Long term follow up of prosthetic valve endocarditis: what characteristics identify patients who were treated successfully with antibiotics alone?

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Abstract
Objective—To identify predictors for the safe use of antibiotic treatment without reoperation in patients with prosthetic valve endocarditis.
Setting—Retrospective study in a tertiary care centre.
Subjects and design—All 49 episodes of definite prosthetic valve endocarditis (Duke criteria) diagnosed at one institution between 1980 to 1997 were analysed. Ten episodes (20%) were treated with antibiotics only (antibiotic group) and 39 episodes (80%) with combined antibiotic and surgical treatment (surgery group).
The analysis included detailed study of hospital records and data on long term follow up which were obtained in all patients by questionnaire or telephone contact with physician or patient. The length of follow up (mean (SD)) was 41 (32) months in the antibiotic group and 45 (24) months in the surgery group (NS). Long term survival was estimated by the Kaplan–Meier method and compared by the log-rank test.
Results—There was no significant difference in age, history of previous endocarditis, number of previous heart operations, vegetations, emboli, type of prosthesis, or percentage of early prosthetic valve endocarditis and positive blood cultures between the two groups. In the antibiotic group, there were more enterococcal (50%; p = 0.005) and in the surgery group more staphylococcal infections (55%; p = 0.048). Annular abscesses (p < 0.0001) and aortoventricular dehiscence (p = 0.02) were more common in the surgery group. No patient in the antibiotic group had heart failure. Long term follow up showed no significant difference between the surgery and antibiotic groups regarding late mortality (14% v 18%) and five year rates of recurrent endocarditis (14% v 16%), event related mortality (14% v 3%, log-rank test), and the need for reoperation (14% v 19%; log-rank test). The only patient with conservatively treated staphylococcal prosthetic valve endocarditis died after reoperation for recurrence.
Conclusions—Haemodynamically stable patients with non-staphylococcal prosthetic valve endocarditis who are carefully supervised can be treated with antibiotics alone without an increased rate of reoperation, reoperation, or death.

Keywords: prosthetic valve endocarditis; antibiotic treatment; complications; long term follow up

Prosthetic valve endocarditis is a rare but serious complication after heart valve replacement, with an incidence of approximately 0.1–4% per year.1–3 This type of endocarditis is associated with high morbidity and mortality rates of between 10% and 59%.1,11 Generally, combined medical and surgical treatment is considered the treatment of choice and thought to be necessary to improve prognosis. Some clinicians, however, recommend reoperation only in the presence of large vegetations with thromboembolic episodes, congestive heart failure, valve dysfunction, and more virulent organisms.2,9 In a multicentre, prospective, unrandomised trial, however, mortality after valve replacement was lower than after medical treatment alone (23% v 56%);10 the authors of that paper recommend early surgery. Another argument for early surgery was the finding of persistently positive bacterial cultures from prosthetic valves removed at operation or necropsy, despite prolonged bactericidal antibiotic treatment in another study.11 Early total excision of the infected annular root was therefore recommended.12 Thus controversy continues about when conservative treatment alone can be safe. There are few data analysing subgroups of patients who can be managed relatively safely with medical treatment alone, with an outcome comparable to that achieved with combined surgical and medical treatment.

Our aim in this study was therefore to analyse data from patients with definite prosthetic valve endocarditis to determine predictors identifying those in whom medical treatment alone may be safe.

Methods
Patients
From January 1980 to September 1997, 49 consecutive patients with definite prosthetic valve endocarditis were admitted to hospital at the University Hospital, Zurich. Three died immediately after admission before treatment decisions could be made and were thus excluded from the study. The remaining 46 patients (nine women, 37 men) had 49 episodes of endocarditis, which are the subject
of this analysis. Ten of these were treated with antibiotics alone (antibiotic group) and 39 with a combination of antibiotics and surgery (surgery group). Episodes were regarded as new rather than recurrent if they occurred more than 12 months after the last treated episode; in our three patients who were included twice, the second episode occurred three to five years after the last episode.

At diagnosis of prosthetic valve endocarditis, the mean (SD) age of the subjects was 52 (14) years (range 16 to 76 years). Clinical data were obtained from a review of the patients’ medical records. The data included clinical presentation and course, laboratory data, results of microbiological tests, echocardiographic findings, duration of antibiotic treatment, time and type of surgery, and type and location of prosthesis. All operations were performed at our hospital in the division for cardiovascular surgery.

**DEFINITIONS**
Patients with mechanical or bioprosthetic valves in the aortic or mitral position were included if they fulfilled the Duke criteria for definite prosthetic valve endocarditis published in detail elsewhere. The pathological criteria include either demonstrable microorganisms or pathological lesions compatible with active endocarditis. For a clinical diagnosis of endocarditis, two major criteria, one major and three minor criteria, or five minor criteria were needed. Major criteria were: positive blood cultures (typical microorganisms or persistently positive blood cultures) and evidence of endocardial involvement (positive echocardiogram for infective endocarditis or new valvar regurgitation). Minor criteria were: predisposing heart condition or intravenous drug use, fever, vascular phenomena, immunological phenomena, microbiological evidence, and echocardiographic criteria not fulfilling the major criteria as described.

Early prosthetic valve endocarditis was defined as occurring ≤ 60 days after valve replacement, and late prosthetic valve endocarditis as occurring after > 60 days.

Emergency surgery was defined as valve replacement performed within 24 hours after hospital admission. Early mortality was defined as death within the first 30 days after surgery or death during the hospital stay for patients in the antibiotic group.

Aortoventricular dehiscence was defined as lack of normal continuity of the muscular left ventricular outflow tract with the sinus portion of the aorta caused by abscess formation involving either part of or the whole circumference of the aortic annulus.

**ECHOCARDIOGRAPHY**
A complete cross sectional and Doppler transthoracic echocardiographic examination was performed in all patients, with detailed examination of each valve. Transoesophageal echocardiography was routinely available in our hospital from 1991 and was performed in 28 patients (49%) between 1991 and 1997 (biplane 5 MHz probe or multiplane 5 MHz probe since 1997). Hewlett-Packard systems (Sonos 1000 and Sonos 2500; Hewlett-Packard Co, Andover, Massachusetts, USA) were used.

**FOLLOW UP**
The patients surviving this hospital admission or their physicians were contacted with a questionnaire to obtain follow up data. These included death, recurrence of prosthetic valve endocarditis, and reoperations. Five patients were interviewed by telephone because the questionnaire was not returned. Follow up was achieved in all patients included in the analysis.

**STATISTICAL ANALYSIS**
All analyses were performed using the StatView 4.51 statistical software package (Abacus Concepts). Nominal data were analysed using Fisher’s exact test. Continuous variables were analysed by the Mann–Whitney test and are presented as mean (SD). Long term follow up was estimated by the Kaplan–Meier method and compared by the log-rank test. A probability (p value) ≤ 0.05 was considered significant.

**RESULTS**

**CLINICAL CHARACTERISTICS**
A comparison of the clinical characteristics of the antibiotic group and the surgery group is shown in table 1. No significant difference was found between the two methods of treatment with respect to age, sex, concomitant heart disease, number of previous heart operations, history of previous endocarditis, onset of endocarditis (early or late), type of prosthesis, position involved (aortic or mitral), or signs for peripheral emboli. Heart failure and catecholamine requirement were comparable in the two groups. Endocarditis occurred at an average of 57 (69) months (range one to 248 months) after the last valve replacement in the surgery group and at 61 (60) months (range one to 192) in the antibiotic group (NS). The mean time from the onset of clinical symptoms to diagnosis was 20 (22) days (range one to 84) and 14 (25) days (range one to 84) in the surgery and antibiotic groups, respectively (NS).
Table 2  Laboratory results and responsible microorganisms

<table>
<thead>
<tr>
<th>Test</th>
<th>Surgery group (n = 39)</th>
<th>Antibiotic group (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm in the first hour)</td>
<td>57 (32)</td>
<td>42 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>WBC (x 10³/l)</td>
<td>11.6 (4.6)</td>
<td>8.4 (3.1)</td>
<td>0.047</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>133 (107)</td>
<td>47 (35)</td>
<td>0.02</td>
</tr>
<tr>
<td>Early PVE</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Culture positive</td>
<td>29</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Staphylococci spp</td>
<td>16</td>
<td>1</td>
<td>0.048</td>
</tr>
<tr>
<td>S aureus</td>
<td>4</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Coagulase negative</td>
<td>12</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Streptococci spp</td>
<td>7</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Enterococci spp</td>
<td>1</td>
<td>4</td>
<td>0.005</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n.

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; PVE, prosthetic valve endocarditis; WBC, white blood cell count.

Table 3  Echocardiographic findings of the surgery group and the antibiotic group

<table>
<thead>
<tr>
<th>Type of valve</th>
<th>Surgery group (n = 39)</th>
<th>Antibiotic group (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>26</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Biological</td>
<td>13</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Localisation of PVE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>35</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Perivalvar leakage</td>
<td>32</td>
<td>1 (&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>32</td>
<td>1 (&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Aortoventricular dehiscence</td>
<td>15</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Vegetations</td>
<td>9</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

PVE, prosthetic valve endocarditis.

LABORATORY RESULTS AND MICROBIOLOGY
The laboratory findings and the microorganisms causing the endocarditis are shown in table 2. There was a significantly higher white blood cell count and plasma C reactive protein concentration in the surgery group (p = 0.05 and p = 0.02, respectively). All but three patients (94%) had antibiotic treatment before being transferred to our hospital. The frequency of culture positive prosthetic valve endocarditis was similar in the two groups. In culture positive patients, staphylococcal infections (S aureus and coagulase negative staphylococci) were more common in the surgery group (p = 0.05), whereas enterococcal infections were more common in the antibiotic group (p = 0.005). In one blood culture negative patient, histopathological examination identified a possible organism (a Gram negative bacillus). In only one patient, with previous infective endocarditis caused by coagulase negative staphylococci, was the same organism cultured in both episodes.

ECHOCARDIOGRAPHIC AND INTRAOPERATIVE FINDINGS
Echocardiographic and intraoperative findings are listed in table 3. Abscess formation, perivalvar leakage, and aortoventricular dehiscence were more commonly detected in the surgery group (p < 0.05). One patient with enterococcal aortic prosthetic valve endocarditis and an annular abscess seen by transoesophageal echocardiography (maximum diameter 1.5 cm) was successfully treated with antibiotics alone, with reduction in the abscess cavity size to less than 1 cm. Echocardiographically detectable abscesses were confirmed surgically in 32 of 33 cases (97%), with a positive predictive value of 100% (95% confidence interval (CI), 89% to 100%) and a negative predictive value of 86% (95% CI, 42% to 100%). Echocardiographically detectable aortoventricular dehiscence was found in 15 of 22 cases (68%), which were all confirmed surgically, with a positive predictive value 100% (95% CI, 78% to 100%) and a negative predictive value 71% (95% CI, 49% to 87%).

TREATMENT
Surgery was performed in 39 patients. The total length of antibiotic treatment was significantly shorter in the surgery group than in the antibiotic group (table 1; p = 0.039). In 32 patients (82%), elective surgery was possible after 35 (43) days of antibiotic treatment (range 28 to 63). Emergency surgery was necessary in seven patients (18%) because of an unstable haemodynamic condition; in these patients, congestive heart failure (p = 0.004) and aortoventricular dehiscence (p = 0.005) occurred significantly more often than in patients with an elective operation. No significant difference was seen in relation to the type of prosthesis, abscess formation, or staphylococcal infection between the emergency and elective surgery groups (NS). Seven patients (18%) in the surgery group died during their hospital admission. One patient died intraoperatively from intractable bleeding and heart failure. Five other patients died within the first 30 days after operation because of multiorgan failure from continuing septicaemia, acute myocardial infarction, retroperitoneal bleeding, or intracerebral haemorrhage. Another patient in the surgery group with severe hypoxic brain damage from preoperative resuscitation died from pneumonia on day 135 (late in-hospital death). Aortoventricular dehiscence (p = 0.05), but not congestive heart failure, abscess formation, or staphylococcal infection, was significantly associated with death after surgery.

No patient in the antibiotic group died during the initial hospital admission for endocarditis. However, the difference in early mortality between the surgery and antibiotic groups was not significant (0% vs 15%; NS).

LONG TERM FOLLOW UP
Follow up was obtained in all patients after 42 (30) months. Length of follow up (41 (32) to 45 (24) months) was not significantly different between the surgery and the antibiotic group.

Recurrence of endocarditis occurred in three patients (9%) in the surgery group after 46, 48, and 49 months, respectively. All three patients had mechanical valves in the aortic position and reoperation was necessary because of valve dysfunction. Two other patients (6%) in the surgery group needed reoperation for dysfunction of the prosthetic valve without signs of recurrent endocarditis. Recurrence of endocarditis also occurred in one patient from the antibiotic group 39 months after a conservatively treated episode of coagulase negative staphylococcal endocarditis (table 4, patient 10). This patient with recurrent coagulase negative staphylococcal endocarditis needed reoperation for congestive heart failure and perivalvar...
leakage. The patient died one hour postoperatively from heart failure. No additional reoperation was needed in the other patients in the antibiotic group. Apart from the above mentioned patient with recurrent staphylococcal endocarditis, the other nine conservatively treated patients had no signs of recurrent infection and good function of the implanted valves after a follow up of 45 (24) months (range five to 91) (table 4). In our analysis, the five year rates for recurrence of prosthetic valve endocarditis were 16% in the antibiotic group and 14% in the surgery group (NS). The cumulative five year rate of freedom from recurrent prosthetic valve endocarditis was 85%. The five year rates for need for reoperation were 19% in the antibiotic and 14% in the surgery group (NS).

In the surgery group, one patient had sudden cardiac death six years after prosthetic valve endocarditis without signs of recurrent endocarditis. This death was therefore considered to be unrelated to the previous endocarditis. Another two patients died from causes not related to prosthetic valve endocarditis: one had pneumonia four years after the episode of endocarditis and one committed suicide. Overall, neither late mortality (18% v 14%; fig 1) nor the five year rate of event related late mortality (3% v 14%) differed significantly between the antibiotic and the surgery group.

The cumulative five year rates for all our patients with prosthetic valve endocarditis were 83% survival, 85% freedom of recurrence, 82% freedom of reoperation, and 68% with no event in this period.

### Discussion

Despite improvements in diagnosis and treatment, prosthetic valve endocarditis remains a serious complication associated with a high mortality. In general, combined medical and surgical treatment is considered the management of choice in patients with prosthetic valve endocarditis. The superiority of surgical treatment compared with antibiotic treatment alone has been demonstrated in several studies, and an aggressive approach recommended. In a large analysis by Calderwood et al, the only variable significantly associated with a worse outcome was initial medical treatment. In some patients with prosthetic valve endocarditis, severe complications clearly require prompt surgical intervention but only few investigators have analysed which patients can be treated safely by antibiotics alone.

Among the 49 episodes with definite prosthetic valve endocarditis in our study, 10 (20%) were treated conservatively. Our study shows that conservative management of prosthetic valve endocarditis guided by echocardiography and clinical data is feasible for well selected patients without an increase in overall mortality, recurrent endocarditis, and reoperation rate.

### Characteristics of Prosthetic Valve Endocarditis in Our Study Group

In our population, 10% of cases of prosthetic valve endocarditis occurred within the first 60 days after heart valve replacement. This differs from previous reports where approximately one third of the cases were early and two thirds late. This may reflect the fact that we included only patients with definite prosthetic valve endocarditis and not those with only bacteraemia and no other major criteria of endocarditis, which may be more common early after surgery. In contrast to other reports, early prosthetic valve endocarditis in our population was not associated with worse outcome than late endocarditis. The overall frequency of complications like abscess formation (69%), perivalvar leakage (67%), and aortoventricular dehiscence (45%) present in our study was similar to that in other published reports.

In the antibiotic group, however, no patient had aortoventricular dehiscence and only one had an annular abscess and another a perivalvar leakage. The number of previous heart operations was comparable in both groups, although eight patients in the antibiotic group...
(80%) had two to three previous operations, compared with 18 (46%) in the surgery group (NS). This might reflect a reluctance to reoperate on patients with two or more previous heart operations. The type of valve, location of the endocarditis, and the presence of vegetations and emboli had a similar frequency in the two groups.

**INFLUENCE OF BACTERIOLOGICAL FINDINGS**

Early prosthetic valve endocarditis is caused by contamination of the artificial valve at the time of its implantation or by perioperative bacteremia. Staphylococci (*S aureus* and coagulase negative staphylococci) and enterococci are common in early prosthetic valve endocarditis. Late prosthetic valve endocarditis can be caused by many different microorganisms. Staphylococci are more prevalent in both early and late prosthetic valve endocarditis compared with endocarditis of the native valves. The type of microorganism involved is affected by the quantity of potentially infective organisms present, by their special adhesion mechanisms, and by the host environment (for example, whether there is immunosuppression). In our study group, in the 37 patients with culture positive endocarditis, staphylococci were the most common organisms, with a prevalence of 46% and no difference between early and late involvement.

It has been said that the type of microorganism seems to influence the therapeutic strategy, with infections by staphylococci, fungi, and Gram negative bacilli more often requiring a surgical approach. This was confirmed in our study: all our patients with staphyloccocal prosthetic valve endocarditis ultimately needed surgery. Conservative management of staphylococcal endocarditis of prosthetic valves therefore does not seem advisable; there appears to be only a single case report of successful conservative treatment, with a follow up of only one year. Our conservatively treated patient with coagulase negative staphylococcal endocarditis had a recurrence after 39 months, possibly with the same microorganism despite initial antibiotic treatment for 212 days. In one analysis, mortality was not influenced by the type of organism but was high, at 41% for the patients treated with antibiotics only, and no recommendations were given for identifying patients who could be treated conservatively. In another study involving 122 patients with prosthetic valve endocarditis, better survival was found for those with combined medical and surgical treatment than with antibiotic treatment alone (45% vs 0%), and none of 20 patients with *S aureus* associated endocarditis survived when treated with antibiotics alone. However, in that analysis only subjects who were admitted to the intensive care unit were included and so there was a bias towards very sick patients. When prosthetic valve endocarditis was not caused by staphylococci, the mortality was similar in patients with combined treatment and with antibiotics only treatment (89% vs 81%) in a four month follow up. The conclusions of John et al that performing valve replacement surgery will reduce mortality among patients with *S aureus* endocarditis even in the absence of cardiac complications may well be true. Why were staphyloccocal infections more devastating than, for example, enterococcal infections, which had a relatively benign course in our study? It has been observed by others that enterococcal prosthetic valve endocarditis has a low mortality, 69% being cured without surgical intervention. This differs completely from enterococcal endocarditis of the native valve, which seems to be very aggressive; the prosthetic valve appears more resistant to destruction. However, despite the common problem of resistance of enterococci to penicillins, bactericidal treatment with combined aminoglycosides and penicillins for at least six weeks is now a well established way of managing enterococcal native and prosthetic valve endocarditis. In contrast, antibiotic treatment of staphyloccocal endocarditis—particularly infections with coagulase negative staphylococci—is not often successful, and this has been confirmed both in vitro and in animal models.

**RECURRENT OF PROSTHETIC VALVE ENDOCARDITIS**

Device related infections are a major clinical issue. Infection in a mechanical valve is located in the sewing ring; therefore antibiotic treatment often fails unless the infected implant is removed. Normally recurrent episodes of endocarditis are defined as relapses occurring within one year of completion of treatment for the initial episode, or as reinfection if they occur more than one year after completion of therapy. In our patients, however, recurrence with possibly the same microorganism (a coagulase negative staphylocooccus) was seen to occur as late as 39 months after valve replacement. We propose, therefore, that recurrence of prosthetic valve endocarditis is defined as any episode of endocarditis occurring with the same organism, even during long term follow up. Only if the organism differs should reinfection be postulated. It was worrying that in all four patients with recurrent endocarditis, this occurred very late in the follow up (39 to 49 months), which could indicate that in such cases it is difficult to be sure of a cure. However, the risk of recurrence or persistent sepsis or infection is low.

**REOPERATION AND MORTALITY**

Early mortality understandably tended to be higher in the surgery group (15%) than in the antibiotic group (0%), though this difference was not significant (p = 0.15). This was because the sicker patients were treated surgically. We were, however, especially interested in the long term follow up data. In a cumulative five year rate, freedom from recurrence was 85% in all our patients after discharge from the initial hospital stay. The five year rate for recurrent endocarditis was not significantly different in the two groups. We had an excellent overall 83% cumulative five year survival rate at follow up. Our late mortality was 14% in the antibiotic group and
18% in the surgery group (NS). Studies published before 1980 reported mortality rates for early and late prosthetic valve endocarditis of 70% and 45%, respectively. More recent studies on the surgical treatment of prosthetic valve endocarditis report an overall in-hospital mortality of approximately 10–25%, and a five year survival ranging from 50% to 75%. The cumulative five year survival rate of 83% in our study group was therefore better than expected. The cumulative five year rate of freedom from any event was 68%. The rates of reoperation for recurrent endocarditis and for late sequelae were also lower in our analysis than in other studies.

In certain patient groups, conservative treatment can thus result in comparable survival to surgical treatment. We chose to perform reoperations on the basis of the following criteria: congestive heart failure from valve dysfunction, recurrent emboli despite treatment, and progression of cardiac complications such as large abscess formation or aortoventricular dehiscence. Early non-staphylococcal prosthetic valve endocarditis as such was not a criterion for reoperation, in contrast to other recommendations.

IMPACT OF ECHOCARDIOGRAPHY

The important role of echocardiography in diagnosis and management of prosthetic valve endocarditis has been emphasised. Echocardiographic signs of prosthetic valve endocarditis include vegetations on and around the prosthetic valve, valve dysfunction (stenosis, regurgitation, paravalvar leak), and invasion of perivalvar tissue by abscesses and fistulae. Early diagnosis of prosthetic valve endocarditis—especially in the presence of negative blood cultures caused by previous use of antibiotics—is thus facilitated by the use of transthoracic echocardiography, and if this is inconclusive transoesophageal echocardiography: four cases.

CONCLUSIONS

Patients with non-staphylococcal prosthetic valve endocarditis without left heart failure and with careful clinical and echocardiographic surveillance to exclude large abscesses or aortoventricular dehiscence may be managed by antimicrobial treatment alone without an increased rate of reinfection, reoperation, or death.

This study was presented as an oral communication at the American College of Cardiology Meeting 1999 in New Orleans, USA, March 1999.
