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CASE REPORT

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# Bacterial endocarditis with AACEK (HACEK) organisms

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## Abstract

**Introduction:** Gram-negative organisms of the AACEK group, formerly known as HACEK, rarely cause endocarditis.

**Case Series:** We present three cases of bacterial endocarditis, involving native and prosthetic valves, caused by AACEK organisms. In two patients, *Cardiobacterium hominis* was the responsible organism, and in a third, *Aggregatibacter aphrophilus* was implicated. A dental source of infection was identified in two patients, and in all three patients, the presentation of endocarditis was subacute.

**Discussion:** This case series highlights the indolent nature of infection with the AACEK organisms. It also demonstrates the crucial role of multimodality imaging, especially transesophageal echocardiography, in the diagnosis of AACEk endocarditis of both native and prosthetic valves, and in delineating the extent of abscess in those with prosthetic valve infection.

KEYWORDS
AACEK, bioprosthesis, endocarditis, HACEK, TEE, valve replacement

## 1 | INTRODUCTION

HACEK organisms, a group of fastidious, gram-negative coccobacilli, are a rare cause of endocarditis, accounting for approximately 3% of all cases of valve infection.[1,2] The HACEK acronym originally referred to the *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species. However, the renaming of the key *Haemophilus* species, *Haemophilus aphrophilus* to *Aggregatibacter aphrophilus* triggered a change in the acronym from HACEK to AACEK. The *Aggregatibacter* species is now recognized as the most common cause of AACEK endocarditis, followed by *Cardiobacterium hominis*. We report three cases of subacute endocarditis due to AACEK organisms – two with *Cardiobacterium hominis* and one with *Aggregatibacter aphrophilus*.

## 2 | CASE 1

A 65-year-old previously healthy and active man presented with a 1-year history of fatigue and generalized malaise. He denied fever, chills, night sweats, or weight loss.

Physical examination was remarkable for a grade 3/6 holosystolic murmur and splenomegaly. Complete blood count revealed a normocytic anemia (hemoglobin 9.5 g/dl) and thrombocytopenia ($85 * 10^3/\mu l$) with a normal white blood count and differential. Erythrocyte sedimentation rate (ESR) was 51 mm/h (normal 0–10 mm/h) and C-reactive protein (CRP) was 72.5 mg/L (normal 0–5 mg/L). Blood cultures were collected. A transthoracic echocardiogram (TTE) revealed a large posterior mitral leaflet vegetation with severe, eccentric, anteriorly directed mitral regurgitation, a dilated left atrium, and a normal size left ventricle with preserved systolic function (Figure 1, Video 1).

The patient was admitted for the management of subacute bacterial endocarditis (SBE). After additional blood cultures were obtained, he was started on empiric broad-spectrum antibiotic therapy with vancomycin and gentamicin. Signs of congestive heart failure ensued. The pre-admission and admission blood cultures grew gram-negative rods in multiple aerobic and anaerobic bottles, which were identified a week later as *Cardiobacterium hominis*. A 2D and 3D transesophageal echocardiogram (TEE) on hospital day 4 revealed a large, partly calcified, fungating vegetation on the P2 scallop of the posterior mitral leaflet (Figure 2, Videos 2 and 3).

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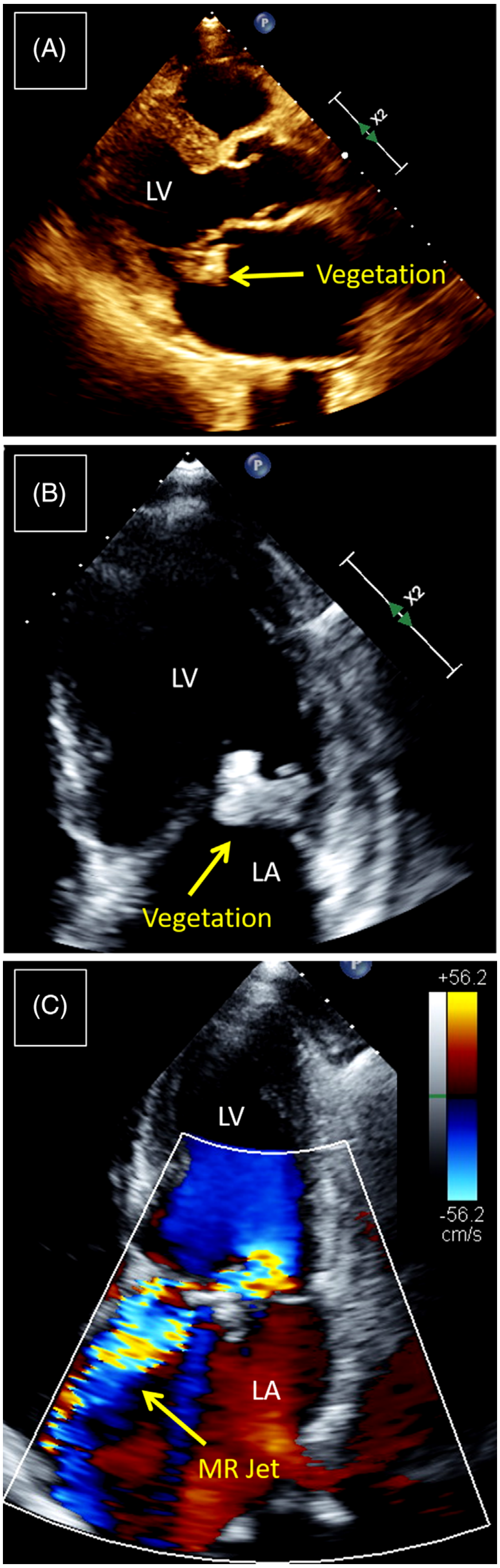



**FIGURE 1** Case 1 – TTE demonstrated a large vegetation on the posterior mitral leaflet (Panels A and B) with severe mitral regurgitation (Panel C). LA, left atrium; LV, left ventricle. Composite Video 1 corresponds to the three panels of this figure.

With the diagnosis of infective endocarditis caused by an AACEK organism, the patient's antibiotic regimen was changed to intravenous ceftriaxone. Due to the large size of the vegetation and the presence of heart failure, he was referred for surgery (Figure 3, Video 4) and underwent mitral valve replacement with a 31-mm Medtronic Mosaic bioprosthesis on hospital day 6. He was discharged four days later and completed 6 weeks of Intravenous antibiotics as an outpatient. He is doing well 2 years later.

## 3 | CASE 2

A 64-year-old man, who had undergone type A aortic dissection repair and mechanical aortic valve replacement with a 27-mm St Jude bileaflet prosthesis (Abbott, Plymouth, Minnesota, USA) 7 years earlier, presented with a 1-month history of generalized weakness, malaise, anorexia, and intermittent night sweats.

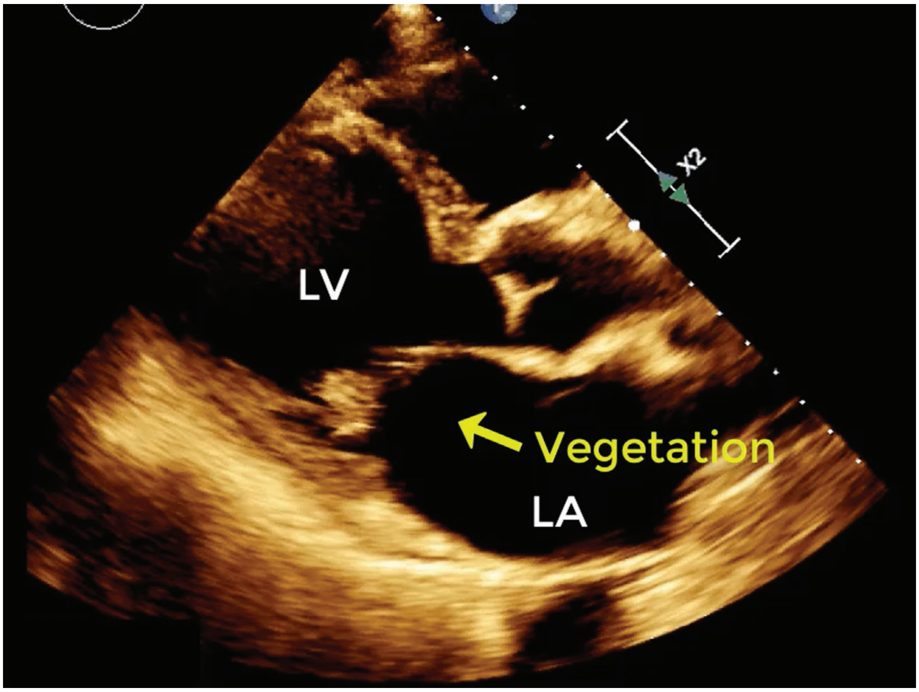
On admission he was afebrile with a heart rate of 87 bpm, a respiratory rate of 20 breaths per minute, and a blood pressure of 103/70 mm Hg. Laboratory tests were significant for normocytic anemia (hemoglobin 8.1 g/dl), leukocytosis (17.6 $*10^3/\mu l$), markedly supratherapeutic international normalized ration (INR 10.6 on warfarin), and mild transaminitis. Electrocardiogram revealed new-onset atrial fibrillation (AF). SBE was suspected, blood cultures were drawn, and the patient was started on intravenous ceftriaxone.

TTE revealed a normally-functioning aortic mechanical prosthesis. No vegetation was seen, but the blood cultures grew gram-negative rods. On hospital day 3, he underwent a 2D/3D TEE, which showed an aortic root abscess encasing the sewing ring of the valve prosthesis. The abscess extended into the intervalvular fibrosa and involved the base of the anterior mitral leaflet, creating a mitral valve perforation. The abscess mass of the intervalvular fibrosa protruded into the left atrial cavity, and a channel through the abscess connecting the left ventricular (LV) outflow tract and left atrium (LA) resulted in mitral regurgitation-like physiology (Figure 4, Videos 5 and 6).

On hospital day 5, the gram-negative rods in the blood were identified as *Aggregatibacter aphrophilus*, and the patient was continued on ceftriaxone therapy. The source of infection was thought to be severe periodontal disease, although no acute odontogenic infection or abscess was identified.

The patient underwent re-operation with extensive debridement of the infected tissue, reconstruction of the aortic root, fibrous trigone, and left atrium, and implantation of aortic and mitral bioprostheses (Figure 5). He was discharged six days after surgery and received several more weeks of intravenous ceftriaxone as an outpatient. The decayed teeth were extracted 1 month after discharge, while he was completing his course of antibiotics.

Unfortunately, 5 months after the surgery, he was diagnosed with recurrent *Aggregatibacter aphrophilus* bacteremia, and TEE showed large vegetation on the bioprosthetic aortic valve extending onto the bioprosthetic mitral valve (Figure 6 and Video 7). He underwent surgical replacement of both prostheses, but he expired two days after surgery.




**VIDEO 1** Case 1 – Composite 3-clip video demonstrates large vegetations on the posterior mitral leaflet with severe mitral regurgitation seen in the parasternal long axis and apical four chamber view with color flow doppler. LA, left atrium; LV, left ventricle. LA, left atrium; LV, left ventricle; MR, mitral regurgitation.

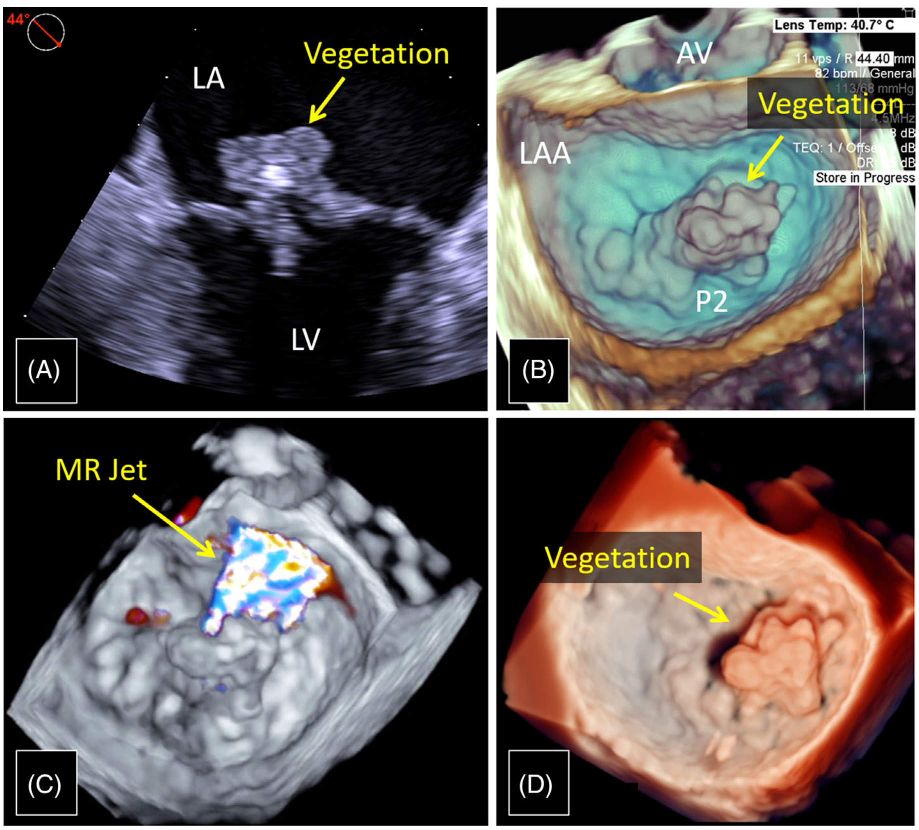



**FIGURE 2** Case 1 – Preoperative 2D TEE revealed a large, vegetation on the P2 scallop and a small vegetation on the A2 scallop of the mitral valve (Panel A). 3D TEE of the mitral valve from the LA perspective showed a massive MV vegetation protruding into the LA (Panels B, C, and D) with an anteriorly directed jet of severe MR (Panel C). AV, aortic valve; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MR, mitral regurgitation. Composite Video 2 corresponds to Panels A and B while composite Video 3 corresponds to Panels C and D.

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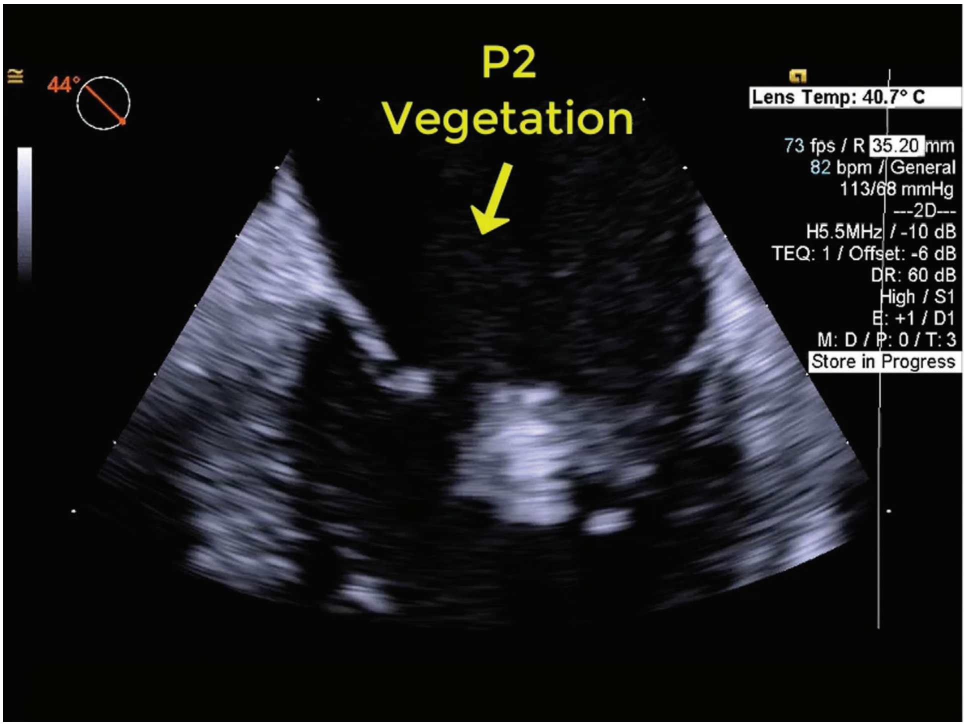
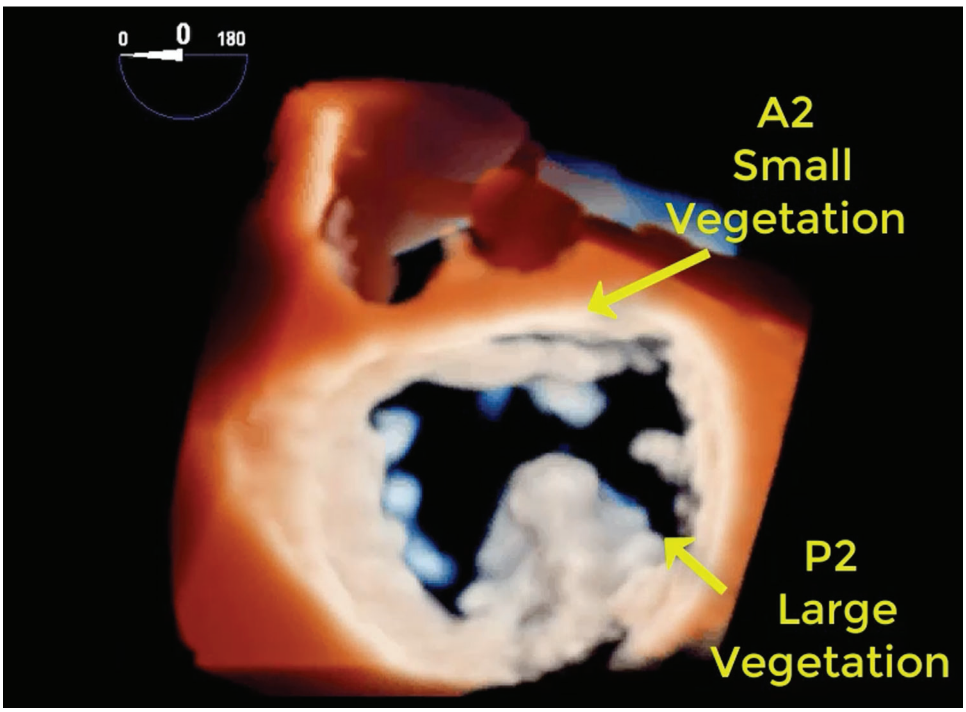



**VIDEO 2** Case 1 – Composite 2-clip video of 2D and 3D TEE demonstrates a large, partly calcified vegetation on the P2 scallop and a small vegetation on the A2 scallop of the mitral valve. 3D TEE imaging of the mitral valve from the LA perspective showed a massive native MV vegetation protruding into the LA. AV, aortic valve; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MR, mitral regurgitation; MV, mitral valve.




**VIDEO 3** Case 1 – Composite 2-clip video shows 3D TEE imaging of the mitral valve from the LA perspective, which demonstrated a massive P2 scallop vegetation protruding into the LA, resulting in an anteriorly directed jet of severe MR. MR, mitral regurgitation.

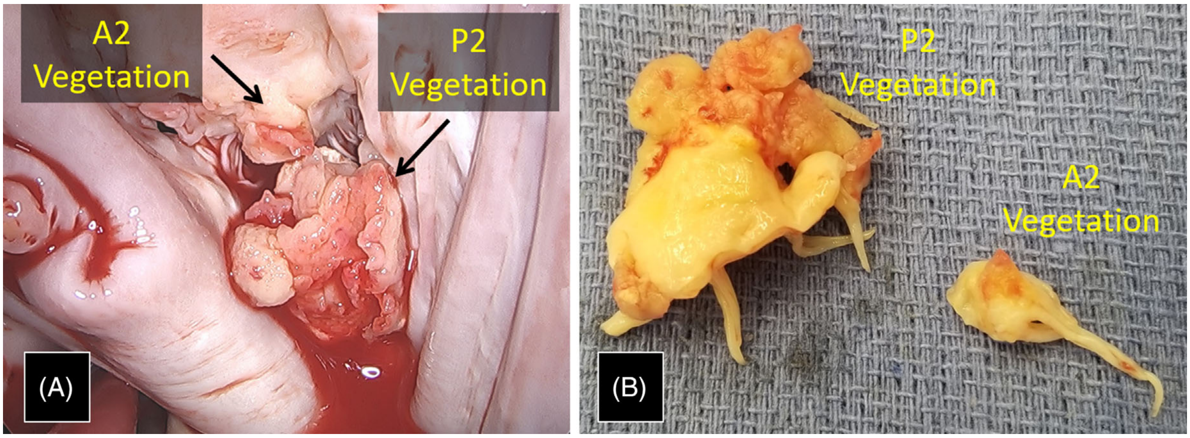
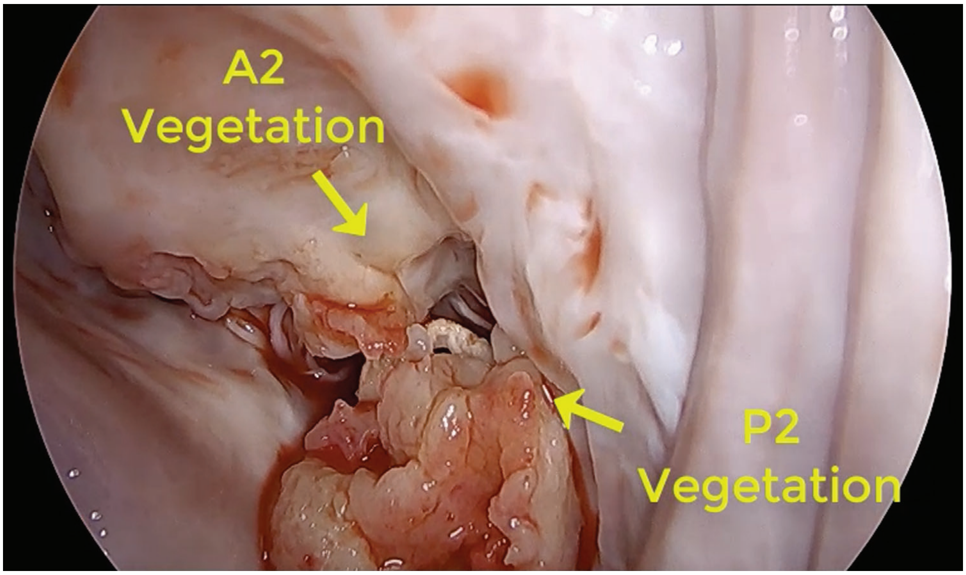



**FIGURE 3** Case 1 –Intraoperative image of the mitral valve revealed the large P2 vegetation and smaller A2 vegetation (Panel A). Both vegetations were resected (Panel B). Video 4 corresponds to Panel A of this figure.




**VIDEO 4** Case 1 –Intraoperative video recording shows a large, partly calcified, fungating P2 vegetation next to a smaller A2 vegetation prior to resection.

## 4 | CASE 3

A 58-year-old woman with rheumatic valve disease and atrial fibrillation, who had undergone bioprosthetic mitral valve replacement and tricuspid valve annuloplasty several years earlier, presented to the emergency department (ED) with 2 months of fatigue, anorexia, progressive lower extremity edema, and abdominal distention.

In the ED, the patient became febrile to 38.3°C and was noted to be in AF with a ventricular response of about 120 beats per minute. Physical examination revealed pulmonary congestion, moderate edema of both lower extremities, and ascites. Laboratory analysis was significant for leukocytosis ($13.1{*}10^3/\mu l$), normocytic anemia (hemoglobin 8.7 g/dl), hyponatremia (126 mmol/L, normal: 136–145 mmol/L), and hypoalbuminemia (2.4 g/dl, normal: 3.5–5.0 g/dl). The INR was 10 on warfarin, and urinalysis showed microscopic hematuria.

SBE was suspected and broad-spectrum antibiotics were started. Blood cultures obtained in the ED confirmed bacteremia with gram-negative rods on hospital day 3. TTE revealed an elevated mean diastolic mitral gradient (11 mm Hg), which was thought to be secondary to AF with rapid ventricular rate. No vegetation was seen.

On hospital day 5, the gram-negative rods were identified as *Cardiobacterium hominis*, and the antibiotic regimen was changed to intravenous ceftriaxone. Oral-maxillofacial surgery evaluation revealed multiple carious teeth believed to be the source of infection. TEE (2D and 3D) demonstrated large vegetations on the three cusps of the bioprosthetic mitral valve (Figure 7 and Video 8). In addition, there were smaller vegetations on the native aortic valve. Neither

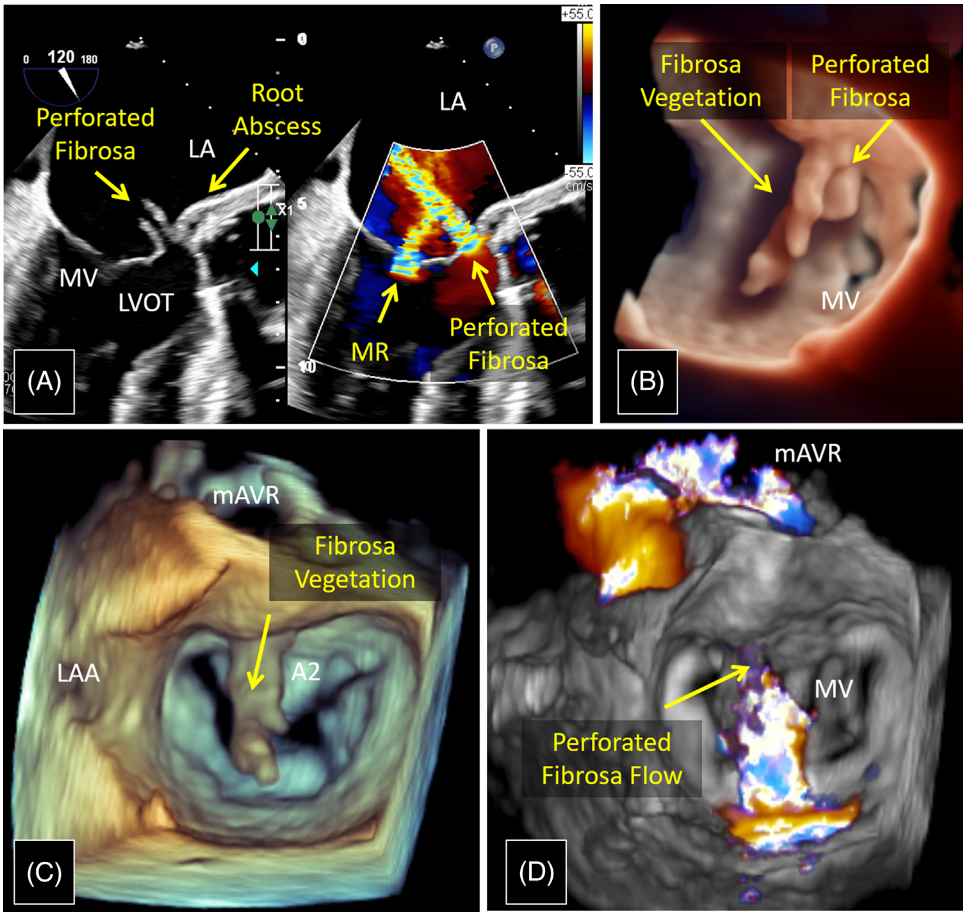



**FIGURE 4** Case 2 –2D TEE revealed a large aortic root abscess adjacent to the sewing ring of the mechanical prosthesis with direct extension into the intervalvular fibrosa and to the base of the anterior mitral leaflet. There was a perforation of the fibrosa and mitral valve perforation with large vegetations surrounding the fistula. Severe valvular MR and MR-like flow through the perforated fibrosa were visualized (Panel A). 3D TEE showed the perforated fibrosa in between two large vegetations above the anterior mitral leaflet. Vegetations on the perforated fibrosa had originally been interpreted as vegetations of the A2 scallop of the native mitral valve (Panels B and C). mAVR, mechanical aortic valve replacement; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MV, mitral valve. Video 5 corresponds to Panel A and Video 6 corresponds to Panels B, C and D.

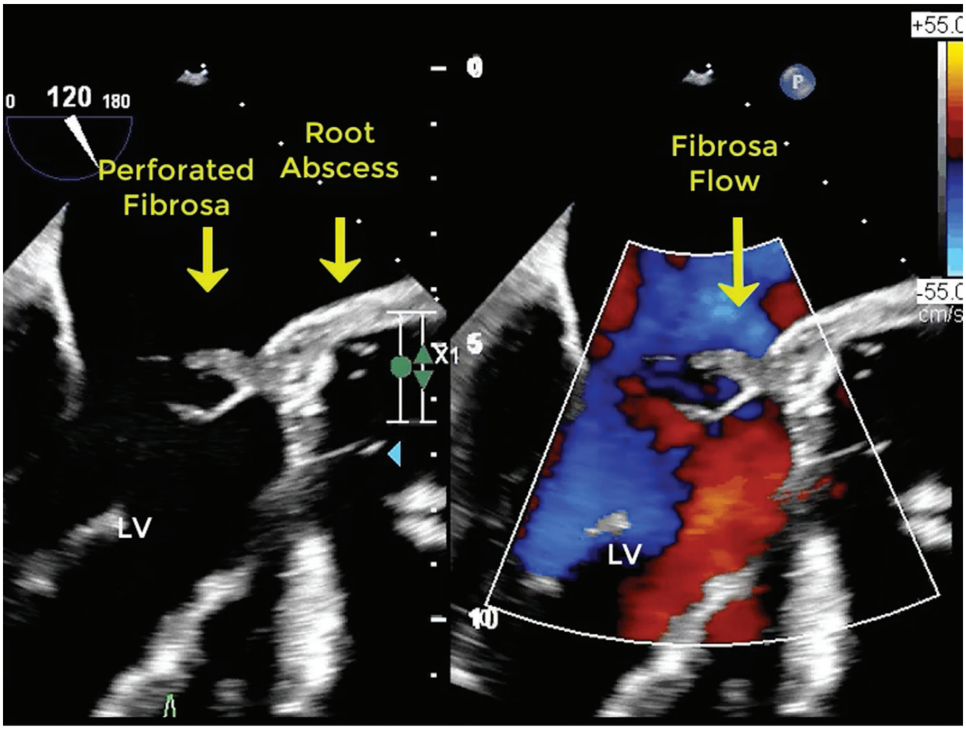
computed tomography of the abdomen and pelvis nor magnetic resonance angiogram revealed any evidence of systemic emboli.

Although the mitral vegetation was large, (a possible indication for surgical intervention), none of the vegetations appeared mobile, and in the absence of emboli, evidence of valvular insufficiency, or persistent bacteremia, medical treatment for the patient's SBE was deemed appropriate. The patient was discharged on hospital day 10 to complete a 6-week course of intravenous ceftriaxone with close follow-up by cardiology and infectious disease. Dental intervention is pending.

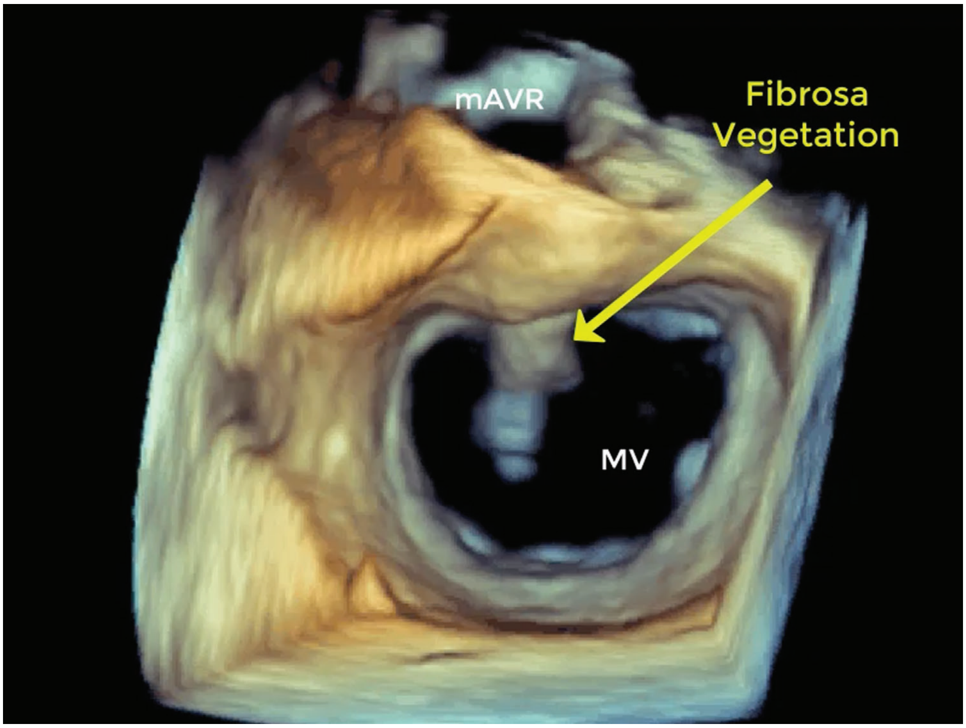
## 5 | DISCUSSION

In this series, we report three cases of infective endocarditis with AACEK organisms – one involving a native mitral valve and two occurring in patients with prosthetic valves. All three patients presented with insidious illnesses and vague constitutional symptoms characteristic of subacute bacterial endocarditis. Although endocarditis with AACEK organisms is rare, pre-existing cardiac disease and the presence of a prosthetic valve are important risk factors. Preceding procedures are also important to note as AACEK endocarditis has been reported after dental procedures, upper endoscopy, and colonoscopy.[3] Increased risk for AACEK endocarditis is also present in patients who use intravenous drugs and increased attention should be paid to these patients.[4] Complicating the diagnosis is the fact that AACEK endocarditis often presents with a particularly long duration of symptoms (greater than 12 weeks) prior to diagnosis.[5] There, suspicion for AACEK endocarditis should not wane even if risk-inducing procedures or behaviors were in the remote past. Concern for AACEK endocarditis in at-risk patients will help to avoid a delay in the collection of blood cultures, diagnostic imaging, and initiation of antibiotic therapy.

For all three patients, TEE provided important anatomic information about the extent of their infections. In the patient with native mitral valve endocarditis, involvement of both leaflets was shown by TEE. It is probably not too surprising that in the two patients with valve prostheses, vegetation was not seen at all on their TTEs, and TEE




**VIDEO 5** Case 2 – 2D TEE video clip shows a large aortic root abscess originating from the sewing ring of the mechanic aortic prosthesis extending into the intervalvular fibrosa and to the anterior leaflet of the mitral valve, resulting in perforation of the fibrosa with surrounding vegetation. Color-flow doppler revealed severe MR and flow through the perforated fibrosa. LV, left ventricle.




**VIDEO 6** Case 2 – Composite 3-clip video of 3D TEE imaging demonstrates the perforated fibrosa in between 2 large vegetations above the leaflets of the mitral valve and involving the base of the anterior mitral leaflet, resulting in LV-LA regurgitation-like flow and mitral valve perforation. mAVR, mechanical aortic valve replacement; MV, mitral valve

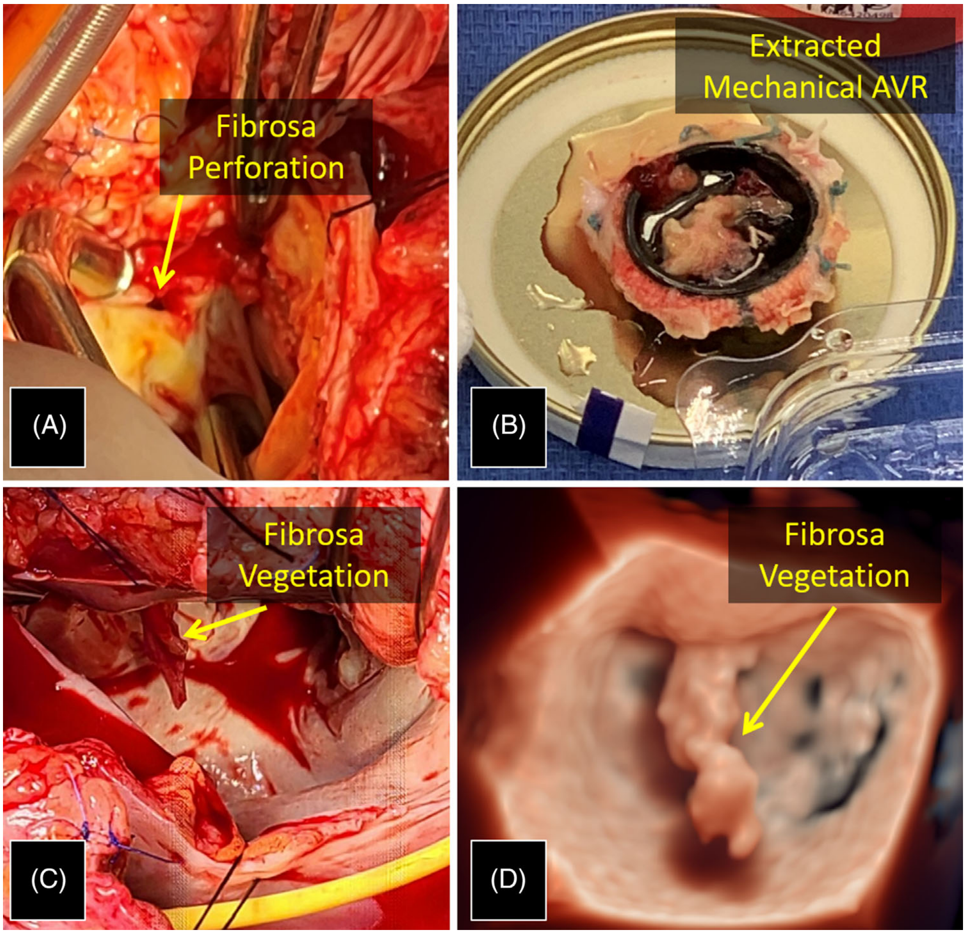



**FIGURE 5** Case 2 – Intraoperative findings included perforated intervalvular fibrosa (Panel A), infected aortic bioprosthesis (Panel B) and fibrosa vegetation (Panel C). The corresponding 3D TEE view of the fibrosa vegetation is shown in Panel D.

was required to reveal their prosthetic valve masses. In the case of one of the two patients with prostheses, TEE also demonstrated the very extensive associated abscess and the LV-LA fistula through the abscessed intervalvular fibrosa.

These cases thus highlight the crucial role of TEE in establishing the diagnosis of AACEK endocarditis and in elucidating some of its anatomic complications. Delay in diagnosis places patients at risk for complications like cardioembolic stroke, which is known to occur more frequently in AACEK compared to non-AACEK endocarditis.[1] Interestingly, two of our patients required surgical intervention. Of course this is less unexpected in patients with prosthetic endocarditis, even subacute bacterial infection. Of the two patients with prosthetic valves described here, the one presenting with a shorter duration of constitutional symptoms (Case 1) had more localized infection that was treated effectively without surgery.

On the other hand, the more expansive infection with which the patient in Case 2 presented – the extension of an aortic root abscess, arising most frequently from prosthetic aortic valve endocarditis, to the intervalvular fibrosa – is acutely life-threatening. The abscess may compress surrounding structures, such as the left-sided coronary artery or the pulmonary artery. It may also result in a mycotic aneurysm or pseudoaneurysm of the fibrous structure (connecting the base of the anterior mitral leaflet with the base of the noncoronary aortic valve cusp) that may rupture, sometimes catastrophically, into the pericardium.

A more contained rupture between the LV and LA, as in our patient, may result in fistula formation, which is seen in 20% of patients with pseudoaneurysm of the intervalvular fibrosa.[6] MR-like flow through such a fistula should be differentiated from eccentric mitral valve regurgitation by comprehensive transesophageal echocardiographic imaging.[6] Additional imaging with computed tomography may be indicated to better visualize surrounding structures prior to surgery, which is the definitive treatment.

Recurrence of infection in patients with AACEK endocarditis is rare. In a study of 118 cases of AACEK endocarditis, only one case of recurrent bacteremia was identified: a relapse of *Cardiobacterium hominis*.[7] Only two cases of recurrent *Aggregatibacter aphrophilus* have been reported[8,9] in the literature. Sadly, the patient presented in Case 2 returned with a relapse of *Aggregatibacter aphrophilus* endocarditis within 6 months of the index infection.

This was, however, a case of prosthetic valve endocarditis with extensive intracardiac abscess. The severity of his infection – and

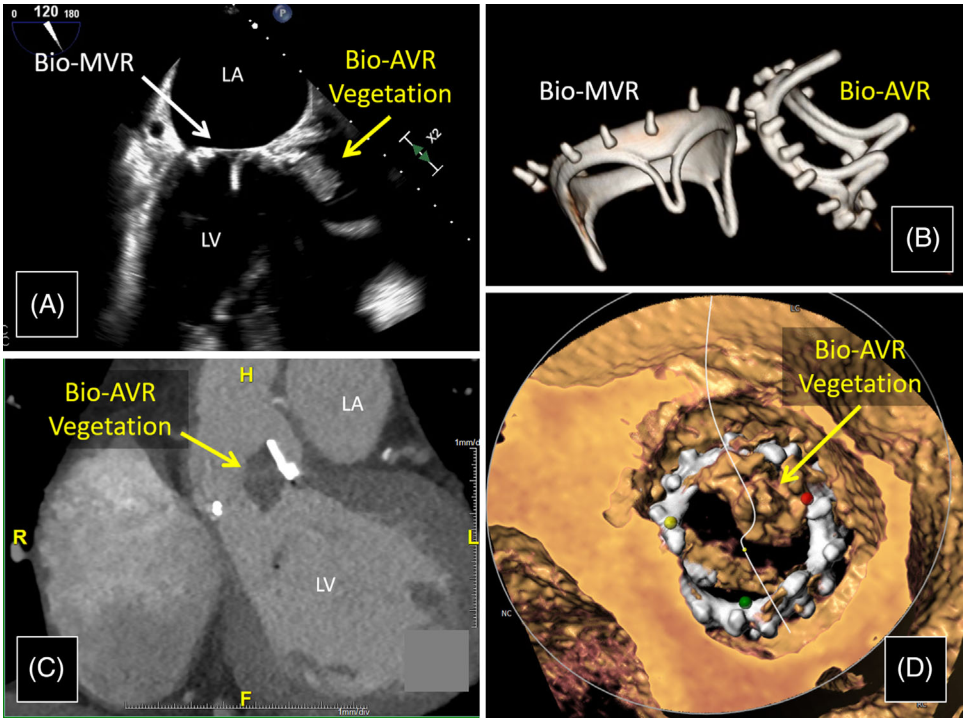
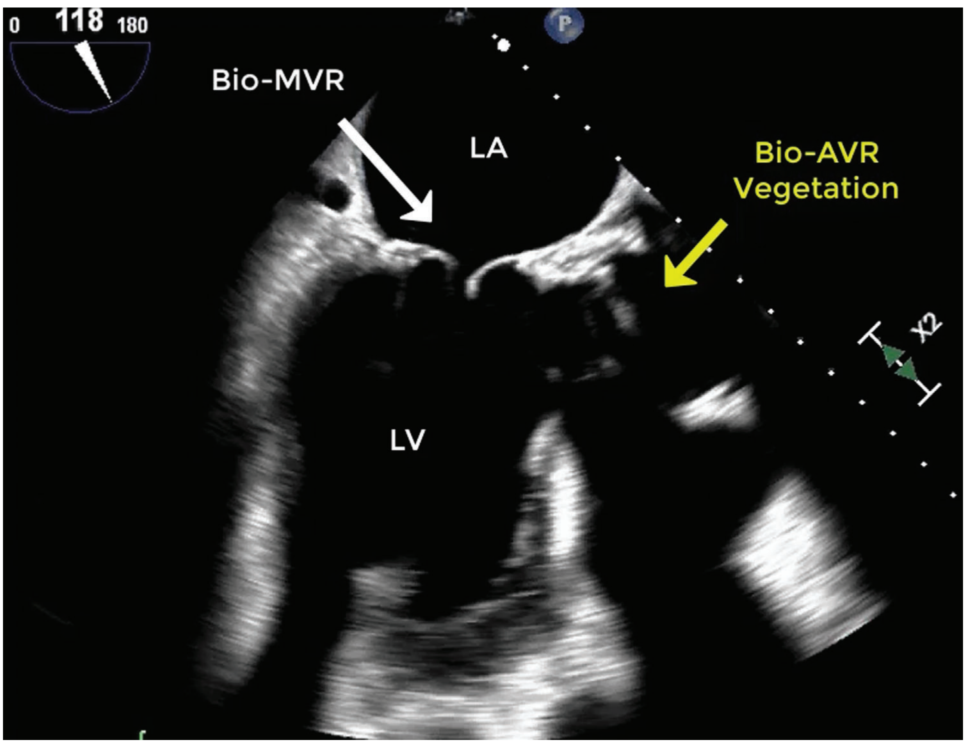



**FIGURE 6** Case 2 – AACEK relapse with infected aortic bioprosthesis was demonstrated on 2D TEE (Panel A). The two valves (Panel B) and the aortic bioprosthetic leaflet vegetations were demonstrated by 2D CT (Panel C) and 3D CT (Panel D). Composite Video 7 corresponds to this Figure. bio-AVR, bioprosthetic aortic valve prosthesis; bio-MVR, bioprosthetic mitral prosthesis; LA, left atrium; LV, left ventricle




**VIDEO 7** Case 2 – Composite 3-clip video of AACEK relapse with infected bioprosthetic aortic valve demonstrated on 2D TEE. The two valves and the bioprosthetic aortic leaflet vegetations are demonstrated by 2D CT and 3D CT. Bio-AVR, bioprosthetic aortic valve; bio-MVR, bioprosthetic mitral valve; LA, left atrium; LV, left ventricle.

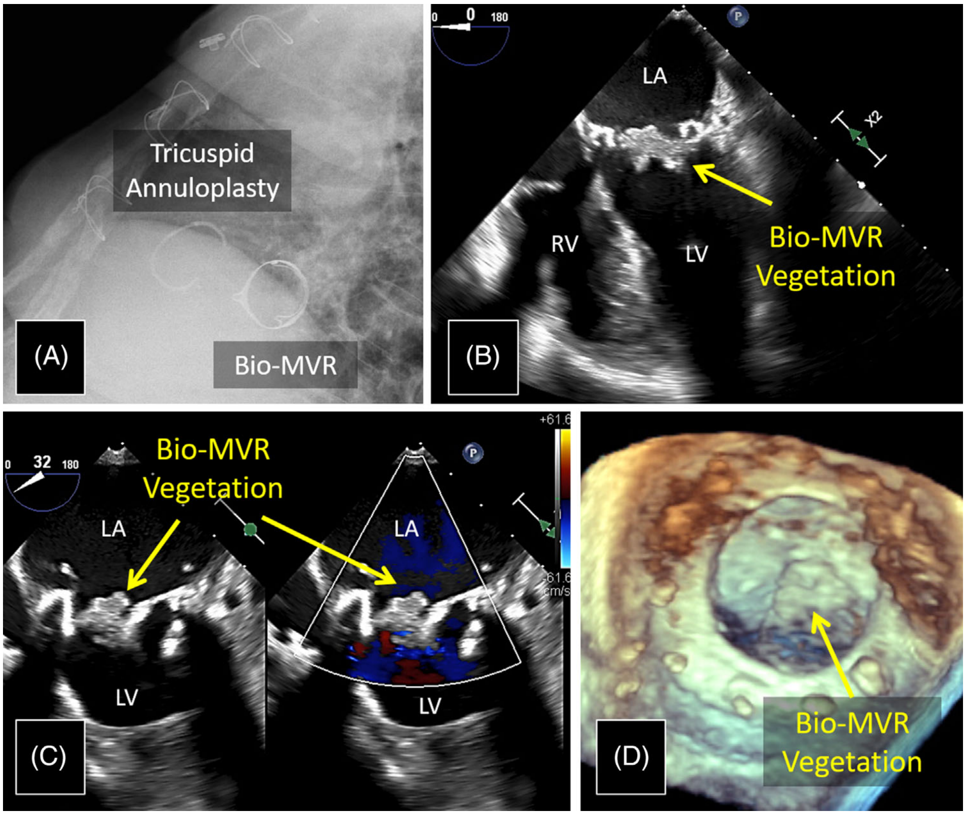
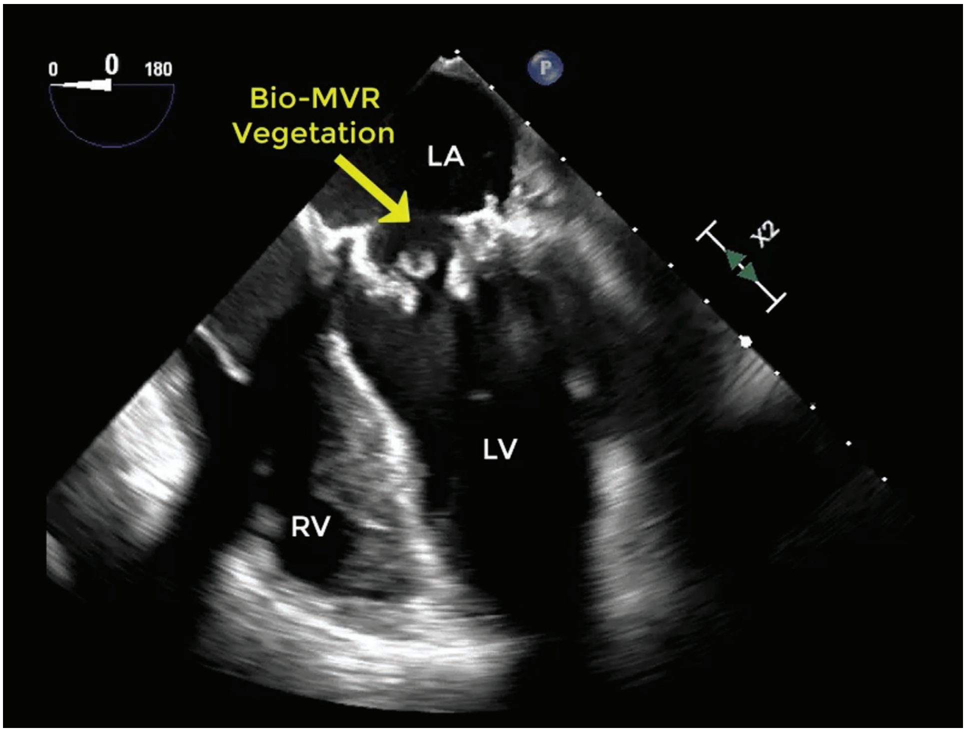



**FIGURE 7** Case 3 – AACEK endocarditis occurred in the setting of prior bioprosthetic MVR and tricuspid annuloplasty (Panel A). Extensive bioprosthetic MV leaflet vegetation was visualized by 2D TEE (Panels B and C) and 3D TEE from the LA perspective (Panel D). Composite Video 8 corresponds to this Figure. Bio-MVR, bioprosthetic mitral prothesis




**VIDEO 8** Case 3 – Composite 3-clip video of AACEK endocarditis occurred in the setting of prior bioprosthetic MVR and tricuspid annuloplasty. Extensive bioprosthetic mitral leaflet vegetations are visualized by 2D and 3D TEE from the LA perspective.

the complexity of the resection and reconstruction of the abscessed tissue (including implantation of two valve prostheses) – would certainly be expected to carry a much higher risk of recurrence, even with longterm (perhaps chronic) antibiotic treatment. Additionally, the source of AACEK infection in this patient, as in Case 3, was thought to be severe periodontal disease, which was likely difficult to eradicate completely despite dental extraction. In Case 1, conversely, the source of infection was not identified.

In conclusion, AACEK (formerly HACEK) organisms are a rare cause of infective endocarditis on both native and prosthetic valves – usually characterized by an insidious clinical course with large vegetations at presentation. Transesophageal echocardiography plays a crucial role in the diagnosis and may help to elucidate the extent of this life-threatening infection. Surgical intervention, in addition to appropriate antibiotic therapy, may be required to facilitate recovery in some patients.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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