Infective endocarditis profile, prognostic factors and in-hospital mortality: six-year trends from a tertiary university center in South America

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Abstract

Background: Infective endocarditis (IE) remains an expressive health problem with high morbimortali-ty rates. Despite its importance, epidemiological and microbiological data remain scarce, especially in developing countries. Aim: This study aims to describe IE epidemiological, clinical, and microbiological profile in a tertiary university center in South America, and to identify in-hospital mortality rate and predictors. Methods: Observational, retrospective study of 167 patients, who fulfilled modified Duke's criteria during a six-year enrollment period, from January 2010 to December 2015. Primary outcome was defined as in-hospital mortality analyzed according to treatment received (clinical vs. surgical). Multivari-ate analysis identified mortality predictors. Results: Median age was 60years (Q1-Q3 50-71), and 66% were male. Echocardiogram demonstrated vegetations in 90.4%. An infective agent was identified in 76.6%, being Staphylococcus aureus (19%), Enterococcus (12%), Coagulase-negative staphylococci (10%), and Streptococcus viridans (9.6%) the most prevalent. Overall in-hospital mortality was 41.9%, varying from 49.4% to 34.1%, in clinical and surgical patients, respectively (p=0.047). On multivariate analysis, diabetes mellitus (OR 2.5), previous structural heart disease (OR 3.1), and mitral valve infection (OR 2.1) were all-cause death predictors. Surgical treatment was the only variable related to better outcome (OR 0.45; 95%IC 0.2-0.9). Conclusion: This study presents IE profile and all-cause mortality in a large patient's cohort, compris-ing a 6-years' time window, a rare initiative in developing countries. Elderly and male patients predom-inated, while Staphylococcus aureus was the main microbiological agent. Patients conservatively treated presented higher mortality than surgically managed ones. Epidemiological studies from developing countries are essential to increase IE understanding.

Introduction

Despite substantial improvements in diagnostic accuracy, medical therapy and surgical techniques, infective endocarditis (IE) remains a high-lethality disease, with an incidence that has not changed in the last two decades [1].

Several studies have evaluated IE epidemiological characteristics and morbimortality data in developed countries. Nonetheless, significant differences in epidemiological and microbiological aspects are evident when developed and developing countries are compared[2-3]. In the setting of developing countries, EI epidemiological studies remain scarce, even known that these data would contribute to IE prevention, diagnosis, and treatment.

A particularly debated issue in IE management is the best time to indicate an intervention since about 30% of patients will be submitted to a cardiac surgery [4]. Historically, it was sought to avoid surgery during the

active phase, due to high postoperative mortality and valve dysfunction risk [5]. However, a new trend is performing earlier operations. Kang et al., for instance, demonstrated that surgery performed within the first 48 hours was associated with a significant reduction in in-hospital mortality and 6-weeks embolic events compared to surgery at any hospitalization time (3% vs. 23%) [6].

Based on these aspects, the present study aims to describe IE epidemiological, clinical and microbiological profiles in a tertiary university center in South America, in order to identify in-hospital mortality predictors and to compare patient's outcomes, based on whether or not they have undergone cardiac surgery.

Materials and Methods

Retrospective cohort of 167 consecutive patients who received an IE diagnosis, according to Duke's modified criteria, from January 2010 to December 2015, in a Brazilian tertiary university hospital. There were no exclusion criteria.

Primary endpoint was all-cause in-hospital mortality, defined as any death occurred during the index hospitalization, regardless of hospital length of stay. This outcome was analyzed according to the treatment received, clinical vs. surgical. Data from medical records were collected and reviewed by two independent reviewers. In case of disagreement, a third review was performed.

Descriptive data were expressed as mean ± standard deviation (SD) or median and interquartile range (Q_1-Q_3). Statistical analyses were performed using the statistical package SPSS (version 18.0; SPSS Inc, Chigaco, IL, USA). Categorical variables were analyzed using Chi-square Test, while continuous variables were analyzed using Student's T-test or Mann-Whitney U test, according to the distribution pattern. Logistic regression was used for univariate analyses. Multivariate analysis model was proceeded to identify independent predictors of mortality. A two-sided p -value lower than 0.05 was considered significant for all analyses. This study was reviewed and approved by the institution's research ethics committee (CAAE:40755515900005327).

Results

Epidemiological, Clinical, and Microbiological Features

Clinical and epidemiological aspects from the 167 patients who fulfilled the Duke's criteria are described in Table 1. The median age was 60 years (Q_1-Q_3 50-71), and 66% were male. Previous structural heart disease was present in 34%, and 31% of patients had already been submitted to a cardiac surgery. The most prevalent comorbidities were arterial hypertension (56%), diabetes mellitus (29%), chronic kidney disease (21%), previous stroke (12%), chronic liver disease (6.6%), and chronic obstructive pulmonary disease (6%).

The median time from symptoms onset to hospital admission was 7 (Q_1-Q_3 3-10) days, and from hospital admission to definitive diagnosis 4 (Q_1-Q_3 1-7) days.

Fever was the most incident symptom at the time of hospital admission (84.3%), followed by decompensated heart failure (25.7%), and a new cerebral or peripheral embolic event (18% and 21%, respectively). New cardiac murmur was observed in 39.5% of the cases (Table 2).

Echocardiographic evaluation demonstrated the presence of one or more vegetations in 90.4%, and abscess in 9.6%. The valve most frequently compromised was the aortic valve (54.5%), and the majority of the cases involved native valves (73%) (Table 3).

A specific infective agent was identified in 76.6% of cases, with Staphylococcus aureus (19%), Enterococcus (12%), Coagulase- negative staphylococci (10.2%), and Viridans streptococci (9.6%) being the most microbiological agents (Table 4).

Surgical Data

Surgical treatment was indicated in 82 patients (49.1%) (Figure 1). The most frequent reasons were: decompensated heart failure (n=32, 39%), prevention of embolism (n=24, 29%), uncontrolled infection (n=9,

11%), recurrent emboli despite appropriate antibiotic treatment (n=5, 6.1%). Figure 1 shows the proportion of clinical versus surgical management across the 6 years of study recruitment.

Male sex (OR 3.3, 95% CI 1.3-8.1), chronic kidney disease (OR 3.2, 95% CI 1.2-8.5), valve regurgitation grade [?] 3+ (OR 6.1, 95% CI 2.5-14.6) and the presence of abscess on echocardiogram (OR 5.7, 95% CI 1.1-31) were the independent predictors of need for surgery. Age was the only variable negatively associated with surgical indication (OR 0.97, 95% CI 0.94-0.99) (Table 5).

In the subgroup of patients who underwent a surgical intervention, the average time between definitive diagnosis and procedure was 9 (Q_1-Q_3 4-19) days. Procedural cardiopulmonary bypass and aortic cross-clamp median times were 82 (Q_1-Q_3 58-110) and 62 (Q_1-Q_3 44-83) minutes, respectively.

Morbimortality

The median hospital length of stay was 39 (Q_1-Q_3 30-49) days, varying from 41 (Q_1-Q_3 32-46) days in the clinical group and 38 (Q_1-Q_3 28-53) in the surgical one (p =0.485).

Overall all-cause in-hospital mortality was 41.9%, a rate significantly lower in patients who underwent a surgical procedure compared to those clinically managed (49.4% in clinical vs. 34.1% in surgical group;p =0.047).

On multivariate analysis (Table 6), diabetes mellitus (OR 2.56, 95% CI 1.1-5.9), previous structural heart disease (OR 3.1, 95% CI 1.4-5.9) and mitral valve infection (OR 2.1, 95% CI 1.1-4.5) were the predictors of in-hospital mortality. Surgical treatment was the only variable related to better outcome (OR 0.45; 95% IC 0.2-0.9).

Discussion

Infective endocarditis was first described by Osler, in 1857 as a pathology of patients with a pre-existent valvular disease[7]. Since then, significant progress in disease understanding has been achieved. The majority of large epidemiological studies come, however, from developed countries, with a gap in solid evidence from developing regions.

IE incidence varies from 2 to 6 cases per 100.000 inhabitants/year, a value quite steady over the last decades [1]. This incidence, associated with prolonged hospital length of stay and elevated hospitalization costs, makes IE a real worldwide burden[8].

The present study provides valuable insights into IE in the current era, bringing data from a tertiary hospital in South America, a complex demographic region with huge contrasts and a lack of comprehensive epidemiological reports.

In the present study, we demonstrated that the primary IE causative organisms were Staphylococcus aureus, followed by Enterococcus, Coagulase-negative staphylococci, and Viridans streptococci. These findings are in accordance with the international literature, which demonstrates a significant increase in Staphylococcus aureus prevalence (21% - 30% in the last five decades)[8], representing, currently, the most frequent microbiological agent in high-income health systems. Besides, our results are similar to the ones from other two Brazilian inquiries[9, 10].

The transition in pathogen pattern, from viridans streptococcus to Staphylococcus aureus, has been associated with population-aging, decrease in rheumatic heart disease burden, and advanced device management, particularly in cardiac patients [11, 12]. Precisely because of these factors, this transition was more pronounced in high-income countries; however, as reported in this study, also in less developed regions, Staphylococcus aureus has emerged as the primary IE pathogen.

A common issue in IE studies from developing countries is the high prevalence of negative blood cultures [2]. In our study, blood cultures were negative in 23.3% of cases, a value beyond the 10% reported in recent scientific publications [12, 13], but similar to other developing countries inquiries (10-55%)[9], and even lower than in Asiatic populations (30–65%) [14-16]. Negative cultures are usually related to infections with highly

fastidious bacterial or non-bacterial pathogens, inadequate microbiological technique, or prior administration of antibiotics before the diagnosis of IE [17].

Most of our patients were males (66%) e the majority of the cases were from native valves (73%), a similar pattern than that reported in other studies from developing countries [10, 18-21]. IE has a well-recognized and consistent male predominance, with a reported male: female ratio of 1.2:1 to 2.7:1 [22]. The explanation for the male predominance could be related to the presence of congenital cardiac conditions, such as a bicuspid aortic valve that also has a male predominance [2].

Diverging from other developing countries reports, we observed a median age of 60 years, resembling western countries trends, in which patients age is typically 60 or 70 years old [23]. According to Yew SH et al., increased longevity, decreased rheumatic heart disease incidence, staphylococci predominance, and increased use of invasive procedures and medically implanted devices represent the current IE scenario in developed countries [2]. Taken these features into consideration, our epidemiological and microbiological profiles seem to be closer to those from developed countries instead of developing regions. This pattern is also disclosed when we analyze the most affected valve. While in developing countries, mitral valve involvement predominates, due to a higher prevalence of rheumatic disease [20, 24, 25], in our series, the aortic valve was the most affected (54.5%).

In terms of mortality, despite improvements in diagnostic accuracy, medical therapy, and surgical techniques, IE mortality rate remains relatively high. In our study, we observed an overall in-hospital mortality of 41.9%, meeting other Latin-American reports (46.4% and 31%) [9, 10], but much superior to that described in high-income healthy systems (15 to 22%) [26]. This higher mortality rate may be justified by differences in patients' profile, with a high prevalence of multiple comorbidities, and a delay in reaching medical assistance. In our study, for instance, the average time between symptoms onset and hospital admission was 7 days, resulting in a remarkable diagnosis and intervention delay. Besides, 25% of our patients were admitted on decompensated heart failure and 39% presenting an embolic event.

Another relevant factor is that our study reflects data from a tertiary referral center, which presents an inherent selection and referral bias. As describe by the International Collaboration on Endocarditis – Prospective Cohort Study (ICE-PCS), patients with IE who require surgery and suffer complications (e.g., stroke, heart failure, and new valvular regurgitation) are referred to tertiary hospitals more frequently than those with an uncomplicated course [27], contributing to increase the in-hospital mortality in referral centers.

In this same line, analyzing IE incidence and mortality in the Veneto Region (Italy) from 2000 to 2008, Fedeli U et al. observed an increase in 36-day mortality from 24.6 % (2000-2002) to 31.5 % (2006-2008), which was, at least partially, attributed to a growing number of the elderly patients (median age was 68 years) [28].

According to the present study, diabetes mellitus, previous structural heart disease, and mitral valve infection were the independent predictors of in-hospital mortality, while patients submitted to surgical treatment had 55% less chance of dying than those handled just with clinical treatment. This finding follows the new trends in IE treatment, which suggests that early valve surgery will result in better outcomes. Liang et al., for instance, conducted a meta-analysis revealing that, compared with non-early surgery, early surgery was associated with reduced in-hospital (OR 0.57) and long-term mortality incidence (OR 0.57) [26].

Last but not least, 49% of our patients received a cardiac surgical intervention, which fits the rate reported in the current IE European guideline (40–50%). This guideline also reinforces that despite early surgery is indicated to avoid progressive HF, irreversible structural damage and to prevent systemic embolism, it is associated with significantly higher risk. Therefore, surgical indication would be justified in patients with high-risk features that make the possibility of cure with antibiotic treatment unlikely, and who do not have comorbid conditions or complications that make the prospect of recovery remote[29].

Unfortunately, the present cohort had not enough power to compare those patients that were submitted to an early intervention versus those that had more delayed surgery. However, our study adds evidence in the

assumption that surgically treated patients have better outcomes than those clinically managed.

The major limitation of our study is its retrospective and single-center design, enrolling patients from a tertiary-care center, which could not represent the profile of entire South American health system. On the other hand, one of the major highlights of our study is that this is one of the largest cohorts of patients from Latin America and the largest in Brazil. It is also important to highlight that the description of temporal trends and associations does not provide evidence of causality. Despite a long-term enrollment period, this study focuses on short-term results. Properly designed trials with long-term follow-up are required to confirm the impact and trends in IE.

Conclusion

This study presents the IE profile and all-cause mortality analyses in a large patient's cohort, comprising a 6-years' time window, which represents a rare initiative in developing countries. Elderly and male patients predominated, while Staphylococcus aureus was the main microbiological agent.

In this cohort, patients conservatively treated presented higher mortality than surgically managed ones. The high mortality rate observed corroborates the impact of IE studies since they provide a better understanding of epidemiological and microbiological characteristics associated with poorer outcomes, thus, leading us to the development of strategies to improve them. We believe that further studies, if possible randomized studies, will demonstrate the superiority of early surgical procedures.

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Table 1. Baseline Characteristics

Preoperative Variable	Total N= 167	Clinical N=85	Surgical N=82	*P-value*
Age – years Median (Q_1-Q_3)	60 (50-71)	65 (54-74)	57 (46-68)	0.013
Male sex – n (%)	110 (66)	48 (56.5)	62 (75.6)	0.015

Preoperative Variable	Total N= 167	Clinical N=85	Surgical N=82	*P-value*
Weight – Kg Mean ± Standard Deviation	72±15	71±17	73±13	0.109
Height – cm Mean ± Standard Deviation	166±10	165±9	166±10	0.514
Previous medical history	**Previous medical history**	**Previous medical history**	**Previous medical history**	**Previous medical history**
Structural heart disease – n (%)	57 (34.1)	36 (42.3)	21 (25.6)	0.023
Hypertension – n (%)	93 (55.7)	52 (61.1)	41 (50)	0.146
Diabetes mellitus – n (%)	48 (29)	23 (17)	25 (30.5)	0.624
Current smoker – n (%) Former smoker	27 (16) 44 (26)	12 (14.1) 23 (27)	15 (18.3) 21 (25.6)	0.464 0.832
Current alcohol abuse – n (%) Previous alcohol abuse	27 (16) 44 (26)	4 (4.7) 1 (1.2)	7 (8.5) 7 (8.5)	0.318 0.026
Chronic kidney disease – n (%)	35 (21)	13 (15.3)	22 (26.8)	0.067
Chronic obstructive pulmonary disease – n (%)	10 (6)	5 (5.8)	5 (6.1)	0.953
Chronic liver disease – n (%)	11 (6.6)	8 (9.4)	3 (3.6)	0.134
Previous stroke – n (%)	20 (12)	11 (12.9)	9 (10.9)	0.696
Arrhythmia – n (%)	23 (14)	15 (17.6)	8 (9.7)	0.242
Previous cardiac surgery – n (%)	52 (31)	32 (37.6)	20 (24.3)	0.057
Left ventricular ejection fraction – % Mean ± Standard Deviation	60.2±12	59±11	60±12	0.539

Table 2. Hospital admission symptoms. n (%)

	Total N= 167	Clinical N=85	Surgical N=82	P-value
Fever	141 (84.3)	72 (84.7)	69 (84.1)	0.921
New cardiac murmur	66 (39.5)	27 (31.7)	39 (47.5)	0.037
Decompensate heart failure	43 (25.7)	15 (17.6)	28 (34.1)	0.015

	Total N= 167	Clinical N=85	Surgical N=82	P-value
Embolism on admission Cerebral Peripheral	30 (18) 35 (21)	16 (18.8) 16 (18.8)	14 (17) 19 (23.1)	0.768 0.490

Table 3. Infective Endocarditis classification. n (%)

	Total N= 167	Clinical N=85	Surgical N=82	P-value
Native valve	122 (73)	61 (71.7)	61 (74.4)	0.796
Intravenous drug abusers	5 (3)	1 (1.2)	4 (4.8)	0.161
Nosocomial Dialytic patients	15 (9) 13 (7.8)	7 (8.2) 5 (5.8)	8 (9.7) 8 (9.7)	0.162
Valve involved	Valve involved	Valve involved	Valve involved	Valve involved
Aortic valve	91 (54.5)	44 (51.7)	47 (57.3)	0.766
Mitral valve	73 (43.7)	37 (43.5)	36 (43.9)	0.764
Tricuspid valve	12 (8.7)	5 (5.8)	7 (8.5)	0.578
Cardiovascular implantable electronic device	8 (4.8)	3 (3.5)	5 (6.1)	0.491
Valve regurgitation degree Mild Moderate Severe	43 (25.7) 36 (21.5) 53 (31.7)	30 (35.3) 19 (22.3) 13 (15.3)	13 (15.8) 17 (20.7) 40 (48.8)	<0.001

Table 4. Blood microorganism. n (%)

	Total N=167	Clinical N=85	Surgical N=82
Staphylococcus aureus	32 (19.16)	21 (24.7)	11 (13.4)
Enterococcus	20 (12)	12 (14.1)	8 (9.7)
Coagulase-negative staphylococci	17 (10.2)	9 (10.6)	8 (9.7)
Viridans streptococci	16 (9.6)	5 (5.9)	11 (13.4)
Other streptococci	22 (13.2)	12 (14.1)	10 (12.2)
Fungus	7 (4.2)	1 (1.2)	6 (7.3)
Other	14 (8.3)	5 (5.9)	9 (11)
Negative culture	39 (23.3)	20 (23.5)	19 (23.1)

Table 5. Multivariate analysis to predict need for surgical intervention

Variable	Odds Ratio (95% Confidence Interval)	*P-value*
Age	0.97 (0.94-0.99)	0.032
Male sex	3.3 (1.3-8.1)	0.008
Chronic kidney disease	3.2 (1.2-8.5)	0.017
Abscess	5.7 (1.1-31)	0.041
Valve regurgitation grade [?] 3+	6.1 (2.5-14)	<0.001

Table 6. Multivariate analysis to predict in-hospital mortality

Variable	Odds Ratio (95% Confidence Interval)	*P-value*
Diabetes mellitus	2.56 (1.1-5.9)	0.028
Previous heart disease	3.1 (1.4-6.8)	0.005
Mitral valve	2.1 (1.1-4.5)	0.046
Surgical treatment	0.45 (0.2-0.9)	0.044

Figure legend:

Figure 1. Clinical versus surgical treatment according to the year of diagnosis.

Author's contributions

APT and OCBW conceived the study. APT and ANK designed the study and coordinated the research. GVS and LMVS collected the data. APT, LMVS and ANK analyzed the data and drafted the manuscript. APT, GVS, LMVS, ANK, and OCBW contributed to interpret the data and revise the article. The authors warrant that all the authors have contributed substantially to the manuscript and approved the final submission.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was reviewed and approved by the institution's research ethics committee (CAAE:40755515900005327).