HACEK Infective Endocarditis: Characteristics and Outcomes from a Large, Multi-National Cohort

To cite this version:
Stephen T. Chambers, David Murdoch, Arthur Morris, David Holland, Paul Pappas, et al.. HACEK Infective Endocarditis: Characteristics and Outcomes from a Large, Multi-National Cohort. PLoS ONE, Public Library of Science, 2013, 8 (5), pp.e63181. 10.1371/journal.pone.0063181. hal-01483758

HAL Id: hal-01483758
https://hal.univ-lorraine.fr/hal-01483758
Submitted on 6 Mar 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
HACEK Infective Endocarditis: Characteristics and Outcomes from a Large, Multi-National Cohort

Stephen T. Chambers1, David Murdoch1, Arthur Morris2, David Holland3, Paul Pappas4, Manel Almela5, Nuria Fernández-Hidalgo6, Benito Almirante6, Emilio Bouza7, Davide Forno8, Ana del Río9, Margaret M Hannan10, John Harkness11, Zeina A. Kanafani12, Tahaniyat Lalani13, Selwyn Lang14, Nigel Raymond15, Kerry Read16, Tatiana Vinogradova17, Christopher W. Woods18, Dannah Wray19, G. Ralph Corey20, Vivian H. Chu21, International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) Investigators

1 Department of Pathology, University of Otago, Christchurch and Christchurch Hospital, Christchurch, New Zealand, 2 Department of Microbiology, Auckland City Hospital, Auckland, New Zealand, 3 Microbiology Laboratory, Middlemore Hospital, Auckland, New Zealand, 4 Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina, United States of America, 5 Department of Microbiology, Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona, Spain, 6 Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain, 7 Clinical Microbiology and Infectious Diseases Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain, 8 Cardiology Department, Maria Vittoria Hospital, Torino, Italy, 9 Department of Clinical Medicine, Infectious and Tropical Diseases, Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona, Spain, 10 Department of Medical Microbiology, Mater Hospitals, Dublin, Ireland, 11 Department of Microbiology, St. Vincent's, Sydney, New South Wales, Australia, 12 Division of Infectious Diseases, American University of Beirut, Beirut, Lebanon, 13 Infectious Disease Clinical Research Program, Uniformed Services University, Bethesda, Maryland, United States of America, 14 Department of Microbiology, Middlemore Hospital, Auckland, New Zealand, 15 Department of Infectious Diseases, Wellington Hospital, Wellington, New Zealand, 16 Department of Infectious Diseases, North Shore Hospital, Auckland, New Zealand, 17 Institute of Experimental Cardiology, Russian Medical State University, Moscow, Russia, 18 Department of Medicine, VA Medical Centre, Durham, North Carolina, United States of America, 19 Infectious Disease Division, Medical University of South Carolina, Charleston, South Carolina, United States of America, 20 Infectious Diseases, Duke University Medical Center, Durham, North Carolina, United States of America

Abstract

The HACEK organisms (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) are rare causes of infective endocarditis (IE). The objective of this study is to describe the clinical characteristics and outcomes of patients with HACEK endocarditis (HE) in a large multi-national cohort. Patients hospitalized with definite or possible infective endocarditis by the International Collaboration on Endocarditis Prospective Cohort Study in 64 hospitals from 28 countries were included and characteristics of HE patients compared with IE due to other pathogens. Of 5591 patients enrolled, 77 (1.4%) had HE. HE was associated with a younger age (47 vs. 61 years; χ²<0.001), a higher prevalence of immunologic/vascular manifestations (32% vs. 20%; χ²<0.008) and stroke (25% vs. 17% p = 0.05) but a lower prevalence of congestive heart failure (15% vs. 30%; p = 0.004), death in-hospital (4% vs. 18%; p = 0.001) or after 1 year follow-up (6% vs. 20%; p = 0.01) than IE due to other pathogens (n = 5514). On multivariable analysis, stroke was associated with mitral valve vegetations (OR 3.60; CI 1.34–9.65; p = 0.008) and younger age (OR 0.62; CI 0.49–0.90; p = 0.001). The overall outcome of HE was excellent with the in-hospital mortality (4%) significantly better than for non-HE (18%; p < 0.001). Prosthetic valve endocarditis was more common in HE (35%) than non-HE (24%). The outcome of prosthetic valve and native valve HE was excellent whether treated medically or with surgery. Current treatment is very successful for the management of both native valve prosthetic valve HE but further studies are needed to determine why HE has a predilection for younger people and to cause stroke. The small number of patients and observational design limit inferences on treatment strategies. Self selection of study sites limits epidemiological inferences.

Introduction

The HACEK group of bacteria (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) are a small, heterogeneous group of fastidious, gram-negative bacteria that frequently colonize the oropharynx and have long been recognised as a cause of infective endocarditis (IE). These organisms have been historically reported as causing infection in <5% of patients of IE [1,2], and 0.8–6% of patients in recent population-based studies [3–5].
Due to the relative rarity of HACEK endocarditis (HE), the clinical description and outcome has, of necessity, been derived from compilation of data from small case series and case reports [6–10]. These reports are limited by non-standardized data collection and selective reporting of patients. Consequently, the features of HE identified cannot be compared rigorously with other forms of IE.

The International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) was designed to provide a large multinational resource of prospectively collected, well defined patients of IE using a standardized data set. The objective is to improve understanding of the clinical characteristics and outcome of IE in a multi-national cohort of patients. In this report we describe the characteristics of patients with HE, and compare the risk factors, clinical characteristics, and outcomes of HE with IE caused by other pathogens (non-HE).

**Patients and Methods**

**Database**

ICE-PCS has been described previously [11,12]. Briefly, participating members from 64 sites in 28 countries reported patients prospectively on a standard case report form from June 2000 through to September 2006. The case report form included 275 variables and was developed by ICE collaborators according to standard definitions [11]. All patients were included from sites that met performance criteria for participation. These criteria include the following: minimum enrolment of 12 patients per year in a centre with access to cardiac surgery; the presence of patient identification measures to ensure consecutive enrolment and to minimise ascertainment bias [11]; high quality data with query resolution.

**Ethical Statement**

Initial institutional review board approval for ICE-PCS came from the Duke International Centre. All participating sites had institutional review board or ethical committee approval or a waiver and informed consent (verbal or written) or a waiver of consent from all patients based on local standards as required by the Duke Coordinating Centre.

**Study Sample**

Patients in the ICE-PCS database were included in this study if they had definite or possible IE according to the modified Duke’s criteria. HACEK isolates were identified and antibiotic susceptibility testing performed in the participating centres. Antibiotic therapy was decided by the treating physician at the individual study site.

**Definitions**

Infective endocarditis was defined according to the modified Duke Criteria [13]. Infective endocarditis was considered to be left sided if no right sided (tricuspid or pulmonary valve) vegetations were present on echocardiographic examination, surgery, or autopsy. Community-acquired IE was defined as signs or symptoms of IE developing before hospitalization in a patient without extensive out-of-hospital contact with health care interventions or systems. Hospital acquired IE was defined as symptom onset and diagnosis occurring in a patient hospitalized for more than 48 hours. Health care–associated infection was defined as cases in which signs or symptoms consistent with infective endocarditis developed before hospitalization in patients with extensive out-of-hospital contact with health care interventions. Extensive out of hospital intervention included one or more of the following: (1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days prior to the onset of IE; (2) visiting a hospital or hemodialysis clinic or receiving intravenous chemotherapy within the 30 days before the onset of IE; (3) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of IE; or (4) residing in a nursing home or long-term care facility [14,15].

Cancer was defined as any malignant neoplasm except basal or squamous cell carcinomas of the skin. The category “other chronic diseases” included connective tissue or rheumatologic disease, chronic liver or kidney disease, chronic neurological conditions, and other chronic infectious and inflammatory conditions. A diagnosis of heart failure was accepted on the basis of clinical evaluation performed by the care team and defined according to the New York Heart Association classification system [16]. Stroke was defined as an acute neurological deficit of vascular aetiology lasting more than 24 hours [17]. Systemic embolisation included embolisation to any organ including the skin. Valve surgery included all surgery performed on heart valves at any time during hospitalisation regardless of urgency. Rates of surgery and mortality include events that occurred during the index hospitalisation and one year follow-up. Repeat IE was defined as a further episode of IE fulfilling the modified Duke criteria. Confirmed relapse was defined as a repeat episode caused by the same microorganism on molecular analysis, as the preceding episode; confirmed new infection as a repeat episode caused by a different species or the same species but a different strain by molecular analysis; and possible relapse as repeat episode caused by a microorganism of the same species within 6 months of the initial episode without molecular analysis [18].

**Geographic regions**

Geographic regions participating in ICE included the following: United States (10 sites), South America (9 sites from Argentina, Brazil, and Chile), Europe (27 sites from Austria, Croatia, France, Germany, Greece, Ireland, Italy, the Netherlands, Romania, Russia, Slovenia, Spain, Sweden, and the United Kingdom), Australia and New Zealand (9 sites), Asia and Middle East (8 sites in India, Israel, Lebanon, Malaysia, Saudi Arabia, Singapore, and Thailand) and South Africa (1 site).

**Microbiological methods**

Blood cultures and sensitivity testing was performed by accredited laboratories using standard methods. Sensitivity testing was most commonly those of the Clinical and Laboratory Standards Institute (CLSI).

**Statistical analysis**

Continuous variables were represented as medians with 25th and 75th percentiles. Categorical variables were represented as frequencies and percentages of the specified group. Simple comparisons were made with the Wilcoxon rank-sum test or the chi square test as appropriate. For all tests, a p value of 0.05 or less was considered statistically significant. Missing data for each variable were excluded from the denominator. Variables found to have a simple association with the outcome of interest (p<0.10) were considered for the final multiple variable model in a stepwise fashion. The variables included in the final multiple variable adjusted regression model were selected based on a combination of statistical significance (p<0.05) and clinical judgment. The generalized estimating equation method was used to produce consistent parameter estimates that measure association between the incidence of outcome and clinical covariates while accounting for the correlation in treatment and outcomes of patients from the
same hospital. Final parameter estimates were converted to ORs
with corresponding 95% Wald CIs. All statistical analyses were
performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Seventy seven (1.4%) of 5591 patients diagnosed with IE in
ICE-PCS had HACEK endocarditis (66 definite and 11 possible)
and PVE was present in 27 (35%). The prevalence of HE differed
significantly between the study sites (p = 0.009), with a low
prevalence in North America and a high prevalence in
Australia/New Zealand. The HE cases by region were: North
America (5/992, 0.5%), South America (8/518, 1.5%), Australia/
New Zealand (23/979, 2.3%), Europe (35/2806, 1.2%), Asia/
Middle East (5/277, 1.8%), and Africa (1/19).

Features of HE by species

The HACEK species were speciated in 76 (99%) cases with
Haemophilus species the most common (40%) (Table 1). Of all
HACEK species, only Kingella spp. was not associated with an
episode of prosthetic valve endocarditis (PVE). PVE was more
common in A. actinomycetemcomitans (6, 86%) and
A. actinomycetemcomitans (6, 32%; p = 0.01). Clinical manifesta-
tions of IE (10, 53%) and A. actinomycetemcomitans (8, 53%)
and H. parainfluenzae IE (6, 55%) than H. parainfluenzae IE (3, 11%;
both p<0.01). Clinical manifestations of IE more than 1 months
duration were recorded more often in A. actinomycetemcomitans
(8, 67% v 5, 18%; respectively p<0.01). Antimicrobial sus-
sceptibility testing

The causative organisms are shown in table 1. Of the isolates
tested 24/25 (96%) were penicillin susceptible (1 resistant
strain of A. aphrophilus, 48/49 (98%) were ampicillin suscep-
tible (1 resistant strain, of A. aphrophilus, 50/50 (100%) were
ceftazidime susceptible, and 30/32 (94%) were gentamicin sus-
cceptible (2 resistant strains of H. parainfluenzae).

Clinical features of HACEK and non-HACEK endocarditis

Baseline characteristics and predisposing factors of HE are
shown in Table 2. The median age of patients with HE (47.4
years; IQR 35.6–57.1) was significantly lower than non-HE (60.5
years; IQR 45.3–72.7) and males predominated (56, 73%). Factors
more commonly associated with HE than Non-HE endocarditis
were Osler’s nodes (7% vs 3%, p = 0.02) and vascular immuno-
logical phenomena (32% vs 20%, p = 0.006) and the presence of
mechanical valves (30% vs 18%, p = 0.02). Factors less commonly
associated with HE than non-HE endocarditis were health care
provision (1% vs 24%, p<0.001), and diabetes mellitus (3% vs
18%, p = 0.02). There was no difference in the proportion with
fever or splenomegaly between HE and non-HE, nor with native
valve predisposition for IE or congenital heart disease (Table 2).

Transfers from another facility

There was no difference in the number of cases transferred from
another facility between HE (30, 39%) and non-HE (2288, 41%;
p = 0.6). In HE there were more cases transferred with native valve
endocarditis (24, 80% vs 23, 49%; p = 0.01 ), new or worsening
murmurs (20, 67% vs 19, 40% p = 0.005), regurgitation on
echocardiography (23, 77% vs 23, 49%; p = 0.02), and need for
valvular surgery (aortic valve 11, mitral valve 12 ( 23, 77% vs 8,
17% p<0.001 ) compared with those directly admitted. There was
a borderline significant increase in stroke among transferees (11,
38% vs 8, 17%; p = 0.06) and CHF (7, 32% vs 4 9%; p = 0.10) and
no difference in the numbers of cases with symptoms longer than 1
month (5, 17% vs 13, 20% p = 0.41) or length of hospital stay
(median 23 IQR 15–42 vs median 27 IQR 14–42, p = 0.56).

Diagnosis

Blood cultures were drawn in all 77 patients with HE. Three of
four patients with negative blood cultures had received antibiotics
in the previous seven days. Additional culture positive sites were
heart valves (20), joint fluid (2), pacemaker wires (1), urine (1),
and other (5). One patient was diagnosed by PCR of infected tissue.
Echocardiography was performed in 97% of HE (transhoracic
only 15, transesophageal only 9, both transthoracic and trans-
esophageal 31). Vegetations were identified in a lower propor-
tion in HE than non-HE (71% vs 83%, p = 0.01) (Table 2). There was
no difference in the proportions of mitral and aortic valve
vegetations identified between HE and non-HE. Only 1 case of
tricuspid valve endocarditis was recorded in HE. New regurgita-
tion and paravalvular complications were not significantly
different from non-HE (Table 2).

Antimicrobial susceptibility testing

The causative organisms are shown in table 1. Of the isolates
tested 42/45 (93%) were penicillin susceptible (1 resistant strain of
A. aphrophilus, 48/49 (98%) were ampicillin susceptible (1 resistant
strain, of A. aphrophilus, 50/50 (100%) were ceftriaxone suscep-
tible, and 30/32 (94%) were gentamicin susceptible (2 resistant
strains of H. parainfluenzae).

Treatment

Antimicrobial therapy was reported in 50 (65%) patients. Of
these 37 (74%) were treated with ceftriaxone (in combination with
an amnikoglycoside in 17 and ampicillin in 6) , 6 with a penicillin
derivative (ampicillin in 3, penicillin G in 2, and penicillinase-
resistant penicillin in one, in combination with an aminoglycoside),
and 3 with cefazolin/cefalothin (in combination with an amino-
glycoside), and 4 unspecified. All cases of HE were treated with
antimicrobial agents that would be active as predicted by

Table 1. HACEK organisms isolated from definite and
probable cases of HACEK endocarditis.

<table>
<thead>
<tr>
<th>HACEK organisms</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus spp.</td>
<td>31 (40)</td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td>28 (36)</td>
</tr>
<tr>
<td>Haemophilus sp. othera</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Aggregatibacter spp.</td>
<td>26 (34)</td>
</tr>
<tr>
<td>Aggregatibacter actinomycetemcomitans</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Aggregatibacter aphrophilus</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Aggregatibacter paraphrophilus</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Aggregatibacter segnis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cardiobacterium spp.</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Cardiobacterium hominis</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Cardiobacterium valvarum</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Eikinella corrodens</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Kingella spp.</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Kingella kingii.</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Kingella denitrificans</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Kingella sp.</td>
<td>1 (1)</td>
</tr>
<tr>
<td>HACEK (not otherwise specified)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
</tr>
</tbody>
</table>

*not specified. doi:10.1371/journal.pone.0063181.t001
Cardiac surgery was performed on 31 (40%) patients a median of four days (IQR 1–19) after admission. The aortic valve was replaced in 17 patients, mitral valve in 13, tricuspid valve in one and an intracardiac device was removed in one patient.

**Table 2. Important features of HACEK endocarditis compared with all other causes of infective endocarditis in database*.**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>HACEK Endocarditis n = 77</th>
<th>Non-HACEK Endocarditis n = 5514</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (interquartile range), y</td>
<td>47.4 (35.6–57.1)</td>
<td>60.5 (45.3–72.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prosthetic valve endocarditis</td>
<td>27/77 (35)</td>
<td>1298/5514 (24)</td>
<td>0.07</td>
</tr>
<tr>
<td>Manifestations &gt;1 month</td>
<td>18/77 (23)</td>
<td>1174/5294 (22)</td>
<td>0.68</td>
</tr>
<tr>
<td>Osler’s nodes</td>
<td>5/71 (7)</td>
<td>132/5260 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Conjunctival haemorrhages</td>
<td>6/72 (8)</td>
<td>214/5261 (4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Vascular/immunologic evidence of endocarditis</td>
<td>25/77 (32)</td>
<td>1118/5514 (20)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Outcomes**

The in-hospital mortality of HE was less than one quarter that of the non-HE (3, 4% vs 998,18%; p<0.001). Of the three HE deaths with one had been treated surgically. Heart failure was significantly less frequent in HE than non-HE (15% vs. 30%,
Heart failure (5.19% vs 6.14%; p = 0.74) or surgical treatment (8.19% vs 10.37%; p = 0.01). The frequency of systemic embolization, excluding central nervous system, intracardiac abscess and mycotic aneurysm were not significantly different in HE than non-HE (Table 2).

At one year follow-up, three additional cases of HE had died (heart failure 1, unrelated causes 1, unknown 1); however the cumulative death rate was significantly lower than non-HE (6.11% vs 16.27%, 39%; p < 0.001) (Table 2). Four cases had undergone valvular surgery; three had been treated medically and one surgically.

There was one possible relapse 4 months after completing therapy with an unspecified HACEK organism. This organism was not available for further speciation. In addition one patient with HE had another episode of endocarditis with a methicillin susceptible S. aureus.

HACEK endocarditis. Comparison of the clinical features of native valve and prosthetic valve HE demonstrated that native valve HE occurred at an older age (median 56.3 (range 41-67) vs median 43.6 (range 32–54) years, p = 0.003), and that a higher proportion had Osler’s nodes (5.20% vs 0.0%; p = 0.002) and systemic embolization (10.37% vs 5.12%; p = 0.01) than prosthetic valve HE (Table 4). There was no significant difference in the proportion with stroke (7.26% vs 11.24%; p = 0.85), or congestive heart failure (3.19% vs 6.14%; p = 0.74) or surgical treatment (8.30% vs 22.45%; p = 0.23) or length of median hospital stay between these groups.

Of those with PVE 8 (30%) required surgical treatment and 19 (70%) were treated with medical therapy alone. There were no in-hospital deaths in either treatment group. Of the 24 PVE patients with 1 year follow-up data, there was one death (cause unknown) and three who required cardiac surgery in the medically treated group, no deaths, relapses or further surgery requirement in the surgically treated group. By comparison, among those with native valve HE, there were two in-hospital deaths and 1 death with-in the 1 year follow-up period.

Discussion

This report describes the findings of a large series of HE and non-HE cases of bacterial endocarditis reported in a standardised manner in which geographic distribution, frequency of clinical features, risk factors and outcomes have been compared. Both groups were subject to referral bias from transfers to the study centres [19,20], but this is unlikely to confound these comparisons as the proportion transferred was very similar in the two groups, and the pattern of features of the transfers with HE was similar to that reported in the ICE cohort. However the frequency of some clinical features are influenced by transfers between hospitals, and the results need to be interpreted in the light of this limitation.

The marked geographic difference in the prevalence of HE (10-fold) between the highest (New Zealand) and the lowest countries (United States of America) confirms the findings of an earlier, smaller sample of cases in the ICE cohort [11]. The range is similar to the range of 0.8–6.1% reported in recent single and multi-centre studies. [3–5]. The high prevalence of HE in New Zealand is unlikely to be due to referral patterns given the low proportion transferred from another facility. Other possible reasons for the variation include the prevalence of risk factors such as frequency of prosthetic devices [12], oral health [21],

### Table 3. Univariate and multivariate analysis for the risk of stroke in HACEK endocarditis*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No Stroke</th>
<th>Stroke</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valve endocarditis</td>
<td>20/57 (35)</td>
<td>3/19 (16)</td>
<td>0.9</td>
<td>0.62 (CI 0.49–0.90) p &lt; 0.01</td>
</tr>
<tr>
<td>Median age (interquartile range), y</td>
<td>51 (38–60)</td>
<td>41 (25–54)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 month from 1st manifestation</td>
<td>13/57 (23)</td>
<td>5/19 (26)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Conjunctival haemorrhages</td>
<td>1/52 (2)</td>
<td>5/19 (26)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Osler’s nodes</td>
<td>4/52 (8)</td>
<td>1/18 (6)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Vascular/immunologic evidence of endocarditis</td>
<td>13/57 (23)</td>
<td>11/19 (58)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Aortic valve vegetation</td>
<td>22/37 (59)</td>
<td>4/16 (25)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mitral valve vegetation</td>
<td>14/37 (38)</td>
<td>11/16 (69)</td>
<td>0.04</td>
<td>3.60 (CI 1.34–9.65) p &lt; 0.01</td>
</tr>
<tr>
<td>Aortic valve surgery</td>
<td>14/21 (67)</td>
<td>4/9 (44)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>6/21 (29)</td>
<td>7/9 (78)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Embolization</td>
<td>10/56 (18)</td>
<td>5/17 (29)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Mycotic Aneurysm</td>
<td>0/57 (0)</td>
<td>3/19 (16)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Median days in hospital (interquartile range)</td>
<td>22 (14–34)</td>
<td>42 (21–60)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>In-hospital death</td>
<td>2/57 (4)</td>
<td>1/19 (5)</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

*Values are reported as n/n (%), unless otherwise noted.
†There was missing data for stroke on one patient.
doi:10.1371/journal.pone.0063181.t003
transmission pathways of HACEK organisms within populations [22], regional health care access, and diagnostic bias.

Some clinical features varied with the causative species. *H. parainfluenzae* was the commonest cause of HE, as has been reported in population based studies [23]. *H. parainfluenzae* endocarditis was less likely to have an insidious onset than both *A. actinomycetemcomitans* and *C. hominis* confirming previous reports [7]. *C. hominis* was strongly associated with aortic valve infection and *A. actinomycetemcomitans* endocarditis was a frequent cause of PVE, and vascular immunological manifestations [6,7,9,10]. Despite this, we found that HE has sufficient important clinical features in common that distinguish it from non-HE to retain clinical usefulness. These features include younger age of presentation, community acquisition, a higher proportion with vascular/immunological manifestations, a lower proportion with co-morbidities and an excellent outcome.

Prosthetic valve endocarditis was common (35%), although the prevalence of HACEK PVE was not significantly higher than non-HE PVE in this study (p = 0.07). However, the comparator includes a heterogeneous group of organisms with variable propensity to cause PVE. For example, previous studies of the ICE cohort have found the proportion of PVE in *Staphylococcus aureus* IE to be 16%, viridans streptococcal IE to be 15%, and coagulase-negative staphylococcal IE to be 32% [11]. Thus it appears that HACEK organisms have a predilection for prosthetic valves. This finding is more marked in late PVE (>1 year after surgery) as HE causes late PVE in a large majority of cases [12], but only about half of cases of *S. aureus* and coagulase-negative staphylococci PVE, suggesting mechanical valves are a particular risk for HE [17]. In addition this study may under estimate the true proportion with PVE because of the high number of native valve HE cases transferred from other centres. Pre-existing native valve and congenital cardiac abnormalities were common in HE but there was no significant increase in these conditions compared with non-HE. Previous studies have suggested these risk factors may occur more frequently in HE, but this will be subject to changes in the epidemiology of native valve lesions such as rheumatic fever and the widespread availability of cardiac surgery [22].

Most cases of HE were treated with a third generation cephalosporin and a minority with ampicillin with or without an aminoglycoside; however there were insufficient cases to correlate outcomes with these recommended regimens [24,25]. The incidence of penicillin resistant strains was limited to an isolate of *A. aphrophilus* species. β-lactamase producing strains of *C. hominis* have been reported but not in *A. actinomycetemcomitans* to our knowledge [26]. The proportion of all HE cases requiring cardiac surgery (40%) was similar to non-HE and to that reported in the literature [12,27]. However in PVE the requirement for surgery was lower (30%) which compares favourably with published rates for PVE overall (49%) [12,27]. The favourable outcome of both medically and surgically treated HACEK PVE demonstrates that HE is readily controlled and treated with antimicrobial agents despite the presence of a prosthetic valve.

The outcome of HE was excellent overall with an in-hospital mortality of 3% which is less than one quarter of the mortality for non-HE and one sixth that of *S. aureus* endocarditis [28]. Heart failure was diagnosed in 15% of cases compared with 30% in non-HE and 37% reported for *S. aureus* endocarditis [27,28]. The younger age group and lack of co-morbidities, in addition to pathogen-specific characteristics may favour a good in-hospital and 1 year outcomes. These results would not be affected by

### Table 4. Comparison between the features of native valve HACEK endocarditis and prosthetic valve HACEK endocarditis.*

<table>
<thead>
<tr>
<th></th>
<th>Native valve Endocarditis</th>
<th>Prosthetic valve endocarditis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 47</td>
<td>n = 27</td>
<td></td>
</tr>
<tr>
<td>Duke diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>definite</td>
<td>43/47 (92)</td>
<td>21/27 (78)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median age</td>
<td>43.8 (32–54)</td>
<td>56.3 (41–67)</td>
<td>0.003</td>
</tr>
<tr>
<td>(interquartile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osler’s nodes</td>
<td>0/43 (0)</td>
<td>5/25 (20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Worsening of old</td>
<td>30/47 (64)</td>
<td>8/27 (30)</td>
<td>0.005</td>
</tr>
<tr>
<td>murmur or presence of new murmur</td>
<td>36/47 (77)</td>
<td>10/27 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECHO evidence</td>
<td>46/78 (78)</td>
<td>15/27 (56)</td>
<td>0.02</td>
</tr>
<tr>
<td>of new regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracardiac</td>
<td>17/36 (47)</td>
<td>9/15 (60)</td>
<td>0.4</td>
</tr>
<tr>
<td>vegetation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve</td>
<td>18/36 (50)</td>
<td>7/15 (47)</td>
<td>0.8</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>11/22 (50)</td>
<td>7/8 (88)</td>
<td>0.06</td>
</tr>
<tr>
<td>Surgery</td>
<td>11/46 (24)</td>
<td>7/27 (26)</td>
<td>0.85</td>
</tr>
<tr>
<td>Stroke</td>
<td>6/11 (55)</td>
<td>4/6 (67)</td>
<td>1.0</td>
</tr>
<tr>
<td>Embolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral</td>
<td>5/11 (45)</td>
<td>2/6 (33)</td>
<td>1.0</td>
</tr>
<tr>
<td>haemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other systemic</td>
<td>1/43 (12)</td>
<td>10/27 (37)</td>
<td>0.01</td>
</tr>
<tr>
<td>Embolization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart</td>
<td>6/44 (14)</td>
<td>5/27 (19)</td>
<td>0.13</td>
</tr>
<tr>
<td>failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>21/47 (45)</td>
<td>8/27 (30)</td>
<td>0.23</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>2/47 (4)</td>
<td>0/27 (0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Death within</td>
<td>21/47 (45)</td>
<td>24/17 (43)</td>
<td>0.2</td>
</tr>
<tr>
<td>1 year of admission</td>
<td>3/33 (9%)</td>
<td>1/22 (5%)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Values are reported as n/n (%), unless otherwise noted.

1 year mortality data was available on 33 (70%) subjects with native valve HE and 22(81%) subjects with prosthetic valve HE.

doi:10.1371/journal.pone.0063181.t004
survivor bias given the very high survival rate of HE. With respect to PVE, the numbers were too small to make meaningful comparison for other major complications including stroke, constrictive heart failure and abscess formation.

The major complication of HE was stroke (25%), and this complication almost doubled the length of hospitalisation. This figure over-represents the true incidence of stroke in HE as there was an increased frequency of stroke in those transferred from other facilities. Nevertheless stroke is comparatively common in HE compared with non-HE, and the reported frequency in S. aureus endocarditis (20%) and viridans streptococcal IE (8%) in the ICE cohort [29]. Mitral valve IE was an important risk factor for stroke as reported previously, but organism specific effects on the nature of the vegetations in HE may also make a significant contribution to the prevalence of stroke, as 44% of patients with mitral valve HE suffering a stroke compared with 24% of non-HE. This may be related to the long antecedent history with organisms such as A. actinomycescomitans [7].

While embolism was the predominant cause of stroke in HE there was relative excess of haemorrhagic stroke. The reasons for this are not clear but it is possible micro-vascular/immunological manifestations of IE which were significantly more frequent in HE than non-HE and might contribute to the development of cerebral microbleeds which are a strong predictor of subsequent intracranial haemorrhage [30]. Anticoagulant therapy is unlikely to contribute to the occurrence of stroke but may increase the conversion of embolic to haemorrhagic events [31].

There are several additional limitations of this study. Because of small numbers both possible and definite cases were included to increase statistical power. Despite this there were a limited number of cases of HACEK endocarditis and the observational design and long-term follow-up limited to one year limits our ability to draw any firm conclusions regarding optimal antimicrobial therapy or surgical treatment strategies. Furthermore the self selection of centres to participate in the ICE study, and the heavy weighting toward Europe, North America and Australasia with few sites in Asia, and Africa has meant that the population sample may not be representative of any specific region. Thus important geographical differences may have been missed and any epidemiological inferences from this study are limited.

Our findings suggest that there is sufficient similarity in presentation and outcome to justify considering the HACEK organisms as a group at present. Despite the high prevalence of stroke, HE has a remarkably low mortality rate, suggesting that current antibiotic therapy with surgery when needed, is very effective. The reasons why HE shows apparent disparities in incidence of stroke are worthy of further investigation.

Acknowledgments

In addition to all of the named ICE investigators at each site, we would like to acknowledge the support given to this project from all of the personnel at each site and at the coordinating center that have allowed this project to move forward.

Study Investigators

**Argentina:** Lilianna Clara, MD, Marisa Sanchez, MD (Hospital Italiano).
Francisco Nacinnovich, MD, Pahlo Fernandez Oses, MD, Ricardo Ronderos, MD, Adriana Suscar, MD, Jorge Thierer, MD (Instituto Cardiovascular), José Casable, MD, PhD, Claudia Cortes, MD (Hospital Universitario de la Fundacion Favaloro)

**Australia:** Denis Spelman, MD (Alfred Hospital), Eugene Athan, MD, Owen Harris, MBBS, (Barwon Health), Karina Kennedy, MBBS, Ren Tan, MBBS (Canberra Hospital), David Gordon, MBBS, PhD, Lito Papanicolas, MBBS (Flinders Medical Centre), Damon Eisen, MBBS, MD, Leanne Gregg, MBBS, Alan Street, MBBS (Royal Melbourne Hospital), Tony Korman, MD, Despina Kostasana, BS (Hons) (Southern Health), Robyn Dever, MD, Phillip Jones, MD, Pam Konecný, MD, Richard Lawrence, MD, David Rees, MD, Suzanne Ryan, MHS (St. George Hospital), Michael P. Fencey, MD, John Harkness, MD, Phillip Jones, MD, Suzanne Ryan, MHS (St. Vincent’s), Austria: Phillip Jones, MD, Suzanne Ryan, MHS (Austria), Jeffrey Post, MD, Forl Reinhott, Suzanne Newman, (The University of South Wales), Rudi L, Franz Wiesbauer, MD (Vienna General Hospital), Brazil: Adriana Ribas Andrade, Ana Claudia Passos de Brito, Arminio Costa Guimarães, MD (Anna Neri Hospital), Max Grinberg, MD, PhD, Alfredo José Mansur MD, PhD, Rinaldo Focaceia Siciliano, MD, Tania Mara Varrejao Strabelli, MD, Marcelo Luiz Campos Vieira, MD (Heart Institute (Incor), University of Sao Paulo Medical School). Regina Aparecida de Medeiros Tranches, MD, Marcelo Goulart Pita, MD (Hospital 9 de Julho), Claudio Querido Fortes, MD (Hospital Universitario Clementino Fogo Filho/UFRRJ), Auriestela de Oliveira Ramos, MD (Instituto Dante Fameccossi di Cardiologia), Giovanna Ferrainoli, MD, Wilma Golecbofski, MD, Cristiane Lamas, MD, Phi, Maria Santos, MD, PhD, Clara Weksler, MD (Instituto Nacional de Cardiologia). Canada: James A. Karkowsky, MD, Yoav Kayem, MD, Andrew M. Morris, MD, Edan Rubinstein, MD, LLB (University of Manitoba), Chiles: Sandra Braam, MD, Patricia Garcia, MD, Hospital Clinico P观光stico de Buenavista (Bolivia de Chile), M Cereceda, MD, Alberto Fica, Rodrigo Montagna Mella, MD (Hospital Clinico Universidad de Chile). Croatia: Bruno Barisi, MD, PhD, Suzana Bukovski, MD, PhD Vladimir Krajnovic, MD, Ana Pangercic, MD, Igor Ruze, MD, Josip Vince, MD, PhD (University Hospital for Infectious Diseases). Czech Republic: Tomas Freiberger, MD, PhD, Jiri Pol, MD, Barbora Zaloudekova, MS (Centre for Cardiovascular Surgery and Transplantation). Egypt: Zainab Ashour, MD, Amani El Kholy, MD, Marwa Miah, MD, Marzouk Rizk, MD (University of Brest - Université de Bretagne Occidentale). France: Aissa, MD, Corentine Alauzet, MD, Francois Alla, MD, PhD, CHU Catherine Camagnac, RN, Thanh Doco-Lecompte, MD, Christine Selluty, MD (CHU Nancy-Bourbuis). Jean-Paul Casalta, MD, Pierre-Eudoard Fournier, MD, Gilbert Habib, MD, Didier Raoult, MD, PhD, Franck Thuny, MD (Faculte de Medecine de Marseille). Francois Delahaye, MD, PhD, Armel Delahaye, Francois Vandenesch, MD (Hospital Louis Pradel). France: Joel Bourguignon, PhD, Pierre Yves Desrues, PhD, Christian Guerra, MD, PhD, Matthieu Revest, MD, Pierre Tattevin, MD, PhD, Jeremie Violette, MD (Ponchatoula University). Florent Chevalier, MD, Antoine Jou, MD, Dan MD Rusinara, MD, Claire Sorel, MD, Christophe Tribouilloy, MD, PhD (South Hospital Amans). Yvette Bernard, MD, Catherine Chirouze, MD, Bruno Hoen, MD, PhD, Joel Leroy, MD, Patrick Pieslat, MD (University Medical Center of Bouamou). Germany: Christoph Naber, MD, Berhard, Universitatsklinik Neunburg (University of Breslau - Universitat Breslau). Germany: Matthias Zumaher, PhD, Christoph Naber, MD, PhD, Carl Neuerburg (University Essen). Greece: Sofia Athanasia, MD, Effthymia Giannitsioti, MD (Athinon University General Hospital), Elena Mylona MD, Olga Panari MD, PhD, Konstantinos Papanicolaou, MD, John Pyros MD, Athanasios Skoutelis MD, PhD (Evangelismos General Hospital of Athens). India: Gautam Sharma, MD (All India Institute of Medical Sciences). Johnson, MD, DM, Lathia Nair, DM, Vinod Thomas, MD, DM, Krishnan Venugopal, MD, DM (Medical College Calicut). Ireland: Margaret Hanon, MB, BCh RAO, MSc, John Hurley, MB, BCh (Water Hospitals). Israel: Dan Gilon, MD, Sarah Israel, MD, Maya Korem, MD, Jacob Scharlievitz, MD (Hadassah-Hebrew University). Ethan Rubinstein, MD, LLLB, Jacob Scharlievitz, MD (Tel Aviv University School of Medicine). Italy: Marie Francoise Tripodi, MD (Università degli Studi di Salerno); Roberta Casalta, MD, PhD, Susanna Cucurullo, MSc, Giovanni Diataldo, MD, Emanuele Durance, MD, PhD, Matteo Imazio, MD, PhD, Enrico Ragone, MD, PhD, Ricardo Ulli, MD, PhD (University di Napoli). Enrico Cecchi, MD, Francesco De Rosa, MD, Davide Forno, MD, Massimo Imazio, MD, Rita Trinchero, MD (Maria Vittoria Hospital). Alessandro Tehini, MD, Paolo Grossi, MD, PhD, Mariangela Lattanzio, MD, Antonio Toniolo, MD (Spedali Civili – Università di Brescia). Lebanon: Tony Bana, MD, Zsina Kafanani, MD, MS, Souha S.Kanj, MD, Jad Stefl, MD, Mohammad Yasmine, MD (American University of Beirut Medical Center). Malaysia: Imran Abidin, MD (University of Malaysia Medical Center), Syahidah Syed Tamin, MD (National Heart Institute) Mexico: Eduardo Rivera Martinez, MD, Gabriel Israel Soto Nieto, MD (Instituto Nacional de Cardiovascular) PLOS ONE | www.plosone.org 7 May 2013 | Volume 8 | Issue 5 | e63181


