Healthcare-Associated Infective Endocarditis: a Case Series in a Referral Hospital from 2006 to 2011

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Abstract

Background: **Healthcare-associated infective endocarditis (HCA-IE), a severe complication of medical care, shows a growing incidence in literature.**

Objective: **To evaluate epidemiology, etiology, risk factors for acquisition, complications, surgical treatment, and outcome of HCA-IE.**

Methods: **Observational prospective case series study (2006–2011) in a public hospital in Rio de Janeiro.**

Results: **Fifty-three patients with HCA-IE from a total of 151 cases of infective endocarditis (IE) were included. There were 26 (49%) males (mean age of 47 ± 18.7 years), 27 (51%) females (mean age of 42 ± 20.1 years). IE was acute in 37 (70%) cases and subacute in 16 (30%) cases. The mitral valve was affected in 19 (36%) patients and the aortic valve in 12 (36%); prosthetic valves were affected in 23 (43%) patients and native valves in 30 (57%). Deep intravenous access was used in 43 (81%) cases. Negative blood cultures were observed in 11 (21%) patients, *Enterococcus faecalis* in 10 (19%), *Staphylococcus aureus* in 9 (17%), and Candida sp. in 7 (13%). Fever was present in 49 (92%) patients, splenomegaly in 12 (23%), new regurgitation murmur in 31 (58%), and elevated C-reactive protein in 44/53 (83%). Echocardiograms showed major criteria in 46 (87%) patients, and 34 (64%) patients were submitted to cardiac surgery. Overall mortality was 17/53 (32%).**

Conclusion: **In Brazil HCA-IE affected young subjects. Patients with prosthetic and native valves were affected in a similar proportion, and non-cardiac surgery was an infrequent predisposing factor, whereas intravenous access was a common one. S. aureus was significantly frequent in native valve HCA-IE, and overall mortality was high. (Arq Bras Cardiol. 2014; 103(4):292-298)**

Keywords: **Endocarditis, Bacterial/mortality; Endocarditis Bacterial/etiology; Risk Factors; Cross Infection.**

Introduction

Infective endocarditis (IE) is a severe disease and is potentially lethal if not treated with antimicrobials or with surgical therapy[1]. A close association between IE and medical care, especially hospitalization and invasive procedures, has been observed since the 1950s[2]. A study done in the United Kingdom showed a seven-fold increase in the incidence of nosocomial or health-care associated IE (HCA-IE) between 1985 and 1996[2]. This increase has been credited to advances in invasive medical procedures, especially the use of intravenous catheters[2,3].

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Manuscript received January 24, 2014; revised March 18, 2014; accepted May 5, 2014.

DOI: 10.5935/abc.20140126

HCA-IE is an important public health problem and represents 10–34% of all cases of IE[4-8]. It is a severe complication of hospitalization and is associated with higher morbidity and mortality when compared to community acquired IE. Chen et al[9] (1992) described a higher incidence of congestive heart failure and hypotension in HCA-IE than in community acquired IE[9]. In-hospital mortality of HCA-IE was also significantly higher (40% vs 18%, p = 0.02) than community acquired IE mortality[9].

In this study, consecutive cases of HCA-IE at a public Brazilian cardiac surgery hospital, from 2006 to 2011, were evaluated, focusing on the epidemiology, risk factors, complications, and surgical outcome.

Methods

This is an observational prospective case series study performed between 2006 and 2011, in a public federal hospital in the city of Rio de Janeiro, the Instituto Nacional de Cardiologia (INC). INC is a referral center for cardiac

surgery, and it receives a large number of cases of IE from other hospitals in the State of Rio de Janeiro, as well as cases originating from its several outpatient units, especially the Valve Department.

Cases were enrolled consecutively when they filled definite or possible criteria for IE, as per the modified Duke criteria[10].

HCA-IE was defined as IE that developed more than 72 hours following hospital admission, or IE acquired as a result of an invasive procedure within the previous eight weeks before the development of signs and symptoms[3,11,12]. Early prosthetic valve endocarditis (PVE) was defined as endocarditis manifesting up to one year following valve surgery and classified as *healthcare-associated*[12-16]. When IE was associated to pacemakers and implantable cardioverter-defibrillators, it was considered hospital-acquired if it occurred within one year from the insertion of the device[15,16].

Patients above the age of 14 years with definite diagnosis of HCA-IE who agreed to participate in the study (or their parents or legal guardian did) were included. All patients or guardians signed an informed consent form and had a case report form (CRF) filled. The CRF used is the model from the International Collaboration on Endocarditis, as INC has been a collaboration site since 2006. Selected data obtained from the CRF were collected and analyzed (descriptive statistics) in Excel charts (Microsoft®). Data were described as mean ± standard deviation. The Statcalc program, CDC's EpiInfo® version 7.1.1.0 was used for chi-square or Fishers' exact tests, as appropriate. Odds ratio and 95% intervals were estimated; a p value of 0.05 was considered statistically significant.

The study was approved by the Ethics Committee from INC under the number 0171/2006.

Results

Between January 1st, 2006, and December 31st, 2011, 151 patients with IE were admitted to the INC. Of these, 53 (35%) met the criteria for HCA-IE. The ratio of HCA-IE and all cases of IE per year between 2006 and 2011 are represented in Graph 1. The proportions were as follows: 33%, 29%, 29%, 42%, 33%, and 38%, respectively, for the years 2006–2011.

According to the modified Duke criteria, cases were definite and possible, in 42 (79%) and 11 (21%) of the cases, respectively. Of the HCA-IE cases, 26 (49%) were males with a mean age of 47 ± 18.7 years, and 27 (51%) were females with a mean age of 42 ± 20.1 years. Age range varied from 14 to 78 years. Distribution of cases by age range is shown in table 1.

Regarding the referral status of the patients, 18 (34%) were referred from other hospitals, and 35 (66%) were patients from the INC.

Clinical presentation of IE was acute in 37 (70%) patients and subacute in 16 (30%). Affected structures are presented in table 2.

Regarding the valve status at the beginning of the episode, 23 (43%) patients had prosthetic valves and 30 (57%) had native valves; two of these patients had native valves and patches for ventricular septal defect repair, and one had a biventricular assist device (he was a candidate for cardiac transplantation due to a non-specified myocarditis). Of the patients with prosthetic valves, 13 (57%) had had valve surgery less than 2 months prior to the episode of IE, 7 (30%) had valve surgery within the last 2 to 12 months and 3 (13%) had valve surgery more than 1 year prior to the IE. Most episodes affecting prosthetic valves were early PVE (20/23, 87%).

Regarding the most prevalent comorbidities, patients with HCA-IE with chronic renal failure in their past medical history were 12 (23%), and half of these patients were on hemodialysis. Nine patients (17%) were affected by diabetes mellitus.

Table 1 – Distribution of cases by age range in 53 cases of HCA-IE, INC, 2006–2011

Age group (years)	Number of cases	Percent (%)
10-20	5	9
21-30	8	15
31-40	7	13
41-50	9	17
51-60	8	15
61-70	10	19
>70	6	11

Table 2 – Affected structures in 53 cases of HCA-IE, INC, 2006-2011

Affected structure	Number of cases	Percent (%)
Mitral Valve	19	36
Aortic Valve	12	23
Mitral + Aortic valves (concomitant)	5	9
ID* + Tricuspid valve (concomitant)	5	9
ID	4	8
Tricuspid valve	3	6
"Patch" in VSD †	2	4
Mitral + Tricuspid valves (concomitant)	1	2
Assist Device ‡	1	2
Mitral valve + ID	1	2

** ID: implanted devices; † VSD: ventricular septal defect; Patch: bovine pericardial patch; ‡ Assist device: device for biventricular myocardial support.*

Microbiological agents are shown in Table 2. Chi square tests were applied comparing all different etiologies between native and prosthetic valves, and the only significant difference in proportion was found for *Staphylococcus aureus*, which was predominant in native valve HCA-IE (30 vs 0%, $p < 0.005$, OR undefined).

Of the 11 patients with blood culture negative endocarditis, seven had their excised valves submitted to polymerase chain reaction (PCR) using primers to identify *C. burnetii, Bartonella spp, Tropheryma whipplei, Staphylococcus aureus, Streptococcus oralis group, Streptococcus bovis group, Enterococcus spp, Mycoplasma spp*, and fungi. Of these seven patients, only one had the agent identified: *Streptococcus oralis* group and *S. gallolyticus* (cross-amplification was likely). This was part of another project in INC[17]. Bartonella and Coxiella serologies are not routinely performed in our center and were not performed for any of the patients in this study.

Regarding clinical manifestations, fever was present in 49 (92%) patients and splenomegaly of recent onset in 12 (23%) patients. A new regurgitation murmur was observed in 31 (58%) patients. Elevated C reactive protein was found in 44/53 (83%), and elevated erythrocyte sedimentation rate in 14/24 (58%) patients.

Major complications were the following: cardiac failure in 28 (53%) patients, pulmonary embolism in 15 (28%), visceral abscess in 8 (15%), and persistent bacteremia in 5 (8%) patients.

Echocardiography was performed in all cases and showed major criteria in 46/53 (87%) of the patients; transesophageal echocardiography was performed in 47/53 (89%) patients, and transthoracic echos in 18/53 (34%). Transesophageal echocardiography was most contributory, with 38/46 (83%) showing major criteria. Vegetations were observed in 42/46 (91%) scans with major criteria, new regurgitation in 27 (59%), paraprosthetic leak in 8 (17%), paravalvular abscess in 5 (11%), valve dehiscence in 5 (11%), leaflet perforation in 4 (9%), and intracardiac fistula in 1 (2%).

Thirty-four (64%) patients were submitted to cardiac surgery for the current episode of HCA-IE, four of which had their intracardiac device removed by an open procedure. Of the patients submitted to surgery, 24/34 (71%) were discharged from the hospital. Nineteen patients (19/53, 36%) were not operated, and 12/19 (63%) were discharged. Overall mortality was 17/53 (32%). There was no statistical difference between the mortality of the patients who underwent surgery and those who did not.

Positive histopathology of the excised valves was observed 14/34 (41%) of the patients who underwent cardiac surgery. Lesions suggestive of IE were observed by the surgeon during cardiac surgery in 24/34 (71%) of the operated patients.

Discussion

The incidence of HCA-IE has been growing in the last decades representing 10–34% of all IE cases[2,4-8]. The incidence of our HCA-IE cases (35%) was in the upper limit described in reported series from the international literature, probably because the hospital where the study was done is a cardiac referral center, with daily insertion of cardiac prosthesis and intracardiac devices, as well as occasional heart transplantation. No previous studies on HCA-IE were found in Brazil. However, a large general series of 300 episodes of IE from INCOR, São Paulo, from 1978 to 1986, describes that in 15/282 episodes (16.5%), the use of intravascular catheters in patients was a predisposing procedure[18]. In the same study, prosthetic valves (age of valve not given) were listed as predisposing in 23% of the cases, and mortality was high in this group (43%).

Table 3 – Microbiological agents in HCA-IE, INC, 2006–2011

Microbiology	Native Valve		Prosthetic Valve				General	
			0–2 months		2–12 months			
	n	%	n	%	n	%	n	%
*Staphylococcus aureus**	9	30%	0	0%	0	0%	9	17%
CoNS†	3	10%	3	15%	0	0%	6	11%
Enterococcus faecalis	4	13%	5	25%	1	33%	10	19%
Gram-positive not identified	2	7%	0	0%	0	0%	2	4%
Enterobacter sp.	1	3%	1	5%	0	0%	2	4%
Pseudomonas aeruginosa	0	0%	2	10%	0	0%	2	4%
Acinetobacter sp.	1	3%	0	0%	0	0%	1	2%
Gram-negative not identified	2	7%	1	5%	0	0%	3	6%
Candida sp.	3	10%	4	20%	0	0%	7	13%
Not identified	5	17%	4	20%	2	67%	11	21%
Total	**30**	**100%**	**20**	**100%**	**3**	**100%**	**53**	**100%**

**S. aureus 9 (5 were methicillin resistant, MRSA); † CoNS: coagulase-negative staphylococcus.*

A more recent study of 180 episodes of IE from Ribeirão Preto, São Paulo, from 1992 to 1997, describes 23 patients with PVE (3 early, 20 late); mortality was high for both early and late PVE (2 of 3 in early, 5 of 20 or 25% in late PVE)[19]. These are not exactly comparable data, but can be used to extrapolate some information on HCA-IE in Brazil. The proportion of prosthetic valves affected varies from 11.8% to 45.5% in published HCA-IE series and is 43% in ours[4,5,11,17,20-23]. Despite the number of prosthetic valves involved, the rate of early PVE in our institution is within the one described by the literature[24].

The mean age of patients was 47.2 years, lower when compared with the mean age of HCA-IE in the literature, which varies between 60.1 and 69 years[4,6,10,20,21]. However, in Terpenning et al[11] and Lamas et al[2], the mean age was comparable to that in our series, 47.8 and 53.8 years, respectively.

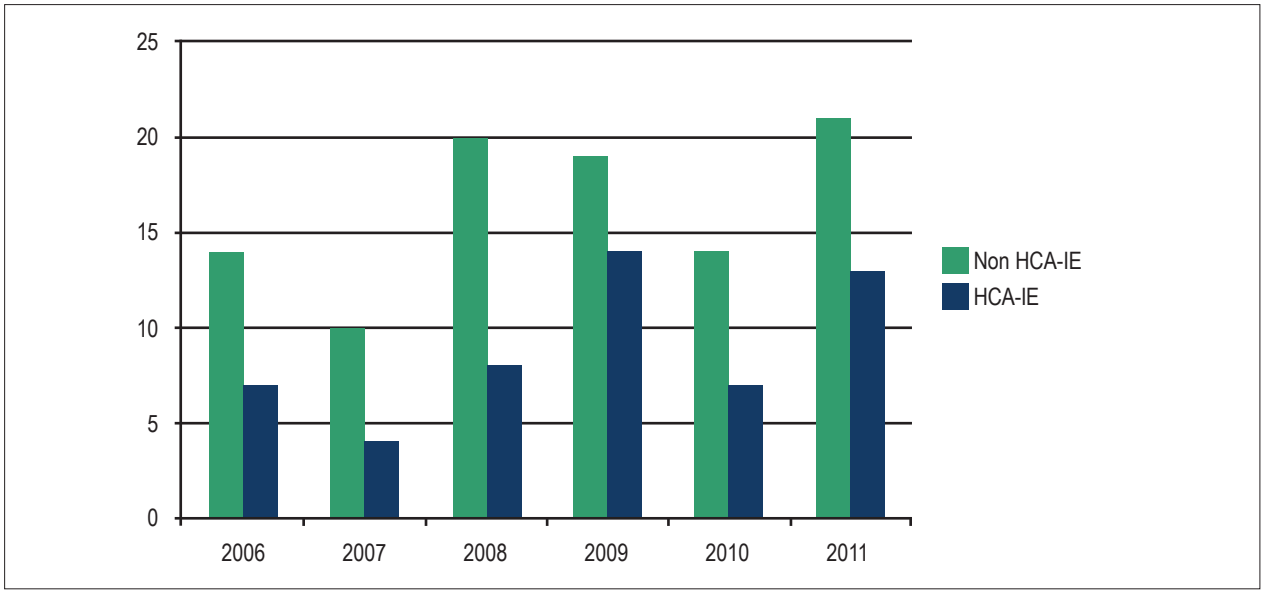
Gender distribution was proportional in HCA-IE (1:1), differently from community-acquired IE (1.7:1)[23]. This is due to other predisposing factors such as prosthetic valves and intravascular catheters that are independent of gender.

The incidence of 11% of patients on hemodialysis (HD) and 17% of patients with diabetes is in accordance with the literature, where it is 11.9%–19.3% for HD and 19–30.9% for diabetes[4,5,20,21]. It has been reported in a study on intravenous catheters from INC that devices used for HD, especially femoral catheters, are a particular risk for bacteremia and endocarditis, thus being an important issue not only for patients with prosthetic valves but also for those with native valves[25,26].

Regarding etiological agents, microbes were not identified in the majority of the cases (21%): a high proportion comparing to other series, where blood cultures are negative in only 2.4%–9.5% of HCA-IE[2,4,20,21]. The previous use of antibiotics is the main cause for this result; indeed patients frequently received antimicrobial therapy, and patients in the post-operative period often had presumptive diagnosis of other infections (pneumonia, blood stream infection). However, some studies[2] only included patients with positive blood cultures, as case definition was based on positive blood cultures identified in the Microbiology Laboratory, not by echocardiographical or clinical definitions[2]. As part of a PCR study of valves between 1998 and 2009 in collaboration with the Unite´ des Rickettsies (Marseille, France), some patients in the present study had their valves analyzed for several pathogens, and only one of 11 valves was positive for *S. oralis/S. gallolyticus*[17]. Bartonella and Coxiella serologies are not routinely performed in our center, and they are not relevant for HCA-IE.

The incidence of *Enterococcus faecalis* (19%) in our study is similar to that in the literature, 17.3%–47%[4-6,20,21,25]. This is a interesting data, since INC is a surgical hospital, not a general one, and the incidence of gastrointestinal or urinary tract diseases are not high. Therefore, as shown in a study by our group, these enterococci are arising primarily from intravenous lines[26]. There was no difference in the proportion of enterococci in native or prosthetic valves in the series.

Staphylococcus aureus accounted for 17% of microbes isolated, and over half of them were methicillin resistant (MRSA). This is a lower incidence than that of other series (20%–36.5%)[4,5,11,20]. However, Giannitsioti et al[21], Massoure et al[27], and Martín-Dávila et al[8] had lower rates of *S. aureus*, varying between 11% and 20%. The incidence of MRSA in the literature varies from 26 to 85%[4-6,8,20]. Curiously, no *S. aureus* was seen in patients with early prosthesis infection; we believe this occurs because of routine pre-operative decolonization with topical mupirocin and chlorexidine for cardiac surgery at INC.



Graph 1 – *Number of cases of HCA-IE and non- HCA-IE, 2006–2011, INC. HCA-IE - healthcare-associated infective endocarditis.*

The incidence of HCA-IE caused by coagulase-negative staphylococcus in our study was 11%, low when compared to the literature where it varies between 21.7% and 27.6%[4,20,21]. Sy et al[5] found a similar incidence to ours (5%).

Gram-negative rods are present in 0%–3% of HCA-IE in published series, but we found them in 16% of the cases[3,8,13,20]. This incidence was not different in native and prosthetic cases, and we hypothesize cefazolin, used as prophylaxis, was insufficient to deter wound contamination with Gram-negatives; also, in developing countries, Gram-negatives are a significant cause of line-associated bacteremia[28,29]. Since April 2012, institutional protocol on antibiotic prophylaxis has changed, including cefuroxime, with or without vancomycin, the last pending number of days in hospital (> 7 days), body mass index > 30, and MRSA colonization (CL, personal communication)

Candida sp. is present in 0% to 11% of HCA-IE cases[3,8,13,20]. The overall incidence was 13% and 10% of native valves in this series. According to França et al[30], the higher incidence of fungi in hospital infections is due to prior antibiotic use and use of intravenous lines, very frequently associated in the studied patients[30].

Fever is present in 81 to 94 % of patients with HCA-IE and was present in 92% of our patients[2,6,23,27]. Splenomegaly, though not considered a major criterion, was found in 23% of the patients. A new cardiac murmur or worsening of a previous murmur was found in 58% of the patients, similar to Benito et al (2009), who found this manifestation in 60% of patients with native valve HCA-IE[6]. Therefore, the finding of fever and murmur in a hospitalized patient should be considered as possible endocarditis.

Heart failure is a frequent and serious complication, and was observed in 53% of the cases; Fernández-Hidálgo et al (2008) found a similar rate in their study (47%)[20]. In other series, heart failure was described in 18%–37% of the cases[2,4-6,20]. Embolic phenomena occurred in 28% of the cases, similar to the literature, where it is described to occur in 11%–27.7% of the patients[5,6,20]. Giannitsioti et al[21] found a 45.2% rate of embolic complications.

Surgical treatment was offered to 34 (64%) patients; in other series, this varied from 19% to 44.1%[4-6,21]. However, the number of cardiac surgeries in our study is high because the INC is a surgical center. Also the four cardiac devices removed by open surgery were included in this number.

Patients who underwent surgery for treatment of HCA-IE were discharged more often from the hospital than the other patients, but this was not statistically significant. However, no follow up at one year was done for this cohort. In-hospital mortality was 32%, which is similar to the literature (22%–50%)[2-6,20,21]. Mortality in community acquired IE is less frequent: 18% and 18.6% in Giannitsioti et al[21] and Chen et al[9], respectively, demonstrating greater severity of HCA-IE.

Conclusion

HCA-IE affected younger patients in this Brazilian series compared to other series described in the literature. This is possibly due to a high incidence and prevalence of rheumatic heart disease, which is predominant in children and teenagers, in our country[4,6,20-22].

Differently from IE acquired in the community, where there is a higher (2:1 to 3:1) ratio of male to female patients affected, HCA-IE does not show a difference in gender distribution.

In this series, non-cardiac surgeries did not predispose to HCA-IE, but this may be due to the fact that the INC is a cardiac surgery hospital, with few non-cardiovascular surgeries performed.

Blood culture negativity was more frequent than in other series, probably due to referral bias and prior use of antibiotics. Moreover, the cases were often detected by clinical and echocardiographic findings.

There was a low incidence of *S. aureus* for early PVE; probably because of routine decolonization with topical mupirocin and chlorexidine at INC. *S .aureus* was significantly more frequent in patients with native valves who were admitted for non-surgical causes, such as congestive heart failure.

The high incidence of Gram-negatives and fungi (Candida sp) infections may be related to prior or concurrent use of antibiotics and to the presence of intravenous catheters.

Despite INC is not a general hospital, the incidence of *E. faecalis* was similar to that of other series, probably because of intravenous catheter use, especially HD catheters inserted in femoral veins[26].

HCA-IE is a condition with significant morbidity and mortality. It was associated with major complications such as heart failure and embolic phenomena, and it also showed high mortality.

Acknowledgments

We acknowledge the entire medical, surgical, nursing, and other staff at the Instituto Nacional de Cardiologia who looked after the patients included in this study.

Author contributions

Conception and design of the research, Acquisition of data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Francischetto O, Silva LAP, Senna KMS, Vasques MR, Barbosa GF, Weksler C, Ramos RG, Golebiovski WF, Lamas CC; Analysis and interpretation of the data: Francischetto O, Barbosa GF, Weksler C, Ramos RG, Golebiovski WF, Lamas CC; Statistical analysis: Lamas CC; Obtaining financing: Francischetto O, Lamas CC.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by FAPERJ.

Study Association

This study is not associated with any thesis or dissertation work.

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