

A rare cause of culture negative bioprosthetic valve endocarditis: a case report of *Aggregatibacter aphrophilus* infection

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Received 15 June 2020; first decision 26 August 2020; accepted 6 December 2020

Background

The prevalence of culture negative infective endocarditis (IEC) is reported as 2–7% though this figure may be as high as 70% in developing countries.¹ This higher rate will, at least in part, be due to reduced diagnostic facilities though some data suggests higher rates even when appropriate cultures were taken. The frequency is significantly elevated in patients who have already been exposed to antibiotics prior to blood cultures.^{1,2} A rare cause of culture negative IEC is the HACEK group of organisms that are normal inhabitants of the oropharyngeal flora and account for 1–3% of native valve endocarditis.³ *Aggregatibacter aphrophilus* (*A. aphrophilus*) is a member of the HACEK group of organisms.

Case summary

A 32-year-old gentleman with a previous bioprosthetic aortic valve presented with a 1-week history of diarrhoea, vomiting, malaise, and weight loss. He was awaiting redo surgery for stenosis of the bioprosthesis, which had been inserted aged 17 for aortic stenosis secondary to a bicuspid valve. The initial blood tests revealed liver and renal impairment with anaemia. A transoesophageal echocardiogram demonstrated a complex cavitating aortic root abscess, complicated by perforation into the right ventricle. He underwent emergency redo surgery requiring debridement of the aortic abscess, insertion of a mechanical aortic prosthesis (St Jude Medical, USA), annular reconstruction and graft replacement of the ascending aorta. Despite antibiotic therapy, he remained septic with negative blood and tissue cultures. Bacterial 16S rRNA gene sequencing confirmed *A. aphrophilus* infection, for which intravenous ceftriaxone was initiated. This was subsequently changed to ciprofloxacin due to neutropenia. The patient self-discharged from the hospital during the third week of antibiotic therapy. One week later, he was re-admitted with fever, night sweats, and dyspnoea. Transthoracic echocardiogram revealed a large recurrent aortic abscess cavity around the aortic annulus fistulating into the right heart chambers; this was confirmed by a computed tomography scan. There was dehiscence of the patch repair. Emergency redo aortic root replacement (25 mm mechanical valve conduit, ATS Medical, USA) and annular reconstruction was performed with venoarterial extracorporeal membrane oxygenation (VA-ECMO) support. VA-ECMO was weaned after 3 days. The patient completed a full course of intravenous meropenem and ciprofloxacin and made a good recovery.

Discussion

IEC with oropharyngeal HACEK organisms is rare and difficult to diagnose, due to negative blood culture results. The broad-range polymerase chain reaction and gene sequencing with comparison to the DNA database is useful in these circumstances. This case demonstrates the importance of the 16S rRNA gene sequencing for HACEK infection diagnosis and appropriate antibiotic treatment.

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Handling Editor: Alberto Bouzas-Mosquera

Peer-reviewers: Erica Tarr; Aref Bin Abdhahk

Compliance Editor: Edwina McNaughton

Supplementary Material Editor: Deepti Ranganathan

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Keywords

Bioprosthetic valve endocarditis • HACEK infection • Bicuspid aortic valve • Mechanical valve endocarditis • Aortic root abscess • Gene sequencing • Case report

Learning points

- HACEK organisms are normal inhabitants of the oropharyngeal flora, they account for 1–3% of endocarditis cases.³
- Blood culture negative infective endocarditis may reach up to 70% of patients. Broad-range polymerase chain reaction testing is a useful tool to identify pathogens causing culture negative endocarditis.²
- Third generation cephalosporins are considered the drugs of choice, with ciprofloxacin as an alternative treatment.

Introduction

Culture negative infective endocarditis (IEC) may reflect culture failure due to prior antibiotic exposure or infection with fastidious organisms including oropharyngeal gram-negative rods such as the HACEK group, *Brucella*, *Listeria*, and *Legionella*. The prevalence of culture negative infective endocarditis (IEC) is reported as 2–7% though this figure may be as high as 70% in developing countries.¹ This higher rate will, at least in part, be due to reduced diagnostic facilities though some data suggests higher rates even when appropriate cultures were taken. The frequency is significantly elevated in patients who have already been exposed to antibiotics prior to blood cultures.^{1,2} A rare cause of culture negative IEC is the HACEK group of organisms that are normal inhabitants of the oropharyngeal flora and account for 1–3% of native valve endocarditis.³ *Aggregatibacter aphrophilus* (*A. aphrophilus*) is a member of the HACEK group of organisms.

Previously, it took 3 weeks to grow these organisms even in optimal media.⁴ However, with current blood culture processing methods, they may be detected within the standard 5-day incubation period.⁵ We present a case of HACEK-induced endocarditis with an *Aggregatibacter aphrophilus* strain.

Timeline

Day 1	A 32-year-old patient with bioprosthetic aortic valve admitted with deranged liver function tests, renal impairment, and weight loss.
Day 4	Transoesophageal echocardiography showed cavitating aortic root abscess with perforation into the right ventricle.
Day 5	Mechanical aortic valve replacement with annular reconstruction and graft replacement of the ascending aorta.
Day 16	16S rRNA gene sequencing showed <i>Aggregatibacter aphrophilus</i> infection and intravenous ceftriaxone was initiated.

Continued

Day 19	Self-discharged from hospital and continued intravenous ceftriaxone.
Week 5	Antibiotic converted to ciprofloxacin due to neutropenia.
Week 6	Readmitted with sepsis and dyspnoea New York Heart Association III. Echocardiography showed a large peri-annular aortic abscess with fistula into the right heart chambers.
Week 7	Redo surgery with aortic root replacement (25 mm ATS valve conduit) with annular reconstruction with venoarterial extracorporeal membrane oxygenation (VA-ECMO). VA-ECMO removed after 3 days.
Week 13	Continued intravenous meropenem and oral ciprofloxacin for 6 weeks.
Week 13	Discharged home.
Month 5	Purpuric viral rash which resolved, diagnosed as 'non-specific viral induced rash' with negative blood cultures.

Case presentation

A 32-year-old Caucasian gentleman had a bioprosthetic aortic valve replacement at the age of 17 for bicuspid aortic stenosis. Whilst awaiting redo surgery for a stenosed bioprosthetic aortic valve, he presented with a 1-week history of abdominal pain, vomiting, and diarrhoea. In addition, he reported malaise, lethargy, and weight loss. He had no history of drug abuse or any recent travel. In addition, he had good dental hygiene with a routine dental check 2 weeks prior to presentation. He had no other past medical history. He had pyrexia and dyspnoea with signs of decompensated right-sided heart failure with raised jugular venous pressure, abdominal tenderness, and jaundice. He had no stigmata of IEC with an ejection systolic murmur on cardiac examination.

Initial blood investigations revealed deranged liver function tests with ALT of 64 IU/L (1–55 IU/L), ALP 190 IU/L (30–130 µ/L), and bilirubin 176 µmol/L (1–20 µmol/L), renal impairment with creatinine of 352 µmol/L (50–98 µmol/L) equating to an estimated glomerular filtration rate of 19 mL/min/1.73 m, and anaemia with a haemoglobin of 87 g/L (120–155 g/L). Electrocardiogram showed sinus rhythm with no abnormalities. Transoesophageal echocardiogram demonstrated a complex, cavitating aortic root abscess adjacent to the left and the

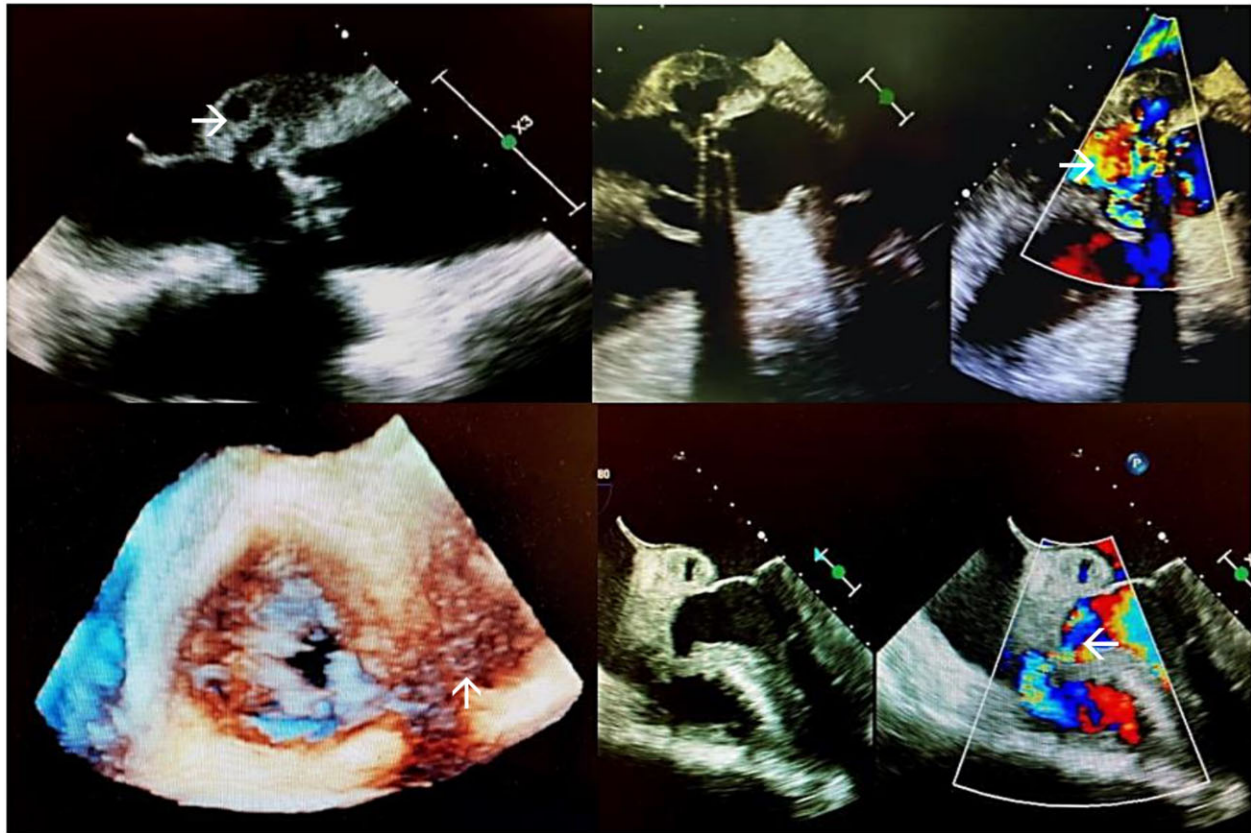


Figure 1 Transoesophageal echocardiography illustrating aortic root abscess and fistula to the right heart chambers. (A) Aortic root abscess, (B) severe aortic regurgitation with root abscess, colour flow, (C) three-D image of the previous bio-prosthetic valve with root abscess, and (D) five-chamber view showing fistula to the right ventricle.

non-coronary cusps of the aortic valve. This was complicated with perforation into the right ventricle. (Figure 1, Video 1) An emergency redo surgery was performed with a mechanical aortic valve replacement (St Jude USA), annular reconstruction and graft replacement of the ascending aorta after debridement of the aortic abscess.

Following the operation, the patient remained septic and continued to spike temperatures with static inflammatory markers. Although all blood cultures and the intraoperative tissue cultures were negative, he was treated with meropenem broad spectrum antibiotic. On his 7th postoperative day, he had pericardial effusion and tamponade for which he had pericardiocentesis. Eventually, bacterial 16S rRNA gene sequencing from the intraoperative tissue valve specimen was performed; revealing *A. aphrophilus* infection and the antibiotic was changed to intravenous ceftriaxone after 2 weeks. He decided to self-discharge from the hospital, but he continued to take his intravenous ceftriaxone. However, 2 weeks after discharge, the patient developed neutropenia and his antibiotic was changed to oral ciprofloxacin.

One week later, he was readmitted with dyspnoea on minimal effort, night sweats, and fever. Transthoracic echocardiography showed an enlarging abscess cavity around the aortic annulus, with fistula formation and significant blood flow into the right heart chambers. (Figure 2, Video 2) computed tomography (CT) scan confirmed the presence of pseudoaneurysms (Figure 3).

He had a further redo sternotomy with a mechanical aortic valve and root replacement (25 mm ATS valve conduit, ATS Medical, USA). Annular reconstruction was performed as the previous patch repair had dehisced revealing a large peri-annular abscess with fistula into the right ventricle. The patient became coagulopathic with fibrinogen of 0.35 g/L (1.5–4.5 g/L) with poor right ventricular function and a venoarterial extracorporeal membrane oxygenation (VA-ECMO) was inserted with femoral venous drainage and arterial return to the right axillary artery. The VA-ECMO was removed after 3 days. The patient continued intravenous meropenem and ciprofloxacin for 6 weeks. He had a follow-up echocardiogram that showed a well seated valve with no abscess, and this was confirmed by a follow-up CT. He made a good recovery and was discharged. Five months later, he had a purpuric rash which resolved, after investigations and blood cultures, he was diagnosed by the dermatologists of having non-specific viral-induced rash, he has been asymptomatic since and remains under follow-up.

Discussion

Aggregatibacter aphrophilus (formerly *Haemophilus aphrophilus* and *Haemophilus paraphrophilus*) is part of the normal oropharyngeal flora,⁶ and one of the organisms of the HACEK group, in addition to

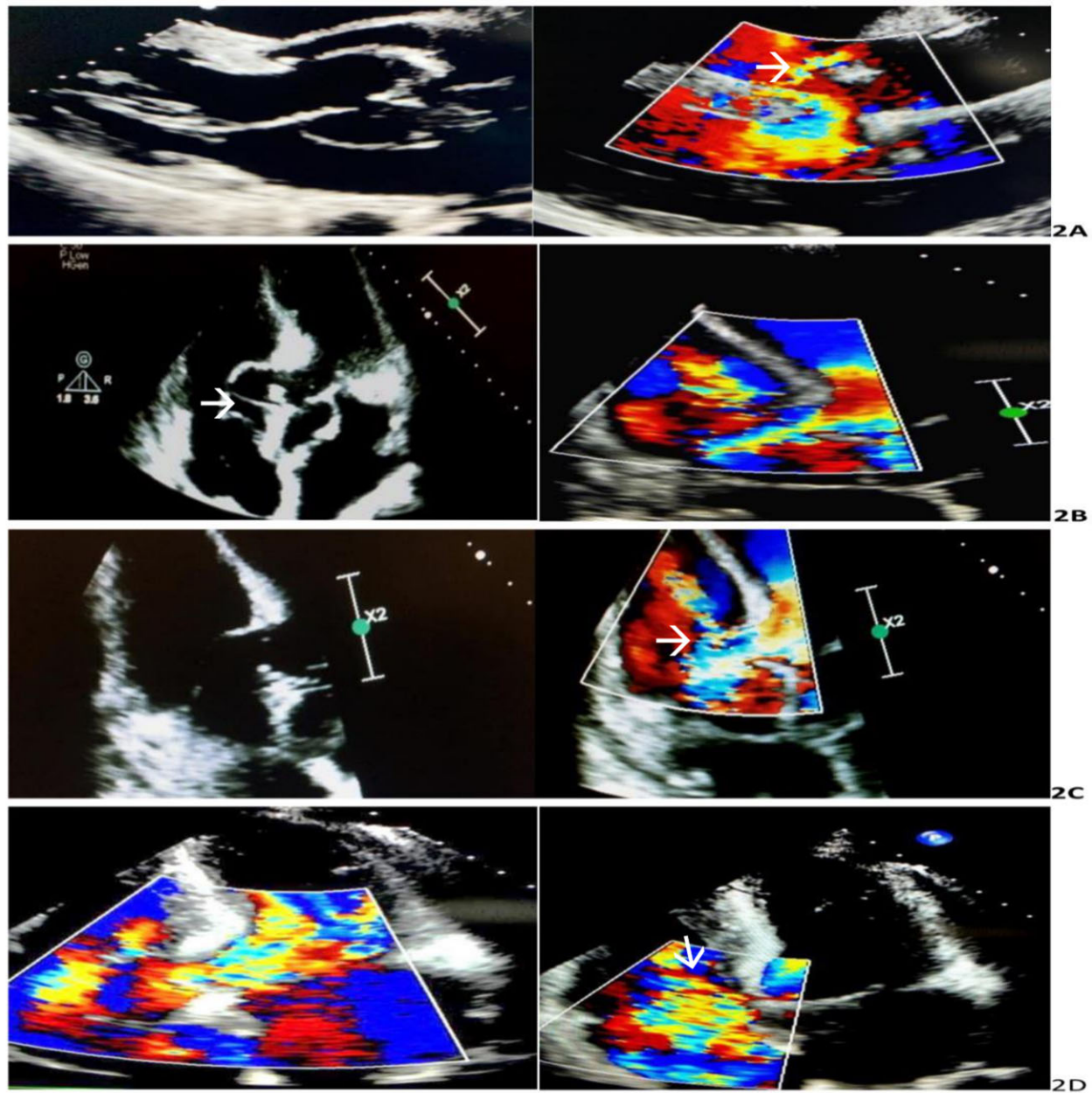


Figure 2 Transthoracic echocardiography showing metallic valve endocarditis. (A) Parasternal long axis showing metallic aortic valve with paravalvular aortic regurgitation. (B) Apical five-chamber view showing aortic root abscess with flow to the right heart chambers. (C) Apical five-chamber view showing communicating fistula. (D) Multiple fistulae with torrential tricuspid regurgitation.

Haemophilus, *Cardiobacter*, *Eikenella corrodens*, and *Kingella*. They account for 1–3% of native valve endocarditis.³

It was first described by Khyarat in 1940 in a PhD thesis, as a new species causing IEC.^{7,8} Dental procedures, tongue piercings, use of tongue scrapers, and upper respiratory tract infections are known causes for bacterial entry into the bloodstream.⁹ In a large multi-centre study by Chambers *et al.*,¹⁰ which included a cohort of 5591 patients, it was noted that HACEK endocarditis was more common in prosthetic valve endocarditis than in non-HACEK endocarditis.

The mechanical valves are of a particular risk for HACEK endocarditis, especially the late prosthetic valve endocarditis occurring more than a year after surgery.

HACEK endocarditis is difficult to diagnose with negative blood cultures.¹¹ *Aggregatibacter* is an oxidase and catalase-negative organism, in contrast to other types of *Haemophilus* strains such as *Haemophilus influenzae* and *Haemophilus parainfluenzae*. Hence, diagnostic cultures have difficulty to identify *A. aphrophilus*.¹² Broad-range polymerase chain reaction (BR-PCR) diagnostic method, is

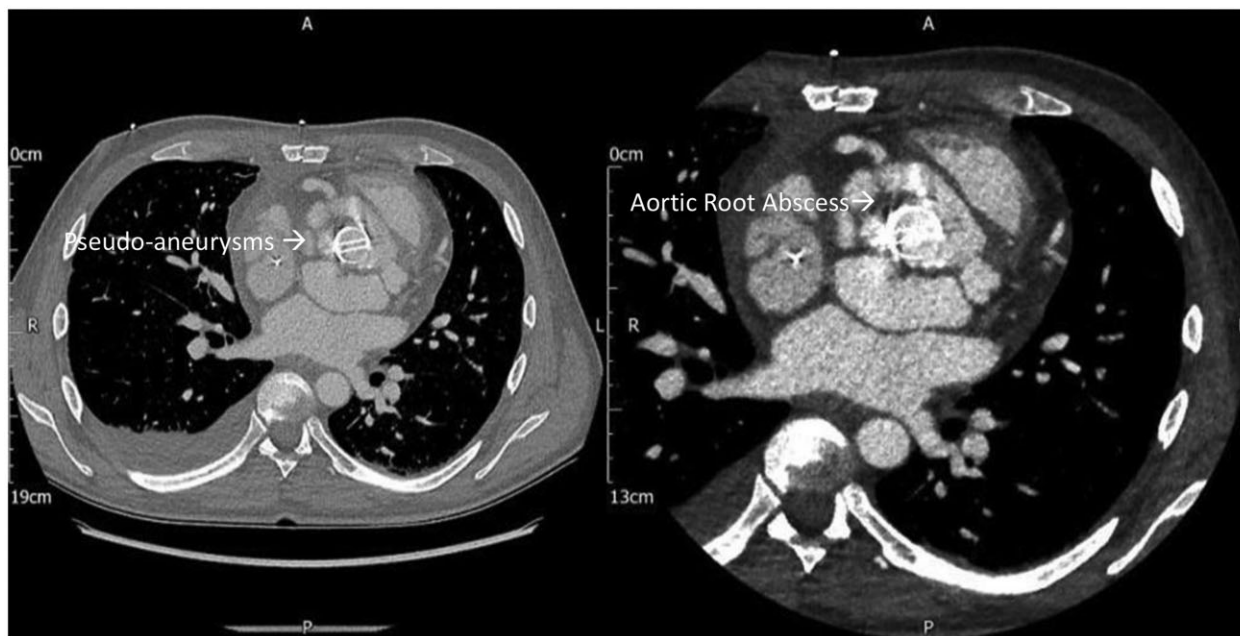
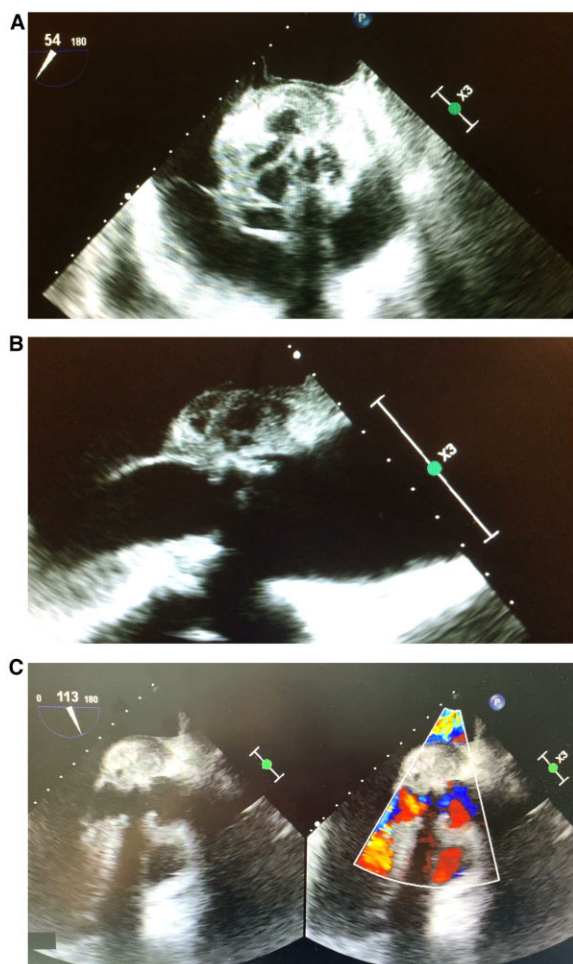


Figure 3 Cardiac computed tomography showing metallic aortic valve with aortic root abscess and pseudoaneurysms.



Video 1 Transoesophageal echocardiography illustrating aortic root abscess and severe aortic regurgitation.

helpful in cases of culture-negative IEC. This includes universal PCR analysis with 16S rRNA gene sequencing and comparison with the DNA database.^{13,14} This is a useful tool for bacterial identification in culture negative infection, as with our case. The BR-PCR result was the first marker that led to microbial diagnosis and appropriate antibiotic treatment.

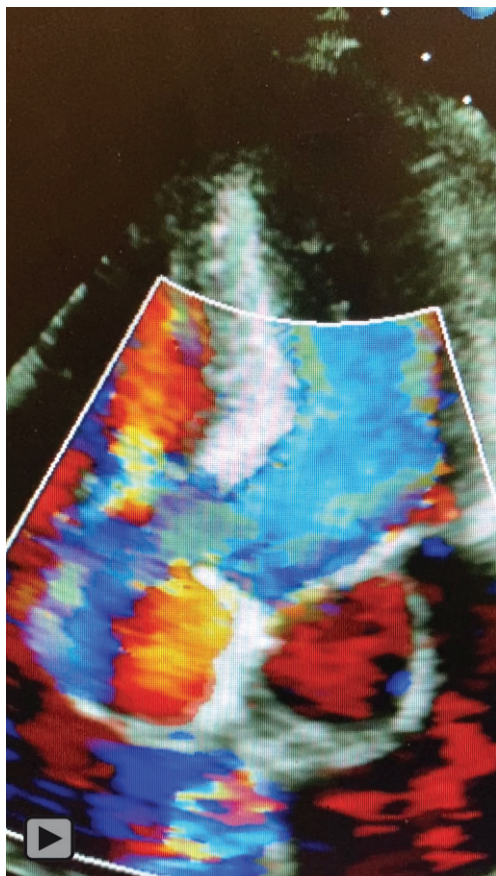
A significant number of *Aggregatibacter* species are resistant to multiple antibiotics. Broad-spectrum cephalosporins and fluoroquinolones are consistently active against HACEK organisms. Third generation cephalosporins, such as ceftriaxone and cefotaxime are considered the drugs of choice. These have a broad-spectrum gram-negative activity, with higher efficacy against resistant HACEK organisms.¹⁵ Ciprofloxacin can be considered an alternative oral agent.¹⁶

HACEK-induced endocarditis is rare and difficult to diagnose due to negative blood culture results. BR-PCR with bacterial 16S rRNA gene sequencing is useful in diagnosing culture-negative IEC.

Lead author biography



Nancy Wassef completed interventional training in the University Hospital of Plymouth Trust, UK and obtained her CCT. Currently, she is an interventional fellow in Kettering General Hospital, UK. Fields of interests include coronary and structural interventions.



Video 2 Transthoracic echocardiography apical five-chamber view showing aortic root abscess with blood flow to the right heart chambers.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and

associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

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