Medical Management of Infective Endocarditis; Limitations and Indication for Surgery

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Problems and limitations of medical management for infective endocarditis were studied and surgical indications were discussed based on the retrospective analysis of 55 episodes. Since perioperative complications still occur during highly active infection, antibiotic treatment was suggested as the primary management. Intractable or progressing heart failure appeared to be a definite indication for emergency surgery, but medical therapy was recommended for mild to moderate heart failure. For uncontrolled infection of more than one month duration despite the best available antibiotics, surgical debridement of the infected tissue was indicated. Occurrence of peripheral or fatal emboli was difficult to predict from clinical features and echocardiogram and therefore presented a therapeutic dilemma. Since major or fatal emboli frequently occurred during highly active infection, early initiation of effective antibiotic therapy was considered to be of primary importance. Demonstration of vegetation by echocardiography alone did not seem to justify urgent surgery. In addition, disseminated intravascular coagulation appeared to be a serious complication and thus sedimentation rate should be followed carefully. In the healed stage, prophylactic surgery seemed unnecessary for prevention of recurrent infection or embolization, as they were relatively rare.

THE introduction of potent antibiotic therapy converted infective endocarditis from frequently fatal disease to one with survival rates ranging from 50% to 90%.¹⁻⁶ However, certain subgroups of patients continue to sustain high mortality rates, determined primarily by major complications of heart failure due to valve destruction, intractable infection and peripheral embolization.^{4-6,17} In an effort to reduce this high mortality, open heart surgery with valve replacement has been recommended even in the

presence of active infection and has demonstrated improvement of the outlook of patients with infective endocarditis.⁷⁻¹⁷ Therefore, it is now a critical issue in daily practice to determine the conditions and timing that surgical intervention is warranted. In the present study, we investigated problems and limitations of medical management for infective endocarditis and discussed surgical indication, based on the retrospective analysis of 55 episodes in the past 10 years.

Key Words:

Heart failure
Uncontrolled infection
Systemic embolization
Disseminated intravascular coagulation
Prosthetic valve endocarditis

MATERIALS AND METHOD

From 1975 through 1983, 54 patients with infective endocarditis were admitted to the 3rd Department of Internal Medicine, Kurume

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University Hospital. These included 26 men and 28 women who ranged in age from 18 to 65 years (37 ± 13 years). A clinical diagnosis of

TABLE I CLINICAL OUTCOME IN 55 EPISODES (54 PATIENTS) WITH INFECTIVE ENDOCARDITIS

	NVE	PVE	Total
No. of episodes	44	11	55
Medical therapy	32	8	40
No. of death	11	5	16
Heart failure	4	0	4
Emboli [†]	6	3	9
Others	1*	2**	3
Emergency surgery	12	3	15
Indications for surgery			
Heart failure	8	0	8
Persistent infection	3	0	3
PV failure	/	3	3
SMA aneurysma	1	0	1
No. of death	3	1	4

[†] = One patient who developed a fatal brain embolism after discharge was excluded; * = renal failure; ** = PV failure and sudden death

PV = prosthetic valve; SMA = superior mesenteric artery; NVE = native valve endocarditis; PVE = prosthetic valve endocarditis

infective endocarditis was based on the following criteria; 1) positive blood cultures plus either predisposing heart disease or vegetation determined by echocardiography, during surgery or at autopsy, 2) negative blood culture and persistent fever with signs of active inflammation (elevated sedimentation rate and positive CRP) plus either vegetation or predisposing heart disease with peripheral embolization.

As one patient developed two episodes of endocarditis, 55 episodes were analysed in the present study. The infecting organisms included streptococcus viridans group (19 patients), Peptostreptococcus (2 patients), other streptococci (2 patients), Staphylococcus aureus (9 patients), Staphylococcus epidermidis (8 patients), gram-negative bacilli (5 patients) and other bacteria (3 patients). Repeated blood cultures were negative in 7 patients.

The diagnosis of a vegetation was made by two dimensional echocardiography with the demonstration of a mobile, rapidly oscillating mass that was attached to, or appeared to replace, normal valve tissue. Increased valve thickness by itself was considered insufficient for the diagnosis of a vegetation. Size, mobility and oscillation of vegetations were evaluated qualita-

TABLE II. RELATION BETWEEN CLINICAL FEATURES AT THE TIME OF ADMISSION AND INTRACTABLE HEART FAILURE*

	No. of patients at risk	No. of heart failure		
		Dead	Operated	Total
<i>Infecting organisms</i>				
Viridans group	12	2	2	4
Staph. aureus	5	0	1	1
Staph. epidermidis	4	1	0	1
Others	6	0	2	2
Negative	6	1	3	4
<i>Dominant hemodynamic lesion</i>				
AR	14	4	4	8
MR	13	0	4	4
Others	6	0	0	0
<i>NYHA functional class on admission</i>				
Class II	10	0	0	0
III	15	2	2	4
IV	8	2	6	8
<i>White blood cell count on admission</i>				
~ 1000/mm ³	10	0	1	1
10000 ~	21	4	6	10

* 12 patients with intractable heart failure who died of or required emergency surgery were compared with 21 patients with successful medical management.

AR = aortic regurgitation; MR = mitral regurgitation

TABLE III PERIPHERAL EMBOLIZATION

	NVE	PVE	Total
<i>Occurrence*</i>	21/44(7)	3/11(3)	24/55(10)
<i>As initial sign*</i>	7	0	7
<i>Frequency*</i> 1	10(4)	3(3)	13(7)
2	8(2)	0	8(2)
≥ 3	3(1)	0	3(1)
<i>Stage of infection**</i>			
Active	33(5)	3(3)	36(8)
Healed	4(2)	0	4(2)
<i>Site of emboli**</i>			
Brain	10(5)	2(2)	12(7)
Coronary	2(1)	0	2(1)
Lung	6(1)	0	6(1)
Abdomen	2(0)	1(1)	3(1)
Others	17(0)	0	17(0)

No. of patients* or No. of episodes (death)**

NVE = native valve endocarditis;

PVE = prosthetic valve endocarditis

tively. Peripheral embolization was assessed clinically by the sudden onset of the following events; 1) cerebrovascular accident, 2) electrocardiographic evidence of myocardial infarction, 3) chest X-ray appearance of pulmonary infarction, 4) severe abdominal pain with or without hematuria and 5) severe pain in the back or thigh followed by gangrene.

RESULTS

The clinical outcomes of 55 episodes (54 patients) of infective endocarditis are presented in Table I. Of 44 episodes of native valve endocarditis, 21 were successfully treated but 11 could not be saved by medical management. Emergency surgery was performed on 12 patients in the active stage of infection before completing an antibiotic regimen and 9 of them survived. Medical management was effective in only 3 of 11 patients with prosthetic valve endocarditis. Three patients underwent emergency surgery and 2 survived.

Twelve patients with native valve endocarditis developed severe and intractable heart failure and the 4 patients who were managed medically did not survive. In contrast, 5 of 8 patients were cured by emergency surgery (Table I). To determine the factors relating to heart failure, the clinical features in these 12 patients were compared with those in 21 patients with successful medical management in Table II. There was no clear association between heart failure

and the type of infecting organism. In contrast, heart failure was frequent in patients with aortic regurgitation and all 4 patients who died of heart failure had aortic regurgitation. Heart failure in patients with mitral regurgitation was less frequent and less progressive than that in aortic regurgitation, so that all 4 patients with heart failure and mitral regurgitation could be successfully managed with emergency surgery. No patients with other cardiac conditions, including aortic or mitral stenosis or right sided lesions, experienced heart failure which was fatal or required surgical intervention. Of 8 patients with NYHA functional class IV on admission, 6 had emergency surgery and 2 died. In 15 patients with NYHA class III, 4 had fatal outcomes or required surgery. However, severe heart failure did not develop in patients with NYHA class II on admission. Patients who had a white blood cell count of 10000/mm³ or more on admission were associated with an increased risk of intractable heart failure. Thus in native valve endocarditis, patients with aortic regurgitation, NYHA class III and IV and white blood cell count of 10000/mm³ or more had a high risk of heart failure and often required emergency surgery.

Peripheral embolization was a frequent and occasionally fatal complication of infective endocarditis (Table III). It was observed in 24 of 55 episodes of endocarditis and developed as an initial symptom in 7 patients. Most patients had the attack once or twice and multiple embolization of 3 or more events was relatively infrequent. Fatal embolization was observed in 10 patients, with 7 of these being brain emboli. It was of note that the first attack was fatal in 7 cases. Although aortic regurgitation tended to result in fatal emboli when it occurred, there were no definite clinical predictors for peripheral embolization nor fatal events, including infecting organisms, site, size, morphology or mobility of vegetations as documented by two dimensional echocardiogram. However, it should be emphasized that 90% of emboli developed in the active stage of endocarditis. In addition, of 8 patients who developed fatal embolization in the active stage, 3 had received no or incomplete antibiotic therapy due to a delay in correct diagnosis (Table IV). Antibiotics were ineffective at the time of the event in the other 5 patients, 2 of them complicated with disseminated intravascular coagulation. Of two patients with fatal emboli in the healed stage, one (case 9) had multiple

TABLE IV PATIENTS WITH FATAL EMBOLIZATION

Age Sex	Infecting organism	Site of infection	Vegetation by 2-D echo	Site of infection	Antibiotic therapy (days)	At the time of emboli				Complication
						Fever (°C)	WBC (/mm ³)	ESR (mm/h)	CRP	
1. 29M	<i>Viridans gr</i>	Aortic NV	Large	Brain	0	37.0	10900	57	3+	no
2. 51M	<i>Staph epidermidis</i>	Aortic PV (early)	no	Brain	0	38.9	10300	64	2+	no
3. 21F	<i>Staph aureus</i>	Aortic NV Mitral NV	Large	Brain	30 (incomplete)	39.0	9700	98	3+	CHF
4. 51M	<i>Serratia</i>	Aortic NV	no	Brain Coronary	7	38.5	11400	29	3+	DIC
5. 18F	<i>Viridans gr</i>	Mitral NV	not examined	Brain Lung	7	39.1	5200	59	1+	DIC
6. 43F	<i>Staph aureus</i>	Aortic PV (late)	no	Brain	7	39.3	27300	116	6+	CHF
7. 22F	<i>Staph aureus</i>	Aortic NV Pulmonic NV	not examined	Lung	7	40.0	8400	24	2+	CHF
8. 35F	<i>Staph epidermidis</i>	Aortic PV Mitral PV (early)	no	Kidney	14	38.1	14600	46	4+	CHF
9. 38M	<i>Staph epidermidis</i>	Mitral NV	small	Brain	60	36.3	7200	85	2+	no
10. 38M	<i>Viridans gr</i>	Aortic NV Mitral NV	small	Coronary	40	36.5	7400	20	1+	CHF

WBC = white blood cell count; ESR = erythrocyte sedimentation rate; NV = native valve; PV = prosthetic valve;
CHF = congestive heart failure; DIC = disseminated intravascular coagulation

emboli and died of a 4th embolus to the brain. Associated heart failure due to aortic regurgitation seemed to allow a coronary embolus to become a fatal event in another patient (case 10).

The present series included 11 patients with

TABLE V PROSTHETIC VALVE
ENDOCARDITIS

	Early (≤ 2 months)	Late (> 2 months)
No. of patients	5	6
Prosthetic valve		
Aortic	2	2
Mitral	2	2
Aortic & mitral	1	1
Tricuspid	0	1
Infecting organisms		
Viridans group	0	1
Staph. aureus	0	2
Staph. epidermidis	3	0
Others	2	3
Clinical outcome		
Cured (operated)	1	4(2)
dead (operated)	4	2(1)
Cause of death		
PV failure	1	1*
Emboli	2	1
Sudden death	1	0

No. of patients, *died after operation
PV = prosthetic valve

prosthetic valve endocarditis (PVE), 5 of them developed within 2 months after surgery (early PVE) as shown in Table V. Although the number of patients was small for detailed analysis, patients with early PVE tended to be infected by organisms other than viridans group streptococci and had a very poor prognosis. On the other hand, 6 patients with late PVE who developed endocarditis two months or more after surgery had similar clinical features to native valve endocarditis.

With the medical management, active infection could not be controlled in 10 patients despite treatment with the best available antibiotics. Three patients who were managed medically died of heart failure, cerebral embolus or renal failure. Surgical intervention was indicated in the remaining 7 patients for persistent infection (3 patients), progressive heart failure (3 patients) or development of prosthetic valve failure (1 patient). Five of them survived the operation. Clinical features of these 10 patients with uncontrolled infection were compared with those of 21 medically managed patients to identify factors relating to the effect of medical therapy (Fig. 1). This analysis excluded 24 patients who had emergency surgery or died within one month after admission. There were no essential differences between the 2 groups of patients with respect to infecting organisms,

Fig.1. Clinical course in patients with controlled (—●—) and uncontrolled (---○---) infection.

TABLE VI PATIENTS COMPLICATED WITH DISSEMINATED INTRAVASCULAR COAGULATION

Age Sex	Infecting organism	CRP	ESR (mm/h)	Platelet ($10^4/\text{mm}^3$)	Fibrinogen (mg/dl)	Prothr. time (sec)	FDP ($\mu\text{g/ml}$)	Bleeding	Outcome
1. 53M	Staph. epidermidis	4+	1	8.8	100	17.8	80	—	Cured
2. 45F	Viridans gr.	2+	7	7.7	30	30.9	20	GI	Cured
3. 27F	Pseudomonas	7+	47	4.0	244	25.9	10	—	† Renal failure
4. 18F	Viridans gr.	4+	29	8.4	175	14.5	40	Lung	† Emboli (brain)
5. 56F	Klebsiella	3+	13	10.5	284	20.0	5	GI	† CHF
6. 51F	Staph. epidermidis	5+	33	2.5	57	69.0	10	—	† CHF
7. 51M	Serratia	4+	8	3.2	144	15.9	40	Lung	† Emboli (Brain, coronary)

† = died

ESR = erythrocyte sedimentation rate; FDP = fibrinogen degradation product; GI = gastrointestinal

temperature, sedimentation rate, CRP, white and red blood cell counts, hemoglobin, or serum levels of Fe and Cu at the time of admission. However most patients who were successfully managed with medical treatment had improved signs of active infection within one month, while fever, positive CRP and increased white blood cell count persisted over one month in the uncontrolled group. Therefore surgical intervention appears to be indicated if medical therapy is ineffective despite use of several possibly effective antibiotics for one month.

In the present study, association of disseminated intravascular coagulation (DIC) was suggested in 7 patients and seemed to be one of the serious complications of infective endocarditis (Table VI). These patients showed a normal or less elevated sedimentation rate despite signs of highly active infection. Abnormal platelet count, fibrinogen and prothrombin time were consistent with DIC, but an increase in fibrinogen degradation product was mild, suggesting a rather chronic form of this condition. Four of them were complicated by bleeding in the gastrointestinal tract or lung and only 2 patients survived.

Emergency surgery was indicated in the active stage before completion of antibiotic therapy in 15 patients for heart failure, persistent infection and prosthetic valve failure (Table I). One patient died of heart failure and 3 of persistent infection after surgery. Perioperative mortality tended to be greater for patient who had surgery within one month after admission, or those who showed highly active infection ($\text{CRP} \geq 3+$, white blood cell count $\geq 9000/\text{mm}^3$) at the time of surgery (Table VII).

Among 24 medically managed patients, 9 underwent successful operations during the healed stage for the correction of underlying cardiac lesions (Table VIII). The remaining 15 patients were followed up medically for an average of 4.3 ± 2.2 years. One patient died of cerebral embolism and another had a recurrence of endocarditis which was cured medically. The other patients were uneventful in the follow-up period, although some of them showed a persistent vegetation by echocardiogram.

DISCUSSION

The role of surgery for infective endocarditis had become increasingly important and the following conditions have been proposed as

TABLE VII RELATION BETWEEN OPERATIVE MORTALITY AND CLINICAL FEATURES

	No. of operated	No. of perioperative death		
		Infection	CHF	Total
<i>Indications for surgery</i>				
Heart failure	8	2	1	3
Persist. infection	4*	0	0	0
PV failure	3	1	0	1
<i>Infecting organisms</i>				
Viridans group	6	0	1	1
Staph. aureus & epidermidis	3	0	0	0
Others	6	3	0	3
<i>Time to operation from admission</i>				
≤ 30 days	6	2	1	3
> 30 days	9	1	0	1
<i>CRP at the time of operation</i>				
< 3 +	9	1	0	1
≥ 3 +	5	2	1	3
<i>WBC at the time of operation</i>				
< 9000/mm ³	9	0	0	0
≥ 9000/mm ³	5	3	1	4

* including one patient with aneurysma of the superior mesenteric artery.

CHF = congestive heart failure; PV = prosthetic valve; WBC = white blood cell count

indications for surgical intervention^{10-12,14}: 1) appreciable or worsening congestive heart failure, 2) infections uncontrolled by antibiotic therapy, particularly fungal, gram-negative bacillary or staphylococcal infections, 3) recurrent systemic embolization, 4) progressive spread of intracardiac infections, as manifested by conduction system disturbances, aneurysma, fistula formation or suppurative pericarditis, 5) prosthetic valve endocarditis. However, the most opportune time for surgical intervention for each individual patient is still difficult to determine. Recent studies⁸⁻¹⁷ have shown that perioperative complications are low even in the active stage of infection and the major determinant for early operative mortality is severity of heart failure, possibly due to delay of surgery. Hence these authors have recommended more aggressive and earlier surgical intervention irrespective of the activity of infectious process before permanent damage and major disability occur. In fact, some of them have claimed that the surgical approach should employed more frequently for patients with mild to moderate heart failure^{13,16,19} or for those with staphylococcal infection regardless of hemodynamic state.¹⁹

However perioperative mortality is still high, ranging from 10 to 30%^{8-11,13,15-18}. Although

TABLE VIII LONG-TERM PROGNOSIS IN PATIENTS WITH SUCCESSFUL MEDICAL MANAGEMENT

	No. of patients	Emboli	Re-currence	Died
<i>Elective operation</i>	9	/	/	0
<i>Medically followed*</i>	15	1	1	1
Vegetation (+)	8	1	1	1
Vegetation (-)	5	0	0	0
Vegetation (?)	2	0	0	0

*Follow-up = 4.3 ± 2.2 years

the frequency of residual postoperative infection has been reported at 3 to 4%^{8,11,14} it is a matter of concern in certain groups of patients with active endocarditis. In the present series, patients with persistent postoperative residual infection tended to have greater white blood cell count or CRP at the time of surgery. Croft et al.¹⁷ also noted that all 3 patients with an early postoperative recurrence of infection had persistent sepsis despite antibiotic therapy. Wilson et al.¹⁸ suggested that the risk of prosthetic valve endocarditis and valve dehiscence may be higher in patients with positive blood cultures in the perioperative period. Another potential problem after valve replacement in

active endocarditis is periprosthetic regurgitation secondary to valve dehiscence.^{11,17} In patients with active or quite recent infection, there may be the difficulties in implanting a prosthetic valve in an area with edema and friable tissue even without residual infection. This complication has been reported to develop in approximately 15% of active endocarditis.^{11,17} Thus patients in a highly active state of infection with or without preceding antibiotic therapy would be considered to have an increased risk of persistent infection or prosthetic valve dehiscence postoperatively. In addition, valve replacement is not curative and it causes many problems associated with the prosthetic valve so that unnecessary valve replacement should be avoided. Hence the decision to recommend surgical treatment in patients with active endocarditis must be based on the particular circumstances in which valve replacement has proven to be superior and when surgery offers a significantly better prospect for survival in the individual patient.

There is increasing recognition that patients with endocarditis who develop significant hemodynamic impairment are best managed surgically with an immediate operation. This is in view of the 50–89% reported mortality rate if managed otherwise.^{8–18} In the present study, all patients with NYHA functional class IV and 27% with class III on admission died or required emergency surgery because of intractable heart failure. Of 8 patients who were managed surgically, 5 have survived. Hence we agree that intractable or progressive heart failure is a definite indication for surgical intervention irrespective of preceding antibiotic therapy. Whether patients with mild to moderate heart failure should have surgery during the active stage is still a matter of controversy. However 73% of patients with NYHA functional class III in the present series were successfully managed with medical therapy. Therefore, we would suggest that patients with heart failure, controlled with conventional medical therapy, should be initially managed with appropriate antibiotics, considering potential perioperative risks. This would be particularly true for patients with mitral regurgitation.

Patients with uncontrolled infection which is not responsive to antibiotics are better managed with surgical debridement and replacement of the infected valve.^{8,11,12,14} Control of infection may be particularly difficult when the organism is located in a myocardial or valve ring abscess,

pericardial space, intracardiac thrombus or in the suture site of prosthetic valves. In the present series, active infection could not be controlled in 10 patients. Three of them died of developing complications, while 5 of 7 patients who were operated on for persistent infection, heart failure or prosthetic valve failure survived. One of them had a large left atrial thrombus, a possible site of infection. Failure of antibiotic therapy could be clearly diagnosed when positive blood culture persisted, but blood cultures became negative with antibiotics in most uncontrolled patients in the present study. Therefore we compared clinical features of patients with uncontrolled infection and those with successful medical management. There were no differences in clinical features at the time of admission including the infecting organisms. However, patients with uncontrolled infection showed signs of persistent infection despite use of several possibly effective antibiotics for one month's duration. Hence patients with signs of persistent infection over one month could be considered to be refractory to medical therapy and to be candidates for surgical intervention. Before undertaking cardiac surgery, however, noncardiac sources of persistent infection must be excluded. In the present study, one patient with infection in an aneurysm of the superior mesenteric artery was successfully operated on. Fungal endocarditis, which has been reported to be an indication of urgent surgery,^{11,12,14} was not observed in the present series.

Association of disseminated intravascular coagulation was observed in 7 patients and considered to be a serious complication. These patients often missed a chance for surgical intervention, resulting in a death. Thus sedimentation rate should be carefully followed in every patient with infective endocarditis.

Peripheral embolization appeared to be a serious therapeutic dilemma, resulting in a lethal outcome even in patients with an otherwise uneventful course. Although recurrent emboli have been proposed as an indication of surgery,^{11,12,14} in the present study the majority of fatal emboli occurred as the first event. Several reports^{19–21} have described that a greater frequency of major embolic events occurs with large and mobile vegetations observed by echocardiography, but others have failed to replicate this.^{23–25} We also could not demonstrate a clear association between the structure

and mobility of vegetation by two dimensional echocardiography and frequency of embolization or fatal events. In contrast, peripheral emboli occurred mostly in the active stage of infection and tended to be fatal in patients with highly active and uncontrolled infection or in those complicated with disseminated intravascular coagulation. It has also been suggested that improper use of oral antibiotics increases the risk of major emboli²⁶. Hence the accurate diagnosis and initiation of effective antibiotic therapy in the early stage of endocarditis is of primary importance in the management of major emboli. At the present time, demonstration of large vegetations by echocardiography alone does not seem to justify urgent valve replacement in most cases. However, if patients have a history of multiple emboli or uncontrolled infection despite optimal antibiotic therapy, or are complicated with heart failure, surgical intervention should be considered.

Prosthetic valve endocarditis is another medical problem²⁷⁻²⁹. Although late endocarditis can be managed medically in uncomplicated cases as in our series or in others^{11,14,27,29}, outcome of medical therapy is poor in patients with early prosthetic valve endocarditis^{11,14,27-29}. Many reports²⁷⁻²⁹ have recommended aggressive surgical intervention for this condition, but operative mortality is also high. In this regard, prophylactic measures for endocarditis would be essential during and after operation for patients with prosthetic valve implantation.

In the healed stage, 9 patients underwent successful elective operation for correction of cardiac abnormalities. In the remaining 15 patients who were followed-up medically, only two patients developed a recurrent infection or peripheral embolus. The other 13 cases were uneventful in the follow-up period. Therefore prophylactic surgical intervention would not be necessary for prevention of recurrent infection or peripheral emboli in the healed stage, as the prosthetic valve itself carries a risk of endocarditis^{27,29}.

In summary, cardiac surgery plays an important role in the care of patients with infective endocarditis, although antibiotic therapy remains the primary management. In order to provide optimal care, it is essential to recognize conditions under which surgery is indicated and to select the appropriate time for surgical intervention. It is of utmost importance to refer patients who may develop complications

which require surgical intervention to a center with facilities for open heart surgery.

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