Editorial

The challenge and the reproach of infective endocarditis

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Bacterial endocarditis, or as it is better and more comprehensively termed infective endocarditis, has long been clearly recognised. Osler¹ and Horder² amplified the original descriptions, and in 1909 Osler commented on the chronic form of the disease. Infective endocarditis was fatal in virtually all patients until the introduction of penicillin. Only 4-6% of patients responded to sulphonamide, which was given before the introduction of penicillin. After its introduction mortality fell from almost 100% to 30%, and there the rate has generally stayed,^{3,4} though lower figures have been quoted from major centres.⁵ The probable increase in the incidence of the disease,⁶ however, tends to offset any fall in mortality in the past decade. The age distribution of patients with infective endocarditis has changed during the past 50 years; the mean age has increased from 32 to 50 years or more, and the disease has become increasingly common in 60-80 year old subjects.

Although the incidence of rheumatic valvar disease has fallen substantially in developed countries, the pattern of infective endocarditis has not changed appreciably. A recent survey of the Medical Services Study Group of the Royal College of Physicians of London associated with the British Cardiac Society has provided information on 541 patients in the United Kingdom who developed infective endocarditis during the years 1981-82.⁷⁻⁹ The mean age was 51, the commonest primary cardiac disorder was rheumatic (in 126 patients), and the commonest organism isolated was *Streptococcus viridans*. Of the 541 patients, 171 had no history of heart disease. The mortality was 30% for staphylococcal infections and 6% for streptococcal infections, but cultures from 54 patients (10%) yielded negative results.

Reasons for the apparently increasing incidence of infective endocarditis could be the development of

infection on prosthetic valves and other materials introduced into the heart and the recognition of unusual forms of infective endocarditis such as coxiella (Q fever), chlamydia (psittacosis), and fungal infections. Fungal infections may paradoxically have increased as a result of more intensive and lengthy chemotherapy for advanced bacterial infective endocarditis.

Patients who are immunologically compromised such as those taking immunosuppressive drugs are especially vulnerable to infection of any sort. Infective endocarditis due to self injection without aseptic precautions by drug addicts can be a serious source of infective endocarditis but is fortunately uncommon in the United Kingdom.

With the development of more powerful antibiotics, improved diagnostic methods such as cross sectional echocardiography, and increased awareness of the problems, why is the mortality so high? If infective endocarditis is curable, why is it not cured more often? As no simple answer is readily forthcoming attention has focused again on prophylaxis. Who should be protected and how? What is the value of prophylaxis? In the survey by the Medical Services Study Group 19% of infections were thought to be dental in origin, but in only 76 of the 544 episodes (14%) of infective endocarditis had a dental procedure been performed within three months of presentation. Organisms of the *S viridans* group were the cause of infection in 33 patients who had dental sepsis but who had not been treated recently. Organisms from the gastrointestinal tract were also isolated, often in connection with operations, investigations, or disease of the alimentary tract.

Prophylaxis

Prophylaxis, therefore, is important during dental work, gastrointestinal tract procedures, and genitourinary investigations. An awareness of the need to

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maintain good dental hygiene is most important, especially in patients with cardiac disease. The regularity of infection with *S. viridans* has emphasised the importance of prophylaxis during dental work, but *S. viridans* can be found in parts of the body other than the mouth or pharynx, while bacteraemia can occur from dental sepsis without any dental work precipitating it, as in the patients in the Medical Services Study Group's survey who developed *S. viridans* endocarditis without recent dental attention. Prophylaxis during dental work is not strikingly effective, but, nevertheless, cannot be neglected. There could be many reasons for its relative ineffectiveness: penicillin is not given or is improperly given; susceptible patients are not identified; or no prophylaxis is given at all to susceptible patients. If all these aspects are to be dealt with who then should be given prophylaxis? Obviously those with known cardiac defects must have prophylaxis, but it is important to know which defects are especially susceptible to infection—that is, those that are concerned with pronounced mechanical stress, especially when blood is driven from a high pressure source through a narrow orifice into a low pressure segment.¹⁰ Thus patients with mild mitral regurgitation, bicuspid aortic valve, ventricular septal defect, and persistent ductus arteriosus are characteristically vulnerable to infection, while those with a low cardiac output, pronounced valve regurgitation, and severe heart failure are less so. At the end of the spectrum is the secundum atrial septal defect, in which infective endocarditis is virtually unknown. Nevertheless, some patients with atrial septal defect have mitral valve lesions that can readily become infected.

The simple answer would be to protect everyone with any suggestion of cardiac disease, and this is often done. Since infection can occur on a normal valve, however, or at least in patients not known to have cardiac disease, should everyone be given dental prophylaxis? Even if this was practicable, would the hazard of penicillin reaction outweigh the benefits? Possibly they would, but the survey by the Medical Services Study Group inclines to the view that perhaps all patients over the age of 60, even without evidence of cardiac disease, should be given prophylaxis. This is a valuable suggestion because of the increase in infective endocarditis found in older patients and the risk of infection from instrumentation of the gastrointestinal and genitourinary tracts that is common in elderly people.

The recommendations of the Medical Services Study Group and the British Society for Antimicrobial Therapy generally agree on the means of prophylaxis¹¹: for dental work in outpatients 2 g amoxycillin should be given by mouth one hour before the work is carried out: for inpatients penicillin

can be injected intramuscularly: for patients undergoing instrumental procedures on the lower gastrointestinal and genitourinary tracts ampicillin or amoxycillin combined with gentamicin should be given—a single dose should cover investigations; and for patients sensitive to penicillin erythromycin is advised.

Treatment

Since over 80% of infections are due to staphylococci or streptococci initial treatment should be with a combination of drugs such as gentamicin and penicillin. Benzylpenicillin should be given for streptococci likely to have come from the mouth; flucloxacillin for staphylococcal infections; and ampicillin for faecal streptococci.¹² Treatment should be given intravenously, preferably by a central subclavian line inserted under full aseptic conditions. The line can be left in position for several weeks, but specimens from the tip should be cultured on removal. A regular weekly injection of amphotericin to prevent secondary fungal infections is useful. The duration of treatment should be not less than four weeks—six weeks for complicated cases and prosthetic valve infections. The dose of benzylpenicillin should be not less than 10 MU daily; some authorities recommend 20 MU daily but this carries some risk of penicillin complications such as convulsions and hyperkalaemia. Low dose heparin (1 U/ml) added to the infusion fluid limits the risk of the formation of thrombi. If heart failure is present, or deemed likely, sodium penicillin should be avoided. The intravenous route should be continued for a minimum of two weeks, preferably three, and then penicillin may be given orally. Treatment with gentamicin must be monitored by blood concentrations. Peak concentrations should not exceed 14 mg/l or fall below 5 mg/l. Trough concentrations should not exceed 2 mg/l.

Special problems of treatment include prosthetic valve endocarditis, endocarditis in drug addicts, fungal endocarditis, and coxiella endocarditis. Prosthetic valve endocarditis occurs either early in the postoperative phase, within two months of operation, or late: early endocarditis is usually due to the entry of staphylococci into the blood from the skin of the patient,¹³ which often occurs when surgical drains are removed from the chest. During this manoeuvre anti-staphylococcal chemotherapy should be given. The prognosis of early endocarditis treated medically is much worse than that of late endocarditis.¹⁴ Westaby *et al* reported 21 patients who suffered 25 attacks of prosthetic valve endocarditis.¹⁵ Nine patients with late prosthetic valve endocarditis were cured by medical treatment alone, two died before operation was possible, and 11 required replacement of prosthetic

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valves after treatment with antibiotics. Three patients died and two needed replacement of their valves after medical treatment.

Surgical treatment is thus often needed for prosthetic valve endocarditis, and constant vigilance is necessary to detect infection early and begin effective medical treatment. If, despite this, infection continues, embolism occurs, or vegetations damage the prosthetic valve further operation should not be delayed. The diagnosis should be suspected if there is unexplained fever, heart failure, embolism, change in the auscultatory characteristics of the prosthetic valve, or persistent anaemia due to mechanical haemolysis. In view of the echoes produced by the metal parts of the valve echocardiography (especially M mode) is of only limited value in diagnosis, but changing patterns of the structure of the valve on repeat examination may be of some help.

Surgical treatment is most important also for native valvar endocarditis, and should be considered in any patient who shows evidence of pronounced valve failure, conduction defects, or embolism and does not respond immediately to medical treatment. Delay in surgical treatment can be disastrous, although operation in the face of continuing infection is no bar to success, in fact the reverse. The need for replacement of valves is particularly great in infections noted for the severe destruction of valves, particularly staphylococcal, coxiella, and fungal infections. Medical treatment practically never cures coxiella endocarditis, and fungal endocarditis, which carries a high mortality, is difficult to treat medically because antifungal drugs (amphotericin B and 5-fluorocytosine) are fungistatic rather than fungicidal and are toxic to the patient.

Delay in diagnosis

When so much time and effort has been put into the prevention, detection, and treatment of infective endocarditis, where lies the reproach? It lies in the failure to reduce mortality appreciably below 30%. Reasons for the failure are multiple and include organisms resistant to antibiotics; more direct exposure of the heart to infection by open operation, and insertion of foreign bodies into it; and older and sicker patients who develop the disease. Probably the most important impediment to good results, however, is late diagnosis. Ranged against these hazards are improved antibiotics and effective surgical treatment for infective endocarditis. Why then have these advances not had an effect on mortality? The answer lies both in the continued delay in diagnosis and in the failure to consult the cardiac surgeon in the early stages of the disease. Diagnosis is delayed because infective endocarditis is a great mimic; it can be hidden by many other

cardiac diseases that it inhabits and can counterfeit many medical diseases, notably renal disease, disease of the connective tissue, and cerebral vascular disease to name a few. Evidence of infection in the early stages may consist of no more than unexplained malaise, anaemia, the insidious development of heart failure for no known cause, rheumatic aches and pains, or even psychoneurosis.

Reliance on special investigations rather than on repeated careful clinical examinations can cause confusion—for example, echocardiography, which is probably the single most important investigation, can be abused if it is wrongly applied. A request for “echocardiogram please to exclude subacute bacterial endocarditis” is to be deprecated. If no vegetations are seen and the report is negative then the possibility of the diagnosis may be erroneously put aside and valuable time lost. Whenever possible, cross sectional as well as M mode echocardiography should be used.

Recommendations

All that has been said is well known to cardiologists and to most readers of the British Heart Journal. Why say it then? My purpose is to appeal to those outside cardiology: patients, dental surgeons, general surgeons, gastrointestinal surgeons, genitourinary surgeons, general practitioners, and consultant physicians for the best available prophylaxis and the earliest possible diagnosis and treatment. Although prophylaxis remains a somewhat imprecise exercise, it should at least be meticulously applied to patients who are especially at risk. Early diagnosis can be greatly helped if, when any patient with known heart disease develops a fever of unknown cause that lasts for more than a few days, blood cultures (or if not possible an erythrocyte sedimentation rate and haemoglobin estimation) are performed before any antibiotics are given. This reduces the risk of damping down the infection temporarily and rendering results of subsequent blood cultures negative. The possibility of infective endocarditis should be considered in any cardiac patient who becomes mysteriously unwell, develops heart failure, arrhythmia, heart block, or, most obvious of all, a new cardiac murmur. Patients with known heart disease should be told about infective endocarditis and how to reduce the risk: they should be asked to be meticulous in prophylactic measures and report to their general practitioner for a blood test if they develop unexplained fever or malaise.

General practitioners should be encouraged to think always of the possibility of infective endocarditis in patients with heart disease, to take the necessary blood tests when indicated before giving antibiotics, and if in doubt to refer the patient to a specialist.

The consultant physician can further the cause of early diagnosis and successful treatment by repeated meticulous clinical examination; by applying echocardiography shrewdly; and by bearing in mind the possibility that surgical treatment may be needed, not as a last resort but as a planned procedure complementary to chemotherapy. Valves that become severely damaged over a short time cause important defects of myocardial function that can seriously worsen prognosis, while uncontrolled infection can burrow malignantly into the great vessels producing aneurysms and deep into the heart causing serious conduction defects.

The combination of enhanced awareness on the part of the patient, the general practitioner, and the physician, together with meticulous prophylaxis, early consultation with the cardiac surgeon, and effective treatment with antibiotics should appreciably reduce the mortality. The challenge must be accepted and the reproach neutralised.

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