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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 paraphrophilus*, *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

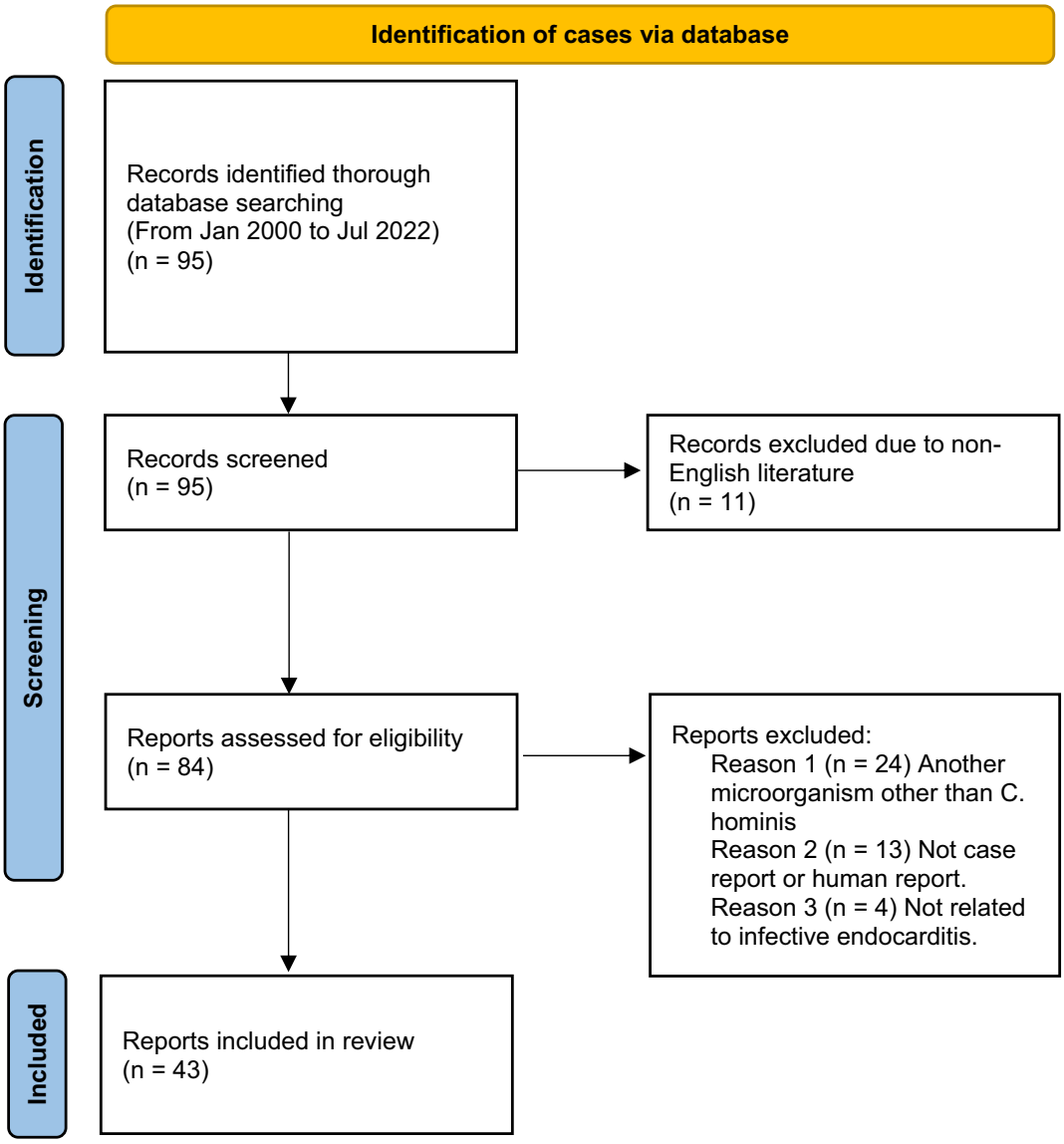

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart outlining the literature search.

%), 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 × 10^3/μL (interquartile range, 8.3–14.1 × 10^3/μL). 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^3)	CRP (mg/dL)	Predisposing factors	Physical examination	Time to identify *C. hominis* 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	Currie	2000 [8]	17	M	Lethargy, night sweats	ND	No	Normal	Negative	Congenital aortic stenosis (post AVR) Dental treatment	Systolic/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, fatigability	ND	No	8,500	Negative	DM Dental caries	Systolic/diastolic murmurs	12	-	TTE, TEE	AR, vegetation (aortic valve)	Aortic	AVR	Ampicillin+gentamicin (2 weeks) Ceftriaxone (3 weeks) Ciprofloxacin (1 week)	6	None	Alive at 8 months
3	Apisarnthanarak	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 bioprosthetic MVR)	Splinter hemorrhages, holosystolic murmur, jugular venous distention, knee swelling	6	-	TEE	MR, thickening and perforation of the medial leaflet	Mitral	-	Ceftriaxone	6	None	Alive at 3 months
4	Nikkari	2002 [11]	48	M	Leg pain, chest discomfort	ND	ND	ND	ND	None	ND	-	Positive	TEE	AR, vegetation (aortic valve), annular 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	-	Ceftriaxone, gentamicin, ampicillin →ciprofloxacin	26	Immune thrombocytopenic purpura	Alive at 7 months
6	Walkty	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	Cefuroxime, azithromycin →Cefotaxime	4	Cardiac tamponade, third-degree heart block	Alive at 12 months
7	Gatselis	2006 [14]	62	M	Appetite loss, fatigue, weakness, diffuse abdominal discomfort, chills, night sweats, diarrhea, fever	39	Yes	14,400	14.3	Dental caries	Pale, palpable liver/spleen, murmur	17	Positive	TTE, TEE, AUS	Vegetation (aortic valve)	Aortic	-	Teicoplanin, 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	Systolic murmur, tenderness near the right trochanteric bursa and sacroiliac joint	15	-	TEE	Vegetation (aortic valve)	Aortic	-	Ceftriaxone (10 weeks) → amoxicillin/clavulanate (24 weeks)	34	Bacterial discitis	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	Systolic/diastolic murmur	7	-	TTE	Aortic valve dehiscence, paravalvular abscess	Aortic	AVR	Vancomycin, gentamicin →ceftriaxone (6 weeks) → amoxicillin (24 weeks)	30	Chronic sternal wound infection	Alive at 6 months
10	Shivaprakash a	2007 [16]	61	M	Fever	38.3	Yes	10,300	ND	Post atrial septal defect closure and MVR	ND	4	-	TTE, TEE	MR, vegetation (mitral valve)	Mitral	-	Vancomycin, gentamicin, ceftriaxone → 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, cefotaxime	6	Cerebral infarction	Alive
12	Braun	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 →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	Systolic murmur, decreased pinprick, light touch, temperature sensation, and proprioception	7	-	TEE	AS, AR, vegetation (aortic valve)	Aortic	-	Vancomycin, ceftriaxone	6	Cerebral infarction	Alive at 6 weeks
14	Maekawa	2011 [20]	5	M	Shortness of breath	37.2	Yes	13,400	1	Post RVOT reconstruction for tetralogy of Fallot with pulmonary atresia, auricular plasty	Systolic/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	Wallet	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 →Cefotaxime	ND	None	Alive
16	El Hajjaji	2012 [22]	56	M	Fever, chill, night sweats	ND	Yes	ND	ND	Post Bentall procedure	Splenomegaly	ND	-	TTE, TEE, PET	Thickening of aortic root, diffuse uptake around the initial portion of the aortic graft	Aortic	-	Aminoglycoside (2 weeks) →cephalosporin (6 weeks)	8	None	Alive at 12 months
17	Courand	2012 [23]	50	M	Chest pain	37	No	22,100	8.8	Renal- Oster- Weber syndrome, splenectomy, dental [illegible]	Holosystolic murmur	2	-	TTE, TEE, MRI	MR, vegetation (mitral valve)	Mitral	-	Gentamicin (2 weeks) and ceftriaxone(6 weeks)	6	Coronary artery occlusion	Alive at 12 months
18	Pousios	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	Cefuroxime, gentamicin	8	Cerebral infarction, splenic infarction	Alive at 12 months
19	Groner	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 collaterals, post placement of a right ventricle-to-pulmonary artery non-valved conduit, post VSD patch closure, patch plasty of the left pulmonary artery	Systolic murmur	2.7	-	TTE	Vegetation (xenograft pulmonic 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	5,930	1.15	Post repair of tetralogy of Fallot with pulmonary atresia and subsequent replacements of the right ventricle to pulmonary artery conduit, poor dentition	Systolic/diastolic murmurs	ND (at least more than 2 days)	-	TTE	Vegetation (conduit valve)	Pulmonic	-	Vancomycin, piperacillin/tazobactam →ceftriaxone →ampicillin/sulbactam →levofloxacin	6	None	Alive

21	Donovan	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 →ceftriaxone, gentamicin, ciprofloxacin	ND	Discitis, cardiac arrest	Alive
22	Wong	2015 [28]	47	M	Malaise, fatigue, night sweats, anorexia, weight loss	36.8	No	14,100	6.4	Dental treatment	Systolic/diastolic murmurs, erythema of the palm/foot	2	-	TEE	Vegetation (aortic valve), paravalvular abscess	Aortic	AVR	Vancomycin, ceftriaxone	6	Cerebral infarction	Alive at 3 months
23	Glucksman	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	Arunachalam	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	Bonavent	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	1st time: Cefuroxime (2 weeks)→ceftriaxone (2 weeks) 2nd time: amoxicillin/clavulanic acid→ ceftriaxone (10 days)→amoxicillin (3 weeks)	4 4	Relapse of IE Pulmonary embolism	Relapse at 2 years Alive
26	Mamdani	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, anemia	36.9	No	9,400	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 lumber vertebra	ND	-	TEE	MR, vegetation (mitral valve)	-	-	Ceftriaxone	4	Lumbar epidural abscess, vertebral osteomyelitis, discitis	Died at 4 weeks (during treatment)
29	Daneshmand	2019 [35]	30	M	Face and arm tingling	ND	ND	ND	ND	Endocarditis 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 hemispatial neglect	37.8	Yes	8,300	7.1	Post AVR/MVR	-	20	-	TTE, TEE	Mitral valve hyperplasia	Mitral	-	Meropenem, vancomycin (16 days) →ceftriaxone (20 days)	5	Subcortical hematoma	Alive at 2 months
31	Diallo	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-clavulanate, gentamicin (2 weeks) →ceftriaxone (2 weeks)	4	Guillain-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	Kolb	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, amoxicillin/clavulanic acid, gentamicin →ceftriaxone	6	None	Alive
35	Blanchot	2019 [6]	59	F	Fever, bruises, multiple pains	39	Yes	60,200	14.7	Septal defect, AR, acute myeloid leukemia	ND	6	Positive	TTE	None	-	-	Piperacillin/tazobactam, vancomycin →gentamicin →cefepime, amikacin	ND	Respiratory distress	Died
34	Holden	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 →ceftriaxone	6	Cerebral infarction	Alive at 24 months
36	Wang	2020 [41]	55	F	Lower extremity petechiae, palpable purpura, fatigue, weight loss, chills, cough, joint aches	ND	ND	ND	ND	Tetralogy of Fallot and bioprosthetic pulmonic valve	Systolic murmur, purpuric papules	2.5	-	TTE, TEE	Right ventricular outflow tract obstruction, vegetation (pulmonic valve)	Pulmonic	Pulmonic valve stent 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, Osler–Weber–Rendu syndrome, severe mitral regurgitation, Barlow's myxomatous degeneration, post MVR, endoscopic resection of a gastric carcinoid 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 →ceftriaxone	ND	-	Alive
38	Saramathi	2020 [7]	35	F	Chest pain, difficulty in breathing, palpitation, 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	ND	Heart transplantation	ND	ND	-	TEE, PET	Uptake spot around the aortic vascular graft	Aortic vascular graft	-	Ceftriaxone	6	None	Alive
40	Terranella	2021 [44]	40	M	Shortness of breath, dyspnea, orthopnea, left leg pain	ND	ND	ND (leukocytosis)	ND	Heart valve abnormality	Systolic murmur, jugular venous distension, 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), paravalvular abscess, AR, vegetation in the right ventricle	Aortic	AVR	Ceftriaxone	6	Cerebral infarction	Alive at 6 months
42	Meledathu	2021 [46]	72	M	Fatigue, chills	ND	No	5,780	ND	Post mitral valve repair, dental treatment	Systolic murmur	4	-	TTE	Vegetation (mitral valve)	Mitral	-	Vancomycin, piperacillin/tazobactam →meropenem →ciprofloxacin	6	Renal failure	Alive
43	Millere	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	Oxacillin, amoxicillin →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 β-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_2. 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 ≥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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