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ORIGINAL ARTICLE

Epidemiological Profile of Patients with Infective Endocarditis at three Tertiary Centers in Brazil from 2003 to 2017

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Abstract

Background: Infective endocarditis (IE) is a disease with high morbimortality and an increasing incidence. With improved diagnosis and treatment, a number of epidemiological changes have been reported over time.

Objectives: We sought to describe the epidemiological profile, mortality predictors, and analysis of a possible microbiological transition in patients admitted to three tertiary centers in Brazil.

Methods: In this cross-sectional retrospective study, data from 211 patients with definite or probable IE were analyzed according to the modified Duke criteria between 2003 and 2017. The association between categorical variables was assessed using the chi-square or Fisher's exact test, and binary logistic models were built to investigate mortality. We considered $p < 0.05$ statistically significant.

Results: The median age of the sample was 48 (33-59) years old, 70.6% were men, and the most prevalent pathogen was *Staphylococcus spp.* (19%). Mortality was 22.3%, with increasing age being the leading risk factor for death ($p = 0.028$). Regarding the location of the disease, native valves were the most affected site, with the aortic valve being more affected in men than women ($p = 0.017$). The mean number of cases of *Staphylococcus* spp. ($\tau = 0.293$, $p = 0.148$) and *Streptococcus* spp. ($\tau = -0.078$, $p = 0.727$) has remained stable over the years.

Conclusion: No trend towards reduced or increased mortality was evident between 2003 and 2017. Although *Staphylococcus* spp. were the most prevalent pathogen, the expected epidemiological transition could not be observed.

Keywords: Infective Endocarditis; Epidemiology; Mortality; Streptococci; staphylococci; Hospitalization; Comorbidities.

Introduction

With improved resources for the prevention, diagnosis, and treatment of infective endocarditis (IE), significant changes in the characteristics of the disease have been reported over time. If, on the one hand, the prevalence of IE due to rheumatic valve disease has decreased, on the other, there has been an increase in IE related to degenerative valve disease in older adults, valve replacement surgery, the implantation of intracardiac devices, and the use of injectables and hemodialysis. Coincidentally, IE cases due to *Staphylococcus* spp. have surpassed those of *Streptococcus* spp., and cases due to atypical microorganisms have also increased.[1,2] This microbiological change is attributed to medical progress and the resulting increase in invasive procedures.[3,4]

Despite efforts to the contrary, IE is still considered a condition with persistently high morbimortality,

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and its incidence has increased over time.[1] However, most studies that observed this change were conducted in developed countries, and it is unclear whether developing countries are susceptible to this epidemiological transition to the same extent and magnitude, given the possible difference in access to medical resources.[3] Furthermore, it is extremely relevant to understand the risk factors associated with mortality as well as the profile of patients affected by IE.[5,6]

Only 10 epidemiological studies on IE have been published in Brazil, and none of them addressed this possible change, especially since their samples were included over a limited time span. Considering the high regional variability and epidemiological transition in IE, the purpose of this study was to survey the characteristics of a population of patients with IE over 14 years to analyze the behavior of variables over time, determine predictors of mortality, and better understand the profile of affected individuals.

Methods

Sample description and design

This observational, retrospective, cross-sectional study included 211 patients admitted to 3 tertiary health centers in Ipatinga and Belo Horizonte in the state of Minas Gerais, Brazil, between 2003 and 2017. An initial survey of medical records containing International Classification of Diseases related to IE (ICD 10 I33.0) was conducted. These records were analyzed and information on epidemiological, microbiological, valvular, and outcome characteristics were collected in an Excel database.

The inclusion criterion was definite or probable IE according to the modified Duke criteria.[7] Patients whose medical records were incomplete, who were transferred during hospitalization, or who were still hospitalized at the time of analysis were excluded. After selection, data from the medical records were collected, including age, sex, blood culture, and prognosis. The microbiology was determined through blood culture results, and the location of the IE was determined through echocardiographic or perioperative findings.

This study was approved by the ethics committee of the Faculty of Medical Sciences of Minas Gerais (CAAE 60893616.7.0000.5134). Informed consent was not required due to the retrospective nature of the study.

Statistical analysis

Categorical variables are presented as absolute and relative frequencies, and quantitative variables are presented as median (1^{st} – 3^{rd} quartile). The normality of quantitative variables was assessed using the Shapiro-Wilk test, while the Wilcoxon-Mann-Whitney test was used to compare quantitative variables among groups. The association between categorical variables was assessed using the chi-square test and Fisher's exact test. Binary logistic models were constructed to verify the association with mortality, and the results are presented as odds ratios (OR) and 95% confidence intervals. The Mann- Kendall test was used to verify the temporal trend. The analysis was performed in R version 3.5.2, with $p < 0.05$ considered significant.

Results

The sample consisted of 211 patients, whose profile has been described in a previous study:[8] 110 from Belo Horizonte and 101 from Ipatinga. Their median age was 48.0 (33-59) years and 70.6% were men. Bacteria of the genus *Staphylococcus* were the most prevalent pathogens, observed in 19% of cases, with *Staphylococcus aureus* occurring in 10% and *Coagulase-negative Staphylococci* in 9%. Native valves were the site of IE in 70.6% of the cases, and the greatest prevalence was in the mitral valve (41.7%), (Table 1).

Mortality

Overall mortality was 22.3%. It was observed that increasing age is a risk factor for death ($p = 0.028$). However, when the sample was stratified into patients younger and older than 65 years of age, there was no statistical relevance (Table 2). Among patients younger than 65 years who died, the native aortic valve was the most affected site (33.3%) and *Staphylococcus* spp. was the most frequent pathogen, representing 30.6% of the cases. Regarding the 11 deaths in patients older than 65 years, most were due to *Streptococcus* spp., and the most prevalent location was the native mitral valve. Sex, blood culture findings, and lesion location had no statistical relevance on mortality. Mortality from IE remained stable between 2003 and 2017 ($\tau = 0.010$). The highest and lowest death rates occurred in 2004 and 2012, respectively.

Table 1 - Characteristics of 211 patients with infective endocarditis

Characteristic	Total (*n=211*)
Sex	
Male	149 (70.6%)
Female	62 (29.4%)
Age (years) (median [1st – 3rd quartile])	48.00 (33-59)
< 18	15 (7.1%)
18 to 29	25 (11.8%)
30 to 44	55 (26.1%)
45 to 64	78 (37%)
65 or more	38 (18%)
Definite infective endocarditis*	118 (56%)
Possible infective endocarditis*	93 (44%)
Deaths	47 (22.3%)
Blood culture findings	
Staphylococcus spp.	40 (19%)
Staphylococcus aureus	21 (10%)
Coagulase-negative Staphylococci	19 (9%)
Streptococcus spp.	31 (14.7%)
Enterococcus spp.	14 (6.6%)
Other†	10 (4.7%)
Not specified	14 (6.6%)
Negative blood culture	71 (33.6%)
Location	
Native valves‡	149 (70.6%)
Mitral	88 (41.7%)
Aortic	56 (26.5%)
Tricuspid	21 (10%)
Pulmonary	3 (1.4%)
Prosthetic valves	51 (24.2%)
Pacemaker cable	9 (4.3%)
Other§	6 (2.8%)
Unidentified location	3 (1.4%)

** According to the modified Duke criteria for infective endocarditis[7].*
† Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis.
‡ Some patients had lesions in more than one place.
§ Right atrium, pulmonary arteries, ostium of the interventricular defect, ostium of the superior vena cava.

Table 2 – Mortality risk analysis in 211 patients with infective endocarditis

Characteristic	Death		OR (CI 95%)	p-value
	No (n=164)	Yes (n=47)		
Sex				
Male	117 (71.3%)	32 (68.1%)	-	-
Female	47 (28.7%)	15 (31.9%)	1.167 (0.568; 2.323)	0.611
Age (years) (median [1st - 3rd quartile])	46.00 (31-59)	52.00 (39-63)	1.020 (1.003; 1.039)	0.028
<65	137 (83.5%)	36 (76.6%)	-	-
65 or more	27 (16.5%)	11 (23.4%)	1.550 (0.263; 3.358)	0.277
Blood culture findings				
Staphylococcus spp.	28 (17.1%)	12 (25.5%)	1.665 (0.750; 3.548)	0.195
Staphylococcus aureus	15 (9.1%)	6 (12.8%)	1.454 (0.493; 3.827)	0.467
Coagulase-negative Staphylococci	13 (7.9%)	6 (12.8%)	1.700 (0.568; 4.590)	0.311
Streptococcus spp.	26 (15.9%)	5 (10.6%)	0.632 (0.204; 1.625)	0.377
Enterococcus spp.	9 (5.5%)	5 (10.6%)	2.050 (0.603; 6.268)	0.219
Other*	10 (6.1%)	-	-	-
Not specified	11 (6.7%)	3 (6.4%)	0.948 (0.208; 3.197)	0.937
Negative blood culture	59 (36%)	12 (25.5%)	0.610 (0.285; 1.237)	0.184
Location				
Native valves†	114 (69.5%)	35 (74.5%)	1.279 (0.627; 2.756)	0.511
Mitral	70 (42.7%)	18 (38.3%)	0.833 (0.423; 1.609)	0.591
Aortic	43 (26.2%)	13 (27.7%)	1.076 (0.506; 2.190)	0.844
Tricuspid	15 (9.1%)	6 (12.8%)	1.454 (0.493; 3.827)	0.467
Pulmonary	2 (1.2%)	1 (2.1%)	1.761 (0.081; 18.779)	0.647
Prosthetic valves	40 (24.4%)	11 (23.4%)	0.947 (0.426; 1.985)	0.889
Pacemaker cable	7 (4.3%)	2 (4.3%)	0.997 (0.145; 4.297)	0.997
Other‡	5 (3%)	1 (2.1%)	0.691 (0.036; 4.428)	0.739
Unidentified location	3 (1.8%)	-	-	-

** Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis. OR: odds ratio.*
† Some patients had lesions in more than one place.
‡ Right atrium, pulmonary arteries, ostium of the interventricular defect, ostium of superior vena cava.
P-value refers to the logistic regression model.

Differences between the sexes

Of the 211 patients, 149 were men and 62 were women. A total of 82.3% of the men and 81.9% of the women diagnosed with IE were younger than 65 years of age (no significant difference). Native valves were most affected, especially the mitral valve, regardless of the patient's sex, representing 40.3% of the infections in men and 45.2% in women, while the pulmonary valve was the least affected site. Of note, prosthetic valve endocarditis occurred in 22.8% and 27.4% of the men and women, respectively, at a ratio of approximately

1:3 in relation to native valves. The native aortic valve was significantly more affected in men than women (p = 0.017). There was no association between the other findings (blood culture, age group, and other IE sites) and sex.

Microbiological agent

Table 3 shows the relationship between microbiological findings, age, and affected valve. There was no association between a specific microorganism and age, with individuals younger or older than 65 being equally affected. Infection by atypical microorganisms was more common in patients with prosthetic valve endocarditis (p = 0.014). Individuals without mitral lesions were more prone to infection by *Coagulase-negative Staphylococci* (p = 0.026). Regarding the main pathogens found during the study period (Figure 1), all had a non-significant trend according to the Mann Kendall test: *Staphylococcus* spp. (τ = 0.293, p = 0.148), *Streptococcus* spp. (τ = -0.078, p = 0.727) and negative blood culture (τ = -0.332, p = 0.100), which indicates that the occurrence of these microorganisms was stable over the years.

Discussion

IE is a serious infectious disease, and a multidisciplinary approach involving specialists is necessary to treat and monitor these patients. Although the incidence of IE has been increasing over the years,[9] few studies have been published on IE in developing countries, which makes a general analysis difficult. The overall mortality in our sample was 22.3%, which is consistent with several other observational studies,[10,11] including some conducted in developing countries.[12] The logistic regression model (Table 2), showed that patient age was directly related to mortality [p = 0.028; OR 1.020, 95% CI 1.003; 1.039], which agrees with other studies, eg, Khan et al.,[13] who obtained a similar result with a sample of 523,432 patients in the United States. Moreover, this study reported a trend over the years toward reduced mortality in IE patients, which the authors ascribed to improved medical services in the USA. However, such a trend was not observed in our analysis.

No significant differences were found regarding microbiological profile and mortality, which contrasts

Table 3 – Distribution of microbial agents according to age and location

Microorganism	Age (years)			Mitral valve affected			Aortic valve affected		
	< 65 n=173	≥ 65 n=38	p-value	No n=123	Yes n=88	p-value	No n=155	Yes n=56	p-value
Staphylococcus spp.	32 (18.5%)	8 (21.1%)	0.892†	29 (23.6%)	11 (12.5%)	0.065†	29 (18.7%)	11 (19.6%)	1.000†
Staphylococcus aureus	18 (10.4%)	3 (7.9%)	0.773‡	13 (10.6%)	8 (9.1%)	0.904†	18 (11.6%)	3 (5.4%)	0.296‡
Coagulase-negative Staphylococci	14 (8.1%)	5 (13.2%)	0.348‡	16 (13%)	3 (3.4%)	0.026‡	11 (7.1%)	8 (14.3%)	0.181†
Streptococcus spp.	25 (14.5%)	6 (15.8%)	1.000†	18 (14.6%)	13 (14.8%)	1.000†	22 (14.2%)	9 (16.1%)	0.905†
Enterococcus spp.	10 (5.8%)	4 (10.5%)	0.286‡	7 (5.7%)	7 (8%)	0.581‡	9 (5.8%)	5 (8.9%)	0.531‡
Other*	7 (4%)	3 (7.9%)	0.391‡	8 (6.5%)	2 (2.3%)	0.199‡	8 (5.2%)	2 (3.6%)	1.000‡
Not specified	10 (5.8%)	4 (10.5%)	0.286‡	10 (8.1%)	4 (4.5%)	0.404‡	9 (5.8%)	5 (8.9%)	0.531‡
Negative blood culture	61 (35.3%)	10 (26.3%)	0.386†	35 (28.5%)	36 (40.9%)	0.082†	53 (34.2%)	18 (32.1%)	0.910†

** Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis. † Chi-square test. ‡ Fisher's exact test.*

Table 3 (continuation) - Distribution of microbial agents according to age and location

Microorganism	Tricuspid valve affected			Prosthetic valves affected		
	No n=190	Yes n=21	p-value	No n=160	Yes n=51	p-value
Staphylococcus spp.	33 (17.4%)	7 (33.3%)	0.139†	31 (19.4%)	9 (17.6%)	0.945†
Staphylococcus Aureus	17 (8.9%)	4 (19%)	0.140‡	17 (10.6%)	4 (7.8%)	0.789†
Coagulase-negative Staphylococci	16 (8.4%)	3 (14.3%)	0.413‡	14 (8.8%)	5 (9.8%)	0.784‡
Streptococcus spp.	29 (15.3%)	2 (9.5%)	0.746‡	25 (15.6%)	6 (11.8%)	0.652†
Enterococcus spp.	12 (6.3%)	2 (9.5%)	0.636‡	10 (6.2%)	4 (7.8%)	0.748‡
Other*	10 (5.3%)	-	-	4 (2.5%)	6 (11.8%)	0.014‡
Not specified	13 (6.8%)	1 (4.8%)	1.000‡	9 (5.6%)	5 (9.8%)	0.334‡
Negative blood culture	62 (32.6%)	9 (42.9%)	0.485†	56 (35%)	15 (29.4%)	0.572†

** Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis.*
† Chi-square test.
‡ Fisher's exact test.

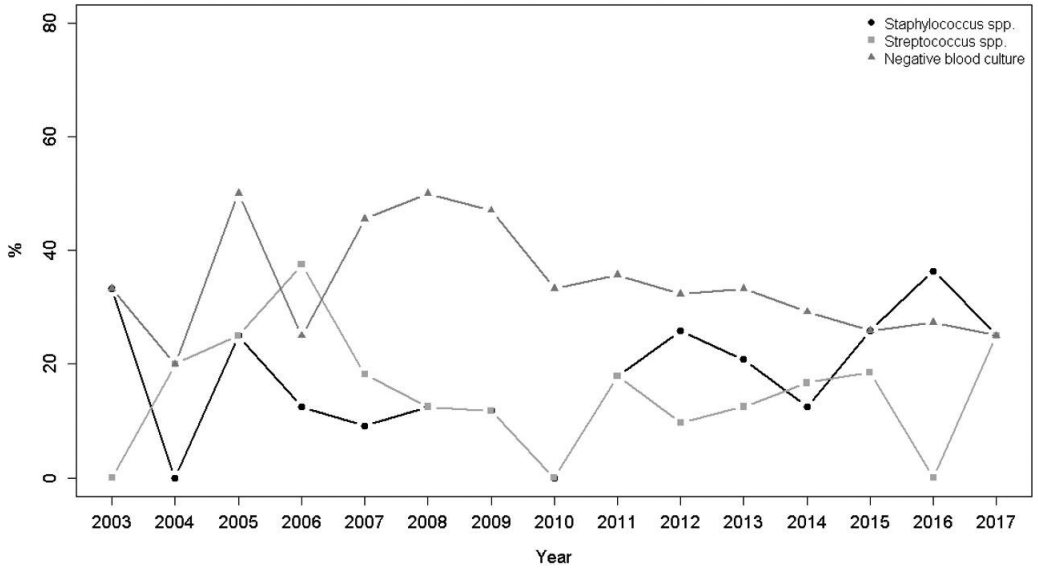

Figure 1 – Main blood culture findings per year. Figure caption: All findings had a non-significant trend according to the Mann-Kendall test (τ = 0.293, p = 0.148, for Staphylococcus spp.; τ = -0.078, p = 0.727, for Streptococcus spp. and τ = -0.332, p = 0.100 for blood culture negative). Source: The authors

with the results of Joffre et al.,[14] who found an association between *Staphylococcus* spp., *Candida* spp. and higher in-hospital mortality, as well as an association between IE due to *Streptococcus* spp. and a more favorable prognosis. It should also be pointed out that these authors found male sex to be a protective factor against death. Other authors have found a direct relationship between mortality and endocarditis location, with the aortic and mitral valves having the worst outcomes.[9,15,16] However, we did not observe this in the present study.

It is possible that comorbidities (e.g. hypertension, heart disease, etc.) and events (e.g. septic shock, need for surgical approach) affect prognosis more than the microbiological or valvular characteristics of the IE. Ren et al.[15] found significant associations between higher mortality and conditions such as hemorrhagic and ischemic stroke, constrictive heart failure, pneumonia, and renal failure. One limitation of our study is the lack of data on these variables.

In general, IE affected men the most (70.6%), at a ratio of 1.7:1. This difference has been found by other authors in Belgium,[17] Saudi Arabia,[18] and Brazil,[9,19] and Bakir et al.,[20] ascribed it to the potential protective role of estrogen against endothelial injury. Other authors have reported a lower prevalence of IE in women, including a lesser likelihood of developing sepsis.[21,22] Nevertheless, none of these mechanisms are fully understood. It is curious that, although IE affects fewer women, it seems to be related to higher in-hospital mortality.[23,24] In fact, prognostic scales such as the EuroSCORE and the results of Martínez-Sellés et al.,[25] indicate a worse outcome among women and a greater likelihood of death.

Furthermore, our analysis showed that native aortic valves are more affected in men than women ($p = 0.017$), which was also described by Sevilla et al.,[26] and Elamragy et al.,[27] who further described that the native mitral valve was more affected in women. Regarding the microbiological profile between the sexes, the most frequent microorganism was *Staphylococcus* spp. (22.6% men vs 17.4% women, $p = 0.501$), a result similar to other authors.[27] The equally high negative blood culture rate in men and women is also of note (32.9% and 35.5% respectively, $p = 0.838$), which may be explained by the indiscriminate use of antibiotics to treat any febrile disease before obtaining cultures, a common practice in Brazil. It should be pointed out that some studies have found a much higher percentage of negative blood cultures than ours, eg, in Egypt (69.5%)[27] and South Africa (55.3%),[28] while others have found lower percentages, eg, in France (9%)[29] and the United Kingdom (12.2%).[30] Thus, it could be cautiously inferred that Brazil is somewhere in the middle of a broad spectrum, which might be associated with improvements to the Brazilian public health system, as well as new and more effective hospital protocols.

The relationship between the affected valve and the blood culture results diverges greatly among studies. What became clear in our study was that a positive blood culture for *coagulase-negative staphylococci* is less related to mitral valve lesion (Table 3), which was also reported by Barrau et al.,[31] These authors also found that *Staphylococcus aureus* affects the aortic valve the least. Another important result of our study was that patients with cardiac prostheses were more likely to be affected by bacteria in the "other" category, which may reflect inadequate laboratory techniques or less strict criteria for diagnosing IE.[32,33]

Finally, we should point out that we found *Staphylococcus* spp. to be the most prevalent pathogen, which agrees with the literature.[1-4,34] However, we did not observe the reported epidemiological transition toward more cases due to *Staphylococcus* spp. and fewer cases due to *Streptococcus* spp. (Figure 1) over the years as consequence of medical progress. Most studies reporting this trend have been conducted in developed countries,[1] and little evidence for such a trend has been found in low/middle income countries, either due to the precariousness of medical systems or the scarcity of new studies.

Limitations

Our study is not without limitations. First, since we performed a retrospective analysis, associations between variables do not necessarily indicate a causal relationship. Second, the sample can be considered small, since we dealt with cases over 15 years at three different centers, as well as the fact that it included many probable IE cases (93 out of 211). However, few studies have been published on the epidemiological profile of Brazilian patients and, to the best of our knowledge, our study involves the largest such sample. It should also be pointed out that most of the probable IE cases involved a negative blood culture, which is related to the use of antibiotics. Third, no data

on comorbidity, heart valve disorder, hemodynamic variables, heart failure, abscess formation, or heart valve surgery were collected. Thus, any discussion of mortality must be extremely limited. Finally, it was not possible to collect blood samples for blood culture in 34 patients, either because they received treatment prior to collection or because they began antibiotic therapy before being transferred to tertiary centers.

Conclusion

In conclusion, among the 211 IE cases included in this study, age had the greatest influence on mortality. However, a trend towards reduced or increased mortality was not evident during the study period. Although more infections occurred in native aortic valves in men than women, no specific bacteria stood out. Additionally, in patients whose IE was due to *coagulase-negative staphylococci*, the mitral valve was less likely to be affected, whereas patients with heart prostheses were more likely to be infected with bacteria in the "other" category. Even though *Staphylococcus* spp. were the most prevalent pathogen in the sample, we did not observe the epidemiological transition described in literature. Finally, further research is needed to better understand the risk factors associated with mortality in developing countries, especially comorbidities, symptoms present at admission, and the effects of surgical interventions.

Author contributions

Conception and design of the research: Bezerra RL, Salgado LS, Silva YM, Figueiredo GGR, Cunha AGJ. Acquisition of data: Bezerra RL, Silva YM. Analysis and interpretation of the data: Bezerra RL, Salgado LS, Silva YM, Figueiredo GGR, Cunha AGJ. Statistical analysis: Gomes IC. Writing of the manuscript: Bezerra RL, Salgado LS, Silva YM, Figueiredo GGR. Supervision: Filho RMB, Machado ELG, Cunha AGJ. Critical revision of the manuscript for intellectual content: Filho RMB, Machado ELG, Cunha AGJ.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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