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Review article

## *Cardiobacterium hominis* infective endocarditis: A literature review

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### ABSTRACT

**Background:** *Cardiobacterium hominis* is a member of the HACEK group, which causes infective endocarditis (IE) but is rarely associated with other infections. It is difficult to biologically identify *C. hominis* because of its slow growth in culture. However, the clinical features of *C. hominis* IE remain unclear.

**Method:** We searched the PubMed database for all articles of *C. hominis* IE published between January 2000 and July 2022.

**Results:** The major clinical features of 44 previously reported cases of *C. hominis* IE were as follows: the median age was 59 years, of which 36 were men; the initial presenting symptoms were chest discomfort (30 %), followed by fever (27 %), night sweats (20 %), fatigability (18 %), weight loss (16 %), and dyspnea (16 %). Almost half of the patients were febrile upon admission. The major predisposing factors were postsurgical valve treatment (57 %), dental treatment or caries (20 %), and congenital valve abnormality (5 %). The median time to identify *C. hominis* in the blood culture was 4 days, but the longest time was 42 days. The most commonly infected valve was the aortic valve, and the most common complication was systemic embolism. Surgical treatment was performed in 23 (52 %) patients. The most frequent initial treatment regimen was cephem antibiotics, with a median treatment duration of 6 weeks. The overall mortality and recovery rates of *C. hominis* IE were 9 % and 91 %, respectively.

**Conclusion:** If *C. hominis* infection is confirmed, physicians should check for the presence of vegetations of the heart valves and understand these characteristics.

### 1. Introduction

*Cardiobacterium hominis*, a Gram-negative pleomorphic and fastidious rod-shaped bacterium, is a member of the *Haemophilus parrophilus*, *Haemophilus parainfluenzae*, *Aggregatibacter actinomycetemcomitans*, *Aggregatibacter aphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* (HACEK) group, which causes infective endocarditis (IE) but is rarely associated with other infections [1,2]. A positive blood culture of typical microorganisms consistent with IE, including the HACEK group, is one of the major criteria in the European Society of Cardiology 2015 modified criteria for the diagnosis of IE [3]. However, IE caused by the HACEK group is rare and accounts for 1.3–1.4 % of IE cases [4,5]. In these HACEK IE cases, *C. hominis* accounts for 13 % of cases; therefore, *C. hominis* IE is significantly rare, with an incidence rate of approximately 0.17–0.18 % [5]. It is difficult to biologically identify *C. hominis* because of its variability in

Gram coloration and slow growth in the culture media [6,7]. Owing to its rare nature, the clinical features and prognosis of *C. hominis* IE remain unclear.

We searched the PubMed database to identify case reports of *C. hominis* IE and found 44 cases reported between January 2000 and June 2022 [1,6–47]. Herein, previously reported cases of *C. hominis* IE were reviewed and summarized.

### 2. Methods

This literature review was reported in concordance with guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Approval from the institutional review board was not required because the data were publicly available.

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2.1. Literature search strategy and data sources

We systematically reviewed the literature for reports of *C. hominis* IE. We searched the PubMed database for all articles published between January 2000 and July 2022 using the following keywords or MeSH terms: (“*cardiobacterium hominis*”[Supplementary Concept] OR “*cardiobacterium hominis*”[All Fields] OR “*cardiobacterium hominis*”[All Fields] OR (“c”[All Fields] AND “*hominis*”[All Fields])) AND (“endocarditis”[MeSH Terms] OR “endocarditis”[All Fields] OR “endocarditides”[All Fields]).

2.2. Case selection

All articles retrieved from the systematic search were exported to the EndNote Reference Manager (version X9; Clarivate Analytics, Philadelphia, Pennsylvania). The articles were then assessed at the title and abstract levels, after which the full text was read to confirm relevance. Two authors (RO and IK) independently reviewed the titles and abstracts of each of the retrieved articles to determine if they met the predefined eligibility criteria and discussed and made final decisions in cases of discrepancies. The following predefined inclusion criteria were used: (1) human case reports of IE, (2) cases associated with *C. hominis*, (3)

English literature, and (4) reports with available clinical data and outcomes.

3. Results

3.1. Literature search

The initial literature search yielded 95 potentially relevant studies. After applying predetermined eligibility criteria, 43 reports (44 cases) were selected for inclusion in the literature review. The PRISMA flowchart summarizes the results of the literature search (Fig. 1).

3.2. Literature review

The major clinical features of the 44 previously reported cases of *C. hominis* IE are summarized in Table 1.

The median age of the population was 59 (interquartile range, 46–66) years, of whom 36 and 8 were male and female, respectively. Four of the patients identified were aged younger than 20 years. The initial presenting symptoms of *C. hominis* IE were chest discomfort or pain (n = 13, 30 %), fever (n = 12, 27 %), night sweats (n = 9, 20 %), fatigability (n = 8, 18 %), weight loss (n = 7, 16 %), dyspnea (n = 7, 16

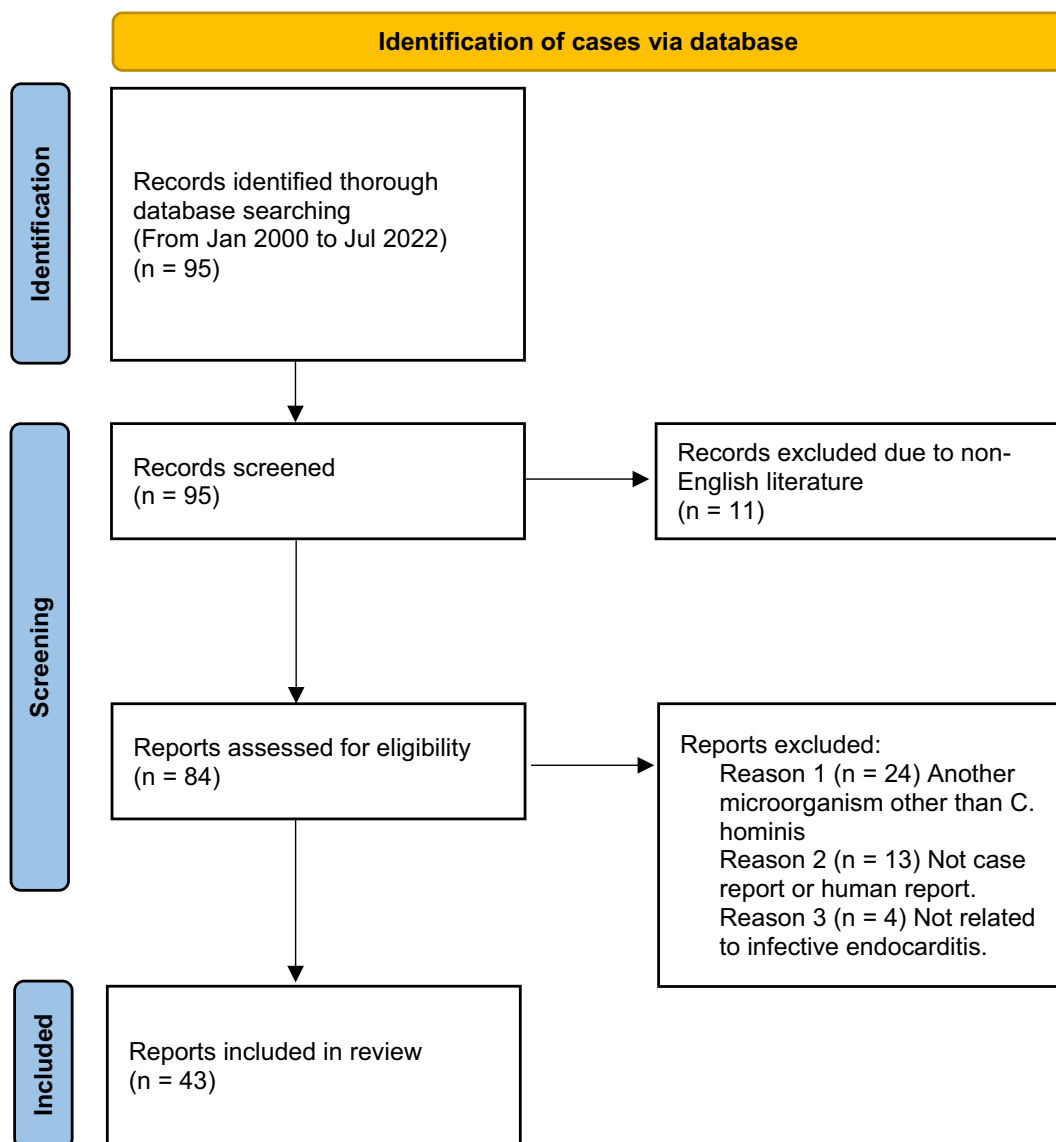


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart outlining the literature search.

%), chills (n = 5, 11 %), myalgia (n = 5, 11 %), and neurological symptoms, such as confusion, diplopia, vertigo, or speech disturbance (n = 5, 11 %). Almost half of the patients (48 %) were febrile on admission. The median white blood cell count was  $10.3 \times 10^3/\mu\text{L}$  (interquartile range,  $8.3\text{--}14.1 \times 10^3/\mu\text{L}$ ). In cases with positive C-reactive protein, the median value was 7.1 (interquartile range, 4.0–11.6) mg/dL. Most patients had predisposing factors. The identified predisposing factors were postsurgical valve treatment (n = 25, 57 %), dental treatment or caries (n = 9, 20 %), congenital valve abnormality (bicuspid or quadricuspid aortic valve) but not receiving treatment (n =

2, 5 %), diabetes mellitus (n = 2, 5 %), steroid use (n = 2, 5 %), pacemaker implantation (n = 2, 5 %), and IE history (n = 2, 5 %). Other factors included heart transplantation (n = 1, 2 %) and rheumatoid arthritis (n = 1, 2 %). Of note, 24 of the 25 patients with postsurgical valve treatment underwent valve replacement, whereas only one patient underwent valve repair. Only three patients had no predisposing factors.

Physical examination revealed a cardiac murmur in 29 (66 %) cases. Splinter hemorrhage was noted in four cases. The median time to *C. hominis* identification in the blood culture was 4 (interquartile range, 3–7) days. Notably, the longest time was 42 days, followed by 20 days.

**Table 1**  
Literature review of *Cardiobacterium hominis* infective endocarditis.

| Case | Author        | Year [Reference] | Age (years) | Sex | Initial presentation  | Body temperature (°C) | Febrile | WBC (mm <sup>3</sup> ) | CRP (mg/dL) | Predisposing factors  | Physical examination  | Time to identify <i>C. hominis</i> of blood culture (days) | 16S rDNA sequencing targeting PCR | Cardiac investigation | Cardiac findings   | Site of infectious valve | Surgery                                      | Antibiotics  | Treatment duration (weeks) | Complication                                      | Outcome            |
|------|---------------|------------------|-------------|-----|---|-----------------------|---------|------------------------|-------------|---|---|--|-----------------------------------|-----------------------|--|--------------------------|--|--|----------------------------|---|--------------------|
| 1    | Curie         | 2000 [8]         | 17          | M   | Lethargy, night sweats  | ND                    | No      | Normal                 | Negative    | Congenital aortic stenosis (post AVR) Dental treatment  | Systemic diastolic murmurs  | 3  | -                                 | TTE                   | AR, vegetation (aortic valve)  | Aortic                   | AVR  | Amoxicillin  | 10                         | None  | Alive at 18 months |
| 2    | Lu            | 2000 [9]         | 66          | F   | Chest discomfort, fatigue   | ND                    | No      | 8,500                  | Negative    | Dental caries   | Systemic diastolic murmurs  | 12   | -                                 | TTE, TEE              | AR, vegetation (aortic valve)  | Aortic                   | AVR  | Amoxicillin (1 week)<br>Ceftriaxone (3 weeks)<br>Ciprofloxacin (1 week)                    | 6                          | None  | Alive at 8 months  |
| 3    | Apharathumrak | 2002 [10]        | 82          | M   | Knee swelling, weight loss, fatigue, night sweats   | 37.8                  | Yes     | 11,000                 | ND          | Ischemic cardiomyopathy (post coronary artery bypass, ventricular aneurysmectomy, and hepatomegaly MVR)   | Splinter hemorrhages, holosystolic murmur, jugular venous distention, heave swelling        | 6  | -                                 | TEE                   | MR, thickening and perforation of the medial leaflet                                   | Mitral                   | -  | Ceftriaxone  | 6                          | None  | Alive at 3 months  |
| 4    | Nikari        | 2002 [11]        | 48          | M   | Leg pain, chest discomfort  | ND                    | ND      | ND                     | ND          | None  | ND  | -  | Positive                          | TEE                   | AR, vegetation (aortic valve), aortic abscess  | Aortic                   | AVR  | Ceftriaxone, gentamicin, ampicillin  | 4                          | None  | Alive at 1 month   |
| 5    | Arnold        | 2004 [12]        | 63          | M   | Weight loss, night sweats, chest pain   | ND                    | No      | 9,300                  | ND          | Aortic stenosis due to bicuspid aortic valve (post AVR)   | Holosystolic murmur, splinter hemorrhages   | 2  | -                                 | TTE                   | AS, AR   | Aortic                   | -  | →ciprofloxacin   | 26                         | Immune thrombocytopenic purpura                   | Alive at 7 months  |
| 6    | Walkey        | 2005 [13]        | 56          | M   | Myalgia, dyspnea, orthopnea, chest pressure, fever  | 38.4                  | Yes     | 29,200                 | ND          | Quadricuspid aortic valve   | Holosystolic murmur, coarse crackles, splenomegaly  | 3  | -                                 | TTE                   | MR   | Mitral                   | MVR, AVR                                     | Ceftriaxone, azithromycin<br>→Ceftriaxone  | 4                          | Cardiac tamponade, third-degree heart block       | Alive at 12 months |
| 7    | Gabels        | 2006 [14]        | 62          | M   | Appetite loss, fatigue, weakness, diffuse abdominal discomfort, chills, night sweats, distended liver | 39                    | Yes     | 14,400                 | 14.3        | Dental caries   | Pale, palpable liver/spleen, murmur   | 17   | Positive                          | TTE, TEE, AUS         | Vegetation (aortic valve)  | Aortic                   | -  | Tekoplanin, ceftriaxone, ampicillin-sulbactam  | 6                          | None  | Alive              |
| 8    | Malani        | 2006 [15]        | 76          | F   | Hip pain  | 38.2                  | Yes     | 12,000                 | ND          | Post AVR, CABG, pacemaker placement, recent endoscopy   | Systemic murmur, tenderness near the right tracheal area and sacrocaudal joint              | 15   | -                                 | TEE                   | Vegetation (aortic valve)  | Aortic                   | -  | Ceftriaxone (10 weeks)<br>amoxicillin/clavulanic acid (24 weeks)                           | 34                         | Bacterial dacryc                                  | Alive at 6 months  |
| 9    | Malani        | 2006 [15]        | 67          | M   | Chest pain, anemia  | 38.1                  | Yes     | 7,000                  | ND          | DM, post AVR, CABG, recent endoscopy  | Systemic diastolic murmur   | 7  | -                                 | TTE                   | Aortic valve paravalvular abscess  | Aortic                   | AVR  | →ceftriaxone (6 weeks)<br>→ amoxicillin (24 weeks)   | 30                         | Chronic sternal wound infection                   | Alive at 6 months  |
| 10   | Shayrakasha   | 2007 [16]        | 61          | M   | Fever   | 38.3                  | Yes     | 10,300                 | ND          | Post aortic regurgitant defect closure and MVR  | ND  | 4  | -                                 | TTE, TEE              | MR, vegetation (mitral valve)  | Mitral                   | -  | → penicillin   | ND                         | Renal failure, pneumonia                          | Died               |
| 11   | Lena          | 2009 [17]        | 59          | M   | Left-sided weakness and numbness, leg edema, cough, chest pain, night sweats, myalgia                 | ND                    | Yes     | Normal                 | 4           | Reactive arthritis  | Murmur, splenomegaly  | 9  | -                                 | TTE, TEE              | AR, MR, vegetation (aortic valve)  | Aortic                   | -  | Gentamicin, ceftriaxone  | 6                          | Cerebral infarction                               | Alive              |
| 12   | Bran          | 2010 [18]        | 61          | M   | Fatigue, lethargy, weight loss, chills, night sweats  | 36.9                  | No      | 8,200                  | 1.7         | Post AVR due to a bicuspid aortic valve, history of endocarditis, colitis   | Murmur  | 5  | -                                 | TTE, TEE              | AR   | Aortic                   | -  | Vancomycin, gentamicin, rifampicin, ceftriaxone<br>→ciprofloxacin, rifampicin, clindamycin | 24                         | None  | Alive at 8 months  |
| 13   | Chentanez     | 2011 [19]        | 31          | M   | Fever, fatigue, headache, numbness of extremity   | 38.1                  | Yes     | 8700                   | 5.4         | Crohn's disease, steroid use  | Systemic murmur, decreased pupillary light touch, temperature sensation, and proprioception | 7  | -                                 | TEE                   | AS, AR, vegetation (aortic valve)  | Aortic                   | -  | Vancomycin, ceftriaxone  | 6                          | Cerebral infarction                               | Alive at 6 weeks   |
| 14   | Mickawa       | 2011 [20]        | 5           | M   | Shortness of breath   | 37.2                  | Yes     | 13,400                 | 1           | Post RVOT reconstruction for tetralogy of Fallot with pulmonary atresia, aortic valve plasty  | Systemic diastolic murmurs, hepatomegaly  | 5  | -                                 | TEE, CT               | PR due to cuspid valve failure, large thrombus on a cusp of RVOT conduit               | Pulmonic                 | RVOT conduit replacement                     | Vancomycin, ceftriaxone, gentamicin  | 6                          | None  | Alive              |
| 15   | Walter        | 2011 [21]        | 60          | M   | Chest constrictive pain   | 37.3                  | No      | 9,100                  | 2.4         | Steroid use   | None  | 3  | Positive                          | TEE                   | AR, vegetation (aortic valve)  | Aortic                   | AVR  | Amoxicillin, gentamicin, levofloxacin<br>→Ceftriaxone                                      | ND                         | None  | Alive              |
| 16   | El Hajji      | 2012 [22]        | 56          | M   | Fever, chills, night sweats   | ND                    | Yes     | ND                     | ND          | Post femoral procedure  | Splenomegaly  | ND   | -                                 | TTE, TEE, PET         | Thickening of aortic root, diffuse uptake around the aortic portion of the aortic root | Aortic                   | -  | Amphotericin B (2 weeks)<br>→cephalosporin (6 weeks)                                       | 8                          | None  | Alive at 12 months |
| 17   | Courand       | 2012 [23]        | 50          | M   | Chest pain  | 37                    | No      | 22,100                 | 8.8         | Renal-vein thrombosis, splenectomy, dental  | Holosystolic murmur   | 2  | -                                 | TTE, TEE, MRI         | MR, vegetation (mitral valve)  | Mitral                   | -  | Gentamicin (2 weeks)<br>ceftriaxone (6 weeks)  | 6                          | Coronary artery occlusion                         | Alive at 12 months |
| 18   | Poniss        | 2012 [24]        | 67          | F   | Confusion, right-sided weakness, speech disturbances  | ND                    | Yes     | 15,800                 | 25          | Post AVR  | Splinter hemorrhages, diastolic murmur  | 42   | -                                 | TEE                   | AR, vegetation (aortic valve), aortic root abscess                                     | Aortic                   | AVR, debridement for the aortic root abscess | Ceftriaxone, gentamicin  | 8                          | Cerebral infarction, splenic infarction           | Alive at 12 months |
| 19   | Goner         | 2013 [25]        | 4           | M   | Cough, irritability, appetite loss  | 38.9                  | Yes     | 16,900                 | 16          | DiGeorge syndrome, tetralogy of Fallot with pulmonary atresia, small pulmonary arteries, and major aortopulmonary collateral, post placement of a right ventricle-to-pulmonary artery non-valved conduit, post VSD patch closure, patch plasty of the left pulmonary artery | Systemic murmur   | 2.7  | -                                 | TTE                   | Vegetation (regrafted pulmonary valve)   | Pulmonic                 | Coil embolization                            | Ceftriaxone  | 6                          | Aneurysm of the right lower lobe pulmonary artery | Died at 3 months   |
| 20   | Suresh        | 2013 [26]        | 12          | M   | Fatigue   | ND                    | ND      | 5930                   | 1.15        | Post repair of tetralogy of Fallot with pulmonary atresia and subsequent replacement of the right ventricle to pulmonary artery conduit, poor dentition   | Systemic diastolic murmurs  | ND (at least more than 2 days)                             | -                                 | TTE                   | Vegetation (conduit valve)   | Pulmonic                 | -  | →ceftriaxone<br>→ampicillin/sulbactam<br>→levofloxacin                                     | 6                          | None  | Alive              |

|    |             |           |    |   |   |      |     |                   |                       |  |  |     |          |  |  |           |   |  |      |   |                    |
|----|-------------|-----------|----|---|---|------|-----|-------------------|-----------------------|--|--|-----|----------|--|--|-----------|---|--|------|---|--------------------|
| 21 | Danovm      | 2014 [27] | 66 | F | Fever, night sweats, fatigue, back pain   | ND   | Yes | ND                | ND                    | Post AVR   | ND   | 3   | -        | TTE  | Vegetation (aortic valve)  | Aortic    | AVR   | Vancomycin, gentamicin, rifampicin   | ND   | Dielect, cardiac arrest   | Alive              |
| 22 | Wong        | 2015 [28] | 47 | M | Malaria, fatigue, night sweats, anorexia, weight loss   | 36.8 | No  | 14,000            | 6.4                   | Dental treatment   | Systolic diastolic murmurs, erythema of the nailbeds                       | 2   | -        | TEE  | Vegetation (aortic valve), paravascular abscess  | Aortic    | AVR   | Vancomycin, ceftriaxone  | 6    | Cerebral infarction   | Alive at 3 months  |
| 23 | Ghakkam     | 2016 [29] | 43 | M | Vertigo, nausea, headache   | ND   | No  | ND                | ND                    | Post AVR, tricuspid valve annuloplasty   | Systolic murmur  | 5   | -        | TEE, CT                                      | Vegetation (aortic valve)  | Aortic    | AVR, aortic arch aneurysm surgical repair         | Ceftriaxone  | 6    | Cerebral infarction, cerebral aneurysm, aortic aneurysm                       | Alive at 12 months |
| 24 | Aranachalam | 2016 [30] | 80 | M | Hematochezia, palpitation   | 38.9 | Yes | ND                | ND                    | Post MVR, dental treatment   | Systolic murmur  | ND  | -        | TTE, TEE                                     | Vegetation (mitral valve)  | Mitral    | -   | Ceftriaxone  | 6    | None  | Alive              |
| 25 | Bouvent     | 2016 [31] | 66 | F | Fever, weight loss  | 39.5 | Yes | ND                | 9.9                   | PMI for SSS  | ND   | 4   | -        | TTE  | Vegetation (pacemaker lead)  | Pacemaker | PM removal/PM reimplantation                      | In time: Ceftriaxone (2 weeks) → Ceftriaxone (2 weeks) 2nd time: amoxicillin-clavulanic acid → ceftriaxone (10 days) → amoxicillin (3 weeks) | 4    | Relapse of IE   | Relapse at 2 years |
| 26 | Mandau      | 2017 [32] | 35 | M | Dyspnea, pleuritic chest pain   | ND   | No  | ND                | ND                    | Hypercoagulability, post AVR   | Systolic murmur  | 3   | -        | CT, TTE                                      | Thrombus/vegetation (aortic valve)   | Aortic    | -   | Ciprofloxacin  | 6    | None  | Alive at 3 months  |
| 27 | Avery       | 2018 [33] | 78 | M | Chest tightness, leg edema, ascites   | 36.9 | No  | 9,800             | 11.4                  | Post AVR, coronary angioplasty, prostate cancer  | Systolic murmur  | 7   | -        | TEE  | Vegetation (aortic valve)  | Aortic    | AVR, CABG   | Ciprofloxacin  | 6.5  | Myocardial infarction, chest hematoma   | Alive at 14 months |
| 28 | Yadava      | 2018 [34] | 75 | M | Back pain   | 38.7 | Yes | 4,330             | 20.5                  | Post AVR   | Systolic murmur, tenderness over the lower lumbar vertebrae                | ND  | -        | TEE  | MR, vegetation (mitral valve)  | -         | -   | Ceftriaxone  | 4    | Lumbar epidural abscess, vertebral osteomyelitis, discitis (during treatment) | Alive at 4 weeks   |
| 29 | Danchand    | 2019 [35] | 30 | M | Face and arm tingling   | ND   | ND  | ND                | ND                    | Embolization of the aortic and mitral valves   | ND   | ND  | -        | ND   | AR, vegetation (aortic valve)  | Aortic    | AVR   | Ceftriaxone  | ND   | Subarachnoid hemorrhage, cerebral aneurysm, cerebral hematoma                 | Alive              |
| 30 | Okumura     | 2019 [36] | 63 | M | Headache, left hemiparetic neglect  | 37.8 | Yes | 8,300             | 7.1                   | Post AVR/MVR   | -  | 20  | -        | TTE, TEE                                     | Mitral valve hyperplasia   | Mitral    | AVR, MVR  | Meningococci, vancomycin (16 days) → ceftriaxone (20 days)   | 5    | Subcortical hematoma  | Alive at 2 months  |
| 31 | Diako       | 2019 [37] | 53 | M | Fever, limb paresthesia, ataxia, transient diplopia   | ND   | Yes | ND                | 11.6                  | Dental treatment   | Proprioceptive ataxia  | 2.7 | Positive | TTE, TEE                                     | AR, vegetation (aortic valve)  | Aortic    | AVR   | Amoxicillin clavulanic acid, gentamicin (2 weeks) → ceftriaxone (2 weeks)  | 4    | Gaikiti-Barré syndrome  | Alive              |
| 32 | Asai        | 2019 [38] | 62 | M | Fever, anorexia, fatigue  | ND   | ND  | 12,000            | ND                    | Post AVR/MVR   | ND   | 2   | -        | TTE, TEE                                     | None   | -         | -   | Ceftriaxone, gentamicin (2 weeks) → ceftriaxone (4 weeks) → moxifloxacin (4 weeks)   | 10   | Cerebral infarction, vertebral embolus  | Alive              |
| 33 | Kob         | 2019 [39] | 58 | M | Breathlessness, chest tightness, chills   | ND   | ND  | 12,400            | 8.7                   | None   | Signs of heart failure   | -   | Positive | TTE, TEE                                     | AR, vegetation (aortic valve)  | Aortic    | AVR   | Amoxicillin-clavulanic acid, gentamicin, ceftriaxone   | 6    | None  | Alive              |
| 35 | Blanchet    | 2019 [6]  | 59 | F | Fever, bruises, multiple pains  | 39   | Yes | 60,200            | 14.7                  | Septal defect, AR, acute myocardial ischemia   | ND   | 6   | Positive | TTE  | None   | -         | -   | Piperacillin-tazobactam, vancomycin → gentamicin → cefepime, ampicillin  | ND   | Respiratory distress  | Deceased           |
| 34 | Hökken      | 2019 [40] | 56 | M | Fever, back pain, lethargy, polyarthralgia  | 38.1 | Yes | 5,200             | 6.5                   | Rheumatoid arthritis   | Systolic diastolic murmurs   | 3   | -        | TTE, TEE                                     | AS, AR, vegetation (aortic valve), abscess   | Aortic    | AVR, pericardial patch closure of the aortic root | Ceftriaxone, gentamicin, moxifloxacin  | 6    | Cerebral infarction   | Alive at 24 months |
| 36 | Wang        | 2020 [41] | 55 | F | Lower extremity paresthesia, palpable purpura, fatigue, weight loss, chills, cough, joint aches | ND   | ND  | ND                | ND                    | Tetralogy of Fallot and bicuspid aortic valve  | Systolic murmur, papular papules   | 2.5 | -        | TTE, TEE                                     | Right ventricular outflow tract obstruction, vegetation (pulmonic valve)               | Pulmonic  | Pulmonic valve aortic angioplasty                 | Piperacillin-tazobactam → ceftriaxone  | ND   | IgA vasculitis  | Alive at 1 month   |
| 37 | Singh       | 2020 [42] | 73 | M | Generalized weakness, weight loss   | ND   | ND  | 15,000            | ND                    | Nonischemic cardiomyopathy, Okai-Welch-Renzli syndrome, severe mitral regurgitation, Barlow's myocardium degeneration, post MVR, endoscopic resection of a gastric carcinoma tumor, dental treatment | Cachexia, poor dentition, bilateral lower extremity edema, systolic murmur | 4   | -        | TTE, TEE                                     | TR, bioprosthetic mitral valve thickening, vegetation (mitral valve)                   | Mitral    | -   | Vancomycin, cefepime   | ND   | -   | Alive              |
| 38 | Saranathi   | 2020 [7]  | 35 | F | Chest pain, difficulty in breathing, palpitations, edema, fever                                 | ND   | Yes | 11,000            | ND                    | None   | ND   | 7   | -        | TEE  | MR, vegetation (mitral valve)  | Mitral    | -   | Ceftriaxone, gentamicin (2 weeks) → ceftriaxone (2 weeks)  | 4    | Thrombus in the left femoral artery   | Alive              |
| 39 | Lievens     | 2021 [43] | 53 | M | ND  | ND   | ND  | ND                | Heart transplantation | ND   | ND   | -   | TEE, PET | Uptake spot around the aortic vascular graft | Aortic vascular graft  | -         | Ceftriaxone                                       | 6  | None | Alive   |                    |
| 40 | Terracelli  | 2021 [44] | 40 | M | Shortness of breath, dyspnea, orthopnea, left leg pain  | ND   | ND  | ND (leukocytosis) | ND                    | Heart valve abnormality  | Systolic murmur, jugular venous distention, crackles, left leg mass        | ND  | -        | TEE  | MR, AR, vegetation (aortic valve)  | Aortic    | AVR, MVR  | ND   | ND   | Aneurysm of the anterior tibial artery  | Alive              |
| 41 | Shingu      | 2021 [45] | 60 | M | Fatigue   | 35.4 | No  | 8,330             | 5.2                   | Valve-sparing aortic root replacement, dental treatment, esophagogastroduodenoscopy, colonoscopy   | Systolic murmur  | 1.7 | Positive | TTE, TEE                                     | Vegetation (aortic valve), paravascular abscess, AR, vegetation in the right ventricle | Aortic    | AVR   | Ceftriaxone  | 6    | Cerebral infarction   | Alive at 6 months  |
| 42 | Mekladou    | 2021 [46] | 72 | M | Fatigue, chills   | ND   | No  | 5,790             | ND                    | Post mitral valve repair, dental treatment   | Systolic murmur  | 4   | -        | TTE  | Vegetation (mitral valve)  | Mitral    | -   | Meropenem → piperacillin-tazobactam  | 6    | Renal failure   | Alive              |
| 43 | Milner      | 2022 [1]  | 41 | M | Dyspnea, chest pain   | 37.1 | No  | 9,100             | 3.5                   | Post aortic coarctation operation  | None   | 3   | Positive | TEE  | AR, vegetation (aortic valve)  | Aortic    | AVR   | → ceftriaxone → amoxicillin  | 4    | None  | Alive              |
| 44 | Radovanovic | 2022 [47] | 54 | M | Generalized weakness, exertional intolerance  | ND   | ND  | ND                | ND                    | Bicuspid aortic valve  | Systolic diastolic murmurs   | 8   | -        | TTE, TEE                                     | AR, perforation of the fused leaflet   | Aortic    | AVR   | Ceftriaxone  | 6    | None  | Alive              |

Note: AR, aortic regurgitation; AS, aortic stenosis; AUS, abdominal ultrasound; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CRP, C-reactive protein; CT, computed tomography; DM, diabetes mellitus; F, female; IE, infectious endocarditis; M, male; MR, mitral regurgitation; MRI, magnetic resonance imaging; MVR, mitral valve replacement; ND, not described; PCR, polymerase chain reaction; PET, positron emission tomography; PM, pacemaker; PMI, pacemaker implantation; rDNA, ribosomal deoxyribonucleic acid; RVOT, right ventricular outflow tract; SSS, sick sinus syndrome; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; VSD, ventricular septal defect; WBC, white blood cell.

In most of the cases, the positivity for blood culture was firstly assessed by the gram staining. Cardiobacterium would be identified if the organisms are catalase-negative and oxidase-positive gram-negative rods. However, 16S ribosomal deoxyribonucleic acid (16S rDNA) sequencing targeting polymerase chain reaction (PCR), which is considered to be the gold standard method for the isolation of the organism, is also used to avoid misidentifying. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is another method to

identify the organism. Eight (18 %) cases were identified using 16S rDNA PCR. Cardiac investigations were performed in all but one patient, and either transthoracic echocardiography or transesophageal echocardiography was performed. Cardiac computed tomography was performed in three patients, and positron emission tomography and cardiac magnetic resonance imaging were performed in one each patient.

Cardiac findings revealed that 32 (73 %), 16 (37 %), 8 (18 %), and 5 (11 %) patients had vegetation, aortic regurgitation, mitral

regurgitation, and paravalvular abscess, respectively. The infectious sites were the aortic valve, mitral valve, pulmonic valve, and pacemaker in 27 (61 %), 9 (20 %), 4 (9 %), and 1 (2 %) patients, respectively. Surgical treatment was performed in 23 (52 %) patients. The median treatment duration was 6 weeks for antibiotic use. The most frequent initial treatment regimen was cephem antibiotics (n = 27), followed by gentamicin (n = 17), vancomycin (n = 11), penicillin antibiotics (n = 9), ciprofloxacin (n = 2), meropenem (n = 1), and teicoplanin (n = 1). Combination therapy with  $\beta$ -lactams and gentamicin was administered to 14 (32 %) patients. The most common complication was thrombosis due to vegetation, including cerebral infarction (n = 8, 18 %), myocardial infarction (n = 2, 5 %), splenic infarction (n = 1), pulmonary embolism (n = 1), vertebral embolus (n = 1), and arteriosclerosis obliterans (n = 1). Other complications included aneurysm (n = 4), discitis (n = 3), and bleeding (n = 3). The overall mortality rate was 9 %, and the recovery rate was 91 % (alive, 40 patients; dead, 4 patients). One patient experienced relapse.

#### 4. Discussion

*C. hominis* is a small, Gram-negative coccobacillus that is part of the normal human oropharyngeal flora but rarely causes human infection [14]. Although *C. hominis* has relatively low virulence, IE complicates 88–95 % of all bacteremia cases [5,40,48]. It is difficult to biologically identify *C. hominis* because of its significantly slow growth and requirement of special enriched media for growth [6,7]. Bacterial culture is usually performed in standard enriched media, and optimal growth is achieved in the presence of 5 % CO<sub>2</sub>. The culture is weak in a microaerophilic atmosphere and negative in an anaerobic atmosphere. Therefore, in some cases, the identification of *C. hominis* requires a significant period of time [2,6,13]. Our review revealed that there was a case in which the culture extended until 6 weeks to identify the organism [24]. Because of its fastidious and slow-growing nature, blood cultures should be continued for  $\geq 14$  days if a patient is suspected with IE [15,49]. In addition, the microbiological identification of IE has dramatically improved over the last decades because molecular biology, especially 16S rDNA PCR, the so-called universal bacterial PCR, allows the identification of causal bacteria, even if antibiotics have already been started before sampling [14,50].

Currently, there are two species of *Cardiobacterium*: *C. hominis* and *Cardiobacterium valvarum*. In these HACEK IE cases, *C. hominis* and *C. valvarum* account for 13 % and 1 %, respectively [5,6]. It is difficult to differentiate between *C. hominis* and *C. valvarum*. The only phenotypic difference described in the literature is the production of raffinose by *C. hominis* [51]. The 16S rDNA PCR test can differentiate between these two *Cardiobacterium* species [14].

Compared with IE associated with other HACEK organisms, a longer duration of symptoms has been reported in *C. hominis* IE. The delayed diagnosis of *C. hominis* IE occurs due to its mild and insidious symptoms and the difficulty in isolating *C. hominis* from the blood culture, as stated above. In fact, our review revealed that nonspecific symptoms, such as fever, night sweats, fatigability, and weight loss, were mainly observed in the initial presentations. Notably, a febrile state was noted in almost half of the patients; in other words, physicians should suspect IE even in the absence of fever. This illness often affects the middle-aged or elderly populations, and the levels of inflammatory markers, such as white blood cells or C-reactive protein, are moderately increased in this illness [14].

Regarding the predisposing factors, we found that three of the four patients aged younger than 20 years had tetralogy of Fallot, and another young patient had congenital aortic stenosis. In adult cases, postsurgical valve treatment and dental treatment were major risk factors. For the past several decades, antimicrobial prophylaxis prior to invasive dental procedures has been considered important to prevent IE caused by oropharyngeal bacteria, including HACEK bacteria. However, the American Heart Association revised its guidelines for IE prevention in a

statement issued in 2008, placing more emphasis on optimal oral hygiene than prophylactic antibiotic administration in dental care [52]. The guidelines for IE do not always recommend antibiotic prophylaxis after dental procedures, but antimicrobial prophylaxis is now recommended for certain high-risk situations, such as the presence of an artificial heart valve, a history of IE, uncorrected or recently corrected congenital heart disease, or the development of valvular heart disease after a heart transplant [53,54]. Therefore, antibiotic prophylaxis for prevention at the time of dental treatment is reasonable and should be considered in patients with postsurgical valve treatment or congenital heart diseases. The aortic valve was the most frequently found site of infection (61 %), followed by the mitral valve (20 %) and pulmonic valve (9 %). If a positive culture for *C. hominis* is noted, a detailed investigation, including transesophageal echocardiography, for these valves should be performed.

Although microbiological cure is achieved by treatment, complications frequently occur during the course of therapy. In our study, 12 (27 %) cases of systemic thrombosis complications occurred in *C. hominis* IE. These included cerebral infarction, myocardial infarction, splenic infarction, pulmonary embolism, vertebral embolus, and arteriosclerosis obliterans. As previously reported, *C. hominis* may tend to form large friable vegetations that can easily cause embolic complications [38]. Other complications included aneurysms, discitis, and bleeding due to infection.

In terms of treatment of HACEK-related species, some HACEK-group bacilli produce beta-lactamases, and ampicillin is no longer the first-line treatment. Therefore, the European Society of Cardiology 2015 recommends ceftriaxone, another third-generation cephalosporin, and quinolone for HACEK IE treatments; the standard treatment is ceftriaxone 2 g/day for 4 weeks in the native valve and for 6 weeks in the prosthetic valve. If they do not produce beta-lactamase, ampicillin (12 g/day in four or six doses) plus gentamicin (3 mg/kg/day divided into two or three doses) for 4–6 weeks is an alternative option. Ciprofloxacin (400 mg/8–12 h intravenously or 750 mg/12 h orally) may be an option for penicillin and cephalosporin intolerance [3]. In fact, our review indicated that most patients were treated with cephem antibiotics for a 6-week duration, which could lead to relatively good outcomes. Surgical treatment was performed in almost half of the patients (52 %). All but one patient who underwent surgical procedures survived. The prognosis showed an overall mortality rate of 9 % and recovery rate of 91 %. Among the four patients who died, the causes of death were renal failure and secondary pneumonia, complicated aneurysm of the right lower lobe pulmonary artery with sudden cardiac arrest due to unknown cause, unknown cause, and respiratory distress and sepsis. One patient experienced relapse, and this relapsed patient firstly had bacteremia of *C. hominis* as well as a small vegetation on the pacemaker lead. The patient received intravenous antibiotics and did not undergo the removal of the pacemaker lead. Repeated blood cultures yielded no longer growth of *C. hominis* and it was initially interpreted that the infection had been successfully treated. However, the patient had *C. hominis* bacteremia again two years later, and the patient received appropriate antibiotics therapy, removal of the pacemaker, and new implantation of the pacemaker, which resolved finally. Therefore, in the case of the bacteremia with the pacemaker, removal of the device should be considered to prevent the relapse.

In conclusion, we systematically reviewed the literature on reports of *C. hominis* IE. Our review of reported cases of *C. hominis* IE suggested that it is often observed in patients with postsurgical valve treatment, congenital heart disease, and recent dental treatments and has mild and insidious symptoms at the initial presentation. Identifying *C. hominis* during cultivation requires a significant period of time. The antibiotic regimens of ceftriaxone, other third-generation cephalosporins, and quinolones, or surgical treatment, if indicated, are usually effective, and the mortality rate is relatively low.



## Ethical statement

Approval from the institutional review board was not required because the data were publicly available.

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## CRediT authorship contribution statement

**Ryohei Ono:** Conceptualization, Methodology, Data curation, Writing – original draft. **Izumi Kitagawa:** Conceptualization, Methodology, Data curation, Writing – original draft. **Yoshio Kobayashi:** Supervision, Writing – review & editing.

## Declaration of competing interest

None.

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