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HACEK infective endocarditis: Epidemiology, clinical features, and outcome: A case–control study☆

Juan Ambrosioni[a,1], Clara Martinez-Garcia[b,1], Jaume Llopis[c], Cristina Garcia-de-la-Maria[a], Marta Hernández-Meneses[a], Adrián Tellez[a], Carles Falces[d], Manel Almela[e], Bàrbara Vidal[d], Elena Sandoval[f], David Fuster[g], Eduard Quintana[f], José M. Tolosana[d], Francesc Marco[e], Asunción Moreno[a], José M. Miró[a,*], The Hospital Clinic Infective Endocarditis Investigators[2]

[a] Infectious Diseases Service, Hospital Clinic — Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain
[b] University of Barcelona, School of Medicine, Barcelona, Spain
[c] Biostatistics Department, Faculty of Biology, University of Barcelona, Barcelona, Spain
[d] Cardiology Service, Hospital Clinic — Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain
[e] Microbiology Service, Hospital Clinic — Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain
[f] Cardiac Surgery Service, Hospital Clinic — Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain
[g] Nuclear Medicine Service, Hospital Clinic — Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain

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ABSTRACT

Objectives: The study aimed to describe the epidemiological, microbiological, and clinical features of a population sample of 17 patients with HACEK infective endocarditis (HACEK-IE) and to compare them with matched control patients with IE caused by viridans group streptococci (VGS-IE).
Methods: Cases of definite (n = 14, 82.2%) and possible (n = 3, 17.6%) HACEK-IE included in the Infective Endocarditis Hospital Clinic of Barcelona (IE-HCB) database between 1979 and 2016 were identified and described. Furthermore, a retrospective case–control analysis was performed, matching each case to three control subjects with VGS-IE registered in the same database during the same time period.
Results: Seventeen out of 1209 IE cases (1.3%, 95% confidence interval 0.69–1.91%) were due to HACEK group organisms. The most frequently isolated HACEK species were *Aggregatibacter spp* (n = 11, 64.7%). Intracardiac vegetations were present in 70.6% of cases. Left heart failure (LHF) was present in 29.4% of cases. Ten patients (58.8%) required in-hospital surgery and none died during hospitalization. In the case–control analysis, there was a trend towards larger vegetations in the HACEK-IE group (median (interquartile range) size 11.5 (10.0–20.0) mm vs. 9.0 (7.0–13.0) mm; p = 0.068). Clinical manifestations, echocardiographic findings, LHF rate, systemic emboli, and other complications were all comparable (p > 0.05). In-hospital surgery and mortality were similar in the two groups. One-year mortality was lower for HACEK-IE (1/17 vs. to 6/48; p = 0.006).
Conclusions: HACEK-IE represented 1.3% of all IE cases. Clinical features and outcomes were comparable to those of the VGS-IE control group. Despite the trend towards a larger vegetation size, the embolic event rate was not higher and the 1-year mortality was significantly lower for HACEK-IE.

Introduction

The HACEK group of bacteria (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) are fastidious Gram-negative bacilli that have long been recognized as a cause of infective endocarditis (IE) (Raoult, 2001). Common features of the HACEK group are frequent colonization of the oropharynx, slow growth, and enhanced growth in the presence of carbon dioxide. Due to these

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* Corresponding author at: Infectious Diseases Service, Hospital Clinic, Villarroel 170, Barcelona 08036, Spain.
E-mail address: jmmiro@ub.edu (J.M. Miró).

[1] Juan Ambrosioni and Clara Martínez García contributed equally to this work.
[2] The names of the Hospital Clinic Infective Endocarditis Investigators are listed in Appendix A.

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microbiological characteristics, organisms may not be detected in routine blood culture systems unless enriched blood media are used (Das et al., 1997; Baron et al., 2005), which may lead to a delay in diagnosis. The reported incidence of IE caused by Gram-negative bacteria ranges from 1.3% to 10%, with HACEK group contributing to the majority of the cases (Raoult, 2001; Chambers et al., 2013; Goldberg, 2006; Nørskov-lauritsen, 2014).

The most commonly reported pathogens among the HACEK group are *Haemophilus spp* (Raoult, 2001; Goldberg, 2006). However, the taxonomy of this group has recently been updated, and today the genus *Aggregatibacter spp* also includes subspecies classically known as *Actinobacillus actinomycetemcomitans*, *Haemophilus aphrophilus*, and *Haemophilus segnis.* With the current classification, *Aggregatibacter spp* might be the dominant aetiology of HACEK-related IE (Nørskov-lauritsen, 2014). HACEK-IE tends to occur in young and middle-aged adults (Raoult, 2001; Chambers et al., 2013) with previous dental procedures and underlying heart disease (Raoult, 2001; Goldberg, 2006; Paturel et al., 2004; Raza and Sohail, 2010).

Clinical features of HACEK-IE remain controversial. Some studies have noted that HACEK-IE is more likely to present with larger vegetations and a higher risk of embolization than non-HACEK-IE (Das et al., 1997; Raza and Sohail, 2010), which may be related to the prolonged clinical course until diagnosis. However, in a recent multicentre study performed by the International Collaboration on Endocarditis (the International Collaboration on Endocarditis Prospective Cohort Study, ICE-PCS), these features were not confirmed in the 77 HACEK-IE cases out of the 5591 IE cases included (Chambers et al., 2013); moreover, lower rates of in-hospital mortality (3.8% vs. 18%; $p = 0.001$) and left-sided heart failure (LHF) (15% vs. 30%; $p = 0.004$) were noted (Chambers et al., 2013). In this previous study, HACEK-IE cases were compared to a control group that included all IE caused by non-HACEK microorganisms.

The present study aimed to characterize HACEK-IE cases at the authors' centre since 1979 and to perform a propensity case–control analysis using patients with IE caused by viridans group streptococci (VGS) (organisms sharing the port of entry and believed to have comparable virulence) as controls, in order to determine possible differences in outcomes and prognosis.

Methods

Study design

This retrospective study included two parts. In the first part, a description of the institutional cases between 1979 and 2016 was performed. The second part consisted of a matched case–control (1:3) study with VGS-IE patients in the Infective Endocarditis Hospital Clinic of Barcelona (IE-HCB) database.

Microbiological methods

HACEK bacteria were identified by the microbiology service of the study hospital using standard methods (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) assay or 16S rRNA-based PCR assay). Sensitivity testing was performed following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (M100-S25 Performance Standards for Antimicrobial Susceptibility Testing, 2015). Species were reported according to the updated taxonomy (Nørskov-lauritsen, 2014).

Cases and controls

The case population included all patients registered in the IE-HCB database between 1979 and 2016 with HACEK blood cultures. Patients from the IE-HCB database had definite or possible IE according to the modified Duke criteria (Durack et al., 1994; Li et al., 2000). Cases of IE related to cardiovascular electronic implantable devices (CEID) were included in the descriptive study but not in the case–control sub-study, in order to preserve the homogeneity of the sample.

A 1:3 matching was established with patients affected by VGS-IE registered in the same database between 1979 and 2016. The matching criteria included identical year of admission (±1 year), age, sex, type of endocarditis (native/prosthetic), valve affected, and major comorbidities (including diabetes mellitus, parenteral drug addiction, HIV infection, haemodialysis, and underlying cardiopathy).

Variables

For echocardiographic findings and complications where transthoracic and transoesophageal echocardiography (TTE, TOE) had both been performed, results from TOE were considered.

The following complications were analyzed: LHF, systemic emboli, central nervous system (CNS) complications, and renal failure. LHF was accepted on the basis of clinical evaluation and was defined according to the Killip classification (Killip and Kimball, 1967). Systemic emboli included embolization to any organ including skin, but excluded pulmonary emboli in right-sided endocarditis in intravenous drug abusers. CNS complications recorded included stroke and/or meningitis.

In-hospital surgery was considered when it was performed within the first 45 days. The outcome was evaluated up until the 1-year follow-up.

Data collection and ethics

Information concerning patient demographics, risk factors, comorbidities, clinical manifestations, echocardiography and microbiological data, treatment, complications, and follow-up was collected retrospectively from the IE-HCB database. Where data were missing, the patient's clinical records were consulted, and this was recorded in a case report form (CRF) specifically designed for the study.

The study was approved by the Ethics Committee of the Hospital Clinic.

Statistical methods

Categorical variables were represented as frequencies (percentages). Continuous variables were expressed as the median and interquartile range (IQR). The Chi-square test and Mann–Whitney *U*-test were used for categorical variables and continuous variables, respectively. All *p*-values were considered significant at <0.05. The statistical analyses were performed using STATA software version 14.0.

Results

Description of institutional HACEK-IE cases

Demographics, risk factors, and type of endocarditis

Seventeen out of 1209 cases of IE were identified as HACEK-IE cases (1.3%; 95% confidence interval (CI) 0.69–1.91). Among the 17 HACEK-IE patients, 14 (82.4%) were male, with a median (IQR) age of 44.0 (35.0–53.0) years. According to the modified Duke criteria, 14 patients (82.2%) had definite IE and three (17.6%) had possible IE. Native valve IE was present in 10 patients (62.5%). Six patients (35.3%) had prosthetic valve IE and one had CEID-related IE (5.9%). All cases were community-acquired IE. An underlying cardiopathy

was identified in 13 patients (76.5%) (one rheumatic valvulopathy, two mitral prolapses, one biological prosthesis, one Marfan's syndrome, two homografts, two mechanical prostheses, two scleroses and calcifications of aortic and/or mitral valves, and one pacemaker). Other risk factors were identified in eight cases (47%). None of the cases were drug abusers, HIV-positive, or on haemodialysis.

Microbiology and treatment

The most common species was *Aggregatibacter spp* (including *A. actinomycetemcomitans* $n = 4$, *A. aphrophilus* $n = 3$, *A. paraphrophilus* $n = 2$, *A. segnis* $n = 1$, and *A. ureae* $n = 1$) isolated in 11 patients (64.7%). *Haemophilus parainfluenzae* was isolated in three cases (17.6%) and *C. hominis* also in three cases (17.6%). No cases of *Eikenella* or *Kingella spp* were identified. *Staphylococcus epidermidis* was also isolated in blood cultures of one IE case caused by *Haemophilus spp*.

Native valve endocarditis was treated for 4 weeks and prosthetic valve endocarditis for 6 weeks. Most patients received a third-generation cephalosporin as monotherapy (52.9%); others received penicillin plus an aminoglycoside (29.4%), a third-generation cephalosporin plus an aminoglycoside (11.8%), or ciprofloxacin (5.9%).

Clinical presentation, echocardiographic findings, and outcomes

The most frequent findings were fever at admission in 16 patients (94.11%), a murmur (previously unreported by the patient) in eight cases (47.1%), and splenomegaly in three patients (17.7%). Osler nodes and CNS signs were present in two cases each (11.8%), and septic metastases, systemic emboli, and petechiae in one case each (5.9%). Echocardiography was performed in all cases. Vegetations were identified in 12 cases (70.6%). The most frequent location for vegetations was the mitral valve (seven cases, 58.3%), followed by the aortic valve (four cases, 33.3%) and tricuspid valve and pacemaker wire (one case each, 8.3%). The median (IQR) size of the vegetations was 11.5 mm (10.0–17.0 mm). Eight patients (47.1%) presented severe valve regurgitation, five (29.4%) a mild regurgitation, and four (23.5%) a moderate regurgitation. Other complications detected were one paravalvular abscess (5.9%), two cases of mitral valve fluttering (11.8%), and two valve perforations (11.8%).

During the episode of IE, five patients (29.4%) suffered LHF (three Killip II and two Killip IV). Other clinical complications were CNS complications (including stroke or meningitis), renal failure and systemic emboli ($n = 2$ each, 11.8%), and atrioventricular blockage ($n = 1$, 5.9%). Surgery during hospitalization was performed for 10 patients (58.8%). Surgical procedures included four mechanical prostheses, two biological prostheses, two homografts, one aortic prosthesis surgery, and one pacemaker extraction. No patient died during hospitalization. Fourteen patients were followed up for 1 year. Surgery after discharge was performed on one (5.9%) patient. One patient died of a non-related cause.

There were no differences in the clinical characteristics and outcomes of IE among the different species of HACEK microorganism (data not shown).

Case–control study

Demography, risk factors, and type of endocarditis

A total of 64 patients were analyzed: 16 cases (one CEID-related HACEK-IE was excluded) and 48 controls. According to the modified Duke criteria, 14 HACEK-IE patients (87.5%) and 41 VGS-IE (87.5%) patients had a definite diagnosis ($p = 1.000$). The median age, type of endocarditis (native or prosthetic), valve involved, underlying cardiopathy, otorhinolaryngological source, and other risk factors were all comparable between the groups (Table 1).

Clinical presentation and echocardiographic findings

The prevalence and duration of fever were comparable in the two groups, as were all other clinical symptoms compared. Echocardiography was performed in all patients, and the proportion of vegetations, valve involved, proportion of regurgitation, and proportion of valve perforation were comparable in the two groups. The median (IQR) size of the HACEK-IE vegetations was 11.5 (10.0–20.0) mm and of the VGS-IE vegetations was 9.0 (7.0–13.0) mm; however the difference between the groups did not reach statistical significance ($p = 0.068$). HACEK-IE and VGS-IE had the same proportion of paravalvular complications ($p = 0.580$). Two VGS-IE cases (16.7%) presented prosthetic valve dysfunction, while no case of HACEK-IE had this complication ($p = 0.141$).

Table 1
Comparative analysis of demographic characteristics and risk factors between the HACEK infective endocarditis (HACEK-IE, case) and viridans group Streptococcus infective endocarditis (VGS-IE, control) groups.[a]

Variable	Total ($n = 64$)	Cases ($n = 16$)	Controls ($n = 48$)	p-Value
Epidemiology				
Sex, male	55 (85.9%)	13/16 (81.3%)	42/48 (87.5%)	0.567
Age (years)	44.0 (35.0–58.0)	42.0 (34.0–52.5)	43.5 (34.0–58.4)	0.457
Type of endocarditis				
Native valve IE	46/64 (71.9%)	10/16 (62.5%)	36/48 (75%)	0.362
Prosthetic valve endocarditis	18/64 (28.1%)	6/16 (37.5%)	12/48 (25.0%)	0.362
Mitral IE	28/64 (43.8%)	8/16 (50.0%)	20/48 (41.7%)	0.564
Aortic IE	23/64 (35.9%)	7/16 (43.8%)	16/48 (33.3%)	0.464
Aortic + mitral IE	11/64 (17.2%)	1/16 (6.25%)	10/48 (20.8%)	0.088
Risk factors				
Underlying cardiopathy	48/64 (75.0%)	12/16 (75.0%)	36/48 (75.0%)	1.000
ORL source	16/64 (25.0%)	4/16 (25.0%)	12/48 (25.0%)	1.000
Previous IE	5 (7.8%)	2/16 (12.5%)	3/48 (6.3%)	0.489
Diabetes mellitus	4 (6.3%)	1/16 (6.3%)	3/48 (6.3%)	1.000
Diagnosis according to the modified Duke criteria				
Definite	55/64 (87.5%)	14/16 (87.5%)	41/48 (87.5%)	1.000
Possible	9/64 (14.1%)	2/16 (12.5%)	7/48 (14.6%)	0.830

IE, infective endocarditis; ORL, otorhinolaryngological.
[a] Results are presented as n (%) or median (interquartile range).

Outcome and 1-year follow-up

Clinical LHF was the most common complication for both groups, followed by systemic emboli, stroke, and meningitis, all equally distributed among the groups. In-hospital surgery was comparable in the two groups. In-hospital death was registered in two controls and in zero HACEK-IE cases. Surgery after discharge was performed in the same proportion in both groups. Clinical presentation, echocardiographic findings, outcomes, and follow-up information are shown in Table 2. In-hospital mortality was comparable, but significantly lower at 1 year for HACEK-IE cases ($p = 0.006$, Table 2 and Figure 1).

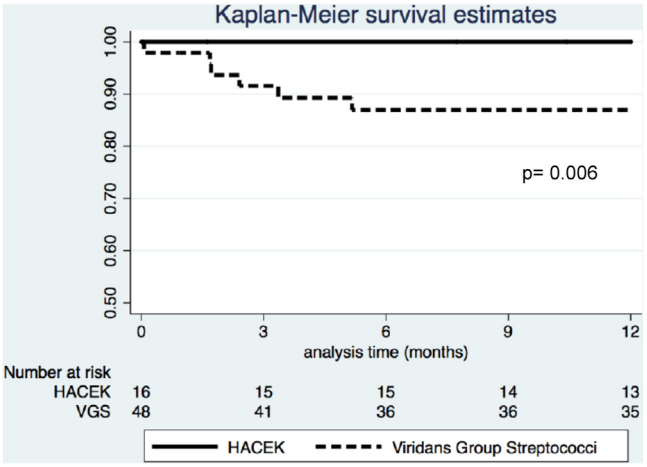

Figure 1. One-year survival of patients with HACEK infective endocarditis (HACEK-IE) and viridans group Streptococcus infective endocarditis (VGS-IE).

Discussion

The existing literature on HACEK-IE remains scarce due to the low incidence of the disease. Previously published studies also have many limitations, such as small sample sizes, long periods of data collection, and non-homogeneous information. This study described a population of 17 cases of HACEK-IE and compared them to 48 patients affected by bacterial endocarditis due to VGS, which is considered to have the most similar clinical course of all causes of IE.

Most patients were male with a median age of 44.0 years. Community-acquired endocarditis was present in all cases. Native-valve endocarditis was more frequent than prosthetic-valve endocarditis, but the latter had a non-negligible 35% prevalence, which reflects previous studies (Chambers et al., 2013). The mitral valve was affected in the majority of the cases.

According to the updated taxonomy, the most common causative pathogen reported was *Aggregatibacter spp*. This differs

Table 2
Comparative analysis of clinical manifestations, echocardiographic findings, outcome, and follow-up between cases and controls.[a]

Variable	Total ($n = 64$)	Cases ($n = 16$)	Controls ($n = 48$)	p-Value
Clinical characteristics at admission				
Fever	59/64 (92.2%)	15/16 (93.8%)	44/48 (91.7%)	0.775
Duration of the fever (days)	2.0 (1.0–3.0)	2.0 (3.0–5.0)	2.0 (1.0–3)	0.982
New murmur	25/63 (38.7%)	8/16 (50.0%)	17/47 (36.2%)	0.338
Vascular phenomena	14/64 (21.9%)	8/16 (18.8%)	11/48 (22.9%)	0.718
Skeletal symptoms	14/64 (21.9%)	3/16 (18.8%)	11/48 (22.9%)	0.718
Splenomegaly	8/64 (12.5%)	3/16 (18.8%)	5/48 (10.4%)	0.439
CNS symptoms	5/64 (7.8%)	1/16 (5.9%)	4/48 (8.3%)	0.775
Ischemic stroke	3/64 (4.7%)	1/16 (6.25%)	2/48 (4.2%)	0.757
Echocardiographic findings				
Intracardiac vegetations	48/64 (75%)	11/16 (68.8%)	37/48 (77.1%)	0.528
Mitral valve	30/48 (62.5%)	7/11 (63.3%)	23/37 (62.2%)	0.947
Aortic valve	25/48 (52.1%)	4/11 (36.4%)	21/37 (56.8%)	0.226
Tricuspid valve	1/48 (2.1%)	1/11 (9.1%)	0/37 (0.0%)	0.299
Vegetation size (mm)		11.5 (10.0–20.0)	9.0 (7.0–13.0)	0.068
Vegetation size $\geq$10 mm	21/38 (55.3%)	7/9 (77.8%)	14/29 (48.3%)	0.085
Mitral valve regurgitation	47/62 (75.1%)	11/15 (73.3%)	36/47 (76.6%)	0.802
Aortic valve regurgitation	33/62 (53.2%)	6/15 (40.0%)	27/47 (57.4%)	0.236
Mild regurgitation	23/80 (28.8%)	5/17 (29.4%)	18/63 (28.6%)	0.946
Moderate regurgitation	14/80 (17.5%)	4/17 (23.5%)	10/63 (15.9%)	0.499
Severe regurgitation	43/80 (53.8%)	8/17 (47.1%)	35/63 (55.6%)	0.535
Valve perforation	15/64 (23.4%)	2/16 (12.5%)	13/48 (27.1%)	0.168
Paravalvular complications	6/64 (9.3%)	1/16 (6.3%)	5/48 (10.4%)	0.580
Prosthetic valve dysfunction	2/18 (11.1%)	0/6 (0.0%)	2/12 (16.7%)	0.141
Outcome				
Left-sided HF	24/64 (37.5%)	5/16 (31.3%)	19/48 (39.6%)	0.541
Moderate HF (II)	14/64 (21.9%)	3/16 (18.8%)	11/48 (22.9%)	0.718
Severe HF (III + IV)	10/64 (15.6%)	2/16 (12.5%)	8/48 (16.7%)	0.674
Systemic emboli	12/64 (18.8%)	2/16 (12.5%)	10/48 (20.8%)	0.414
Stroke/meningitis	11/64 (17.2%)	2/16 (12.5%)	9/48 (18.8%)	0.534
Renal failure	10/64 (15.6%)	2/16 (12.5%)	8/46 (17.4%)	0.626
AVB (first to third degree)	2/62 (3.2%)	1/16 (6.25%)	1/46 (2.2%)	0.528
In-hospital surgery	29/64 (45.3%)	9/16 (56.3%)	20/48 (41.7%)	0.312
In-hospital mortality	2/64 (3.1%)	0/16 (0.0%)	2/48 (4.2%)	0.154
Days of hospitalization	32.0 (18.0–42.0)	37.0 (28.0–70.0)	29.5 (19.5–40.5)	0.065
Follow-up				
Surgery after discharge	9/64 (14.1%)	1/16 (6.3%)	8/48 (16.7%)	0.203
1-year mortality	7/64 (10.9%)	0/16 (0.0%)	7/48 (14.6%)	0.006

CNS, central nervous system; HF, heart failure; AVB, atrioventricular block.
[a] Results are presented as n (%) or median (interquartile range).

from other published studies, which have reported *Haemophilus spp* as the most prevalent microorganism (Chambers et al., 2013; Goldberg, 2006). Treatment with a third-generation cephalosporin was used in the majority of the patients, in monotherapy or in combination, as recommended in guidelines. Although some patients in the sample were treated with ampicillin, this treatment is no longer a first-line empirical treatment, since some HACEK group bacilli produce beta-lactamases (Baddour et al., 2015; Baddour, 2005; Habib et al., 2015).

The case–control analysis showed overall similar characteristics of HACEK-IE when compared to VGS-IE. Infection of the otorhinolaryngological area, which has been described as a risk factor for HACEK-IE, was present in 25% of both case and control subjects (Raoult, 2001; Goldberg, 2006; Paturel et al., 2004; Raza and Sohail, 2010).

Intracardiac vegetations were present in 68.8% of cases and 77.1% of controls. Classically, HACEK-IE-related vegetations have been thought to be larger due to the prolonged clinical course of the disease (Sharara et al., 2016; Nwaohiri et al., 2009; Feder et al., 2003; Berbari et al., 1997). In the present study, HACEK-IE vegetations tended to be both larger (median 11.5 mm, IQR 10.0–20.0 mm) than in VGS (median 9.0 mm, IQR 7.0–13.0 mm) and more numerous when <1 cm. Vegetations >1 cm in diameter have shown a trend towards higher embolic rates in some studies (Das et al., 1997; Erbel et al., 1988; Sanfilippo et al., 1991). Despite expecting a higher risk of embolization, the study results showed a similar risk of systemic emboli for the two groups ($p = 0.414$). This may be explained by the extreme sensitivity to beta-lactams of the HACEK group, reducing the embolization rate once treatment has been started.

In both cases and controls, the most prevalent complication was clinical heart failure ($p = 0.541$). This finding differs from observations in other studies in which the main complication has tended to be stroke due to the possible increased embolization risk (not detected in the present study). In the ICE-PCS cohort, stroke was present in 25% of patients and embolization (excluding CNS) in 21% of patients, whereas in the present study these complications were both only present in 12.5% of the cases (Chambers et al., 2013). Other studies have shown an even greater risk of embolization, especially for the *Haemophilus spp* cases (Feder et al., 2003).

Surgery was performed in 56.3% of the cases, in line with the general indication for surgery in cases of IE due to other aetiologies (Habib et al., 2015). The overall outcome of HACEK-IE was excellent with an in-hospital mortality rate of 0% and a significantly lower rate at the 1-year follow-up compared to VGS-IE: seven cases in the VGS-IE group died compared to none in the HACEK-IE group ($p = 0.006$). The ICE-PCS also demonstrated lower rates of 1-year mortality among the HACEK group patients compared to the non-HACEK patients (6% vs. 39%; $p = 0.001$).

This study has several strengths. It appears to be the first case–control comparative study reported in the literature. Since HACEK is a rare aetiology for IE, previous studies have been limited to descriptions of cases. ICE-PCS was the first study comparing HACEK-IE to IE due to other microorganisms, but since all non-HACEK-IE were included in the control group, the results obtained from the analysis may be difficult to interpret. It is believed that the present study provides more specific information about the clinical characteristics and outcomes of HACEK-IE compared to VGS-IE, which shares the same port of entry and pathogenesis.

This study also has some limitations. Despite spanning 20 years, the cohort only comprised 17 cases, and the statistical power of the study was too low to observe more statistically significant results. Moreover, the retrospective long-term design meant that some data were missing, especially for echocardiographic findings, and there may also have been a potential data collection bias.

In conclusion, the HACEK group is a rare cause of IE, and this predominantly affects young males, is generally community-acquired, and involves the native valves. Vegetations are detected in most cases and their size tends to be greater than those due to VGS-IE. However, although there was an expectation of a higher risk of embolization, systemic emboli were similar regardless of the size of the mass. The outcome of HACEK-IE was excellent, with a remarkably low 1-year mortality rate. More powerful, multicentre studies may be necessary to confirm these results.

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Conflict of interest

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Appendix A.

Investigators of the Hospital Clinic Infective Endocarditis Study Group: Jose M. Miró, Juan Ambrosioni, Juan M. Pericàs, Adrian Téllez, Marta Hernandez-Meneses, Asunción Moreno (Infectious Diseases Service); Cristina Garcia de la Mària, Javier Garcia-Gonzalez (Experimental Endocarditis Laboratory); Francesc Marco, Manel Almela, Jordi Vila (Microbiology Service); Eduard Quintana, Elena Sandoval, Juan C. Paré, Carlos Falces, Daniel Pereda, Ramon Cartañá, Salvador Ninot, Manel Azqueta, Marta Sitges, Barbara Vidal, José L. Pomar, Manuel Castella, José M. Tolosana, José Ortiz (Cardiovascular Institute); Guillermina Fita, Irene Rovira (Anaesthesiology Department); David Fuster (Nuclear Medicine Service); Jose Ramírez, (Pathology Department); Mercè Brunet (Toxicology Service); Dolors Soy (Pharmacy Service); Pedro Castro (Intensive Care Unit), and Jaume Llopis (Department of Statistics, Faculty of Biology, University of Barcelona).

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