K, Gabriel H et al. Prosthetic valve endocarditis due to Candida tropicalis coimplicated by multiple pseudoaneurysms. Infection 2001;29:177-9.

457. Nasser RM, Melgar GR, Longworth DL et al. Incidence and risk of developing fungal prosthetic valve endocarditis after nosocomial candidemia. Am J Med 1997;103:25-32.

458. Uddin MJ, Sanyal SC, Mustafa AS et al. The role of aggressive medical therapy along with early surgical intervention in the cure of Brucella endocarditis. Ann Thorac Cardiiovasc Surg 1998;4:209-13.

459. Quiroga J, Miralles A, Farinola T et al. Surgical treatment of Brucella endocarditis. Cardiovasc Surg 1996;4:227-30.

460. Raoult D, Houpikian P, Tissot Dupont H et al. Treatment of Q-fever endocarditis: comparison of two regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch Int Med 1999;159:167-73.

461. Raoult D, Raza A and Marrie TJ. Q fever endocarditis and other forms of chronic Q fever. In: Marrie TJ, ed. Q Fever. Volume I: The Disease. Boston:CRC Press, 1990:179-99.

462. Madkour MM. Brucellosis. In: Fauci AS et al., eds. Harrison's Principles of Internal Medicine, 14th Edition. Volume I: Chapter 162. McGraw Hill 1998, pp 970.

463. Bruneval P, Choucair J, Paraf F et al. Detection of fastidious bacteria in cardiac valves in case of blood-culture negative endocarditis. J Clin Pathol 2001;54:238-40.

464. Cerubin CE and Sapira JD. The medical complications of drug addiction and the medical assessment of the IV drug user. Ann Intern Med 1993;119:1017-28.

465. Haverkos HW and Lange WR. Serious infection other than human immunodeficiency virus among IV drug abusers. J Infect Dis 1990;894-902.

466. Heldman AW, Hartert TV, Ray SC et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users:prospective randomized comparison with parenteral therapy. Am J Med 1996;101:68-76.

467. Botsford KB, Weinstein RA, Nathan CR and Kabis SA. Selective survival in pentazocine and tripelennamine of Pseudomonas aeruginosa serotype 011 from drug addicts. J Infect Dis 1985;151:209-16.

468. Bisbe J, Miro JM, Latone X et al. Disseminated candidiasis in addicts who use brown heroin. Report of 83 cases and review. Clin Infect Dis 1992;15:910-23.

469. Fortun J, Novase E, Martinez-Beltran J et al. Short-course therapy for right-side endocarditis due to Staphylococcus aureus in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. Clin Infect Dis 2001;33:120-5.

470. Cicalini S, Forcina G and De Rosa FG. Infective endocarditis in patients with human immunodeficiency virus infection. J Infect 2001;42:267-71.

471. Rerkpattanapipat P, Wongpraparut N, Jacobs LE et al. Cardiac manifestations of acquired immunodeficiency syndrome. Arch Intern Med 2000;160:602-8.

472. DiNubile MJ. Short-course antibiotic therapy for right-sided endocarditis caused by Staphylococcal aureus in injection drug users. Ann Intern Med 1994;89:2279.

473. Fernandez Guerrero ML, Torres Perera R, Gomez Rodrigo J et al. Infectious endocarditis due to non-typhi Salmonella in patients infected with human immunodeficiency virus:report of two cases and review. Clin Infect Dis 1996;22:853-5.

474. Currie PF, Sutherland GR, Jacob AJ et al. A review of endocarditis in acquired immunodeficiency syndrome and human immunodeficiency virus infection. Eur Heart J 1985;16(Suppl B):15-18.

475. Kinney EL, Monsuez JJ, Kitzis M and Vittecoq D. Treatment of AIDS-associated heart disease. Angiology 1989;40:970-6.

476. Nahass RG, Weinstein MP, Bartels J and Gocke DJ. Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type1-negative and -positive patients. J Infect Dis 1990;162:967-70.

477. Heinonen CP, Slone D and Shapiro S. Birth defects and drugs in pregnancy. Littleton MA, Littleton Publishing Sciences Group, 1977.

478. Dashe JS and Gilstrap LC. Antibiotic use in pregnancy. Obstet Gynecol Clin North Am 1977;24:617-29.

479. King CT, Rogers PD, Cleary JD and Chapman SW. Antifungal therapy during pregnancy. Clin Infect Dis 1998;27:1151-60.

480. Horstkotte D, Weist K and Rueden H. Better understanding of the pathogenesis of prosthetic valve endocarditis – recent perspectives for prevention strategies. J Heart Valve Dis 1998;7:313-15.

481. Hyde JAJ, Darouiche RO and Costeron JW. Strategies for prophylaxis against prosthetic valve endocarditis. A review article. J Heart Valve Dis 1998;7:316-26.

482. Cowgill LD, Addonizio VP, Hopeman AR and Harken AH. Prosthetic valve endocarditis. Curr Probl Cardiol 1986;11:617-64.

483. Tornos P. Management of prosthetic valve endocarditis: a clinical challenge. Heart 2003;89:245-6.

484. Akowuah EF, Davies W, Oliver S et al. Prosthetic valve endocarditis: early and late outcome following medical or surgical treatment. Heart 2003;89:269-72.

485. DiSesa VJ, Sloss LJ and Cohn LH. Heart transplantation for intractable prosthetic valve endocarditis. J Heart Transplant 1990;9:142-3.

486. Brottier E, Gin H, Brottier L et al. Prosthetic valve endocarditis: diagnosis and prognosis. Eur Heart J 1984;5(Suppl C)123-7.

487. Cowgill LD, Addonizio VP, Hopeman AR and Harken AH. A practical approach to prosthetic valve endocarditis. Ann Thorac Surg 1987;43:450-7.

488. Leport C, Vilde JL, Bricaire F et al. Fifty cases of late prosthetic valve endocarditis: improvement in prognosis over a 15 year period. Br Heart J 1987;58:66-71.

489. Dismukes WE. Prosthetic valve endocarditis. Factors influencing outcome and recommendations for therapy. In Bisno AL (ed) Treatment of infective endocarditis,. New York, Grune & Stratton, 1981, pp 167-191.

490. Durack DT. Infective endocarditis. In: Schlant R, Hurst WJ. Eds. The Heart, 7th edition companion handbook. New York: McGraw Hill, 1990, pp 153-67.

491. Scheld WM and Sande MA. Endocarditis and intravascular infections. In: Mandell GL, Douglas RG Jr, Dolin R. eds. Principles and practice of infectious diseases, 4th edn. New York: Churchill Livingstone, 1995, pp 740-83.

492. DiNubile MJ, Calderwood SB, Steinhaus DM and Karchmer AW. Cardiac conduction abnormalities complicating native valve active endocarditis. Am J Cardiol 1986;58:1213-17.

493. Tucker KJ, Johnson JA, Ong T et al. Medical management of prosthetic aortic valve endocarditis and aortic root abscess. Am Heart J 1993;125:1195-7.

494. Guzman F, Cartmill I, Holden MP and Freeman R. Candida endocarditis: report of four cases. Int J Cardiol 1987;16:131-6.

495. Douglas JL and Cobbs CG. Prosthetic valve endocarditis. In: Kaye D ed., Infective endocarditis, 2nd edn. New York: Raven Press, 1992, pp 375-96.

496. Yu VL, Fang GD, Keys TF et al. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy only. Ann Thorac Surg 1994;58:1073-7.

497. Saffle JR, Gardner P, Schoenbaum SC et al. Prosthetic valve endocarditis: the case for prompt valve replacement. J Thorac Cardiovasc Surg 1977;3:416-20.

498. Lytle BW, Taylor PC, Sapp SK et al. Surgical treatment of prosthetic valve endocarditis. J Thorac Cardiovasc Surg 1996;111:198-210.

499. Farina G, Vitale N, Piaza L et al. Long term results of surgery for prosthetic valve endocarditis. J Heart Valve Dis 1994;2:165-71.

500. Moon MR, Miller DL, Moore KA et al. Treatment of endocarditis with valve replacement: the question of tissue versus mechanical prosthesis. Ann Thorac Surg 2001;71:1164-71.

501. Trunninger K, Attenhofer CH, Seifert B et al. Long term follow up of prosthetic valve endocarditis: what characteristics identify patients who were treated successfully with antibiotics alone. Heart 1999;82:714-20.

502. Karchmer AW, Dismuke WE, Buckley MJ et al. Late prosthetic valve endocarditis: clinical features influencing therapy. Am J Med 1978;64:199-206.

503. Kuyvenhoven P, Rijk-Zwikkere GL, Hermans J et al. Prosthetic valve endocarditis: analysis of risk factors for mortality. Eur J Cardiothoracic Surg 1994;8:420-4.

504. Ivert TS, Dismukes WE, Cobbs CG et al. Prosthetic valve endocarditis. Circulation 1984;69:223-32.

505. Chow AW and Azar RM. Glycopeptides and nephrotoxicity. Intensive Care Med 1994;20(Suppl 4):23-9.

506. Leport C, Perronne C et al. Evaluation of teicoplanin for treatment of endocarditis caused by gram-positive cocci in 20 patients. Antimicrob Agents Chemother 1989;33:871-6.

507. Karchmer AW and Bisno AL. Infections of prosthetic heart valves and vascular grafts. In: Bisno AL, Waldvogel F eds. Infections associated with indwelling medical devices. Washington: ASM, 1989:129-59.

508. Blumberg EA, Robbins N, Adimora A and Lowy FD. Persistent fever in association with infective endocarditis. Clin Infect Dis 1992;15:983-90.

509. Vuille C, Nidorf M, Weyman AE and Picard MH. Natural history of vegetations during successful medical treatment of endocarditis. Am Heart J 1994;128:1200-9.

510. Mansur AJ, Dal Bo CM, Fukushuma JT et al. Relapses, recurrence, valve replacement and mortality during the long-term follow-up after infective endocarditis. Am Heart J 2001;141:78-86.

511. Nathwani D and Conlon C on behalf of the OHPAT Workshop. Outpatient and home parenteral antibiotic therapy (OHPAT) in the UK: a consensus statement by a working party. Clin Microbiol Infect 1998;4:537-51.

512. Fancioli PB and Stamboulian D for the Endocarditis Working Group of the International Society for Chemotherapy. Outpatient treatment of infective endocarditis. Clin Microbiol Infect 1998;4(3)S47-55.

513. Verheul HA, van den Brink RB, van Vreeland T et al. Effects of changes in management of active infective endocarditis on outcome in a 25-year period. Am J Cardiol 1993;72:682-7.

514. Middlemost S, Wisenbaugh T, Meyerowitz C et al. A case for early surgery in native left-sided endocarditis complicated by heart failure: results in 203 patients. J Am Coll Cardiol 1991;18:663-7.

515. Bogers AJJC, van Vreeswijk H, Verbaan CJ et al. Early surgery for active infective endocarditis improves early and late results. Thorac Cardiovasc Surg 1991;39:284-7.

516. Jubair KA, Al Fagih MR, Ashmeg A et al. Cardiac operations during active endocarditis. J Thoracic Cardiovasc Surg 1992;104:487-90.

517. Vlessis AA, Hovaguimian H, Jaggers J et al. Infective endocarditis: ten-year review of medical and surgical therapy. Ann Thorac Surg 1996;61:1217-22.

518. Dehler S and Elert O. Early and late prognosis following valve replacement for bacterial endocarditis of the native valve. Thorac Cardiovasc Surg 1995;43:83-9.

519. Castillo JC, Anguita MP, Ramirez A et al. Long-term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. Heart 2000;83:525-30.

520. Alexiou C, Langley SM, Stafford H et al. Surgery for active culture-positive endocarditis: determinants of early and late outcomes. Ann Thorac Surg 2000;69:1448-54.

521. Douglas A, Moore-Gillon J and Eykyn SJ. Fever during treatment of infective endocarditis. Lancet 1986;I:1341-3.

522. Graupner C, Vilacosta I, SanRoman J et al. Periannular extension of infective endocarditis. J Am Coll Cardiol 2002;39:1204-11.

523. Choussat R, Thomas D, Isnard R et al. Perivalvular abscess associated with endocarditis: clinical features and prognostic factors of overall success in a series of 233 cases. Perivalvular Abscess French Multicentre Study Eur Heart J 1999;20:232-41.

524. Stinson EB. Surgical treatment of infective endocarditis. Prog Cardiovasc Dis 1979;22:145-68.

525. Becher H, Hanrath P, Bleifeld W and Bleese N. Correlation of echocardiographic and surgical findings in acute bacterial endocarditis. Eur Heart J 1984;5(Suppl C):67-70.

526. Arnett EN and Roberts WC. Prosthetic valve endocarditis: clinicopathologic analysis of 22 necropsy patients with comparison of observations in 74 necropsy patients with active endocarditis involving natural left-sided cardiac valves. Am J Cardiol 1976;38:281-92.

527. Blumberg EA, Karalis DA, Chandrasekaran K et al. Endocarditis-associated paravalvular abscesses: do clinical parameters predict the presence of abscess? Chest 1995;107:898-903.

528. Scarvelis D and Malcolm I. Embolization of a huge tricuspid valve bacterial vegetation. J Am Soc Echocardiogr 2002;15:185-7.

529. Stewart WJ and Shan K. The diagnosis of prosthetic valve endocarditis by echocardiography. Semin Thorac Cardiovasc Surg 1995;7:7-12.

530. Ergin MA. Surgical techniques in prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:54-60.

531. David TE. The surgical treatment of patients with prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:47-53.

532. Joyce F, Tingleff J and Pettersson G. The Ross operation in the treatment of prosthetic aortic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:38-46.

533. Camacho MT and Cosgrove DM 3rd. Homografts in the treatment of prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:32-7.

534. McGiffin DC and Kirklin JK. The impact of aortic valve homografts on the treatment of aortic prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:25-31.

535. Gordon SM and Keys TF. Bloodstream infections in patients with implanted prosthetic cardiac valves. Semin Thorac Cardiovasc Surg 1995;7:2-6.

536. Lytle BW. Surgical treatment of prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995;7:13-9.

537. Lytle BW. Prosthetic valve endocarditis. Introduction. Semin Thorac Cardiovasc Surg 1995;7:1.

538. Tornos P, Alnurante B and Mirabet S. Infective endocarditis due to Staphylococcus aureus: deleterious effect of anticoagulant therapy. Arch Intern Med 1999;159:473-5.

539. Nihoyannopoulos P. Tricuspid valvectomy following tricuspid valve endocarditis in an intravenous drug addict. Heart 2001;86:144.

540. Carozza A, Penzulli A, De Feo M et al. Tricuspid repair for infective endocarditis: clinical and echocardiographic results. Tex Heart Inst J 2001;28:96-101.

541. Yee ES and Khonsari S. Right-sided infective endocarditis:valvuloplasty, valvectomy or replacement. J Cardiovasc Surg 1989;30:744-8.

542. Hughes CF and Noble N. Vegetectomy:an alternative surgical treatment for infective endocarditis of the atrioventricular valves in drug addicts. J Thorac Cardiovasc Surg 1988;95:857-61.

543. Reinhartz O, Herrmann M, Redling F and Zerkowski HR. Timing of surgery in patients with acute infective endocarditis. J Cardiovasc Surg 1996;37:397-400.

544. Wilson WR, Davidson GK, Giuliani ER et al. Cardiac valve replacement in congestive heart failure due to infective endocarditis. Mayo Clin Proc 1979;54:223-6.

545. Moon MR, Stinson EB and Miller DC. Surgical treatment of endocarditis. Prog Cardiovasc Dis 1997;40:239-64.

546. Karchmer AW and Stinson EB. The role of surgery in infective endocarditis. In: Remington JS, Schwartz MN, eds. Current Clinical Topics in Infectious Diseases. New York, NY: McGraw-Hill;1980:124-157.

547. Jung JY, Saab SB and Almond CH. The case for early surgical treatment of left-sided primary infective endocarditis: a collective review. J Thorac Cardiovasc Surg 1975;70:509-18.

548. Acar J, Michel PL, Varenne O, Michaud P, Rafik T. Surgical treatment of infective endocarditis. Eur Heart J 1995;16(Suppl B):94-8.

549. Saffle JR, Gardner P, Schoenbaum SC and Wild W. Prosthetic valve endocarditis: the case for prompt valve replacement. J Thorac Cardiovasc Surg 1977;73:416-20.

550. Peri CM, Vuk F, Huski CR. Active infective endocarditis: low mortality associated with early surgical treatment. Cardiovasc Surg 2000;8:208-13.

551. Karchmer AW. Treatment of prosthetic valve endocarditis. In: Sand MA, Kaye D and Root RT eds. Endocarditis. New York, Edinburgh, London and Melbourne: Churchill Livingstone, 1984.

552. Richardson JV, Karp RB, Kirklin JW and Dismukes WE. Treatment of infective endocarditis: a 10 year comparative analysis. Circulation 1978;58:589-97.

553. Parrino PE, Kron IL, Ross SD et al. Does a focal neurological deficit contraindicate operation in a patient with endocarditis? Ann Thorac Surg 1999;67:59-64.

554. Gillinov AM, Shah RV, Cxurtis WE et al. Valve replacement in patients with endocarditis and acute neurologic deficit. Ann Thorac Surg 1996;61:1125-9.

555. Parrino PE, Kron IL, Ross SD et al. Does a focal neurologic deficit contraindicate operation in a patient with endocarditis. Ann Thorac Surg 1999;67:59-64.

556. Eishi K, Kawazoe K, Kuriyama Y et al. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrosective study in Japan. J Thorac Cardiovasc Surg 1995;110:1745-55.

557. Ting W, Silverman N and Levitsky S. Valve replacement in patients with endocarditis and cerebral septic embolism. Ann Thorac Surg 1991;51:18-21.

558. Piper C, Wiemer M, Schulte HG and Horstkotte D. Stroke is not a contraindication for urgent valve replacement in acute infective endocarditis. J Heart Valve Dis 2001;10:703-11.

559. Vilacosta I and Gomez J. Complementary role of MRI in infectious endocarditis. Echocardiography 1995;12:673-6.

560. Bertorini TE, Laster RE Jr., Thompson BF and Gelfand M. Magnetic resonance imaging of the brain in bacterial endocarditis. Arch Intern Med 1989;149:815-7.

561. Turtz AR and Yocom SS. Contemporary approaches to the management of neurosurgical complications of infective endocarditis. Curr Infect Dis Rep 2001;3:337-46.

562. Utoh J, Miyauchi Y, Goto H et al. Endovascular approach for an intracranial mycotic aneurysm associated with infective endocarditis. J Thorac Cardiovasc Surg 1995;110:557-9.

563. Salgado AV, Furlan AJ and Keys TF. Mycotic aneurysm, subarachnoid hemorrhage, and indications for cerebral angiography in infective endocarditis. Stroke 1987;18:1057-60.

564. Dodge A, Hurni M, Ruchat P et al. Surgery in native valve endocarditis: indications, results and risk factors. Eur J Cardiothoracic Surg 1995;9:330-4.

565. Aranki SF, Santini F, Adams DH et al. Aortic valve endocarditis. Determinants of early survival and late morbidity. Circulation 1994;90(Suppl II):175-82.

566. Olaison L, Hogevik H, Myken P et al. Early surgery in infective endocarditis. QJM 1996;89:267-78.

567. Reinhartz O, Herrmann M, Redling F et al. Timing of surgery in patients with acute infective endocarditis. J Cardiovasc Surg 1996;37:397-400.

568. Lytle BW, Priest BP, Taylor PC et al. Surgical treatment of prosthetic valve endocarditis. J Thorac Cardiovasc Surg 1996;111:198-207.

569. Cimbollek M, Nies B, Wenz R and Kreuter J. Antibiotic-impregnated heart valve sewing rings for treatment and prophylaxis of bacterial endocarditis. Antimicrob Agents Chemother 1996;40:1432-7.

570. Mullany C, Chau Y, Schaff H et al. Early and late survival after surgical treatment of culture-positive active endocarditis. Mayo Clin Proc 1995;70:517-25.

571. Middlemost S, Wisenbaugh T, Meyerowitz C et al. A case for early surgery in native left-sided endocarditis complicated by heart failure:results in 203 patients. J Am Coll Cardiol 1991;18:663-7.

572. Espersen F, Frimodt-Noller N. Staphylococcus aureus endocarditis. A review of 119 cases. Arch Intern Med 1986;146:1118-21.

573. Delany D, Pellerini M, Carrier M et al. Immediate and long-term results of valve replacement for native and prosthetic valve endocarditis. Ann Thorac Surg 2000;70:1219-23.

574. Knosalla C, Weng Y, Yankah AC et al. Surgical treatment of active infection aortic valve endocarditis with associated periannular abscess – 11 year results. Eur Heart J 2000;21:490-7.

575. d'Udekem Y, David TE, Feindel CM et al. Long-term results of operation for paravalvular abscess. Ann Thorac Surg 1996;62:48-53.

576. Nomura F, Penny DJ, Menahem S et al. Surgical intervention for infective endocarditis in infancy and childhood. Ann Thorac Surg 1995;60:90-5.

577. Mathew J, Abreo G, Namburi K et al. Results of surgical treatment for infective endocarditis in intravenous drug users. Chest 1995;108:73-7.

578. Niwaya K, Knott-Craig CJ, Santangelo K et al. Advantage of autograft and homograft valve replacement for complex aortic valve endocarditis. Ann Thorac Surg 1999;67:1603-8.

579. Grandmougin D, Prat A, Fayad G et al. Acute aortic endocarditis with annular destruction: assessment of surgical treatment with cryopreserved valvular homografts. J Heart Valve Dis 1999;8:234-41.

580. Haydock D, Barratt-Boyes B, Macedo T et al. Aortic valve replacement for active infectious endocarditis in 108 patients. A comparison of freehand allograft valves with mechanical prostheses and bioprostheses. J Thorac Cardiovasc Surg 1992;103:130-9.

581. Petrou M, Wong K, Albertucci M et al. Evaluation of unstented aortic homografts for the treatment of prosthetic aortic valve endocarditis. Circulation 1994;90(part 2):198-204.

582. Zwischenberger JB, Shalaby TZ and Conti VR. Viable cryopreserved aortic homograft for aortic valve endocarditis and annular abscesses. Ann Thorac Surg 1989;48:365-70.

583. Pagano D, Allen SM and Bonser RS. Homograft aortic valve and root replacement for severe destructive native or prosthetic endocarditis. Eur J Cardiothorac Surg 1994;8:173-6.

584. Dossche KM, Defauw JJ, Ernst SM et al. Allograft aortic root replacement in prosthetic aortic valve endocarditis: a review of 32 patients. Ann Thorac Surg 1997;63:1644-9.

585. O'Brien MF, Stafford EG, Gardner MA et al. A comparison of aortic valve replacement with viable cryopreserved and fresh allograft valves, with a note on chromosomal studies. J Thorac Cardiovasc Surg 1987;94:812-23.

586. McGiffin DC, Galbraith AJ, McLachlan GL et al. Aortic valve infection. Risk factors for death and recurrent endocarditis after aortic valve replacement. J Thorac Cardiovasc Surg 1992;104:511-20.

587. Dearani JA, Orszulak TA, Schaff HV et al. Results of allograft aortic valve replacement for complex endocarditis. J Thorac Cardiovasc Surg 1997;113:285-91.

588. Edwards MB, Ratnatunga CP, Dore CJ et al. Thirty-day mortality and long-term survival following surgery for prosthetic endocarditis: a study from the UK heart valve registry. Eur J Cardiothorac Surg 1998;14:156-64.

589. D'Udekem Y, David TE, Feindel CM et al. Long-term results of surgery for active infective endocarditis. Eur J Cardiothorac Surg 1997;11:46-52.

590. Jault F, Gandjbakhch I, Rama A et al. Active native valve endocarditis: determinants of operative death and late mortality. Ann Thorac Surg 1997;63:1737-41.

591. Ladowski JS and Deschner WP. Allograft replacement of the aortic valve for active endocarditis. J Cardiovasc Surg 1996;37(Suppl 1):61-2.

592. Wos S, Jasinski M and Bachowski R. Results of mechanical prosthetic valve replacement in active valvular endocarditis. J Cardiovasc Surg 1996;37(Suppl 1):29-32.

593. Robi C and Sek E. Are allografts the "choice" in infectious endocarditis with perivalvular abscess? Eur Heart J 2000;21:421.

594. Yankah AC, Klose H, Petzina R et al. Surgical management of acute aortic root endocarditis with valve homograft:13 year experience. Eur J Cardiovasc Surg 2002;21:260-7.

595. Guerra JM, Tornos MP, Permanye-Miralda G et al. Long-term results of mechanical prostheses for treatment of active endocarditis. Heart 2001;86:63-8.

596. Aranki SF, Adams DH, Rizzo RJ et al. Determinants of early mortality and late survival in mitral valve endocarditis. Circulation 1995;92:143-9.

597. Mansur AJ, Grinberg M, Cardoso RH et al. Determinants of prognosis in 300 episodes of infective endocarditis. Thorac Cardiovasc Surg 1996;44:2-10.

598. Malquarti V, Saradarian W, Etienne J et al. Prognosis of native valve infective endocarditis. A review of 253 cases. Eur Heart J 1984;5(Suppl C)11-20.

599. Bayliss R, Clark C, Oakley CM et al. Incidence, mortality and prevention of infective endocarditis. J R Coll Physicians 1986;20:15.

600. Delahaye F, Echchard R, de Gevigney G et al. The long-term prognosis of infective endocarditis. Eur Heart J 1995;16(Suppl B):48-53.

601. Renzulli A, Carozza A, Romano G et al. Recurrent infective endocarditis: a multivariate analysis of 21 years of experience. Ann Thorac Surg 2001;72:39-43.

602. Tornos MP, Permanyer-Miralda G, Olona M et al. Long term complications of native valve infective endocarditis in non addicts. Ann Intern Med 1992;117:567-72.

603. Calderwood SP, Swinsky LA, Karchmer AW et al. Prosthetic valve endocarditis. Analysis of factors affecting outcome of therapy. J Thorac Cardiovasc Surg 1986;92:776-83.

604. Tornos P, Almirante B, Olona M et al. Clinical outcome and long-term prognosis of late prosthetic valve endocarditis: a 20-year experience. Clin Infect Dis 1997;24:381-6.

605. Mihaljevic T, Byrne JG, Cohn LH and Aranki SF. Long-term results of multivalvar surgery for infective multivalve endocarditis. Eur J Cardiothoracic Surg 2001;20:842-6.

606. Lacassin F, Hoen B, Leport C et al. Procedures associated with infective endocarditis in adults. A case control study. Eur Heart J 1995;16:1968-74.

607. Roberts RB, Krieger AG, Schiller NL and Gross KC. Viridans streptococcal endocarditis: the role of various species including pyridoxal-dependent streptococci. Rev Infect Dis 1979;1:955-66.

608. Coykendale AL. Classification and identification of the viridans streptococci. Microbiol Rev 1989;2:315.

609. Harder EJ, Wilkowske CJ , Washington JA 2nd and Geracci JG. Streptococcus mutans endocarditis. Ann Intern Med 1974;80:364-8.

610. Stein DS and Nelson KE. Endocarditis due to nutritionally deficient streptococci: Therapeutic dilemma. Rev Infect Dis 1987;9:908-16.

611. Gelfand MS and Threlkeld MG. Subacute bacterial endocarditis secondary to Streptococcus pneumoniae. Am J Med 1992;93:91-3.

612. Ugolini V, Pacifico A, Smitherman TC and Mackowiak PA. Pneumococcal endocarditis update: analysis of 10 cases diagnosed between 1974 and 1984. Am Heart J 1986;112:813-9.

613. Powderly WG, Stanley SL and Medoff G. Pneumococcal endocarditis: report of a series and review of the literature. Rev Infect Dis 1986;8:786-91.

614. Sands M, Brown RB, Ryczak M and Hamilton W. Streptococcus pneumoniae endocarditis. South Med J 1987;80:780-2.

615. Lindberg J and Fangel S. Recurrent endocarditis caused by Streptococcus pneumoniae. Scand J Infect Dis 1999;31:409-10.

616. Marshall JB and Gerhardt DC. Polyposis coli presenting with Streptococcus bovis endocarditis. Am J Gastroenterol 1981;75:314-6.

617. Kupferwasser I, Darius H, Muller AM et al. Clinical and morphological characteristics in Streptococcus bovis endocarditis: a comparison with other causative microorganisms in 177 cases. Heart 1998;80:276-80.

618. Seglenieks A and Black RB. Streptococcus bovis and its association with bowel cancer. Aust N Z J Surg 1998;68:542-3.

619. Ben-Haim SA, Nechmad M, Edoute Y et al. Colonic villous adenoma, polyp and leiomyoma presenting with Streptococcus bovis endocarditis. Am Heart J 1988;115:192-5.

620. Zuccollo R and Boyd RV. Streptococcus bovis endocarditis and carcinoma of the colon. Br J Clin Pract 1987;41:1022-3.

621. Wong A, Rosenstein AH, Rutherford RE and James SP. Bacterial endocarditis following endoscopic variceal sclerotherapy. J Clin Gastroenterol 1997;24:90-1.

622. Baskin G. Prosthetic endocarditis after endoscopic variceal sclerotherapy: a failure of antibiotic prophylaxis. Am J Gastroenterol 1989;84:311-2.

623. Bortolotto LA, Mansur AJ, Grinberg M et al. Infective endocarditis related to acute cholecystitis. Thorac Cardiovasc Surg 1988;36:237-8.

624. Kreuzpaintner G, Horstkotte D, Heyll A et al. Increased risk of bacterial endocarditis in inflammatory bowel disease. Am J Med 1992;92:391-5.

625. Nicholls DP and Stanford CF. Infective endocarditis due to ulcerative endocarditis. Ulster Med J 1991;60:114-6.

626. Wong JS. Infective endocarditis in Crohn’s disease. Br Heart J 1989;62:163-4.

627. Ward RL. Endocarditis complicating ulcerative colitis. Gastroenterology 1977;73:1189-90.

628. Hoffman MA, Steele G and Yalla S. Acute bacterial endocarditis secondary to prostatic abscess. J Urol 2000;163:245.

629. Jones BL, Ludlam HA and Brown DF. High dose ampicillin for the treatment of high-level aminoglycoside resistant enterococcal endocarditis. J Antimicrob Chemother 1994;33:891-2.

630. Mandell GL, Kaye D, Levison ME and Hook EW. Enterococcal endocarditis: An analysis of 38 patients observed at the New York Hospital-Cornell Medical Center. Arch Intern Med 1970;125:258-64.

631. Maki DG and Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis and management. Medicine 1988;67:248-69.

632. Moellering RC Jr, Watson BK and Kunz LJ. Endocarditis due to group D streptococci. Comparison of disease caused by Streptococcus bovis with that produced by enterococci. Am J Med 1974;57:239-50.

633. Leport C, Bure A, Leport J and Vilde JL. Incidence of colonic lesions in Streptococcus bovis and enterococcal endocarditis. Lancet 1987;1:748.

634. Emiliani VJ, Chodos JE, Comer GM et al. Streptococcus bovis brain abscess associated with an occult colonic villous adenoma. Am J Gastroenterol 1990;85:78-80.

635. Wiseman A, Rene P and Crelinstein GL. Streptococcus agalactiae endocarditis: an association with villous adenomas of the large intestine. Ann Intern Med 1985;103:893-4.

636. Arber N, Pras E, Copperman Y et al. Pacemaker endocarditis. Report of 44 cases and review of the literature. Medicine 1994;73:299-305.

637. Vlay SC. Prevention of bacterial endocarditis in patients with permanent pacemakers and automatic internal cardioverter defibrillators. Am Heart J 1990;120:1490-2.

638. Kobayashi H, Sugiuchi R, Tabata N et al. Guess what! Acute infective endocarditis with Janeway lesions in a patient with atopic dermatitis. Eur J Dermatol 1999;9:239-40.

639. Grabczynska SA and Cerio R. Infective endocarditis associated with atopic eczema. Br J Dermatol 1999;140:1193-4.

640. Ostlere LS, Akhras F, Langtry JA and Staughton RC. Generalized pustular psoriasis associated with bacterial endocarditis of the anterior papillary muscle. Br J Dermatol 1992;127:187-8.

641. Pike MG and Warner JO. Atopic dermatitis complicated by acute bacterial endocarditis. Acta Paediatr Scand 1989;78:463-4.

642. Gowda TK, Sriprasad S, Korath MP and Jagadeesan K. Right ventricular mural infective endocarditis in a patient with burns. J Assoc Physicians India 1992;40:52-4.

643. Hassan IJ and Carmichael A. Endocarditis following skin procedures. J Infect 1993;27:341-2.

644. Speechly-Dick ME and Swanton RH. Osteomyelitis and infective endocarditis. Postgrad Med J 1994;70:885-90.

645. Speechly-Dick ME, Vaux EC and Swanton RH. A case of osteomyelitis secondary to endocarditis.Br Heart J 1994;72:298.

646. Weidmann B, Hanseler T, Jimenez C and Niederle N. Tricuspid endocarditis induced by implantable venous access. J Clin Oncol 1994;12:1103-5.

647. Bernardin G, Milhaud D, Roger PM et al. Swan-Ganz catheter-related pulmonary valve infective endocarditis: a case report. Intensive Care Med 1994;20:142-4.

648. Kaye GC, Rodgers H, Smith DR and Turney J. Bacterial endocarditis of the tricuspid valve after insertion of a central venous catheter. Br J Clin Pract 1990;44:762-3.

649. Finkielman JD, Gimenez M, Pietrangelo C and Blanco MV. Endocarditis as a complication of a transjugular intrahepatic portosystemic stent-shunt. Clin Infect Dis 1996;22:385-6.

650. Julander I. Staphylococcal septicaemia and endocarditis in 80 drug addicts. Aspects on epidemiology, clinical and laboratory findings and prognosis. Scand J Infect Dis 1983;41:(Suppl)49-55.

651. Levine DP, Crane LR and Zervos MJ. Bacteremia in narcotic addicts at the Detroit Medical Center. II. Infectious endocarditis: A prospective comparative study. Rev Infect Dis 1986;8:374-96.

652. Eichacker PQ, Miller K, Robbins M et al. Echocardiographic evaluation of heart valves in IV drug abusers without a previous history of endocarditis. Clin Res 1984;32:670A.

653. Bellamy CM, Roberts DH and Ramsdale DR. Ventriculo-atrial shunt causing tricuspid endocarditis: its percutaneous removal. Int J Cardiol 1990;28:260-2.

654. Molina JM, Leport C, Bure A et al. Clinical and bacterial features of infections caused by Streptococcus milleri. Scand J Infect Dis 1991;23:659-92.

655. Ullman RF, Miller SJ, Strampfer MJ and Cunha BA. Streptococcus mutans endocarditis:report of three cases and review of the literature. Heart Lung 1988;17:209-12.

656. Boenning DA, Nelson LP and Campos JM. Relatively penicillin-resistant Streptococcus sanguis endocarditis in an adolescent. Pediatr Infect Dis J 1988;7:205-7.

657. Endara A, Corkerton MA, Diqer AM, Neal AJ and Kang D. Pneumococcal aortic valve endocarditis causing aortopulmonary artery fistula. Ann Thorac Surg 2001;72:1737-8.

658. Siegel M and Timpane J. Penicillin-resistant Streptococcus pneumoniae endocarditis: a case report and review. Clin Infect Dis 2001;32:972-4.

659. Wall TC, Peyton RB and Corey GR. Gonococcal endocarditis: a new look at an old disease. Medicine 1989;68:375-80.

660. Owens JE and Kelchak JA. Gonococcal endocarditis:report of a case and review of the literature. J.S.C. Med Assoc 1990;86:93-6.

661. Jackman JD Jr., and Glamann DB. Gonococcal endocarditis: twenty-five year experience. Am J Med Sci 1991;301:221-30.

662. Gunn J, Gaw A and Trueman AM. A case of meningococcal endocarditis. Eur Heart J 1992;13:1004-5.

663. Candrick J, Segasothym M, Wheaton G et al. Meningococcal endocarditis in a patient with rheumatic heart disease. Aust N Z Med 1999;29:749-50.

664. Lynn DJ, Kane JG and Parker RH. Haemophilus parainfluenzae and influenzae endocarditis: a review of forty cases. Medicine 1977;56:115-28.

665. Ellner JJ, Rosenthal MS, Lerner PI and McHenry MC. Infective endocarditis caused by slow-growing, fastidious, Gram-negative bacteria. Medicine 1979;58:145-58.

666. Schack SH, Smith PW, Penn RG and Rapoport JM. Endocarditis caused by Actinobacillus actinomycetemcomitans. J Clin Microbiol 1984;20:579-81.

667. Lane T, MacGregor RR, Wright D and Hollander J. Cardiobacterium hominis: an elusive cause of endocarditis. J Infect Dis 1983;6:75-80.

668. Decker MD, Graham BS, Hunter ER and Liebowitz SM. Endocarditis and infections of intravascular devices due to Eikenella corrodens. Am J Med Sci 1986;292:209-12.

669. Jenny DB, Letendre PW and Iverson G. Endocarditis due to Kingella species. Rev Infect Dis 1988;10:1065-6.

670. Cohen PS, Maguire JH and Weinstein L. Infective endocarditis caused by gram-negative bacteria: a review of the literature. Prog Cardiovasc Dis 1980;22:205-42.

671. Komshian SV, Tablan OC, Palutke W and Reyes MP. Characteristics of left-sided endocarditis due to Pseudomonas aeruginosa in the Detroit Medical Center. Rev Infect Dis 1990;12:693-702.

672. Johansen HK, Kjeldsen K and Hoiby N. Pseudomonas mendocina as a cause of chronic infective endocarditisin a patient with situs inversus. Clin Microbiol Infect 2001;7:650-2.

673. Carvajal A and Frederiksen W. Fatal endocarditis due to Listeria monocytogenes. Rev Infect Dis 1988;10:616-23.

674. Spyrou N, Anderson M and Foale R. Listeria endocarditis: current management and patient outcome – world literature review. Heart 1997;77:380-3.

675. Baddour LM. Listeria endocarditis following coronary artery bypass surgery. Rev Infect Dis 1989;11:669.

676. Castro Cabezas M, Cramer MJ, de Jongh BM and de Maat CE. Listeria monocytogenes endocarditis in a patient with an aortic prosthetic valve. Neth J Med 1996;48:15-7.

677. Johnston PW and Trouton TG. Dietary precautions and listeria endocarditis? Heart 1998;79:206.

678. Alonso J, Revuelta JM, Marce L et al. Successful surgical treatment of a case of Listeria monocytogenes endocarditis. J Cardiovasc Surg 1988;29:140-2.

679. Gallagher PG and Watanakunakorn C. Listeria monocytogenes endocarditis: a review of the literature 1950-1986. Scand J Infect Dis 1988;20:359-68.

680. McIntosh CS, Vickers PJ and Isaacs AJ. Spirillum endocarditis. Postgrad Med J 1975;51:645-8.

681. Etienne J, Ory D, Thouvenot D et al. Chlamydial endocarditis: a report of 10 cases. Eur Heart J 1992;13:1422-6.

682. Norton R, Schepetiuk S and Kok TW. Chlamydia pneumoniae pneumonia with endocarditis. Lancet 1995;345:1376-7.

683. Lamaury I, Sotto A, Le Quellec A et al. Chlamydia psittaci as a cause of lethal bacterial endocarditis. Clin Infect Dis 1993;17:821-2.

684. Baorts E, Payne RM, Slater LN et al. Culture-negative endocarditis caused by Bartonella henselae. J Pediatr 1998;132:1051-4.

685. Keller LS, Sanders P, Shaw D and Broun MA. Salmonella prosthetic valve (mechanical) endocarditis managed conservatively. Intern Med J 2001;31:364-5.

686. Flannery MT, Le M and Altus P. Endocarditis due to Salmonelli. South Med J 2001;94:427-8.

687. Gomez-Moreno J, Moar C and Roman F. Salmonella endocarditis presenting as a cerebral haemorrhage. Eur J Intern Med 2000;11:96-7.

688. Rosenbach KA, Poblete J and Larkin I. Prosthetic valve endocarditis caused by Pasteurella dagmatis. South Med J 2001;94:1033-5.

689. Elsaghier AA, Kibbler CC and Hamilton-Miller JM. Pasteurella multocida as an infectious cause of endocarditis. Clin Infect Dis 1998;27:410-1.

690. LeMoal G, Roblot F, Paccalin M et al. Pacemaker endocarditis due to Yersinia enterocolitica. Scand J Infect Dis 2001;33:397.

691. Watson A, French P and Wilson M. Nocardia asteroides native valve endocarditis. Clin Infect Dis 2001;32:660-1.

692. Mannaerts HF, Hekker T and Visser CA. A rare case of aortic valve endocarditis caused by Tropheryma whippelii with left coronary cusp perforation diagnosed by transoesophageal echocardiography and PCR. Heart 1999;81:217.

693. Fenollar F, Lepidi H and Raoult D. Whipple's endocarditis:review of the literature and comparisons with Q fever, Bartonella infection and blood culture-positive endocarditis. Clin Infect Dis 2001;33:1309-16.

694. Gubler JG, Kuster M, Dutly F et al. Whipple endocarditis without overt gastrointestinal disease: report of four cases. Ann Intern Med 1999;1341:112-6.

695. Smith MA. Whipple endocarditis without gastrointestinal disease. Ann Intern Med 2000;132:595.

696. Antony S, Dummer S and Stratton C. Lactobacillus bacteremia and endocarditis. Clin Infect Dis 1998;26:1483-4.

697. Atkins MC, Nicolson L, Harrison GA et al. Lactobacillus jensenii prosthetic valve endocarditis. J Infect 1990;21:322-4.

698. Cohen CA, Almeder LM, Israni A and Maslow JN. Clostridium septicum endocarditis complicated by aortic-ring abscess and aortitis. Clin Infect Dis 1998;26:495-6.

699. Mendes CM, Oplustil CP, dos Santos TJ and Mady C. Clostridium perfringens as a cause of infectious endocarditis in a patient with a vascular prosthesis. Clin Infect Dis 1996;22:866-7.

700. Chen TT, Schapiro JM and Loutit J. Prosthetic valve endocarditis due to Legionella pneumophila. J Cardiovasc Surg 1996;37:631-3.

701. Kundsin RB and Walter CW. Legionella prosthetic-valve endocarditis. N Engl J Med 1988;319:581.

702. Tompkins LS, Roessler BJ, Redd SC et al. Legionella prosthetic-valve endocarditis. N Engl J Med 1988:530-5.

703. Klinger K, Brandli O, Doerfler M et al. Valvular endocarditis due to Mycobacterium tuberculosis. Int J Tuberc Lung Dis 1998;2:435-7.

704. Isaacson JH and Grenko RT. Rothia dentocariosa endocarditis complicated by brain abscess. Am J Med 1988;84:352-4.

705. Gorby GL and Peacock JE Jr. Erysipelothrix rhusiopathiae endocarditis: microbiologic, epidemiologic and clinical features of an occupational disease. Rev Infect Dis 1988;10:317-25.

706. Samuel L, Bloomfield P and Ross P. Gemella haemolysans prosthetic valve endocarditis. Postgrad Med J 1995;71:188.

707. Martin MJ, Wright DA and Jones AR. A case of Gemella morbillorum endocarditis. Postgrad Med J 1995;71:188.

708. Wilmshurst PT, Venn GE and Eykyn SJ. Histoplasma endocarditis on a stenosed aortic valve presenting as dysphagia and weight loss. Br Heart J 1993;70:565-7.

709. Ena J, Amador C, Parras F and Bouza E. Ciprofloxacin as an effective antibacterial agent in Serratia endocarditis. J Infect 1991;22:103-5.

710. Sanyal SK, Wilson N, Twum-Danso K et al. Moraxella endocarditis following balloon angioplasty of aortic coarctation. Am Heart J 1990;119:1421-3.

711. Lam S, Samraj J, Rahman S and Hilton E. Primary actinomycotic endocarditis: case report and review. Clin Infect Dis 1993;16:481-5.

712. Mossad SB, Tomford JW, Stewart R, Ratliff NB and Hall GS. Case report of Streptomyces endocarditis of a prosthetic aortic valve. J Clin Microbiol 1995;33:3335-7.

713. Gallagher PG and Watanakunakorn C. Group B streptococcal endocarditis: report of seven cases and review of the literature, 1962-1985. Rev Infect Dis 1986;8:175-88.

714. Simmons NA. Dentistry and endocarditis. Br Dent J 1990;169:74-5.

715. McGowan DA. Dentistry and endocarditis. Br Dent J. 1990;169:69.

716. Daly CG, Mitchell DH, Highfield JE and Grossberg DE. Bacteraemia due to periodontal probing:a clinical and microbiological investigation. Periodontol 2001;72:210-4.

717. Lamey PJ, MacFarlane TW, Patton DW et al. Bacteraemia consequential to sialography. Br Dent J;158:218-20.

718. DeLeo AA, Schoenknecht FD, Anderson MW and Peterson JC. The incidence of bacteraemia following oral prophylaxis on pediatric patients. Oral Surg 1974;37:36-45.

719. Lucas VS and Roberts GJ. Odontogenic bacteremia following tooth cleaning procedures in children. Pediatr Dent 2000;22:96-100.

720. Hunter KM, Holborow DW, Kardos TB et al. Bacteraemia and tissue damage resulting from air polishing. Br Dent J 1989;167:275-8.

721. Felix JE, Rosen S and App GR. Detection of bacteremia after the use of an oral irrigation device in subjects with periodontitis. J Periodontol 1971;42:785-9.

722. Bender IB, Seltzer S, Tashman S and Meloff G. Dental procedures in patients with rheumatic heart disease. Oral Surgery, Oral Med and Oral Pathol 1963;16:466-73.

723. Doerffel W, Fietze I, Baumann G and Witt C. Severe prosthetic valve-related endocarditis following dental scaling: a case report. Quintessence Int 1997;28:271-4.

724. Bandt CL, Korn NA and Schaffer EM. Bacteraemis from ultrasonic and hand instrumentation. J Periodontol 1964;35:214-5.

725. Ali MT, Tremewen DR, Hay AJ and Wilkinson DJ. The occurrence of bacteraemia associated with the use of oral and nasopharyngeal airways. Anaesthesia 1992;47:153-5.

726. Gerber MA, Gastanaduy AS, Buckley J and Kaplan EL. Risk of bacteremia after endotracheal intubation for general anesthesia. South Med J 1987;73:1478-80.

727. Dinner M, Tjeuw M and Artusio JF. Bacteremia as a complication of nasotracheal intubation. Anesth Analg 1987;66:460-2.

728. Stone JM, Karalliedde LD, Carter ML and Cumerland NS. Bacteraemia and insertion of laryngeal mask airways. Anaesthesia 1992;47:77.

729. Brimacombe J, Shorney N, Swainston R and Bapty G. The incidence of bacteraemia following laryngeal mask insertion. Anaesth Intensive Care 1992;20:484-6.

730. Longman CP and Martin MV. A practical guide to antibiotic prophylaxis in restorative dentistry. Dent Update 1999;26:7-14.

731. Berry FA, Yarbrough S, Yarbrough N et al. Transient bacteremia during dental manipulation in children. Pediatrics 1973;51:476-9.

732. Roberts GJ, Radford P and Holt R. Prophylaxis of dental bacteraemia with oral amoxycillin in children. Br Dent J 1987;162:179-82.

733. Kralovic SM, Melin-Aldana H, Smith KK and Linnemann CC Jr. Staphylococcus lugdunensis endocarditis after tooth extraction. Clin Infect Dis 1995;20:715-6.

734. Roberts GJ, Gardner P, Longhurst P, Black A and Lucas VS. Intensity of bacteraemia associated with conservative dental procedures in children. Br Dent J 2000;188:95-8.

735. Sonbol H, Spratt D, Roberts GJ and Lucas VS. Bacteraemia from conservative (restorative) procedures. Proceedings of 7th International Symposium on Modern Concepts in Endocarditis. 2002

736. Lineberger LT and De Marco TJ. Evaluation of transient bacteraemia following routine periodontal procedures. J Periodontol 1973;44:757-63.

737. Debelian GJ, Olsen I and Tronstad L. Bacteremia in conjunction with endodontic therapy. Endod Dent Traumatol 1995;11:142-9.

738. Farrington FH. The incidence of transient bacteremia following pulpotomies onprimary teeth. ASDC J Dent Child 1973;40:175-84.

739. Beechen II, Laston DJ and Garbarino VE. Transitory bacteremia as related to the operation of vital pulpotomy. J Oral Surg 1956;9:902-5.

740. Khurana M and Martin MV. Orthodontics and infective endocarditis. Br J Orthod 1999;26:295-8.

741. Roberts GJ, Watts R, Longhurst P and Gardner P. Bacteraemia of dental origin and antimicrobial sensitivity following oral surgical procedures in children. Pediatr Dent 1998;20:28-36.

742. McLaughlin JO, Coulter WA, Coffey A and Burden DJ. The incidence of bacteremia after orthodontic banding. Am J Orthod 1996;109:639-44.

743. Biancaniello TM and Romero JR. Bacterial endocarditis after adjustment of orthodontic appliances. J Pediatr 1991;118:248-9.

744. Peterson LJ and Peacock R. The incidence of bacteremia in pediatric patients following tooth extraction. Circulation 1976;53:676-9.

745. Burket LW and Burn CG. Bacteremias following dental extraction. Demonstration of source of bacteria by means of a non pathogen (Serratia marcesens). J Dental Research 1937;16:521-30.

746. Flood TR, Samaranayake LP, Macfarlane TW et al. Bacteraemia following incision and drainage of dento-alveolar abscesses. Br Dent J 1990;169:51-3.

747. Robinson L, Kraus FW, Lazansky JP, Wheeler RE and Johnson V. Bacteremias of dental origin. II. A study of factors influencing occurrence and detection. Oral Surgery, Oral Med and Oral Path 1950;3:923-6.

748. Heimdahl A, Hall G, Hedberg M et al. Detection and quantitation by lysis-filtration of bacteraemia after different oral surgical procedures. J Clin Microbiol 1990;28:2205-9.

749. Giglio JA, Rowland RW, Dalton HP and Laskin DM. Suture removal induced bacteremia: a possible endocarditis risk. J Am Dent Assoc 1992;123:69-70.

750. Brown AR, Papasian J, Shultz P, Thiesen D and Shultz RE. Bacteremia and intraoral suture removal: can an antimicrobial rinse help? J Am Dent Assoc 1998;129:1455-61.

751. King RC, Crawford JJ and Small EW. Bacteraemia following intraoral suture removal. Oral Surg Oral Med Oral Pathol 1988;65:23-8.

752. Zuccaro G Jr, Richter JE, Rice TW et al. Viridans streptococcal bacteremia after esophageal stricture dilation. Gastrointest Endosc 1998;48:568-73.

753. Meyer GW. Endocarditis prophylaxis for esophageal dilation: a confusing issue? Gastrointest Endosc 1998;48:641-3.

754. Subhani JM, Kibbler C and Dooley JS. Review article: antibiotic prophylaxis for endoscopic retrograde cholangio-pancreatography (ERCP). Aliment Pharmacol Ther 1999;73:103-16.

755. Breuer GS, Yinnon AM and Halevy J. Infective endocarditis associated with upper endoscopy: case report and review. J Infect 1998;36:342-4.

756. Norfleet RG. Infectious endocarditis after fiberoptic sigmoidoscopy. With a literature review. J Clin Gastroenterol 1991;13:448-51.

757. Watanakunakorn C. Streptococcus bovis endocarditis associated with villous adenoma following colonoscopy. Am Heart J 1988;116:1115-6.

758. Logan RF and Hastings JG. Bacterial endocarditis: a complication of gastroscopy. Br Med J 1988;296:1107.

759. Baskin G. Prosthetic endocarditis after endoscopic variceal sclerotherapy: a failure of antibiotic prophylaxis. Am J Gastroenterol 1989;84:311-2.

760. Foster E, Kusumoto FM, Sobol SM and Schiller NB. Streptococcal endocarditis temporally related to transesophageal echocardiography. J Am Soc Echocardiogr 1990;3:424-7.

761. Kullman E, Jonsson KA, Lindstrom E et al. Bateremia associated with extracorporeal shockwave lithotripsy of gallbladder stones. Hepatogastroenterology 1995;42:816-20.

762. Schlesinger Y and Urbach J. Circumcision and endocarditis prophylaxis. Arch Pediatr Adolesc Med 1998;152:412.

763. Roblot F, Le MG, Irani J et al. Infective endocarditis after transrectal prostatic biopsy. Scand J Infect Dis 2002;34:131.

764. Fervenza FC, Contreras GE, Garratt KN and Steckelberg JM. Staphylococcus lugdunensis endocarditis: a complication of vasectomy? Mayo Clin Proc 1999;74:1227-30.

765. Kessler RB, Kimbrough RC 3rd and Jones SR. Infective endocarditis caused by Staphylococcus hominis after vasectomy. Clin Infect Dis 1998;27:216-7.

766. Zimhony O, Goland S, Malnick SD et al. Enterococcal endocarditis after extracorporeal shock wave lithotripsy for nephrolithiasis. Postgrad Med J 1996;72:51-2.

767. Murai N, Katayama Y, Imazeki T et al. Post parturition infectious endocarditis in a patient with a normal mitral valve. Jpn J Thorac Cardiovasc Surg 1999;47:171-3.

768. Hughes LO, McFadyen IR and Raftery EB. Acute bacterial endocarditis on a normal aortic valve following vaginal delivery. Int J Cardiol 1988;18:261-2.

769. Pantanovitz L, Hodkinson J, Zeele R and Jones N. Gonococcal endocarditis after threatened abortion: a case report. J Reprod Med 1998;43:1043-5.

770. Panigrahi NK, Panda RS and Panda S. Tricuspid valve endocarditis following elective abortion. Indian J Chest Dis Allied Sci 1998;40:69-72.

771. Kangavari S, Collins J, Cercek B et al. Tricuspid valve group B streptococcal endocarditis after an elective termination of pregnancy. Clin Cardiol 2000;23:301-3.

772. Cobbs CG. IUD and endocarditis. Ann Intern Med 1973;78:451.

773. Mong K, Taylor D, Muzyka T et al. Tricuspid endocarditis following a Papanicolaou smear: case report. Can J Cardiol 1997;13:895-6.

774. Jurado RL and Klein S. Infective endocarditis associated with fiberoptic bronchoscopy in a patient with mitral valve prolapse. Clin Infect Dis 1998;26:768-9

775. Vigla M, Oren I, Bentur L et al. Incidence of bacteraemia following fiberoptic brochoscopy. Eur Respir J 1999;14:789-91.

776. Finelli PF and Ross JW. Endocarditis following nasal packing: need for prophylaxis. Clin Infect Dis 1994;19:984-5.

777. Cacoub P, Leprince P, Nataf P et al. Pacemaker infective endocarditis. Am J Cardiol 1998;82:480-4.

778. Wagshal AB, Tager S, Maor E et al. Implantable defibrillator endocarditis. Pacing Clin Electrophysiol 1999;22:1120.

779. Da Costa A, Kirkorian G, Cucherat M et al. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. Circulation 1998;97:1796-801.

780. Latson LA, McManus BM, Doer C et al. Endocarditis risk of the USCI PDA umbrella for transcatheter closure of patent ductus arteriosus. Circulation 1994;90:2525-8.

781. Bullock AM, Menahern S and Wilkinson JL. Infective endocarditis on an occluder closing an atrial septal defect. Cardiol Young 1999;9:65-7.

782. Goldstein JA, Beardslee MA, Xu H et al. Infective endocarditis resulting from CardioSEAL closure of a patent foramen ovale. Cathet Cardiovasc Interv 2002;55:217-20.

783. Moriyama Y, Toyohira H, Saigenji H et al. Infective mitral valve endocarditis after percutaneous transvenous mitral commissurotomy. Eur J Cardiothorac Surg 1995;9:111-2.

784. Park S, Montoya A, Moreno N et al. Infective aortic endocarditis after percutaneous balloon aortic valvuloplasty.Ann Thorac Surg 1993;56:1161-2.

785. Shrivastava S and Agarwal R. Infective endocarditis after balloon mitral dilatation. Int J Cardiol 1992;36:373.

786. Kalra GS, Wander GS and Anand IS. Right sided endocarditis after balloon dilatation of the pulmonary valve. Br Heart J 1990;63:368-9.

787. Cujec B, McMeekin J and Lopez J. Bacterial endocarditis after percutaneous aortic valvuloplasty. Am Heart J 1988;115:178-9.

788. Aziz S, Palmer N, Newall N and Ramsdale DR. Bacteraemia following complex percutaneous coronary intervention. TCT Meeting 2003, Washington, USA. Am J Cardiol 2003;64(Suppl):112L.

789. Palmer ND and Ramsdale D.R (2004). Mitral valve endocarditis resulting from Coagulase-negative Staphylococcus after stent implantation in a saphenous vein graft. Cardiology in Review 2004;12:in press.

790. Ramsdale D.R., Aziz S, Newall N and Palmer ND. (2004) Incidence of bacteraemia following complex percutaneous coronary intervention. J Invasive Cardiol 2004;in press.

791. Grech V, Sammut P and Parascandolo R. Bacterial endocarditis following lacrimal duct probing. J Pediatr Opthalmol Strabismus 2001;38:49-50.

792. Haas AF and Grekin RC. Antibiotic prophylaxis in dermatologic surgery. J Am Acad Dermatol 1995;32:155-76.

793. Flanagan PG and Carmichael A. Endocarditis following skin procedures. J Infect 1993;27:341-2.

794. Paterson P and Dunn KW. Bacterial endocarditis following minor burn injury. Case report and review. Burns 1999;25:515-7.

795. Apple J, Hunt JL, Wait M and Purdue G. Delayed presentations of aortic valve endocarditis in patients with thermal injury. J Trauma 2002;52:406-9.

796. Nambiar P and Ratnatunga C. Prosthetic valve endocarditis in a patient with Marfan's syndrome following acupuncture. J Heart Valve Dis 2001;10:689-90.

797. Scheel O, Sundsfjord A, Lunde P and Andersen BM. Endocarditis after acupuncture and injection – treatment by a natural healer. JAMA 1992;267:56.

798. Ramage IJ, Wilson N and Thomson RB. Fashion victim: infective endocarditis after nasal piercing. Arch Dis Child 1997;77:187.

799. Tronel H, Chaudemanche H, Pechier N et al. Endocarditis due to Neisseria mucosa after tongue piercing. Clin Microbiol Infect 2001;7:275-6.

800. Ochsenfahrt C, Friedl R, Hannekun A and Schumacher BA. Endocarditis after nipple piercing in a patient with a bicuspid aortic valve. Ann Thorac Surg 2001;71:1365-6.

801. Satchithananda DK, Walsh J and Schofield PM. Bacterial endocarditis following repeated tattooing. Heart 2001;85:11-2.

802. The Task Force on Infective Endocarditis of the European Society of Cardiology. Guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis. Executive Summary. Eur Heart J 2004;25:267-276.

803. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G and von Graevenitz A. The Task Force on Infective Endocarditis of the European Society of Cardiology. Guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis. Full Text. Eur Heart J 2004;00:1-37. www.escardio.org

804. Littler WA. Clindamycin suspension and endocarditis prophylaxis. Br Dent J 2001;190:407.

805. Wilson AP. Antibiotic prophylaxis in cardiac surgery. J Antimicrob Chemother 1988;21:522-4.

806. Wilson APR and Gaya H. Treatment of endocarditis with teicoplanin: a retrospective analysis of 104 cases. J Antimicrob Chemotherap 1996;38:507-21.

807. Burkert T and Watanakunakorn C. Group A streptococcus endocarditis: report of five cases and review of literature. J Infect 1991:23:307-16.

808. Plastino KA, Connors JE and Spinler SA. Possible synergy between aminoglycosides and vancomycin in the treatment of Staphylococcus epidermidis endocarditis? Ann Pharmacother 1994;28:737-9.

809. Whitby M. Fusidic acid in septicaemia and endocarditis.. Int J Antimicrob Agents 1999;12(Suppl 2):S17-22.

810. Fantin B, Leclerq R, Duval J and Carbon C. Fusidic acid alone or in combination with vancomycin for therapy of experimental endocarditis due to methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 1993;37:2466-9.

811. Eykyn SJ. Staphylococcal bacteraemia and endocarditis and fusidic acid. J Antimicrob Chemother 1990;25(Suppl B):33-8.

812. Fichtenbaum CJ and Smith MJ. Treatment of endocarditis due to Pseudomonas aeruginosa with imipenem. Clin Infect Dis 1992;14:353-4.

813. Sailler L, Marchou B, Lemozy J et al. Successful treatment of Actinobacillus actinomycetemcomitans endocarditis with ofloxacin. Clin Microbiol Infect 2000;6:55-6.

814. Hoeprich PD. Clinical use of amphoteracin B and derivatives: lore, mystique and fact. Clin Inf Dis 1992;14(Suppl 1):S114-9.

815. Woods GL, Wood P and Shaw BW Jr. Aspergillus endocarditus in patients without prior cardiovascular surgery: report of a case in a liver transplant recipient and review. Rev Infect Dis 1989;11:263-72.

816. Fowler VG and Durack DT. Infective endocarditis. Curr Opin Cardiol 1994;9:389-400.

817. Kawamoto T, Nakano S, Matsuda H et al. Candida endocarditis with saddle embolism: a successful surgical intervention. Ann Thorac Surg 1989;48:723-4.

818. Tanka M, Toshio A, Hosokawa S et al. Tricuspid valve Candida endocarditis cured by valve-sparing debridement. Ann Thorac Surg 1989;48:857-8.

819. Isalska BJ and Stanbridge TN. Fluconazole in the treatment of Candidal prosthetic valve endocarditis. Br Med J 1988;297:178-9.

820. Scottish Intercollegiate Guidelines Network (SIGN). http://www.sign.ac.uk

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 witrh 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 th 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

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 (**Timentin**^{R}) which is active against beta-lactamase producing bacteria resistant to ticarcillin. The ureidopenicillin **piperacillin** is more active than ticarcillin against *P.aeruginosa*. **Tazocin**^{R} (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 **ceftriaxone** 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 cephamycin antibiotic, is active against *Bacteroides fragilis*.

Beta-lactam antibiotics include **aztreonam, imipenem** and **meropenem. Aztreonam** 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 concentrastion 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.

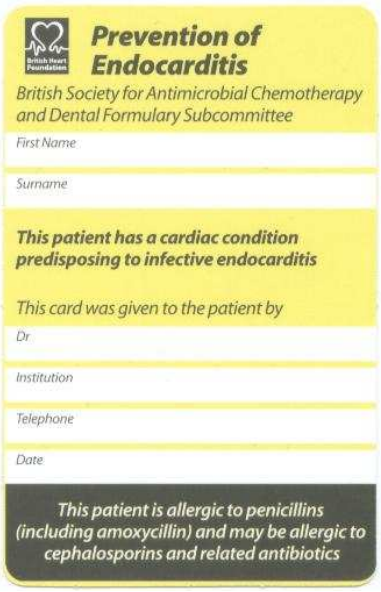
Synercid$^{\mathbf{R}}$ - a combination of the streptogramin antibiotics **quinupristin** and **dalfopristin** may be useful for Gram-positive bacterial endocarditis with MRSA or for patients who cannot be treated with other agents. It is not active against *Enterococcus faecalis*.

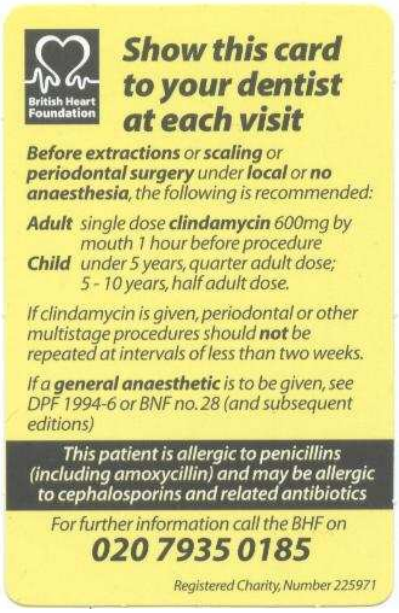
APPENDIX 3 ABBREVIATIONS

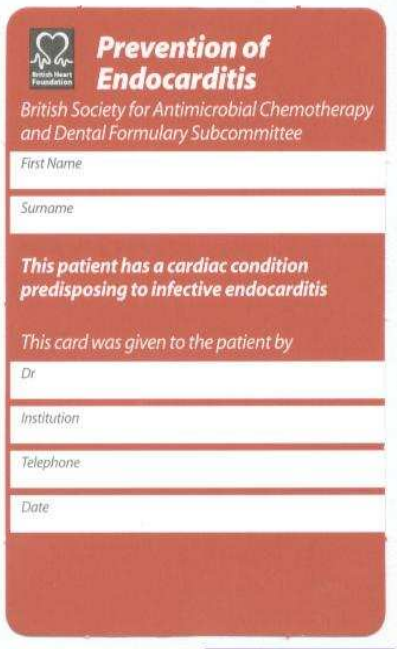
Abbreviation

AIDS	Acquired immuno-deficiency syndrome
AS	Aortic stenosis
AR	Aortic regurgitation
CNE	Culture negative endocarditis
CO_2	Carbon dioxide
CRP	C-reactive protein
CSF	Cerebrospinal fluid
ECG	Electrocardiogram
ECHO	Echocardiography
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
5-FC	5-flucytosine
G	gram
GA	General anaesthesia
GISA	Glycopeptide intermediate resistance *S. aureus*
hr	hour
IE	Infective endocarditis
IM	Intramuscular
IV	Intravenous
kg	kilogram
MBC	Minimal bactericidal concentration
MIC	Minimal inhibitory concentration
MIF	Microimmunofluorescence
min	minute
mls	milliliters
mg	milligram
MR	Mitral regurgitation
MRSA	Methicillin-resistant *S. aureus*
NVE	Native valve endocarditis
PAE	Post antibiotic effect
PCR	Polymerase chain reaction
PDA	Patent ductus arteriosus
PVE	Prosthetic valve endocarditis
spp	species
TOE	Transoesophageal Echocardiography
TTE	Transthoracic Echocardiography
TV	Tricuspid valve
VISA	Vancomycin intermediate resistance *S. aureus*
VRE	Vancomycin Resistant Enterococci

FIGURE 1. British Heart Foundation "Endocarditis Dental Warning Cards" for patients requiring dental prophylaxis with antibiotics







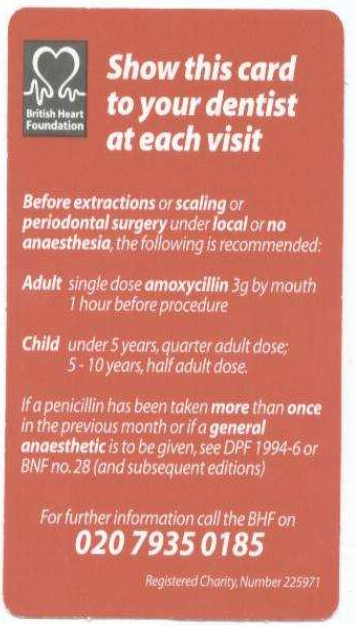


FIGURE 2. ALGORITHM FOR MANAGEMENT OF PATIENTS WITH INFECTIVE ENDOCARDITIS