Infective endocarditis: incidence and mortality in the North East Thames Region

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SUMMARY A survey of infective endocarditis in the North East Thames Regional Health Authority was carried out over a period of 30 months from 1982 to 1984. The incidence, clinical characteristics, and in-hospital mortality were studied. Important causes of endocarditis were dental treatment, the presence of dental disease, drug abuse, and cytotoxicity. The omission or incorrect administration of antibiotic prophylaxis in patients with valve disease was noted, but failure of correctly prescribed antibiotic prophylaxis was not recorded. Adverse prognostic features were increased age, prosthetic valve infection, Gram negative or staphylococcal infections, and aortic valve involvement. In contrast, mortality was lower in patients with mitral valve prolapse, ventricular septal defect, and streptococcus viridans infection. Deaths were usually attributable to irreversible complications present at the time of diagnosis. Vegetations were detected on the echocardiogram in half of those studied and mortality was higher in those with vegetations than without. Operation for native valve infection was associated with a low mortality and it is likely that the overall mortality for infective endocarditis has been improved by surgical intervention.

Since 1909¹ infective endocarditis has been the subject of several important surveys. The most recent was from the Medical Services Study Group of the Royal College of Physicians and was completed in 1982.²⁻⁴ Earlier reports often came from referral centres and patients were enrolled for up to 10 years so that sufficiently large study groups could be accumulated by single institutions.⁵⁻⁸ Many patients with infective endocarditis are now managed in district general hospitals whereas in these earlier studies more complex cases sent to referral centres were over-represented. Published data on incidence, mortality, and clinical features are unlikely to reflect accurately the impact of current preventive, diagnostic, and therapeutic interventions.

We set out to document the current features of infective endocarditis within the North East Thames regional population, aiming to obtain accurate incidence and mortality figures. This approach differed from that of the Medical Services Study Group²⁻⁴ which reported from the whole of the United Kingdom with a relatively low sampling

rate and consequently encountered difficulties in assessing incidence and mortality.⁹

Patients and methods

All physicians in the North East Thames Region were asked to register cases of infective endocarditis at the time of diagnosis and to complete a questionnaire after the discharge or death of the patient. A nominated physician in each health district acted as a coordinator to encourage case reports from all physicians, geriatricians, surgeons, and pathologists.

Because we expected that case reporting might be incomplete we also actively sought cases. The Regional Hospitals Activity Analysis centre provided details of all cases coded as endocarditis on death or discharge. These were followed up and the consultants responsible were asked to complete the questionnaire on these cases. Five cases diagnosed at necropsy were similarly followed up to obtain clinical data. The survey lasted 30 months (June 1982 to November 1984). Patients registered more than once (that is intraregional transfer or multiple admissions) were counted as a single case.

Reports were received from most of the hospitals in the region and in most instances the case notes were reviewed in the study centre where the ques-

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tionnaire was completed. The topics covered in the questionnaire included causative events, antibiotic prophylaxis, clinical and microbiological features, echocardiography, and the outcome of medical or surgical treatment.

The 1981 census records and more recent census monitors¹⁰ gave mid-year population figures for the North East Thames Region adjusted for births, deaths, and migration. These figures were used to estimate incidence.

Results

INCIDENCE

The regional hospital activity analysis statistics showed 197 cases coded as infective endocarditis during the survey period. We studied 173 (88%) of these; the remaining 24 case records were not made available to the survey despite repeated attempts to include them. We found that 18 cases were incorrectly coded. A further 20 cases registered through the District coordinators had not been coded by the hospital activity analysis at the end of the survey period. There were a further 10 cases from the London Chest Hospital; these are not reported through the regional hospital activity analysis system. In total 185 cases of infective endocarditis were included in this survey which lasted 30 months.

The regional population was 3.375 million; therefore the incidence per annum of patients treated for infective endocarditis was 23 per million. There were five extra-regional patients and when they were excluded the estimate of incidence was marginally reduced. If all cases not made available are assumed to be accurately coded then the maximum estimate of incidence would be 25 cases per million. Extrapolation to the whole of the United Kingdom gives an annual incidence of 1150–1300 cases per year.

MORTALITY

Overall mortality was 21% (39 of 185 cases) but mortality in the different subgroups varied considerably. Infection associated with native valve or congenital heart disease had a mortality of 7% (2/29) for those coming to operation and 19% (27/137) for those treated medically. Prosthetic valve infection had a mortality of 53% (10/19).

Increased age adversely influenced outcome with a 34% mortality (28/82) among patients aged ≥ 60 years compared with 9.5% mortality (10/96) in those < 60 years. The mean (SD) age for the whole group was 54.5 (18) years and the mean age of those who died was 63.0 (15) years.

CAUSE OF DEATH

Each of the 39 deaths was reviewed in detail to

Fig 1 Source of infection.

establish the major cause of death and whether different management might have altered the outcome.

It was clear that in the majority of these cases major complications were present, often being the cause of admission to hospital. The major causes of death were heart failure (10), uncontrolled infection (9), stroke (8), sudden death (6), renal failure (2), pancreatitis (1), and unknown in two. When the information on the cases was examined in greater detail there was usually a combination of complications that had contributed considerably to the death. This is shown by the fact that six of the nine patients with uncontrolled infection had advanced renal failure and two others had systemic embolisation before death. The majority of deaths appeared to be unavoidable but in three patients with heart failure operation could have been considered and three might have benefited from earlier in-hospital diagnosis.

Table 1 Unusual sources of infective endocarditis in 23 cases

Source	No	Source	No
Colonic surgery	2	Cardiac pacing	1
Eczema	2	Chiropody	1
Haemodialysis	2	Coarctation repair	1
Intravenous cannula	2	Labour	1
Prostatism	2	Obstructive jaundice	1
Septic arthritis	2	Sinusitis	1
Skin abscess	2	Gland infection	1
Cardiac catheter	1	Urethral surgery	1

SOURCES OF INFECTION LEADING TO INFECTIVE ENDOCARDITIS (FIG 1, TABLE 1)

No source of infection was identified in over half the cases. The most frequent single cause for infective endocarditis was dental treatment within three months of symptoms; this occurred in 26 (14%) patients. In 21 (11%) patients untreated dental disease was present and was thought to be the source of infection. Thus dental treatment or disease was implicated in 25% of all cases.

Drug abuse (6.5%) was an important cause of infective endocarditis, with tricuspid valve infection occurring in 11 of the 12 cases reported. Although poor compliance tended to reduce the length of treatment in these patients the early in-hospital mortality was only 8% (one death in 12 patients).

Cytoscopy or prostatism preceded *Streptococcus faecalis* (6 patients) or *Str enterococcus* (1 patient) infection. The variety of other causes (table 1) indicates the many situations in which bacteraemia (and hence endocarditis) may occur.

ANTIBIOTIC PROPHYLAXIS

In seven patients it was suggested that prophylactic antibiotics had been given before endocarditis developed; on close examination none was established as a failure of antibiotic prophylaxis. One patient received appropriate antibiotics but only after dental treatment had been completed. In three patients appropriate antibiotic cover had been given but clinical and microbiological data indicated that the subsequent infective endocarditis was unrelated to the procedure for which the antibiotics had been given. In one case which occurred after dental treatment the patient had not received adequate doses of erythromycin.¹¹ One case of streptococcus viridans endocarditis that occurred six weeks after labour is of uncertain origin. An intramuscular dose of amoxycillin was given two hours before the start of the second stage of labour and plasma concentrations would have been low at the time of greatest risk of bacteraemia. In another patient who had had dental extraction correctly covered with amoxycillin

Fig 2 Site of infection.

a year earlier, streptococcus viridans endocarditis was attributed to the presence of further dental sepsis.

Six patients had not been given antibiotic prophylaxis despite recognised cardiac indications for its use. Two patients were not given antibiotics because it was thought unnecessary for dental scaling. Another had dental treatment without cover, but no reason was given for this omission. Excision of an abscess (two cases) and chiropody (one case) were reported to precede staphylococcal infection and no antibiotics had been given before these procedures in patients known to have prosthetic cardiac valves.

CLINICAL FEATURES

The symptoms and signs at presentation (table 2) reflect the recognised features of infective endocarditis. The mean (SD) duration of symptoms was 6.2 (5.5) weeks but the symptomatic period before diagnosis was shorter among those patients who died than in those who survived (4.2 (3.3) weeks vs 6.8 (5.9) weeks). This was true for patients treated medically or surgically. Staphylococcal and Gram negative infections were associated with a short duration of symptoms (3.0 (3.2) weeks) and were more frequently found in the patients who died. For each organism there was no difference in the symptomatic period before diagnosis in survivors and non-survivors.

Endocarditis was more frequent on the mitral valve than on the aortic valve (55% vs 35%) and carried a lower mortality (21% vs 28%) (fig 2).

Mitral valve prolapse (19%) and rheumatic heart disease (18%) were the most frequently recognised valvar abnormalities but in many patients (29%) no underlying cardiac abnormality was recognised. Mortality associated with infection on rheumatic valves (24%) and bicuspid aortic valves (28%) was much higher than that for mitral prolapse (6%). Mortality was high (53%) in patients with prosthetic

Table 2 Symptoms of infective endocarditis

Sign or symptom	%
Fever	79
Malaise	79
Weight loss	39
Dyspnoea	42
Pyrexia	84
Pallor	47
Splinter haemorrhage	26
Splenomegaly	21
Clubbing	9
Ocular emboli	6

Fig 3 Microbiological results.

**Haemophilus parainfluenzae* (3), *Lactobacillus* (2), Mixed culture (4), diphtheroid sp. (1), Q fever (2).

valve endocarditis whereas infective endocarditis in patients with congenital heart disease had a low mortality (7%).

MICROBIOLOGICAL RESULTS (FIG 3)

Our data show the continuing importance of streptococcal infection, with 113 (61%) cases recorded. Viridans group streptococci caused 45% of cases (83 patients) and only 38% (31 patients) of these were associated with dental treatment or disease. The mortality for viridans infection was 7% while infection with the other streptococci carried a mortality of 20%. Staphylococcal infection occurred in 21% (39 cases), the mortality being greater for *Staphylococcus epidermidis* (67%, eight out of 12) than *Staphylococcus aureus* (30%, eight of 27 cases). All five patients with *Staph epidermidis* infection on a prosthetic valve died.

Six of the seven patients with Gram negative infection died. There were 14 (8%) culture negative cases but all had clinical, surgical, or necropsy features to support the diagnosis of infective endocarditis.

ECHOCARDIOGRAPHY

Echocardiography was performed on 140 (76%) patients in the survey. Vegetations were detected in only 23% (six out of 26 patients) who had M mode studies compared with 49% (55 of 114) when combined M mode and cross sectional echocardiography was performed.

In native valve infection mortality was 13% (8/60) in patients with vegetations on the echocardiogram and 8% (5/64) in those without. In two cases persisting mobile vegetations were taken as an indication for operation, one of these patients having experienced a systemic embolus. Vegetations were identified in only one of 16 patients with prosthetic valve infection.

HAEMATOLOGICAL AND BIOCHEMICAL INVESTIGATIONS

Initial or peak values (mean) for plasma urea and creatinine were high in those patients who subsequently died. The early haemoglobin concentrations and white cell counts were similar in survivors and non-survivors and most patients had values within the normal range. The erythrocyte sedimentation rate varied considerably and in eight patients the initial rate was under 20 mm/h. Microscopic haematuria was detected in 28% (52 cases) and was more common in those who died (41% (16 of 39)) than in the survivors (24% (36 of 146)).

PROSTHETIC VALVE INFECTION

Mortality was high (53%) in the 19 patients with infection on a prosthetic valve. Aortic and mitral valve involvement were equally common and there were five deaths associated with infection at each of these sites. Because the numbers are low no conclusions can be made about the relation between type of prosthesis and outcome, although infection was more common on mechanical (13) than bioprosthetic (6) valves. *Staph epidermidis* infection was more common in patients with prosthetic valves, and all five cases died.

SURGICAL TREATMENT

The results of surgical treatment were good. Eighty two per cent (28 patients) survived and 18% (six patients) died. When those treated for native valve infection are considered separately the mortality is much lower at 7% (2/29) and is better than that recorded for medically treated patients. Since most operations were performed because of acute and severe haemodynamic complications the results can be regarded as encouraging. Surgery for prosthetic valve endocarditis was successful in only one of five patients who had an operation.

Discussion

This is the second large survey of infective endocarditis to be reported from the United Kingdom in the 1980s, the Medical Services Study Group of the Royal College of Physicians in collaboration with the British Cardiac Society having published data on 541 patients.²⁻⁴

Our study was designed to encompass the whole population of patients with infective endocarditis in the North East Thames Region, without a bias towards those presenting to referral centres, and to permit the estimation of overall incidence and mortality. We found the annual incidence to be 23-25 cases per million and extrapolation of this figure to the whole of the United Kingdom gives a total inci-

dence of 1150–1300 cases. These figures are higher than those from earlier series, but they resemble the incidence reported from a population of 1.8 to 2.0 million around Lyons in France (40–50 cases per year).¹²

The Royal College of Physicians survey reported a relatively low number of cases associated with drug abuse (2%), a relatively high number of prosthetic valve infections (17%), and a low overall mortality (14%), supporting the authors' view that there was a low sampling rate and some sampling bias in the study that prevented accurate estimates of incidence and mortality.⁹

We found the overall mortality to be 21% and this should replace the widely quoted figure of 30% which was based on data from the 1960s and 1970s^{5–8} when surgical intervention was not widely practised. The number of deaths from infective endocarditis registered in the United Kingdom is approximately 250 cases per year.⁹ Based on the mortality rate of 21% from our survey the calculated incidence of infective endocarditis is 1250 cases per year which closely matches our estimated incidence.

We found that a considerable proportion of cases (25%) was related to either dental treatment or the presence of dental disease. Recent investigation of dental causes of endocarditis showed that 103 (19%) of 541 cases were associated with dental procedures or dental sepsis. It was estimated in 1978 that 20–30% of the United Kingdom population had dental or periodontal disease¹³; this accords with the amount of dental disease we found in the population with infective endocarditis. An improvement in the dental health of the population should, therefore, reduce the incidence of infective endocarditis arising because of chronic dental infection. Increased detection of asymptomatic heart valve disease, followed by appropriate advice would allow the population at risk to be better protected, but would prove a formidable logistic exercise. Endocarditis can arise in previously normal hearts and three patients treated surgically in our series were seen to have "normal" valves apart from the damage from vegetations. The value of offering prophylactic antibiotic treatment to all patients over 60 years receiving dental treatment has been examined^{2,14,15} but no definitive recommendation has emerged. In our study only 35 of 83 patients with viridans infection were over 60 years and, of these, endocarditis followed dental treatment in only seven. Routine prophylaxis for dental treatment in all subjects over 60 years would therefore offer only limited reduction in the incidence of infective endocarditis in this age group.

There has been considerable interest in the usefulness of antibiotic prophylaxis in patients known

to be at risk, and advice on this has been available for some years.^{16,17} We found that there were no failures of prophylaxis when the appropriate antibiotic had been given in the correct dose and at the optimum time to cover a particular procedure. Closer analysis of the nine cases of possible prophylaxis failure among 541 cases³ shows that only three are likely to be true failures of antibiotic prophylaxis for dental treatment. A recent case report gave a further example of a true failure of prophylaxis, but in a complex clinical setting.¹⁸ Our impression is that if only three from a total of over 700 cases of endocarditis are thought to result from true failure of prophylaxis it is reasonable to conclude that there is a high rate of protection obtained when prophylaxis is properly used for the large number of patients for whom it is recommended.

The current advice on antibiotic prophylaxis was simplified and widely published in 1982.¹⁶ In at least eight of our 185 patients and in several examples from the Royal College of Physicians report,³ antibiotics were not given when they should have been or they were incorrectly prescribed. An alarmingly high rate of ignorance about some aspects of antibiotic prophylaxis for endocarditis was found among physicians, surgeons, dentists, and general practitioners in a recent survey,¹⁹ and cardiologists and others should ensure that both patients and doctors are aware of the oral amoxycillin prophylaxis regimen.

Our findings confirm the continuing importance of streptococci, which accounted for 61% of infections. The incidence of viridans infection (45%) is of the same order as that found in the 1960s and 1970s.^{6–8} In our series 15% of cases (28 patients) had infections from organisms normally found in the bowel or genitourinary tract, and a similar incidence was reported by the Royal College of Physicians' survey.⁴ We found specific causes for *Strep faecalis* infection in five of 10 cases (cystoscopy three, and prostatic disease two). Among 18 infections with other bowel organisms, only two had a clear cause identified. In both a colostomy had been fashioned, one for carcinoma of the colon and one for carcinoma of the prostate. The high mortality (67%) found with *Staph epidermidis* infections suggests that the traditional view that this organism is not an important pathogen should be altered in the context of infective endocarditis particularly when a prosthetic valve is affected.

The clinical features (table 2) confirm the findings in other series. A short duration of symptoms before diagnosis was a striking feature among those with a higher mortality and this probably relates mainly to the characteristics of the infecting organism in these cases.

Echocardiography is of diagnostic value in infective endocarditis. In this study the rate of detection of vegetations was doubled by the use of combined M mode and cross sectional studies compared with M mode studies alone. The overall sensitivity of echocardiography in detecting vegetations was only 49%. This detection rate has been reported in the past²⁰ although others have reported a detection rate of up to 73%.²¹ This re-emphasises the important point that a normal echocardiogram does not exclude the diagnosis of endocarditis. Clinical and microbiological findings remain the main diagnostic criteria and the role of echocardiography is to confirm the diagnosis. There was a higher mortality in patients in whom vegetations were detected (13% *vs* 8%). Vegetations were imaged echocardiographically in only one of 16 patients with prosthetic valve endocarditis although several who had operation were found to have large vegetations around the valve. This is because of the highly echogenic nature of the prosthesis which makes differentiation of the features of vegetations difficult.

The important contribution of surgical treatment to the management of infective endocarditis is evident from the results reported here and other recent surveys.^{6 22-24} We suspect that this is the major reason for the fall in overall mortality from 30% to 21%. Many patients with severe haemodynamic deterioration because of valvar regurgitation had a favourable outcome after operation. The mortality for surgical patients was considerably better than for medical treatment of native valve infection (7% *vs* 19%). This indicates that the haemodynamic consequences of infective endocarditis can be effectively treated by operation whereas other complications (for example, uncontrolled infection, sudden death, stroke) do not necessarily respond so well to the use of antibiotic chemotherapy or other medical interventions. After analysing the case records of the patients who died we believe that most deaths were unavoidable, mainly because serious complications were already established at the time of admission to hospital. It is clear that many of the complications of endocarditis are unresponsive to treatment and therefore prevention of the infection or early diagnosis are the best means of reducing overall mortality.

It is likely that endocarditis will continue to be a major clinical challenge mainly because of the unknown aetiological factors in nearly half the cases, the number of individuals presenting who were not previously known to have cardiac abnormalities, and increasing numbers of patients with prosthetic valves. A reduction of incidence might occur with improvements in the use of antibiotic prophylaxis or in the dental health of the population. Surgical results are good and have contributed to a reduction

in mortality to 21%. The mortality figures might have been further improved by earlier diagnosis or operation in six of the 39 patients who died.

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