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The microbiology and pathogenesis of infective endocarditis

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SUMMARY Some details of 544 episodes of infective endocarditis occurring in 541 patients during 1981 and 1982 are reported. The mean age of patients was 51·6 years and there was a greater proportion of males (2:1). Of the 544 episodes 347 (63%) were due to streptococci, 19% to staphylococci, and 14% to bowel organisms. A wide variety of other organisms were responsible for a few cases, and 10% were culture negative. In 60% the portal of entry of the infection could not be ascertained: 19% were probably of dental origin: 16% arose from the alimentary, genitourinary, or respiratory tracts or from the skin or in association with drug addiction, fractures, or pregnancy; the remaining 5% were related to cardiac or other vascular surgery, cardiac catheterisation, haemodialysis, or other procedures involving the blood stream. Seventy-four (14%) of the 541 patients (mean age 59·0 years) died; the mortality was 30% in staphylococcal cases, 14% in infections due to bowel organisms, and 6% in other streptococcal infections. One hundred and seventy-one (32%) of the patients appeared to have had normal hearts before the onset of illness and another 59 (11%) had cardiac lesions not previously recognised. The aortic valve was the most common site of infection. Ninety (17%) of the patients had prosthetic valves or had undergone other cardiac surgery while 34 (6%) had had a previous episode of infective endocarditis. Nine (1·6%) episodes were not diagnosed until necropsy or operation and 34 (6·3%) required urgent valve replacement.

Since Horder's classic description of infective endocarditis nearly three quarters of a century ago[1] antibiotics and valve replacement have transformed the then hopeless prognosis. Studies have shown a changing pattern of the disease,[2–9] but despite the enormous advances in microbiology, particularly the speciation of the streptococci, the source of the infection is often not known and the proportion of cases related to dental procedures or sepsis is probably smaller than previously believed. A recent study of 541 patients with infective endocarditis with particular reference to dental prophylaxis has confirmed this.[10] The number of patients studied was so large compared with previous reports that we considered it appropriate to present some of the other findings in respect of microbiology and pathogenesis.

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Patients and methods

The investigation covered two years, and the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians endeavoured, with the help of fellows and members of the college, to study all patients with infective endocarditis in the British Isles during 1981 and 1982. A short proforma was used with the main object of ascertaining the incidence of cases of dental origin and the efficacy of dental prophylaxis. There was a considerable shortfall in reporting, but a survey of the hospitals staffed by physicians and cardiologists who did contribute does not suggest any significant bias in the sample and we do not believe that the unreported cases would affect the validity of the conclusions presented.

Table 1 *Causal organism in 544 episodes of infective endocarditis*

Organism	*No of cases*
Streptococci	
Group A	1
Group B	3
Group C	1
Group D	1
Enterococci	19
Str bovis	27
Str durans	1
Str faecalis	13
Group F	1
Str milleri	9
Str mitior	24
Str mutans	12
Str salivarius	7
Str sanguis	26
α haemolytic	183
β haemolytic	3
Non-haemolytic	8
Microaerophilic	1
Unspecified	2
Str pneumoniae	5
Total	347
Staphylococci	
Staph aureus	60
Coagulase negative (*Staph albus, Staph epidermidis, Staph hominis, Staph saprophyticus*)	43
Total	103
Micrococci	
Gram negative bacilli	2
Escherichia coli and coliforms	7
Proteus sp	2
Pseudomonas sp	3
Other	1
Total	13
Haemophilus sp	
H influenzae	1
H parainfluenzae	2
H aphrophilus	1
Total	4
Corynebacteria and diphtheroids	
Cor haemolyticum	1
Cor pyogenes	1
Cor xerosis	1
Corynebacterium sp	2
Diphtheroids	2
Total	7
Neisseriae	
Neisseria sp	1
Others	
Cardiobacterium hominis	1
Fusobacterium necrophorum	1
Bacteroides fragilis	1
Others less precisely identified	4
Total	7
Culture negative but cause established	
Coxiella burnetii	7
Chlamydiae	1
Total	8
Negative blood cultures	53
Blood cultures not done	2
Organisms not stated	1
Total	548*

*In four episodes two organisms were cultured.

Results

A total of 544 proformas were received concerning 541 patients, three of whom had two episodes of infective endocarditis in the two years. The age range of the patients was 2–87 years (mean age 51·6) and there was a greater proportion of males (ratio 2:1).

Table 1 shows the causative organisms grown on blood culture or otherwise, and Table 2 gives their source, as far as this could be ascertained. In four episodes more than one organism was cultured. Seventy-four (14%) of the 541 patients died, and brief clinical details are given in Table 3.

Table 4 shows the primary cardiac abnormalities in the 541 patients. Instances in which the doctors, dentists, and patients themselves were unaware of the presence of a pre-existing lesion are also shown, as are patients with previously normal hearts. The valve, valves, or other sites affected by endocarditis, as far as they are known, are shown in Table 5. Table 6 summarises the factors predisposing to infective endocarditis in the 544 episodes, and Table 7 gives details of the 77 patients with prosthetic valve endocarditis. In five patients the diagnosis was not made until necropsy and in another four not until operation. Thirty-four patients required emergency valve replacement.

Discussion

The mean age of the patients was high (51·6 years), a trend indicated in many recent reports.[3 4 6 8 9] Twenty-two of the 541 patients were 15 years of age or less, and 21 of them had known congenital heart disease. By contrast there were 155 patients aged 65 and over, and in 59 of these there was no evidence of any pre-existing cardiac abnormality. Among Horder's[1] 150 cases there were only 12 over the age of 50, and 30 years ago most of Cates's and Christie's[2] patients were between the ages of 15 and 35, but only 13·7% of the 541 reported here were in this age range. Several factors doubtless contribute to this change, the decreasing incidence of rheumatic heart disease and the greater longevity of the population being among the most important. There was a greater proportion of

Table 2 *Source of causal organism in 544 episodes of infective endocarditis*

Possibly dental	103
Alimentary tract	22
Genitourinary tract	23
Respiratory tract	17
Skin	14
Drug addiction	6
Fractures (3 compound, 1 closed)	4
Pregnancy and parturition	3
Related to cardiac operations, non-cardiac vascular procedures, cardiac catherisation, venograms, blood donation, anticoagulant treatment or chronic haemodialysis	26
No portal of entry apparent	326
Total	544

Table 3 *Details of the 74 patients who died from infective endocarditis*

Case No	*Sex*	*Age (yr)*	*Organism*	*Cardiac abnormality**	*Clinical features*
6	M	75	Enterococcus	None	Followed TUR
13	M	60	*Str faecalis*	None	Followed right hemicolectomy
24	M	61	Enterococcus	Yes	AVR for congenital aortic stenosis 1 yr previously
40	M	58	Negative	Yes	
60	M	72	Group D streptococcus	None	
69	F	55	Coagulase negative staphylococcus	Yes	Followed MVR
71	M	27	*Staph aureus*	Yes	Followed AVR
73	M	63	*Staph aureus*	Yes	AVR in 1973
75	M	69	*Staph aureus*	None	
76	M	52	*Staph aureus*	None	Bicuspid aortic valve
85	M	62	Micrococcus	Yes	Followed AVR
88	F	49	*Staph albus*	Yes	Followed AVR
108	M	48	α haemolytic streptococcus	Yes	Died from subarachnoid haemorrhage
113	F	74	*Staph albus*	Yes	
118	M	60	*Staph albus*	Yes	Followed MVR
130	M	?	*Staph albus*	Yes	AVR in 1980
131	M	57	*Staph aureus*	Yes	IE and VR in 1973, followed urethral dilatation and urinary tract infection
137	M	66	Non-haemolytic streptococcus	None	Diabetic
146	F	73	*Str faecalis*	None	Followed reduction of Colles fracture
166	M	53	*Staph albus*	Yes	Dental extraction without antibiotic cover 5–8 wk previously
167	F	76	Negative	None	
176	F	76	*Str sanguis*	None	
186	M	10	*Staph aureus*	Yes	Followed operation for congenital heart disease
190	M	15	Negative	Yes	ASD, died from cerebral embolism
192	M	66	*Str viridans*	Yes	Followed dilatation of oesophageal stricture
204	M	68	*Str faecalis*	None	
209	F	72	*Proteus* sp	None	Diabetic, pyelonephritis, *Proteus* sp in urine
211	M	17	Negative	None	Required AVR for IE, renal failure followed
214	F	63	*Staph albus*	Yes	Previous MVR
249	M	23	*Staph aureus*	None	Chronic renal failure on haemodialysis, IE on tricuspid valve
257	M	57	*H parainfluenzae*	Yes	CAGS and AVR in 1980
259	M	68	*Str bovis*	Yes	
262	F	61	*Staph aureus*	None	Renal biopsy for ARF, retroperitoneal haemorrhage, exfoliative dermatitis, steroids
276	F	57	Negative	Yes	
296	M	53	Negative	Yes	Known aortic stenosis, CAGS 5 m before onset
297	F	62	*Staph albus*	Yes	MVR in 1974
298	M	49	Negative	None	Alcoholism and chronic renal failure
305	M	51	*Str viridans*	None	Congenital heart disease
311	F	66	*Staph aureus*	Yes	AVR in 1973, followed infected thumb
317	F	82	*Str viridans*	None	Died cerebral embolism
324	M	26	*Str mitior*	None	Bicuspid aortic valve, 3 months before onset dental extraction without antibiotic cover
330	F	?	*Staph aureus*	Yes	AVR in 1980
333	F	23	*Str viridans*	None	Severe dental sepsis, ? Marfan's syndrome
338	M	51	*Str viridans*	None	Scaling 5–8 wk before onset without antibiotic cover
348	M	70	*Staph epidermidis*	Yes	Followed AVR 9 weeks previously
350	M	48	Microaerophilic streptococcus	Yes	Bicuspid aortic valve, died from ruptured cusp
353	F	65	Negative	Yes	Endocarditis found at AVR
354	M	57	Negative	Yes	Followed AVR and MVR
359	M	71	*Staph aureus*	Yes	Venesections
360	M	63	*Str mitior*	None	Scaling and polishing without antibiotic cover 9 wk previously
361	F	70	No blood culture done	None	Diagnosed at necropsy
369	F	31	*Staph aureus*	None	Marrow transplant for acute myeloid leukaemia
376	M	78	α haemolytic streptococcus	None	Diagnosed at necropsy
392	F	40	*Staph aureus*	Yes	IE twice previously
393	F	71	*Staph aureus*	Yes	Diabetic
398	F	86	*Str mitior*	None	
424	F	62	*Staph albus*	Yes	Previous MVR
433	M	68	*Staph albus*	Yes	Calcific aortic stenosis, rheumatoid arthritis, followed TUR
438	F	81	*Staph aureus*	None	Diagnosed at necropsy
444	M	70	Group G streptococcus	None	Diagnosed at necropsy
454	M	29	*Corynebacterium* sp	None	Had bicuspid aortic valve
458	F	71	*Str mitior*	Yes	
461	M	63	*Str bovis*	None	Followed liver biopsy
464	M	77	*Str viridans*	Yes	Followed acupuncture
465	M	68	*Str sanguis*	Yes	
486	F	55	*Staph aureus*	Yes	Previous MVR
494	M	46	*Staph aureus*	None	
496	M	57	*Staph aureus*	Yes	
506	M	59	*Str faecalis*	Yes	Dental sepsis
507	M	71	*Str salivarius*	None	Dental sepsis
508	F	46	*Actinobacillus actinomycetencomitans*	Yes	AVR in 1975
515	M	81	*Staph aureus*	None	
526	M	43	*Staph aureus*	None	Chronic haemodialysis, died cerebral haemorrhage, IE found at necropsy
541	F	58	Negative	Yes	AVR and MVR in 1977

*Previously known. TUR, transurethral resection; AVR, aortic valve replacement; MVR, mitral valve replacement; IE, infective endocarditis; CAGS, coronary artery graft surgery; ARF, acute renal failure.

Table 4 *Primary cardiac abnormalities of the 541 patients with 544 episodes of infective endocarditis*

	Known before onset of IE	*Not known before onset of IE*
Rheumatic heart disease	116*	10
Congenital heart disease	76*	23
Other cardiac abnormality (for example, mitral valve prolapse, calcific aortic valve disease)	115*	26
No apparent cardiac abnormality	—	171
Not stated	4	—
Total	311	230

*These figures include 90 who had had valve replacement or other cardiac surgery before the episode of infective endocarditis studied and 34 who had previously had infective endocarditis (Table 6).
IE, infective bacterial endocarditis.

Table 5 *Valve or other site affected by infective endocarditis in 544 episodes*

Aortic valve	142*
Mitral valve	119*
Aortic and mitral valves	24*
Tricuspid valve	6*
Tricuspid and mitral valves	3*
Tricuspid and aortic valves	1*
Tricuspid, mitral, and aortic valves	1*
Pulmonary valve	1
Congenital heart lesion	46
Pacemaker	2
Uncertain	199
Total	544

*These figures include 77 patients with prosthetic valves.

Table 6 *Factors predisposing to infective endocarditis*

Prosthetic valves	77
Other cardiac surgery	13
Previous infective endocarditis	34*
Drug addiction	6
Diabetes	8
Alcohol dependence	4
Immunosuppression	8
Renal failure with or without haemodialysis	7

*Includes nine of the 77 who had had valve replacements.

Table 7 *77 patients with prosthetic valve endocarditis*

	*Early endocarditis**	*Late endocarditis†*
Number	11	66
Mean age (years)	46·9	52·9
Mortality	45%	21%
Previous infective endocarditis		9
Organisms:		
Staphylococci	8‡	21
Micrococci	1	2
Corynebacteria and diphtheroids	1	2
Str viridans	1‡	16
Pseudomonas sp	1‡	
Bowel organisms		6
Other organisms		6
Negative cultures	1	10
Negative-*Coxiella burnetii*		3
Valves:		
Mitral	3	24
Aortic	5	25
Mitral and aortic	3	8
Mitral and tricuspid		2
Mitral, aortic, and tricuspid		1
Aortic and tricuspid		2
Tricuspid		1
Uncertain		3

*Within eight weeks of insertion of prosthetic valve.
†More than eight weeks after insertion of prosthetic valve.
‡Two patients' blood grew two organisms.

males, another trend indicated by most recent writers.[4 6 8 11 12] The reasons for this are uncertain, although it may be related to the higher incidence of bicuspid aortic valves and calcific aortic stenosis in males and to the diminishing importance of rheumatic heart disease, which is more common in females.

The causal organisms (Table 1) were streptococci in 63·3%, staphylococci in 18·9%, and organisms probably originating from the bowel in 14%; 75·5% of the streptococci were of the viridans group. In 10% blood cultures were negative or not done. These findings are in general agreement with other recent series.[6 8 9]

The portal of entry to the blood stream of the causal organisms is much more difficult to identify (Table 2). In 60·3% of the 544 episodes there was no clue, and though in 122 of the episodes the patient had dental sepsis or had undergone a dental procedure with or without antibiotic cover during the three months before the onset of illness, the relevance of this history is uncertain because a dental background of this pattern is much the same as that of those enjoying normal health.[10] Nevertheless, in 103 of the 122 cases a dental origin was probable. The importance of infective, malignant, and other lesions in the alimentary, genitourinary, and respiratory tracts and the procedures used in their investigation and treatment in the causation of infective endocarditis is much more firmly established,[3 4 8 12–16] as are cutaneous lesions and injuries,[6 8 12 13] drug addiction,[6 8 9 11–14] fractures,[4] pregnancy and parturition,[14–16] and any procedure involving the blood stream, particularly haemodialysis[9 12 16] and cardiac catheterisation.[15]

Of the 22 patients in whom the alimentary tract seemed to be the portal of entry the causal organisms

were enterococci, *Streptococcus faecalis* or *Str bovis* in 11. Two followed gastroscopy and one followed liver biopsy; in the latter patient the casual organism was *Str bovis* and malignant disease was probably present. Right hemicolectomy, closure of a colostomy, diverticular disease, rectal carcinoma and adenomas, or polypi of the colon or stomach seemed responsible for seven others. Piles and gall bladder disease and operations for these conditions accounted for another five, while operations for hernia, appendicectomy, oesophageal dilatation, and infections of the gastrointestinal tract were the apparent cause in the remainder. Most of these diseases and procedures have been previously shown to be associated with bacteraemia and infective endocarditis.[15-21]

In 23 patients the infection seemed to come from the genitourinary tract. Enterococci, *Str faecalis*, coliforms and *Proteus* or *Pseudomonas* spp were responsible in 15 of the 23. In five, transurethral or retropubic prostatectomy (one for carcinoma) was responsible, in nine urinary tract infections, in two urethral dilatation, in one nephrectomy for pyelonephritis, in one renal calculus, in one cystoscopy, and in one carcinoma of the bladder. In the female genital tract vaginal hysterectomy, repair of vaginal prolapse, insertion of a ring pessary to control prolapse, and carcinoma of the cervix were each responsible in one patient. Again, the causal association of most of these conditions and procedures with bacteraemia and infective endocarditis have been recorded previously.[15 17 22-24]

Fourteen of the 17 patients in whom the respiratory tract was the portal of entry had bronchopulmonary infection. Two of the other three cases followed bronchoscopy and the remaining one developed after a nasal polypectomy in a patient taking steroids. Pneumococcal endocarditis followed the aspiration of a pneumococcal pleural effusion in one patient and developed shortly after bronchoscopy in another, but in many of the remainder the association of respiratory disease or instrumentation and endocarditis may have been temporal rather than causal, although the evidence appears stronger than in many of those of possible dental origin.

In 14 patients the source of infection was the skin. Four patients had gravitational or varicose leg ulcers, five cases followed traumatic skin lesions, and one followed acupuncture; one patient had chronic generalised eczema, one ulcerated rheumatoid nodules, one a septic thumb, and one an infected chest wound after mitral valve replacement.

There were only six drug addicts among the 541 patients, which is fewer than some might anticipate and possibly reflects underrepresentation of hospitals with catchment areas in parts of London and other large cities to which such young people tend to gravitate. Five were staphylococcal and one was due to *H parainfluenza*. None had any pre-existing cardiac disease.

Four cases of infective endocarditis followed fractures, three of which were compound. In the fourth a Colles fracture occurred two months before the onset of infective endocarditis; there was no known previous heart disease and the responsible organism was *Str faecalis*. The fracture may have been unrelated or the infective endocarditis may have been caused in some way by the anaesthetic, but endocarditis has been reported after closed fractures.[4]

In two patients the endocarditis occurred during pregnancy and in another it followed parturition. This association has been noted by others.[15 17 25-27] In 26 patients the portal of entry was related to cardiac or vascular surgery, cardiac catheterisation, haemodialysis, blood donation, venography, or anticoagulant treatment. In the remaining 326 episodes there was no evidence as to how or where the organisms had entered the blood stream.

Mortality was affected by age, the causative organism, and previous cardiac surgery. The 74 patients who died (Table 3) were older (mean age 59·0 years) than those who survived (mean 50·5 years). The mortality was 30% in staphylococcal infections, 14% in infections due to bowel organisms, and only 6% in other streptococcal infections. Other workers[4 7 8 9 12] report broadly similar findings. Among the 74 patients who died were five in whom the diagnosis was not made until necropsy and 22 who had had valve replacements or who had undergone other cardiac surgery.

Table 4 shows that 43% (230 of 541) of the patients were not known to have any cardiac abnormality before the onset of infective endocarditis. In 59 (26%) of these 230 patients an undiagnosed pre-existing lesion was undoubtedly present, but in most of the remaining 171 the heart was probably normal; it is possible, however, that in some who recovered without valve replacement a bicuspid aortic valve or degenerative changes in the aortic valve or an unrecognised mitral valve abnormality may have been present. Pre-existing rheumatic heart disease was present in 23·2%, a proportion similar to that in other recent reports,[6 8] and the incidence of congenital heart disease was only slightly lower (17·9%). Among the 141 with other cardiac abnormalities most had mitral incompetence (prolapsing mitral valve) or calcific aortic valve disease.

Table 6 shows the vulnerability of those with prosthetic valves, those who had undergone other cardiac surgery, and those who had previously had infective endocarditis. These three groups comprised 21% of the patients. The high incidence of infective endocarditis in those with prosthetic valves has been

emphasised in other reports,[6 8 11 12] which suggest that the danger is greatest in the early postoperative period, when the organism is usually a staphylococcus.[8 9 13] Table 7 shows that in this series 77 of the 544 episodes of infective endocarditis were prosthetic valve endocarditis. One seventh occurred during the two months after valve replacement and most of these were staphylococcal. The mortality among them was 45%. In the late cases of prosthetic valve endocarditis staphylococci remained the dominant organism, but three were caused by *Coxiella burnetii* and the normal microbiological pattern of the disease was more evident. The mortality in late cases was 21%.

Table 5 shows the valve, valves, or other cardiac sites affected by the infective endocarditis. In nearly two fifths it was uncertain or not stated, but where known the aortic valve alone was attacked most often and the mitral valve a little less often.

Infective endocarditis is often difficult to diagnose. Of the 544 episodes studied the diagnosis was not made until operation in four cases and not until necropsy in five others. In addition, 34 of the patients required urgent valve replacement for cardiac or renal failure. There can be little doubt that the best hopes of reducing mortality (which is probably already lower than the widely quoted figure of 30%) lie in early diagnosis, close collaboration with microbiologists, and prompt recognition of the need for surgical intervention and many believe that all patients with infective endocarditis should be under the clinical supervision of cardiologists and cardiac surgeons. Certainly, the investigation of murmurs by ultrasound and non-invasive techniques identifies lesions which place patients at special risk such as mitral valve prolapse and bicuspid aortic valves.

An additional difficulty is that bacteraemia if not becoming increasingly common is certainly being recognised more often, and in such patients it may be difficult to be certain whether endocarditis has or has not developed. Fortunately it makes little difference as treatment is unchanged unless valve replacement becomes necessary, by which time cardiac involvement will have been evident at least for some days.

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