Infection Prevention in Practice 6 (2024) 100343

Available online at www.sciencedirect.com

Infection Prevention in Practice

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

Epidemiological differences, clinical aspects, and short-term prognosis of patients with healthcare-associated and community-acquired infective endocarditis

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ARTICLE INFO

Article history:
Received 13 September 2023
Accepted 25 January 2024
Available online 2 February 2024

Keywords:
Infective endocarditis
Healthcare-associated infections
Community-acquired
Epidemiology
Hospital mortality
Staphylococcus
Meticillin-resistant
Staphylococcus aureus

SUMMARY

Background: The prevalence of healthcare-associated infective endocarditis in Brazil is poorly known.
Aim: To analyze the epidemiological, clinical and microbiological characteristics, and the prognosis of healthcare-associated infective endocarditis (HAIE) compared with community-acquired infective endocarditis (CIE) and identify the associated factors with hospital mortality.
Method: A historical cohort study was carried out, with a data collection period from January 2009 to December 2019 at the *Federal University of São Paulo*. Data were collected from medical records of patients with infective endocarditis (IE) hospitalized during the study period. Patients were classified into three groups: CIE, non-nosocomial HAIE (NN-HAIE) and nosocomial HAIE (NHAIE).
Results: A total of 204 patients with IE were included; of these, 127 (62.3%) were cases of HAIE, of which 83 (40.7%) were NN-HAIE and 44 (21.6%) were NHAIE. *Staphylococcus spp.* Were the main causative agents, especially in HAIE groups ($P<0.001$). *Streptococcus spp.* were more prevalent in the CIE group ($P<0.001$). In-hospital mortality was 44.6%, with no differences between groups. Independent risk factors for in-hospital mortality were age $\geq$ 60 years (*odds ratio* (OR): 6.742), septic shock (OR 5.264), stroke (OR 3.576), heart failure (OR 7.296), and Intensive Care Unit admission (OR 7.768).
Conclusion: HAIE accounted for most cases in this cohort, with a higher prevalence of non-nosocomial infections. *Staphylococcus spp.* were the main causative agents. Hospital mortality was high, 44.6%, with no difference between groups.

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https://doi.org/10.1016/j.infpip.2024.100343

Introduction

Healthcare-associated infections are a problem of global magnitude. About 24% of cases of sepsis treated in hospitals are associated with healthcare, reaching almost half of cases treated in adult Intensive Care Units (ICU) [1].

In this context, infective endocarditis (IE), a disease with high morbidity and mortality, despite improvement in diagnosis and treatment, has shown an increase in incidence rates in recent years [2—4]. This increase can be attributed to a change in the microbiological profile with the emergence of *staphylococcus* and *streptococcus* as the main causes, and in the epidemiological pattern, such as the aging population, greater exposure to the healthcare system, and increased use of intracardiac and vascular devices [3—6], Previous studies indicated an incidence of 30% of cases of healthcare-associated IE (HAIE) in developed countries, mainly in hospital settings [7,8]. However, more recent studies highlight the importance of HAIE acquired outside hospital environments in patients undergoing invasive medical procedures in an outpatient setting [9,10]. Several studies show a worse prognosis and higher mortality in patients with HAIE [7,10—15]. Regarding Latin America, the region with the highest estimated IE incidence rates, and Brazil, the country with the highest global increase in IE incidence rates in 2019 [4], there are only two studies in which the differences between HAIE and community-acquired IE (CIE) were analyzed [16,17].

This study aimed to analyze the epidemiological, clinical, and microbiological characteristics, the risk factors and prognosis of healthcare-associated infective endocarditis (HAIE) compared with community-acquired infective endocarditis (CIE) and identify the associated factors with hospital mortality.

Method

Ethical aspects: The study was approved by the Research Ethics Committee of the *Universidade Federal de São Paulo* (673/2019, Opinion 3,588,513).

Study design, period, and location: A historical cohort study was carried out, with a data collection period from January 2009 to December 2019 at the University Hospital of the Federal University of São Paulo, Brazil. It is a tertiary centre, with reference services in cardiology, cardiac surgery, and haemodialysis.

Inclusion criteria and sample: Patients over 18 years old, hospitalized with a diagnosis of confirmed or possible IE according to the modified Duke criteria [18] and complete data in medical records, were included. Using the Echocardiography Department database, patients with suspected IE, hospitalized during the study period and who underwent transoesophageal echocardiography, were selected. The initial sample consisted of 278 patients with suspected IE; of these, 204 met the inclusion criteria. Thus, 74 patients were excluded: 16 due to incomplete data in medical records; and 58 because they did not meet the modified Duke criteria.

Data collection and analysis of results: Demographic data, comorbidities, predisposing cardiac condition, clinical and echocardiographic findings, causative microorganisms, complications, and outcomes (survival and death) were collected. Medical record analysis and insertion of data into the database were independently reviewed by two investigators. For analysis of results, patients were classified into three groups: CIE, non-nosocomial HAIE (NN-HAIE) and nosocomial HAIE (NHAIE). HAIE groups were compared separately with the CIE group.

Variable definitions

- Non-nosocomial HAIE (NN-HAIE) was defined as occurring before or within 48 hours of hospital admission in a patient with extensive out-of-hospital exposure to medical interventions such as: receiving intravenous therapy, haemodialysis, intravenous chemotherapy, wound care, or skilled nursing care in the 30 days prior to onset of IE; hospitalization for two or more days within 90 days before onset of IE; residence in a Nursing Home or long-term care facility prior to hospital admission;
- Nosocomial HAIE (NHAIE) was defined as those whose signs and symptoms compatible with IE developed after 48 hours or more of hospital admission.
- CIE was defined as IE whose signs and symptoms developed before or within 48 hours of hospital admission and who did not meet the criteria for NN-HAIE [2,10,15].
- Early prosthetic valve IE was defined as IE occurring within one year after prosthetic valve surgery, and was classified as HAIE [19,20].
- Predisposing cardiac condition was defined as a history of heart valve replacement (bioprosthesis or mechanical prosthesis), congenital heart defects, valve disease, including rheumatic and other acquired valve disease, previous episode of IE, and implantation of a cardiac device such as a pacemaker or defibrillator.
- Complications of IE included acute heart failure, arterial embolisms such as stroke, splenic, renal, gastrointestinal, and pulmonary infarction, sepsis and septic shock, and acute kidney injury (AKI) requiring haemodialysis.
- Sepsis was defined as organ dysfunction caused by a dysregulated response to infection. Septic shock was defined as sepsis with resistant hypotension that requires vasopressors to maintain mean arterial pressure (MAP) $\geq$ 65 mmHg [21].
- AKI was defined according to the KDIGO criteria [22].

Statistical analysis: Data were collected from patients' medical records (physical and electronic), which were stored in Excel 2016 spreadsheets and analyzed using the free software R version 4.2.2 for Windows. In the descriptive data analysis, qualitative variables are presented as numbers and percentages, and quantitative variables are summarized through mean, standard deviation (SD), median, interquartile range according to the type of distribution. Likewise, comparative statistical analyses between groups were performed using

Student's t test or Mann-Whitney test for quantitative variables. Regarding qualitative variables, the chi-square test, Fisher's exact test were used. Logistic regression was performed to identify variables related to death. The Odds Ratio (OR) was calculated with a 95% Confidence Interval. After univariate analysis, variables with *P*-values less than 0.05 were included in the multivariate logistic regression. *P*-values less than 0.05 were considered statistically significant.

Results

A total of 204 cases of IE were registered during the study period; of these, 77 cases (37.7%) were classified as CIE, and 127 cases (62.3%) met criteria for HAIE, 83 (40.7%), for NN-HAIE, and 44 (21.6%), for NHAIE. In the NN-HAIE group, 32 (38.6%) were hospitalized for two or more days in the 90 days prior to admission and 63 patients (76%) were on haemodialysis (Table I). In the NHAIE group, the main primary causes of hospitalization were infections, cardiovascular diseases, and neurological disorders (Supplementary Table A1).

Predisposing factors, clinical, microbiological, and echocardiographic findings

The mean age of the patients was 53 years. Men accounted for 57.8% of patients, with no statistical differences in the analyzed groups. In the CIE group, there was a greater number of patients with valve disease and previous cardiac surgery compared to the HAIE groups ($P<0.001$). Chronic diseases such as hypertension and diabetes were observed in greater proportion in HAIE groups ($P<0.001$). Compared to the CIE group, the NN-HAIE group had significantly more patients with chronic kidney disease on haemodialysis (1.3% vs 76%, $P<0.001$) and greater use of intravascular catheters (1.3% vs 65%, $P<0.001$). Recent bloodstream infection (BSI) was observed in 18% of patients in the NN-HAIE ($P<0.001$) group and 9% in the NHAIE group ($P=0.016$), while there were no cases in the CIE group. Fever was observed in nearly 90% of patients, with no differences between groups. Heart murmur was observed in 75% of patients in the CIE group, 47% in the NN-HAIE subgroup and 22.7% in the NHAIE subgroup ($P<0.001$).

Gram-positive bacteria accounted for more than 70% of cases of IE. There were no cases of IE caused by Gram negative bacteria and fungi in the CIE group. Negative blood cultures were more common in the CIE group (29.9%) than in the NN-HAIE group (8.4%) ($P=0.001$), but not different when compared to NHAIE group (15.9%) ($P=0.087$). *Staphylococcus aureus* was the causative agent in almost half of cases in HAIE groups (NN-HAIE $P=0.028$; NHAIE $P=0.082$), followed by coagulase-negative *Staphylococcus* (CoNS), with 30% of cases in these groups. CoNS were responsible for 15.6% of cases in the CIE group, of which 71.3% had a history of previous cardiac surgery. *Streptococci* accounted for about 25% of infections in the CIE group (CIE *vs* NN-HAIE $P<0.001$). There were no cases of infection caused by *Streptococcus spp.* in the NHAIE group. (Figure 1). Meticillin-resistant *Staphylococcus aureus* (MRSA) strains were observed in almost 30% of the samples and meticillin-resistant strains were observed

Table I
Main clinical characteristics of patients with CIE and (non-nosocomial and nosocomial) HAIE and echocardiographic findings in exams performed

	CIE	HAIE		Total	*P-value*	
		Non-nosocomial	Nosocomial			
	N=77	*N*=83	*N*=44	*N*=204	(CIE vs NNHAIE)	(CIE vs NHAIE)
Male	49 (63.6)	42 (50.6)	27 (61.4)	118 (57.8)	0.096	0.804
Median age	51.21 [38; 65]	52.89 [40; 66.5]	57 [46; 68.5]	53.14 [40.75; 67]	0.526 ǂ	0.071**
Predisposing cardiac conditions						
Previous valvular disease	25 (32.5)	8 (9.6)	8 (18.2)	41 (20)	<0.001	0.089
Rheumatic heart disease	15 (19.5)	2 (2.4)	2 (4.5)	19 (9.3)	<0.001	0.023
Previous IE episode	11 (14.3)	6 (7.3)	2 (4.5)	19 (9.3)	0.148	0.130*
Cardiac device	6 (7.8)	3 (3.6)	5 (11.4)	14 (6.9)	0.315	0.526
Previous cardiac surgery	31 (40.3)	13 (15.7)	7 (16)	51 (25)	<0.001*	0.005*
Coronary artery bypass grafting	1 (1.3)	5 (6)	1 (2.3)	7 (3.4)	0.212*	1*
Valve surgery	23 (29.9)	3 (3.6)	4 (9.1)	30 (14.7)	<0.001	0.008
Others	7 (9)	5 (6)	2 (4.5)	14 (6.9)	0.286	0.485*
Comorbidities						
Cancer	12 (15.6)	8 (9.9)	6 (13.6)	26 (12.9)	0.281	0.772
High blood pressure	34 (44.2)	70 (84.3)	27 (61.4)	131 (64.2)	<0.001	0.068
Diabetes	8 (10.4)	32 (38.5)	16 (36.4)	56 (27.5)	<0.001	<0.001
Haemodialysis	1 (1.3)	63 (76)	13 (29.5)	77 (37.7)	<0.001	<0.001

(continued on next page)

Table I (*continued*)

	CIE	HAIE		Total	*P-value*	*P-value*
		Non-nosocomial	Nosocomial			
	N=77	*N*=83	*N*=44	*N*=204	(CIE vs NNHAIE)	(CIE vs NHAIE)
Intravascular catheter (central)	1 (1.3)	54 (65)	11 (25)	66 (32.4)	<0.001	<0.001*
Recent blood stream infection	0	15 (18.3)	4 (9)	19 (9.4)	<0.001	0.016*
Recent hospital admission	14 (18.2)	32 (38.6)	11 (25)	57 (27.9)	0.004	0.373
Clinical finding at presentation						
Fever	68 (88.3)	73 (88)	40 (90.9)	181 (88.7)	0.944	0.767*
Heart murmur	58 (75)	39 (47)	10 (22.7)	107 (52.5)	<0.001	<0.001
Echocardiographic findings						
Exam day						
Mean (SD)	7.307 (5.261)	8.607 (5.092)	25.64 (23.770)	11.83 (13.987)	0.047‡	<0.001‡
Vegetation						
Mitral valve	44 (57.1)	26 (31.3)	7 (15.9)	77 (37.7)	0.001	<0.001
Aortic valve	20 (26)	21 (25.3)	15 (34.1)	56 (27.4)	0.922	0.343
Tricuspid valve	5 (6.5)	11 (13.3)	2 (4.5)	18 (8.8)	0.154	1*
Pulmonary valve	2 (2.6)	0	0	2 (0.9)	-	-
Right atrium	4 (5.2)	3 (3.6)	2 (4.5)	9 (4.4)	0.712*	1*
Superior vena cava	0	3 (3.6)	2 (4.5)	5 (2.5)	-	-
Vascular and cardiac devices	6 (7.8)	11 (13.3)	12 (27.3)	29 (14.2)	0.263	0.004
Vegetation size (mm)						
<10 mm	28 (36.4)	28 (33.7)	22 (50)	78 (38.2)	0.727	0.143
≥10 mm	37 (48.1)	45 (54.2)	20 (45.5)	102 (50)	0.436	0.783
Dysfunction degree						
Moderate and Important						
Mitral valve	42 (54.5)	21 (25.3)	8 (18.2)	71 (34.8)	<0.001	<0.001
Aortic valve	23 (29.9)	15 (18.1)	6 (13.6)	44 (21.6)	0.079	0.044
Tricuspid valve	16 (20.8)	10 (12)	2 (4.6)	28 (13.7)	0.135	0.016
Pulmonary valve	1 (1.3)	0	0	1 (0.5)	-	-
Right ventricle	4 (5.2)	2 (2.4)	1 (2.3)	7 (3.4)	0.429*	0.652*
Left ventricle	8 (10.4)	9 (10.8)	7 (15.9)	24 (11.8)	1	1

Data are expressed as the mean (SD), number (percentage) or median [interquartile range]. Applied tests: Chi-square test; * Fisher's exact test; ** Student's t test; ǂ Mann-Whitney. CIE — community-acquired infective endocarditis; HAIE - healthcare-associated infective endocarditis.

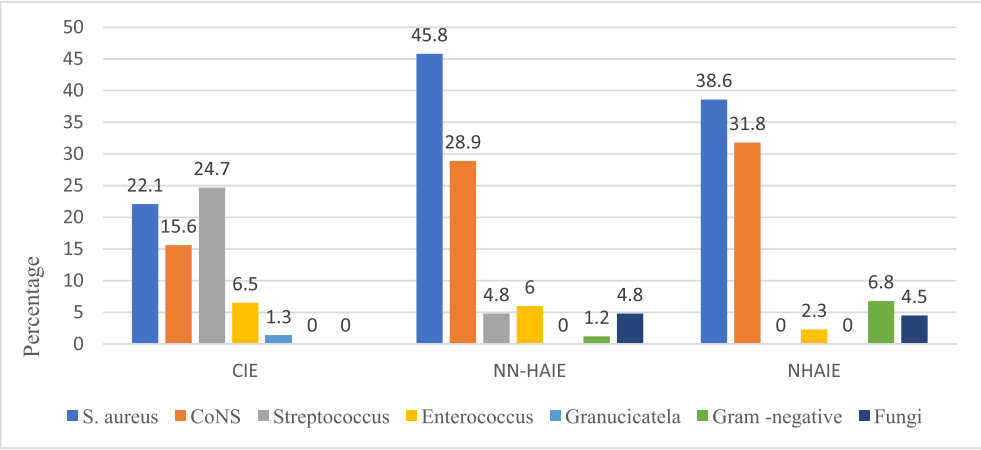

Figure 1. Etiologic IE agents in patients with CIE and HAIE.

in 85% of CoNS samples, with no significant difference between groups (Supplementary Table A2).

Transoesophageal echocardiogram (TOE) was performed in all patients in the study. The mitral valve was more affected in the CIE group than in HAIE groups (NN-HAIE P=0.001, NHAIE P<0.001). In the NHAIE group, a greater number of vegetations were observed in intravascular and cardiac devices, superior vena cava and right atrium wall (P=0.004) (Table I). Complications such as abscess, leaflet perforation and valve pseudoaneurysm were observed in greater number in the CIE group compared to HAIE groups, with greater involvement of the mitral (NN-HAIE P=0.004; NHAIE P=0.006) valve (Supplementary Table A3). Vegetations $\geq$ 10 mm were found in half of the exams, with no statistical differences between groups. In the CIE group, there were more patients with moderate and severe dysfunction in the mitral valve compared to HAIE groups (P<0.001).

Complications and outcomes

Compared with the NHAIE group, embolic events were observed more frequently in the CIE group (P=0.026). The central nervous system (CNS) was the most affected site (P=0.028). Splenic, renal and intestinal emboli were observed more frequently in the CIE group than in HAIE groups (NN-HAIE P=0.001, NHAIE P=0.029) (Table II). Higher frequency of sepsis was observed in HAIE groups (NN-HAIE P=0.044; NHAIE P=0.036) compared to CIE. Septic shock was observed in approximately 37% of the study patients, with no differences between groups. HAIE groups patients had more associated infections during hospitalization. In the NHAIE group, 75% acquired BSI (P<0.001), 52.3%, pneumonia (P=0.064), 31.8%, urinary tract infection (P=0.012), and 20.5%, other associated infections (P=0.002) during hospitalization.

About half of patients had AKI during hospitalization and about 30% required haemodialysis during hospitalization, with no statistical differences between groups. Acute heart failure was observed in 19.6% in the NN-HAIE group and 39% of patients in the CIE group (P=0.006). Surgical treatment was indicated in 70% of patients in the CIE group compared to 30% in HAIE groups (P<0.001). In the CIE group, almost 60% of patients underwent surgical treatment, against 20% in HAIE groups (P<0.001) (Supplementary Table A4). ICU admission was required in approximately 80% of patients in this cohort, with no statistical differences between groups. The NHAIE group had a longer length of stay in hospital compared to the CIE group (P=0.019). Thus, 91 (44.6%) patients died during hospitalization; of these, 34 (44.2%) were from the CIE group, 32 (38.6%) from the NN-HAIE group, and 25 (56.8%) from the NHAIE group, with no statistical differences between groups.

Risk factors for healthcare-associated infective endocarditis

In univariate analysis, previous valvular disease, previous cardiac surgery, diabetes, hypertension, haemodialysis, central venous catheter use, and recent hospital admission were associated with non-nosocomial IE (NN-HAIE). In the multivariate analysis, haemodialysis (OR 9.851; P<0.001) and recent hospital admission (OR 2.72; P=0.02) were independent risk factors to NN-HAIE. Healthcare-associated infections, embolic events, stroke and performing cardiac surgery during hospitalization were associated with nosocomial IE (NHAIE) in univariate analysis. Multivariate analysis showed that infections associated with hospitalization were independent risk factors for contracting nosocomial IE (OR 5.231; P<0.001) (Supplementary Table A5).

Risk factors for in-hospital mortality

In univariate analysis, age $\geq$ 60 years, arterial hypertension, care-associated infections, septic shock, ICU admission, embolic events, stroke, and acute heart failure were associated with mortality. In the multivariate analysis, age $\geq$ 60 years (OR 6.742; P<0.001), septic shock (OR 5.264; P<0.001), stroke (OR 3.576; P=0.029), heart failure (OR 7.296; P<0.001) and ICU admission (OR 7.768; P=0.003) were independent risk factors for in-hospital mortality (Table III).

Discussion

The results of this study show that patients with HAIE accounted for most cases of IE in the cohort studied (62.3% of the total). Two studies carried out in Brazil found similar results

Table II
Complications and outcomes in patients with CIE and (non-nosocomial and nosocomial) HAIE

	CIE	HAIE		Total	*P-value*	*P-value*
		Non-nosocomial	Nosocomial			
	N=77	*N*=83	*N*=44	*N*=204	(CIE vs NNHAIE)	(CIE vs NHAIE)
Embolic events	33 (42.9)	28 (33.7)	10 (22.7)	71 (34.8)	0.235	0.026
Central Nervous System	22 (28.6)	21 (25.3)	5 (11.4)	48 (23.5)	0.641	0.028
Pulmonary	2 (2.6)	8 (9.6)	2 (4.5)	12 (5.9)	0.101*	0.621*
Osteoarticular	5 (6.5)	4 (4.8)	1 (2.3)	10 (0.5)	0.739*	0.415*
Others	17 (22.1)	4 (4.8)	3 (6.8)	24 (11.8)	0.001	0.029
Infectious complications						
Sepsis	12 (15.6)	24 (28.9)	14 (31.8)	50 (24.5)	0.044	0.036
Septic shock	27 (35.1)	31 (37.4)	17 (38.6)	75 (36.8)	0.764	0.694
Healthcare-associated infections						
Bloodstream infection	22 (28.6)	33 (39.8)	33 (75)	88 (43.1)	0.137	<0.001
Pneumonia	27 (35.1)	31 (37.4)	23 (52.3)	81 (39.7)	0.764	0.064
Urinary tract infection	10 (13)	9 (10.8)	14 (31.8)	33 (16.2)	0.675	0.012
Others	2 (2.6)	9 (10.8)	9 (20.5)	20 (9.8)	0.039	0.002*
Acute kidney injury (AKI)	44 (57.1)	32 (38.6)	27 (61.4)	103 (50.5)	0.014	0.447
AKI without haemodialysis	22 (28.6)	12 (14.5)	11 (25)	45 (22.1)	0.029	0.671
AKI with haemodialysis	22 (28.6)	20 (24.1)	16 (36.4)	58 (28.4)	0.520	0.374
Heart failure	30 (39)	16 (19.3)	15 (34.1)	61 (29.1)	0.006	0.594
Intensive Care Unit (UCI)	61 (79.2)	60 (72.3)	36 (81.8)	157 (77)	0.307	0.730
Indication for surgical treatment	54 (70.1)	25 (30.1)	8 (18.2)	87 (42.6)	<0.001	<0.001
Surgery	45 (58.4)	17 (20.5)	7 (15.9)	69 (33.8)	<0.001	<0.001*
Post-operative IE	0	0	5 (11.4)	5 (2.5)	-	-
Length of stay Mean (SD)	41.9 (22.287)	40 (26.551)	58.34 (38.873)	44.67 (29.037)	0.327‡	0.015‡
Outcomes						
Death	34 (44.2)	32 (38.6)	25 (56.8)	91 (44.6)	0.555	0.152

Data are expressed as the mean (SD) or number (percentage). Applied tests: Chi-square test; * Fisher's exact test; ‡ Mann-Whitney test.

Table III
Risk factors for in-hospital death in patients with infective endocarditis

Risk factor	Univariate		Multivariate	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Age ≥ 60 years	4.583 [2.507; 8.582]	<0.001	6.742 [2.821; 17.418]	<0.001
Male	1.114 [0.636; 1.959]	0.706		
Previous valvular disease	1.689 [0.844; 3.423]	0.14		
Diabetes	1.355 [0.729; 2.521]	0.335		
High blood pressure	1.88 [1.044; 3.440]	0.037	1.061 [0.454; 2.469]	0.889
Haemodialysis	1.061 [0.598; 1.877]	0.839		
Staphylococcus aureus infection	1.182 [0.662; 2.111]	0.57		
CoNS infection	0.781 [0.404; 1.487]	0.456		
Negative blood culture	0.995 [0.476; 2.050]	0.988		
Other healthcare-associated infections	3.144 [1.712; 5.943]	<0.001	1.385 [0.553; 3.464]	0.484
Septic shock	10.364 [5.356; 21.022]	<0.001	5.264 [2.211; 13.168]	<0.001
Embolic events	1.912 [1.068; 3.448]	0.029	0.404 [0.136; 1.117]	0.089
Stroke	4.25 [2.142; 8.820]	<0.001	3.576 [1.153; 11.715]	0.029
Heart failure	5.489 [2.854; 11]	<0.001	7.296 [3.122; 18.382]	<0.001
Intensive Care Unit admission	10.2 [4.166; 30.735]	<0.001	7.768 [2.213; 33.174]	0.003
Surgical IE treatment	1.274 [0.708; 2.292]	0.418		
Mitral valve endocarditis	0.915 [0.522; 1.598]	0.754		
Aortic valve endocarditis	0.708 [0.382; 1.296]	0.267		
Vegetation ≥ 10 mm	1.697 [0.972; 2.985]	0.064		
Type of IE				
CIE	1.002 [0.562; 1.783]	0.993		
Non-nosocomial (NN-HAIE)	0.659 [0.371; 1.163]	0.153		
Nosocomial (NHAIE)	1.769 [0.909; 3.482]	0.094		

OR — Odds Ratio; CI — Confidence Interval.

[16,17], but other recent Latin American and Caribbean studies found lower rates [23,24]. The prevalence of HAIE in this cohort was higher than that reported in European and Asian studies (18—46%) [7,9—12,15,25,26], but closer to North American results (50—58%) [13,27].

Regarding the studied cohort's profile, very clear differences can be traced among the groups. Some differences in the profile of the patients were observed. The CIE group included predominantly patients with a profile like those of high-income countries, such as, middle-aged, predisposing cardiac conditions for endocarditis (valve disease and previous cardiac surgery), *Streptococcus* or *Staphylococcus* infections, greater involvement of the mitral and aortic valves, higher prevalence of embolic events, heart failure and indication for surgical treatment. On the other hand, patients with NN-HAIE had chronic diseases such as hypertension, diabetes, chronic kidney disease undergoing haemodialysis and history of hospitalization in the 90 days prior to admission. Patients with NHAIE were mostly older men, with chronic diseases, whose initial cause of hospitalization was not related to IE, but the exacerbation of chronic diseases or other infections; also, the patients of this group had IE in central catheters and cardiac devices, greater occurrence of complications such as AKI and ICU admission, longer length of stay in hospital, mainly higher incidence of healthcare-associated infections, especially BSI, urinary tract infection and pneumonia.

Staphylococcus aureus was the main causative agent in patients with HAIE, a profile like that found in high-income countries [28]. CoNS also played a relevant role, accounting for one third of infections in HAIE groups. The emergence of CoNS is related to immunocompromised patients and use of intravascular devices [29], a characteristic of patients with HAIE. About 85% of meticillin resistance was found in CoNS samples and in 40% of MRSA in patients with NHAIE. In a Spanish multicentre study, published in 2020, MRSA was associated with HAIE [30]. *Staphylococcus aureus* and CoNS are the main agents involved in central line-associated ICS in the United States. Like CoNS, MRSA is strongly associated with biofilm formation on intravascular devices, making infections persistent and difficult to treat [29,31,32]. Negative blood cultures occurred in about a third of the samples collected from the CIE group, a percentage similar to other Latin American studies [33,34]. This result can be explained by economic limitations resulting in restrictive access to serological tests and molecular biology techniques for diagnosing infections by fastidious bacteria and by using antimicrobials before collecting cultures. A previous study reported that there is a relevant role of infections by *Staphylococcus* and mainly, *Streptococcus*, in cases of IE with blood culture sterilized by previous antimicrobial treatment [35]. In the present cohort, more than half of patients received or were being treated with antimicrobials at the time of blood culture collection, which could explain the high percentage of negative samples.

In-hospital mortality was 44.6%, higher than the mean reported in studies from high-income countries [36]. Although NHAIE had a higher mortality rate, there were no statistical differences between groups analyzed. Other national studies reported similar rates [16,17,37], placing Brazil as one of the

countries with the highest risk of death from IE [4,38]. Regarding cases of HAIE in this study and in other Latin American studies [16,23,33,34], the use of central intravascular catheters and BSI had a strong relationship with patients of nosocomial and non-nosocomial IE. Therefore, strengthening of infection prevention and control teams, healthcare professional training regarding insertion and care in central catheter management and staff awareness regarding compliance with care-related infection prevention measures are feasible actions to reduce HAIE rates [39]. Furthermore, multicentre studies are needed to draw a more reliable picture of the epidemiology of IE, in particular HAIE, at the national and regional levels.

Despite the results, the present study has limitations. First, it was conducted at a single centre, with retrospective data analysis through medical records, which can lead to loss of information. Moreover, there was no longitudinal follow-up of survivors and, therefore, these patients' long-term prognosis cannot be assessed. Failure to perform serological tests and molecular biology techniques for cases of negative blood culture prevented the diagnosis of infections by fastidious bacteria. Although the results were similar to national prospective studies carried out in southeastern Brazil, the results of the present study may not reflect HAIE's and CIE's real situation in other areas of the country, making it necessary to carry out national multicentre studies including all regions.

Conclusion

HAIE accounted for the majority of cases of IE in this cohort. There was a higher prevalence of NN-HAIE, and haemodialysis and recent hospitalization were factors associated with IE in this group. In the NHAIE group, acquiring other infections during hospitalization was a risk factor for IE. *Staphylococcus aureus* and CoNS were the main causative agents of HAIE. There was a higher prevalence of MRSA infections in patients with NHAIE. In-hospital mortality was high, with 44.6%. Independent risk factors for in-hospital death were age over 60 years, heart failure, CNS embolization, ICU admission, and septic shock.

Conflict of interest

The authors have no conflicts of interest to declare.

Sources of funding

There was no source of funding for the research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.infpip.2024.100343.

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