International Journal of Infectious Diseases 14 (2010) e394–e398

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Profile of infective endocarditis at a tertiary care center in Brazil during a seven-year period: prognostic factors and in-hospital outcome

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ARTICLE INFO

Article history:
Received 15 January 2009
Received in revised form 15 April 2009
Accepted 19 June 2009

Corresponding Editor: Andy I.M. Hoepelman, Utrecht, the Netherlands

Keywords:
Infective endocarditis
Echocardiography
Prognosis

ABSTRACT

Objectives: To describe the epidemiological, clinical, and laboratory profile of infective endocarditis (IE) at a Brazilian tertiary care center, and to identify the predictors of in-hospital mortality.
Methods: Data from 62 patients who fulfilled the modified Duke's criteria for IE during a seven-year period were gathered prospectively. The Cox proportional hazards model was used to identify predictive factors for death.
Results: The mean age of patients was 45 years, and 39 patients (63%) were male. The median time from admission to diagnosis was 15 days. Rheumatic heart disease was the predominant underlying heart condition (39%), followed by valvular prosthesis (31%). Neurological complications were observed in 12 patients (19%). Echocardiography demonstrated one or more vegetations in 84% of cases. The infective agent was identified in 65% of cases, and the most frequent causative agents were staphylococci (48%), followed by streptococci (20%). The median duration of hospitalization was 39 days. Surgery was performed during the acute phase of the IE in 53% of cases. The overall in-hospital mortality was 31%. On multivariate analysis, vegetation length >13 mm remained the only independent predictor of in-hospital mortality (hazard ratio 1.05 per millimeter, 95% confidence interval 1.003–1.110, $p = 0.038$).
Conclusions: IE remains a severe disease affecting the young population in Brazil, and rheumatic heart disease continues to be the most common underlying heart condition. Large vegetation size, assessed early in the course of IE by transesophageal echocardiography, along with the clinical and microbiological features, may predict in-hospital death.

1. Introduction

In spite of the great advances made in diagnosis and treatment, infective endocarditis (IE) remains a life-threatening condition with a high mortality rate.[1–4] However, its epidemiological characteristics have changed significantly over the past decades.[5,6] In developed countries, the epidemiological features of IE are changing as a result of increasing longevity, new predisposing factors, and the higher frequency of nosocomial cases.[5–7] Information on the profile of IE in developing countries is relatively scarce,[8] but differences have been reported.[9,10] This fact emphasizes the necessity of carrying out regional studies in order to describe the local characteristics of this disease, which may help the prevention, diagnosis, and management of this complex condition.

Therefore, we undertook the present study with the aim of describing the clinical manifestations, echocardiographic and laboratory findings, microbiological profile, management strategies, and in-hospital outcome of patients with IE who were admitted to a tertiary care hospital in Brazil over a seven-year period.

2. Methods

2.1. Patient population

From June 2001 to July 2008, 62 consecutive adult patients with definite ($n = 49$) or possible ($n = 13$) IE according to the modified Duke's criteria,[11] who were admitted to the University Hospital, Federal University of Minas Gerais, Belo Horizonte, Brazil, were included in the study. There were no exclusion criteria. Written informed consent was obtained from all patients, as required by the institutional ethics committee. Clinical evaluation, echocardiography, blood cultures, and routine laboratory tests were performed within the first 72 h of admission. For the participants

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doi:10.1016/j.ijid.2009.06.024

who presented repeated episodes of IE, only the first one was taken into account.

2.2. Clinical and laboratory data

In accordance with a detailed protocol, clinical and laboratory parameters were collected prospectively at diagnosis and during hospitalization, until discharge from the hospital.

Briefly, the clinical data recorded were: age, sex, previous heart disease, intravenous drug abuse, HIV infection, diabetes mellitus and other co-morbidities, fever and other constitutional manifestations, peripheral stigmata of IE, splenomegaly, congestive heart failure, stroke, and other embolic events. The antibiotic regimen, aspects related to the surgical approach, and in-hospital outcome were also recorded. Early surgery was defined as valve replacement or repair performed during the course of the antibiotic therapy.

Complete blood count, C-reactive protein (CRP), serum chemistry, and urine analysis comprised the routine laboratory investigations that were recorded.

2.3. Echocardiography

Transthoracic (TTE) and/or transesophageal echocardiography (TEE), as clinically indicated, were performed as previously described.[12] The presence of the following characteristics was investigated: vegetation, abscess, new dehiscence, and new moderate or severe valvular regurgitation. A vegetation was defined as an irregularly shaped echogenic mass attached to a valve or myocardial surface.[13] Measurements of the vegetation length were performed in various planes, and the maximal length was selected. An abscess was defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance.[13] In order to determine the severity of the valvular regurgitation, semiquantitative analysis was performed with the use of color flow Doppler echocardiography.

2.4. Statistical analysis

Data were summarized as the means ± standard deviation (SD), medians and interquartile range, or proportions. The primary outcome selected was in-hospital death. Baseline clinical, echocardiographic, and microbiological variables were tested as potential predictors of in-hospital mortality. Variables associated with a *p*-value of <0.10 under univariate analysis were included in a Cox proportional hazards model in order to identify independent characteristics associated with in-hospital death.

In order to investigate the association between the microorganism and in-hospital mortality from IE, the patients infected with *Staphylococcus aureus* were compared with a second group, which included all the other microbiological etiologies and culture-negative IE cases.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value of vegetation length that best predicted the end-point. A cumulative survival curve for the occurrence of in-hospital death was performed by the Kaplan–Meier method and tested by the log-rank test. Values of $p < 0.05$ were considered significant. The analyses were performed using SPSS statistical software (version 13.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical characteristics on admission

Baseline clinical features are shown in Table 1. The mean age of patients was 45 ± 17 years (range 15–76 years), and 39 patients (63%) were male. The median time between onset of symptoms and diagnosis of IE was 15 days (interquartile range 7–60 days; total range 1–210 days). The portal of entry and source of the bacteremia was identified in 25 patients (40%); dental procedures predominated (16%), followed by cutaneous infections (6%).

Table 1
Patient baseline characteristics

Age (years), mean ± standard deviation	45 ± 17
Male, *n* (%)	39 (63%)
Duration of symptoms before diagnosis (days), median (range)	15 (1–210)
Site of infection	
Left-sided endocarditis, *n* (%)	
Native mitral valve	14 (23%)
Native aortic valve	10 (16%)
Native mitro-aortic valves	2 (3%)
Prosthetic mitral valve[a]	10 (16%)
Prosthetic aortic valve	3 (5%)
Prosthetic mitro-aortic valves	6 (10%)
Right-sided endocarditis, *n* (%)	
Tricuspid valve	3 (5%)
Pacemaker and ICD	12 (19%)
Other[b]	2 (3%)
Previous infective endocarditis,[c] *n* (%)	14 (23%)
Rheumatic heart disease, *n* (%)	25 (40%)
Diabetes mellitus, *n* (%)	5 (8%)
Drugs use, *n* (%)	5 (8%)
Renal failure, *n* (%)	6 (10%)
Neurological complications, *n* (%)	12 (19%)

ICD, implantable cardioverter-defibrillator.
[a] Biological and mechanical prostheses.
[b] Central venous catheters and hemodialysis.
[c] Including 24 patients with rheumatic diseases, 19 with prosthetic valve, nine with mitral valve prolapse, seven with congenital heart diseases, and four with degenerative valve diseases.

Fever was the most common symptom (80%) at the initial evaluation. Other observed symptoms were anorexia (62%), weight loss (46%), night sweats (34%), and myalgia (12%). Neurological complications were present in 12 patients (19%); nine of them were embolic events. The other sites of embolization were the spleen (three cases), peripheral arteries (three cases), and kidney (two cases).

Physical examination revealed a systolic murmur in 49 patients (79%), and manifestations of heart failure were observed in 22 (35%). Other physical findings related to the IE included: Janeway lesions (four cases), petechiae (one case), and Osler's nodes (one case).

The most common underlying heart disease was rheumatic valvular disease, which was responsible for 39% of the cases of IE, followed by valvular prosthesis (31%), and devices such as pacemaker and implantable cardioverter-defibrillator (19%). The mitral valve was the most frequently involved, affecting 48% of cases, followed by the aortic and tricuspid valves, which affected 21% and 5% of the cases, respectively. The site of infection could not be identified in two cases. Anemia was present in 86% of the patients, and the inflammatory parameters were constantly elevated.

A pathogenic microorganism was isolated from blood cultures in 40 cases (65%). The frequencies of the causative agents are shown in Table 2. Staphylococci were the most common causative organisms (48%), followed by streptococci, which were identified in 20% of cases. Community-acquired methicillin-resistant *S. aureus* was found in 13 patients (32%) and coagulase-negative staphylococci in 15%. The next most common etiologic agents were enterococci (15%). Other pathogens including fungi accounted for 17% of the cases. Culture-negative endocarditis occurred in 22 patients (35%). Persistently negative blood cultures occurred as commonly in the patients who received antibiotics prior to the diagnosis of IE as in those who did not ($p = 0.666$).

Table 2
Etiologic agents of infective endocarditis

Microorganisms	Episodes, number (%)
Streptococci (viridans, pyogenes)	8 (20%)
Staphylococci	
Staphylococcus aureus	13 (32%)
Coagulase-negative staphylococci	6 (15%)
Enterococci	6 (15%)
Fungi	2 (5%)
Other[a]	5 (13%)
Negative-blood cultures[b]	22 (35%)

[a] Including HACEK group (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella; $n = 2$), *Escherichia coli* ($n = 1$), and polymicrobial ($n = 2$).
[b] Definite infective endocarditis diagnosis using the clinical Duke's criteria: one major and three minor criteria or five minor criteria.

3.2. Echocardiographic findings

TTE was performed in 19 (31%) cases and TEE in 43 (69%). The echocardiographic findings, specified according to the Duke's criteria, are shown in Table 1. A vegetation was evident in 84% of the cases, and the majority of these were attached to a cardiac valve (89%). Among the patients who died during hospitalization, aortic or mitral valve vegetations were observed in 58% and right-sided vegetations in 31% of the cases. The localization of the vegetations did not predict mortality ($p = 0.750$).

Echocardiographic evidence of prosthetic valve dehiscence or intracardiac abscess (Figure 1) was apparent in only a few cases (six and three cases, respectively). New moderate or severe regurgitation was observed in 20% of the cases, and its frequency was similar between patients who survived and those who died in hospital ($p = 0.697$).

3.3. Follow-up during antibiotic therapy

The mean (± SD) duration of hospital stay was 41 (± 30) days and the median (interquartile range) duration of hospital stay was 39 (24–53) days, with a total range of 1–179 days. During this period, 19 patients died, corresponding to an overall mortality of 31%. Early surgery was performed in 33 cases (53%) with a mean time from admission to operation of 2 weeks. The indications for these operations were: congestive heart failure (17 patients (27%)), persistent signs of septicemia despite antibiotic treatment (14 patients (22%)), and recurrent embolization (two patients (3%)). Patients with device-associated IE had the device removed after a week of antibiotic treatment. In-hospital mortality rates were not significantly different between the group of patients who underwent cardiac surgery and those who did not (31% and 29%, respectively; $p = 0.867$). The principal causes of death were severe heart failure, multiorgan failure, and septic shock.

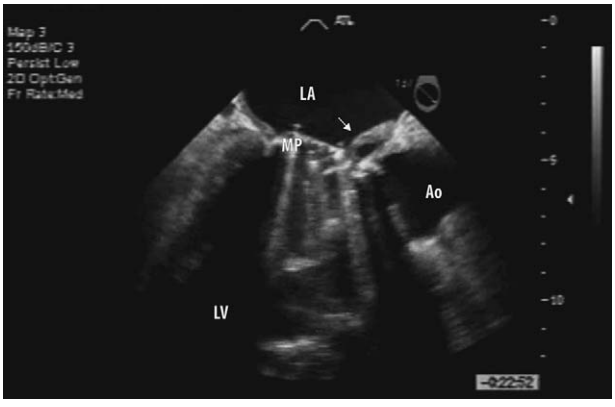

Figure 1. Transesophageal long-axis view showing a small abscess at the mitral–aortic intervalvular fibrosa. The abscess is the abnormal echolucent area within the intervalvular fibrosa.

Table 3
Univariate predictors of in-hospital mortality

Variables	Hazard ratio	(95% confidence interval)	*p*-Value
Age (years)	0.985	0.957–1.013	0.297
Rheumatic heart disease	1.217	0.442–3.353	0.704
Cardiac device-related	0.627	0.204–1.928	0.415
Cardiac surgery	0.837	0.303–2.312	0.731
Prosthetic valve IE	1.932	0.628–5.942	0.251
Heart failure	1.113	0.493–2.511	0.796
C-reactive protein (mg/l)[a]	1.004	1.000–1.008	0.035
Leukocytes (cells/μl)[b]	1.874	1.061–3.310	0.030
Negative blood culture results	1.386	0.510–3.767	0.522
Staphylococcus aureus	3.393	1.110–10.372	0.032
Neurologic events	0.636	0.243–1.664	0.357
Abscesses	2.029	0.486–8.478	0.332
Vegetation length (mm)	1.055	1.003–1.110	0.038
Vegetation extent[c]	2.830	1.025–7.817	0.045

[a] Serum level at admission; the reference value was less than 5 mg/l.
[b] Quartiles of the leukocytosis.
[c] Single versus multiple on a single leaflet, multiple leaflets or extending to extravalvular structures.

Factors affecting mortality in the univariate analysis were: *S. aureus* infection, high CRP levels, high white blood cell count, long vegetation length, and multivalvular involvement (Table 3). After adjusting for age, presence of abscess, multivalvular involvement, and *S. aureus* infection, vegetation length remained as the only independent predictor of in-hospital mortality on multivariate analysis (hazard ratio (HR) 1.05 per millimeter, 95% confidence interval (CI) 1.003–1.110, $p = 0.038$). According to the ROC curve, vegetation length >13 mm is associated with the best predictive value, with a sensitivity of 88% and specificity of 75% (area under the curve: 0.797) (Figure 2). A Kaplan–Meier curve was constructed using the 13 mm-vegetation length as the cut-off value (Figure 3).

4. Discussion

The present study provides several important insights into IE in the current era at a referral hospital in a developing country.

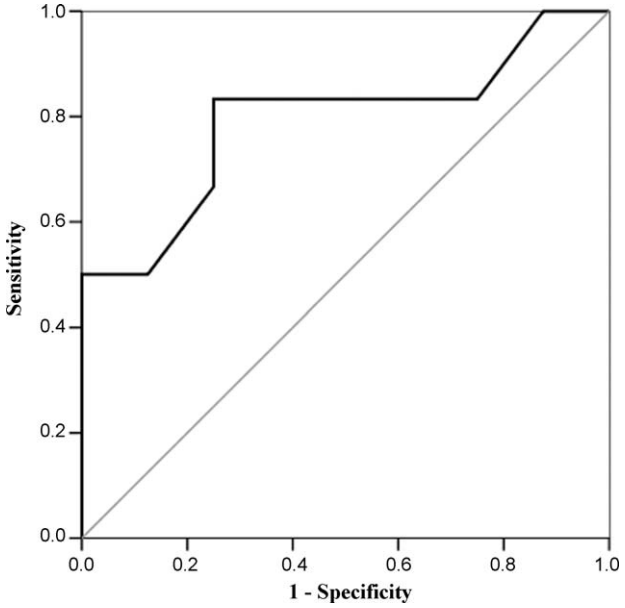

Figure 2. Receiver operating characteristics (ROC) curves for vegetation length at diagnosis of infective endocarditis.

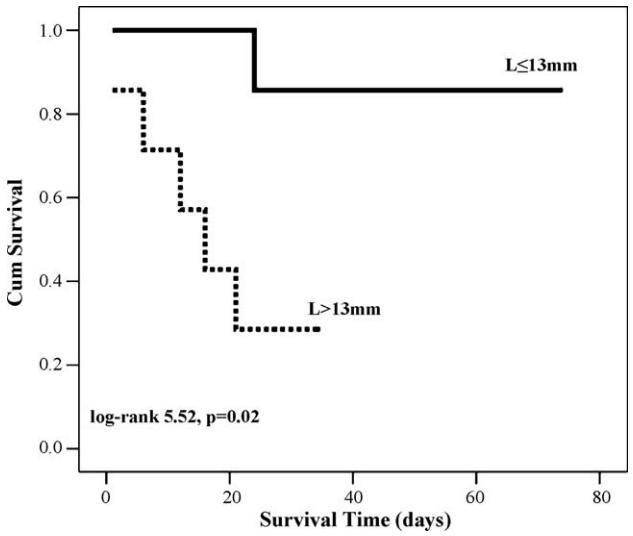

Figure 3. Kaplan–Meier curves demonstrating in-hospital survival according to vegetation length.

Despite advances in diagnostic imaging methods, blood culture techniques, antibiotic therapy, and the surgical approach, IE is still associated with a severe outcome. The overall in-hospital mortality rates for both native valve and prosthetic valve IE remain high.[1–4,14] In our study, the in-hospital mortality was 31%, which is slightly higher than that observed in other countries,[4,7,15–18] including some developing countries.[8,19] We hypothesize that this difference could be explained, at least in part, by the high risk profile of the patients admitted to our institution, such as cases of late diagnosis, which already have complications at admission, the high prevalence of patients with valve prostheses, and the high proportion of IE involving staphylococci. It is well known that the clinical features of IE substantially differ between patients from referral centers and those seen in primary-care centers.[20,21]

According to our study, rheumatic valvular disease remains the most common underlying heart disease. As a result, our patients were younger, which is consistent with previously published studies from developing countries.[9,18,19] In contrast, literature data have demonstrated a gradual increase in the mean age of IE patients in developed countries,[8,22,23] which is largely attributed to both the high prevalence of undiagnosed degenerative valve disease[4] and the increased use of invasive procedures and implanted medical devices.[22] Similar to the results of other studies, men were found to be affected more often than women (male:female ratio, 1.7:1).[14]

Our results confirm many of the clinical features of IE occurring in other parts of the world. For example, most of our cases involved native valves, and the mitral valve was the most frequently affected, followed by the aortic valve. Fever was the most common presenting feature in our cohort, as observed by others.[9,14,18,19] As described previously, in most of our cases some clinical manifestations were present for weeks before the diagnosis. Other investigators have reported an even more prolonged duration of symptoms.[24] The long duration of hospitalization in our series is similar to that reported in other studies,[17] and denotes the important cost burden. Peripheral manifestations of IE have been decreasing as a result of early diagnosis and therapy.[4]

In our study cohort, valve surgery was carried out in a large proportion of patients during antibiotic therapy, which is in accordance with the new trends in IE treatment, i.e., early valve surgery.[7,17,19] However, the frequency of surgery in our series was considerably higher than that reported in some recent studies from other parts of the world.[8,9] These numbers reflect not only a good adherence to modern care standards, aiming to further integrate surgery in the initial management strategy of IE, but also the particular severity in our patients. Although the highest risk patients are those who are generally referred for surgical intervention, surgery was not found to be associated with mortality in our investigation. Further studies are needed to evaluate whether early surgical intervention for patients at higher risk of death will improve outcome.[16]

The proportion of negative blood cultures was high in our series at 35%, which is far beyond the 10% rates reported in recent publications.[8,17] The prevalence of culture-negative IE is more frequent in developing contries.[9,10,25,26] This fact has been ascribed to three major reasons: previous administration of antimicrobial agents, inadequate microbiological techniques, and infection with highly fastidious bacteria or non-bacterial pathogens.[25,26] Although the use of antibiotics without prescription is a common practice in Brazil, our results suggest that this fact did not play a major role in the high rate of negative blood cultures in our study; however, it is not possible to completely rule out this possibility in some of our cases. The culture technique, volume of blood, number of blood cultures, and meticulous care in obtaining the blood are important determinants of the accuracy of blood culture results. Although a standard blood culture system is used at our institution, we cannot entirely exclude the possibility of some oversights, such as a prolonged specimen transport time. Finally, fastidious microorganisms were probably responsible for some negative blood cultures in our series.

As reported recently, staphylococcal species have emerged, along with streptococci, as the major causative microorganisms.[7,17,21] An acceptable explanation for this could be the increasing access to medical facilities and the expanding use of invasive procedures in Brazil, favored by economic development.

Prosthetic valve endocarditis has accounted for 7–25% of cases of IE in most developed countries.[14] In our study, the frequency of IE involving prosthetic valves was around 30%, probably reflecting an increase in surgical treatment of rheumatic valvular heart disease. Prosthetic valve endocarditis accounted for over 20% of all IE cases in a recent prospective, multicenter, international registry,[7] reflecting a considerably higher proportion in comparison with reports from the last decade,[27] but similar to the findings of a one-year survey of IE in France, which was published five years before.[17] Altogether these data point towards a progressive increase in the frequency of prosthetic valve endocarditis. In addition, the high sensitivity of TEE probably enhanced the detection of prosthetic valve endocarditis in our series.

The in-hospital mortality and early surgical intervention rates were similar for native valve and prosthetic valve IE in our investigation. Although prosthetic valve IE is associated with a very high mortality rate, only five of our patients presented early-prosthetic valve IE, which is caused by more virulent organisms and has a worse outcome.

Some studies have attempted to evaluate the prognostic role of echocardiography in IE, focusing on the association between vegetation size and risk of embolic events.[16,28,29] However, the relationship between echocardiographic findings and survival remains undefined. The specific echocardiographic findings of the Duke's criteria assessed early in the course of IE were not predictive of in-hospital death in the study by Chu et al.[15] These results suggest that echocardiography may have greater diagnostic utility than prognostic significance in early IE. One challenging aspect of this disease is the dynamic nature of its clinical and echocardiographic findings during the active phase.

Interestingly, we found, in the multivariate analysis, that vegetation length >13 mm was a predictor of in-hospital death, even after adjustment for the other predictors. Older series failed to demonstrate a prognostic value of the presence and/or size of the vegetation, probably because of both the small number of

patients studied and the use of TTE only.[12] However, our results are in agreement with the recent prospective multicenter study by Thuny et al.,[16] which showed a direct relationship between the size of the vegetation and mortality. Moreover, the results of that study demonstrated that large vegetations (>10 mm) and/or high vegetation mobility were associated with an increased embolic risk. Similarly, with the systematic use of TEE, Hill et al.[29] observed that vegetation length >10 mm was independently associated with six-month mortality. Thus, our findings and the above literature data suggest that echocardiography, performed early in the course of IE, may have a prognostic value. Along with baseline clinical and microbiological features, the assessment of vegetation characteristics may contribute to the identification of those patients who are at high risk of death. However, these aspects need further investigation.

4.1. Study limitations

Our study group was relatively small and included patients from a single large tertiary-care center, to which many patients with IE were referred from other hospitals. These facts may have caused selection bias resulting in limitations to the generalization of the results. TEE was performed in 69% of the cohort; more frequent use of this method could have influenced the results related to the echocardiographic findings and their association with outcome. Furthermore, the small sample size could have exerted some influence on the results of the multivariate analysis. Thus, studies including a larger number of events are necessary to confirm (or not) our findings regarding the independent predictors of in-hospital death.

4.2. Conclusions

Our study demonstrates that IE remains a severe disease affecting a young population in Brazil, and is associated with high in-hospital mortality. Rheumatic heart disease continues to be the most common underlying heart condition. Survival was similar for patients with native valve or prosthetic valve IE, and also for patients who underwent early surgery or did not. Specific echocardiographic findings, particularly the vegetation size, assessed early in the course of IE, along with clinical and microbiological features, may predict in-hospital death. Recognition of these factors could improve risk stratification and, therefore, the selection of patients for more intensive treatment.

Conflict of interest: We declare that we have no conflicts of interest.

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