Infective Endocarditis: Mid-Term Prognosis in Patients with Good In-Hospital Outcome

José Zamorano, Leopoldo Pérez de Isla, Gracieta Malangatana, Carlos Almería, José Luis Rodrigo, Adalia Aubele, Isidre Vilacosta, Enrique Rodriguez, Carlos Macaya

Unidad de Ecocardiografía e Imagen Cardiaca, Instituto Cardiovascular, Hospital Clínico San Carlos, Madrid, Spain

Background and aim of the study: **The study aim was to analyze the mid-term prognosis of infective endocarditis (IE) in patients managed with medical therapy during the in-hospital phase and who had a good initial outcome. Comparison was made with the prognosis of patients treated surgically during this period.**
Methods: **A total of 151 patients diagnosed with IE was studied, and in-hospital outcome, clinical characteristics and mid-term follow up data were analyzed. The main end-point was a composite of death and need for surgical repair.**
Results: **Among 151 patients, 84 (56%) underwent surgery or died during the in-hospital phase, while 67 patients (44%) received medical treatment and were discharged clinically stable with a final diagnosis of healed infective endocarditis. A better baseline profile was seen in the medically treated group, but outcome in this group showed extensive mid-term morbidity/mortality. In total, 52.2% of patients underwent surgery to correct complications and 60% died as a consequence of the disease. The event-free survival rate was 20% at five years.**
Conclusion: **Despite a favorable in-hospital clinical course and successful medical treatment, patients with IE are at risk of late complications that result in a need for surgical repair, or in death. A close follow up should be made in order to treat late complications.**

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Despite important advances in the management of patients with infective endocarditis having been made in recent years, the disease remains a life-threatening condition. Early diagnosis resulting from the use of echocardiography, improvements in antimicrobial treatment and a combined medical-surgical approach have reduced mortality and complications during the active phase of the disease. However, serious sequelae - namely, valve incompetence, recurrence or relapse, congestive heart failure and death - persist as major threats long after patients have been discharged from hospital following successful treatment of the active disease. Although several studies have focused on the issue of short-term patient survival, few data exist regarding the mid-term prognosis. Thus, the study aim was to analyze the prognosis in terms of the morbidity and mid-term survival of patients managed successfully with medical therapy during the in-hospital phase of the disease, and to compare these data with the prognosis of patients treated surgically during the same period.

Address for correspondence:
José Luis Zamorano, Laboratorio de Ecocardiografía, Hospital Clínico San Carlos, C/ Professor Martín Lagos s/n. 28040, Madrid, Spain
e-mail: jlzamorano@vodafone.es

Clinical material and methods

Study population

The authors' institution is both a primary care hospital for a local population of 500,000 people and a university-based referral center for cardiac diagnostic procedures and surgery. Data pertaining to all patients admitted between 1991 and January 2003 with a definite diagnosis of infective endocarditis based on Duke criteria were collected and followed up.

All patients in whom infective endocarditis was suspected underwent transthoracic echocardiography (TTE) on at least one occasion; most patients also underwent transesophageal echocardiography (TEE).

Echocardiography

Bidimensional, M-mode and Doppler echocardiographic studies (pulsed, continuous and color modalities) were performed systematically in all patients by experienced echocardiographers. Consent was

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obtained from each patient to perform TEE. In all cases, local anesthesia of the oropharynx (10% xylocaine spray) and sedation (1 mg intravenous diazepam plus 12.5 mg intravenous meperedine) was carried out if necessary prior to introduction of the probe.

Data acquisition and definitions

Demographic, clinical and predisposing factors for infective endocarditis were recorded for each patient. The in-hospital phase referred to the period of active disease when the patient was receiving antibiotic treatment in hospital. Predisposing factors to infective endocarditis were both cardiac and extracardiac. Increased susceptibility to infection (including infective endocarditis) was also described for chronic liver disease (1,2). Patients who were intravenous drug abusers and those with HIV infection were included, for obvious reasons.

Fever was defined as a confirmed temperature of 38ºC, or higher. Embolization referred to the presence of signs of secondary involvement of any organ due to the displacement of an infected embolus.

With regard to echocardiographic definitions, a patient was said to have a vegetation when any echogenic, mobile mass attached to a valve, its supporting structures, the endocardial surface (usually on the path of regurgitant jets) or to a prosthetic intracardiac device was detected. An abscess/pseudoaneurysm was diagnosed whenever an abnormal paravalvular echogenic or relatively echo-free space was detected. A fistula was defined as the presence of an abnormal anatomic pathway communicating two different cavities. A systolic displacement beyond the plane of the annulus in the long-axis view of one or more leaflets met the diagnostic criteria of prolapse.

A case of infective endocarditis was considered to have negative blood cultures when at least two different cultures had been obtained, all of which were negative by the time of hospital discharge.

Patients underwent surgical treatment when they fulfilled the indications established by the respective guidelines for each period. Those patients who died or underwent cardiac surgery (defined as valve repair or replacement) during the in-hospital phase comprised the surgical/death group; those discharged alive but not requiring cardiac surgery during the in-hospital phase comprised the medically treated group.

Follow up

Patients were studied and followed up for a mean (± SD) period of 25.4 ± 42.0 months. The clinical characteristics were assessed, and demographic data, risk factors for endocarditis and clinical, echocardiographic and outcome data evaluated. The main end-point was the composite end-point of death or need for surgical repair or replacement during follow up. No event was considered after the composite end-point had been reached. All patients discharged from hospital were diagnosed as 'healed infective endocarditis'. After discharge, in case of any clinical suspicion of recurrence or reinfection or in case of fever, new blood cultures were analyzed in order to diagnose the new event.

Table I: Clinical characteristics of the patient groups.

Parameter	Patient group		p-value
	Medical treatment	Surgical treatment/ death	
Age (years)	46.9 ± 20.0	55.2 ± 16.3	0.008
Male gender	44 (65.7)	56 (66.7)	NS
Cardiac risk factors			
Prosthetic valve	14 (21)	35 (42)	0.005
DVD	11 (16)	8 (10)	NS
CHD	6 (9)	11 (13)	NS
Rheumatic valve disease	13 (19)	18 (21)	NS
Pacemaker	0	7 (8)	0.015
Prior IE	6 (9)	8 (10)	NS
Non-cardiac risk factors			
Intravenous drug abuse	27 (40)	14 (17)	0.002
HIV infection	18 (27)	9 (11)	0.013
Hepatic disease	13 (19)	13 (16)	NS
Diabetes mellitus	5 (8)	8 (10)	NS

Values in parentheses are percentages.
CHD: Congenital heart disease; DVD: Degenerative valve disease; IE: Infective endocarditis; NS: Not significant.

Table II: Clinical course during follow up.

Condition	Patient group		p-value
	Medical treatment	Surgical treatment/ death	
Fever	53 (79)	60 (71)	NS
Renal failure	18 (27)	18 (21)	NS
Systemic emboli	26 (39)	16 (19)	0.010
Congestive heart failure	22 (33)	40 (48)	0.047
Re-infection	26 (38.8)	23 (34.3)	NS
Recrudescence	15 (22.4)	18 (25.3)	NS
Surgery during follow up	35 (52.2)	48 (67.6)	NS
Death during follow up	40 (60)	29 (40.8)	0.010

Values in parentheses are percentages.
NS: Not significant.

Statistical analysis

Normally distributed continuous variables were expressed as mean (±SD) and compared using the unpaired two-sided Student's *t*-test (independent sample *t*-test). Non-parametric continuous variables were tested with the Mann-Whitney *U*-test. Discrete variables were expressed as proportions (percentages) and compared using the chi-square test or Fisher's exact test. Data analysis was conducted for the entire study population, whilst survival analysis was performed for the medical group only. Survival curves were computed using the Kaplan-Meier method. Survival analysis was calculated from the date of diagnosis to the date of death or cardiac surgery due to infective endocarditis, or the last follow up. A Cox analysis was performed to detect predictors of worse prognosis in this group of patients. Data relating to patients who died from causes other than infective endocarditis or its complications were censored at the time of death. Censored times were also considered when patients were lost to follow up. A p-value <0.05 was considered to be statistically significant.

Results

During the observation period a total of 151 patients was admitted to hospital with infective endocarditis. A diagnosis of infective endocarditis was made according to the aforementioned criteria, and was definite in all 151 patients.

Clinical presentation and in-hospital outcome

Among the patients, 84 (56%) underwent surgery or died during the in-hospital phase of the disease, while 67 (44%) received medical treatment and were discharged as clinically stable with a final diagnosis of healed infective endocarditis. All patients discharged alive from hospital (in both groups) had three or more negative blood cultures after treatment.

The clinical characteristics of both patient groups are listed in Table I, while results related to the clinical course during follow up are listed in Table II. The left ventricular ejection fraction was normal (>55%) in all patients in the medically treated group. In all cases, residual valvular regurgitation was less than moderate before discharge from hospital. None of the patients showed left ventricular dilatation.

Location of infective endocarditis

The native mitral and aortic valves were equally affected in both groups, though there was a higher incidence of infected tricuspid valve (25% versus 12%, p = 0.035) in the medical group, most likely due to a higher prevalence of intravenous drug abusers. Prosthetic valves, either mitral (12% versus 26%, p = 0.023) or aortic (8% versus 19%, p = 0.033) were present more frequently in the surgery/death group. Simultaneous infection of two valves occurred in five (8%) of the medical group patients, and in eight (10%) of the surgical group (p = NS) (Table III).

The etiological bacterium

Blood cultures were positive in 117 patients (78%), with no significant difference between groups. The isolated bacteria were mostly *Staphylococcus aureus*, *Staph. epidermidis* and *Streptococcus viridans*, with no differences between both groups, except for *Staph. aureus* which was more frequent in the medical group (42% versus 23%, p = 0.009). Simultaneous infection by two or more bacteria was found in 10 patients (7%); prevalence was 8% in the medical group and 6% in the surgical treatment/death group (Table IV).

Table III: Location of infective endocarditis.

Location	Patient group		p-value
	Medical treatment	Surgical treatment/ death	
Infected native valve			
Mitral	22 (33)	19 (23)	NS
Aortic	20 (30)	22 (26)	NS
Tricuspid	17 (25)	10 (12)	0.035
Pulmonic	2 (3)	0	NS
Infected prosthetic valve			
Mitral	8 (12)	22 (26)	0.023
Aortic	5 (8)	16 (19)	0.033
More than one valve affected	5 (8)	8 (10)	NS

Values in parentheses are percentages.
NS: Not significant.

Medically treated group follow up

The average follow up for the medical group (n = 67) was 28.9 ± 6.8 months. Survival without cardiac surgery was 54% at one year, 29% at three years, and 20% at five years. Thirty-five patients (52.2%) underwent late surgery to correct sequelae of the infection, while 40 patients (60%) died from cardiovascular causes as a direct consequence of infective endocarditis (development of sepsis) or due to worsening of the underlying cardiac disease. Twenty-one patients (68%) of those who underwent cardiac surgery after discharge, died during the follow up.

Twenty-nine patients (21 in the medically treated group) persisted in using intravenous drugs; among these, 17 (12 in the medically treated group) died as direct consequence of continuing drug abuse.

Congestive heart failure developed in 22 patients (33%) in the medically treated group. Among these patients, eight (39%) had at least one embolic episode, four (17%) had an abscess or a pseudoaneurysm, and three (13%) had a cardiac rupture or perforation. The analysis did not show any statistically significant dif-

Table IV: Microbiological characteristics.

Causative organism	Patient group		p-value
	Medical treatment	Surgical treatment/ death	
Staphylococcus aureus	28 (42)	19 (23)	0.009
Staphylococcus epidermidis	11 (16)	9 (11)	NS
Streptococcus viridans	7 (10)	13 (16)	NS
Streptococcus pyogenes	0	2 (2)	NS
Enterococcus	4 (6)	5 (6)	NS
Streptococcus pneumoniae	0	0	NS
Streptococcus milleri	0	2 (2)	NS
Neisseria spp.	0	1 (1)	NS
Corynebacterium	0	1 (1)	NS
Escherichia coli	1 (1)	1 (1)	NS
Candida spp.	0	3 (4)	NS
Others	0	2 (2)	NS
More than two bacteria	5 (8)	5 (6)	NS
Negative blood cultures	11 (16)	21 (25)	NS

Values in parentheses are percentages.
NS: Not significant.

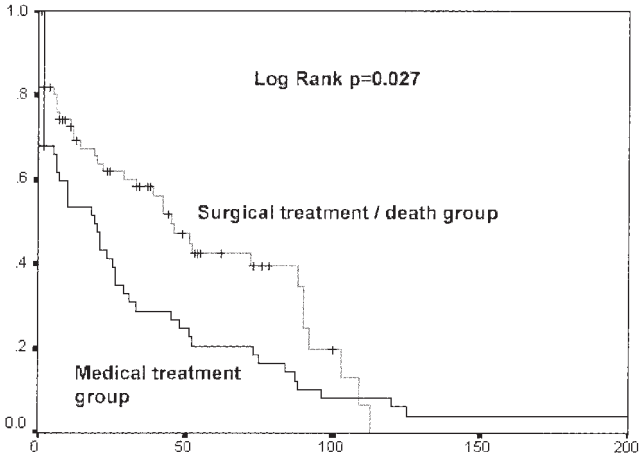

Figure 1: Survival without cardiac surgery of patients in the medically treated group.

ferences between patients with negative and positive blood cultures and patients with single- or mixed-organism infections in both groups (log rank test, p = NS).

In order to assess mid-term follow up, the outcomes of patients in the medically treated group were compared with those of the subgroup of patients treated surgically and discharged alive from hospital. Follow up results for the predefined end-point were worse for the former group than for the latter (Fig. 1; log rank test, p = 0.027)

Predictors of middle-term survival of patients in the medically treated group

Using the univariate Cox analysis, diabetes mellitus (odds ratio (OR) = 4.74; p = 0.25), renal failure (OR = 4.02; p = 0.014), the development of heart failure after hospital discharge (OR = 3.34; p = 0.03) and the appearance of a pseudoaneurysm (OR = 5.7; p = 0.024) were each identified as predictors of poor outcome. In the multivariate analysis, only the appearance of a pseudoaneurysm (OR = 9.44; p = 0.009) was identified as an independent predictor of poor prognosis.

Discussion

Over the past 50 years, important advances have been made in the diagnosis and treatment of infective endocarditis, and this has led to radical modifications of the clinical course and natural history of the disease. However, persistently high rates of morbidity and mortality are seen for this condition among different subgroups of patients (3-6). This is true either for the early in-hospital phase or for late follow up following the cure of endocarditis, and as a consequence the important sequelae of this disease include congestive heart failure, major embolus, or rupture of a mycotic aneurysm (7). Several studies have been conducted to assess short-term survival, but few data are available relating to mid-term prognosis. Consequently, the present study was initiated to investigate the prognosis in terms of morbidity and mid-term survival of those patients managed successfully only with medical therapy during the in-hospital phase of the disease. The study included 151 patients with infective endocarditis followed up for an average 28.9 ± 6.8 months; the mean age of the patients (46.9 years) was consistent with that in other studies (8-11).

Predisposing cardiac risk factors for infective endocarditis were encountered more often within the surgical group than the medical group (60% and 41%, respectively; p <0.0005), thus reflecting the trend that patients with underlying cardiac disease develop complications that require surgical management. Prosthetic valve and pacemaker lead infection were also seen more often in the surgical/death group (42% versus 21%, p = 0.005; and 10% versus 0%, p = 0.015, respectively), for the same reasons. In addition, the numbers of intravenous drug abusers and HIV patients were greater in the medical group (40.3% versus 16.7%, p = 0.013) and, according to one report, most of these patients have no known heart disease (15).

Intravenous drug abusers and HIV-infected patients - who usually are also drug abusers - were predominant among the medical group, most likely due to their younger age and because they usually develop right-sided infection which holds a better clinical course and therefore offers good outcome with medical treatment only (12-17). One possible explanation for the higher predominance of right-sided infective endocarditis in intravenous drug abusers is that long-term drug addiction results in continuous endothelial damage due to bombardment of the tricuspid valve by impurities and adulterants contained in injected drugs (16). Indeed, in the present study tricuspid valve infection occurred significantly more often in the medical group (25.4% versus 11.9%, p = 0.035).

Staphylococcus aureus infection was encountered more often in the medical group (41.8% versus 22.6%), again probably as a consequence of the greater proportion of intravenous drug abusers and HIV-infected patients. It has been reported previously that although the phenomenon of *Staph. aureus* is not unique to drug addicts, the high frequency is characteristic (16,18).

Among the present patients, aortic valve involvement occurred equally in both groups. This was a surprising finding as, according to several series, infection of the aortic valve tends to be more refractory to antibiotic therapy and therefore more prone to develop complications than are the mitral and tricuspid valves, and requires early surgical intervention (19).

During the follow up period, several complications occurred that reflected the complexity of the disease. Systemic embolus most frequently affected the medical group (39%), and this was similar to data reported in other studies (9,11), most likely because these patients were given more time to develop these complications, the occurrence of which may extend far beyond the first week of effective antibiotic treatment, albeit with a lower incidence (3).

In the present series, the high rates of surgery or death which occurred during the in-hospital phase may be explained by selection bias as the hospital, being a referral centre, not only receives the most severe cases but also has easier access to surgery. This may also explain the high proportion of patients with negative blood cultures (22%) and mixed organisms (7%). Another possible explanation may be a delay in diagnosing the disease, as this dictates a more complicated clinical course and, consequently, a need for surgery and a less favorable outcome.

During the follow up period, 35 patients (52.2%) in the medical group underwent surgery, this rate being slightly higher than was previously reported (9 to 47%) (8-11). Forty patients (60%) died during the follow up period; again, this was similar to one report (21) but higher than others (range: 23 to 37%) (9,10), perhaps because the latter studies included both medical and surgically treated patients. In addition, a selection bias due to the authors' hospital receiving critically ill patients may also have been present. As in earlier studies, mortality was higher during the first months after discharge and stabilized thereafter (8,20). The event-free survival rate of 20% at five years was similar to that of some previous studies (22,23), but poorer than others (67%) (11). At no time could any variable related to the prognosis of these patients be detected, although this may have been due to the relatively small sample of patients involved.

The present results indicate that infective endocarditis is a disease with poor short- and mid-term prognoses. An initial good response to aggressive medical treatment should not lead to these patients being considered as low risk, and precautions must be taken to follow them very closely. In particular, the presence of pseudoaneurysms should be sought as this is a clear indication of a poor prognosis.

Study limitations

Although the present study was started in 1991, and surgical indications have since changed as new guidelines to treat infective endocarditis have been developed, the conclusions were not significantly affected. Indeed, recent reports have shown the prognosis of patients with infective endocarditis and heart failure to be poor if surgery is not carried out, but significantly improved if it is (21). This approach was generally followed before these reports were made, and patients with these characteristics have undergone surgery unless a major contraindication was found.

In conclusion, the results of the present study showed that despite a good initial clinical course after medical treatment, infective endocarditis has a high rate of mid-term complications and a poor life expectancy. Hence, a close clinical and echocardiographic follow up of this subgroup should be conducted in order to prevent and treat the late complications that usually appear in these patients.

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Erratum

In the contents of the March 2005 issue the degrees of the authors of the article Acoustic Diagnosis of Aortic Stenosis were incorrectly printed. The correct degrees are as follows:

Zhanyu Sun	M. Eng
Kian-Keong Poh	M.B.B.Chir., M.R.C.P
Lieng H. Ling	M.B.B.S., F.R.C.P
GS Hong	Ph.D
Chye-Heng Chew	Ph.D