Factors influencing mortality from infective endocarditis in two district general hospitals

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Summary: Factors influencing mortality were studied in 92 consecutive cases of infective endocarditis admitted to two district general hospitals between January 1975 and April 1982. Thirty two patients died, an overall mortality of 35%, 13 patients died before diagnosis and 19 despite aggressive antimicrobial therapy. Bactericidal antibiotic levels were monitored in 39 cases but these did not appear to influence outcome.

Mortality was lowest for *Streptococcus viridans* infection (15%) but rose to 50% for infections with *S. faecalis* and other less common organisms. Most deaths were in patients over 50. Cardiac failure on admission was a poor predictor of mortality, although this was the principal cause of death during treatment (14 cases). Eight patients had emergency valve replacement and 3 died post-operatively.

When the diagnosis was missed during life (13 cases) arterial embolus was a common presenting feature (46%). Classical signs of endocarditis, other than pyrexia, were absent. A cardiac murmur (always mitral incompetence) was noted in only 6 cases and considered to be insignificant.

Introduction

Following the introduction of antibiotics, mortality from infective endocarditis fell, but remains at 14–46% in Great Britain.^{1–3} Possible causes of variation in reported mortality include differences in the types of hospital from which the patients were recruited (e.g. regional cardiological centre or district general hospital), and in the age distribution of cases in the reported series. We report the general clinical findings and discuss the factors influencing outcome in an unselected group of patients presenting at two district general hospitals in the Midlands.

Methods

Cases of infective endocarditis admitted to two Nottingham hospitals between January 1975 and April 1982 were identified by examining medical, microbiological and post-mortem records.

Cases were included if positive blood cultures or serology were obtained with clinical evidence of endocarditis; if, despite negative blood cultures, there was strong clinical evidence of endocarditis (fever, changing heart murmur and splinter haemorrhages); or if typical endocarditic lesions were detected at

autopsy and histological or bacteriological examination of the lesions confirmed the presence of infection.

Minimum inhibitory and minimum bactericidal concentrations of antibiotics were determined by the tube dilution method for most bacterial isolates. The bactericidal activity of the patient's serum against the organism isolated was determined during treatment, before (trough level) and 1 hour after (peak level) an antibiotic dose.

Results

There were 92 cases of infective endocarditis during the study period. Thirty two patients died (35%) including 13 patients in whom the diagnosis was missed during life.

Of the 79 patients in whom the diagnosis of endocarditis was established in life, 44 were men and 35 were women. There was a peak incidence in patients aged 61–70 (Figure 1). Only 3 of the 28 patients aged 50 or less died, whereas 16 of 51 patients over the age of 50 died. Mortality in men (15 deaths) exceeded that in women (4 deaths).

Predisposing causes

Twenty-three of the total 92 patients were known to have had rheumatic heart disease and a further 22

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patients had a known heart murmur, usually mitral incompetence. Seven patients had congenital heart lesions and 8 had prosthetic heart valves. The remaining 32 patients (35%) were not known to have had valvular heart disease.

Only 4 patients presented following dental manipulation, 3 of whom had infection with viridans streptococci. Four patients developed enterococcal endocarditis, 3 following urinary catheterization and one following hysterectomy.

Clinical and laboratory findings

These are summarized in Tables I and II. The infecting organism was identified in 75 patients (95%) (Table I). Viridans streptococci accounted for 42 cases of which 6 (14%) died. Mortality rose to 50% for infections with *S. faecalis* and other unusual organisms. The mean duration of symptoms before admission was longest in infection with viridans streptococci (11.1 weeks) but the range was large (1.5–28 weeks). The duration of symptoms for all organisms is shown in Table 1.

Pyrexia and a cardiac murmur were found on admission in 80% of cases. Cardiac failure was present in 32 patients of whom 9 (28%) died. Seventeen patients presented with major embolic episodes and 5 (29%) died. Mortality in patients with mitral or aortic involvement was similar: 21% and 28% respectively. Mixed aortic and mitral valve involvement did not increase the mortality (24%). There were 8 'late onset' cases of prosthetic valve infection (i.e. occurring more than 2 months after cardiac surgery) and 3 (37%) died.

Of 65 patients in whom the ESR was measured, 14 had exhibited normal values (< 25 mm/h) and only 2 of these died. In contrast 9 (53%) of 17 patients in whom the ESR was greater than 75 mm/h died. The difference was significant ($P < 0.05$, Fisher's exact test). Microscopic haematuria was found in 47 of the 72 specimens tested.

Treatment

Fifteen patients were treated with benzylpenicillin and 48 with a combination of penicillin and aminoglycoside. After 1977 streptomycin was replaced by gentamicin as the aminoglycoside of choice. Cloxacillin in combination with an aminoglycoside was used in 12 patients. Two patients with penicillin allergy were treated with cephalosporins and one patient with *Coxiella burnetii* infection received tetracycline alone. One patient with *Candida albicans* infection was referred for emergency surgery before antimicrobial treatment. Most surviving patients received a minimum of 2 weeks intravenous therapy and the total treatment period was usually 6 weeks or more.

Serum trough and peak bactericidal titres were measured during intravenous therapy in 32 survivors and in 7 patients who died (Figure 1) but did not appear to influence outcome. Among the survivors the serum at trough was bactericidal at a mean dilution of 1 in 158 (range 2–2048) and at peak at 1 in 820 (range 8–2048). In the patients who died the serum at trough was bactericidal at a mean dilution of 1 in 464 (range 16–1024) and at peak at 1 in 1074 (range 32–2048).

Eight patients had emergency valve replacement and 3 of these died postoperatively.

Missed diagnosis

Among patients in whom the diagnosis was missed in life, there was a female preponderance of 9:4. Six patients (46%) presented with a major arterial embolus, of whom 5 had hemiplegia. Mitral incompetence was detected on admission in 6 patients and considered to be insignificant. Heart failure was present in only one patient. Six had unexplained pyrexia and 3 had anaemia.

Table I Relationship of the duration of illness and outcome to the infecting organism

Organism	No. of cases	(%)	Percent mortality	Mean age years	Duration of symptoms (weeks)	
					Mean	(Range)
'Viridans' streptococci*	42	(56)	14	52	11.1	(1.5–28)
Group G streptococci	3	(4)	33	73	0.33	(0–1)
<i>Streptococcus faecalis</i>	6	(8)	50	68	3.4	(0.5–12)
<i>Staphylococcus aureus</i>	11	(15)	27	52	2.8	(0.5–8)
<i>Staphylococcus epidermidis</i>	3	(4)	33	48	8.3	(1–12)
Others†	10	(13)	50	49	8	(1–24)

**Streptococcus bovis* biotype I (9); *Str. mitior* (8); *Str. sanguis* (7); *Str. mutans* (3); *Str. milleri* (1) – identified by the Streptococcal Reference Laboratory of the Central Public Health Laboratory, Colindale; not speciated (24)

†Others: *Erysipelothrix rhusiopathiae*, coryneform bacterium, *Rothia dentocariosa*, *Str. pneumoniae*, *Haemophilus aphrophilus*, *Cardiobacterium hominis*, *Neisseria gonorrhoeae*, *Escherichia coli* *Candida albicans*, *Coxiella burnetii* – one of each.

Table II Presenting features and laboratory investigations in 92 cases of infective endocarditis

Presenting features/ investigations	Total n = 79	Number of cases		Deaths n = 19 (%)	Undiagnosed in life n = 13
		Diagnosed Survivors n = 60	Deaths n = 19		
Cardiac failure	32	23	9	(28)	1
Cardiac murmur	63	44	19	(30)	6
Emboli:					
cerebral	12	8	4	(33)	5
Peripheral	5	4	1	(20)	1
Pyrexia	63	53	10	(15)	6
Valve involved:					
mitral	28	20	8	(28)	9
aortic	19	15	4	(21)	3
mixed	17	13	4	(24)	
prosthetic	8	5	3	(37)	
congenital abnormality	7	7	—		
other				—	1
Haemoglobin:					
< 10g/dl	27	18	9	(33)	3
< 10g/dl	51	42	9	(17)	7
Erythrocyte sedimentation rate:					
< 25mm/h	14	12	2	(14)	5
> 25mm/h	51	36	15	(29)	5
> 50mm/h	38	27	11	(28)	3
> 75mm/h	17	8	9	(53)	1

*Figures in brackets represents percentage of patients in each category who died.

Figure 1 Relationship of age and sex to mortality in 79 cases treated for infective endocarditis.

Discussion

Despite advances in the medical and surgical treatment of infective endocarditis mortality remains unacceptably high.¹⁻³ Most published series have reported experience from regional secondary referral centres and a recent review from the UK presented multicentre data collected by means of a questionnaire.³ In contrast, this study has reviewed cases of endocarditis in two district general hospitals serving a well defined population. The estimated incidence of endocarditis in the locality was 16 per million per year.

The age distribution, the dominance of male cases and the higher mortality among the elderly agree with observations made by others.^{1,3,4} Although more men died during treatment, more of the patients who died undiagnosed were female. We obtained a bacteriological diagnosis in all but 4 of the 79 patients who were treated. A portal of entry was identified in only 8 patients (10%), 4 of whom had had recent dental surgery. This contrasts with the findings of a multicentre survey where a probable portal of entry was ascertained in 40% of cases.³ Four of our 6 cases of *S. faecalis* infection developed endocarditis in hospital following genito-urinary procedures. These should have been prevented by appropriate chemoprophylaxis. Staphylococcal infection was less common than in the other series.^{5,6} This may have been due to the absence of a cardiac surgical unit in our hospitals. As in other series,⁷ cases of viridans streptococcal endocarditis often had a protracted course of illness before admission, although there was a marked variation among patients. In contrast, infection with Group G streptococci, *S. faecalis* and *Staph. aureus* was associated with a shorter antecedent illness and tended to have a more dramatic presentation.^{8,9}

The association between anaemia, high ESR and mortality has not been reported in other series and may simply reflect other factors such as age and chronic disease. No other investigations were helpful in predicting outcome. The proportion of patients who had microscopic haematuria (65%) was lower than the incidence of 93% reported by Shinebourne who considered the diagnosis unlikely in its absence.¹⁰ In contrast, Lerner & Shnurr found the incidence of haematuria to be 26% and 27% respectively.^{7,11}

How can diagnosis be improved? Clearly the classical signs of endocarditis are not always present. In half the patients in whom the diagnosis was missed, no heart murmur was heard on admission to hospital. In the remainder mitral incompetence was detected, but considered haemodynamically insignificant. We suspect that aortic incompetence is likely to alert the clinician to the possibility of endocarditis whereas mitral incompetence, particularly in the elderly patient, may often fail to do so. Cardiac failure occurred in only one undiagnosed patient but 5

presented with cerebral embolus. A safe rule is to consider infective endocarditis in any sick patient with signs of valvular incompetence, particularly those presenting with stroke.

Echocardiography is now regarded as a valuable aid to diagnosis, allowing characterization of the valve lesion and visualization of vegetations and abscesses,^{12,13} although a normal echocardiogram does not exclude the diagnosis. In our series, echocardiograms were performed infrequently during the early years, but were used increasingly in the later years. Furthermore, one hospital performed only M mode studies instead of the now preferred two-dimensional echocardiograms. For these reasons it was not possible to assess the value of echocardiography in this series.

Why do patients still die of endocarditis? Uncontrolled sepsis is now uncommon and in this series there were no cases of relapsing infection. Although antibiotic therapy should be monitored by titration of the patient's serum,¹⁴ high bactericidal levels clearly do not guarantee therapeutic success. Most deaths in this and in other series^{11,14} were attributable to haemodynamic complications arising from the valve lesion, and not surprisingly, older patients are at particular risk. Acute aortic incompetence is said to be the main cause of intractable cardiac failure, but in the present study, mitral valve involvement appeared equally important. However, it is important to note that acute aortic incompetence may not be recognized since the well known signs associated with chronic compensated aortic incompetence are often absent.¹⁵ Cardiac failure on admission to hospital was a poor predictor of mortality, although it was the main cause of death. Although it may be possible to treat mild heart failure by medical means most patients with this complication are at considerable risk, and certainly severe heart failure at presentation is an indication for urgent surgical referral.¹⁶ Reluctance to refer such patients because antimicrobial therapy has not been completed may have disastrous consequences.

Future advances in the treatment of endocarditis will require more careful liaison between microbiologist, physician and surgeon. When surgical facilities are not close at hand the physician must refer patients with cardiac failure and major arterial emboli since emergency valve replacement may offer the only hope of survival.

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