Factors Affecting Survival in Prosthetic Valve Endocarditis

Review of the Effectiveness of Prophylaxis

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We review factors affecting survival of 44 episodes of prosthetic valve endocarditis occurring in 39 patients from 1965 to 1982. The mortality was 31.8 percent (14/44), and 21.6 percent (8/37) if the fungal cases are excluded. The development of a new murmur of valvular regurgitation in 18 patients led to valve replacement or death in every patient. Streptococcal endocarditis in 11 patients resulted in no deaths and only two valve replacements; staphylococcal infections had a mortality of 27.1 percent (6/22). Length of medical therapy before valve replacement did not relate to a successful outcome. Eight cases of early staphylococcal endocarditis occurred in which the organism was susceptible to the prophylactic antibiotic therapy. Changes in prophylaxis have led to no cases of early endocarditis over the past three years in 261 valve replacements.

Endocarditis remains a feared major complication of prosthetic cardiac valve replacement. The mortality in early endocarditis (onset within two months) is reported at 68, 88, and 87 percent. The mortality for late onset endocarditis is reported as 42, 40, and 36 percent by the same authors. The incidence of early endocarditis is 0.78 percent; for late endocarditis it is 1.1 percent. Good surgical technique and antibiotic prophylaxis are the mainstays for prevention of early onset endocarditis, while antibiotic prophylaxis is used to prevent late endocarditis. We evaluated the effects of the type of organism, antibiotic susceptibility, time of onset postoperation, and the development of a new murmur on the outcome of the endocarditis.

We also looked at the effects of valve replacement and the length of medical treatment prior to operation on survival. In addition, we compared the antibiotic susceptibility of the infecting organisms to the antimicrobial agent used during the presumed infecting procedure to determine the effectiveness of the prophylactic regimens.

METHODS

There were 47 episodes of endocarditis in 42 patients from 1965 to 1982. The records for three patients were not obtainable, so they were excluded from this analysis. Therefore, in this study there were 44 episodes of endocarditis occurring in 39 patients. Five of the cases were referred from outside hospitals. Since 1970, in 40 of the 44 episodes the patients have been interviewed personally by one of the authors (J. T. S.) to determine the precipitating event leading to endocarditis and the antibiotic prophylaxis used during that event. The antibiotic susceptibilities of the organism cultured from the blood were obtained from the bacteriologic laboratory report of the University Hospital.

The time from the onset of symptoms to the institution of antibiotics was noted. The duration of medical treatment prior to valve replacement was also recorded.

The diagnosis of endocarditis was based on the presence of positive blood cultures and no other source for the bacteremia other than the prosthetic valve. In two patients without bacteremia, the diagnosis was made by surgical and autopsy findings. Statistical significance was determined by the $t^2$ method to look for differences in survival in infections caused by different organisms. The two-sample $t$ test was used to evaluate the effect of the duration of medical treatment prior to the operation upon patient survival.

RESULTS

This report covers 44 episodes of endocarditis in 39 patients. There were ten women and 29 men in the study, with a mean age of 50.2 years, ranging from 24 to 71. The Starr-Edwards ball valve prosthesis was present at the time of endocarditis in 30 cases, while seven had the Bjork-Shiley disk valve, and seven had a heterograft. The aortic valve was involved in 21 cases and the mitral valve in 14. Nine patients had two valves. The Starr-Edwards ball valve was infected by the following organisms: staphylococcal, 16; streptococcal, four; and fungal, four; and the Bjork-Shiley prosthesis, staphylococcal, five; streptococcal, one; and fungal, one; the heterograft prosthesis, staphylococcal, one; streptococcal, four; and one fungal infection.

New murmurs developed in 18 patients (Table 1). All 18 patients who developed new murmurs before or during the treatment period died or had to have valve replacements. Nine major embolic complications were present in 20 percent (9/44). Splinter hemorrhages were present in seven cases, Roth’s spots in six, and petechiae alone in three patients. Twenty-four patients had no evidence of major or minor embolic events.

The number of cases of endocarditis per year has
remained constant for our institution, averaging from
two to six cases. However, within the past three years
we have had no cases of staphylococcal endocarditis
within two months of operation and only one case
within the first year for 261 operations. Six of the seven
cases of fungal endocarditis occurred before 1975.
Otherwise, the spectrum of organisms has remained
similar over the course of this review. The types of
organisms responsible for the endocarditis are listed
in Table 2 by time of onset following operation.

The mortality for the entire series was 31.8 percent
(14/44). The group with early onset of symptoms,
within two months following operation (group 1), had a
25 percent (4/16) mortality. One patient had clearing of
an early staphylococcal infection, but seven months
later developed a fatal Candida endocarditis. Group 2
had the onset of endocarditis from two months to one
year and had a 53.3 percent (8/15) mortality. The late
(group 3) had a 15.4 percent mortality (2/13). The
differences in mortality between the groups is not sig-
nificant. The mortality rate by organisms is listed in
Table 3. The mortality in the patients with streptococ-
cal organism infection is significantly lower than the
staphylococcal (p<0.05). If the cases from group 1 are
excluded, there were no deaths (0/10) in the streptococ-
cal and a 50 percent (6/12) mortality in the staphylococ-
cal cases (p<0.01).

Valve replacement was carried out in nine patients in
group 1, with two postoperative deaths and one late
death from Candida endocarditis. There were two
deaths in the seven unoperated patients (one Serratia
and the other Candida). The organism present in the
patients dying in this period was fungal in two; Gram-
negative, one; and Serratia, one. There were nine

<table>
<thead>
<tr>
<th>Organism</th>
<th>Group 1, 2 mo</th>
<th>Group 2, 2 mo-1 yr</th>
<th>Group 3, 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus epidermidis (13)</td>
<td>7</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>S. aureus (9)</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Viridans (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcal (II)</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Candida (6)</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Gram-negative (3)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous (3)</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total no.</td>
<td>16</td>
<td>15</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 3—Mortality by Type of Organism in Prosthetic Valve Endocarditis

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcal</td>
<td>6/22 (27.1)</td>
</tr>
<tr>
<td>Epidermidis</td>
<td>2/13 (15.3)</td>
</tr>
<tr>
<td>Aureus</td>
<td>4/9 (44.4)</td>
</tr>
<tr>
<td>Streptococcal</td>
<td>0/11 (0)</td>
</tr>
<tr>
<td>Fungal</td>
<td>6/7 (85.7)</td>
</tr>
<tr>
<td>Miscellaneous (Gram-negative, Nocardia)</td>
<td>2/4 (50)</td>
</tr>
</tbody>
</table>

reoperations in group 2, with five deaths. Three of the
six unoperated patients died (two of embolism and one of
cerebral hemorrhage). Five patients had valve
replacement in group 3. The two patients dying in this
group both had reoperation (one fungal and the other
staphylococcal-coag positive).

We compared our early to our more recent experience.
The operative death rate was 45 percent (9/20)
prior to 1975 compared to 20.8 percent (5/24) since
then (p = NS). The reoperation rates were 60 percent
(12/20) for the early period and 45.8 percent (11/24)
for the later period (p = NS). If one removes the fungal
cases from the mortality calculation, the death rate for
the pre-1975 group is 35.7 percent (5/14) compared to
17.4 percent (4/23) for the late group (p = NS).

Data concerning anticoagulant management were
available in 40 cases. There was a 28.6 percent (4/14)
embolic incidence in those patients who did not receive anticoagulation and 20 percent (1/5) in those
receiving heparin. There was a 14.3 percent (3/21)
embolic incidence in the patients who continued receiving warfarin (Coumadin). One patient had a fatal
CNS bleeding episode in the Coumadin-treated
group. Two of the embolic episodes in the non-
anticoagulated patients were fatal.

The presumed sources of the infecting organisms are
listed in Table 4.

Data concerning the antibiotics used for prophylaxis
and the susceptibility of the infecting organisms were
available for 20 patients. The presumed source of
infections was classed as from the operative procedure
if the infection occurred within two months of the
operation. Eleven of the 20 organisms were suscepti-
ble to the agent given during the procedure. Seven of

Table 4—Source of Infesting Organisms in Prosthetic Valve Endocarditis

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve surgery*</td>
<td>15</td>
</tr>
<tr>
<td>Dental</td>
<td>8</td>
</tr>
<tr>
<td>Intravascular procedure</td>
<td>4</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5</td>
</tr>
</tbody>
</table>

*Listed for cases occurring during the first two months postopera-
tion.
the resistant organisms were fungal. Therefore, of the 13 remaining bacterial organisms, 11 were susceptible to the antibiotic used for prophylaxis (one dental, eight valve replacements, and two others). Table 5 gives the antibiotic dosage and frequency during the operative procedure for the nine patients who had endocarditis within two months of the operation. The antibiotic susceptibilities for the organisms of the entire series are listed in Table 6.

We compared the duration of medical treatment prior to valve replacement for operative deaths and survivors; it was 51.9 ± 32.5 days for the 13 survivors and 49.4 ± 42.8 days for the nonsurvivors (p = NS). Information was available in 43 patients for the time between the onset of symptoms and the start of therapy. The 28 survivors had an interval of 15.7 ± 19.8 days compared to 19.8 ± 24.1 days for the 15 nonsurvivors (p = NS).

**Discussion**

The diagnosis of prosthetic valve endocarditis is usually not difficult. Fever was present in most of our

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**Table 5—Type and Dosage of Perioperative Antibiotics and to the Antibiotic Susceptibility of the Infecting Organism**

<table>
<thead>
<tr>
<th>Case</th>
<th>Organism</th>
<th>Preop</th>
<th>Intraop</th>
<th>Postop</th>
<th>Antibiotic Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Staphylococcus epidermidis</em></td>
<td>Cefazolin</td>
<td>1 g IM (PM and AM day of operation) 0</td>
<td>Cefazolin 1 g IV q6hr two days then 500 mg qid x 5 d</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td><em>S epidermidis</em></td>
<td>Cefazolin</td>
<td>1 g IM PM and AM day of operation 0</td>
<td>Cefazolin 1 g IV q6hr two days then 500 mg qid x 4 d</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td><em>S epidermidis</em></td>
<td>Cephalothin</td>
<td>2 g IV AM of operation 0</td>
<td>Cephalothin 2 g IV q6hr two days then 2 g q4hr (q4d)</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td><em>S epidermidis</em></td>
<td>Cephalothin</td>
<td>2 g IV q6hr two days and Clindamycin</td>
<td>Cephalothin 2 g IV q6hr (2 wk)</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td><em>S aureus</em></td>
<td>Cefazolin</td>
<td>1 g IM PM and AM day of operation 0</td>
<td>Cefazolin 1 g IV q6hr two days then 500 mg q6hr (5d)</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td><em>S epidermidis</em></td>
<td>Cefazolin</td>
<td>500 mg IM PM and AM day of operation 0</td>
<td>Streptomycin 0.5 g IM bid x 8 doses then 500 mg q6hr (24d)</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td><em>S epidermidis</em></td>
<td>Oxacillin 0.5 g and penicillin V 600,000 units qid (1 d preop)</td>
<td>Oxacillin 500 mg Penicillin V (0) qid (10d)</td>
<td>Streptomycin 0.5 g q12 hr (3d) and Lincomycin 500 mg q6hr (15d)</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td><em>S epidermidis</em></td>
<td>Erythromycin 100 mg 1M preop Streptomycin 0.5 g 1M preop</td>
<td>Erythromycin 250 mg IM q6hr (3d) Streptomycin 0.5 g q12 hr (3d) and Lincomycin 500 mg q6hr (15d)</td>
<td>Streptomycin 0.5 g bid and Lincomycin 600 mg IM (4d)</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td><em>S aureus</em></td>
<td>Erythromycin 100 m 1M preop and Streptomycin 0.5 g 1M preop</td>
<td>Lincomycin 1 g (via pump)</td>
<td>Streptomycin 0.5 g bid and Lincomycin 600 mg IM (4d)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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**Table 6—Antibiotic Susceptibility for Organisms Causing Prosthetic Valve Endocarditis**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Penicillin</th>
<th>Erythromycin</th>
<th>Cephalosporins</th>
<th>Clindamycin</th>
<th>Vancomycin</th>
<th>Methotrexate</th>
<th>Gentamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus epidermidis aureus</em></td>
<td>8/13</td>
<td>6/13</td>
<td>11/12</td>
<td>4/11</td>
<td>7/7</td>
<td>7/9</td>
<td>9/9</td>
</tr>
<tr>
<td></td>
<td>3/8</td>
<td>5/7</td>
<td>8/8</td>
<td>7/8</td>
<td>6/6</td>
<td>6/6</td>
<td>6/6</td>
</tr>
<tr>
<td>Total</td>
<td>11/21</td>
<td>11/20</td>
<td>19/20</td>
<td>11/19</td>
<td>13/13</td>
<td>13/15</td>
<td>15/15</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>8/8</td>
<td>7/8</td>
<td>4/6</td>
<td>2/4</td>
<td>5/5</td>
<td>2/3</td>
<td>3/3</td>
</tr>
</tbody>
</table>
patients (40/43), and blood cultures were positive in all 42 patients in whom they were available (positive blood cultures were a requirement to enter the study). Quensar et al. reported fever in all 24 patients with prosthetic valve endocarditis, and Block et al. noted fever in all 12 patients of his series. In our study, splenomegaly was present in only six patients and noted in only one of 22 patients with staphylococcal endocarditis. A normal leukocyte count was present in 17 patients, and 30 had an absence of hematuria. Quensar and co-workers noted hematuria in 29.2 percent of cases and splenomegaly in 54.2 percent. Therefore, it is not unusual to have an absence of splenomegaly, leukocytosis, and hematuria in a patient with prosthetic valve endocarditis.

The failure of antibiotic prophylaxis to prevent infection, even when the organism is susceptible to the agent, is of concern. This is especially true of the staphylococcal infections occurring early after valve replacement, as in the eight such cases in our series. This could relate to a heavy inoculum of organisms at the time of surgery. In the report by Kluge et al., 16 of 31 cardiac prostheses cultured at the end of implantation had positive results, usually Staphylococcus epidermidis. The bed in which the valve is sutured may be avascular, leading to low antibiotic concentrations. Soaking the valves in a vancomycin solution prior to implantation is presently being done in our program. Kluge et al. also documented inadequate cephalosporin blood levels in adults during cardiopulmonary bypass, especially if the last dose was given more than four hours prior to the operation. This may be important, since only one of the nine patients described in Table 5 received antibiotics in the pump during the operation. We now add the antibiotics to the pump during the procedure. The absence of early onset endocarditis from staphylococcal organisms over the past three years may indicate the success of this approach. Prolonged antibiotic administration following operation does not appear to be important in the prevention of endocarditis. The antibiotic susceptibilities noted in Table 6 support the continued use of cephalosporins during valve replacement, as well as penicillin for dental procedures. Vancomycin is an excellent choice for penicillin-allergic patients. Adequate blood levels of the prophylactic antibiotic during the valve replacement must be attained.

Operatively induced infection of the prosthetic valve may develop beyond two months following operation. S epidermidis infection was present in one of 13 cases developing after one year postoperation, while there were five of 15 such infections from two months to one year postoperation. In addition, the high mortality and frequent need for valve replacement within the first year also support this concept. This is supported by the report of Karchmer et al. of methicillin-resistant staphylococcal organisms being found in 87 percent (53/61) of cases up to one year following operation but only in two of nine patients after one year. Methicillin-resistant organisms also are usually resistant to cephalosporins. Two of our patients had positive cultures without fever, which suggests an asymptomatic period of infection in patients with endocarditis. An embolic event within the first year should also raise the possibility of endocarditis.

Our data do not answer the question about whether to continue anticoagulants during the medical treatment of prosthetic valve endocarditis. The occurrence of four episodes of embolism resulting in two deaths in the 14 patients not given anticoagulants is of concern. Our current policy is to continue anticoagulant therapy in patients with mechanical valves during the endocarditis treatment period. Wilson et al. in a review of anticoagulants in prosthetic valve endocarditis, also recommend continuing anticoagulants during treatment in these patients.

Surgical intervention is important for these patients. The presence of a streptococcal organism would generally not require valve replacement in the absence of valve dehiscence. We successfully replaced the infected valve in two of 11 patients with streptococcal endocarditis. Patients having a new murmur of valvular insufficiency should be considered for valve replacement, since a fatal outcome or need for valve replacement occurred in all 18 patients with this finding. The presence of a staphylococcal organism, especially within the first year, suggests that valve replacement may be necessary. Only three of 17 staphylococcal infections were successfully treated without operation during the first postoperative year. There were five survivors of 22 cases of staphylococcal endocarditis in the nonreoperated patients. Certainly, a fungal infection indicates early valve replacement, and all seven of our patients with this infection required operation or died from their fungal endocarditis. Our one survivor from a Candida infection was a late infection arising from a dental procedure which allowed a successful outcome after medical and surgical treatment.

The low mortality of 25 percent in those patients developing endocarditis within two months following operation is lower than that previously reported. Bacteremia without infection of the prosthetic valve is unlikely, since these patients had left the postoperative intensive care unit and were free of indwelling lines or wound or urinary tract infections. These differences most likely reflect a random variation in outcomes and a larger number of more recent cases. There was no difference in the length of medical treatment between the operative survivors and deaths—51.9 days for the survivors compared to 49.4 days for those dying following operation. The time of medical treatment for
those surviving operation and the patients having a fatal postoperative course was the same (51.9 v 49.4 days, respectively).

Our present policy is to control the sepsis and then replace the valve if the patient has evidence of (1) new valvular insufficiency, (2) a fungal organism, or (3) infection with a staphylococcal organism within two months of the operation.

ACKNOWLEDGMENT: Appreciation is expressed to Evelyn Mitchell for help in the manuscript preparation.

REFERENCES
7 Kluge RM, Calia FM, McLaughlin JS, Hornick RB. Sources of contamination in open heart surgery. JAMA 1974; 230:1415-18

The Leading Edge in Diagnostic Ultrasound

This three-day program will be held at the Resorts International Hotel Casino, Atlantic City, May 10-12, under sponsorship of the Department of Radiology, Thomas Jefferson University Hospital. For information, contact Ms. Kathy Bonner, Education Coordinator, Division of Ultrasound and Radiologic Imaging, Thomas Jefferson University, 1015 Walnut Street, Philadelphia 19107 (215:928-8533).

Annual Meeting, European Academy of Allergology and Clinical Immunology

The Annual Meeting of the European Academy of Allergology and Clinical Immunology will be held May 16-19 in Brussels, Belgium. For further information, contact Prof. R. Pauwels, Department of Respiratory Diseases, De Pintelaan 185, B9000 Ghent, Belgium.