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Corynebacterium freneyi as a cause of early prosthetic valve endocarditis

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SUMMARY

Infective endocarditis (IE) is associated with severe complications and a high mortality rate. Identification of the causative pathogen is crucial to optimise treatment. We present a case of prosthetic valve endocarditis caused by *Corynebacterium freneyi*, a very rare cause of human infection and not previously reported as a cause of IE. Despite proper antibiotic therapy, the patient eventually needed surgery after progression of the infection. After surgery, he quickly recovered without evidence of relapse during an 8-month follow-up period. This report highlights critical decision making in a complex and potentially life-threatening situation, where neither guidelines nor previous clinical or microbiological experience were able to give clear treatment recommendations.

BACKGROUND

Infective endocarditis (IE) is associated with severe complications and a high mortality rate.[1] Numerous pathogens have been described as potential causes of IE, and the risk for complications and disadvantageous outcome is associated with the causative organism. Therefore, correct identification of the pathogen is crucial for clinical decision making regarding antibiotic therapy, indications for surgical treatment and timing of surgery. Prosthetic valve endocarditis (PVE) is associated with particularly poor outcome.[2]

The *Corynebacterium* species are aerobic, non-sporulating, pleomorphic, gram-positive rods and normal constituents of the skin flora.[3] They are rare causes of human infections and usually regarded as contaminants when grown in blood cultures. However, a few published cases have reported *Corynebacterium* species as causes of severe infections, including PVE.[4–6] It has been suggested that they have aggregative adhering invasive mechanisms that predispose to infection of prosthetic devices.[7]

We report a case of PVE caused by *Corynebacterium freneyi* in a patient with mitral and aortic bioprosthetic valves and a pacemaker. *C. freneyi* was first described in 2001,[8] and a MEDLINE search of English literature for the keywords 'Corynebacterium', 'freneyi' and 'endocarditis' returned no cases. Thus, we believe this represents the first report of *C. freneyi* IE.

CASE PRESENTATION

A man in his mid-seventies was admitted to a community hospital with fever, chills and malaise. He had well-controlled hypertension and was anticoagulated with apixaban because of atrial fibrillation.

Two months prior to admission, he had finished treatment for IE due to *Streptococcus mitis*, complicated by destruction of the aortic and mitral valves, aortic root infection and complete atrioventricular block. The infection had been considered

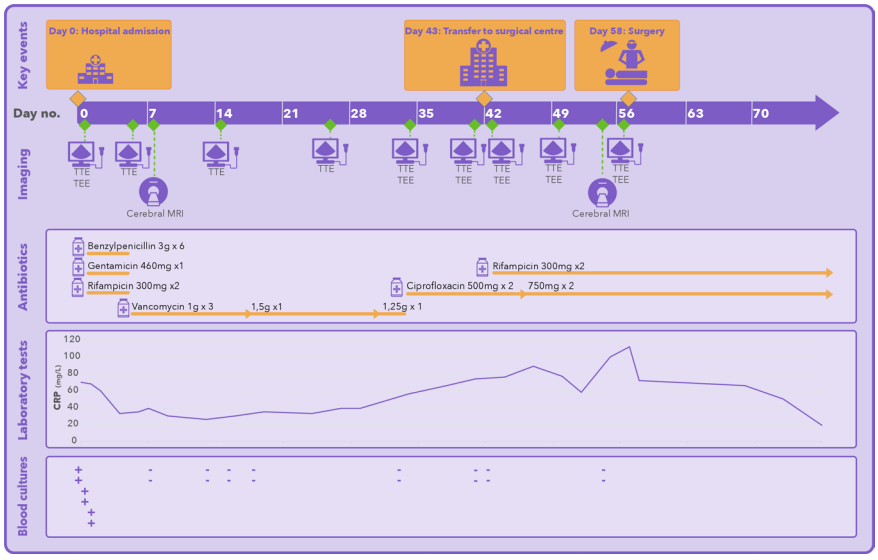


Figure 1 Outline of the clinical course following hospital admission. CRP, C reactive protein; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography. Figure made by BG.

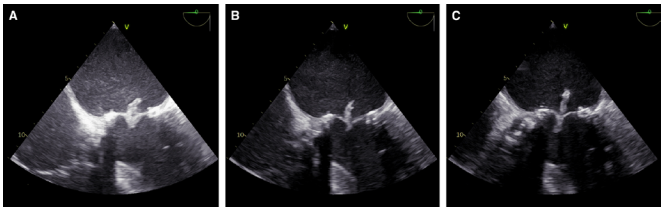


Figure 2 Mid-oesophageal transoesophageal views demonstrating a large vegetation attached to the prosthetic mitral valve. (A) Findings at presentation, revealing a 29 mm long mobile vegetation on the posterior valve leaflet. There was only trace regurgitation and no obstruction of transmitral flow. No definitive evidence was found of paravalvular pathology or involvement of the aortic prosthetic valve, pacemaker leads or right-sided valves. (B) Findings at presentation to the university hospital, after 6 weeks of antibiotic treatment. A large vegetation of the mitral bioprosthesis and trace regurgitation was confirmed. There was an increased transvalvular diastolic gradient of 9 mm Hg. No evidence of prosthesis dehiscence or other signs of paravalvular infection were found. (C) Findings the day before surgery, revealing a more mobile and irregular vegetation, and apparent thickening of the posterior leaflet compared with previous examinations.

successfully treated with appropriate antibiotics (empirical treatment with cloxacillin and gentamicin for 2 days, followed by benzylpenicillin according to susceptibility testing) and open-heart surgery with implantation of bioprosthetic valves in mitral and aortic position and reconstruction of the aortic annulus with a pericardial patch. A biventricular pacemaker was implanted postoperatively due to persistent complete atrioventricular block and reduction of left ventricular function with dyssynchronous contraction. Antibiotic treatment with benzylpenicillin was continued for 6 weeks postoperatively. Transthoracic echocardiography at completion of therapy demonstrated proper function of the prosthetic valves without evidence of vegetations.

Nine weeks after completion of antibiotic therapy, he was readmitted to the community hospital (Molde Hospital, Molde, Norway) with persistent symptoms of fever with chills, reduced general condition and impaired sense of taste during the last 2 weeks, despite amoxicillin prescribed by the general practitioner 1 week earlier (figure 1). At admission, he had fever with temperature 38.6 °C. Blood pressure was 136/72 mm Hg, heart rate 88/min, respiratory rate 12/min, oxygen saturation 98%. Physical examination revealed no murmur or abnormal organ findings. C reactive protein (CRP) was 70 mg/L (normal <10), white blood cell count 13×10^9/L (normal 4–9) and haemoglobin 93 g/L (normal >13.8). Chest X-ray and urinary tests were normal. COVID-19 and influenza tests were negative. Amoxicillin was discontinued and several blood cultures were drawn.

Table 1 Antibiotic susceptibility of the *Corynebacterium freneyi* growing in blood cultures

Drug	MIC	Sensitivity
Ciprofloxacin	0.064	S
Clindamycin	0.25	S
Doxycycline	0.125	S
Gentamicin	0.125	S
Linezolid	0.25	S
Benzylpenicillin	>32	R
Rifampicin	0.008	S
Vancomycin	0.25	S

MIC, minimum inhibitory concentration; R, resistant; S, sensitive.

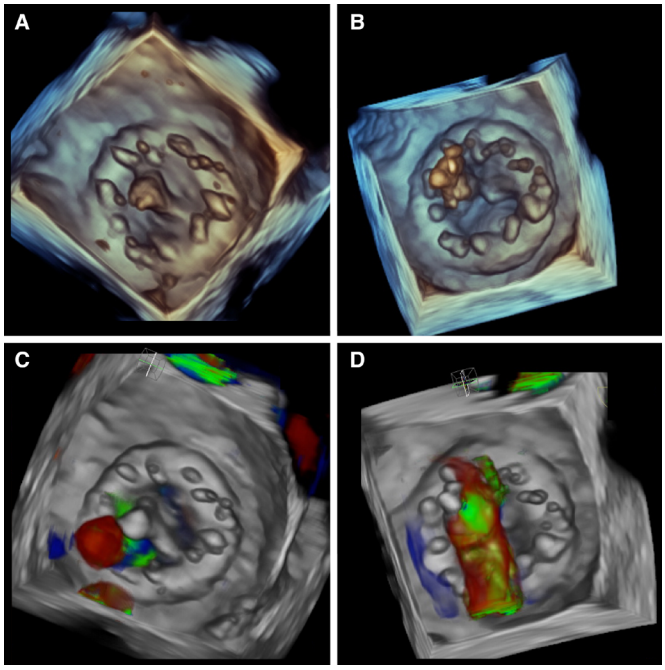
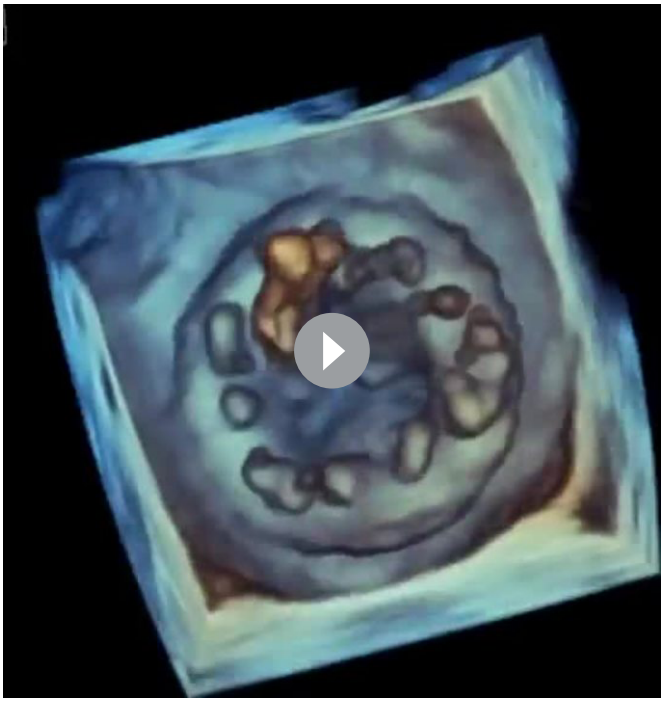


Figure 3 Three-dimensional transoesophageal views of the of the prosthetic mitral valve as seen from the left atrium ('surgeons view'). There was growth of the vegetation size and profound increase of the regurgitation from admission at the university hospital (A and C) to the day before surgery (B and D).

Transthoracic and transoesophageal echocardiography revealed a vegetation susceptive of endocarditis on the prosthetic mitral valve, and empirical antibiotic therapy was initiated (figures 1 and 2A). Four days after admission, gram-positive bacteria were grown in all six blood cultures. Blood culture isolates were identified as *C. freneyi* using matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF) with a match of 99.9% with the MALDI-TOF reference database (table 1).

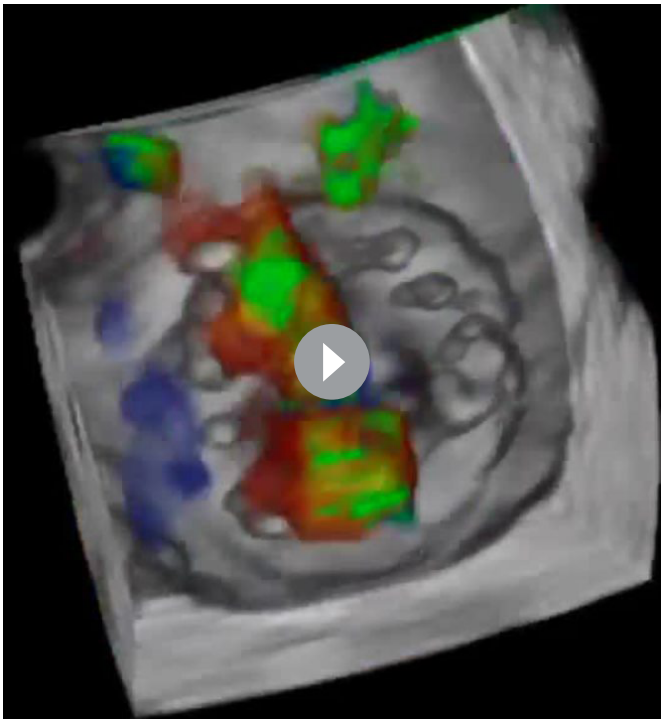
Treatment with vancomycin was initiated after discussion with the surgical centre at the university hospital, with daily clinical evaluation, blood tests and regular echocardiograms. The target range for vancomycin predose serum concentration was 15–20 mg/L throughout the duration of treatment. The patient's general condition was stable the following weeks, with no fever. Vancomycin was replaced with ciprofloxacin monotherapy due to high blood concentrations and increasing creatinine (figure 1). No microbe was grown in later repeated blood cultures. Cerebral MRI revealed no evidence of embolisation. However, CRP and white blood cells were slowly increasing, and echocardiographic examinations demonstrated a persistent vegetation. Therefore, after 6 weeks, the patient was transferred to the cardiac surgical centre (St Olavs University Hospital, Trondheim, Norway) for further evaluation.

Transthoracic and transoesophageal echocardiography at the university hospital confirmed a large vegetation (size approximately 18×9 mm) of the mitral valve bioprosthesis, trace mitral regurgitation and no evidence of other infective involvement (figure 2B). The patient was discussed by the endocarditis team. Surgery was considered to involve high risk due to previous extensive thoracic surgery, renal failure and age, and there was no definitive evidence for progression of the infection. A continued conservative strategy was therefore decided, with addition of rifampicin to the antibiotic therapy. However,



Video 1 Three-dimensional transoesophageal view of the prosthetic mitral valve as seen from the left atrium ('surgeons view') the day before surgery. A large pendulating vegetation was attached to the posterior leaflet.

the patient developed fever and CRP was increasing to a peak of 112 mg/L. He had recurrent episodes of localised pain and rubor in the right leg without evidence of local infection, and



Video 2 Colour Doppler 3D transoesophageal view of the prosthetic mitral valve as seen from the left atrium ('surgeons view') the day before surgery. There was a significant regurgitation originating from the infected part of the bioprosthesis.

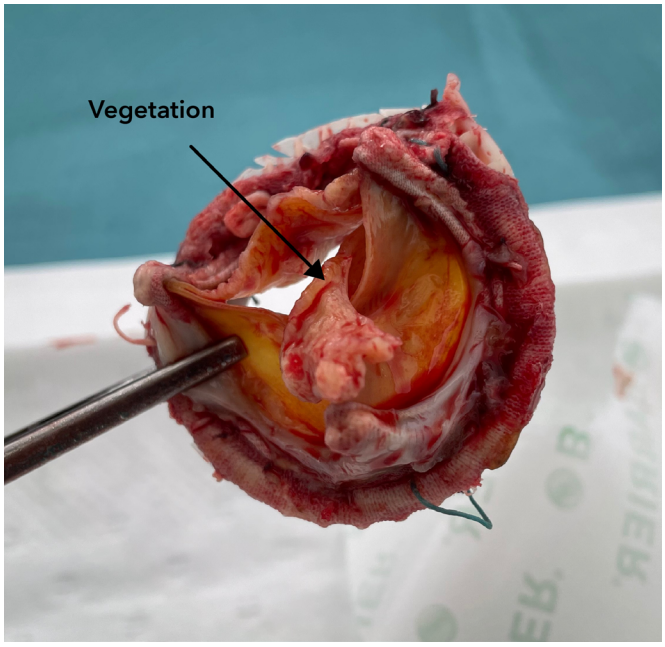


Figure 4 The mitral valve bioprosthesis after extraction, as seen from the ventricular side of the prosthesis. There is a large vegetation protruding through the valve, attached to the atrial surface of the posterior leaflet.

peripheral embolisations were suspected. Transoesophageal echocardiography revealed increasing mitral valve regurgitation and at day 57 the vegetation at the prosthetic mitral valve had become profoundly irregular and mobile (figures 2C and 3, videos 1 and 2). Surgery was now considered inevitable, and reoperation was performed on day 58. The pacemaker leads and generator were detached and removed, and the prosthetic mitral valve extracted. There was a large vegetation attached to the atrial side of the posterior valve leaflet, which was thickened and partially destructed (figure 4). Thorough inspection revealed no evidence of infectious involvement of the mitral annulus, the aortic root or the aortic valve prosthesis. Removal of the aortic valve prosthesis and adjacent patch was deemed to involve too high risk, and the procedure was therefore completed with replacement of the prosthetic mitral valve only. A new bioprosthetic valve was inserted.

OUTCOME AND FOLLOW-UP

Following surgery, the patient's general condition improved rapidly. A new biventricular pacemaker was implanted on day 68. There was no growth on the extracted pacemaker leads or the valve prosthesis during extended testing. However, bacterial sequencing of tissue from the valve was positive and based on the PCR product (partial 16S rRNA-gene, 541 nucleotides) consistent with *C. freneyi*. Antibiotic treatment was continued for 6 weeks post-surgery. The patient has now been followed for 8 months since surgery, with no recurrence of fever or other IE-related symptoms. Weekly CRP and white blood cell tests during the first 3 months were normal. Transoesophageal echocardiography at 4 months' follow-up revealed no evidence of IE relapse.

DISCUSSION

To the best of our knowledge, this is the first case report of IE caused by *C. freneyi*. The report highlights treatment decisions

in a complex and potentially life-threatening situation where neither guidelines nor clinical or microbiological experience were able to give clear recommendations. The case presentation has important clinical implications: first, we demonstrate that *C. freneyi* may cause IE. Second, the case highlights the particular challenges faced by PVE and considerations regarding redo surgery in a patient with multiple cardiac implants. Third, it emphasises the importance of thorough clinical, laboratory and imaging follow-up in patients with IE, and the need of an endocarditis team with close collaboration between cardiologists, cardiothoracic surgeons, imaging experts and infectious disease specialists.

The *Corynebacterium* species are aerobic, non-sporulating, pleomorphic, gram-positive rods and normal constituents of the skin flora.[3] Traditionally classified as culture contaminants, *Corynebacterium* species have later been associated with life-threatening infections in patients with intravenous catheters or prosthetic heart valves.[4–6] Within the *Corynebacterium* species, *Corynebacterium diphteriae* is the most well-known cause of human infection. However, both *Corynebacterium jeikeium* and *Corynebacterium striatum* are increasingly recognised as causes of severe infections, including IE.[4 6 9–11] A case report from 2018 reviewed 10 published cases of *C. jeikeium* IE, of which 5 had prior valve replacement.[11] Of these, all had PVE. In a paper from 2020, 35 published cases of *C. striatum* IE were found, including 8 reports of PVE.[10] In a recent study, 335 cases of *Corynebacterium* bacteraemia were identified during 2012–2017, of which 30 (9%) episodes were classified as true infections.[6] Eight episodes of IE were identified, all in patients with prosthetic valves. Infections both early and late after surgery were described, suggesting intraoperative as well as haematogenous spread of bacteria. Based on this study, the incidence of *Corynebacterium* IE was estimated to be around one in a million per year. In patients with *Corynebacterium* endocarditis, both the requirement for valve replacement and the mortality have been high.[4]

Our patient met the Modified Duke criteria for diagnosis of IE, based on a vegetation identified by echocardiography (major criterion), a prosthetic mitral valve as a predisposing condition (minor criterion), fever (minor criterion) and growth of *C. freneyi* in several blood cultures (minor criterion). Although *C. freneyi* is not a typical IE organism, growth in six out of six blood cultures drawn at separate time points was considered as highly suspicious of clinically relevant infection and not solely contamination. The diagnosis was ultimately confirmed by PCR products consistent with *C. freneyi* in the removed prosthetic valve vegetation after surgery.

C. freneyi was first characterised in 2001 as a fermentative, α-glucosidase-positive *Corynebacterium* species related to *Corynebacterium xerosis*.[8 12] The species has been reported to be sensitive to linezolid, meropenem, vancomycin, doxycycline, gentamicin and rifampicin.[12] There are no clear recommendations for treatment of *Corynebacterium* IE and obviously not for *C. freneyi*. Based on reported cases of successful treatment without surgery for other *Corynebacterium* species IE, we initially opted for a conservative strategy of antibiotic therapy with vancomycin, which has been suggested as a treatment of choice for IE caused by *Corynebacterium* species.[11]

In patients with IE, the decision to perform surgery in addition to antibiotic therapy is complex.[1] Guidelines recommend early surgery for patients with IE who have heart failure with refractory pulmonary oedema due to severe valve dysfunction, heart block, perivalvular abscess or persistent large vegetations after one or more embolic episodes.[1] PVE, as in our case, involves particular challenges. There is risk of residual infected tissue related to prosthetic valves and pacemaker leads, despite adequate antibiotic therapy. Surgical treatment with complete removal of all foreign material is therefore often required. Thus, approximately 50% of patients with PVE ultimately undergo surgery, and another 20% do not receive valve replacement because of prohibitive surgical risk.[13] Our patient had a history of complex surgery with two prosthetic valves and patch reconstruction in the aortic annular region, as well as a biventricular pacemaker system. Complete removal of all foreign material and surgical reconstruction with reinsertion of both mitral and aortic valvular prostheses, as well as aortic reconstruction and implantation of a new pacemaker, was deemed to comprise very high risk. The risks associated with surgery in PVE has previously been demonstrated in a large meta-analysis, where early surgery with valve replacement did not reduce mortality compared with medical therapy alone.[14]

However, in the presented patient, adequate antibiotic therapy failed to control the infection and redo surgery was considered unavoidable. It was obvious that the damaged mitral valve bioprosthesis had to be removed. Moreover, extraction of the pacemaker system was decided. The patient was not pacemaker dependent, and the leads were only a few months old, so lead extraction was considered safe. However, uncertainty remained whether to remove the aortic valve prosthesis. Transoesophageal echocardiography revealed no evidence for infectious involvement of the aortic valve prosthesis. Nuclear imaging by 18F-FDG PET/CT has evolved as a useful adjunctive diagnostic tool in the evaluation of diagnostically challenging cases of IE, particularly in PVE,[15] and was discussed in our patient. However, the accuracy during the first months after cardiac surgery is low. Final decision with regard to the aortic valve prosthesis was therefore postponed until thorough examination during surgery, where no sign of infection was revealed beyond the mitral valve bioprosthesis. A long follow-up period without any recurrence supports that there was no infection related to the aortic valve prosthesis or native tissue.

In conclusion, this case establishes *C. freneyi* as a causative pathogen for PVE. Longstanding adequate antibiotic therapy failed to eradicate the infection, and the patient eventually needed surgery. There was no infection of native human tissue or involvement of other cardiac implants and the patient rapidly recovered after surgery with no evidence of infectious relapse during 8 months of follow-up.

Learning points

- *Corynebacterium freneyi* is a possible causative pathogen for prosthetic valve endocarditis.
- *Corynebacterium* species grown in blood cultures should not always be considered a contaminant, particularly in patients with prosthetic heart valves.
- Antibiotic therapy is the mainstay of treatment in patients with infective endocarditis, however, surgery is often required to eradicate the infection and treat complications.
- An endocarditis team is essential for successful management of these complex patients.
- Comprehensive follow-up to evaluate the need for concomitant surgery is required in patients with infective endocarditis who are treated with an initial antibiotic strategy, in particular with prosthetic valve endocarditis.

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Contributors Each author contributed to the concept and design of this manuscript. All authors were central members in decisions on diagnostics and handling as part of the endocarditis team. BG, HD, EH and TS-A were central to the diagnostic work-up, acquired echo images and had the main responsibility for follow-up after surgery. DON was the chief surgeon and contributed importantly to the surgical perspective throughout the manuscript. OCM was central for decisions on the patient treatment, and in particular, handling of the pacemaker. JKD was a key member of the endocarditis team with profound knowledge in infectious medicine and contributed importantly to the infectious medicine and microbiology perspective of the manuscript. BG drafted the manuscript and prepared the illustrations. All authors contributed importantly to the final manuscript and have read the final version. All authors are accountable for the manuscript and its content.

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