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Major Article

Epidemiological and clinical profile of infective endocarditis at a Brazilian tertiary care center: an eight-year prospective study

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Abstract

Introduction: Infective endocarditis (IE) is a systemic infectious disease requiring a multidisciplinary team for treatment. This study presents the epidemiological and clinical data of 73 cases of IE in Rio de Janeiro, Brazil. **Methods**: This observational prospective cohort study of endocarditis patients during an eight-year study period described 73 episodes of IE in 70 patients (three had IE twice). Community-associated (CAIE) and healthcare-acquired infective endocarditis (HAIE) were diagnosed according to the modified Duke criteria. The collected data included demographic, epidemiologic, and clinical characteristics, including results of blood cultures, echocardiographic findings, surgical interventions, and outcome. **Results:** Analysis of data from the eight-year study period and 73 cases (70 patients) of IE showed a mean age of 46 years (SD=2.5 years; 1–84 years) and that 65.7% were male patients. The prevalence of CAIE and HAIE was 32.9% and 67.1%, respectively. *Staphylococcus aureus* (30.1%), *Enterococcus* spp. (19.1%), and *Streptococcus* spp. (15.0%) were the prevalent microorganisms. The relevant signals and symptoms were fever (97.2%; mean 38.6 $\pm$ 0.05°C) and heart murmur (87.6%). Vegetations were observed in the mitral (41.1%) and aortic (27.4%) valves. The mortality rate of the cases was 47.9%. **Conclusions:** In multivariate analysis, chronic renal failure (relative risk [RR]= 1.60; 95% confidence interval [CI] 1.01–2.55), septic shock (RR= 2.19; 95% CI 1.499–3.22), and age over 60 years (RR= 2.28; 95% CI 1.44–3.59) were indirectly associated with in-hospital mortality. The best prognosis was related to the performance of cardiovascular surgery (hazard ratio [HR]= 0.51; 95% CI 0.26–0.99).

Keywords: Infectious endocarditis. HAIE. CAIE. *Staphylococcus aureus*. *Enterococcus* spp. *Streptococcus* spp.

INTRODUCTION

Infective endocarditis (IE) is a systemic infection for which a multidisciplinary team is required to approach treatment of this life-threatening disease[1-4]. In past years, the overall incidence of IE in the general population in developed nations has ranged between 3 and 10 cases per 100,000 individuals per year. However, recent epidemiological studies have suggested an increasing incidence of IE[5,6]. Despite trends toward earlier diagnosis and surgical intervention in IE patients in the 21st century, in-hospital mortality rates have not improved over the last three decades[2,3,5]. In developed countries, IE is associated with high mortality rates of approximately 20%, despite medical and surgical advances[3,5,7]. In low- and middle-income countries, the mortality of IE ranges from 19 to 46%[8]. In these countries, the morbidity and mortality rates of IE are similar to those reported in the middle of the 20th century in North America and European countries[7,8].

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The aim of this observational and prospective cohort study, which started in June 2009 at the Hospital Universitário Pedro Ernesto (HUPE), was to evaluate the epidemiological, microbiological, clinical characteristics, and outcomes of 73 cases of definitive IE in a major urban teaching Hospital in Rio de Janeiro, Brazil. An overview of infective endocarditis in low- and middle-income countries in 2002–2017 was also performed.

METHODS

The HUPE is a 600-bed public medical hospital facility that serves as both a tertiary care referral center and a primary and secondary care institution for public assistance security (Sistema Único de Saúde -SUS/Brazil). The HUPE provides care in all medical and surgical specialties and subspecialties.

Study design

The study was developed as an observational prospective cohort study, over a period of 97 months, from June 2009 to June 2017, at HUPE, Rio de Janeiro, Brazil, to which 92,634 patients were admitted in the last eight years. The database consists of 73 episodes in 70 patients (three had IE twice) with infective endocarditis (IE) who were all interviewed by the same senior infectious diseases physician (IDP). Community-associated (CAIE) and healthcare-acquired infective endocarditis (HAIE) were diagnosed according to the modified Duke criteria. Two major or one major (typical microorganism for IE from two separate blood cultures, evidence of endocardial involvement, new valvular regurgitation) and three minor clinical criteria (predisposing heart condition or intravenous drug use, fever, vascular or immunologic phenomena, echocardiogram findings consistent with IE but not meeting major criteria, blood culture but not meeting major criteria, or serologic evidence of active infection with organism consistent with IE) were used. The major clinical criteria included positive blood culture and evidence of endocardial involvement. The minor clinical criteria were fever >38.0º C, predisposing heart conditions, and vascular or immunologic phenomena[2]. These criteria were used for definite diagnosis or rejection of IE cases.

HAIE subjects were categorized as either IE-manifesting, occurring >48h after hospital admission, or IE-acquired, in association with a significant invasive procedure performed in the six months preceding the following situations: (a) a stay and/or treatment in a hospital setting (nosocomial health-associated IE); or (b) patients with extensive outpatient contact with health-care interventions[9].

The collected data included demographic characteristics, epidemiologic and clinical data in first medical care in the hospital, results of blood cultures, echocardiographic findings, cardiac surgical interventions, and outcomes. Mortality was defined as in-hospital death.

Clinical data

After patient anamnesis by the IDP, all relevant clinical variables for this study such as time between the onset of symptoms, fever, chills, myalgia, arthralgia, back pain, pleuritic pain, abdominal pain, headache, dyspnea, prostration, weight loss, heart murmur, change of murmur, arterial emboli, Osler sign, Janeway lesions, petechiae, Roth spots, and comorbidities were recorded in patient questionnaires.

Echocardiographic data

Transthoracic and transesophageal echocardiography was performed at the echocardiography service of HUPE. All echocardiography exams in which IE was suspected were reviewed by an expert in echocardiography.

Microbiological data

Bloodstream samples were collected, placed in at least three aerobic bottles (Plus Aerobic), and incubated for five days in a BACTEC 9240 blood culture instrument (BATEC/ALERT®, BioMérieux, Durham, NC, USA). Bacterial identification and antimicrobial susceptibility testing were performed using an automated VITEK 2 System (BioMérieux). Additionally, the vancomycin minimal inhibitory concentration (MIC) was determined by E-test and microdilution for *Enterococcus* sp. and methicillin-resistant *Staphylococcus aureus* (MRSA), respectively.

*Mec*A and SCC*mec* typing were carried out by multiplex polymerase chain reaction (PCR) analysis that generated specific amplification patterns for SCC*mec* types I, II, III, IV, and V[10]; in addition, molecular characterization based on multilocus sequence typing (MLST) was performed for all MRSA isolates[11].

Microorganisms obtained from blood culture or after valve biopsies were identified by 16SrRNA sequencing or by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF). Serological and molecular *Coxiella burnetii* analyses were performed in all blood culture-negative endocarditis cases (BCNE) using an indirect immunofluorescence assay (Focus Diagnostics TM, Cypress, CA, USA) and PCR amplification of a fragment of the repetitive element IS1111 of a heat-shock protein gene[12].

Statistical analysis

Data were input to Excel 2007 and analyzed using STATA™ version 9.1. A descriptive analysis of the variables was performed. The relative risks (RRs) or hazard ratio (HRs) with 95% confidence intervals (CIs) were calculated for categorical variables, and v2 or Fisher's exact tests for expected values of <5 were also used to determine statistical significances. Logistic regression was used to examine the potential associations between variables and multivariate analysis was performed to identify risk factors independently associated with mortality. Variables with p >0.05 were excluded from the final model. P-values <0.05 were considered statistically significant.

Ethical considerations

This study was approved by the institutional board of HUPE (CAAE: 01247512.3.0000.5259).

RESULTS

Demographic and Epidemiologic findings

Demographic, clinical, microbiological, and complication data in the cohort of IE patients are shown in **Table 1**.

In the past eight years, 73 cases (70 patients) with IE were followed-up, with 0.75 episodes per 1,000 patients in the

TABLE 1: Epidemiology, etiology, and outcomes of infective endocarditis (IE) among inpatients from an urban university hospital.

Cases of IE in HUPE	73
Average age (years)	46.0 ± 2.5
Male sex	48 (65.7)
Time to IE diagnosis (mean ± SD, day)	27.5 ± 3.7
Diagnosis of IE on admission	28 (38.4)
Type of IE	
Community-associated	24 (32.9)
Healthcare-associated	49 (67.1)
Blood culture	
Blood culture performed	73 (100)
Blood cultures collected (mean ± SD)	3.5 ± 0,3
Negative blood culture	8(10.9)
Positive blood culture	65 (89.0)
Staphylococcus aureus	22 (30.1)
MSSA	16 (21.9)
MRSA	6 (8.2)
Coagulase-negative Staphylococci	7 (9.5)
Streptococcus spp	11 (15.0)
Viridans group *Streptococcus*	8 (10.9)
Streptococcus mutans	2 (2.7)
Streptococcus agalactiae	1 (1.3)
Abitrophia defective	1 (1.3)
Enterococcus spp	14 (19.1)
VRE (*E. faecium*)	4 (5.4)
Enterococcus faecalis	10 (13.6)
HACEK	0 (0.0)
Gram-Negative bacilli non-HACEK	6 (8.2)
Serratia marcences	3 (4.1)
Burkholderia cepacea	1 (1.3)
Acinetobacter baumannii complex	1 (1.3)
Escherichia coli	1 (1.3)
Corynebacterium spp.	1 (1.3)
Microbacterium testaceum	1 (1.3)
Yeasts	3 (4.1)
Candida spp.	2 (2.7)
Rhodotorula muscilaginosa	1 (1.3)
Discharge from hospital	38 (52.0)
Mortality rate in CAIE	8 (10.9)
Mortality rate in HAIE	27 (36.9)
Mortality rate	35 (47.9)

HUPE: *Hospital Universitário Pedro Ernesto*; **MRSA:** vancomycin-resistant *S. aureus*; **VRE:** vancomycin-resistant enterococci; **HACEK:** Haemophilus species; Aggregatibacter species; Cardiobacterium hominis; Eikenella corrodens; Kingella species. **CAIE:** community-associated Infective endocarditis; **HAIE:** healthcare-acquired infective endocarditis.

university hospital. The mean age of the patients was 46 (SD 2.5 years) (range: 1–84 years) and 65.7% of patients were male. The mortality rate of all cases of IE was 47.9%.

The results of two-dimensional transthoracic (TTE) or transesophageal echocardiography (TEE) of the 73 cases showed a mean diameter of valve vegetation of 1.3 ± 0.1 cm. In all IE cases, the mitral valve (41.1%) was the most frequent site of vegetation, followed by the aortic valve (27.4 %). Most patients developed native endocarditis (90.4%).

Clinical data

All 73 cases of IE fulfilled the Duke criteria. Only 38.4% of patients had classic clinical evidence of IE at hospital admission (**Table 1)**. The clinical signs and symptoms that helped the physicians to diagnose IE upon admission to the university hospital are described. The median time between symptom onset and hospital admission was 27.5 ± 3.7 days. The most relevant classical signs and symptoms of IE were fever (97.2%; mean 38.6 ± 0.05°C) and heart murmur (87.6%). Change in heart murmur was observed in only 17.8% of patients and the following stigmas of IE were found: arterial embolic phenomenon (20.5%), Janeway lesion (5.5 %), petechiae (4.1%), and Roth spot (4.1%). The principal antecedent factors in our cohort were central venous catheterization (43.8%), hemodialysis (32.8%), antecedents of IE (16.4%), rheumatic fever (12.3%), previous dental manipulation (9.5%), and intravenous additive (1.3%) **(Table 2)**.

TABLE 2: Echocardiographic, risk factors and clinical findings of 73 cases of infective endocarditis (IE).

Clinical findings of IE patients	Number (%)	Major antecedent factors	Number (%)
Vegetation	70 (95.8)	Rheumatic fever	9 (12.3)
Vegetation diameter (mean ± SD, cm)	1.3 ± 0.1		
Compromised valve		Congenital heart disease	12 (16.4)
Mitral	30 (41.1)	Mitral prolapse	10 (13.7)
Aortic	20 (27.4)	Prior IE episode	12 (16.4)
Mitral-aortic	10 (13.7)	Intracardiac devices	12 (16.4)
Tricuspid	10 (13.7)	Central venous catheterization	32 (43.8)
Other	3 (4.1)	Hemodialysis	24 (32.8)
Native valve	66 (90.4)	HIV positive	7 (9.6)
Mechanical valve	7 (9.5)	Dental procedure	7 (9.6)
Valvular abscess	8 (10.9)	Urinary tract manipulation	3 (4.1)
Dehiscence of prosthesis	2 (2.7)	Corticosteroid therapy	12 (16.4)
Signals and symptoms		Prior cardiac valve surgery	11 (15.0)
Heart murmur	64 (87.6)	Intravenous additive	1 (1.3)
Change in heart murmur	13 (17.8)	**Comorbidities**	
Murmur of mitral regurgitation	42 (57.5)	Chronic renal insufficiency	27 (36.9)
Arterial emboli	15 (20.5)	Diabetes mellitus	8(10.9)
Pulmonary infarction	2 (2.7)	HAS	8(10.9)
Intracerebral hemorrhage	1 (1.4)	Polycystic renal disease	3 (4.1)
Janeway lesions	4 (5.5)	transplant renal	7(9.5)
Petechiae	3 (4.1)	Polipose intestinal	1 (1,3)
Roth spots	3 (4.1)	Cardiomyopathy	4(5.4)
Glomerulonephritis	2 (2.7)	Hematologic neoplasia	5(6.8)
Rheumatoid factor	2 (2.7)	Solid neoplasm	4(5.4)
Temperature (38,6 ± 0,05, °C)	71 (97.2)	Cirrhosis hepatic	2(2.7)
Chills	13 (17.8)	SLE	1 (1.3)
Myalgia	9 (12.3)	**Complications**	
Arthralgia	17 (23.3)	Splenic infarction	6 (8.2)
Backache	14 (19.2)	Splenic abscess	2 (2.7)
Pleuritic pain	1 (1.4)	Mycotic aneurysm	4 (5.4)
Chest pain	13 (17.8)	Septic embolization CNS	6 (8.2)
Abdominal pain	14 (19.1)	Acute renal failure	18 (24.6)
Headache	10 (13.7)	Sepsis	19 (26.0)
Dyspnea	25 (34.2)	Septic shock	14 (19.1)
Prostration	30 (41.1)	Congestive heart failure	11 (15.0)
Weight loss	28 (38.3)	Cardiac shock	6 (8.2)

HAS: arterial hypertension; **SLE:** systemic lupus erythematosus; **HIV:** human immunodeficiency virus; **CNS:** central nervous system.

Our data also showed a higher number of patients with different types of comorbidities, including chronic renal failure in 27 patients (36.9%), diabetes mellitus in eight patients (10.9%), HIV in seven patients (9.5%), kidney transplants in seven patients (9.5%), and neoplasia six patients (8.2%) (**Table 2).**

The prevalence of CAIE and HAIE was 32.9% and 67.1%, respectively. Of the 73 IE cases, 32.8% were classified as non-nosocomial HAIE and 34.3% as classical nosocomial IE, as previously described[1]. Only three patients developed a second episode of endocarditis during the study period **(Table 1)**. The most frequent complications due to IE were sepsis (26.0%), acute renal failure (24.6%), and septic shock (19.1%) **(Table 2)**.

Prevalence of identified organisms in IE

At least three blood cultures were collected from each patient, resulting in 89.0% positive blood cultures, whereas only 9.6% remained without an identified etiology. In total, an isolate was obtained in 90.4% of cases (89.0% of cases of IE with positive blood culture and one with a positive valve culture) **(Table 1)**.

The classic agents of IE included *S. aureus* (30.1% of cases), *Enterococcus* spp. (19.1%) and *Streptococcus* spp. (15.0%). Six of the *S. aureus* isolates were methicillin resistant and contained the *mec*A gene. The MIC for vancomycin by microdilution ranged from 0.5 to 2.0 μg mL^{-1}. Analysis of the MRSA strains by MLST revealed five different sequence types (ST) (1, 5, 25, 105, and 188). Among MRSA strains, the SCC*mec* types included I, II, and IV. PVL toxin genes were detected in 33.3% of all MRSA strains (ST105 and ST1). In addition, two of six MRSA isolates belonged to known epidemic lineages (USA400 and USA800).

Four cases (5.4%) of IE due to vancomycin-resistant *Enterococcus faecium* (VRE) were found. MRSA and VRE strains were only diagnosed in HAIE patients.

As mentioned, *Streptococcus* spp. was identified in 15.0% of patients with IE in Rio de Janeiro. The viridans group was isolated most frequently (10.9% of all IE cases). Non-hemolytic *S. mutans* was isolated from two positive cases and one β-hemolytic *S. agalactie* strain was also isolated. The MIC E-test values for penicillin G ranged from 0.094 to 0.016 μg mL^{-1}. In addition, coagulase-negative *Staphylococcus* (CNS, seven strains; 9.5%) and *Abiotrophia defectiva* (one strain; 1.5%) were also identified.

The prevalence of IE caused by Gram-negative bacteria was 8.2%, corresponding to six patients. Five patients developed HAIE after Gram-negative bacteremia in our hospital, in which vascular catheters were the major source of these microorganisms. Three bacteremia cases were due to *Serratia marcescens*, one to *Burkholderia cepacea*, one to *Acinetobacter baumannii* complex, and one to *Escherichia coli*.

One patient developed CAIE due to *E. coli* bacteremia from a urinary infection. *E. coli* analysis by whole genome sequencing (WGS) identified the isolate as ST-69. The isolate was resistant to ampicillin, trimethoprim, and trimethoprim/sulfamethoxazole and had different virulence genes associated with iron uptake systems (*aer*, *chuA*, *fepA*, *fhuA*, *fhuE*, *fyuA*, *irp2*, and *sitA*) and adhesion (*fimH* and *fimA*).

Endocarditis due to rare and fastidious pathogens (ERFP)

Endocarditis due to rare and fastidious pathogens (ERFP) similar to *Bartonella* spp., *Tropheryma whipplei*, *Coxiella burnetii*, *Corynebacterium spp*., and fungi has been previously reported[18]. In our cohort, five patients had ERFP, four patients of which had HAIE. Two developed IE after candidemia. The other two cases of HAIE are described hereafter. The first case involved a woman with a kidney transplant who was investigated for fever of unknown origin (FUO), from which we isolated *Rhodotorula mucilaginosa* in aortic valve culture. In the second case, *Corynebacterium* spp. was initially found in the blood culture. However, 16S rRNA sequencing identified *Microbacterium testaceum*. Only one patient developed CAIE due to *Corynebacterium* spp.

Serological and molecular analyses of *Coxiella burnetii* were performed in all blood culture-negative endocarditis cases (BCNE) using an indirect immunofluorescence assay. One case showed serological evidence for *C. burnetii* but Q fever was excluded because the male patient was diagnosed with systemic lupus erythematosus with Libman-Sacks endocarditis and antiphospholipid syndrome (**Table 2**).

Statistical analysis

In bivariate analysis, after comparisons of in-hospital mortality and discharged hospital patients, age (56 ± 3,4 years), mitral-aortic valve involvement, VRE, chronic renal failure, sepsis and septic shock, and the lack of cardiovascular surgery to treat active endocarditis were significantly associated with mortality ($p < 0.05$) (**Table 3**). As expected, the best prognosis was for patients with valve and cardiovascular surgery (HR = 0.51; 95% CI 0.26–0.99; $p < 0.05$) (**Table 3**). In multivariate analysis, only chronic renal failure (RR = 1.60; 95% CI 1.01–2.55; $p < 0.05$), septic shock (RR = 2.19; 95% CI 1.499–3.22; $p < 0.01$) and age over 60 years (RR = 2.28; 95% CI 1.44–3.59; $p < 0.01$) were indirectly associated with in-hospital mortality (**Table 4**).

TABLE 3: Univariate analysis of the risk of mortality in 73 cases with infective endocarditis (IE).

Variable	Discharge from hospital	In-hospital mortality	p-value
Age (mean, yr)	37.8 ± 3.2	56 ± 3,4	<0.01
Mitral-aortic	9 (23.7)	1 (2.8)	<0.05
Tricuspid	7 (18.4)	3 (8.5)	<0.05
VRE	-	4 (12.1)	<0.05
Chronic renal failure	10 (26.3)	17 (48.5)	<0.05
Sepsis	4 (10.5)	15 (42.8)	<0.01
Septic shock	2 (5.2)	12 (34.3)	<0.01
Surgery to treat the current IE episode	17 (44.7)	7 (20)	<0.05

VRE: vancomycin-resistant enterococci.

TABLE 4: Multivariate analysis of the risk of mortality in 73 patients with infective endocarditis.

Variable	RR	95%CI	p-value
Chronic renal failure	1.60	1.01-2.55	<0.05
Septic shock	2.19	1.49 -3.22	<0.01
Age>60 years	2.28	1.44 -3.59	<0.01

RR: relative risk; **CI:** confidence interval.

DISCUSSION

IE is a life-threatening systemic infectious disease, in which a multidisciplinary group of specialists is required for the case treatment and follow-ups[2]. Despite IE being a rare pathology, its incidence has increased in developed countries and few studies are available in developing countries[2,6]. Endocarditis is the fourth most important life-threating infectious syndrome after urosepsis, pneumonia, and intra-abdominal sepsis in medical departments in developed countries[13].

In this IE cohort, the prevalence of CAIE and HAIE was 32.9% and 67.1%, respectively. In addition, 32.8% were episodes of non-nosocomial HAIE and 34.3% were nosocomial IE. Therefore, a higher prevalence of HAIE was observed than those reported in recent epidemiological studies of IE in low- and middle-income countries[7,8].

In this investigation, the main etiologic agents identified in blood culture were *S. aureus* (30.1%), *Enterococcus* spp. (19.1%), and *Streptococcus* spp. (15.0%). Among the 49 cases of HAIE, the most prevalent agents were *S. aureus* (38.7%), *Enterococcus* spp., (20.4%), and CNS (10.2%). The principal etiology in 24 episodes of CAIE was *Streptococcus* spp. (45.8%). Our findings show that *S. aureus* and *Enterococcus* spp. are emerging agents of IE in Rio de Janeiro. This scenario has probably changed because a higher proportion of our patients had classic risks for *S. aureus* or *Enterococcus* spp. bacteremia, as observed previously[14-17].

All patients with MRSA bacteremia as the cause of IE developed HAIE and we did not observe any case of MRSA due to CAIE. Among the six MRSA IE cases, five different STs were found, in which two isolates were related to known epidemic lineages (USA400/ST1/SCCmec IV and USA 800/ ST105/SCCmec IV). Some epidemic clones with worldwide distribution can be identified by the characterization of SCC*mec*, ST, and PVL, as we presented in our results.

The in-hospital mortality in six patients with MRSA IE was 50%. In the present cohort, 100% (n=4) of the patients with vancomycin-resistant *E. faecium* HAIE died during treatment. The overall in-hospital mortality was 47.9% and 10.9% and 36.9% in the CAIE and HAIE patient groups, respectively. We observed the best outcome in the group of patients that received clinical and surgical treatment for the IE episode, according to the guidelines for the management of IE[2].

In most developing countries, the epidemiology of IE remains similar to the rates reported in North America and Europe in the twentieth century; the disease often affects a younger age group, is associated with rheumatic heart disease, and is predominantly caused by streptococci[6,8]. The present study showed a different scenario in Rio de Janeiro, where, in 73 cases of IE, *S. aureus* was the most frequent cause of IE, followed by *Enterococcus* spp and *Streptococcus* spp. The current epidemiology of IE in Brazil may be more similar to that of North America, where *S. aureus* and *Enterococcus* spp are the most significant agents of IE[16,18].

In general, the prevalence of positive blood cultures in IE patients was 87.6%. **Figure 1** reviews 21 IE studies performed in low- and middle-income countries during the same period of our investigation. The authors specified the frequency of positive and negative blood cultures and only elicited papers included studies presenting the data for etiology, prevalence of CAIE and HAIE, and outcome of disease. This resulted in 3,592 patients with IE, as defined by the Duke criteria, of which 2,362 (65.7%) and 1,109 (30.8%) had positive and negative blood culture results, respectively (**Figure 1**). Among the positive blood cultures, *Streptococcus* spp. was isolated in 852 cases (23.7%), *S.aureus* in 687 (19.1%), and *Enterococcus* spp. in 102 (2.8%). The prevalence of CAIE and HAIE were 46–94% and 9–56.3%, respectively. The mortality rate of inpatients was 7.3–46.4%.

The difference in the etiology of IE and outcome in our study may have been due to the high proportion of patients with many comorbidities and the low prevalence of rheumatic heart disease. The principal comorbidities in our patients with IE were chronic renal insufficiency (36.9%), diabetes mellitus (10.9%), kidney transplantation, and neoplasia (8.2%), similar to those observed in the ICE cohort study[18]. In our series, one reason for the high prevalence of *S.aureus* and *Enterococcus* spp. IE may have been due to the fact that many patients had vascular devices (**Table 2**) compared to the proportions in other studies of IE in developing countries.

The most relevant classical signs and symptoms of IE were fever (97.2%), and heart murmur (87.6%), similar to those found in other studies[19]. The classic Oslerian manifestations of endocarditis were present only in 38.4% of patients with IE at admission, which corroborates to the indication for echocardiography in cases of bacteremia due to *Staphylococcus* spp., *Enterococcus* spp., and *Streptococcus* spp. in teaching hospitals[2-5,19].

In our multivariate analysis, chronic renal failure (RR = 1.60; 95% CI 1.01–2.55; p <0.05), septic shock (RR 2.19; 95% CI 1.499–3.22; p <0.01), and age over 60 years (RR 2.28; 95% CI 1.44–3.59; p <0.01) were indirectly association with in-hospital mortality. As expected, the best prognosis was for valve and cardiovascular surgery (HR = 0.51; 95% CI 0.26–0.99; p <0.05).

FIGURE 1: Review of IE studies in low- and middle-income countries. **References** [1,29-30].

Year	Country	IE Patients number	Follow-up (years)	Type of study	Multi-centric	Age (average; years-old)	Sex (male %)	Community associated (%)	Healthcare associated (%)	*Streptococcus* spp. number (%)	*Staphylococcus aureus* number (%)	CNS number. (%)	*Enterococcus* spp. number (%)	HACEK number (%)	Negative cultures number (%)	Mortality Risk Factors	Mortality rates (%)	Reference
2002	Lebanon	91	15	R	+	48	54.9	81	9	35 (50.7)	18 (26)	7 (10.1)	3 (4.3)	-	20 (22.5)	-	18.0	20
2004	Pakistan	66	5	R	-	28.6	66	94	6	20 (59)	3 (9)	5 (15.0)	1 (3)	-	32 (48)	-	27.0	21
2005	India	192	10	R	-	27.6	73.4	-	-	46 (23.2)	30 (15.1)	-	16 (8.1)	-	64 (32.3)	CHF, RF, prosthetic dysfunction	18.6	22
2006	Argentina	452	1.5	P	+	58.5	70	-	-	139 (38.3)	108 (29.8)	-	37 (10.2)	22 (6.1)	42 (10.8)	Age >60 years, CHF, septic shock	24.0	23
2006	Taiwan	315	9	R	-	50.6	59.3	-	-	97 (30.8	83 (26.3)	18 (5.7)	17 (5.4)	5 (1.6)	62 (20)	Nosocomial IE, neoplasm, RF	21.6	24
2006	Turkey	112	2	R	+	45.2	50	-	-	7 (28.7)	33 (35.1)	-	15 (16)	-	18 (16.1)	Hemodialysis, mobile vegetation, mental alteration	28.6	25
2007	Tunisia	435	10	R	+	32.4	55	-	-	70 (34.5)	71 (34.5)	-	17 (7.9)	6 (2.7)	193 (44.3)	-	20.6	26
2008	Tunisia	134	9	R	-	34.2	58	-	-	33 (24.8)	24 (18)	6 (4)	1 (1)	-	47(35)	CHF, vegetations> 15 mm	19.4	27
2010	Brazil	62	7	P	-	45	63	-	-	8 (20)	13 (32)	6 (15)	6 (15)	2 (5)	22 (35)	vegetations> 13 mm	31.0	28
2011	India	104	2	P	-	23.5	54.8	-	-	9 (31.5)	7 (20)	-	5 (17.5)	-	69 (66)	Underlying heart disease, septic shock	26.0	29
2013	Turkey	248	7	R	+	47	54.4	-	-	27 (11)	53 (21)	-	28 (11)	-	93 (37.5)	-	33.0	30
2014	Brazil	71	4	P	N	49.8	57.7	46	56.3	15 (25)	8 (30)	-	16 (26.7)	-	11 (15.4)	Age >45 years, RF	46.4	1
2015	New Caledonia	51	5	R	Y	52.4	60.8	84.3	15.7	15 (29.4)	16 (31.1)	7 (13.7)	2 (3.9)	-	7 (13.7)	-	21.5	31
2015	Lao PDR	36	1	P	N	25	41.7	-	-	7 (25)	2 (7.6)	-	2 (15.3)	2 (15.3)	22 (61.1)	-	38.9	32
2015	Turkey	325	3	R	N	46.9	57.5	76.9	23.9	63 (19.4)	65 (20.1)	52 (16)	22 (6.8)	-	92 (24)	CHF, dialysis, CNS emboli, coronary artery disease	27.8	33
2016	China	174	8	R	N	47.5	66	-	-	65 (61.9)	1 (10.4)	13 (12.3)	5 (4.7)	-	69 (39.7)	-	10.9	34
2016	Czech Republic	106	8	R	N	57	80	-	-	16 (13.5)	36 (30.8)	17 (14.5)	15 (12.8)	-	21 (17.9)	-	16.9	35
2017	Lebanon	166	27	R	N	53.5	62	-	-	55 (33.1)	33 (15)	-	15 (9)	4 (2.1)	45 (28)	Paravalvular complications, aortic vegetation	15.6	36
2017	Iran	55	3	R	N	33.9	78.2	-	-	3 (17.6)	6 (35.3)	3 (17.6)	2 (11.8)	-	38 (69.1)	-	7.3	37
2017	Martinique	201	13	R	N	58	67	59.7	38.3	61 (30.3)	46 (22.9)	12 (6)	10 (5)	8 (4)	42 (20.9)	-	19.0	38
2017	China	196	8	R	N	43.5	69.4	-	-	1 (42.7)	18 (18.8)	-	10 (10.4)	-	100 (51)	CHF, diabetes mellitus, age ≥60 years, *S. aureus* or GNB	-	39

+: positive; **-:** negative; **R:** retrospective; **P:** prospective; **CHF:** congestive heart failure; **RF:** rheumatic fever; **CNS:** central nervous system; **HACEK**: *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* species; **CNS:** coagulase-negative *Staphylococcus*; **GNB:** Gram-negative bacilli.

In our review of IE in developed countries, we had access to only 12 studies that included data from multivariate analysis of in-mortality rates in IE patients. These studies showed statistically significant relationships for age over 45 years, dialysis, chronic renal failure, septic shock, heart failure, prosthetic dysfunction, nosocomial IE, neoplasia, mobile vegetation, mental alteration, central nervous system emboli, coronary artery disease, aortic vegetation, and large vegetation.

The experience from a single teaching hospital and failure to investigate all patients by transesophageal echocardiography may have been limiting factors in the results of the present study. However, this eight-year prospective study of endocarditis highlights the epidemiologic and microbiologic features in Brazilian hospitals. In the near future, further investigation will be developed in different hospital centers.

In conclusion, among 73 episodes of IE reported in the last eight years in our hospital, located in the metropolitan area of Rio de Janeiro, *S. aureus*, *Enterococcus* spp., and *Streptococcus* spp. were the main causes of infection. *Enterococcus* spp. was also identified as an emerging etiology agent of HAIE in our country.

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Conflict of Interest

The authors declare no conflict of interest and affirm that there was no financial affiliation (e.g., employment, direct payment, stock holdings, retainers, consultantships, patent licensing arrangements or honoraria), or involvement with any commercial organization with a direct financial interest in the subject or materials discussed in this manuscript.

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