Contemporary Themes

Prosthetic valve endocarditis

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Abstract

During 1965 to 1982, 32 episodes of infective endocarditis on prosthetic valves in 30 patients were treated at this hospital. In early endocarditis (presenting within four months of operation) staphylococci were the organisms most commonly responsible. Early endocarditis appears to be declining in incidence and is largely preventable; sternal sepsis was the main predisposing factor, requiring urgent and effective treatment. Streptococci were the most common organisms in late onset disease, but as with natural valve endocarditis a wide range of organisms was responsible. All but one of the patients with early onset disease were treated conservatively, but mortality was high; prompt surgical replacement of infected prostheses is probably indicated in such patients. Medical management was effective in most patients with late onset disease, and for them early surgical intervention may not be justified.

Introduction

Infective endocarditis on prosthetic valves has been the subject of numerous reviews since it was first reported in the late 1950s,[1-8] yet agreement has not been reached on criteria either for diagnosis or for division into "early" and "late" forms of the disease. Mortality in the early postoperative period continues to be high and the management of late onset disease is controversial.

Since prosthetic valves were first used at St Thomas's Hospital in 1965 all patients with infective endocarditis on these valves have been studied prospectively and their clinical features, laboratory findings, management, and progress documented. We present our experience with the disease up to 1982.

Patients and methods

During the 18 years of the study, 920 aortic, 851 mitral, and 65 tricuspid prostheses were inserted in the course of 1545 valve replacement operations. All patients received antistaphylococcal antibiotic prophylaxis, initially with methicillin but later with cloxacillin and then flucloxacillin. In addition, over half the patients also received prophylactic ampicillin. The antibiotics were given with the premedication and continued for a variable time after surgery but always for at least three days. Mechanical tilting disc or ball and cage prostheses were used in virtually all cases until late 1980. Over the next two years a quarter of the valves inserted were porcine xenografts.

All patients with suspected prosthetic valve endocarditis had blood taken for culture by department of microbiology staff, as described.[9] Wound discharge, sputum, and urine were cultured when indicated. Valves removed at operation or necropsy were examined for vegetations and cultured.

Prosthetic valve endocarditis was diagnosed when results of blood cultures were persistently positive in a patient with the clinical features of endocarditis or when significant organisms were recovered from the excised prosthesis of such a patient. Clinical features considered suggestive of endocarditis included fever, malaise and weight loss, haemodynamic deterioration, embolic and vasculitic lesions, new cardiac murmurs, and an enlarged spleen.

Results

There were 32 episodes of endocarditis in 30 patients during the study period. Nineteen of the patients were men (mean age 50 years; range 28-69) and 11 women (mean age 51 years; range 28-67). All except one of the patients had mechanical valves in situ; the exception (case 15) had an aortic allograft. No case of endocarditis has yet occurred among patients with porcine xenografts. Thirteen episodes were diagnosed within four months of operation, giving an incidence of 0·84% in this period. The mean time of diagnosis was 38 days from operation (range four days to four months). Nineteen episodes were diagnosed in 17 patients more than four months from operation, the mean time of diagnosis being five years nine months (range 10 months to 14 years) and the mean yearly incidence 0·12% of those at risk. These two groups are referred to as "early" and "late" endocarditis, respectively. Tables I and II give details of the patients, infecting organisms, and outcome in the two groups.

EARLY ENDOCARDITIS (13 patients)

Clinical features—All patients were severely ill with high fever, and three had rigors. Overt circulatory shock was present at the time of diagnosis in four patients, and all but one of the others showed

TABLE I—*Patients with early onset prosthetic valve endocarditis*

Case No	Age and sex	Valve(s)	Latency* (weeks)	Infecting organism	Outcome
1	46 M	M	12	*Staphylococcus aureus*	Died
2	51 F	M	4	*Candida albicans*	Died
3	36 M	M, A	2	*Pseudomonas thomasii*†	Died
4	28 F	M, A, T	11	*Pseudomonas thomasii*†	Survived
5	50 M	M	3	*Staphylococcus epidermidis*	Survived
6	65 M	A	3	*Staphylococcus aureus*	Died
9	44 F	M, A	3	*Staphylococcus aureus*	Died
10	63 M	A	3	*Candida albicans*	Died
11	64 M	M	5	*Staphylococcus aureus*	Died
12	66 M	A	16	*Streptococcus mitior*	Died
16	53 F	M	3	*Staphylococcus aureus*	Died
21	47 F	M	6	*Corynebacterium* spp	Survived
22	67 F	M, A	<1	*Pseudomonas aeruginosa*	Died

M = Mitral. A = Aortic. T = Tricuspid.
*Interval between insertion of prosthetic valve and bacteriological diagnosis of prosthetic valve endocarditis.
†Now *Ps picketii*.

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TABLE II—*Patients with late onset prosthetic valve endocarditis*

Case No	Age and sex	Valve(s)	Interval*	Infecting organism	Outcome
7	38 M	M	10 months	*Brucella melitensis*	Survived
8	56 M	A	3 years	*Streptococcus sanguis*	Survived
13	55 M	A	13 months	Viridans streptococcus	Survived
14	69 M	A	8 years 2 months 8 years 8 months 10 years	Viridans streptococcus Viridans streptococcus Viridans streptococcus	Survived
15	49 M	A	11 years	*Streptococcus mitior*	Survived
17	59 F	A	11 years	*Streptococcus salivarius*	Survived
18	61 F	M	8 years	*Staphylococcus aureus*	Survived
19	39 M	M, A	6 years	*Streptococcus mitior*	Survived
20	41 M	A	5 years	*Staphylococcus aureus*	Died
23	61 F	M, T	14 years	*Streptococcus mitior*	Survived
24	64 M	A	5 years	*Streptococcus sanguis*	Survived
25	49 M	A	5 years	*Streptococcus mitior*	Survived
26	48 F	M, A	3 years	*Pseudomonas thomasii*†	Survived
27	51 M	A	15 months	*Rhodococcus* spp	Survived
28	28 M	M, A	32 months	*Haemophilus parainfluenzae*	Survived
29	52 M	A	17 months	*Corynebacterium* spp	Survived
30	46 F	A	5 years	*Actinobacillus actinomycetem comitans*	Died

M = Mitral. A = Aortic. T = Tricuspid.
*Interval between insertion of prosthetic valve and bacteriological diagnosis of prosthetic valve endocarditis.
†Now *Ps picketii*.

signs of a low cardiac output. Roth spots and vasculitic skin lesions were each present in one patient, and a third patient had both splinter haemorrhages and a new cardiac murmur.

Laboratory investigations—Twelve patients had a polymorphonuclear leucocytosis. The erythrocyte sedimentation rate was raised in all patients in whom it was recorded.

Microbiological findings—Results of multiple blood cultures were positive in all 13 patients (table I). *Staphylococcus aureus* was the commonest pathogen, accounting for five cases. A purulent wound infection or retrosternal abscess was detected during life or at necropsy in all five patients infected with *Staph aureus* and in the patient infected with *Corynebacterium* spp, but no local infection was found in the seven patients infected with other organisms. In the pseudomonas infections the same organism was isolated from intravenous fluids (cases 3 and 4) or from the water bath used for warming blood in the theatre (case 22).

Progress, treatment, and outcome—Of the 13 patients with early endocarditis, only three survived: one of these (case 4) received prolonged co-trimoxazole for *Pseudomonas thomasii* (*Pseudomonas picketii*) infection; the second patient (case 5) was successfully treated for *Staph epidermidis* infection with flucloxacillin and fusidic acid; and the other patient (case 21) was the only one with early onset disease to undergo emergency surgery. This last patient had initially been treated with penicillin and vancomycin for corynebacterium endocarditis, but after seven days urgent surgery was required for dehiscence of the prosthesis. Vegetations on the prosthesis and material from a paravalvular abscess found at operation were sterile on culture. All five patients with *Staph aureus* infections died, four within a week of diagnosis and the fifth within four weeks, despite intensive antistaphylococcal treatment. Both patients infected with *Candida albicans* had received numerous antibiotics for persistent postoperative fever before the diagnosis was made, and one died within 24 hours of this; the other patient survived three weeks of treatment with flucytosine before unexpected and unexplained death. Two of the three patients with pseudomonas endocarditis died, one (case 3) within two weeks of diagnosis and the other (case 22) within five weeks, having initially made an apparently good recovery with tobramycin and azlocillin. Both patients came to necropsy, and in both cases gross vegetations were found which yielded the same *Pseudomonas* spp that had been repeatedly isolated from the blood. The only patient with streptococcal early onset disease (case 12) was feverish, with sterile blood cultures, for six weeks after valve replacement despite empirical treatment with ampicillin, gentamicin, and lincomycin. Low grade malaise and weight loss continued until he presented in acute left ventricular failure 10 weeks later. Blood cultures grew *Streptococcus mitior* and he died within a week despite intravenous benzylpenicillin.

LATE ENDOCARDITIS (17 patients, 19 episodes)

Clinical features—Fever was present in all but one patient, and four had rigors. Only one patient had circulatory shock. Three patients had splinter haemorrhages, one had developed a new murmur and an enlarged spleen, and in one all three of these physical signs were noted.

Laboratory investigations—A polymorphonuclear leucocytosis was present in 12 patients. The sedimentation rate was normal in one patient but exceeded 30 mm in the first hour in the other 10 in whom it was measured.

Microbiological findings—Results of multiple blood cultures were positive in all patients except case 27 (table II). The organism isolated from the blood was also isolated from antral washings in case 19 (*Str mitior*) and from sputum in case 18 (*Staph aureus*). Organisms were cultured from the excised valve in two of the four patients who came to operation: in case 7 the *Brucella melitensis* isolated from successive blood cultures was also grown from the valve, and in case 27 a pure heavy growth of *Rhodococcus* spp was isolated from the vegetations, although numerous blood cultures had failed to grow an organism. The same *Staph aureus* as had been isolated from the blood in case 20 was subsequently isolated from the valve at necropsy.

Progress, treatment, and outcome—Two patients died; the other 15 survived 17 episodes of endocarditis. All except one of the patients were treated with antibiotics, the remaining patient (case 20) dying on the day of admission. Surgery was undertaken for deteriorating valve function in four patients. In case 7 an emergency operation was required within days of the diagnosis of *Br melitensis* endocarditis. In case 29 valve replacement was performed after two weeks of antibiotic treatment for corynebacterium endocarditis. Surgery was performed six weeks after the clinical diagnosis of endocarditis in case 27. In this patient a two week trial of antibiotic treatment with intravenous penicillin and gentamicin had failed to control the disease and numerous blood cultures had been sterile. In the only patient with streptococcal late onset disease to require valve replacement this was undertaken as an elective procedure after completion of six weeks of antibiotic treatment. Streptococcal endocarditis was treated with intravenous benzylpenicillin (8-12 MU daily) in all cases, and this was later followed by oral antibiotics in four. The antimicrobial treatment of non-streptococcal endocarditis was determined by the in vitro sensitivity of the pathogen.

Discussion

Infection of cardiac valve prostheses was recognised soon after they came into use,[10] but uniformly satisfactory diagnostic criteria for prosthetic valve endocarditis have yet to be established. Bacteraemia does not of itself necessarily imply the diagnosis,[11] and Dismukes *et al*[2] suggested as minimum criteria bacteraemia with the same organism in two or more blood cultures in a patient with a clinical picture consistent with endocarditis. Later workers added, as alternative criteria, detection of typical vegetations at necropsy or surgery, or recovery of organisms from the excised prosthesis.[4] Some patients with the disease may still fall outside these diagnostic confines, particularly those infected with micro-organisms not readily cultured by routine methods such as *Coxiella burneti* and *Chlamydia* spp, and less rigorous criteria may have to be accepted in planning the management of a possible case of prosthetic valve endocarditis.

Division of cases into "early" and "late" onset has also proved difficult. These groups differ both in causative organisms and in prognosis. Dismukes *et al*[2] regarded the limit for early onset cases as 60 days after valve replacement, but Petheram and Boyce[4] thought that such a division was artificial: their patients presented within four months or after 14 months. If an arbitrary time scale is to be defined our experience also suggests a figure of around four months. Although "late" infections are assumed to be acquired some time after surgery, such infections may occur with organisms introduced at operation but dormant until later presentation; this occurred in one of our patients (case 26), in whom *Ps thomasii* was known to have been introduced at operation but did not result in endocarditis until three years later. The incidence of these latter infections is unknown but they are very uncommon.

Our incidence of early infections (0·84%) compares with those of 1·1-1·7% reported in other series.[3 5 6] It fell to 0·3% in the last six years of the study but was 1·14% over the first 12 years. Although *Staph aureus* was the commonest organism

causing early disease, there were no cases in the last six years. Staphylococcal (and other) sternal infections still occur but are now recognised and treated more promptly. The three cases of pseudomonas endocarditis were associated with contaminated infusion fluids, described in detail elsewhere.[12 13]

The true incidence of late infections is difficult to assess, and our figure of 0·12% a year is almost certainly an underestimate. Patients may be lost to follow up and present elsewhere with endocarditis, or die with undiagnosed endocarditis. In a recent review Oakley suggested a figure of at least 1% a year.[14]

All the patients with early endocarditis were overtly septicaemic and very ill compared with only three patients (two with rapidly fatal disease) in the late onset group; and in none of these three was the disease streptococcal. A polymorphonuclear leucocytosis was present in all but one of the early cases but in only 12 of 19 late cases.

The range of infecting organisms differed between the two groups: staphylococci accounted for half of the early infections but streptococci for only one. In contrast, streptococci accounted for almost half of the late infections and staphylococci for only two. Late prosthetic valve endocarditis is thus caused by the same organisms as natural valve endocarditis, oral streptococci being predominant.

All staphylococci isolated from cases of prosthetic valve endocarditis were sensitive in vitro to the prophylactic antibiotics given, but the other organisms were relatively insensitive or frankly resistant. Such data beg the question of antibiotic prophylaxis for valve replacement. No controlled trial has been done—nor would one now be thought ethical—and the subject is steeped in surgical folklore. Rigorous asepsis, improvements in surgical technique, shorter operating times, and improvements in perioperative and postoperative cardiorespiratory management may all have contributed to the declining incidence of early onset disease as well as earlier recognition and treatment of sternal wound infections, however minor they may initially appear. Early onset prosthetic valve endocarditis is largely preventable.

Mortality among our early onset cases was 77% and was comparable to that in other reported series; mortality among our late onset cases (11%), however, was lower than the 33-67% reported by others.[3-6 15] Masur and Johnson[6] concluded that their "unacceptably high mortality rate" suggested that the usual indications for reoperation (persistent infection, fungal prosthetic valve endocarditis, relapse of prosthetic valve endocarditis, prosthesis dysfunction) should be extended so that "all patients with prosthetic valve endocarditis should be candidates for early valve replacement except those with uncomplicated streptococcal PVE." A recent review of reported series came to the same broad conclusion.[8] Our results accord with these views but, in common with other workers, our experience with non-streptococcal late onset disease is limited. Provided that the infecting organism and its sensitivity are known, and optimal bactericidal chemotherapy can be given, then in the absence of a severely compromised haemodynamic state this treatment appears to be acceptable for patients with late onset streptococcal disease and possibly also for late onset non-streptococcal disease. Continuous cardiological assessment is necessary to monitor deteriorating valve function, but a small and stable degree of impairment may not of itself be an indication for immediate reoperation. Four of our late onset cases required surgery; three (none streptococcal) as an emergency procedure within days or a few weeks of the diagnosis, and the fourth (streptococcal) an elective valve replacement after the infection had been controlled.

We suggest that in dividing prosthetic valve endocarditis into early and late cases a period of four months may be more acceptable than the 60 days often used. The incidence of early endocarditis appears to be declining, but sternal sepsis—particularly staphylococcal—may still result in endocarditis and must be treated urgently and effectively. We believe that early, aggressive surgical management of late onset endocarditis, as often advocated, may not be indicated in streptococcal infection. Close cooperation between cardiologist, cardiac surgeon, and microbiologist is necessary to achieve a successful outcome.

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In countries where the water supply is likely to be contaminated could you advise on the best method of sterilisation? Do you have to boil the water for as long as 10 minutes? Ordinary bacteria are killed after 60 seconds but I am not sure about cysts and other protozoa. Is filtration essential if the water is then going to be chlorinated? How much iodine should be added as an alternative? I use commercial tablets made by Kirby (Puritabs). Do these contain some sort of chlorine producing compound?

Boiling gives the surest sterilisation of water, whereas the use of halogens is more convenient. Most gut pathogens are killed by boiling for two minutes. The exceptions are heat resistant strains of *Bacillus cereus* and *Clostridium perfringens*. One tablet of Puritabs, containing 17 mg of sodium dichloroisocyanate, dissolved in one litre of water liberates 10 ppm of available chlorine and this will kill viruses, bacteria, and encysted protozoa at temperatures around 20°C at neutral pH after a contact time of 30 minutes. Organic matter in cloudy water will reduce available chlorine concentrations so turbidity should be allowed to settle and clear water decanted off for chlorination. Lower temperatures, below 10°C, and increasing pH both reduce the cysticidal activity of halogens and in those conditions filtration, using a Millbank bag, for example, is also necessary. Tincture of iodine, a 2% solution, may be used to sterilise water; add five drops, 0·05 ml per drop, to one litre of clear water and 10 drops per litre of cloudy water and allow a contact time of 30 minutes. Turbidity may reduce the efficiency of sterilisation for the reason given above.—S G WRIGHT, honorary consultant physician, London.

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