Clinical and Echocardiographic Predictors of Morbidity and Mortality in Infective Endocarditis: The Significance of Vegetation Size

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Key words: endocarditis, vegetation, abscess, prosthetic valve

Abstract

Background: Infective endocarditis is a common disease with significant morbidity and mortality.

Objectives: To define clinical and echocardiographic parameters predicting morbidity and in-hospital mortality in patients with infective endocarditis hospitalized in a tertiary hospital from 1991 to 2000.

Methods: All patients with definite infective endocarditis diagnosed according to the Duke criteria were included. We examined relevant clinical features that might influence outcome.

Results: The study group comprised 100 consecutive patients, 77 with native valve and 23 with prosthetic valve endocarditis. The overall in-hospital mortality rate was 8%. There was a higher mortality in the PVE group compared to the NVE group (13% vs. 7%, $P = 0.07$). The mortality rate in each group, with or without surgery, was not significantly different. Clinical predictors of mortality were older age and hospital-acquired endocarditis. The presence of vegetations and their size were significant predictors of major embolic events and mortality. *Staphylococcus aureus* was a predictor of mortality (25% vs. 5%, $P < 0.005$) and abscess formation. Multivariate logistic analysis identified vegetation size and *S. aureus* as independent predictors of mortality.

Conclusions: Mortality is higher in older hospitalized patients. *S. aureus* is associated with a poor outcome. Vegetation size is an independent predictor of embolic events and of a higher mortality.

IMAJ 2007;9:365–369

Infective endocarditis is a serious disease with a significant morbidity and mortality. William Osler emphasized the importance of the disease, and for nearly a century the diagnosis was based on the classical clinical picture and a positive blood culture. A decrease in the prevalence of rheumatic heart disease, the use of valve prostheses, an increase in the use of chronic instrumentation and implantable devices, and the emergence of drug-resistant organisms have influenced the clinical spectrum of the disease [1-3]. The normal healthy population is living longer today and a new and older population of patients is surviving. They have more chronic debilitating disease and are exposed to instrumentation, foreign bodies and invasive procedures. Great improvements in echocardiographic imaging and now the use of high resolution multiplane transesophageal echocardiography permit better identification of valve pathology, vegetations and intracardiac abscesses, making echocardiography the basis for non-invasive pathological diagnosis of infective endocarditis. The Duke criteria incorporate the echocardiographic findings and currently constitute the new basis for diagnosis [4]. Nonetheless, the impact of these advances on the morbidity and mortality from this disease has yet to be determined.

We examined the clinical and echocardiographic predictors of in-hospital morbidity and mortality in infective endocarditis during a 10 year period in a tertiary clinical hospital.

Patients and Methods

Hadassah-Hebrew University Medical Center is a tertiary referral center. The files of all patients admitted with a definite diagnosis of endocarditis during the years 1991–2000 were reviewed. A diagnosis of definite endocarditis was based on the Duke criteria (two major criteria, one major and three minor, or five minor criteria) [4]. Major criteria include a positive blood culture or evidence of endocardial involvement on echocardiography. Minor criteria include an underlying heart lesion, fever, vascular or immunological phenomena, indefinite echocardiography, or positive microbial cultures [4].

Analysis of data

Epidemiological data, risk factors for endocarditis including previous endocarditis and valve abnormalities, and prior invasive procedures (dental or surgical interventions), occurring within 60 days of the development of endocarditis were evaluated. The presence of a foreign body that was related to the infection (infected indwelling catheters or pacemakers) and a specific extracardiac site of infection origin (abscesses or other infected sources) that was present prior to the onset of endocarditis were recorded. Hospital-acquired endocarditis was defined as an infection that was acquired during the hospital stay. Co-morbid conditions included diabetes mellitus, chronic renal failure (creatinine > 250 mmol/L), neoplastic disease, and regular systemic corticosteroid or other immune suppressive therapy prior to the infection. Clinical findings including fever, immunological and embolic phenomena were evaluated. Immunological phenomena were defined as the occurrence of Roth's spots, glomerulonephritis or Osler nodes. Embolic events were defined as the occurrence of major emboli including arterial emboli, intracranial hemorrhage, pulmonary infarcts and mycotic aneurysms, and minor emboli were defined as splinter hemorrhage, Janeway

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PVE = prosthetic valve endocarditis
NVE = native valve endocarditis

lesions and conjuctival hemorrhage. Echocardiographic findings including transthoracic and transesophageal echocardiography were evaluated from reports with regard to pathology, complications and vegetation size. The examinations were made on HP SONOS 1500 machines (Hewlett-Packard, Andover MA, USA). A vegetation was defined as a mass adherent to a cardiac structure with a distinct shape and independent motion. The measurements of vegetation size were obtained on different echocardiographic views, and the maximal length was used for analysis. Where there were multiple vegetations, the size of the largest vegetation was measured. The results of blood cultures and the indications and timing of surgery were recorded. We evaluated the outcome of patients, including the duration of hospital stay, presence of heart failure, recurrence of endocarditis, and in-hospital mortality.

Statistical analysis

The data were compared and analyzed statistically using the Student *t*-test for continuous variables and the chi-square test for discrete variables. Data are represented as mean ± standard deviation. Multivariant logistic regression analysis was performed in order to define independent predictors of mortality and embolic events. Variables included in the analysis were those parameters that were significant in the univariate analysis. These variables included patient age as a continuous variable, presence of vegetations, vegetation size and the infectious organism (*Staphylococcus aureus* versus other organisms). We did not include two parameters, hospital-acquired endocarditis and an extracardiac source, despite being highly significant on the univariate analysis, since data were missing from these parameters, reducing the size of the analysis and precluding a meaningful result. All analyses were done with the SPSS statistical package (SPSS Inc, Chicago, IL, USA).

Results

A total of 103 patients were admitted with the diagnosis of infective endocarditis; 3 patients were excluded since they did not fulfill the Duke criteria, leaving 100 patients with a definite diagnosis of endocarditis. Of the 100 study patients 77 had native valve and 23 had prosthetic valve endocarditis. Five patients with PVE had early-onset endocarditis (infection that developed within 60 days after cardiac surgery).

Clinical manifestations

The patients' demographic data, clinical characteristics, complications and treatment are presented in Table 1A. The overall in-hospital mortality rate was 8%. The mortality rate with or without surgery was similar; 2 of 25 patients (8%), and 6 of 75 (8%) respectively. There was a higher mortality rate in the PVE group (13%) as compared to the NVE group (7%), $P = 0.07$. The mortality rate in both groups, with or without surgery, did not differ significantly (NVE 7% vs. 6%, PVE 12.5% vs. 14%). Patients who died were older (66 ± 13 vs. 54 ± 19 years, $P < 0.05$) and they tended to have a shorter duration of symptoms before admission to hospital (13 ± 23 vs. 24 ± 27 vs. days, $P = 0.1$). Time to diagnosis was longer but the difference was not statistically significant (6 ± 6 vs. 5 ± 5 days, $P = 0.6$). There was no difference in mortality with regard to the valve involved, a previous valve abnormality, the underlying etiology, previous episodes of endocarditis, the occurrence of embolic phenomena or the development of heart failure. Embolic phenomena were evident in 23% of the patients. Major emboli, defined as arterial emboli, intracranial hemorrhage, pulmonary infarcts or mycotic aneurysms occurred in 14% of patients.

Table 1A. Demographics, clinical characteristics, complications and treatment in patients with infective endocarditis

Age (yrs)	55 ± 20 (1–97)
Male/Female	55/45
Native/prosthetic valve	77/23
Symptom duration (days)	23 ± 27 (1-110)
New murmur	5/96 (5%)
Immunological phenomena*	18/99 (18%)
Valves involved	
Mitral	51 (51%)
Aortic	33 (33%)
Tricuspid	4 (4%)
Multiple valves	7 (7%)
Non-valve	2 (2%)
Unidentified	3 (3%)
Time to diagnosis (days)	5 ± 5 (1–30)
Hospital duration (days)	28 ± 19 (7–101)
Complications	
Patients with clinical heart failure	31/97 (32%)
Embolic phenomena	23/100 (23%)
Major**	14
Minor***	15
Echocardiographic manifestations	
Vegetation	66/99 (67%)
New valve regurgitation	18
Valve deformity	8
Valve dehiscence	6
Abscess	9
Treatment	
Surgery	25/100 (25%)
Replacement	23/25 (92%)
Repair	2/25 (8%)
Time to surgery (days)	13 ± 34 (1–180)
Indication for surgery	
Persistent infection	11
Heart failure	10
Abscess	5
Emboli	1
Recurrence	12/99 (12%)

* Defined as the occurrence of Roth's spots, Osler nodes or glomerolonephritis.

** Defined as the occurrence of arterial emboli, intracranial hemorrhage, pulmonary infarcts or mycotic aneurysms.

*** Defined as the occurrence of splinter hemorrhage, Janeway lesions or conjuctival hemorrhage.

Table 1B. Risk factors and co-morbid conditions of infective endocarditis

Risk factors	
Previous valve abnormality	59/97 (60%)
Previous endocarditis	22/100 (22%)
Previous invasive procedure	21/100 (21%)
Hospital-acquired	12/84 (14%)
Foreign body	10/100 (10%)
Definite infectious origin	33/86 (38%)
Co-morbid conditions	37/100 (37%)
Diabetes	17 (17%)
Renal failure	13 (13%)
Cancer	5 (5%)
Steroid treatment	9 (9%)
Immunosuppressive drugs	3 (3%)

Risk factors

Risk factors [Table 1B] that were significant predictors of mortality were hospital-acquired endocarditis occurring in 14% of the patients (27% vs. 3% mortality, $P < 0.0001$) and a definite extracardiac source of infection evident in 38% of patients (18% vs. 0%, $P < 0.001$). There was a trend towards a higher mortality in patients with a recent invasive procedure (21% of patients, 13% vs. 2% mortality, $P = 0.05$), patients with co-morbid conditions (37% of patients, 14% vs. 5% mortality, $P = 0.08$), and the presence of a foreign body (10% of patients, 8% vs. 5% mortality, $P = 0.09$)

Echocardiographic findings

TTE was performed in all patients and TEE in 69 patients. Vegetations were evident by TTE or TEE in 66 of the 99 patients (67%) who had an echo available for analysis. TTE detected vegetations in 42 of 99 patients (42%), while TEE detected them in 42 of 69 patients (61%). When we compared only cases where both modalities were available (69 patients), TTE detected vegetations in only 18 of the 42 vegetations evident by TEE (43%). Overall, TEE detected vegetations in 24 of 69 cases (35%) that were not detected by TTE. There was no difference in the rate of detecting vegetations by TTE in native valves compared to prosthetic valves (42% vs. 40%) or by TEE (60% in both groups). Vegetations were more common in patients who died although this was not statistically significant (85% vs. 65%, $P = 0.2$), however the average vegetation size was larger in these patients (17 ± 10 vs. 11 ± 7 mm, $P = 0.03$). Vegetation size was also significantly larger in patients with major embolic complications (12 ± 10 vs. 5 ± 7mm, $P < 0.01$). Vegetation detected by echocardiography was a significant predictor of mortality (12% vs. 3%, $P < 0.05$) and of major embolic events (19% vs. 3%, $P < 0.02$). Vegetation size by itself (available for analysis in 50 of the 66 patients with vegetations) was also a significant predictor of mortality (5.3%, 10% and 27% in vegetations < 10 mm, 10–15 mm and > 15 mm respectively, $P < 0.02$) and of major embolic events (10%, 30%, 27% in vegetation size 0–10 mm, 10–15 mm and > 15 mm respectively, $P < 0.005$ [Figure 1]. However, vegetations were not predictors of surgery or the development of heart failure. Large vegetations were also predictive of S. *aureus* infection (19% without a vegetation vs. 54% with a vegetation > 15 mm, $P < 0.004$). The presence of an abscess was evident in 9% of patients with a trend towards a higher mortality rate (22% vs. 7%, $P = 0.09$).

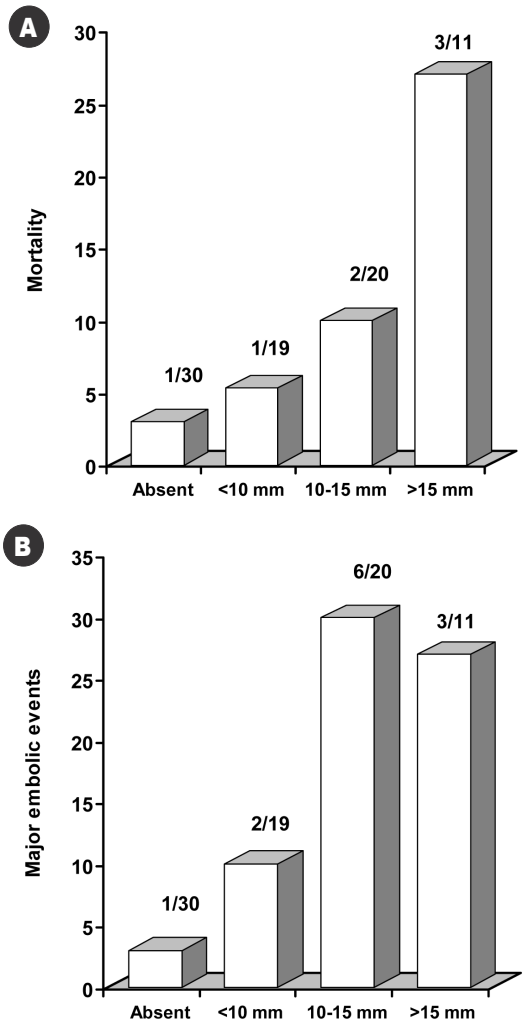

Figure 1. Echocardiographic vegetation presence and size were significant predictors of mortality and major embolic events. **[A]** Vegetation presence and size were significant predictors of mortality (3%, 5.3%, 10% and 27% in patients without vegetations, vegetations of < 10 mm, 10–15 mm and > 15 mm respectively, $P < 0.02$). **[B]** Vegetation presence and size were also a significant predictor of major embolic events (3%, 10%, 30% and 27% in patients without vegetations, vegetations of < 10 mm, 10–15 mm and > 15 mm respectively, $P < 0.005$).

Microbiological findings

The pathogenic organisms causing endocarditis are shown in Table 1C. Culture-positive endocarditis was present in 89% of patients. Culture-positive endocarditis patients had on average

TTE = transthoracic echocardiography
TEE = transesophageal echocardiography

Table 1C. Microbiological characteristics of infective endocarditis

Culture positive	85/96 (89%)
Culture negative	11/96 (11%)
Gram-positive bacteria	
Streptococcus (all)	47 (49%)
Streptococcus viridans	21 (22%)
Streptococcus bovis	7 (7%)
Enterococci	4 (4%)
Other streptococci	19 (20%)
Staphylococcus (all)	24 (25%)
Staphylococcus aureus	16 (17%)
Staphylococcus epidermis	5 (5%)
Staphylococcus, unidentified	3 (3%)
Gram-negative bacteria	8 (8%)
Fungi	1 (1%)
HACEK	1 (1%)

larger vegetation size as compared to culture-negative patients (6.5 ± 8.2 vs. 1.4 ± 2.7 mm, $P < 0.01$), and culture-positive patients were more likely to have surgery (24% vs. 14% in culture-negative patients, $P = 0.1$). They were also more likely to have a major embolus, however the difference was not significant (15% vs. 0%, $P = 0.14$). Mortality rates were not significantly different between the groups (8% vs. 14%, $P = 0.5$). S. *aureus* infection occurred in 16% patients. These patients were older (69 ± 11 vs. 53 ± 15 years, $P < 0.01$), had larger vegetations (10.8 ± 14 mm vs. 5.0 ± 4.8, $P < 0.05$) and were more likely to have hospital-acquired endocarditis (31% vs. 11%, $P = 0.06$). Major emboli were also more common in these patients (25% vs. 11%, $P = 0.11$). S. *aureus* was a significant predictor of mortality (25% vs. 5%, $P < 0.005$). It was also associated with more frequent abscess formation (a 25% incidence with S. *aureus* vs. 6% with other organisms, $P < 0.01$).

Univariate and multivariate analysis for major emboli and mortality

The univariate predictors of major embolic complications that were significant were the occurrence of immunological phenomena (33% vs. 8%, $P < 0.01$), vegetation presence (19% vs. 3%, $P < 0.02$) and vegetation size [Figure 1A]. Multivariate analysis revealed that vegetation size was the only independent predictor of major embolic events ($P < 0.01$). Univariate analysis of the predictors of mortality is presented in Table 2. Multivariate analysis showed that vegetation size ($P = 0.03$) and S. *aureus* ($P = 0.01$) were the only independent predictors of mortality.

Table 2. Univariate analysis of the predictors of mortality

Parameter	**Dead vs. Alive (Mean)**	***P***
Age (yrs)	66 ± 13 vs. 54 ± 19	< 0.05
Symptom duration (days)	13 ± 23 vs. 24 ± 27	0.1
Time to diagnosis (days)	6 ± 6 vs. 5 ± 5	0.6
Hospital duration (days)	28 ± 19 vs. 28 ± 28	0.9
Vegetation size (mm)	17 ± 10 vs.11 ± 7	< 0.05
Parameter	**Mortality (%)**	***P***
Male/Female	9.1% vs. 6.7%	0.7
Native/Prosthetic valve	7% vs. 13%	0.07
Surgery/No surgery	7% vs. 6%;	0.8
Native/Prosthetic valve	12.5% vs. 14%	0.7
Previous valve abnormality/None	7% vs. 10%	0.7
Previous endocarditis/None	9% vs. 7%	0.8
Previous invasive procedure/None	13% vs. 2%	0.05
Hospital-acquired/No	27% vs. 3%	< 0.0001
Foreign body/None	8% vs. 5%	0.09
Definite infectious origin/None	18% vs. 0%	< 0.001
Co-morbid conditions/None	14% vs. 5%	0.08
Immunological phenomena/None	11% vs. 7%	0.6
All embolic phenomena/None	5% vs. 9%	0.6
Major emboli	8% vs. 8%	0.6
Clinical heart failure/None	10% vs. 8%	0.7
Abscess formation/None	22% vs. 7%	0.09
Vegetation presence/None	12% vs. 3%	< 0.05
Culture positive/Negative	8% vs. 14%	0.5
S. *aureus*/Other organism	25% vs. 5%	< 0.005

Discussion

We evaluated the clinical manifestations of endocarditis in our institution – a tertiary university hospital – during the last decade in order to identify the clinical features that have the greatest influence on the morbidity and mortality in these patients. We found on univariate analysis that predictors of mortality were older age, prosthetic valve disease, hospital-acquired endocarditis, a definite extracardiac source of infection, a previous invasive procedure, a foreign body, and the presence of co-morbid conditions including diabetes, chronic renal failure and immunosuppressive therapy. These features are typical of an increasing population of debilitated elderly patients who are treated in a modern, highly invasive medical environment. This is an important trend shift from the classical Oslerian endocarditis seen in earlier decades that included community patients admitted with an underlying valve abnormality. A recent study has shown that co-morbid conditions, including hemodialysis and immune suppression, have increased significantly in the last decade in patients with endocarditis and have been shown to be significant predictors of 1 year mortality [3].

In this study the presence of vegetations as well as their size was shown to have an independent association with embolic events and mortality. The data in our study demonstrate that not only the presence of vegetations but also their size are significant predictors of embolic events. This is consistent with previous studies showing that the presence of vegetations and some of their features predict embolic events [5-8]. Vegetation size has been shown to be the most important characteristic in predicting embolic events [9]. Embolic events are more frequent in patients with a vegetation length > 10 mm and are particularly frequent with very large vegetations (vegetation > 15 mm) [9]. The presence and size of vegetations as a predictor of mortality is less well described in the literature. We found that the presence of vegetations and their size were independent predictors

of in-hospital mortality. Mortality was especially increased in patients with large vegetations and had a definite linear relationship. In a recent study, the presence of vegetations detected by echocardiography was associated with increased mortality and was also a significant predictor of mortality at 6 months [10]. In addition, the size of mitral valve vegetations was a significant independent predictor of mortality at 30 days and 1 year in another study [11].

We have shown that S. *aureus* was another predictor of mortality and was associated with abscess formation. S. *aureus* is known to be associated with poor outcome and has also been reported as an independent predictor of mortality [3] with a high mortality rate [12]. Prolonged life expectancy has increased the proportion of older and often debilitated patients exposed to invasive procedures (as seen in our patient cohort) so that more infections today are due to S. *aureus* [3,13]. This predisposes to a more fulminant endocarditis and a worse outcome. Therefore, earlier diagnosis and a more aggressive approach may be warranted in this population subset.

The 8% mortality rate in this study is lower than reported in earlier published series of infective endocarditis, where it ranged from 15% to 20%. If we compare the mortality rate in the present study to another comparable study from our own hospital covering the period 1971–1980, the mortality has decreased by 50% from 15% to 8% [14]. This was due to a reduction of mortality in prosthetic valves (37% in the earlier period compared to 13% in our series). A recently published study from a community hospital in the same city as the present study reported an in-hospital mortality of 12% with mortality of 8.5% in NVE and 18% in PVE over the past decade [15]. In addition, a recent multicenter study from France reported an overall mortality of 11% [16]. This reduction in mortality is multifactorial. Improved diagnostic techniques and the earlier recognition of complications with the use of TEE may be important factors. In addition, surgical techniques and outcomes have improved in general, and the latter was comparable to that in the medically treated patients in our series.

A limitation of the present study is its retrospective nature. Due to some missing data in two clinical parameters, these were excluded from the multivariate analysis. Nonetheless, we had nearly complete data for the majority of clinical and echocardiographic parameters. It is also important to point out that only one patient, with right-sided endocarditis, was an intravenous drug abuser since IV drug abuse is uncommon in Israel. This differs from other series reported in the literature and may limit the implications of this study to this specific patient cohort.

The strength of this study is the selection criteria of the patients. Only patients with a definite diagnosis of infective endocarditis were included, therefore the data represent patients with unequivocal endocarditis encountered in a large referral medical center and provide an accurate estimation of the predictors of morbidity and mortality in our cohort.

Conclusions

The mortality rate from infective endocarditis has decreased in the last decade. Mortality is higher in older hospitalized patients undergoing invasive procedures. S. *aureus* is a determinant of poor outcome, associated with abscess formation and a higher mortality rate. Vegetation presence and size are the most important predictors of embolic events and in-hospital mortality.

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