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# Journal Pre-proof

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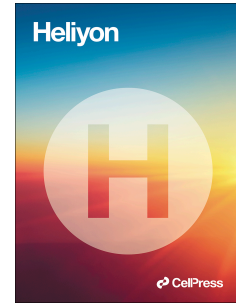
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A “Fishy” Situation, Rare Pathogen and Presentation in Prosthetic Valve Infective Endocarditis

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### Abstract

1 *Lactococcus garviae* (*L. garviae*) is a gram-positive coccus belonging to the Streptococcaceae  
2 family. While primarily a pathogen in fish farms causing hemorrhagic sepsis, it can act as a rare  
3 opportunistic pathogen in humans. A 2021 case report by Bravo *et al.* documented less than 30  
4 cases of infective endocarditis caused by *L. garviae* worldwide at that time.<sup>1</sup> This case report  
5 describes the 27<sup>th</sup> documented case globally and 7<sup>th</sup> documented case in the USA of *L. garviae*  
6 causing infective endocarditis of a prosthetic valve.<sup>1</sup>

7 *L. garviae* is found in unpasteurized dairy products, raw fish, and meat (pork, beef, and poultry),  
8 but the route of human transmission remains unclear.<sup>3</sup> It seems to have a predilection for  
9 individuals with prosthetic valves, immunocompromised states, prior gastrointestinal surgery,  
10 gastrointestinal disorders (colon polyps and diverticulosis), and the use of acid-reducing  
11 medications.<sup>1-3</sup> Infective endocarditis is the most common systemic disease caused by *L. garviae*  
12 <sup>1-4</sup>

13 This report details the case of a 75-year-old male, with multiple comorbidities and risk factors for  
14 *L. garviae* infection who was admitted for “symptomatic anemia”. High clinical suspicion,  
15 coupled with an inadequate hemoglobin response to transfusion, a normal anemia workup, and  
16 blood cultures positive for *L. garviae*, promoted a transesophageal echocardiogram (TEE).  
17 However, the results were negative. Consequently, an <sup>18</sup>F-fluorodeoxyglucose positron emission  
18 tomography/computed tomography scan (<sup>18</sup>FDG PET/CT) was performed. The scan revealed  
19 increased uptake in the aortic valve replacement consistent with prosthetic valve endocarditis in  
20 the setting of *Lactococcus garviae* bacteremia.

**Keywords:** *Lactococcus garviae*, endocarditis, bacteremia, symptomatic anemia, gastrointestinal disease, gastrointestinal disorders, radiology, cardiology, prosthetic valve

21 A 75-year-old white male with a complex medical history presented to the emergency department  
22 with general weakness, fatigue, and dizziness. His past medical history included heart failure with  
23 a preserved ejection fraction, stroke, essential hypertension, atrial fibrillation (on Warfarin),  
24 coronary artery disease, non-rheumatic aortic stenosis requiring transcatheter aortic valve  
25 replacement (TAVR) 8 months prior, insulin-dependent diabetes, gastroesophageal reflux disease,  
26 diverticulosis, chronic back pain, morbid obesity status post gastric bypass, severe peripheral  
27 arterial disease, and ruptured abdominal aortic aneurysm (previously underwent aortobifemoral-  
28 popliteal graft).

29 On arrival, he was hemodynamically stable and afebrile. Workup revealed significant anemia  
30 (hemoglobin [[Hgb] 7.2g/dL normal range 13.2–16.6 g/dL) and a subtherapeutic prothrombin-  
31 international normalized ratio (PT/INR) of 1.6. He was admitted for further evaluation of his  
32 symptomatic anemia.

33 According to the initial evaluation, the patient reported fatigue, general weakness, and intermittent  
34 dizziness that had progressed over 4 weeks, affecting his daily activities. He denied bleeding but  
35 admitted to holding his Warfarin due to a supratherapeutic PT/INR of 6.2 a week prior. He  
36 described the dizziness as fleeting, non-positional, with no clear aggravating or alleviating factors.  
37 He denied other symptoms.

38 Due to his cardiac history and low Hgb, two units of packed red blood cells were ordered for  
39 transfusion. Notably, his baseline Hgb was typically close to 12g/dL. Additionally, admission  
40 laboratory tests included fecal occult blood testing, a complete anemia panel (including serum iron  
41 studies), inflammatory markers, thyroid levels, liver function tests, and vitamin B-12, and folate  
42 levels.

43 On the day following admission, vitals were as follows: blood pressure was 128/45 mmHg, heart  
44 rate 71 beats per minute, oral temperature 99.3°F, respiratory rate 17 breaths per minute, and  
45 oxygen saturation 97%. Weight 195lb (88.5kg) and body mass index was 31.47kg/m<sup>2</sup>.

46 The patient appeared pleasant, cooperative, pale, alert, and oriented. He was hemodynamically  
47 stable, with no signs of acute distress. A systolic ejection murmur was noted on the right sternal  
48 border. Lungs clear to auscultation. The abdomen was obese soft non-tender, non-tender, and non-  
49 distended. Splinter hemorrhages were observed on both right and left index fingers. The patient  
50 had intact neurovascular function with no evidence of infection or ischemia. Examination findings  
51 did not suggest osteomyelitis, epidural abscess, discitis, cauda equina, or conus medullaris  
52 syndrome.

53 A review of the patient's labs revealed normocytic anemia with Hgb 7.6 g/dL despite a transfusion  
54 of two units (previous Hgb 7.2 g/dL, baseline 11.6 g/dL). Platelets decreased slightly from 210  
55 g/dL to 186 g/dL (normal range 150-400 x10<sup>9</sup>/L). Iron studies and the remainder of the anemia  
56 workup were normal except for elevated lactic dehydrogenase (LDH) at 449 U/L (normal  
57 range 135-225 U/L for males), erythrocyte sedimentation rate (ESR) 36 mm/hr (normal range  
58 males >50 years is ≤20 mm/hr) and C-reactive protein (CRP) at 8.7 mg/dL (normal range < 3  
59 mg/dL). Notably, the PT/INR remained subtherapeutic at 1.6 (previously 6.2 a week before  
60 admission). Other labs were unremarkable.

61 The elevated LDH, ESR and CRP despite normal iron studies and no evidence of bleeding,  
62 prompted further discussion with the patient regarding the onset of other potential symptoms.

63 These lab values are elevated in patients with sepsis.<sup>1,7</sup>

64 Following this discussion, the patient revealed new atraumatic, asymmetric polyarthralgia, and an  
65 exacerbation of his chronic back pain unresponsive to his usual medication. He also admitted  
66 experiencing anorexia, unintentional weight loss of 7 lbs, nocturnal fevers, and night sweats for 7  
67 weeks, longer than the previously mentioned 4 weeks. He initially dismissed these symptoms as  
68 irrelevant.

69 Considering this new information, physical examination findings, the combination of symptoms  
70 above and below the diaphragm, and the abnormal laboratory values, a high clinical suspicion  
71 for infective endocarditis arose particularly given his recent TAVR 8 months prior. Blood cultures  
72 and a transthoracic echocardiogram (TTE) were ordered for further evaluation. Antibiotics were  
73 not yet initiated. While bacteremia was suspected, the patient did not meet sepsis or systemic  
74 inflammatory response criteria at that time. The team opted to monitor for potential fever.

75  
76 Overnight, the patient developed a fever with a maximum temperature of 101°F (38.3°C).  
77 Following the sepsis protocol, he underwent blood cultures from multiple sites (pan cultures) and  
78 was started on intravenous ceftriaxone 2 g every 24 hours. The following morning, preliminary  
79 results from all four blood cultures showed gram-positive cocci in pairs.

80 More than 72 hours after collection, final blood culture results identified *Lactococcus garviae*, an  
81 opportunistic human pathogen. Susceptibility testing revealed sensitivity to ceftriaxone but  
82 resistance to clindamycin.

83 Upon receiving preliminary blood culture results, the cardiology and infectious disease  
84 departments were consulted, and a transesophageal Ultrasound (TEE) was ordered to evaluate for  
85 potential infective endocarditis.



86 Later that afternoon during rounds, the patient again reported experiencing his previous dizziness  
87 while lying in bed. The team initially questioned whether this symptom was related to the infection.  
88 However, given the reoccurrence of this non-peripheral symptoms in the context of *L. garviae*  
89 bacteremia and recent TAVR procedure, concerns for infective endocarditis and possible septic  
90 emboli as a cause of the dizziness heightened. To investigate further, a brain computed tomography  
91 (CT) scan without contrast was performed to rule out septic emboli.

92  
93 TTE and TEE revealed normal right and left ventricular function with an ejection fraction of 65%.  
94 There was mild thickening of the mitral valve with mild regurgitation (graded +1). Mild  
95 regurgitation (graded +1) of the pulmonic valve a normal tricuspid valve, and an aortic valve  
96 replaced with an Edwards S3 prosthetic valve (#26) during TAVR. While aortic valve leaflets  
97 appeared thin with a normal opening, there was no evidence of prosthetic valve stenosis,  
98 vegetation, or abscess. Additionally, no wall motion abnormalities were observed.

99  
100 A brain CT scan revealed new areas of hypoattenuation and focal sulcal effacement in the  
101 inferolateral aspect of the right frontal lobe measuring 3.5 cm x 4.2 cm. These findings are  
102 consistent with a subacute infarct. Furthermore, multiple punctate foci of hyperattenuation within  
103 the lower part of the subacute infarct are compatible with petechial hemorrhages.

104  
105 Despite negative TTE and TEE findings for vegetation, the patient now met five minor Duke  
106 criteria for infective endocarditis. Additionally, the CT scan showed evidence of multiple septic  
107 petechial hemorrhages and an infarct in the setting of *L. garviae* bacteremia, raising high suspicion  
108 for infective endocarditis.

109 To investigate further, an  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography/ CT  
110 (PET/CT) scan was performed. The results revealed increased FDG activity in the aortic valve  
111 replacement activity exceeding both the reference activity in the left ventricle and the liver. This  
112 pattern as shown in Figure 1 from the patient's PET/CT scan is consistent with a prosthetic valve  
113 inflammatory process most likely due to prosthetic valve endocarditis. Notably, this activity was  
114 intense on non-attenuated and corrected images confirming its validity and ruling out artifacts. <sup>11</sup>

115  
116 Due to the patient's high surgical risk and in the absence of valvular abscess or abnormal valve  
117 function on cardiac imaging, the team opted for conservative medical management. The  
118 recommended infectious disease regimen of intravenous IV ceftriaxone 2g every 12 hours was  
119 administered over 6 weeks. Blood cultures repeated after 24 hours of afebrile therapy and initiation  
120 of ceftriaxone were negative, indicating a good initial response to treatment. Following the  
121 completion of ceftriaxone therapy, the patient will transition to a maintenance regimen of cefdinir  
122 300mg orally twice a day.

123 The patient was initially discharged to a skilled nursing facility to receive intravenous antibiotics.  
124 During post treatment follow up, he reported complete resolution of all symptoms, including his  
125 dizziness, back pain and joint pain. He regained his functional capacity and can perform his regular  
126 activities without limitations. Notably blood cultures remained negative throughout treatment,  
127 both after the initial 6-week course of ceftriaxone monotherapy and the suppressive therapy with  
128 cefdinir.

129 *L. garviae* is an uncommon but increasingly prevalent human pathogen. While the first case of  
130 infective endocarditis caused by *L. garviae* was reported in 1991, its presence in humans appears  
131 to be rising worldwide.<sup>2</sup> This opportunistic microbe can cause various systemic diseases, including

132 osteomyelitis, peritonitis, meningitis, and infective endocarditis. Notably, *L. garviae* is a catalase  
133 negative pathogen which induces alpha hemolysis and is known well to the aquatic farming  
134 industry for causing hemorrhagic sepsis in saltwater fish.<sup>1</sup> This case exemplifies this risk as the  
135 patient with *L. garviae* bacteremia developed multiple septic petechial emboli identified on a brain  
136 CT scan.

137 Fewer than 30 documented cases of *L. garviae* induced infective endocarditis have been reported  
138 globally. Due to its similarities to *Enterococcus* and its prior classification within the streptococcus  
139 genus, the underdiagnosis of *L. garviae* as a human pathogen is suspected. This opportunistic  
140 bacterium appears to have a predilection for immunocompromised individuals, particularly those  
141 with prosthetic valves, a history of gastric bypass surgery, or those taking acid-reducing  
142 medications (which may elevate gastrointestinal (GI) tract pH and facilitate bacterial growth).  
143 Additionally, *L. garviae* has been isolated from patients with various cardiovascular diseases who  
144 consume raw fish, meat, or unpasteurized dairy.<sup>1-5</sup>

145  
146 The exact source of the *L. garviae* infection remains unclear. While undercooked shrimp has been  
147 implicated in some cases, the patient frequently consumed it before the before symptom onset and  
148 even several months after his TAVR procedure. Further investigation revealed he had undergone  
149 a dental cleaning around the same times as his symptoms, receiving clindamycin prophylaxis. It is  
150 possible that the combination of these factors along with his history of gastroesophageal reflux  
151 disease, bariatric surgery, diverticulosis, and multiple cardiovascular conditions with prior  
152 surgeries (particularly his aortic valve replacement), created a suitable environment for the  
153 pathogen to establish itself.

154

155 Another potential contributing factor is the patients chronic use of acid reducing medications.  
156 Studies suggest, these medications may weaken the natural barrier in the gut, promoting bacterial  
157 growth.<sup>16</sup> Given his significant GI medical history, outpatient follow up with a gastroenterologist  
158 for endoscopy and colonoscopy was recommended, along with other evaluations deemed  
159 necessary. While an association between *L. garviae* and various GI disorders exists, the rarity of  
160 this organism causing severe human disease makes it unclear if a link to GI carcinoma exists.<sup>16</sup>

161

162 Unlike most reported cases of *L. garviae* prosthetic valve endocarditis, this patient did not present  
163 with acute or subacute fever or altered mental state. While initially evaluated for symptomatic  
164 anemia, his presentation shifted to a concern for infective endocarditis due to multiple vague  
165 constitutional symptoms above and below the diaphragm reported over 7 weeks and months  
166 following his TAVR procedure. Additionally, his physical examination did not correlate well with  
167 these symptoms. Notably, his hemoglobin level remained unchanged despite transfusions. The  
168 cause of the anemia remained unclear, and his renal function was normal. He developed a fever  
169 his second night in hospital.

170

171 Based on these concerns, blood cultures, TTE, additional labs ordered, and cardiology and  
172 infectious disease consultations were performed. Both TTE and subsequent TEE yielded negative  
173 results. However, final blood cultures ultimately identified *L. garviae*.

174 Furthermore, the patient's dizziness in the absence of peripheral symptoms, mildly elevated LDH  
175 and inflammatory markers coupled with positive cultures, maintained infective endocarditis as a  
176 top diagnosis. A brain CT brain was performed to evaluate for possible septic emboli and infarct,  
177 fulfilling the five minor Duke criteria for infective endocarditis: splinter hemorrhages, septic

178 emboli with infarct, fever, a predisposing heart condition and positive blood cultures (although *L.*  
179 *garviae* is not classified as major HAECK criteria microbe).

180 Given these findings, the treatment team ordered an <sup>18</sup>F-FDG PET/CT scan. This scan revealed  
181 increased radiotracer uptake in the aortic valve replacement, consistent with prosthetic valve  
182 endocarditis.

183 Traditionally, TTE followed by TEE is the standard diagnostic imaging approach for infective  
184 endocarditis. However, for patients with prosthetic valves and other intracardiac devices the  
185 effectiveness of ultrasound and modified Duke criteria may be limited.<sup>7</sup> A prospective study by  
186 Pizzi *et al.* suggests that PET CT and PET CT angiography (PET/CTA) offer greater sensitivity  
187 and specificity in this patient population.<sup>2,6,7</sup> This case supports these findings and highlights the  
188 potential limitations of echocardiography in patients with cardiac devices where device artifacts  
189 can obscure vegetations. As suggested by previous authors utilizing PET/CT and PET CTA can  
190 offer greater sensitivity as demonstrated in this case.<sup>2,6,7</sup>

191 There is currently no standardized diagnostic, or treatment guidelines for *L. garviae* infective  
192 endocarditis. However, due to its similarities with streptococcal infections, monotherapy options  
193 include ceftriaxone, vancomycin, amoxicillin, and ampicillin. Dual therapy with gentamycin is  
194 also used. Notably, this patient's *L. garviae* strain exhibited resistance to penicillin and  
195 clindamycin.<sup>1-3,7-10</sup>

196 Ceftriaxone was chosen for this patient due to its favorable side effect profile, ease of  
197 administration, and good tolerability. The patient responded well to treatment and transitioned to  
198 lifelong maintenance therapy with cefdinir 300mg orally twice daily. Close monitoring by  
199 multidisciplinary team is ongoing. Suppressive maintenance therapy was selected for this patient

200 due to high risk of recurrence. This risk stems from his aforementioned risk factors and his  
201 ineligibility for surgical intervention.

202 Prosthetic valve replacements are a risk factor for infective endocarditis, accounting for  
203 approximately 20% of diagnosed cases and affecting 6% of patients who undergo the procedure.

204 <sup>7,8</sup> *L. garviae* endocarditis typically presents sub-acutely and mortality is comparable to  
205 streptococcal infective endocarditis (approximately 16-20%)<sup>9</sup>

206 Therefore, early recognition of the constitutional symptoms in high-risk patients, is crucial. When  
207 Clinical suspicion is high and ultrasound is inconclusive, <sup>18</sup>F-FDG PET/CT can be a valuable tool  
208 to aid in the diagnosis of infective endocarditis. Early identification, diagnosis, and treatment can  
209 significantly improve patient outcomes.<sup>6-11</sup>

210

#### **Conflict of Interest:**

The authors declare no known conflicts of interest or personal relationships that could appear to influence this paper.

#### **Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### **Ethical Statement**

We hereby confirm that we have read and complied with the policy on ethical conduct.

All participants/patients (or their proxies/legal guardians) provided informed consent for the publication of their anonymized case details and images.

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#### **Data Availability**

Has data associated with your study been deposited into a publicly available repository?

No. All data pertinent to the case is presented in this publication with verbal and written patient consent.

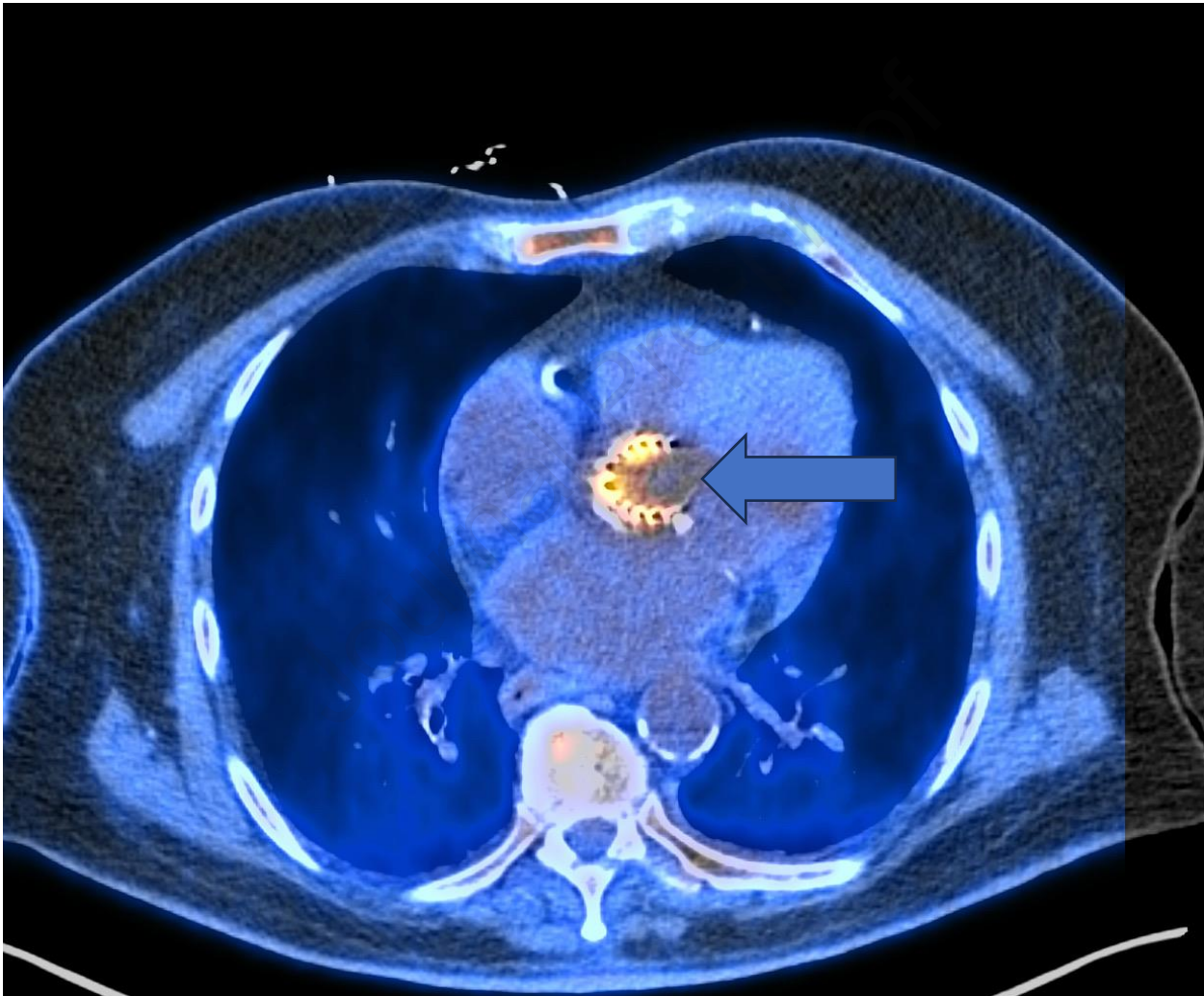
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**Figure 1:**  $^{18}\text{F}$ -FDG PET/CT axial fused image from the patient below depicts the uptake of the  $^{18}\text{F}$  FDG radiotracer isotope as shown by the blue arrow in the aortic valve replacement, consistent with prosthetic valve endocarditis. This intense activity shown in yellow below was present on nonattenuation corrected images and therefore, deemed not to be a valve artifact.



- Mortality caused by *L. garviae* is proportionate to streptococcus
- *Lactococcus garviae* is a rare human pathogen
- Early recognition improves overall morbidity/mortality in infective endocarditis
- <sup>18</sup>F-FDG PET/CT(A) aids diagnosis with prosthetic valves and negative TTE/TEE
- Ultrasound and modified Duke Criterion are limited with prosthetic valves

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