Heart failure associated with infective endocarditis

A review of 40 cases

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SUMMARY Thirty one (78%) of 40 consecutive patients (aged 13-79, mean 44 years) with infective endocarditis had congestive heart failure at presentation. Twenty six (65%) had had rheumatic heart disease and 17 (43%) patients had prosthetic valves. Eight (20%) patients had undergone dental procedures within three months of presentation. Blood cultures were positive in only 22 (55%) of the patients. In nine (41%) of them streptococci of the viridans group were isolated and in seven (32%) patients endocarditis was due to *Staphylococcus aureus*. Eight patients had Q fever endocarditis. Sixteen patients required operation because of haemodynamic deterioration while they were in hospital; 11 patients had native valves and five had prosthetic valves. Seven had emergency operations and were pyrexial at that time. Four of the seven died in hospital. Of the 12 who were alive and well after surgery only two required further surgery two and three years after the initial operation.

Twelve (30%) of the 40 patients died in hospital; in 10 death was mainly due to left ventricular failure or congestive heart failure. All patients died who had renal failure (four cases), myocardial infarction (two cases), complete heart block (one case), or ventricular fibrillation (two cases) before operation. Six (33%) of the 18 patients with culture negative endocarditis died. Two of the four patients seen and treated more than 12 weeks after the onset of symptoms died, as did three of the five patients with prosthetic valves who required surgery while in hospital. Three patients with neurological complications survived and only two (29%) of the seven patients with blood cultures that were positive for *Staphylococcus aureus* died.

Of these 40 high risk patients optimal antibiotic treatment and early surgery for haemodynamic difficulty ensured that 28 (70%) were discharged from hospital alive and well.

There are no accurate figures for the incidence of infective endocarditis in the United Kingdom, but it has been estimated that there are currently 40-50 cases per 1.8-2 million population per year.¹ The incidence of the disease does not seem to have fallen with antibiotic use. Infective endocarditis remains an important cause of mortality and morbidity, with rheumatic heart disease as its chief underlying cause, though to a much lesser extent today than a few decades ago. Heart failure significantly increases the risk of death in patients with infective endocarditis

managed either medically or medically and surgically.

We have reviewed the presentation, management, and short term outcome in 40 consecutive patients with infective endocarditis. Thirty one (78%) of them presented clinically in congestive heart failure and in nine there was difficulty in establishing the diagnosis of infective endocarditis mainly because of negative blood cultures. All patients were admitted to this hospital between 1974 and 1980 during the acute phase of the illness.

Patients and methods

The patient was considered to have endocarditis if the clinical picture was suggestive of the disease and blood cultures or serology were positive, or if in the presence of negative blood cultures the clinical pic-

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Figure Age distribution of the 40 patients with infective endocarditis.

ture was typical or vegetations were found on the endocardium at operation or necropsy. All patients were either referred to this centre because their clinical condition was deteriorating, usually due to congestive heart failure, or because of difficulty in the diagnosis of infective endocarditis (tertiary referral). There were 28 male and 12 female patients (male to female ratio 2.3:1). Their mean age was 44 years (range 13–79 years) (Figure).

Results

At presentation 31 of these patients were clinically in congestive heart failure. Before infective endocarditis developed 26 patients had had rheumatic heart disease, six patients had a bicuspid aortic valve, two a ventricular septal defect, one a mitral valve prolapse, one an atrioventricular canal, and one a persistent ductus arteriosus. Three patients had no predisposing cardiac abnormality. Infective endocarditis was present in 17 patients with prosthetic heart valves; 10 patients had Starr-Edwards valves, three had Björk-Shiley prostheses, two patients had fascia lata, one a homograft, and one a Carpentier-Edwards prosthesis. In all endocarditis developed more than 60 days after the initial valve replacement. There was evidence of a predisposing event in 32 (80%) patients. Eight patients had had dental procedures within three months of presentation. The eight patients who had Q fever endocarditis had all been in contact with cattle or sheep before their illness; one of them had drunk unpasteurised milk. Seven patients had had a sore throat and five patients a respiratory tract infection. Of the remaining four, one patient had had a cholecystectomy for gall stones and had positive blood cultures for *Streptococcus faecalis*, one patient had had a toe infected with *Staphylococcus aureus* and *Staph aureus* was grown from blood cultures, one patient had had a Meckel's diverticulum removed

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but had negative blood cultures, while the oldest patient in the group, whose blood cultures grew *Strep faecalis* had had a recent head injury.

Causative organisms were isolated from blood cultures in only 22 (55%) patients. These were streptococci of the viridans group in nine (41%) patients, *Staph aureus* in seven (32%) patients, *Streptococcus pneumoniae* in two, *Streptococcus faecalis* in two, *Staphylococcus epidermidis* in one, and β haemolytic streptococcus in one. None of the patients had a mixed positive culture. Eighteen (45%) patients had negative blood cultures. In 10 of these causative organisms were later identified—in eight patients serum samples were positive for chronic Q fever (*Coxiella burnetii*) and organisms were identified post mortem in two (*Staph aureus* and *Strep faecalis* were grown from the vegetations in one patient and *Candida albicans* was identified in the other).

At admission all our patients complained of fever and night sweats. Thirty five (87%) also reported malaise, weakness, headache, or tiredness. Abdominal pain was a presenting symptom in 17 (42%) patients and anorexia in 12 (30%). Eight patients complained of arthralgia and a further five (12%) patients complained of chest pain. Nine patients had symptoms from embolic episodes; most of these lesions were in the fingers and toes. Cerebral emboli, as manifest by meningeal symptoms or focal neurological deficit or both, occurred in two patients, while one other patient had a Roth spot in the fundus of the eye. The major clinical findings at presentation were hepatomegaly of 1–6 fingerbreadths in 25 patients and splenomegaly of 1–8 fingerbreadths in 22 patients. Thirteen patients had clubbing of the fingers and toes and 10 patients had purpura during the course of their illness. On routine ward testing 28 patients had haematuria.

On admission 35 of the 40 patients had a haemoglobin concentration of <12 g/dl. Four patients had a leucopenia (white cell count <4000/ μ l) and 28 patients had leucocytosis. In 37 the erythrocyte sedimentation rate was more than 20 mm an hour. Platelet counts were <150 000/ μ l in 11 of the 32 patients in whom they were measured. Two of our patients, both with Q fever, had pancytopenia. A third patient with Q fever endocarditis had a normal haemoglobin concentration but pronounced reduction of the white cell and platelet counts. Gamma globulin concentration was raised in 23 of the 31 patients in whom it was measured. IgG and IgM concentrations were measured in 29 patients; they were raised in 14 and 15 patients respectively. IgA was measured in 25 patients, and it was raised in 10 of them. A latex test for rheumatoid arthritis was positive in eight of 24 patients. C3 complement was mea-

sured in 10 patients; it was raised in four, depressed in two, and normal in the remaining four.

Echocardiography was carried out in 24 patients; 18 patients had vegetations on one or several valves and in five of them blood cultures were negative—one had Q fever endocarditis and one had gram positive and gram negative organisms grown from the vegetations on the aortic valve at necropsy and one was considered to have fungal endocarditis.

Of the 31 patients in congestive heart failure at presentation two had abnormalities of the central nervous system on admission—there were signs of meningitis in one and a Roth spot in one—while in hospital four patients developed renal failure, two patients had myocardial infarction, and one had complete heart block. Ventricular fibrillation developed in two patients before operation. One patient who did not have congestive heart failure developed a transient left hemiparesis. Thus, these 40 patients were a high risk group in that throughout hospital stay only eight had no clinical evidence of congestive heart failure, renal failure, cerebral emboli, myocardial infarction, complete heart block, or ventricular fibrillation.

The duration of illness before treatment was known in 34 patients: in six it was <1 week, in 10 it was 1–4 weeks, in 14 it was 4–12 weeks, and in four it was >12 weeks. Eight patients with Q fever endocarditis were treated for ≤29 months with oral tetracycline and co-trimoxazole or tetracycline alone.² The remaining 32 patients were treated for eight days to eight weeks and usually received at least two bactericidal antibiotics, depending on the bacteriological sensitivities for the organism isolated. In this group all antibiotics were given intravenously except for streptomycin which was administered intramuscularly. The empirical treatment in those patients who were culture negative was two bactericidal antibiotics, one with a maximal effect on gram negative organisms and the other with a maximal effect on gram positive organisms. These were usually benzylpenicillin and an aminoglycoside. One patient who was culture negative and who was considered to have fungal endocarditis, though this could not be proved, had six weeks' treatment with intravenous amphotericin B and oral flucytosine.

During hospital stay 16 patients (13 male) required operation because of haemodynamic deterio-

Table 1 Details of the 12 patients who died of endocarditis

Age	Sex	Organism in blood cultures	Presenting valve lesion	Prosthetic valve in situ at presentation	Valve replacement as emergency procedure	Necropsy	Cause of death
67	M	Culture negative (Q fever serology positive)	Mitral incompetence	Starr-Edwards mitral	No (poor left ventricular function)	No	Congestive heart failure and renal failure
79	M	<i>Strep faecalis</i>	Aortic incompetence and mitral incompetence	None	Refused	No	Left ventricular failure and renal failure
34	F	Culture negative (<i>C albicans</i> on tricuspid valve at post mortem)	Mitral and tricuspid incompetence	Starr-Edwards mitral and tricuspid	No	Yes	Congestive heart failure and cardiogenic shock (stuck tricuspid valve)
13	M	Culture negative	Aortic incompetence (bicuspid aortic valve)	None	Yes	Yes	Left ventricular failure and myocardial infarction
41	M	<i>Staph albus</i>	Aortic incompetence	Starr-Edwards aortic	Yes	Yes	Left ventricular failure
53	M	Culture negative	Mitral incompetence	Starr-Edwards mitral	Yes	Yes	Congestive heart failure
25	F	<i>Staph aureus</i>	Aortic incompetence	Björk-Shiley aortic	Yes	Yes	Left ventricular failure
20	F	Streptococci of the viridans group	Aortic incompetence from a prolapsed aortic valve cusp and atrioventricular canal from right atrium to left ventricle	None	No	Yes	Rupture left ventricular wall and haemopericardium
76	M	Streptococci of the viridans group	Aortic stenosis and aortic incompetence	None	No	Yes	Pulmonary embolus
61	M	<i>Staph aureus</i>	No valve lesion	Starr-Edwards aortic	No	Yes	Left ventricular failure and renal failure
51	F	Culture negative (<i>Strep faecalis</i> and <i>Staph aureus</i> grown post mortem)	Mitral stenosis and tricuspid stenosis, aortic stenosis and aortic incompetence	None	No	Yes	Congestive heart failure and renal failure
63	F	Culture negative	Mitral stenosis, aortic stenosis and aortic incompetence	None	No	Yes	Left ventricular failure

ration (heart failure). Eleven had native valve lesions and five had prosthetic valve endocarditis. Seven of the 16 patients had emergency surgery and were pyrexial at that time. Four of the seven patients who had emergency operation died in hospital (Table 1). Only two of the 12 patients who were alive and well on discharge after operation required further operation. One patient required re-suturing of the mitral valve three years later because of a paravalvar leak, together with a saphenous vein graft to the left anterior descending coronary artery, and the other had re-operation two years later when a clotted mitral Björk-Shiley valve was replaced with a St Jude's prosthesis.

Fifteen patients who had congestive heart failure at admission did not have operation. Six of these died in hospital (Table 1). In two patients operation was contraindicated because they had poor left ventricular function, two had advanced renal failure and congestive heart failure, one patient refused surgery, and in one patient the tricuspid valve jammed suddenly and death followed rapidly despite attempted resuscitation (Table 1). In the remaining nine patients atrial fibrillation complicated congestive heart failure. Digoxin and diuretic treatment produced a dramatic response and all these patients were out of heart failure and alive and well on discharge.

Twelve (30%) patients (seven male, five female) died in hospital (Table 1). Seven of them were >50 years old, and all deaths took place between five and 117 days of admission (mean 32 days). Half the deaths occurred in patients with prosthetic valves. Six patients had endocarditis affecting the aortic valve alone, in four it affected at least two valves, and in two patients the mitral valve only was involved. In 10 patients death was mainly the result of left ventricular or congestive heart failure. Six of the 12 patients who died were culture negative (Table 1).

Six (35%) of the 17 patients with an aortic valve lesion associated with endocarditis died, two (22%) of the nine with a mitral valve lesion died, and two (18%) of the 11 patients with aortic and mitral lesions died. Both patients with a mitral and tricuspid or mitral, tricuspid, and aortic lesion died. The remaining patient, who had a ventricular septal defect alone, survived. Two (29%) of the seven patients in whom *Staph aureus* was identified as the causative organism from blood cultures died. Six (33%) of the 18 patients with culture negative endocarditis died. However, half the patients in whom no organisms (other than those causing Q fever) were cultured died.

Both patients with myocardial infarction, one with complete heart block, four patients who developed renal failure, and two patients who developed ventricular fibrillation before operation all died in

hospital. Three of the five patients with prosthetic valves who required operation because of haemodynamic deterioration during hospital stay died. Two of the four patients seen and treated more than 12 weeks from the onset of symptoms died. Both of the patients with central nervous system abnormalities at presentation survived, as did the one in whom a transient left hemiparesis developed.

Twenty eight patients were out of congestive heart failure and alive and well on discharge from hospital.

Discussion

In the days before antibiotic treatment infective endocarditis was always fatal. Nowadays the overall mortality is reported to be approximately 30%.³⁻⁵ Nevertheless, in a recent study only 14% of 541 patients with infective endocarditis died while in hospital.⁶ This further fall in mortality is undoubtedly related to the use of early appropriate bactericidal/rickettsicidal agents and also to early cardiac valve replacement.

Despite systemic antibiotic treatment and early valve replacement the prognosis in patients with infective endocarditis remains poor, particularly for those with congestive heart failure which is now the major cause of death. In a recent review of 253 patients with infective endocarditis of native valves, low cardiac output or severe heart failure developed in 82 patients and in hospital mortality was 57%.⁷ In the same series severe preoperative heart failure was present in 58 patients who had an in hospital mortality of 41%. Furthermore, mortality was 62% in patients when haemodynamic deterioration occurred in the 24 hours preceding valve replacement. The severity of the heart failure and the time between deterioration of the haemodynamic status and operation are probably the most important determinants of outcome. Twelve (30%) patients died in this series in which 31 of the 40 patients were clinically in congestive heart failure at presentation and in which 16 patients required operation during the acute phase because of haemodynamic deterioration.

It is widely accepted that there is a higher mortality among patients with coronary emboli, arrhythmias, and conduction disturbances associated with infective endocarditis. The respective mortality rates in one study were 60%, 49%, and 50%.⁷ Also those with atrioventricular block, neurological complications, renal insufficiency, and those with *Staph aureus* endocarditis have been reported to have a significantly higher mortality.⁶⁻⁸ In this series all patients with probable coronary emboli giving rise to myocardial infarction (two cases), with complete heart block (one case), with renal failure (four cases),

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and with ventricular fibrillation before operation (two cases) died. All three patients with neurological complications survived, however, and only two (29%) of the seven patients who had *Staph aureus* endocarditis, as identified by blood cultures, died.

In our study the aortic valve was the most common single site of infection (42%). This has been found by other workers.⁶ In medically treated patients mortality was thought to be higher in those with infective endocarditis on the aortic valve. When valve replacement is undertaken at an opportune time, however, there is no significant difference in mortality rate between those with endocarditis of the aortic or mitral valves. In this series the mortality rate for those with infective endocarditis associated with an aortic valve lesion was 35%, for those with a mitral lesion it was 22%, and for those with aortic and mitral lesion it was 18%.

The average age of patients in this series was 44 years; the oldest patient was aged 79 years at diagnosis (Figure). An increasing incidence in the older age groups has been noted in other series, and it has been suggested that the most important factor appears to be the decreasing incidence of rheumatic heart disease and the increased longevity of the population.^{6,9-11}

The ratio of males to females was 2.3:1 in this series. Others have reported a high incidence among males.^{6,10,12} This increase in men is not related to the aetiology of the disease. It has been reported to be partly due to the decreasing incidence of rheumatic valvar disease, which tended to be higher in women than men, and also to the high incidence of congenital aortic valve disease, which is more common in males. Male predominance increased as infective endocarditis became a disease of older patients.¹² In our series 26 (65%) of the 40 had had previous rheumatic heart disease and 17 had prosthetic valves. McNeill *et al* found that rheumatic heart disease accounted for 75% of their patients with pre-existing heart disease,¹³ whereas Schnurr *et al* noted rheumatic heart disease to be a predisposing factor in <25% of their cases.¹⁴

The risk of endocarditis in an individual with valvar heart disease after particular procedures or

illnesses is unknown. It may depend on the age of the person, the type of valve lesion, and the type and pathogenicity of the causal organism. In our series 20% of our patients had had recent dental procedures, which are known to cause bacteraemia. There is a considerable variation in the reported incidence of dental procedures before infective endocarditis.⁵ Bayliss *et al* reported that 13.7% of their cases of infective endocarditis had had dental procedures within three months of the onset of their illness.⁵ All our patients with Q fever endocarditis had been in contact with animal or cattle products. In none of our patients was drug addiction a factor in the pathogenesis of endocarditis, no patients were receiving immunosuppressive drugs, and none had had infective endocarditis before.

The symptoms and signs of infective endocarditis were described by Horder in a series of 150 cases in 1909; they have remained relatively unchanged despite the availability of antibiotics.¹⁵ Fever is the most common sign. The rise in temperature may be minimal or absent, however, especially if the patient has received antibiotics that eradicate the bacteraemia but not the disease. All our patients had pyrexia. Other signs or symptoms in our patients were similar to those noted by other workers, though their frequency varied considerably. Splenomegaly has long been considered to be an important diagnostic feature of this disease, but a greater number of our patients had hepatomegaly. This was probably due to the high incidence of congestive heart failure. Lerner and Weinstein have indicated that the incidence of clubbing has decreased; they found this sign in only 13% of their patients.¹⁶ Its frequency (32%) in our group resembled that reported by Shinebourne *et al*.¹⁷ Twenty two per cent of our patients had evidence of emboli, and haematuria was noted in 70% of our patients, which resembles findings reported by other workers.^{10,16} It has been suggested that thrombocytopenia, as a feature of infective endocarditis, is more frequent in Q fever endocarditis than in bacterial endocarditis. Turck *et al* found thrombocytopenia in 12 of their 16 patients with Q fever endocarditis.¹⁸ It was present in three of our eight patients. In most cases of infective endo-

Table 2 Frequency of organisms in patients with infective endocarditis^{6,20}

Category	%
Streptococci of the viridans group	40-50%
Streptococci group D	10-20%
<i>Staphylococcus aureus</i>	10-15%
<i>Staphylococcus epidermidis</i>	5-10%
Gram negative bacilli	6-8%
Other microorganisms	2-5%
Culture negative	8-12%

Table 3 Organisms isolated in prosthetic valve endocarditis²³

Category	%
Staphylococci	37%
Streptococci	20%
Gram negative organisms	13%
Fungi	9%
Mixed infections	21%

carditis there is a polyclonal immunoglobulinopathy, with high concentrations of IgG, IgM, IgA, and rheumatoid factors have been noted in 43% to 85% of patients with infective endocarditis.

Vegetations are detected by ultrasound in 13% to 78% cases of endocarditis.¹⁹ When heart failure follows valve destruction, however, large vegetations are often seen. Seventy five per cent of the 24 patients in the study who were examined by echocardiography were positive for this sign. But the technique is limited if the duration of symptoms is short and in the presence of calcified or prosthetic valves (which are echo dense) when identification of echoes caused by vegetations is difficult.

Although the type of organisms giving rise to infective endocarditis has changed in the past decade, streptococci remain the largest group of organisms (Table 2). The incidence of culture negative infective endocarditis varies markedly from series to series and has been reported to be as low as 3% and as high as 64%.^{21 22} In recent years the percentage of culture negative endocarditis patients has fallen. This was thought to be due to improved culture techniques. Pesanti and Smith, however, reported that patients with infective endocarditis and negative blood cultures were twice as likely to have clinically evident congestive heart failure and major embolic episodes on admission than patients with positive blood cultures.²¹ Also, such patients were more likely to be on antibiotic treatment before culture. Case selection may also reduce the frequency of culture negative infective endocarditis. Pesanti and Smith found unusual organisms only occasionally; most patients were infected with common organisms, or organisms were no longer evident within the vegetations.²¹ Thus, one group has suggested that many cases of culture negative infective endocarditis represent an immunological, rather than an infectious disease, that is one which is triggered by an infectious agent. The immediate mortality of patients with culture negative infective endocarditis was higher than that of patients with culture positive disease and was comparable to that seen in staphylococcal or prosthetic valve endocarditis.²¹ Six (33%) patients in our series of 18 with culture negative endocarditis died. When those with Q fever endocarditis were excluded, however, five (50%) of 10 died.

Table 3 shows the infecting organisms found in a reported study of prosthetic valve endocarditis. In early prosthetic valve endocarditis, however, the incidence of staphylococci, gram negative pathogens, and fungi has been reported to be significantly higher.²³ Of 17 cases of late prosthetic valve endocarditis eight (47%) infections were due to strep-

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tococci, four (24%) to staphylococci, and 5 (29%) to mixed infection.²³ In another series of late prosthetic valve endocarditis a similar incidence was reported with 31 causative organisms identified in 29 cases; 15 (48%) cases were due to streptococci, 11 (35%) to staphylococci, and five to other species.²⁴ In our series of 17 patients with late prosthetic valve endocarditis, 14 had causative organisms identified by culture or serology or at necropsy. Six (43%) patients had Q fever endocarditis, four (29%) had staphylococci, three (21%) had streptococci, and one (7%) had *C. albicans*. Aortic prosthetic valve endocarditis is reported to be 1.6 times more common than mitral prosthetic valve endocarditis.²³ Infective endocarditis is more common in multiple valve replacement than in isolated valve replacements. Seven of the 17 patients in our study with prosthetic valve endocarditis had an aortic prosthesis, five had a mitral prosthesis, and five had either mitral and aortic (four cases) or mitral and tricuspid prostheses (one case). The mortality rate for late prosthetic valve endocarditis can reach 45%.²³ In our series six (35%) of 17 patients with prosthetic valves died, but three of the five with prosthetic valves in whom haemodynamic deterioration led to a further operation while they were in hospital died. Apparently the two factors with the greatest influence on the prognosis in patients with prosthetic valve endocarditis are the infecting organism and the degree of cardiac dysfunction.²⁵

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