ORIGINAL ARTICLE

Analysis of infectious endocarditis cases in a tertiary hospital

Análise dos casos de endocardite infecciosa em um hospital terciário

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ABSTRACT

Introduction and objective: infectious endocarditis (IE) is a disease with high morbidity and mortality despite improvements in diagnosis and antimicrobial therapy. The early identification of patients at high risk of death or complications can improve the outcome of this disease. The objective was to analyze IE cases in a tertiary hospital and their in-hospital outcomes. **Patients and methods:** 93 episodes of IE were retrospectively analyzed in 91 patients, between January of 2001 and December of 2008. The analyzed variables were: clinical and infectious data, therapeutic modality, and outcomes during hospital developments. The statistical analysis employed the Chi-square, odds ratio, and Mann-Whitney tests. **Results:** the in-hospital mortality occurred in 35% (IC 95%; 26-41%), valve prostheses were involved in 60.23% of cases, and blood cultures without isolation occurred in 36.56%. In positive blood cultures, the main etiological agent isolated was Staphylococcus aureus in 31.18%, multi sensitive S. aureus in 22.8%, and S. aureus MARSA in 8.6%. Surgical intervention was performed in 48.39% of the patients and the main surgical indicator was failure of clinical treatment (20.43%) Patients who have had ICC as outcome presented 57.14% mortality (p = 0.004 and OR of 3.76, IC 95%; 1.41-10.03); mortality rate of 66.67% as observed in those with pacemakers as the site of infection. **Conclusions:** IE remains with high morbidity and mortality. Mortality rates vary according to the etiological agent, prior cardiac state, site of infection, and increased age.

Key words: Endocarditis; Hospital Mortality; Risk Factors.

RESUMO

Introdução e objetivos: *a endocardite infecciosa (EI) é uma doença com alta morbimortalidade, apesar do aprimoramento do diagnóstico e da terapia antimicrobiana. A identificação precoce de pacientes com alto risco de morte ou complicações pode melhorar o desfecho dessa doença. O objetivo foi analisar os casos de EI em um hospital terciário e seus desfechos intra-hospitalares.* ***Pacientes e métodos:*** *analisados retrospectivamente 93 episódios confirmados de EI, em 91 pct, no período de janeiro de 2001 a dezembro de 2008. As variáveis analisadas foram: dados clínicos, infecciosos, modalidade terapêutica e desfechos na evolução hospitalar. A análise estatística utilizou teste do qui-quadrado,* Odds Ratio *e teste de* Mann-Whitney. ***Resultados:*** *a mortalidade intra-hospitalar ocorreu em 35% (IC 95%; 26-41%), as próteses valvares foram acometidas em 60,23% dos casos, as hemoculturas sem isolamento ocorreram em 36,56%. Nas hemoculturas positivas, o principal agente etiológico isolado foi o* Staphylococcus aureus *(31,18%), o* S. aureus *multissensivel em 22,8% e o* S. aureus *MARSA em 8,6%. A intervenção cirúrgica foi realizada em 48,39% e o principal indicador cirúrgico foi a falha ao tratamento clínico (20,43%). Pacientes que tiveram a ICC como desfecho apresentaram mortalidade de 57,14% (p= 0,004 e OR de 3,76, IC 95% ; 1,41-10,03) e aqueles com marca-passo como sítio de infecção, mortalidade de 66,67%.* ***Conclusões:*** *a EI permanece com elevada morbimortalidade. A mortalidade*

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difere em relação aos agentes etiológicos, estado cardíaco prévio, sítio de infecção e aumento da idade.

Palavras-chave: Endocardite; Mortalidade Hospitalar; Fatores de Risco.

INTRODUCTION

Infective endocarditis (IE) is a peculiar disease that presents itself under a wide range of initial clinical manifestations depending on the individual characteristics of patients, their underlying cardiac status, micro-organisms involved, and presence or absence of complications.[1]

In the last 30 years, despite the improvement in diagnosis and antimicrobial therapy, there has not been a reduction in its incidence and mortality, remaining as a disease of high morbidity and mortality.[2] Because of its low incidence, the literature only reports case series studies with limited number of meta-analyses and no randomized studies.[3, 4]

The objective of the present study was to analyze IE cases in a tertiary hospital and their in-hospital outcomes.

METHODS

A total of 93 IE confirmed episodes were examined retrospectively in 91 patients, consecutively admitted at the Madre Teresa Hospital, in Belo Horizonte, between January of 2001 and December of 2008. The study was approved by the Research Ethics Committee from the institution according to the Declaration of Helsinki.

The data collection was conducted through a questionnaire previously developed with the following variables: age, time of symptoms until hospitalization, presence or absence of fever, embolic phenomena or cutaneous lesion, possible bacteremia manipulation (PBM) until three months, previous use of antimicrobials between symptoms and hospitalization, site of infection, blood cultures and etiological agents, antimicrobials (AAM) and time of use, previous heart condition, vegetation and/or abscess detected by echocardiogram (ECHO), therapeutic modality, surgical indication, operative finding (vegetation), positive valve culture, surgical procedure, in hospital complications, evolution to death, and laboratory analysis.

When the same patient presented repeated IE episodes caused by the same microorganism within less than six months after the initial episode, the infection was considered recurrent and was not computed as a new episode. The infection by a different microorganism or a repeated IE episode caused by the same organism after six months from the initial diagnosis was considered reinfection and computed as a new episode.

PBMs were of dental origin, cardiac surgery, pacemaker implant (PM), injectable drug use, and vascular access. The following were considered previous heart conditions: valvulopathy, congenital heart disease, cardiac prosthesis, and the absence of heart disease. The therapeutic modality was divided into clinical and surgical clinical. The analyzed surgical indications were: refractory heart failure (RHF), repeated arterial embolisms, progressive renal failure, failed to clinical treatment, and paravalvular abscess. The surgical procedure consisted of valve replacement, vegectomy, or removal of PM electrodes. Infection that occurred in less than 12 months after a surgical intervention was considered a hospital infection.

The occurrence of death was analyzed, and the outcomes during the hospital development were: RHF, cerebrovascular accident (CVA), and acute renal failure (ARF). ARF was based on increases of 0.5 mg/dL in serum creatinine or an increase of 25% compared to the creatinine baseline during hospitalization.

The laboratory data analyzed during hospital evolution and at discharge or death were values of serum creatinine, hemoglobin, leukocytes, mucoprotein, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and platelets. The lowest value during the hospital evolution was considered for platelets, the highest value was considered for all other parameters.

Statistical analyses were performed using the Stata 10 software. The Chi-square test was used for comparisons between two categorical variables. In the case of two still dichotomous variables, the Odds Ratio was also obtained as a measure of the association magnitude. When one of the variables was continuous, the nonparametric Mann-Whitney test was used for comparisons of groups such as, for example, between individuals who evolved or not to death. The significance level $p<0.05$ was considered in all tests.

RESULTS

Out of the 93 analyzed cases, 28 patients (30%) had community infection, and 65 patients (70%) had nosocomial infection.

There was a predominance of males with 53 cases (56.99%), and 40 patients (43.01%) were older than 60

years. Fever occurred in 83 cases (89.25%), blood cultures were positive in 59 cases (63.44%), and 26 patients (27.96%) had made previous use of AAM (Table 1).

Table 1 - Characteristics of the analyzed cases

Data	Number (n= 93)	Proportion (%) 100%	Confid. Interval 95% p/proportion
Sex	53	56.99%	43.74 – 67.25
	40	43.01%	32.76 – 53.26
Age	53	56.99%	43.74 – 67.25
	40	43.01%	32.76 – 53.26
Fever	83	89.25%	82.83 – 95.66
	10	10.75%	4.34 – 17.17
Blood culture*	34	36.56%	26.59 – 46.53
	59	63.44%	53.47 – 73.41
Previous AAM	26	27.96%	18.66 – 37.25
	67	72.04%	62.75 – 81.34

AAM – antimicrobial Confid. interval– confidence interval; * negative blood culture were those without isolation of the etiologic agent.

Physical examination was performed in 25 patients (26.88%); petechia was observed in 5.38%, skin lesions in 3.23%, and embolic phenomena in 18.28% being 10.75% cerebral and 7.53% extra-cerebral.

PBM occurred in 71 cases (65.61%) with a predominance of valve replacement surgeries in 46.24% (Figure 1).

In relation to previous cardiac condition, 56 patients (60.22%) had heart valve prosthesis (Figure 2).

As for the site of infection, valvular prostheses were involved in 57 cases (60.23%), followed by native in 30 cases (33.36%), and PM in six cases (6.45%) (Figure 3).

All patients were submitted to ECHO. The transesophageal echocardiography (TEECHO) was conducted on 79 patients, and vegetation and abscess were visualized in 74 cases (93.67%) and 12 cases (12.90%), respectively.

Blood cultures without microorganism isolation occurred in 34 cases (36.56%) and *Staphylococcus aureus* was the main etiological agent isolated in positive blood cultures in 29 cases (31.18%), with the multi-sensitive *S. aureus* in 21 (22.8%), and MARSA *S. aureus* in eight (8.6%) (Figure 4).

In 29 cases with blood culture positive for *S. aureus*, 11 evolved to death (37.93%). Five out of these 29 showed an infection by MARSA *S. aureus* and six by the multi-sensitive *S. aureus*.

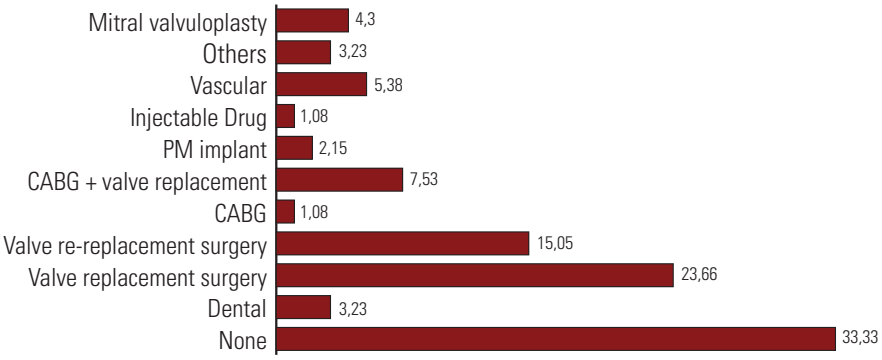

Figure 1 - Possible bacteremia manipulation until three months before symptoms in percentage – % Legend: CABG – coronary artery bypass grafting.

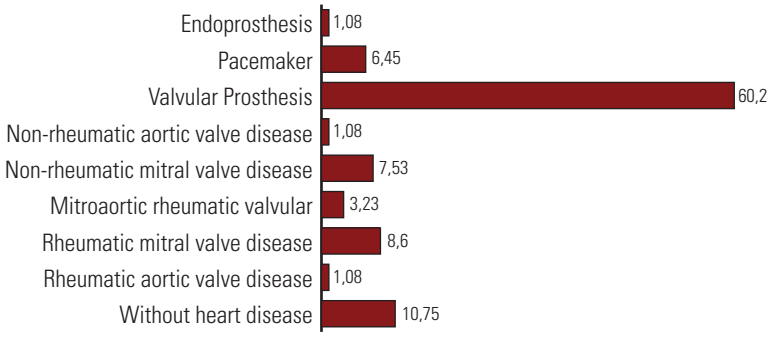

Figure 2 - Cardiac condition before in percentage – %.

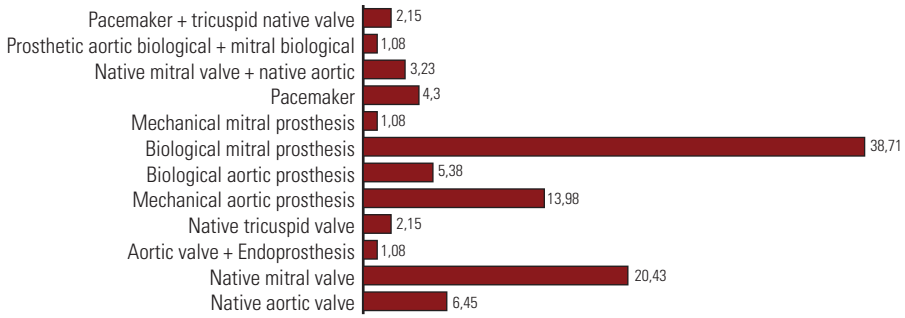

Figure 3 - Localization of the infection site in percentage – %.

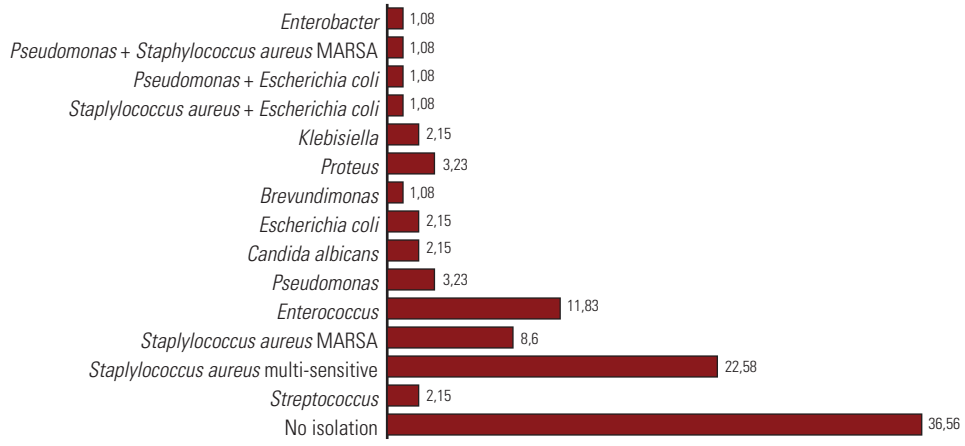

Figure 4 - Etiologic agent isolated in blood culture in percentage – %.
Legend: MARSA – *Staphylococcus aureus* methicillin resistant.

Pseudomonas aeruginosa was isolated in 3.23% and *Candida albicans* in 2.15%. The presence of these two etiological agents was associated with 100% mortality.

Surgery was performed in 45 cases (48.39%) and the surgical indicators were: refractory RHF in 16.13%, clinical treatment failure in 20.43%, arterial embolisms in 3.23%, and paravalvular abscess in 1.08%. In this group of patients, mortality was the outcome in 19 cases (42.22%)

In the analyzed outcomes, ARF was detected in 30 cases (32.26%), RHF in 28 (30.8%), and CVA in eight (8.60%).

Death occurred in 33 cases (35.48%), IC 95%; 26%-41%. In this group the patients, those aged ≥ 60 years showed higher mortality rates, 50% (p = 0.01 and 3.08 OR; IC 95%, 1.23 to 7.71); those with RHF as outcome, 57.14% mortality (p = 0.004 and 3.76 OR, IC 95%; 1.41-10.03); and those with the pacemaker as the site of infection, mortality of 66.67%.

The laboratory data that showed a relationship with mortality were: elevation of serum creatinine, elevated CRP and leucocytes, and reduction in platelet counts (Table 2).

Table 2 - Analysis of continuous variables and relation to in-hospital death

	In-hospital deaths		
	No Median	Yes Median	p-value (Mann-Whitney)
Age	50	64	0.0035
Creatinine	1	1.2	0.0299
Platelets	195500	152000	0.0430
CRP	48	107.5	0.0014
ESR	85	85	0.5763
Leukocytes	9700	11400	0.0234
Hemoglobin	11.05	11.1	0.8096

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

The following factors had no relationship with mortality: gender, vegetation and ECHO abscess, embolic phenomena (p = 0.044 and 2.6 OR, IC 95%; 0.99 to 6.85), fever (p = 0.3125), positive blood culture (p = 0.353), increased ESR values, reduction in hemoglobin, and ARF as the complication (p = 0.043 and OR = 2.59, IC 95%; 0.99 to 6.31) (Tables 2 and 3).

Table 3 - Univariate analysis per death

Data	In-hospital deaths n (%)		Total (n)	p-value	*Odds-ratio*	Conf. Interval 95%
	No	Yes				
Males	32(60.38)	21(39.62)	53	0.3396	1.53	0.63-3.7
Age ≥ 60 years	20(50.00)	20(50.00)	40	0.01	3.08	1.23-7.71
No fever	5(50.00)	5(50.00)	10	0.3125	1.95	0.52-7.46
Positive blood culture	36(61.02)	23(38.98)	59	0.353	1.53	0.62-3.82
No vegetation at TEECHO	3(60.00)	2(40.00)	5	0.826	1.23	0.19-7.94
ECHO abscess	7(58.33)	5(41.67)	12	0.631	1.35	0.39-4.69
Surgical clinic tto.	26(57.78)	19(42.22)	45	0.189	1.77	0.74-4.24
ARF complic.	15(50)	15(50)	30	0.043	2.59	0.99-6.31
RHF complic.	12(42.86)	16(57.14)	28	0.004	3.76	1.41-10.03
CVA complic.	4(50.00)	4(50.00)	8	0.369	1.93	0.44-8.41

TEECHO: transesophageal echocardiogram; ECHO: echocardiogram; tto.: treatment; ARF complic.: acute renal failure as the complication; RHF complic.: refractory heart failure as the complication; CVA complic.: cerebrovascular accident as the complication.

Among the studied patients, 50 (43.01%) presented age ≥ 60 years, median age of 72 years, and mortality occurred in 20 cases in this group (50%).

DISCUSSION

IE is a disease with high morbidity and mortality despite improvements in diagnosis and drug therapies. In-hospital mortality rates range from 9.6 to 26% and differs considerably from patient to patient.[1,5] The early identification of patients at high risk of death and complications can improve the disease outcome.

In this study, a high number of nosocomial infections were observed (65 patients – 70%). It should be noted that our service is a tertiary non-pediatric hospital that belongs to the referential network of the Unified Health System (SUS) for complex surgeries and receives patients transferred from other institutions.

Blood cultures were negative in 34 cases (36.56%) and 26 patients out of the total group (27.96%) made previous use of AAM, which may have elevated the number of negative blood cultures found. Negative blood cultures occur around 2.5 to 31% of all cases of IE reported in the literature with delay in diagnosis and early treatment and impact on clinical outcomes.[6]

Literature data report *Staphylococcus aureus* as the microorganism associated with an increase in rates of complications and mortality,[7] and its involvement into valvular prostheses presents mortality rates > 45%, requiring early valve replacement in most cases.[8] In our material, the primary isolated etiological agent was *S. aureus* in 29 cases (31.18%). Its presence was associated with a mortality rate of 37.93%.

Surgery was performed in 45 cases (48.39%). Of these, 16 presented negative blood cultures and 29 presented positive blood cultures. In the positive blood cultures, *S. aureus* occurred in 17 cases (three with MARSA and 14 with multi-sensitive), followed by *Pseudomonas aeruginosa* with three cases, and *Candida albicans*, *Proteus sp.*, *Enterecoccus sp.*, and *Streptococcus sp.* with two cases each. *Brevundimonas* was isolated in one case.

The analysis of the surgical group showed that 19 cases evolved to death (42.22%). Of these, negative blood culture was present in seven cases (36.84%), infection by *S. aureus* in five patients (26.31%), and all who showed infection by *Pseudomonas aeruginosa* and *Candida albicans* evolved to death.

PM as the site of infection occurred in six cases (6.45%) and four of these patients (66.67%) evolved to death. This group of patients had peculiar characteristics, with difficult diagnosis and therapeutics and high mortality rate.[5] In these patients, the Duke criteria presented low sensitivity, making the diagnosis more difficult.[9]

In our material, age ≥ 60 years was present in 40 cases (43.01%) and, in this group, 20 episodes (50%) ended in deaths. This group of patients has the most severe clinical course with insidious symptoms, delayed diagnosis, and a high incidence of more aggressive pathogens. These patients have high preoperative risk related to age and comorbidities. Advanced age is associated with a worse prognosis in most studies.[10, 11]

In the analysis of outcomes, embolic phenomena occurred in 18.28% and ARF in 27.96% as a complication. Studies identify these events as predictors of mortality. [1, 12] In our material, its occurrence was not associated with in-hospital mortality.

In the group of patients that have evolved to death, 57.14% had RHF as the outcome and RHF was the indication in 16.13% in the surgical intervention group. RHF in IE is caused by a problem in the valve and requires surgical intervention, as well as perivalvular abscess. Studies show that patients with these characteristics have a high risk of mortality and should be submitted to surgery in the acute phase of the disease.[13]

The laboratory parameters examined that were associated with in-hospital mortality were serum creatinine, with median of 1.2 mg/dL (p = 0.0299); thrombocytopenia, with median of 152,000 (p = 0.043); CRP, with median of 107.5 (p = 0.0014); and leukocytosis, with median of 11,400 (p = 0.0234).

Several studies have shown that leukopenia or leukocytosis implies worse IE prognosis.[14, 15] The magnitude of inflammation reflects a systemic response to infection and suggests that IE can be considered an infection of the whole organism.[16]

Thrombocytopenia during IE infection indicates damage to host's response to sepsis and predicts increased mortality.[17] A strong association between thrombocytopenia and infection by *Staphylococcus aureus* has also been found in this study.

It should be emphasized that, because this is a retrospective study, it is possible that not all complications that occurred during the in-hospital evolution have been reported. In addition, this is a convenience sample of patients admitted in a single center, with a diagnosis of infective endocarditis.

CONCLUSION

IE remains with high morbidity and mortality, and these rate differs according to etiological agents, prior cardiac conditions, sites of infection, and increasing age.

The predominance of nosocomial infection (70%) and high mortality rate (35%) were observed in our material.

We highlight that our service is a tertiary non-pediatric hospital that belongs to referential network of the Unified Health System (SUS) for complex surgeries and receives patients transferred from other institutions.

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