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713–22. WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease (2004). Rheumatic fever and rheumatic heart di- sease: report of a WHO Expert Consultation, Geneva, 29 October–1 November 2001. WHO Technical Report Series 923, World Health Organization, Geneva. Zuhlke L, et al. (2016). Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income coun- tries: two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). Circulation, 134(19), 1456–66. 16.9.2 Endocarditis James L. Harrison, John L. Klein, William A. Littler, and Bernard D. Prendergast ESSENTIALS Endocarditis predominantly affects the aortic and mitral valves; in- volvement of the tricuspid valve occurs in approximately one-fifth of cases and pulmonary valve involvement is rare. In the developing world rheumatic heart disease is the most common predisposing factor. In developed countries endocarditis is more common in older people with native valve disease and in patients with prosthetic valves and intracardiac devices (pacemakers and defibrillators). In these countries up to 50% of cases have no predisposing cardiac lesion and more cases are related to intravenous drug abuse and nosoco- mial infection related to invasive procedures. Mortality remains high (30%) despite advances in antimicrobial therapy and surgery, and at least 50% of cases require valve surgery. Early diagnosis, specialist management, and timely intervention are key to successful outcome. Clinical features Presenting symptoms and signs include those of a bacteraemic illness, tissue destruction (heart valve(s) and adjacent structures); phenomena thought to be related to circulating immune com- plexes (e.g. splinter and conjunctival haemorrhages, Osler’s nodes, Janeway lesions, vasculitic rash, Roth spots, and nephritis; and sys- temic and septic pulmonary emboli in left- and right-sided lesions, respectively). Blood culture is the most important laboratory investigation, with prolonged incubation requested in circumstances where endocar- ditis is strongly suspected. Serological tests can aid in the identifi- cation of organisms that are difficult to isolate. Echocardiography should be performed as soon as possible when endocarditis is sus- pected: its principal role is to detect vegetations, but it is not suf- ficiently sensitive to allow the clinician to exclude the diagnosis confidently on the basis of a negative result. Diagnosis is based on pathological criteria (demonstration of microorganisms by cul- ture or histological examination, or histological evidence of active endocarditis) or—more usually—a combination of major and minor clinical criteria, with the major clinical criteria relating to (1) positive blood cultures of ‘typical’ or ‘consistent’ organisms, and (2) evidence of endocardial involvement detected on physical examination (new murmur) or with echocardiography. Causes and management Worldwide the principal causes of endocarditis are viridans strepto- cocci (up to 58%) and Staphylococcus aureus (30% of community- acquired and 46% of hospital-acquired disease) with Streptococcus bovis, enterococcus species, fungi, coagulase-negative staphylo- cocci, and the HACEK group of organisms making up the remainder. However, in developed countries the epidemiological profile has changed in recent decades: rheumatic heart disease is now rare, and with more cases related to prosthetic valves (20% of all cases) device therapy and nosocomial infection, Staph. aureus has overtaken oral streptococci as the most common pathogen. Best management is provided by a multidisciplinary team involving cardiologists, microbiologists, infectious disease specialists, and car- diac surgeons. Bactericidal antibiotics are the mainstay of treatment. Recommended empirical therapy for the patient with suspected na- tive valve endocarditis is amoxicillin or ampicillin (12 g/day IV in four divided doses) plus gentamicin (1 mg/kg body weight IV 8-hourly, modified according to renal function), substituting vancomycin for amoxicillin/ampicillin in patients with penicillin allergy. This should be modified to a definitive antibiotic treatment regimen when the pathogen is known. Surgery is required in about 50% of cases, with the main indications being haemodynamic instability, persistent in- fection, annular or

aortic abscesses, and significant residual valve re- gurgitation once antibiotic therapy is complete.

section 16 Cardiovascular disorders 3520 Prevention Until recently, antibiotic prophylaxis in at-risk patients—meaning any with a wide variety of cardiac lesions undergoing a wide var- iety of dental, medical, and surgical procedures—was accepted as reasonable, but there is no good evidence to support this prac- tice. Recommendations from relevant United Kingdom, European, and American professional bodies are now much more restrictive. National Institute for Health and Clinical Excellence (United Kingdom) guidelines state that antibiotic prophylaxis should only be given to high-risk patients (including those with prosthetic car- diac valves or other prosthetic material within their hearts, previous endocarditis, and some forms of congenital heart disease) if they are undergoing a gastrointestinal or genitourinary procedure at a site where there is suspected infection. Most cardiologists feel that this is too restrictive and prefer European and American guidelines that recommend prophylaxis before dental and nondental procedures for patients at high risk. When prophylaxis is recommended for dental and other pro- cedures, regimens typically include amoxicillin (or clindamycin if penicillin-allergic), with the addition of gentamicin if risks are thought to be high, and substitution of vancomycin (or teicoplanin) for amoxicillin if the patient is penicillin-allergic (or has taken more than a single dose of penicillin in the previous month). Historical background Lazarus Riverius recorded the first case of what is now known as endocarditis in 1723. He described a French magistrate with an ir- regular pulse, oedema, and congestion, who at autopsy had fleshy masses ‘the size of hazelnuts’ obstructing the aortic ostia. Some 50 years later, Morgani (1769) made the link between infection (fulminating gonorrhoea) and ‘whitish polypus concretions on the upper part of the aortic valve near its borders’. The clinical picture of endocarditis was first described by Jean Baptiste Bouillard, in 1835: ‘fever, an irregular pulse, cardiomegaly (by percussion) and a bellows murmur in the heart’. He gave the dis- ease the name ‘endocarditis’, or an inflammation of the inner mem- brane of the heart and fibrous tissues of the valve, and was the first to use the term ‘vegetations’ for the valvular lesions. Winge used the term ‘mycoses endocardi’ for the groups of microorganisms that he saw when he examined vegetations under the microscope in 1870. In 1886, Wyssecokowitch cultured Staphylococcus aureus from an endocardial vegetation. Lenthartz, in 1901, was the first to use blood cultures in the diagnosis of endocar- ditis. ‘Infective endocarditis’ was the term used by Thomas Horder, in 1901, to describe the syndrome consisting of (1) the presence of valvular disease, (2) the occurrence of systemic embolism, and (3) the discovery of microorganisms in the bloodstream. Epidemiology Endocarditis was universally fatal before the advent of antibiotic therapy. Despite significant advances in diagnosis and treatment, it remains a dangerous disease, particularly for people at risk (prosthetic valves, congenital heart disease, previous endocarditis), in whom morbidity and mortality approach 50%. About 200 deaths are recorded each year in the United Kingdom, but this is almost certainly an underestimate. A recent review of papers published be- tween 1993 and 2003 found the mean age of patients varied between 36 and 69 years, the median incidence being 3.6 per 100 000 popu- lation per year (range 0.3–22.4), increasing from 5 or less per 100 000 population per year in individuals aged younger than 50 years to 15 or more per 100 000 population per year in those older than 65 years. The median in-hospital mortality rate was 16% (range 11– 26%). The incidence is greater in men, in those over 65 years of age, and in those with prosthetic heart valves. In intravenous drug users, the incidence of endocarditis is estimated as 150–200 per 100 000 person years. Pathogenesis Normal vascular endothelium is resistant to microbial infection and very few patients potentially at risk actually develop endocar- ditis. Bacteraemia may occur spontaneously during chewing, tooth brushing, and other normal activities.

Since low-grade bacteraemia occurs frequently in everyone, a defence mechanism must exist that can eradicate microbes adherent to fibrin-platelet aggregates at the site of injured endothelium. Platelets play a pivotal role in the antimicrobial host-defence mechanism and human platelets have been found to contain at least 10 different bactericidal proteins or ‘thrombocidins’. Damage to the endothelial surface of the heart or blood vessels induces platelet and fibrin deposition producing a sterile thrombotic vegetation; endocarditis is initiated by the binding of microbes, dis- charged into the general circulation from a peripheral site, to these vegetations. These microbes become rapidly encased in further de- positions of platelets and fibrin, and multiply. The pathogenesis of endocarditis involves complex interactions between microbes and the host-defence mechanisms, both circu- lating and at the site of endothelial damage. An essential step is the activation of the clotting system and the formation of a fibrin clot on the endothelial surface. Experimental evidence suggests that the main pathogens in endocarditis (streptococci and staphylococci) can bind to endothelial cells and induce functional changes within these cells causing monocyte adhesion. The endothelial cells respond to local inflammation by expressing β1-integrins which promote the adhesion of pathogens that carry fibronectin-binding proteins on their surface. The combination of damaged endothelial cells, bac- teria, and endothelial bound monocytes results in the induction of tissue-factor-dependent procoagulant activity which initiates clot formation. Polymorphonuclear leucocytes which are recruited to the infected endothelial site may be subsequently involved in the disease progression, with the contents of lysosomes released by the activated leucocytes probably causing softening and separation of valve tissue, leading to its destruction. In endocarditis, the vegetations are found predominately on the left side of the heart (85%). In a large autopsy series of more than 1000 cases reported over 50 years ago, the mitral valve was involved in 86%, the aortic in 55%, the tricuspid in 20%, and the pulmonary valve in only 1%. The predominance of left-sided lesions has led to the belief that the higher pressures and velocities encountered in the

16.9.2 Endocarditis 3521 left side of the heart and the proximal aorta must impose a greater mechanical stress on the valves and endocardium, which in turn leads to local damage. Endocarditis is classically associated with ‘jet lesions’, where blood flowing from a high-pressure area through an orifice to an area of lower pressure produces a high-velocity jet. Vegetations are usually found in the lower-pressure area (e.g. on the atrial surface of the mitral valve in mitral regurgitation, or the ventricular surface of the aortic valve in aortic regurgitation). This particular deposition of vegetations has been explained on the basis of the Venturi effect. Once a vegetation is established, it determines the subsequent clinical picture by four basic processes: bacteraemia, local tissue de- struction, embolization, and the formation of circulating immune complexes. Clinical features Early reports of endocarditis described a low-grade, febrile illness caused by viridans streptococci from the mouth in a patient with chronic rheumatic heart disease. Night sweats, anorexia, and weight loss were followed by the development of splinter haemorrhages and Osler nodes, finger clubbing, and splenomegaly. The infection pro- gressed relentlessly with increasing cachexia, and the patient died from cardiac failure or a major embolic episode. The term ‘subacute bacterial endocarditis’ was used to describe this illness. ‘Acute or malignant endocarditis’ described an aggressive form of the disease, usually caused by Staph. aureus or other virulent bacteria. During the past 50 years, there has been a striking change in the pattern of endocarditis. The proportion of patients in developed countries with endocarditis who have no known pre-existing car- diac lesion has risen to almost 50%. This change is related both to the decline in rheumatic heart disease and to the increase in extracardiac predisposing factors, including intravenous drug abuse, haemodi- alysis, and the use of intravascular devices. Prosthetic

heart valves are an important predisposing factor and cardiac surgery for com- plex congenital lesions has increased the lifespan of patients who would previously have died prematurely. Antibiotic-resistant organ- isms have emerged. The longevity of the populations of developed countries has resulted in an increasing age of patients with endo- carditis, with mean age rising from under 40 years before 1940, to 60–70 years today. For the general physician, the diagnosis of endocarditis is de- pendent upon a high index of suspicion. In the older population, with a high incidence of degenerative valvular disease, an early pres- entation of endocarditis may often be misdiagnosed and treated as a urinary or upper respiratory tract infection with an incidental finding of a heart murmur. Routine investigation with blood cultures of all patients with a history of valvular heart disease presenting with fever, sepsis, or malaise is therefore recommended. Features of a bacteraemic illness Discharge of the infecting agent into the circulation produces constant bacteraemia which may present as pyrexia, rigors, mal- aise, anorexia, headache, confusion, arthralgia, and anaemia. Some cases of endocarditis, particularly in older people, may present without fever. Features of tissue destruction Endocarditis initially affects valve cusps, leaflets, or chordae tendineae. Tissue destruction results in valvular incompetence, cusp perforation, or rupture of the chordae, producing an appropriate cardiac murmur that may change in character during the course of the illness: 80% of patients present with a murmur, and 15–20% develop one during their hospital stay. Large vegetations rarely ob- struct a native valve, but mechanical obstruction of prosthetic valves is more common and clinically more difficult to detect. As the infective process progresses, it may extend beyond the valve into the paravalvular structures. Aortic root abscess is a serious complication: extension through the aortic wall into other tissues or cavities can create a fistula or pseudoaneurysm. Particular prob- lems can include the development of a sinus of Valsalva aneurysm and involvement of the coronary ostia. Septal abscesses can lead to progressive conduction defects evidenced by prolongation of the PR interval on the electrocardiogram (ECG) and, eventually, complete heart block. Paravalvular abscess is more common in native aortic valve endo- carditis than in mitral valve infection. Infection of a mechanical valve involves the sewing ring and may lead to valve dehiscence. In the case of a mechanical aortic valve, where infection is often local- ized to the junction between the sewing ring and the aortic annulus, a large false aneurysm may develop in this area. Free-wall myocar- dial abscesses may rupture and cause sudden death. Features of systemic or pulmonary emboli Fragments of an infected vegetation may be dislodged into the sys- temic or pulmonary circulation, producing emboli in 20–40% of cases (up to 50% reported in autopsy series). These may lodge in any part of the circulation and present as a cerebrovascular accident, limb arterial occlusion, myocardial infarction, sudden unilateral blindness, or infarction of the spleen or a kidney. Septic embolism from the left side of the heart may result in the formation of a cere- bral abscess. In right heart endocarditis, recurrent septic pulmonary emboli may be misinterpreted as ‘pneumonia’. Mycotic aneurysms arise from embolism of the vasa vasorum that weakens the arterial wall: these have been reported in almost 3% of clinical cases but are found in up to 15% at autopsy. In the cerebral circulation, such aneurysms may produce subarachnoid haemor- rhage or intracerebral haemorrhage. The popliteal artery is also a common site for mycotic aneurysms. Emboli are characteristic of Staph. aureus infections and large em- boli are a feature in HACEK and fungal endocarditis. They usually occur before or within the first few days after starting antimicro- bial therapy. Anterior mitral valve-leaflet vegetations are more likely to embolize than aortic valve vegetations, especially if they are highly mobile. Vegetation size does not predict systemic embolism, but large vegetations (>10 mm) are associated with poor overall outcome. After an embolic complication, recurrent episodes are likely to follow, especially if vegetations persist on

echocardiography. In more than 50% of cases, such recurrence occurs within 30 days of the first episode. The risk of embolism falls rapidly after the initiation of anti- biotic therapy but is not reduced by treatment with anticoagulants or antiplatelet therapy: both may increase the risk of bleeding and should be avoided unless they are essential.

section 16 Cardiovascular disorders 3522 Features of circulating immune complexes The infected vegetation acts as an antigen that triggers an im- mune response. Chronic antigenaemia stimulates generalized hypergammagloblinaemia such that after several weeks of infection a variety of autoantibodies can be detected. Immune complex de- position probably causes many of the extracardiac manifestations of endocarditis, but these classical signs are relatively uncommon and frequently absent in acute presentations. • Splinter haemorrhages (5–15% of cases)—found in the nail bed of the fingers and, less commonly, the toes (Fig. 16.9.2.1). • Conjunctival haemorrhages. • Osler's nodes (5–10% of cases)—transient painful erythema- tous nodules that are found at the ends of fingers and toes and the thenar and hypothenar eminences which may be due to mi- nute infected emboli rather than immune complex deposition (Fig. 16.9.2.2). • Janeway lesions—irregular painless erythematous macules found in roughly the same distribution as Osler's nodes (Fig. 16.9.2.3); they tend to blanch with pressure. • Vasculitic rash—due to immunoglobulin and complement de- posits in the walls of skin capillaries (Fig. 16.9.2.4). • Roth spots (5% of cases)—boat-shaped haemorrhages in the retina are often called Roth spots, but true Roth spots are white retinal exudates that may be surrounded by haemorrhage that consist of perivascular lymphocyte collections. • Splenomegaly—clinical splenomegaly is less common than was reported in earlier literature (20% of cases); however, abdominal CT scanning demonstrates splenomegaly in at least 50% of cases, often with associated splenic infarcts (Fig. 16.9.2.5). Splenic ab- scesses may occur, and splenic rupture can be fatal. • Nephritis (10–15% of cases)—immune complexes can cause glomerulonephritis, manifest as proteinuria, haematuria, and de- cline in renal function, with immunoglobulin and complement deposition within glomeruli on renal biopsy. Key investigations are simple dipstick testing of the urine (with microscopy if more than 1 + positive for blood and/or protein) and measurement of serum creatinine. • Arthralgia—joint manifestations may result from immune com- plex deposition in the synovial membrane. Fig. 16.9.2.1 Splinter haemorrhages. Fig. 16.9.2.2 Osler's nodes involving the fingers and the thenar and hypothenar eminences. Fig. 16.9.2.3 Janeway lesions on the under surface of the left big toe. Fig. 16.9.2.4 Vasculitic rash of the lower limb.

16.9.2 Endocarditis 3523 Other features Up to 30% of patients with endocarditis present with neurological symptoms: these are most common in staphylococcal infection, in which one-third present with the clinical features of menin- gitis. Headaches, confusion, and toxic psychosis can be present as well as encephalomyelitis. It is not certain whether some of these neurological manifestations result from repeated small emboli or from a vasculitic process within the cerebral circulation as a consequence of immune complex deposition. The cerebrospinal fluid can show an increase in white cells, but is usually sterile on culture. Very occasionally it may be positive for staphylococcal infection. Although immune-mediated glomerulonephritis has been re- garded as the typical renal lesion of endocarditis, this assumption was based on small series predating modern treatment regimens. More recent work indicates that the most common histological finding is renal infarction. Circulatory compromise can rarely cause severe renal impairment as a result of renal cortical necrosis. Finger clubbing is one of the classical features of endocarditis, usually seen after 1 or 2 months of the illness. It is seldom seen now, but when present is still a useful sign

because it rarely occurs in con- ditions with which endocarditis can be confused. Specific types or circumstances of endocarditis Prosthetic valve endocarditis Patients with prosthetic heart valves have a small, but constant, risk of endocarditis, estimated at 0.2–1.4 events per 100 patient years. The incidence of prosthetic valve endocarditis is about 3% in the first postoperative year, with the highest risk during the first 3 months. Prosthetic valve endocarditis is five times more common in the aortic area than the mitral area and may involve mechanical, xeno- graft, and homograft valves. Prosthetic valve endocarditis has been classified as early or late ac- cording to its temporal relationship to surgery. Early prosthetic valve endocarditis usually occurs within 60 days of open heart surgery and accounts for 30% of cases. It is caused either by contamination of the prosthetic valve at implantation or by perioperative bacter- aemia from intravenous catheters, arterial lines, urethral catheters, or endotracheal tubes. The most common organisms are coagulase- negative staphylococci. Late prosthetic valve endocarditis accounts for 70% of cases and usually occurs 60 days or more after surgery. The pathogens are those seen in native valve endocarditis, with a preponderance of viridans streptococci and staphylococci, but with a higher incidence of other organisms. Some patients with late prosthetic valve endocarditis will have acquired the infection at the time of surgery, but a bacteraemia is usually the principal cause. Bacteraemia in a patient with a prosthetic valve must always be taken seriously, but it may not always be the result of endocarditis. The clinical picture of prosthetic valve endocarditis is typically fever, malaise, and weakness, with the more classical signs usually absent. The condition is often insidious and clinically difficult to diagnose. A new murmur may appear, and heart failure and embolic phenomena cause high mortality (20–50%). Infection in a mech- anical valve is located in the sewing ring, from which the infection can spread into the host tissues producing annular/myocardial ab- scesses, paravalvular leak, and prosthetic dehiscence. Infection of a tissue valve usually involves the valve leaflets, resulting in destruc- tion or perforation and valvular incompetence. Vegetations may cause obstruction with all forms of prosthetic valve. The diagnosis of prosthetic valve endocarditis requires a high index of clinical suspicion, blood cultures, and transoesophageal echocardiography, which is far superior to the transthoracic ap- proach for detecting vegetations and identifying periprosthetic spread of infection. Vegetations are more difficult to identify in pa- tients with mechanical valves than those with bioprostheses. Right-sided endocarditis Right-sided endocarditis accounts for only 5% of cases overall, but centres that treat large numbers of intravenous drug users will have a higher incidence. The clinical picture differs significantly from left-sided disease. It is usually associated with intravenous drug ad- diction or indwelling intravascular devices, including pacemakers, implantable defibrillators, central venous lines of all types, and septal occluder devices. Staph. aureus is the most common pathogen and the tricuspid valve is more commonly affected (80%) than the pul- monary valve. Fever is almost always present and a cardiac murmur is found in 80% of cases. There may be septic pulmonary emboli (Fig. 16.9.2.6) and the resultant pulmonary infarcts may cavitate. Symptoms include cough, haemoptysis, and pleuritic chest pain; a chest radiograph shows pulmonary infiltrates, which are often mis- interpreted as ‘patches of pneumonia’. Renal involvement (most commonly abscess formation or diffuse pyelonephritis) has been described in over one-half of cases. Myocarditis is more common in right-sided involvement than left. Peripheral stigmata, spleno- megaly, and central nervous system involvement are rare (no more than 5% of cases). Death is most commonly due to sepsis, rarely to heart failure. Fig. 16.9.2.5 CT scan showing multiple splenic infarcts within an enlarged spleen.

section 16 Cardiovascular disorders 3524 Endocarditis in intravenous drug users Endocarditis is a serious complication of intravenous drug abuse. The right side of the heart is affected most commonly, but the left may also be involved in a substantial number of patients (37%), and both right and left side in a few (7%). On the left side, mitral and aortic valves are equally infected. A history of previous heart disease is found only in some 25% of cases. Staph. aureus is responsible for 40% of all cases. Streptococci and enterococci are the next most common pathogens. Less com- monly, fungi and Gram-negative bacilli can cause endocarditis in intravenous drug users, and polymicrobial endocarditis accounts for 5% of cases. The skin is the most common site from which pathogens enter the bloodstream via needles. Gram-negative bacilli are rarely recovered from needles or the drug itself, and it has been suggested that these organisms come from tap water, sinks, or lavatory pans. The clinical picture of endocarditis associated with intravenous drug use depends on which side of the heart is affected. Right-sided disease is described earlier; left-sided disease behaves like that seen in nondrug cases, with a high incidence of heart failure, arterial embolism, central nervous system involvement, and peripheral stigmata. The overall mortality depends on when the patient presents: it is high if they present late, reflecting among other things the frequent challenges in dealing with intravenous drug users, because of poor compliance and failure to discontinue drug use. The principles of management are similar to those in patients who are not drug users. The duration of intravenous antibiotics should be at least 4 weeks, but this is frequently impossible in practice. Furthermore, there are often legitimate concerns regarding the risk of reinfection of a pros- thetic valve and surgery requires very careful consideration in this patient group. Endocarditis in children Endocarditis does occur in children but is rare, especially in the first decade of life. In the early literature, tetralogy of Fallot was the cardiac problem most commonly associated with endocarditis. Complex cyanotic disease, congenital heart disease corrected with prosthetic material, and small ventricular septal defects now make up the bulk of cases. Diagnosis of endocarditis Laboratory methods Blood culture This is the most important laboratory investigation in the diag- nosis of endocarditis (Table 16.9.2.1). Isolation of the pathogen enables an effective antibiotic treatment regimen to be devised. Optimal technique is necessary to avoid false-positive cases due to contaminating skin organisms. The recommended regimen for obtaining blood cultures is that three sets of blood cultures should be taken from a separate venepuncture sites over 24 h at least 1 h apart, with at least 10 ml of blood injected into one aerobic and one anaerobic culture bottle. Blood cultures should be taken be- fore antibiotics are given; if they have already been given, cultures should still be done and, if possible, the administration of further antibiotics delayed for a few days. However, previous antibiotics may render the blood sterile for some time, and the chances of re- covering the pathogen, particularly when it is a sensitive organism such as viridans streptococcus, are very low. Much mystique has been attached to the number and timing of blood cultures in cases of suspected endocarditis. What is known is that the bacteraemia is usually constant and in most cases all bottles will grow the pathogen whenever the blood is obtained for culture and however many sets are taken. There are, of course, rare exceptions when only a few bottles taken are positive, and this is one reason why it is conventional to take three sets. Another reason for several cultures is to assess the relevance of the common skin contaminants (par- ticularly coagulase-negative staphylococci and Corynebacterium) that can cause endocarditis. In most laboratories, blood culture systems are automated, with continuous monitoring to flag up growth for further investiga- tion. Most cultures become positive within 48 h and after this the chances of isolating the pathogen recede (with the exception of fas- tidious organisms of the HACEK group that may take much longer to recover). In most laboratories, blood cultures are incubated for 5–7 days, but this may not be long enough for

the rare fastidious slow grower. The onus is on the clinical microbiologist or clinician to request prolonged incubation for blood cultures from patients in whom endocarditis is strongly suspected, who have not had pre- vious antibiotics, and whose blood cultures are sterile after a week's incubation. Other routine blood tests In endocarditis, an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are almost invariable, and these in- flammatory markers are used most commonly to monitor the ac- tivity of the disease. A normochromic normocytic anaemia is often present and a polymorphonuclear leucocytosis is found in most cases. Hypergammaglobulinaemia and a low serum complement may be present, together with a false-positive rheumatoid factor. Circulating immune complexes may be detected. Fig. 16.9.2.6 CT scan of the chest showing multiple pulmonary infarcts in a case of right-sided endocarditis of the tricuspid valve in an intravenous drug abuser.

16.9.2 Endocarditis 3525 Serological tests aid in the identification of organisms that are difficult to isolate, including bartonella, coxiella (Q fever), myco- plasma, legionella, brucella, and fungi. Candida antibodies are of no diagnostic value. Echocardiography In suspected cases of endocarditis, transthoracic echocardiography should be performed as soon as possible and interpreted by an ex- perienced cardiologist. Its principal role is to detect vegetations (Fig. 16.9.2.7), but it is not sufficiently sensitive to allow the clin- ician to exclude the diagnosis confidently on the basis of a negative result. The sensitivity depends on the size of the vegetations and the time course of the disease: it can resolve vegetations as small as 1–2 mm, but confident identification is more difficult with pros- thetic than native valves and more difficult with mechanical than biological prostheses. Vegetations appear as thick, ragged, nonuniform echoes oscillat ing on or around a cardiac valve or in the path of a regurgitant jet. They need to be differentiated from other conditions which produce echo-density on cardiac valves, including calcification, myxoma- tous degeneration, and atrial myxoma. Vegetations do not usually restrict leaflet mobility and exhibit valve-dependent motion. On na- tive valves, vegetations are usually attached to the ventricular side of the aortic valve and the atrial side of the mitral and tricuspid valves (Fig. 16.9.2.8). Vegetations tend to be larger on the right side and can be demonstrated in 80–100% of cases. Transoesophageal echocardiography improves the rate of diag- nosis of endocarditis over that of transthoracic echocardiography, particularly in the presence of a prosthetic valve. It also makes it easier to recognize many complications of prosthetic valve endocar- ditis, such as abscesses, fistulae, and paravalvular leak. Table 16.9.2.1 Microbiological diagnosis of endocarditis Organism Proportion of cases Relevant clinical history Blood cultures Serology Staphylococcus aureus 30% of community community-acquired; 70% of hospital-acquired IVDU/IV access devices Usually positive Not routinely available (antilipid S antibodies have shown some promise) Coagulase-negative staphylococci 5–10% Prosthetic valves/cardiac devices Usually positive Not available Viridans group streptococci 20–30% Dental abscess/poor oral hygiene Positive, if no recent antibiotics Not available Streptococcus bovis group 5–10% Gastrointestinal neoplasia//older patient population Positive, if no recent antibiotics Not available HACEK group 3% Dental treatment/URTI Most positive in 6 days Not available Fungal <5% Prosthetic valves/IVDU/ immunosuppression/long-term IV lines Filamentous fungi rarely positive, candida usually positive Galactomannan and β-D glucan tests may have a role, but few studies in endocarditis Enterococcus spp. 10% Urological procedures/urinary catheterization/older patients Positive, if no recent antibiotics Not available Brucella spp. <% Endemic area/contaminated milk or dairy product consumption Positive in 80%. May need prolonged incubation Reference assay = tube agglutination Coxiella burnetii

(Q fever) 1% Farming background/exposure to domestic ruminants/raw milk consumption/previous valvulopathy Rarely positive. Tissue cell culture reported as optimal method Major criteria for modified Duke criteria: Antiphase 1 IgG >800 and IgA antibody

> 100 is highly sensitive Reference assay = microimmunofluorescence Bartonella spp. 13% Homelessness (body lice)/ alcoholism/exposure to cats Rarely positive Reference assay = microimmunofluorescence Legionella spp. <1% May be associated with an outbreak Rarely positive. Urinary antigen. Bronchial washings/sputum High antibody levels Reference assay = microimmunofluorescence IV, intravenous; IVDU, intravenous drug use; URTI, upper respiratory tract infection. Fig. 16.9.2.7 A transthoracic echocardiogram showing a large vegetation involving the mitral valve.

section 16 Cardiovascular disorders 3526 Examination of the heart valve and other tissues Histology Histology remains the gold standard for explanted valves. When valve replacement is undertaken, valvular tissue (including vegeta- tion) should be examined histologically and cultured for the pres- ence of microorganisms, which may allow postoperative antibiotics to be tailored accordingly. However, the isolation of microorganisms by valvular culture is infrequent: only 15% in one large series, with staphylococci being most common. Fastidious and rare microorgan- isms have been demonstrated on heart valves by various staining techniques and, more recently using tissue polymerase chain reac- tion techniques. Nucleic acid-based techniques Polymerase chain reaction (PCR) techniques are now widely used for samples obtained from heart valves and embolic tissue in pa- tients with suspected endocarditis. Most laboratories use a broad range strategy, with primers designed to capture all bacteria (e.g. targeting the 16s rRNA gene). Such tests have a sensitivity of around 80% due to the high concentration of bacteria, and hence bacterial DNA, in vegetations. Where available, PCR-based tests should be applied routinely to explanted heart valves in cases of endocarditis of unknown aetiology. By contrast, broad range PCR tests applied to whole blood have a much lower sensitivity and hence are not rou- tinely recommended. Criteria for the diagnosis of endocarditis In 1994, Durack and colleagues introduced criteria for the diag- nosis of endocarditis that have been accepted as the ‘Duke criteria’ and categorize patients into definite, possible, and rejected groups. Although these criteria have been shown to be superior to previous diagnostic tools, they have limitations: in particular, there is a pos- sibility of misclassification when blood cultures remain negative or echocardiography is inconclusive. Negative blood cultures occur in 5–31% of cases of endocarditis, commonly due to prior antibiotic therapy, but also as a result of infection with fastidious and atyp- ical microorganisms. Transthoracic echocardiography visualizes vegetations in only about 50% of cases: transoesophageal echocar- diography has a higher sensitivity for detection on both native and prosthetic valves, but will only be diagnostic in 50–94% of cases. These issues mean that the number of patients who may be incor- rectly diagnosed as having possible endocarditis, as opposed to def- inite, could be as high as 24%. Modification of the Duke criteria to increase their sensitivity has been suggested by several authors (Table 16.9.2.2). Positive serology for typical microorganisms and the use of polymerase chain reaction techniques have been suggested as major criteria, and the following additional minor criteria have been proposed: newly diagnosed clubbing; splenomegaly; splinter haemorrhages and petechiae; microscopic haematuria; a high ESR

or CRP; and the presence of central nonfeeding lines and peripheral lines. Microbiology Although almost any microorganism can cause endocarditis, par- ticularly when this involves a prosthetic valve, certain species do so much more commonly than others. The predominant species involved in the infection have not changed significantly in their incidence in the past three decades. Overall, viridans streptococci and staphylococci account for about two-thirds of cases. However, endocarditis cannot be considered as a microbiologically homo- geneous entity as the incidence of any specific organism depends (1) on the patient, whether an intravenous drug user or not; (2) on the valve, whether native or prosthetic—and if native, whether pre- viously abnormal or not, and if prosthetic whether mechanical or a bioprosthesis, and whether the infection was acquired early or late; and (3) where (and how) the infection was acquired, whether in the community or (as increasingly these days) in hospital, usually via an infected intravascular device. The more common species encountered are considered individually. Streptococci The genus Streptococcus includes species of differing virulence and pathogenicity as well as differing normal habitat in humans. Viridans streptococci For many years, it has been conventional to refer to a group of streptococci that produce greening (α-haemolysis) on blood agar as viridans streptococci; indeed, many still refer (inaccurately) to a microbe ‘Streptococcus viridans’. Although most of these strepto- cocci are virtually specific to the normal oropharyngeal flora and are rarely encountered at other sites, some are not found in the oro- pharynx at all (e.g. Strep. bovis), and others are found at many sites including the oropharynx (e.g. the milleri group of streptococci). The most common species of the viridans streptococci specific to the oropharynx are Strep. sanguis, Strep. oralis, and Strep. mutans, but there are others. Dextran formation may be a virulence factor in these streptococci. Contrary to popular belief, they do not re- quire a dental extraction to enter the bloodstream and cause fre- quent bacteraemias after chewing, tooth brushing, and so on. They are organisms of low virulence and thus usually only infect previ- ously abnormal heart valves. Whereas Strep. oralis and Strep. sanguis are occasionally isolated from blood cultures of patients who do not have endocarditis, the isolation of Strep. mutans from the blood is virtually synonymous with endocarditis. Fig. 16.9.2.8 Bacterial vegetations on the mitral valve—the patient had died as a result of a large cerebral embolism.

 Streptococcus bovis This streptococcus, which may appear ‘viridans’ on blood agar, is part of the normal intestinal flora, but may initially be mistaken for an oral streptococcus. In common with the enterococci, it bears the Lancefield group D antigen and thus can also be mistaken for Enterococcus faecalis, though it is sensitive to penicillin whereas the latter is resistant. There is a significant association between Strep. bovis bacteraemia (and hence endocarditis) and colonic pathology, and any patient with Strep. bovis endocarditis thus warrants appro- priate investigation. Strep. bovis endocarditis is much less common than that caused by oral streptococci. Pyogenic streptococci These organisms, often referred to as β-haemolytic streptococci, cause endocarditis less frequently than the viridans strepto- cocci, but are more aggressive microbes and likely to affect (and often rapidly destroy) a previously normal valve. The commonest pyogenic streptococcus to cause endocarditis is the Lancefield group B β-haemolytic streptococcus (GBS), sometimes referred to as Strep. agalactiae. This organism is found as normal flora in the genital and gastrointestinal tracts. As with Staph. aureus, any patient with community-acquired group B β-haemolytic strepto- coccus bacteraemia should be assumed to have infection in bone, Table 16.9.2.2 Duke criteria for the diagnosis of endocarditis and proposed modifications Duke criteria Suggested modifications Pathological criteria Microorganisms demonstrated by culture or histological examination Active endocarditis demonstrated by histological examination

Major criteria Positive blood cultures To be added: Typical microorganisms consistent with endocarditis from two separate blood cultures Positive serology for Coxiella burnetii Microorganisms consistent with endocarditis from persistently positive blood cultures Bacteraemia due to Staph. aureus Positive molecular assay for specific gene targets and universal loci for bacteria and fungi Positive serology for Chlamydia psittaci Positive serology for Bartonella spp. Evidence of endocardial involvement Echocardiography—oscillating structures, abscess formation, new partial dehiscence
of prosthetic valve Clinical—new valvar regurgitation Minor criteria Predisposing heart disease To be omitted: Fever >38 °C Suspect echocardiography (no major criterion) Vascular phenomena To be added: Immunological phenomena Elevated CRP, elevated ESR, splenomegaly, haematuria, clubbing, splinter haemorrhages, petechiae, purpura Microbiological evidence (no major criterion) Identified IE organism from metastatic lesions Suspect echocardiography (no major criterion) Categories Definite: Pathological criteria positive or 2 major criteria positive or 1 major and 2 minor criteria positive 1 major and 1 minor criterion positive or 5 minor criteria positive 3 minor criteria positive Possible: All cases which cannot be classified as definite or rejected Rejected: Alternative diagnosis Resolution of the infection with antibiotic treatment for <4 days No histological evidence CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IE, infective carditis. Reproduced from Heart, Prendergast BD, Vol 92, pp. 879–85. The changing face of infective endocarditis. Copyright (2006) with permission from BMJ Publishing Group Ltd.

section 16 Cardiovascular disorders 3528 joint, or on a heart valve until proved otherwise. Groups C and G β-haemolytic streptococci occasionally cause endocarditis, and group A even more rarely. The milleri group of streptococci are best regarded as pyogenic streptococci: they form part of the normal flora of all mucous membranes and occasionally cause endocarditis, though much more often cause abscesses at many different sites. The milleri group consists of three species, Strep. constellatus, Strep. intermedius, and Strep. anginosus. Streptococcus pneumoniae (pneumococcus) Pneumococcal endocarditis accounted for about 10% of cases of endocarditis in the preantibiotic era, but is now rarely seen, although it is sometimes diagnosed at autopsy of patients with fatal pneumo- coccal infection. The pneumococcus is a virulent pathogen and attacks normal heart valves. Patients with endocarditis generally have pneumonia and sometimes meningitis. Enterococci Enterococci form part of the normal gastrointestinal flora. They are more virulent than viridans streptococci and more resistant to anti- biotics. The incidence of enterococcal endocarditis is increasing, particularly in older people, but this infection is still much less common than that caused by viridans streptococci. While there are many species of enterococci, those causing endocarditis are usually E. faecalis and occasionally E. faecium. Most cases are community acquired, but the infection can sometimes be acquired in hospital as a result of urological instrumentation. Any patient admitted from the community with E. faecalis in the blood should be investigated for endocarditis. Staphylococci Staphylococci now account for about one-third of cases of community-acquired endocarditis and are the most common cause of hospital-acquired endocarditis. Most of these staphylococci are Staph. aureus, but an increasing proportion are now coagulase- negative staphylococci. All staphylococci are skin organisms and patients become infected from their own skin flora, or in the case of methicillin-resistant Staph. aureus (MRSA) from that of others by cross-infection. Staphylococcus aureus Staph. aureus is an important and aggressive pathogen in community- acquired native valve endocarditis. Sometimes a trivial skin lesion can be identified as the source of the organism, but there is often no obvious lesion. Staph. aureus, and increasingly now MRSA, is the most common cause of hospital-acquired endocarditis.

Prosthetic valves can become infected with Staph. aureus, both early as result of sternal wound sepsis and late as with native valves. Staph. aureus is the commonest pathogen causing endocarditis in intravenous drug users. Coagulase-negative staphylococci Although still regarded by many as pathogens of prosthetic rather than native valves, coagulase-negative staphylococci also cause na- tive valve infection. This has become more common, or certainly more commonly recognized, in the last two decades. The infecting species is most often Staph. epidermidis, but in many reports the des- ignation ‘Staph. epidermidis’ tends to be used for any unspecified coagulase-negative staphylococcus. As in community-acquired Staph. aureus endocarditis, there is sometimes a presumptive predisposing skin lesion. Most patients have a pre-existing cardiac abnormality. Many of these staphylococci (particularly Staph. lug- dunensis) can be as virulent as Staph. aureus and share some of the same virulence factors. Other organisms A wide variety of organisms account for the few cases of endocar- ditis that are not caused by streptococci, staphylococci, or entero- cocci: only a few warrant specific mention. HACEK group These are fastidious, slow-growing species that are oropharyn- geal commensals and have a predilection for heart valves such that their presence in blood cultures is virtually synonymous with this infection. The group consists of Haemophilus parainfluenzae, Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens, and Kingella spp. The large vegetations thought to be characteristic of HACEK organisms in native valve infection may be the result of diagnostic delay and prolonged illness rather than any inherent property of the microbes. Organisms that cannot be cultured by routine techniques Endocarditis is a rare (and late) sequel of acute Coxiella burnetii (Q fever) infection, mostly in middle-aged men with pre-existing valve disease. The reservoir of the organism is usually sheep or cattle, but the source and mode of transmission in many cases is unknown. The diagnosis is usually made serologically, although C. burnetii can be recovered from the blood and excised valves by special techniques. The disease is almost certainly underdiagnosed, with some cases labelled culture-negative endocarditis. Bartonella infection is usually diagnosed by serology, although these bacteria can be recovered from the blood and excised valves by special culture techniques and their presence detected by poly- merase chain reaction. Fungi Fungal endocarditis is very rare and more likely to occur on pros- thetic than native valves, except in intravenous drug users. Most cases are hospital-acquired and associated with infection at intra- vascular access sites and prior use of broad-spectrum antibiotics. Candida species, usually Candida albicans, are the most common fungi, but aspergillus and more exotic genera have also been re- ported. Blood cultures are only likely to be positive with candida, and often only intermittently; for other fungi, the diagnosis must be made by serology and culture of the fungus from the excised valve or detection on valve histology. Culture-negative endocarditis The possibility that an illness is not due to endocarditis should al- ways be entertained when blood cultures are repeatedly negative. However, the blood cultures will be negative in 5–31% of definite cases of endocarditis. The most common explanation for this is pre- vious administration of antibiotics. In a few cases the pathogen will be recovered from another site, including the excised valve, excised emboli, or—specifically in right-sided endocarditis—respiratory specimens. Other causes of negative blood cultures are infection

 with organisms that cannot be grown by conventional blood cul- ture methods, and infections that are diagnosed by serology such as C. burnetii, bartonella, and chlamydia. Treatment Initial therapy The treatment of endocarditis should ideally be undertaken by a multidisciplinary team involving cardiologists, microbiologists, in- fectious disease specialists, and cardiac surgeons. Where possible, patients should be treated in cardiac centres that undertake

cardiac surgery. Bactericidal antibiotics are the mainstay of treatment. The choice and duration of treatment depend on the type of micro- organism and its susceptibility profile, whether infection involves a native or prosthetic valve, and whether the patient is allergic to any antimicrobials. In those patients who have been ill for many weeks, antibiotic treatment can be deferred until the blood cultures are positive and the pathogen known. Antibiotic treatment should be started immediately after taking blood cultures in patients who are acutely ill, using a broad-spectrum combination that can be adjusted when the pathogen is known. However, endocarditis is often not suspected initially in many patients who are acutely ill with native valve in- fection: there may be no obvious signs of this and antibiotics are started for ‘septicaemia’. When methicillin-resistant staphylococci (whether Staph. aureus or coagulase-negative staphylococci) are likely pathogens, vancomycin or teicoplanin is an essential com- ponent of any combination. If empirical therapy is indicated the choice of antimicrobial agent should be dictated by the type of presentation, whether or not there is an intracardiac prosthesis in place, and the likely causative organism as suggested by the clinical picture (Table 16.9.2.3). Definitive therapy There are various international guidelines for the treatment of spe- cific organisms. It is important to realize that these are based on consensus, because there are no randomized controlled trials to show the efficacy of any particular regimen. It is conventional to estimate the minimum inhibitory concentration (MIC) of the antibiotic for the pathogen, but in practice routine disc sensitivity tests are satis- factory in many cases. Although it is widely believed that prosthetic endocarditis requires a longer duration of antibiotic treatment than native valve infection, there are few data to support this. Recommendations for the treatment of the most common causative organisms are taken from guidelines published by the British Society for Antimicrobial Chemotherapy (Tables 16.9.2.4, 16.9.2.5, 16.9.2.6). HACEK endocarditis Treatment should be with a β-lactamase-stable cephalosporin, or with amoxicillin if the organism is sensitive, plus gentamicin 1 mg/kg body weight according to renal function (for the first 2 weeks only) and with regular monitoring of drug levels. An alternative agent is ciprofloxacin. Other uncommon causes of endocarditis Treatments for uncommon causes of endocarditis are shown in Table 16.9.2.7. Table 16.9.2.3 Recommendations for empirical therapy of suspected endocarditis Antimicrobial Dose/route Comment

1. NVE—indolent presentation Amoxicillina AND (optional) 2 g q4 h IV If patient is stable, ideally await blood cultures Better activity against enterococci and many HACEK microorganisms compared with benzylpenicillin Use regimen 2 if genuine penicillin allergy Gentamicina 1 mg/kg ABW The role of gentamicin is controversial before culture results are available
2. NVE, severe sepsis (no risk factors for Enterobacteriaceae, Pseudomonas) Vancomycina AND Dosed according to local guidelines In severe sepsis, staphylococci (including) need to be covered If allergic to vancomycin, replace with daptomycin 6 mg/kg q24 h IV Gentamicina 1 mg/kg IBW q12 h IV If there are concerns about nephrotoxicity/acute kidney injury, use ciprofloxacin in place of gentamicina
3. NVE, severe sepsis AND risk factors for multiresistant Enterobacteriaceae, Pseudomonas Vancomycina AND Dosed according to local guidelines, IV Will provide cover against staphylococci (including MRSA), streptococci, enterococci, HACEK, Enterobacteriaceae and P. aeruginosa Meropenema 2 g q8 h IV
4. PVE pending blood cultures or with negative blood cultures Vancomycina AND 1 g q12 h IV Gentamicina AND 1 mg/kg q12 h IV Rifampicina 300–600 mg q12 h po/IV Use lower dose of rifampicin in severe renal impairment ABW, actual body weight; IBW, ideal body weight;

IV, intravenous; MRSA, methicillin-resistant staphylococci; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis;
po, orally; q4 h, every 4 h; q8 h, every 8 h; q12 h, every 12 h. a Doses require adjustment according to renal function. From Gould FK, et al. (2012). Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. Antimicrob Chemother, 67, 269–89. Reproduced with permission from the British Society for Antimicrobial Chemotherapy.

section 16 Cardiovascular disorders 3530 Fungal endocarditis For Candida, echinocandins (e.g. caspofungin or anidulafungin) or lipid-based amphotericin B preparations are first-line therapies. For aspergillus, voriconazole is first-line treatment. Expert advice on dosing should be sought. Monitoring of treatment Serum bactericidal titres against the infecting organism are no longer recommended. There was always great variation in the moni- toring methods used for these tests and in the interpretation of their results. At best, they could only predict bacteriological not clinical cure, and bacteriological failure is very rare. The most useful labora- tory test for monitoring the response to treatment (which is usually obvious clinically) is serial estimation of CRP; this is of greater use than the ESR, which is much slower to fall. If there is a relapse of endocarditis, this usually occurs within 2 months of cessation of treatment. The relapse rate is lowest for pa- tients with native valve endocarditis caused by penicillin-sensitive viridans streptococci. Relapse rate in prosthetic valve endocarditis is 10–15%. Prevention and prophylaxis Until recently, antibiotic prophylaxis in at-risk patients, including those with native valve disease undergoing a wide variety of dental, medical, and surgical procedures, was accepted as reasonable. This was largely based on indirect data from in vitro studies, ex- perimental animal models, and studies of clinical bacteraemia, but there were many uncertainties about its value, and data confirming its clinical effectiveness were lacking. This lack of evidence has led international bodies to propose more restrictive guidelines in recent years. The most controversial area for the use of prophylactic antibiotics concerns dental treatment. Innovative French guidelines published in 2002 challenged conventional practice, suggesting prophylaxis only for those with the highest benefit to risk ratio, and empha- sizing the importance of oral hygiene. A working party of the British Society of Antimicrobial Chemotherapy recommended in 2006 that the practice of giving antibiotics to all patients with cardiac abnor- malities before dental treatment should be stopped, except for those with a history of previous endocarditis, prosthetic heart valves, or surgically constructed conduits. Many other groups vigorously op- posed this recommendation, not least because some cases of endo- carditis that involve dental procedures have resulted in litigation, and in most of these legal cases endocarditis was judged to be caused by dental manipulations on the basis of the dental procedure, cardiac pathology, infecting microorganism, and the temporal link between the onset of endocardial infection and the dental manipulation. In 2007 the American Heart Association (AHA) revised its guidelines limiting the use of antibiotic prophylaxis to the highest- risk patients who were undergoing the highest-risk procedures Table 16.9.2.4 Summary of treatment options for streptococcal endocarditis Regimen Antimicrobial Dose and route Duration (weeks) Comment Treatment options for streptococci (penicillin MIC ≤0.125 mg/litre) 1. Benzylpenicillina monotherapy 1.2 g q4 h IV 4–6 Preferred narrow-spectrum regimen, particularly for patients at risk of C. difficile or high risk of nephrotoxicity 2. Ceftriaxone monotherapy 2 g once a day IV/IM 4–6 Not advised for patients at risk of C. difficile infection; suitable for OPAT 3. Benzylpenicillina AND 1.2 g q4 h IV 2 Not advised for patients with PVE, extracardiac foci of infection, any indications for surgery, high risk of nephrotoxicity, or at risk of C. difficile Gentamicin 1 mg/kg q12 h IV 2 4.

Ceftriaxone AND 2 g once a day IV/IM 2 Not advised for patients with PVE, extracardiac foci of infection, any indications for surgery, high risk of nephrotoxicity, or at risk of C. difficile Gentamicin 1 mg/kg q12 h IV 2 Treatment of streptococci (penicillin MIC >0.125 to ≤0.5 mg/litre) 5. Benzylpenicillina AND 2.4 g q4 h IV 4–6 Preferred regimen, particularly for patients at risk of C. difficile Gentamicin 1 mg/kg q12 h IV 2 Treatment of Abiotrophia and Granulicatella spp. (nutritionally variant streptococci) 6. Benzylpenicillina AND 2.4 g q4 h IV 4–6 Preferred regimen, particularly for patients at risk of C. difficile Gentamicin 1 mg/kg q12 h IV 4–6 Treatment of streptococci penicillin MIC >0.5 mg/litre Treatment of streptococci in patients with significant penicillin allergy 7. Vancomycin AND 1 g q12 h 4–6 Or dosed according to local guidelines Gentamicin 1 mg/kg q12 h IV ≥2 8. Teicoplanin AND 4–6 Preferred option when high risk of nephrotoxicity Gentamicin 1 mg/kg IV q12 h ≥2 IM, intramuscularly; IV, intravenously; OPAT, outpatient antimicrobial therapy; PVE, prosthetic valve endocarditis; q4 h, every 4 h; q12 h, every 12 h. All drug dosages to be adjusted in renal impairment; gentamicin, vancomycin, and teicoplanin levels to be monitored. a Amoxicillin 2 g every 4–6 h may be used in place of benzylpenicillin 1.2–2.4 g every 4 h. From Gould FK, et al. (2012). Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. Antimicrob Chemother, 67, 269–289. Reproduced with permission from the British Society for Antimicrobial Chemotherapy.

16.9.2 Endocarditis 3531 Table 16.9.2.5 Recommended regimens for treatment of staphylococcal endocarditis Agent Dose/route Duration (weeks) Comment NVE, methicillin-susceptible Staphylococcus spp. Flucloxacillin 2 g every 4–6 h IV 4 Use q4 h regimen if weight >85 kg NVE, methicillin-resistant, vancomycin-susceptible (MIC ≤2 mg/litre) rifampicin-susceptible Staphylococcus or penicillin allergy Vancomycin AND 1 g IV q12 h 4 Or dose according to local guidelines. Modify dose according to renal function and maintain predose level 15–20 mg/litre Rifampicin 300–600 mg q12 h po 4 Use lower dose of rifampicin if creatinine clearance <30 ml/min NVE, methicillin-resistant, vancomycin-resistant (MIC >2 mg/litre), daptomycin-susceptible (MIC ≤1 mg/litre) Staphylococcus spp. or patient unable to tolerate vancomycin Daptomycin AND 6 mg/kg q24 h IV 4 Monitor creatine phosphokinase weekly. Adjust dose according to renal function Rifampicin OR 300–600 mg q12 h po 4 Use lower dose of rifampicin if creatinine clearance <30 ml/min Gentamicin 1 mg/kg IV, q12 h 4 PVE, methicillin, rifampicin-susceptible Staphylococcus spp. Flucloxacillin AND 2 g every 4–6 h IV 6 Use q4 h regimen if weight >85 kg Rifampicin AND 300–600 mg q12 h po 6 Use lower dose of rifampicin if creatinine clearance <30 ml/min Gentamicin 1 mg/kg IV, q12 h 6 PVE, methicillin-resistant, vancomycin-susceptible (MIC ≤2 mg/litre), Staphylococcus spp. or penicillin allergy Vancomycin AND 1 g IV q12 h 6 Or dose according to local guidelines. Modify dose according to renal function and maintain predose level 15–20 mg/litre Rifampicin AND 300–600 mg q12 h po 6 Use lower dose of rifampicin if creatinine clearance <30 ml/min Gentamicin 1 mg/kg q12 h IV ≥2 Continue gentamicin for the full course if there are no signs or symptoms of toxicity PVE, methicillin-resistant, vancomycin-resistant (MIC >2 mg/litre), daptomycin-susceptible (MIC ≤1 mg/litre) Staphylococcus spp. or patient unable to tolerate vancomycin Daptomycin AND 6 mg/kg q24 h IV 6 Increase daptomycin dosing interval to 48 hourly if creatinine clearance <30 ml/min Rifampicin AND 300–600 mg q12 h po 6 Use lower dose of rifampicin if creatinine clearance <30 ml/min Gentamicin 1 mg/kg q12 h IV ≥2 Continue gentamicin for the full course if there are no signs or symptoms of toxicity IV, intravenously; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; po, orally; q12 h, every 12 h; q24 h, every 24 h. From Gould FK, et al. (2012). Guidelines for the antibiotic treatment of endocarditis in adults: report

of the Working Party of the British Society for Antimicrobial Chemotherapy. Antimicrob Chemother, 67, 269–289. Reproduced with permission from the British Society for Antimicrobial Chemotherapy.
Table 16.9.2.6 Recommended regimens for treatment of enterococcal endocarditis Regimen Antimicrobial Dose and route Duration (weeks) Comment 1. Amoxicillin OR 2 g q4 h IV 4–6 For amoxicillin-susceptible (MIC ≤4 mg/litre), penicillin MIC ≤4 mg/litre AND gentamicin-susceptible (MIC ≤128 mg/litre) isolates Penicillin AND 2.4 g q4 h IV 4–6 Duration 6 weeks for PVE Gentamicina 1 mg/kg q12 h IV 4–6 2. Vancomycina AND 1 g q12 h IV or dosed according to local guidelines 4–6 For penicillin-allergic patient or amoxicillin- or penicillin-resistant isolate; ensure vancomycin MIC ≤4 mg/litre Gentamicina 1 mg/kg IBW q12 h IV 4–6 Duration 6 weeks for PVE 3. Teicoplanina AND 10 mg/kg q24 h IV 4–6 Alternative to Regimen 2, see comments for Regimen 2; ensure teicoplanin MIC ≤2 mg/litre Gentamicina 1 mg/kg q12 h IV 4–6 4. Amoxicillina, b 2 g q4 h IV ≥6 For amoxicillin-susceptible (MIC ≤4 mg/litre) AND high-level gentamicin resistant (MIC >128 mg/litre) isolates IBW, ideal body weight; IV, intravenously; PVE, prosthetic valve endocarditis; q4 h, every 4 h; q12 h, every 12 h; q24 h, every 24 h. a Amend dose according to renal function. b Streptomycin 7.5 mg/kg every 12 h intramuscularly can be added if isolate is susceptible. From Gould FK, et al. (2012). Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. Antimicrob Chemother, 67, 269–289. Reproduced with permission from the British Society for Antimicrobial Chemotherapy.

section 16 Cardiovascular disorders 3532 (Tables 16.9.2.8 and 16.9.2.9). In the case of dental treatment these were manipulation of gingival tissue or the periapical re- gion of teeth, or perforation of the oral mucosa. More recently the American College of Cardiology (ACC)/AHA Task Force on Practice Guidelines has downgraded the recommendation for antibiotic prophylaxis for high-risk patients from Class 1 (manda- tory) to Class 2 (reasonable practice). The National Institute for Health and Care Excellence (NICE) developed guidelines in 2008 for adoption by the National Health Service in England, Wales, and Northern Ireland. Based on its findings that (1) there is no consistent association between having an interventional procedure and endocarditis, (2) the clinical ef- fectiveness of antibiotic prophylaxis is not proven, (3) the risk of antibiotic-associated adverse effects exceeds the benefits, and (4) prophylaxis is not cost-effective, NICE concluded that antibiotic prophylaxis should not be given to any at-risk patients undergoing an interventional procedure. NICE made one exception, namely in patients undergoing a gastrointestinal or genitourinary procedure where there is suspected pre-existing infection, who should receive an antibiotic that covers endocarditis causative organisms. NICE have reiterated the same advice in guidelines published in 2015. In 2009 the European Society of Cardiology also suggested re- stricting prophylaxis to those with the highest risk of endocarditis undergoing the highest-risk procedures and have reiterated the same advice in guidelines published in 2015. Dental procedures re- quiring prophylaxis mirror the AHA guidelines. Not surprisingly these departures from established practice have met with mixed reaction; the dental profession in the United Kingdom has welcomed the NICE proposals, but many British cardi- ologists and cardiovascular surgeons have opposed them. A sensible approach would appear to be to allow individual doctors to do what they feel is best for their patients and to be encouraged to discuss their reasons for taking a particular stance on antibiotic prophylaxis with them. Patients themselves should be taught the importance of good oral hygiene and to recognize symptoms that might indicate endocarditis and when to seek expert help. Suitable prophylactic antibiotic regimens are described in Table 16.9.2.9. Surgical treatment of endocarditis Surgery is required in about

50% of cases. Since surgery may be re- quired at any time during an episode of endocarditis, it is essential to involve a cardiac surgeon in the overall management from the outset, which in practice means transferring the patient to a centre with cardiac surgery whenever possible. Surgery for endocarditis carries a 10–25% mortality risk, and up to 10% of patients develop a paravalvular leak requiring a further operation. The main predictive factors for mortality associated with surgery are prosthetic valve endocarditis, infections due to staphylococci or candida, periopera- tive shock, or late referral. Table 16.9.2.7 Management of uncommon causes of endocarditis Pathogen Proposed treatment Brucella spp. Doxycycline plus rifampicin plus cotrimoxazole (>3 months treatment) Coxiella burnetii Doxycycline plus hydroxychloroquine (>18 months treatment) Bartonella spp. Doxycycline (for 4–6 weeks) plus aminoglycoside (for 2 weeks) Mycoplasma spp. Doxycycline or new fluoroquinolones (>12 weeks' treatment) Legionella spp. Macrolides plus rifampicin or new fluoroquinolones (>6 months' treatment) Tropheryma whipplei Doxycycline plus hydrochloroquine (≥18 months) Adapted from Heart, Prendergast BD, Vol 92, pp. 879–85. The changing face of infective endocarditis. Copyright (2006) with permission from BMJ Publishing Group Ltd.
Table 16.9.2.8 Guidelines for antibiotic prophylaxis in endocarditis American Heart Association, 2007 National Institute for Health and Clinical Excellence, 2008 and 2015 European Society of Cardiology, 2009 and 2015 High-risk patients Previous IE Previous IE Previous IE Prosthetic valve Prosthetic valve Prosthetic valve or prosthetic material used for valve repair Unrepaired or incompletely repaired cyanotic congenital heart disease Acquired valvular heart disease with stenosis or regurgitation Cyanotic congenital heart disease (without surgical repair or with residual defects, palliative shunts, or conduits) Congenital heart disease repaired with prosthetic material (for 6 months after the procedure) Structural congenital heart disease, including surgically corrected, or palliated structural conditions; excluding isolated ASD, fully repaired VSD/PDA, endothelialized closure devices Congenital heart disease repaired with prosthetic material (for 6 months if complete repair, indefinite if residual defect) Valve disease in cardiac transplant recipients Hypertrophic cardiomyopathy Procedures requiring prophylaxis Dental procedures involving manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa Gastrointestinal and genitourinary procedures where there is suspected pre-existing infection Dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa Invasive procedures of the respiratory tract needing incision or biopsy of the mucosa ASD, atrial septal defect; IE, infective endocarditis; PDA, patent arterial duct; VSD, ventricular septal defect. Adapted from Harrison JL, Prendergast BD, Habib G (2009). The European Society of Cardiology 2009 guidelines on the prevention, diagnosis, and treatment of infective endocarditis. Key messages for clinical practice. Pol Arch Med Wewn, 119, 773–6.

16.9.2 Endocarditis 3533 The timing of surgery is all-important and demands experience and clinical judgement. The main indications are haemodynamic in- stability, persistent infection, and annular or aortic abscesses. In such cases surgery should never be delayed, even if only hours or days of antibiotic treatment have been given. The primary goals of the surgeon are to remove all infected material and to reconstruct the heart and/ or restore valvular function at the lowest operative risk. An under- standing of the surgical anatomy of endocarditis is a precondition for surgical success, which means the involvement of an experienced sur- gical team. Wherever possible, surgeons now strive to preserve the na- tive valve, either by removal of the vegetation(s) or by valve repair. In prosthetic valve endocarditis, removal of all foreign material is man- datory. Actuarial survival figures indicate a 75% survival at 5 years and a 61% survival at 10 years after cardiac surgery for endocarditis. There are several unresolved issues with regard to the surgical treatment of endocarditis. First, the use of surgery when embolism has already taken place

remains controversial. Recurrent emboli, persistent vegetation after a major systemic embolus, and vegeta- tion size (>10 mm) have all been put forward as indications, but there are no controlled trials to support a firm recommendation. Secondly, the optimal timing of surgery in patients who have had a cerebrovascular accident, either as a result of an embolic stroke or from haemorrhage due to a ruptured mycotic aneurysm: as a general rule, delay of at least 4 weeks is suggested if haemorrhage is detected by CT scanning, but surgery can be undertaken within 72 h if no haemorrhage is present. Thirdly, the duration of anti- biotic treatment postoperatively: a short postoperative course is appropriate if the excised valve is sterile, whereas continuation for 4 to 6 weeks seems reasonable if the pathogen is isolated from the excised valve. FURTHER READING

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Revision #1
Created 2026-01-22 16:39:37 UTC by Omar Ayman
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