CASE REPORT

Subacute bacterial endocarditis caused by Cardiobacterium hominis: A case report

D Davie Wong MD1, Julie Carson MD2,3, Andrew Johnson MD4

Cardiobacterium hominis, a member of the HACEK group of organisms, is an uncommon but important cause of subacute bacterial endocarditis. First-line therapy is a third-generation cephalosporin due to rare betalactamase production. The authors report a case involving endovascular infection due to C hominis that initially tested resistant to third-generation cephalosporins using an antibiotic gradient strip susceptibility method (nitrocephin negative), but later proved to be susceptible using broth microdilution reference methods (a ‘major’ error). There are limited studies to guide susceptibility testing and interpretive breakpoints for C hominis in the medical literature, and the present case illustrates some of the issues that may arise when performing susceptibility testing for fastidious organisms in the clinical microbiology laboratory.

Key Words: Cardiobacterium hominis; Etest; Infective endocarditis

CASE PRESENTATION

A 47-year-old man was admitted to hospital with worsening malaise, fatigue, drenching night sweats, anorexia and a 15 kg weight loss. Four months previously, he developed dyspnea, orthopnea, exertional chest heaviness and a single episode of hemoptysis, for which he had been empirically treated with two 10-day courses of oral antibiotics (cefuroxime, then clarithromycin). Transient swelling, erythema and tenderness over his shins ensued, followed by numbness of his fingers and the left side of his body. These neurological symptoms had improved, but not resolved, at presentation. A dental procedure (unknown) had been performed 12 months before symptom onset.

On examination, he appeared unwell. His temperature was 36.8°C, heart rate 80 beats/min, blood pressure 95/50 mmHg, respiratory rate 18 breaths/min and oxygen saturation 99% on 3 L nasal prongs. Cardiovascular examination revealed a soft S2, an S3, a grade II/VI aortic systolic ejection murmur and a grade III/VI diastolic decrescendo murmur at the left lower sternal border, without signs of congestive heart failure. Fundoscopic examination revealed changes consistent with hypertension, but did not demonstrate retinal hemorrhages or Roth’s spots. Oral hygiene was unremarkable. There was a tender area of induration on the palm of his left hand and the dorsum of his left foot (Figure 1A), but no erythema nodosum. The spleen was palpable.

Abnormal laboratory investigations included a white blood cell count of 14.1 × 10^9/L (normal values 2 × 10^9/L to 8 × 10^9/L), neutrophils 14 × 10^9/L (normal values 2 × 10^9/L to 8 × 10^9/L), a normocytic, normochromic anemia with a hemoglobin level of 117 g/L (normal level 137 g/L to 180 g/L) and elevated inflammatory markers (C-reactive protein level 64 mg/L [normal level 0 mg/L to 8 mg/L] and erythrocyte sedimentation rate 28 mm [normal value 0 mm to 10 mm]). Three temporally distinct sets of blood cultures were obtained, and empirical therapy with intravenous vancomycin and ceftriaxone was initiated. Magnetic resonance angiography of the brain and a transesophageal echocardiogram were obtained.

Figure 1) A Focal area of induration on dorsum of left foot. B Transesophageal echocardiogram (parasternal short axis view) demonstrating a bicuspid aortic valve with a large vegetation. C Gram stain of blood culture demonstrating Gram-negative bacilli consistent with Cardiobacterium hominis. D Etest (bioMérieux Canada, Inc) results for ceftriaxone with a double zone of inhibition at a minimum inhibitory concentration of 0.023 µg/mL and 16 µg/mL. Bacteria within the intermediate zone of inhibition could not be cultured

and empirical therapy with intravenous vancomycin and ceftriaxone was initiated. Magnetic resonance angiography of the brain and a transesophageal echocardiogram were obtained.

1Internal Medicine, University of Manitoba, Winnipeg, Manitoba; 2Section of Microbiology, Department of Pathology and Laboratory Medicine, University of Calgary; 3Calgary Laboratory Services; 4Section of Infectious Diseases, Department of Medicine, University of Calgary, Calgary, Alberta

Correspondence: Dr Julie Carson, Calgary Laboratory Services, 9 – 3535 Research Road Northwest, Calgary, Alberta T2L 2K8. Telephone 403-770-3338, e-mail julie.carson@cls.ab.ca

OPEN ACCESS This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (http://creativecommons.org/licenses/by-nc/4.0), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes. For commercial reuse, contact support@pulsus.com

Can J Infect Dis Med Microbiol Vol 26 No 1 January/February 2015
TABLE 1
Summary of minimum inhibitory concentrations for Cardiobacterium hominis isolates

| Antibiotic                      | Minimum inhibitory concentration (µg/mL) by method and media | CLSI interpretive criteria (µg/mL) |
|---------------------------------|--------------------------------------------------------------|-----------------------------------|
|                                 | Etest-MHB | Etest-BBA | BMD-CAMBH-LHB | Sensitive | Resistant |
| Penicillin                      | 0.5       | ≤0.016    | ≤0.06         | ≤0.5      | ≥4        |
| Ampicillin                      | 0.094     | 0.023     | ≤0.06         | ≤0.5      | ≥4        |
| Amoxicillin-clavulanate         | 0.5†      | 0.023†    | ≤0.5/0.25     | ≤4/2      | ≥8/4      |
| Imipenem                        | 0.032     | 0.006     | No data       | ≤0.5      | ≥2        |
| Meropenem                       | 0.006     | ≤0.002    | ≤0.06         | ≤0.5      | ≥2        |
| Ceftriaxone                     | 16        | 0.016     | ≤0.25         | ≤2        | –         |
| Cefotaxime                      | 32        | 0.094     | ≤0.25         | ≤2        | –         |
| Levofloxacin                    | 0.012     | 0.008     | ≤0.25         | ≤2        | –         |
| Trimethoprim-sulfamethoxazole   | 0.094†    | 0.016†    | ≤0.25/4.75    | ≤0.5/9.5  | ≥4/76     |

*Clinical Laboratory Standards Institute methodology (CLSI); †Amoxicillin concentration; ‡Trimethoprim concentration. BMD Broth microdilution; BBA Brucella blood agar; CAMBH-LHB Cation-adjusted Mueller-Hinton broth with 5% lysed horse blood; MHB Mueller-Hinton agar with 5% sheep blood

**DIAGNOSIS**
Traneseophageal echocardiogram demonstrated a 1.7 cm vegetation on a previously unrecognized bicuspid aortic valve, with severe aortic insufficiency (Figure 1B). Magnetic resonance angiography of the brain revealed a focus of restricted diffusion in the corpus callosum, concerning for an infarct. By 48 h, all blood cultures yielded a Gram-negative bacillus (oxidase positive, catalase negative and urease negative) identified as *Cardiobacterium hominis* (Figure 1C). The identification was confirmed by matrix-assisted laser desorption ionization-time-of-flight (Vitek MS) and the Vitek NH identification card (bioMérieux Canada Inc, Canada). At the time of aortic valve replacement, both native aortic leaflets were markedly thickened and a perivalvular abscess was observed at the aortic valve root, which subsequently grew *C. hominis*. Initial Etest (bioMérieux Canada Inc) results, using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood (MHB), demonstrated resistance to ceftriaxone and cefotaxime (Figure 1D). The nitrocefin-based test (Nitrocefin SR112, Oxoid Microbiology Products, USA) for beta-lactamase production was negative. Subsequently, broth microdilution (BMD) in cation-adjusted Mueller-Hinton broth supplemented with 5% lysed horse blood (CAMHB-LHB) as well as Etest susceptibilities using Brucella blood agar (1) demonstrated susceptibility to all agents tested (Table 1).

**DISCUSSION**
Endovascular infection with *C. hominis*, a member of the HACEK group of microorganisms (*Haemophilus species*, Actinobacillus actinoymcomitans, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella species*), is usually insidious in onset, with a prolonged subacute course characterized by leukocytosis, anemia, splenomegaly, embolic phenomena, congestive heart failure and weight loss (2). Dental work (as well as routine oral hygiene/quality of dentition) and bicuspid aortic valve are both well-described risk factors for endocarditis, noted in 51% and 21% of cases, respectively, especially when the aortic valve is involved (3,5,6). Extravascular infection is unusual (7). Prognosis is generally favourable, with a 93% cure rate for both native and prosthetic valve infection (3). A third-generation cephalosporin is the third-generation cephalosporins. We were unable to reproduce this major error with other recent *C. hominis* isolates (n=5) in our laboratory (data not shown).

Penicillin resistance due to beta-lactamase production has been documented in *C. hominis* (9,10), but cephalosporin resistance has only been described in a single case report (9) based on disc diffusion testing. Guidelines for susceptibility testing of fastidious organisms, including the HACEK group, are relatively new (1). For Cardiobacterium species, the recommended testing method is BMD in CAMBH-LHB (as for pneumococcus and other fastidious organisms). Although not endorsed by CLSI, many laboratories use Etest or other gradient strip methodologies for ease of use and accessibility. In the present case, use of a non-CLSI-approved antibiotic gradient strip susceptibility testing methodology resulted in a major error. The risk of a very major error cannot be ascertained.

The likely cause of the major error was the use of an antibiotic gradient susceptibility testing method with media (MHB) not adequately validated in microbiological studies. MHB agar has previously been used in agar dilution and Etest methodologies for other HACEK-group organisms (11-13). The Etest application guide recommends using either Brucella blood agar or Mueller-Hinton agar with 1% hemoglobin and 1% IsoVitalex (BD, USA) for HACEK organisms (14); however, the cited literature provides no data on the use of Mueller-Hinton agar for susceptibility testing of *C. hominis*. Penicillillase or cephalosporinase production appeared to be unlikely based on a negative nitrocefin test. A subpopulation of *C. hominis* with isolated resistance to cephalosporins due to specific penicillin-binding protein mutations (as has been described in *Streptococcus pneumoniae* [15]) was also considered to be unlikely given that the intermediate zones did not grow when subcultured to another agar plate and the repeated susceptibility testing using BMD did not show any evidence of resistance.

Returning to the case, the patient received six weeks of intravenous ceftriaxone following his aortic valve replacement, rather than a standard four-week course (8), because of his septic cerebral embolus. Repeat echocardiography demonstrated complete resolution of his perivalvular abscess and a properly functioning prosthetic aortic valve.

In our patient, initial minimum inhibitory concentration determinations using Etest methodology on MHB agar demonstrated resistance to third-generation cephalosporins (nitrocephin negative). This complicated early management of the patient because it appeared to preclude the use of first-line therapy for *C. hominis* endocarditis.

Repeat testing with Clinical and Laboratory Standards Institute (CLSI)-approved reference methods (1) demonstrated susceptibility to third-generation cephalosporins. We were unable to reproduce this major error with other recent *C. hominis* isolates (n=5) in our laboratory (data not shown). Penicillin resistance due to beta-lactamase production has been documented in *C. hominis* (9,10), but cephalosporin resistance has only been described in a single case report (9) based on disc diffusion testing. Guidelines for susceptibility testing of fastidious organisms, including the HACEK group, are relatively new (1). For Cardiobacterium species, the recommended testing method is BMD in CAMBH-LHB (as for pneumococcus and other fastidious organisms). Although not endorsed by CLSI, many laboratories use Etest or other gradient strip methodologies for ease of use and accessibility. In the present case, use of a non-CLSI-approved antibiotic gradient strip susceptibility testing methodology resulted in a major error. The risk of a very major error cannot be ascertained.

The likely cause of the major error was the use of an antibiotic gradient susceptibility testing method with media (MHB) not adequately validated in microbiological studies. MHB agar has previously been used in agar dilution and Etest methodologies for other HACEK-group organisms (11-13). The Etest application guide recommends using either Brucella blood agar or Mueller-Hinton agar with 1% hemoglobin and 1% IsoVitalex (BD, USA) for HACEK organisms (14); however, the cited literature provides no data on the use of Mueller-Hinton agar for susceptibility testing of *C. hominis*. Penicillinase or cephalosporinase production appeared to be unlikely based on a negative nitrocefin test. A subpopulation of *C. hominis* with isolated resistance to cephalosporins due to specific penicillin-binding protein mutations (as has been described in *Streptococcus pneumoniae* [15]) was also considered to be unlikely given that the intermediate zones did not grow when subcultured to another agar plate and the repeated susceptibility testing using BMD did not show any evidence of resistance.

Returning to the case, the patient received six weeks of intravenous ceftriaxone following his aortic valve replacement, rather than a standard four-week course (8), because of his septic cerebral embolus. Repeat echocardiography demonstrated complete resolution of his perivalvular abscess and a properly functioning prosthetic aortic valve. His neurological symptoms continued to improve, although he still had residual left-sided numbness at three-month follow-up. This case highlights both the typical clinical presentation of endovascular infection with *C. hominis* and the potential issues that may arise when performing susceptibility testing for fastidious organisms in the clinical microbiology laboratory.

**ACKNOWLEDGEMENTS:** The authors thank Dr Johann Pitout for his assistance in this case.
REFERENCES
1. Clinical Laboratory Standards Institute. Methods for Antimicrobial
dilution and disk susceptibility testing of infrequently isolated or
fastidious bacteria; Approved Guideline – Second Edition. CLSI
document M45-A2. Wayne: Clinical and Laboratory Standards
Institute, 2010.
2. Steinberg JP, Burd EM. Other Gram-negative and Gram-variable
bacilli. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 7th edn. Philadelphia: Elsevier,
2010:3019.
3. Malani AN, Aronoff DM, Kauffman CA. Cardiobacterium hominis
endocarditis: Two cases and a review of the literature. Eur J Clin
Microbiol Infect Dis 2006;25:587-95.
4. Chambers ST, Murdoch D, Morris A, et al. HACEK infective
endocarditis: Characteristics and outcomes from a large,
multi-national cohort. PLoS One 2013;8:e63181.
5. Chentaner T, Khawchaneporn T, Chokrungvaranon N, et al.
Cardiobacterium hominis endocarditis presenting as acute embolic
stroke: A case report and review of the literature. Heart Lung
2011;40:262-9.
6. Lena TS, De Meulemeester C. A case of infective endocarditis
carried by C. hominis in a patient with HLAB27 aortitis. Can J Neurol Sci 2009;36:385-7.
7. Wormser GP, Bottone EJ. Cardiobacterium hominis: Review of
microbiologic and clinical features. Rev Infect Dis 1983;5:680-91.
8. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis:
Diagnosis, antimicrobial therapy, and management of complications:
A statement for healthcare professionals from the Committee on
Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on
Cardiovascular Disease in the Young, and the Councils on Clinical
Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia,
American Heart Association. Circulation 2005;111:394-434.
9. Le Quellec, Bessis D, Perez C, et al. Endocarditis due to
β-lactamase-producing Cardiobacterium hominis. Clin Infect Dis
1994;19:904-5.
10. Lu PL, Haseh PR, Hung CC, et al. Infective endocarditis complicated
with progressive heart failure due to β-lactamase-producing
Cardiobacterium hominis. J Clin Microbiol 2000;38:2015-7.
11. Maurissen W, Eyskens B, Gewillig M, et al. Beta-lactamase-positive
Cardiobacterium hominis strain causing endocarditis in a pediatric
patient with tetralogy of Fallot. Clin Microbiol News 2008;30:132-3.
12. Yagupsy P, Katz O, Peled N. Antibiotic susceptibility of Kingella
kingae isolates from respiratory carriers and patients with invasive
infections. J Antimicrob Chemother 2001;47:191-3.
13. Goldstein EJ, Cherubin CE, M Shulman. Comparison of microtiter
broth dilution and agar dilution methods for susceptibility testing of
Eikenella corrodens. Antimicrob Agents Chemother 1983;23:42-5.
14. Kugler KC, Biedenbach DJ, Jones RN. Determination of the
antimicrobial activity of 29 clinically important compounds tested
against fastidious HACEK group organisms. Diagn Microbiol Infect Dis 1999;34:73-6.
15. Smith AM, Botha RF, Koornhof HJ, Klugman KP. Emergence of a
pneumococcal clone with cephalosporin resistance and penicillin
susceptibility. Antimicrob Agents Chemother 2001;45:2648-50.

Cardiobacterium hominis endocarditis