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Difficult Gram staining: a case of endocarditis due to *Cardiobacterium hominis* and review of the literature

Difficile examen direct par coloration de Gram : à propos d'un cas d'endocardite à Cardiobacterium hominis *et revue de la littérature*

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Abstract. *Cardiobacterium hominis* is a Gram negative rod causing infectious endocarditis (IE), mainly in patients with congenital heart disease or prosthetic valves. The identification of this bacterium is often difficult and could be responsible for a delay in the diagnosis and the treatment that could be a source of cardiac complications. We report here a case of sepsis with infectious endocarditis due to *Cardiobacterium hominis*, its identification and treatment as well as a review of the literature.

Key words: *Cardiobacterium hominis, Cardiobacterium spp., bacteriemia*

Résumé. *Cardiobacterium hominis* est un bacille à Gram négatif responsable d'endocardites infectieuses, principalement chez les patients atteints de pathologies cardiaques ou porteurs de valves. L'identification de cette bactérie est souvent complexe et peut être la cause d'un diagnostic et d'une prise en charge tardifs, source de complications cardiaques. Cet article présente la prise en charge d'une endocardite infectieuse associée à un sepsis à *Cardiobacterium hominis*, les difficultés d'identification de cette bactérie, ainsi qu'une revue de la littérature sur les infections dues à cette bactérie.

Mots clés: *Cardiobacterium hominis, Cardiobacterium spp., bactériémie*

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Cardiobacterium hominis is a Gram-negative rod described for the first time by Slotnick and Dougherty in 1964 after observation of some cases of endocarditis caused by a *Pasteurella*-like organism [1]. This respiratory tract's commensal bacterium, strictly human, belongs to the HACCEK group. These bacteria are responsible for rare cases of endocarditis infections (EI) [2], associated with a 3% of in-hospital mortality [3]. Long time incubation of blood-culture and slow-growing nature make *C. hominis* infections hard to diagnose and treat. We reported here a case of EI due to *C. hominis,* as well as a review of the literature on *C. hominis* infections (*table 1*), identification techniques and drug treatments.

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Case report

A 59-years-old woman with a past medical history of Laubry-Pezzi syndrome (septal defect and aortic insufficiency), appendectomy, uterine fibroids and ovarian cysts was admitted to our hospital in a context of acute leukemia suspicion. The patient reported a fever, bruises and multiple pains for a few days. Complete blood count performed in a medical laboratory had revealed the presence of blast cells. She was then admitted to the hematology ward and type 4 acute myeloid leukemia was diagnosed.

At the admission, clinical examination revealed 39°C fever, a weight of 52 kg for 1.5 m high, no nodal, splenic or cutaneous tumor syndrome. Echocardiography found a cardiac murmur due to her ventricular septal defect. Laboratory assessments showed white cells count as follows: 60.2 G/L with 2.4 G/L neutrophils, 7.2 G/L lymphocytes,

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Table 1. Review of the literature about *Cardiobacterium hominis* infectious endocarditis.

References	Medical history	Symptoms	Cardiac symptoms	Method of identification	Direct examination results	Empirical treatment	Treatment after documentation	Outcome
[9]	Quadri-cuspid aortic valve	Myalgia Dyspnea Orthopnea Slight chest pressure Fever	Holosystolic murmur with severe mitral insufficiency	Not stated	Gram negative bacillus	Cefuroxime Azithromycin	Cefotaxime 4 weeks	Two surgeries with replacement of aortic valves and placement of pacemaker
[13]	Diabetes mellitus	Chest discomfort Fatigability	Systolic and diastolic murmur TTE : vegetation at the aortic valves	Not stated	Not stated	Ampicillin Gentamicin	Not stated	Not stated
[15]	Multiple myeloma Porcine aortic valve replacement Pacemaker and coronary artery bypass graft surgery	Anemia Fever	Murmur in the aortic position TTE : vegetation after 26 days	Not stated	Gram negative bacillus	Not stated	Ceftriaxone 6 weeks	4 weeks of ceftriaxone for presumed bacterial discitis Ampicillin/clavulanic acid for 6 months
[15]	Diabetes mellitus Porcine aortic valve replacement and coronary artery bypass	Anemia Chest pain Fever	Atrial fibrillation aortic and diastolic murmur Paravalvular abscess	Not stated	Gram negative bacillus	Vancomycin Gentamicin	Ceftriaxone 6 weeks Amoxicillin 6 months	Replacement of the porcine aortic and chronic sternal wound infection by coagulase negative staphylococci
[16]	Asthma Rheumatoid arthrisis and psoriasis DDP-MM implanted because of sino-atrial node	Fever Fatigability Weightloss of 40 kg in 5 years Anemia	Negative TTE and transesophageal echocardiogram (TEE) Repeat echocardiography : small vegetation on pacemaker	Immuno electrophoresis	Not stated	Cefuroxime	Cefuroxime 2 weeks Ceftriaxone 2 weeks	Gains weight and afebrile Two years later : pneumonia with blood culture to *Cardiobacterium hominis* : ceftriaxone 10 days, and amoxicillin 3 weeks
[7]	Dental procedure 12 months before symptoms	Worsening malaise Drenching Night sweats Anorexia 15 kg weight loss	Aortic and diastolic murmur TTE : vegetation in bicuspid aortic valve	VITEK MS and NH	Gram negative bacillus	Not stated	Ceftriaxone 6 weeks	Aortic valve replacement

Table 1. *Continued.*

References	Medical history	Symptoms	Cardiac symptoms	Method of identification	Direct examination results	Empirical treatment	Treatment after documentation	Outcome
[17]	Carpentier-Edwards prosthesis aortic valve replacement 3 episodes of *Streptococcus sanguis* endocarditis	Lethargy Weight loss for months Chills Night sweats for 2 months	TTE : minimal calcifications and an aortic insufficiency with jet TEE : no signs of endocarditis	Biochemical characterization 16S rRNA gene sequencing	Gram negative bacilli in rosette cluster	Vancomycin Gentamicin Rifampicin Ceftriaxone	Ceftriaxone	5 weeks after diagnosis, new nodular vegetation on the aortic valve and a minimal insufficiency of the aortic valve
[18]	Tissue aortic valve replacement	Fever Sweats Fatigability Chronic back pain	Ventricular fibrillation cardiac arrest TTE : large mobile aortic valve vegetations TEE posterior root abscess	MALDI-TOF-MS	Gram negative rods	Vancomycin Gentamycin Rifampicin	Ceftriaxone Gentamicin Ciprofloxacin	Aortic homograph placement
[19]	Congenital aortic stenosis Homograph aortic valve replacement Dental treatment	Lethargy Night sweats	Not stated	Not stated	Gram negative bacillus	Not stated	Ceftriaxone Gentamicin 18 days Amoxicillin 4 weeks	Aortic valves replacement
[12]	Arterial hypertension Toothache and gum bleeding 4 weeks prior to admission	Poor dietary intake Weakness Diffuse abdominal discomfort Chills Night sweats	No vegetation to the entrance TTE : small vegetation in the aortic valve 2 weeks later	Broad-range bacterial PCR Biochemical characteristic	Gram negative bacillus	Teicoplanin Ceftriaxone Ampicillin sulbactam	Ceftriaxone Ampicillin-sulbactam 6 weeks	Good outcome
[20]	Dermatological lesion treated with corticoids 15 days before	Atypical chest Constrictive pain	Diastolic murmur TTE : large valvular vegetation on a right coronary aortic cusp	MALDI TOF-MS VITEK 2 NH 16S rRNA PCR	Pleomorphic Gram negative rod in pairs, short chains, with a Gram-positive stain in the end or in central portions	Amoxicillin Gentamycin Levofloxacin	Cefotaxime Gentamycin Levofloxacin	Mechanical prosthesis
[21]	DiGeorge syndrome Complex congenital heart disease	Fever Irritability Decreased appetite	Systolic heart murmur TTE : vegetation near a xenograft valve	VITEK	Small Gram negative bacilli	Ceftriaxone Azithromycin	Ceftriaxone 6 weeks	Not stated

Table 1. *Continued.*

References	Medical history	Symptoms	Cardiac symptoms	Method of identification	Direct examination results	Empirical treatment	Treatment after documentation	Outcome
[22]	Atrial septal defect closure Mitral valve replacement	Fever	Congestive cardiac failure with severe mitral regurgitation TTE : no vegetation	Biochemical characteristic	Pleomorphic Gram negative bacilli	Vancomycin Gentamicin Ceftriaxone	Penicillin	Deceased due to renal failure and secondary pneumonia
[23]	Non-Q wave myocardial infraction Coronary angioplasty and stent of proximal left circumflex Repeat cardiac catheteriza-tion Aortic stenosis with transcatheter aortic valve replacement with SAPIEN valve	Chest tightness radiating in jaw Bilateral peripheral edema Severe anemia	TEE : small vegetation or mass on the aortic valve Mild to moderate perivalvular leak and no abscess	Not stated	Not stated	No treatment	Intravenously ciprofloxacin 2.5 weeks Oral ciprofloxacin 4 weeks	Myocardial infarction with anterolateral ST elevation follows by post-operative mediastinal and left chest hematoma leading to a cardiogenic shock Return home fourteen month later
[24]	Crohn's disease Oral prednisone one month before admission	Low-grade fever and fatigue Headache Numbness of his left arm and leg	Mild aortic stenosis and regurgitation TEE : a 1cm mobile vegetation	Not stated	Gram variable rods	Ceftriaxone Vancomycin	Home intravenous ceftriaxone 6 weeks	Good outcome
[25]	Weaned smoking Overweight	Pelvic girdle and scapular pain Anemia	TTE : isolated tricuspid valve endocarditis TEE : 20 mm vegetation on tricuspid valve associated with three protuberance on the atrial side Chest scan : septic pulmonary embolism	Phenotypic and genotypic (16S rRNA PCR) analyses	Gram negative rods	Intravenous ceftriaxone Gentamicin	Intravenous amoxicillin Gentamicin	Short improvement Day 12 : new event of pulmonary embolization, switch of amoxicillin by ceftriaxone Day 43 : tricuspid surgery Day 54 : stopping antibiotics Good outcome

27.6 G/L dystrophic monocytes and 23.0 G/L blast cells. Hemoglobin rate was 8.2 g/dL and platelets count were 26.0 G/L.

Two days after her admission, chemotherapy was started, including cytarabine and daunorubicin. Aplasia was reached in a few days. Because of persistence of fever and biological inflammatory syndrome with 147 mg/L CRP, intravenous antimicrobial drugs were started with piperacillin/tazobactam 4,000 mg/500 mg every eight hours and vancomycin 30 mg/kg/day. At this time, white cells were at 0.8 G/L with 0.2 G/L neutrophils. Meanwhile, peripheral aerobic blood culture was reported positive in 2 days and 23 hours to Gram-positive rods with a very unusual grouping mode in stack like sea urchin (*figure 1A*). Rods remained somehow Gram-positive in other area of the smear despite pink-colored red blood cells (*figure 1B*). After 72 hours, subcultures on blood agar revealed grey, round, smooth, opaque and glistening colonies with a size about 3 to 8 mm. Conversely to the first Gram-staining obtained from the culture bottle, the ones obtained from the colony showed Gram-negative rods in rosette suggesting *C. hominis* (*figure 1B*). Identification was performed using MALDI-TOF-MS (Microflex mass spectrometer, database MBT IVD Library -6763, Biotyper® 2.3, Brucker Daltonics, Bremen, Germany) and identified *C. hominis* with a 1,48 score despite complete extraction by formic acid and acetonitrile. Regarding this insufficient score, identification was confirmed using a phenotypic method using Vitek2 XL (bioMérieux, Marcy l'Etoile, France). The biochemical characteristics identified *C. hominis* with 85% of probability. For a complete characterization of the strain regarding this case report, we performed sequencing of the 5' end of the 16S rRNA gene using 515F and 1492R primers [4], confirming *C. hominis* identification (accession number M35014), based on a 100% identity, using the BIBI and the NCBI database (*figure 2*). Interestingly, peripheral anaerobic blood culture of this series remained sterile after 5 days of incubation.

The next day, other blood culture samples (peripheral anaerobic and aerobic catheter blood cultures) turned positive to Gram-positive rods in rosette suggesting, once again, *C. hominis*. Delays of positivity were to 71h35 and 74h50, respectively. *C. hominis* identification was then confirmed using MALDI-TOF-MS also with a low score as mentioned above.

The minimal inhibitory concentration (MIC) of this *C. hominis*, determined using E-test method (bioMérieux, Marcy l'Etoile, France) on Muller Hinton agar were: amikacin (MIC = 0,25 mg/L), piperacillin/tazobactam (MIC < 0,016 mg/L), gentamicin (MIC = 0,064 mg/L) and cefepime (MIC = 0,064 mg/L). β-lactamase chromogenic assay was negative.

Transthoracic echography (TTE) showed a 65% left ventricular ejection fraction and no evidence of vegetation. Nonetheless, IE diagnosis was strongly considered given the very high link between *C. hominis* and IE and the past medical history of ventricular septal defect of the patient. Cerebral computer tomography (CT) did not show embolic lesions but hardly characterizable liver injurie were found on the thoraco-abdominopelvic CT. Due to the identification of the microorganism and the aplasia, treatment was switched to discontinuous intravenous piperacillin/tazobactam 4,000 mg/500 mg every eight hours and daily injection of gentamicin 8 mg/kg/day.

Two weeks later, 10^3 CFU/mL of AmpC overproducing-*Citrobacter freundii* was isolated in urine sample and in blood culture, leading to the change of the antimicrobial treatment for intravenous cefepime 2 g/j and amikacin 30 mg/kg/day. The patient was in remission and the aplasia ended three days later. Unfortunately, one week later, she showed respiratory distress and was transferred to the intensive care unit. She died one day later of severe sepsis associated with a multi-system organ failure, without any clue of the source of infection and without any microbiological documentation.

Discussion

C. hominis is an opportunistic bacterium belonging to the normal microbiota of oral and upper respiratory tract of human. Two species of *Cardiobacterium* can currently be described: *C. hominis* and *C. valvarum*. They belong to the HACCEK group, responsible for bacteremia and EI, and composed of *Haemophilus* spp (*H. parainfluenzae*), *Aggregatibacter* spp (*A. aphrophilus*, *A. actinomycetemcomitans* and *A. segnis*), [formerly *Actinobacillus actinomycetemcomitans*, *Haemophilus aphrophilus* and *Haemophilus segnis* until 2006 [5], *Cardiobacterium* spp, *Capnocytophaga* spp (*C. ochracea*, *C. sputigena* and *C. gingivalis* for the human species), *Eikenella corrodens* and *Kingella* spp (*K. kingae* and *K. denitrificans*). A monocentric study of 45 cases of HACCEK endocarditis managed in the Mayo clinic (Minnesota, USA) between years 1970-1992 described that the HACCEK group was responsible for 1-3% of EI, with a proportion of 13-27% due to *C. hominis* and only 1% due to *C. valvarum* [6]. *C. hominis* is responsible for insidious EI, mainly in patients with congenital heart disease or prosthetic valves. In such cases, the disease is characterized by prolonged sub-acute courses associated with fever, splenomegaly, heart failure, anorexia and malaise. Relation between *C. hominis* bacteremia and EI is up to 95% which explains why EI was diagnosed in the presence of only one major and two minor

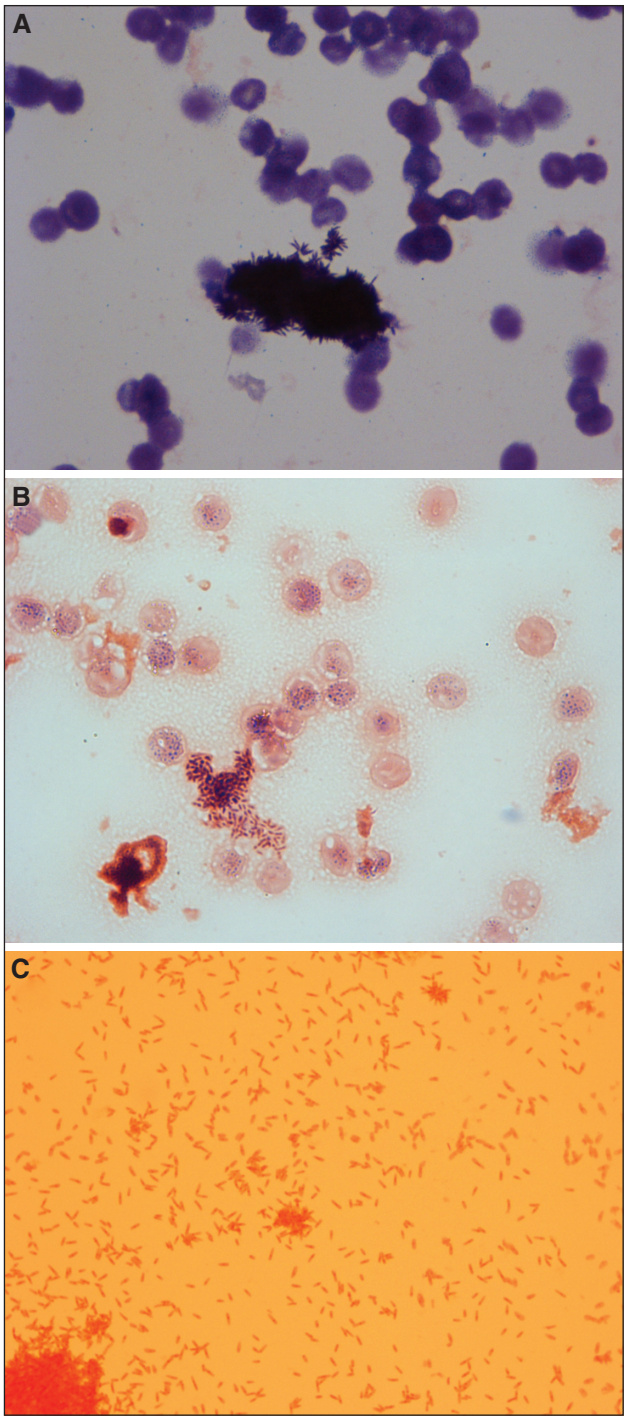

Figure 1. Gram staining of *C. hominis* from blood culture bottle (**A** and **B**) and from colony (**C**).

criteria of IE [7, 8]. Ventricular septal defect, presented by our patient, corresponds to a failure of the inter-ventricular septum and is a congenital heart defect driving to an increased volume load, excessive pulmonary blood flow, reduced systemic cardiac outputs and high pulmonary artery pressure. Presence of a heart murmur is frequent with this pathology and can mask some endocarditis symptoms. Ventricular septal defects and others cardiac malformations have been described as predisposing causes of *C. hominis* EI [9].

C. hominis is a pleomorphic Gram-negative rod presenting a characteristic mode of grouping like rosettes [1]. This case report highlights the difficulty of the biological identification of *C. hominis* due to the variability of the Gram coloration. Culture of these bacteria is usually performed in standard enriched media and optimal growth is obtained with presence of 5% CO_2. Culture is weak in microaerophilic atmosphere and negative in anaerobic atmosphere. Classically, 3.3 days are required to obtain a positive blood culture without treatment, but in some cases, culture could be extended until 14 days [9, 10]. *C. hominis* can be identified and differentiated from the other HACCEK bacteria by its biochemical characteristics which are fermentation of glucose, maltose, mannose, sucrose, mannitol, sorbitol and the production of indole [10]. However, these characteristics do not allow to differentiate *C. hominis* to *C. valvarum*. The only phenotypical difference described in the literature is the production of raffinose by *C. hominis* [11]. Differentiation between the two *Cardiobacterium* species can be made by broad-range 16S rRNA PCR/sequencing test on a culture colony or directly from the sample as described by Gatselis *et al.* [12]. Further studies used 16S rRNA PCR/sequencing to identify *C. hominis*, but with the arrival of MALDI-TOF-MS, 16S rRNA PCR/sequencing is now mainly used at distance of the infection or in case of negative culture. Today, detection of HACCEK bacteria and *Cardiobacterium spp* has been largely facilitated by the introduction of MALDI-TOF-MS, allowing a rapid and reliable identification, in particular between the two species of *Cardiobacterium spp,* with one spectrum of *C. hominis* and one of *C. valvarum* present in the database (MBT IVD Library - 6763). However, as described in the case report, a weak score of MALDI-TOF-MS may require a confirmation using complementary techniques. One of the main difficulties when determining antibiotic susceptibility of the HACCEK bacteria is based on the lack of clinical breakpoints by the European committee on antimicrobial susceptibility testing. Typically, HACCEK group bacteria are susceptible to β-lactams. Ampicillin and ampicillin/clavulanic acid were therefore generally used to treat HACCEK infection. However, a rapid increase of β-lactamase producing-strains led to a modification of the guidelines [13]. Nowadays, third generation cephalosporins for 4 weeks are the first line to treat IE due to the HACCEK group [8]. Fluoroquinolones can be used as an alternative and aminopenicillin are now reserved for the non β-lactamase

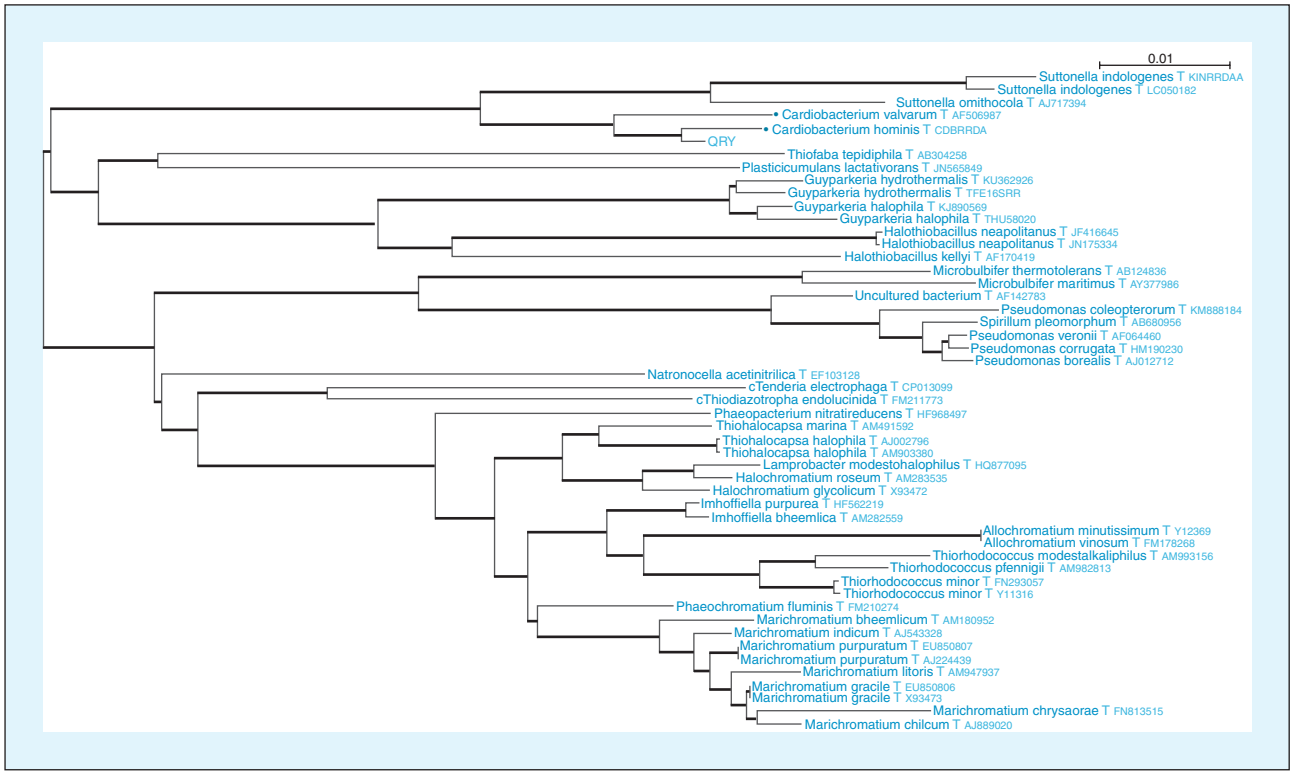

Figure 2. Relationship of *C. homininis* QRY with the species of *Cardiobacter* genus using nearly full 16S rRNA gene sequencing using the BIBI database. Phylogenetic tree based on 16S rRNA genes sequences showing *C. hominis* position of QRY and the genus *Cardiobacterium*. Bootstrap values, expressed as percentage of 1,000 replications, are given at the branching points. Reference type and sequence from a related isolate is shown.

producing-strains. Conversely to the other HACCEK group bacteria, β-lactamase producing-*C. hominis* are still very rare and only few cases of β-lactams resistance have been reported in literature [13, 14].

Conclusion

The present case illustrates the difficulties and the diagnostic approach allowing to identify *C.hominis*, a Gram-negative rod mainly responsible for EI. Prognosis of *Cardiobactrium spp* EI is generally favorable, but the delayed diagnosis caused by the late identification of the bacteria can have severe consequences, particularly at cardiac level. Despite emergence of few antimicrobial resistance determinant, *Cardiobacterium* spp remains susceptible to the third generation cephalosporins which provides a quickly and efficient therapy. The arrival of the MALDI-TOF-MS has greatly facilitated the diagnosis of this infection, but bacterial phenotypical and biological characteristics, as well as the 16S rRNA PCR may still be used to confirm the identification in case of low score.

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