Management of Infective Endocarditis

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Since the dramatic fall in mortality that followed the introduction of penicillin (Fig. 1), deaths from infective endocarditis (IE) have continued to decrease gradually.
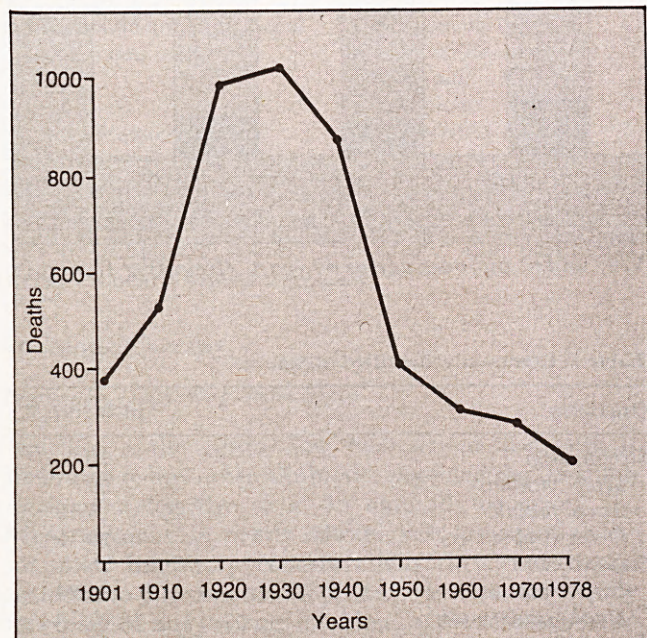

Fig. 1. *Annual mortality from infective endocarditis in England and Wales, 1901-1978. (Registrar General's figures.)*

This may have been due as much to a falling incidence as to a falling mortality rate. In pre-antibiotic times (Fig. 2) there was a high mortality (and therefore incidence) in young people, whereas in 1978 only 20 under the age of forty died from IE (in England and Wales). Deaths among older subjects have fallen very little. The main reason for the falling incidence in the young is almost certainly the decline in rheumatic heart disease, and one of the causes of the continuing, or increasing, incidence in older patients is the longer survival of an earlier generation with rheumatic disease, some of whom have undergone valve replacement. My own experience in the 1960s and 1970s bears this out (Table 1). The mean age increased from 39 to 44 years; the percentage of those with rheumatic valve disease decreased from 48 to 22 per cent, and involvement of a natural mitral valve from 43 to 22 per cent. Increases occurred in post-operative infections and in prosthetic valve endocarditis.

Diagnosis

Early recognition of IE becomes more important as

Table 1. Pre-existing lesions.

	1960-1969	1970-79
Number of Cases	58	58
Mean Age	39.3 yr (16-68)	44.4 yr (9-79)
Mitral Valve	25 (43%)	13 (22%)
Rheumatic	15	7
Non-rheumatic	4	3
Not known	6	3
Aortic Valve	13 (22%)	16 (28%)
Rheumatic	5	4
Aortic stenosis	4	6
Other	4	6
Mitral and Aortic Valves		
Rheumatic	8	2
Total rheumatic valves	28 (48%)	13 (22%)
Post-operative valve	3	7
Prosthetic valve (late)	0	15 (26%)
Other	0	1

methods of treatment improve (Table 2). We now realise that many valves that previously were normal or nearly so are infected, although it is usual for a murmur to be

Table 2. Clinical features of infective endocarditis.

1. *Cardiac Lesion*
   Known pre-existing murmur, or prosthetic valve.
   Change in physical signs.
2. *Source of Infection*
   Recent operation, instrumentation, dental extraction.
   Intravenous drug abuse, dialysis, cannulation, etc.
3. *Septicaemia*
   Fever, malaise, night sweats, loss of weight, fatigue, splenomegaly.
4. *Autoimmune Manifestations*
   Petechiae, Osler nodes, Roth spots, splinter haemorrhages.
   Microscopic haematuria, nephritis, arthritis, myocarditis, finger clubbing (?).
5. *Arterial Emboli*
   Cerebral, renal, splenic, mesenteric, peripheral limb, coronary, pulmonary (rt. heart lesion).
6. *Mycotic Aneurysm*
7. *Cardiac Failure*
   Valve destruction, myocarditis, intracardiac shunt, PV obstruction, coronary embolism.
8. *Laboratory Findings*
   Anaemia, low serum Fe. Increased ESR. Increased serum globulin, rheumatoid factor present.
   Microscopic haematuria. Positive blood culture (75%).
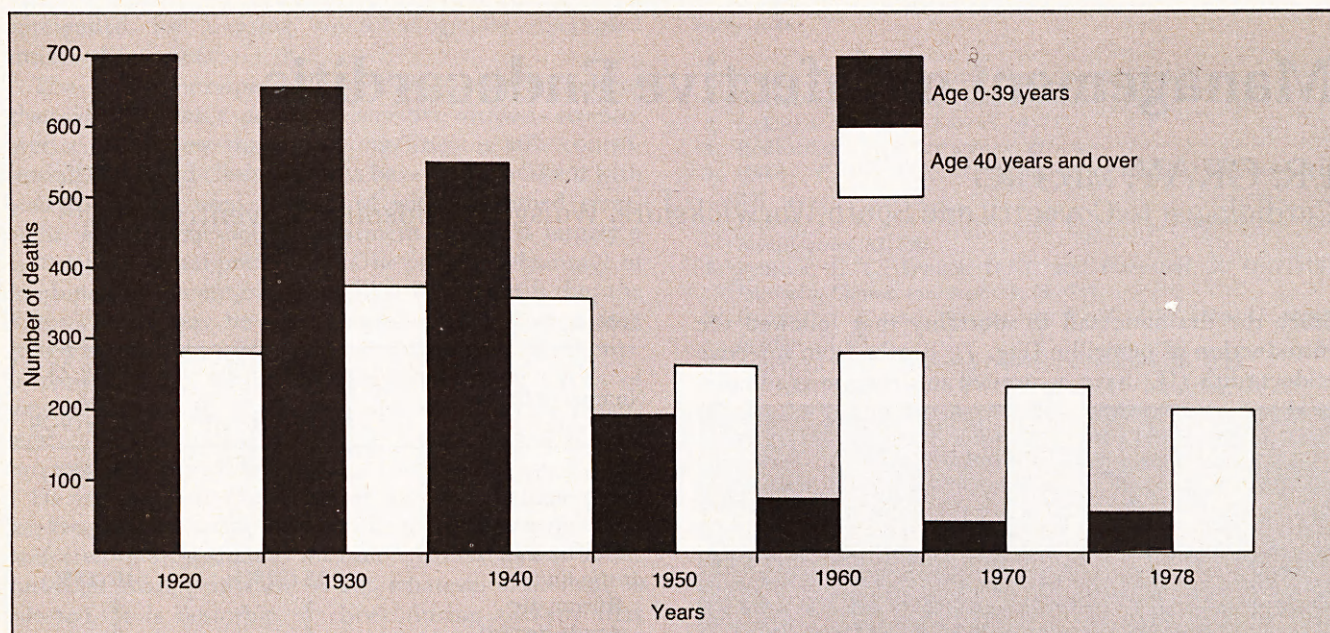   Increased antibody titres—chlamydia, rickettsia.

Fig. 2. *Deaths per annum from infective endocarditis, 1920-1978, under and over age of 40 years. (Registrar General's figures for England and Wales.)*

heard at the time of diagnosis. We also appreciate how vulnerable to infection prosthetic heart valves are. Recent dental or surgical procedures, and intravenous instrumentation or drug abuse, should always arouse suspicion. Symptoms of septicaemia such as fever, night-sweats and loss of weight are usual. Some manifestations of the disease are now thought to be caused by circulating immune complexes; these include Osler's nodes, Roth spots, and splinter haemorrhages as well as nephritis and probably, myocarditis. Systemic emboli in a patient in sinus rhythm should always suggest IE, just as pulmonary emboli can be caused by IE involving the right side of the heart; but the sooner the disease is diagnosed and treated, the less common are emboli likely to be. Congestive heart failure or, more often, left ventricular failure may occur. It can be caused by destruction of the mitral or aortic valve, or by obstruction of a prosthetic valve, or, occasionally, because an intracardiac shunt has developed. Myocardial failure can be caused by myocarditis or infarction following coronary embolism. Blood culture is the most important laboratory investigation, but anaemia and increased sedimentation rate occur almost invariably. A rising antibody titre is usually the only way of diagnosing rickettsial or chlamydial infection, unless the affected valve is excised.

Classification of Infective Endocarditis

Antibiotic treatment should be started immediately IE has been diagnosed clinically and blood samples have been taken for culture. It may take several days for an organism to be identified and its antibiotic sensitivities assessed; blood culture is sterile in as many as 25 per cent of cases. The initial treatment, pending the report of the microbiologist, has to be based on a clinical judgement of the probable infecting organism (Table 3). Streptococci

Table 3. Commonly identified organisms.

Organism	Incidence %
Streptococci	70
Strep. viridans	50
Strep. faecalis	5-10
Other streptococci	10-15
Staphylococci	25
Staph. aureus	10-20
Staph. epidermidis	5-10
Other micro-organisms, including diphtheroids, Gram-negative organisms, *H. influenzae*, fungi.	5-10

are responsible for about 70 per cent of infections, and varieties of *Strep. viridans* account for more than half of these. Staphylococci, mainly the *aureus* variety, but increasingly often *albus* strains, cause most of the other infections. A few are due to a wide variety of other micro-organisms and fungi.

In planning the treatment of patients with IE it is helpful to classify them (Table 4) into those with 'naturally occurring' and those with 'extraneous' infections[1]. The two varieties are distinct from each other in regard to the source of infection, the infecting organisms, the antibiotic regime likely to be effective, and even the role of surgical treatment.

'Naturally occurring' infection can happen at any time in susceptible patients; there may have been a dental or surgical procedure beforehand. Streptococci are usually responsible, the majority of which are highly sensitive to penicillin. 'Extraneous' infections are altogether different. They include those following shortly after cardiac surgery, and those associated with intravenous drug abuse and sometimes with intravenous instrumentation

Table 4. Types of bacterial endocarditis.

Naturally occurring	Extraneous infection
At any time	Shortly after operation
Sometimes following dental treatment, GU instrumentation, etc.	Intravenous drug abuse Haemodialysis Intravenous instrumentation
Strep. viridans *Strep. faecalis* Other streptococci Diphtheroids Rickettsia	*Staph. aureus, staph. epidermidis* Gram-negative organisms Fungi
Oral therapy: Amoxycillin and probenecid Tetracycline i.m. Gentamicin	Intravenous therapy initially (later possibly oral) Flucloxacillin Fucidic acid Gentamicin Amphotericin B

Table 5. Serum penicillin (μg/ml) one hour after single oral dose of 250 mg[4-6].

	Total penicillin	Free penicillin	Recovered from urine %
Phenoxymethyl penicillin	2.27	0.45	26
Phenethicillin	3.37	0.84	32
Propicillin	3.58	0.40	29
Phenbenicillin	5.60	0.17	20
Ampicillin	2.19	1.80	37
Amoxycillin	4.60	3.75	64

Fig. 3. *Serum ampicillin levels in a patient on 500 mg six-hourly, with and without probenecid.*

or haemodialysis. Staphylococci, Gram-negative organisms or fungi are usually the cause, and parenteral therapy is nearly always necessary.

Antibiotic Therapy

'Naturally Occurring' Infections

Penicillin is the outstanding bactericidal drug and is preferable to any other antibiotic, provided the infecting organism is sensitive to it. In naturally occurring IE, *Strep. viridans* is nearly always very sensitive to it; minimum inhibitory concentrations (MIC) of benzyl penicillin to different strains of *Strep. viridans* are usually between 0.02 and 0.05 μg/ml. Many of the semi-synthetic penicillins, such as phenethicillin, ampicillin and amoxycillin, are equally effective. When these forms of penicillin became available it seemed likely that serum concentrations sufficient to control such infections could be obtained with oral therapy.

McCarthy and Finland[2] observed a discrepancy between the antibacterial activity of different penicillins in serum, and the actual serum concentrations. We in Coventry[3] found that MICs of penicillins were higher when estimated in the presence of serum than in broth culture, and Bond *et al.*[4] demonstrated that this difference corresponded with the binding of a fraction of the penicillin to serum protein. This fraction is different for each penicillin, and the effective serum level of a penicillin is related to its degree of protein binding. This varies from 97 per cent with propicillin, 59 per cent with benzyl penicillin, to 18 and 17 per cent with ampicillin and amoxycillin respectively. Absorption of oral penicillins (Table 5) also varies from one to another, so that the level of unbound penicillin in the serum ranges from 0.17 to 3.75 μg/ml after a single oral dose of 250 mg, amoxycillin giving by far the highest level. Amoxycillin, with only 17 per cent protein binding, excellent absorption in the fasting and non-fasting state, and a broad antibacterial spectrum, emerges as the drug of choice for oral therapy (Fig. 3). Probenecid delays the excretion of

an oral penicillin so that serum concentrations are 25 to 50 per cent higher than normal and are maintained for longer periods (Fig. 4). Given with probenecid, 500 mg amoxycillin six-hourly produces peak serum levels of 10 to 30 μg/ml, and levels have seldom fallen below 3 μg/ml.

Oral therapy with amoxycillin and probenecid has therefore been my choice for treating 'naturally occurring' infections. I have treated 90 patients with oral antibiotics over the last 15 years. The organisms in 66 culture-positive cases were nearly all penicillin-sensitive streptococci and *Staph. epidermidis* (Table 6). Most were given ampicillin or amoxycillin, usually with probenecid (Table 7). Nine patients died (10 per cent) (Table 8). One of the deaths could be regarded as an antibiotic failure, the relapse of a *Strep. faecalis* infection some weeks after apparently successful treatment with ampicillin. Some strains of *Strep. faecalis* are not sensitive to amoxycillin alone, but do respond to amoxycillin together with gentamicin. An infection following gastrointestinal or genito-urinary surgery or instrumentation should be treated with an aminoglycoside in addition to a penicillin, pending the culture and sensitivity report.

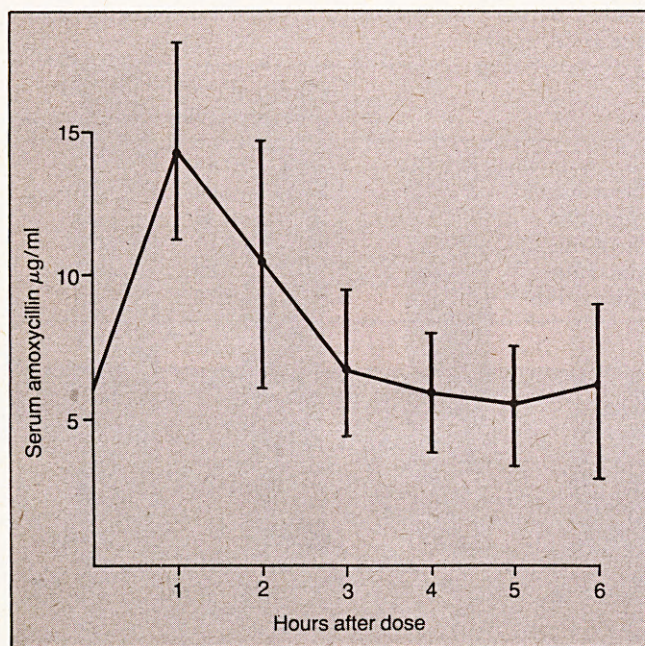The duration of antibiotic treatment is a controversial

Fig. 4. *Serum amoxycillin levels in 15 patients taking 500 mg amoxycillin and 500 mg probenecid six-hourly.*

matter. Geraci[7] championed the short course of therapy and reported that two weeks of antibiotic treatment were adequate for penicillin-sensitive infections. Certainly, in two recent cases in our unit, excised valves were sterile when removed 9 and 13 days respectively after starting treatment. Nonetheless, caution inclines me to giving antibiotics for four weeks, partly because of the

Table 6. Infective endocarditis treated with oral antibiotics (personal series).

Infecting organisms	No. of cases
Strep. viridans	41
Non-haemolytic streptococci	7
Staph. aureus	2
Staph. epidermidis	8
Diphtheroid	3
Strep. faecalis	2
Other bacteria	3
Culture positive	66 (73%)
Sterile culture	24
Total	90

Table 7. Infective endocarditis (personal series). Drugs used in oral therapy.

Drugs	No. of cases
Amoxycillin and probenecid	25
Ampicillin and probenecid	26
Phenethicillin and probenecid	13
Propicillin and probenecid	7
Other drug combinations with probenecid	5
Other drugs without probenecid	14
Total	90

Table 8. Cause of death in 90 orally treated cases.

	No. of cases
Cardiac arrest	3 (all *Strep. viridans*)
LV failure from aortic valve rupture	2 (one *Strep. viridans*, one sterile)
Coronary embolism following valve replacement	1 (Diphtheroid)
Obstructed mitral prosthesis	1 (Non-haemolytic Strep.)
Heart failure with complete heart block and ruptured sinus of Valsalva	1 (*Strep. viridans*)
Relapse of infection	1 (*Strep. faecalis*)
Total deaths	9 (10%)

importance of rest to the patient who may have myocarditis, and partly because of the importance of close clinical supervision at this stage of the illness.

'Extraneous' Infections

These infections, which usually occur shortly after heart operations and in drug addicts, are most often caused by staphylococci but sometimes by Gram-negative organisms and fungi. Five of 7 cases of post-operative endocarditis I have treated, and 7 of 9 such cases at St Thomas's Hospital in the last decade were caused by staphylococci[8]. Intravenous drug abuse is not a big problem in the area where I work, but of 93 cases in the St Thomas's series six were addicts and all were staphylococcal. In Detroit, 65 per cent of cases of IE between 1968 and 1972 were heroin addicts[9], but a more recent collaborative study from 26 American centres found only 8 per cent of cases to be addicts[10].

A summary of data from several American cities showed that 47 per cent of 215 cases of IE in drug addicts was caused by *Staph. aureus,* with pseudomonas as the next most common organism[11].

Although some strains of *Staph. aureus* are penicillin-sensitive, many produce penicillinase and so are resistant to penicillin. Semi-synthetic isoxazole penicillins such as flucloxacillin, which are resistant to penicillinase, have largely overcome this problem and should be given in the first instance. They should be given by six-hourly intravenous injection, changing to oral therapy if the organism is a highly sensitive one. In case the staphylococcus is resistant to all forms of penicillin, fucidic acid should also be given by continuous intravenous infusion pending the results of antibiotic sensitivity testing.

In post-operative IE, infection often co-exists in the operation wound, in a pressure sore, or in the respiratory or urinary tract. The same organism is very often responsible for both infections. If an organism has already been identified, say from an infected wound, this same organism should be regarded as the likeliest cause of the endocarditis, and appropriate antibiotics should be given until the results of blood culture are obtained.

Culture-Negative Endocarditis

Blood culture is sterile in 20 to 30 per cent of cases in

which there are strong clinical grounds for a diagnosis of IE. This is sometimes because a previous short course of an antibiotic has suppressed, but not eradicated, the infection. Rickettsial and chlamydial infection cannot be diagnosed by blood culture, and antibody titres to them should be obtained in culture-negative cases. IE may also be caused by fungi, particularly Candida, and this should be suspected when the blood culture is sterile in a patient who has previously been treated intensively with antibiotics, particularly if they have been administered intravenously. Culture-negative IE should first be treated with an anti-streptococcal or an anti-staphylococcal regime, according to the circumstances. If the response is unsatisfactory, a careful reappraisal of the situation must be made.

Assessment of Antibiotic Therapy

The clinical response may be obvious enough to indicate that infection is coming under control, but this is not always so; fever may not abate immediately and haemoglobin and sedimentation rate may take a long time to improve. It is important to know whether antibiotics are exerting a bactericidal effect. The MICs of antibiotics to the cultured bacteria are helpful in the first instance. They indicate the antibiotic likely to be effective and show, at the outset, whether the organism is a highly sensitive one that should respond readily, or whether it is a relatively resistant one requiring an individualised antibiotic regime. After treatment has begun the adequacy of serum antibiotic levels should be ascertained. Levels estimated 1, 3, and 6 hours after a dose can be compared with the MIC previously estimated, taking protein-binding into account. A simpler method, applicable to any antibiotic regime, is to incubate serial dilutions of the patient's serum with cultures of the organism, the greatest dilution inhibiting growth being reported. If the inhibited cultures are sub-cultured, the figure representing the dilution of serum that is completely bactericidal can be obtained.

These methods are not applicable to culture-negative cases, in which more weight must be placed on the clinical response, although serum antibiotic levels should be estimated. Should surgery be carried out, microscopy and culture of excised tissue will help in showing whether an infection has been controlled.

The Place of Surgery in Infective Endocarditis

In 1940, Touroff and Vessell[12] described the recovery of a patient with IE after ligation of a patent ductus. This gave a preview of the roles that were to be played by the surgeon in this disease. The more important indications for surgery were realised only after valve replacement became possible. This procedure is most often necessary when the mitral or aortic valve is so damaged by the infective process that severe valve regurgitation develops, caused sometimes by perforation of a cusp, sometimes because an entire cusp of the aortic valve has become detached, and sometimes by ruptured chordae of the mitral valve. Such damage may occur at any stage of IE

and even a few weeks after infection has been eradicated. It is particularly likely when a normal or non-rheumatic valve is infected. The delicate normal valve tissue is more easily perforated and destroyed than the thickened fibrotic valve of rheumatic disease. Severe symptoms often come on quickly because the regurgitant flow causes an acute volume overload of a small non-compliant recipient chamber in which the pressure quickly rises. This pressure is transmitted to the pulmonary veins and leads to acute or subacute pulmonary oedema. Heart failure occurs the more readily if there is co-existing myocarditis.

Recognition of valve rupture is extremely important in the care of patients with IE. Signs of aortic or mitral regurgitation may become apparent on clinical examination, and complaints of dyspnoea, cough or signs of heart failure should be taken very seriously. Left heart failure after valve rupture still kills patients who could have been saved by emergency valve replacement[13-15].

Mitral or aortic valve rupture occurs quite frequently when the valves are affected by IE; between 10 and 20 per cent are likely to require valve replacement, although operation can sometimes be deferred until the infection has been completely cured. It is not only when the infection is primarily on a valve that rupture occurs; I have treated two patients in whom infection has spread from a small ventricular septal defect to involve a normal aortic valve which has had to be replaced. Infection may also spread from a diseased aortic valve to cause rupture of chordae of an otherwise normal mitral valve. When a prosthetic valve is infected, a paraprosthetic leak may also cause severe valve regurgitation and require surgical treatment.

If pulmonary oedema occurs in a patient with IE, or if signs of aortic or mitral regurgitation develop, vigorous anti-failure treatment should begin straightway and cardiac investigation should be carried out unless there is a very prompt response to initial treatment. Because valve rupture may occur quite early in the disease, it may not be possible to postpone surgery until the infection has been eradicated[16]. If possible, it is desirable to avoid valve replacement at the height of infection because of the difficulties of suturing a prosthesis into an oedematous or inflamed valve ring, the added hazards of major cardiac surgery in a patient who may have active myocarditis, and the risk of contaminating the prosthesis.

Another mechanical problem that may complicate prosthetic valve endocarditis, and, rarely, the infection of a natural valve, is the obstruction of the valve by vegetations, so that the ball or disc of the valve is immobilised, causing acute mitral or aortic valve stenosis[17]. Such obstruction nearly always leads to acute intractable pulmonary oedema, which is sometimes the first sign of prosthetic valve endocarditis. Changes in the prosthetic valve sounds may be apparent. Such an obstructed prosthesis must be replaced straightway, for a delay even of hours may be fatal.

Large systemic emboli occur in some cases of IE and may cause severe brain damage or other disastrous consequences. Such major emboli are a particular feature of fungal infection, but they also occur in bacterial

endocarditis. They suggest the presence of extensive vegetations, and these can sometimes be identified by echocardiography. Such infected valves may be found to have festoons of thrombus trailing from them. A major systemic embolus should always be regarded as a relative indication for valve replacement in the hope of preventing a further episode.

Although fungal and rickettsial infections can be controlled to some extent by antibiotics, they are not killed by them, so the infection may not be eradicated. Such infections, together with a small minority of antibiotic-resistant bacterial infections, are best treated by replacement of the affected valve under cover of the most effective antibiotic regime that can be devised[18-20].

Once a cardiac lesion has been the seat of IE, it is more likely to become infected again. The question of surgical treatment after the infection is cured should therefore be considered. This does not apply to an affected valve, because of the high risk of infection of a prosthesis. It does, however, apply to a patent ductus and coarctation. A small ventricular septal defect, which might otherwise be left alone, should be considered for surgical repair if it has once been infected.

An infected tricuspid valve in a drug addict may be the source of multiple pulmonary emboli, and the infection in such cases is often antibiotic-resistant. Some of those most familiar with this form of IE recommend removal of the infected tricuspid valve, with either immediate replacement[21] or the later insertion of a prosthetic valve.

Other Complications

Large systemic emboli may require embolectomy if they are threatening the survival of a limb or endangering life in some other way. Mycotic aneurysms, usually a sequal to systemic embolus, always pose a threat and, provided they are accessible, or indeed recognisable, surgery is usually indicated. The most disastrous mycotic aneurysms are on the intracerebral arteries, which rupture to cause subarachnoid haemorrhage. Unfortunately, these are unlikely to be detected unless they do rupture.

Attention has been drawn[22] to neurological complications other than cerebral embolus and subarachnoid haemorrhage. Toxic encephalopathy and meningitis are particularly important, as they can sometimes be presenting symptoms of IE. Nephritis may lead to renal failure, which has to be managed in the same way as acute nephritis and renal failure from any other cause. It should indicate the need for particular care in deciding the dosage of antibiotics if such drugs as aminoglycosides are used.

Antibiotic hypersensitivity, particularly to penicillin, may pose a problem. It is usually desirable to continue with the same antibiotic if at all possible. Some recommend desensitisation to penicillin but in my experience symptoms can nearly always be well controlled by steroids while continuing with the antibiotic as before.

This article is based on a paper read at the Cardiology Conference held at the Royal College of Physicians in November 1980.

References

1. Gray, I. R. (1975) *Quarterly Journal of Medicine*, **44**, 449.
2. McCarthy, C. G. and Finland, M. (1960) *New England Journal of Medicine*, **263**, 315.
3. Gray, I. R., Tai, A. R., Wallace, J. G. and Calder, J. H. (1964) *Lancet*, **2**, 110.
4. Bond, J. M., Lightbown, J. W., Barber, M. and Waterworth, P. M. (1963) *British Medical Journal*, **2**, 956.
5. Knudsen, E. T., Rolinson, G. N. and Stevens, S. (1961) *British Medical Journal*, **2**, 198.
6. Sutherland, R., Croydon, E. A. P. and Rolinson, G. N. (1972) *British Medical Journal*, **2**, 13.
7. Geraci, J. E. and Martin, W. J. (1953) *Circulation*, **8**, 494.
8. Moulsdale, M. P., Eykyn, S. J. and Phillips, I. (1980) *Quarterly Journal of Medicine*, **49**, 315.
9. Arbulu, A. and Asfaw, I. (1980) *Abstracts of the Proceedings of the Eighth European Congress of Cardiology*, Paris. Sandoz.
10. Kaplan, E. L., Rich, H., Gersony, W. and Manning, J. (1979) *Circulation*, **59**, 327.
11. Stimmel, B. and Dack, S. (1978) *Infective Endocarditis* (ed S. H. Rahimtoola.) New York: Grune and Stratton.
12. Touroff, A. S. W. and Vessell, H. (1940) *Journal of the American Medical Association*, **115**, 1270.
13. Barratt-Boyes, B. G. (1963) *British Heart Journal*, **25**, 415.
14. Yeh, T. J., Hall, O. P. and Ellison, R. G. (1964) *American Surgeon*, **30**, 766.
15. Windsor, H. M. and Shanahan, M. X. (1967) *Thorax*, **22**, 25.
16. Wilson, W. R., Danielson, G. K., Giuliani, E. R., Washington, J. A., Jannin, P. M. and Geraci, J. E. (1978) *Circulation*, **58**, 585.
17. Prasquier, R., Gibert, C., Witchitz, S., Valere, P., Beaufils, P. and Vachon, F. (1978) *British Medical Journal*, **1**, 9.
18. Kay, J. H., Bernstein, S., Feinstein, D. and Biddle, M. (1961) *New England Journal of Medicine*, **264**, 907.
19. Wallace, A. G., Glenn Young, W. and Osterhout, S. (1965) *Circulation*, **31**, 450.
20. Kristinsson, A. and Bentall, H. H. (1967) *Lancet*, **2**, 693.
21. Arneborn, P., Bjork, V. D., Rodriguez, L. and Svanbom, N. (1977) *British Heart Journal*, **39**, 1276.
22. Royden Jones, H., Siekert, R. G. and Geraci, J. E. (1969) *Annals of Internal Medicine*, **71**, 21.