

CASE REPORT

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Implantable cardioverter-defibrillator infection by *Streptococcus intermedius* identified by next-generation sequencing

Chris Parsons, Stephen Vickery, Aaron Timins, Ivan Gowe, Adam Parsons, Ashley Reyes

ABSTRACT

Introduction: Culture-negative endocarditis refers to inflammation of endocardial structures with no etiology identified using standard diagnostic methodology. This entity continues to pose a challenge for clinicians. Definitive approaches for identifying infectious etiologies of culture-negative endocarditis are not feasible in clinical practice, including cultures or molecular testing performed directly on valvular tissue. Serologic assays for key pathogens and standard polymerase chain reaction (PCR) methodology applied to peripheral blood have increased diagnostic acumen in these cases. Yet, even with application of these methods, etiologies often remains elusive. Next-generation sequencing (NGS) and categorization of DNA using a large library of DNA sequences can be performed following extraction of microbial cell-free DNA (mcfDNA) from peripheral blood. Through advances in this technology and clinical application, these methods are now available through commercial laboratories utilizing high-throughput systems, and NGS of mcfDNA now offers an important

advance in the diagnostic evaluation for culture-negative endocarditis.

Case Report: A 49-year-old male with an indwelling implantable cardioverter-defibrillator (ICD) developed progressive weight loss, chills, diaphoresis, and hypotension. Echocardiography revealed an ICD lead vegetation. Standard blood cultures revealed no growth, but NGS applied to mcfDNA isolated from peripheral blood identified *Streptococcus intermedius* as the etiologic agent. The patient made a full recovery with antibiotics targeting this organism.

Conclusion: Next-generation sequencing led to successful targeted antibiotic therapy, avoidance of unnecessary surgical procedures, and a full recovery for our patient with culture-negative endocarditis involving his ICD and offers an important diagnostic advance for patients with indwelling devices.

Keywords: Bacteremia, Culture-negative, Endocarditis, Next-generation sequencing

How to cite this article

Parsons C, Vickery S, Timins A, Gowe I, Parsons A, Reyes A. Implantable cardioverter-defibrillator infection by *Streptococcus intermedius* identified by next-generation sequencing. J Case Rep Images Infect Dis 2025;8(1):1–7.

Article ID: 100016Z16CP2025

doi: 10.5348/100016Z16CP2025CR

INTRODUCTION

Culture-negative endocarditis involves inflammation of endocardial structures with no etiology identified using standard diagnostic testing. This entity continues to pose a challenge for clinicians and patients, often resulting in

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Received: 05 April 2025
Accepted: 15 May 2025
Published: 12 June 2025

the use of extended broad-spectrum antibiotic therapy which incurs greater risk of adverse events and inactive therapy for some pathogens. We present an illustrative case of bacteremia and ICD infection, ultimately requiring NGS using mcfDNA to identify the pathogen and which led to effective targeted therapy.

CASE REPORT

A 49-year-old male suffered a cardiac arrest and anoxic brain injury approximately seven years prior, resulting in cardiomyopathy. Anoxic injury resulted in neurologic deficits including Parkinsonism, dystonia, and vocal cord paralysis with residual dysphagia and dysarthria. Despite these challenges, the patient remained relatively independent over the years, including driving and other activities, and with no need for supplemental oxygen. A dual-chamber ICD was eventually placed about two years prior due to ongoing cardiac dysfunction.

Over a 1-year period prior to admission, he suffered unintentional weight loss of about 40 pounds. This was attributed to progression of his neurologic deficits and his decline of percutaneous endoscopic gastrostomy (PEG) tube placement for supplemental nutritional support. About two months prior to admission, a two-dimensional echocardiogram (2D echo) revealed an ejection fraction of 10–15% with mild mitral and tricuspid regurgitation. About six weeks prior to admission, he had several teeth extracted with no complications or requirement for antibiotic treatment. Then about three weeks prior to admission, he and his wife developed nasal congestion and rhinorrhea. His wife's symptoms improved, but the patient's overall health declined, and he required a suction device to clear secretions from his oral cavity. He monitored his vital signs at home and several days prior to admission, his blood pressure was as low as 60/40 mmHg with accompanying tachycardia. On the day of admission, his ICD discharged three times, and he developed chills and significant diaphoresis. He was hypotensive on arrival, and electrocardiogram (ECG) revealed ventricular tachycardia and fibrillation, prompting initiation of intravenous (IV) amiodarone. He had a temperature of 38.3°C. Initial physical exam revealed bilateral rhonchi on auscultation of his posterior chest wall, a well-appearing ICD site over his anterior chest, onychomycosis of his left fifth toe and right great toe, and chronic-appearing, patchy, darkened skin over the dorsum of both feet symmetrically, consistent with chronic venous stasis and edema in these areas. There were no overt areas of drainage at any location on his feet. He had no audible heart murmur. Initial laboratory assessment revealed a peripheral white blood cell count of 28,700 cells/mm³ (2% bands, 22% monocytes, and 76% neutrophils). Other labs revealed reduced hemoglobin (13.8 g/dL), elevated platelet count (552,000 × 10⁹/L), reduced serum sodium (132 mmol/L) and potassium (3.2 mmol/L), elevated serum

creatinine (1.79 mg/dL), reduced serum albumin (3.0 g/dL), elevated total protein (8.6 g/dL), mild elevation of procalcitonin (1.1 ng/mL), mild elevation of serum lactate (2.1 mmol/L), and normal blood sugar, aspartate and alanine aminotransferase levels. Nasopharyngeal swabs were performed with negative results for COVID-19 and influenza by PCR, and a nares PCR screen for methicillin-resistant *Staphylococcus aureus* was negative. Quantitative urinalysis revealed only 6 leukocytes. Initial high-sensitivity troponin levels peaked at 1591 ng/L. Electrocardiogram following initiation of amiodarone revealed sinus tachycardia with normal intervals, as well as mild ST segment depression and T wave inversion in lateral leads, suggestive of ischemia. Chest radiograph revealed bilateral consolidative opacities in the lower lobes.

Two sets of blood cultures were collected and given initial concern for community-acquired pneumonia as the cause of non-ST segment elevation myocardial infarction (NSTEMI), he was initiated on IV cefepime and doxycycline (avoiding azithromycin and fluoroquinolones with possible drug interactions with amiodarone). Later, on the day of admission following single doses of cefepime and doxycycline, two additional sets of peripheral blood cultures were collected. Repeat 2D echo revealed an ejection fraction of 15%, no valvular vegetations, trivial left pleural and pericardial effusions, and possible vegetation adjacent to his intraventricular ICD wire. In response, his IV antibiotics were adjusted to include vancomycin, ceftriaxone, and doxycycline. Norepinephrine was initiated for blood pressure support, and he was transferred to the intensive care unit (ICU).

On Day 2, his temperature remained below 38°C. There was no meaningful change in his white blood cell (WBC) count (27,700 cells/mm³), troponin improved (to 762 ng/L), and he denied chest pain. His blood cultures revealed no growth. ICD removal was discussed although his blood pressure improved quickly, and norepinephrine was withdrawn. Transesophageal echocardiogram (TEE) revealed a left ventricular ejection fraction of 15–20%, mild mitral valve regurgitation with no valvular vegetations, and a small pericardial effusion. Confirming findings on his 2D echo, a hypermobile echo density was noted on the ventricular lead of his ICD (Figure 1). The resolution of his fever and hypotension, coupled with the lack of echocardiographic evidence of valvular compromise or worsening cardiac function, was reassuring. Nevertheless, he was transferred to a tertiary center for consideration of ICD extraction.

All four sets of blood cultures collected on admission revealed no growth after standard 5-day incubation. He was maintained on IV vancomycin, ceftriaxone, and doxycycline and remained hemodynamic stable. Given negative results for standard blood cultures and echocardiogram findings, additional peripheral blood was collected on Day 2 and sent to a reference lab for extraction of mcfDNA and NGS. Follow-up labs on Day 4 revealed improved WBC (18,700 cells/mm³), as well

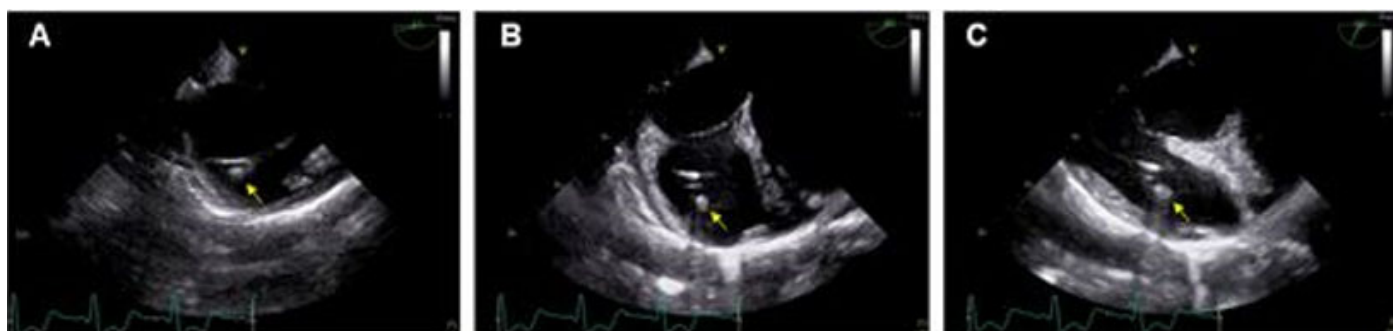


Figure 1: TEE identifies ICD lead wire vegetation. Transesophageal echocardiography was performed with mid-esophageal probe views 15° (panel A), 50° (panel B), and 60° (panel C) in the horizontal plane (probe position noted in upper right portion of each panel). A large mobile vegetation was noted on the ICD lead positioned within the right ventricle (yellow arrows), and within each angle utilized in probe views, underscoring its size and clinical relevance.

as elevated inflammatory markers including C-reactive protein (CRP; 134 mg/L), and erythrocyte sedimentation rate (ESR; 71 mm/h). Two sets of routine peripheral blood cultures were collected on Day 4, ultimately revealing no growth. Other studies performed to identify infectious etiologies included urine antigen tests for *Streptococcus pneumoniae* and *Legionella*, and serologic assays for *Bartonella* and *Coxiella burnetii*, all of which were negative. Intravenous doxycycline was discontinued on Day 4. Interrogation of his ICD revealed discharges related to supraventricular tachycardia thought to be driven by his infection. The cardiothoracic surgery team discussed the risks of ICD removal unique to this patient (specifically, his neurologic dysfunction). They decided against removing his ICD or lead wires while awaiting additional evaluation. He had improved clinically with stable cardiac function and normalization of his heart rhythm with resolution of ICD discharges and ventricular tachycardia. Amiodarone was discontinued in favor of beta-blockers for longitudinal ventricular rate control.

On Day 9, the patient was discharged from the hospital to receive prolonged IV vancomycin and ceftriaxone therapy. Prior to discharge, additional peripheral blood was collected for a serologic immunoassay for *Brucella* species, with detection of IgM but not IgG antibodies. Therefore, following discharge, additional blood was collected and sent to a reference laboratory for confirmatory latex agglutination testing for *Brucella*. This result was negative with titer <1:80. In speaking at length with the patient and his family, he had not consumed raw or other unpasteurized dairy products. The patient's mother owned and cared for horses on a local farm, but the patient had no direct contact with these horses and to their knowledge, none of the horses had been ill or diagnosed with brucellosis. The patient denied more recent consumption of raw meat, homelessness, work in slaughterhouses or food handling service, ownership of pets, exposure to livestock/petting zoos, or military service. Therefore, the initial serologic test result was felt likely to represent a false positive IgM response as has been documented due to cross reactivity with various

Gram-negative rods and possibly other unidentified non-pathogenic bacteria [1].

Peripheral blood which had been collected on Day 2 of hospitalization (after several doses of IV antibiotic therapy) was processed for NGS at a reference laboratory [2]. In short, blood samples were collected in K2-EDTA tubes and shipped to the reference laboratory at 20°C. mcfDNA was isolated from plasma in the Karius Clinical Laboratory (an accredited laboratory certified by the College of American Pathologists, Redwood City, CA, USA). After mcfDNA was extracted and NGS performed, sequences were aligned to a curated database of approximately 1400 organisms. mcfDNA copies from organisms identified above a statistical threshold were reported and quantified in molecules per unit volume. This assay revealed a positive result with 151 DNA molecules/uL of *Streptococcus intermedius* (*S. intermedius*)—the only pathogen identified. With this result, vancomycin was stopped and IV ceftriaxone (2 g infusions every 24 hours) continued. He completed a 6-week duration of IV ceftriaxone, and follow-up laboratory assessment revealed

TEST REPORT		KARIUS	
KA-182448		Page 2 of 4	
KARIUS TEST REPORT Karius ID: KA-182448			
SPECIMEN TYPE: PLASMA			
SPECIMEN INFORMATION		Collected May-01-2023	Received May-03-2023
PATIENT INFORMATION		First Name [REDACTED]	Specimen ID 23NUL121X00231
INSTITUTION INFORMATION		Ordering Physician JOHN SCHULSH	Date of Birth [REDACTED]
TEST RESULTS		Address Greenview Memorial Hospital 751 Green Road Greenview BC 28005	
MICROORGANISM DETECTED		DNA MOLECULES PER MICROLITER (uL)	REFERENCE INTERVAL (uL/uL)
<i>Streptococcus intermedius</i> (<i>Streptococcus</i> <i>anginosus/milleri</i> group)		151	< 10
* Molecules Per Microliter = Number of DNA fragments present in one microliter of plasma ** Reference Interval = The 97.5th percentile of the 1000 specimens detected in PVT plasma from a cohort of 104 asymptomatic donors Results may differ from those obtained via our online access portal Karius and/or its affiliates do not warrant the accuracy of these results. Phone: (800) 452-7447 Email: info@karius.com Karius is a covered entity under HIPAA			
Printed by Vickary, Stephen, CPP [211548] at 5/7/2023 5:04 PM			

normalization of his peripheral white blood cell count (7100 cells/mm³), serum creatinine (0.97 mg/dL), ESR (8 mm/h), and CRP (0.47 mg/L). He returned to his prior functional status and regained 10 pounds. Follow-up with his cardiology team indicated a well-functioning ICD, and as of two months following hospital discharge, he had not required ICD replacement.

DISCUSSION

Culture-negative endocarditis remains a diagnostic challenge for clinicians. This may result from the use of empiric antibiotics which mask standard culture results, or infection with fastidious microorganisms or intracellular bacteria which do not grow optimally in routine culture media. In the absence of infection, other underlying conditions such as cancer or autoimmune diseases are associated with this condition [3]. Timely diagnosis of culture-negative endocarditis is crucial for preventing complications [4]. Our patient's presentation with progressive respiratory symptoms, chills, hypotension, and fever, coupled with vegetations noted on TEE, was consistent with ICD lead wire infection. His routine blood cultures were negative, but NGS sequencing revealed *S. intermedius*. After appropriate antibacterial therapy for this organism his symptoms resolved, and he made a full recovery.

S. intermedius is a component of normal oral, upper respiratory, and gastrointestinal microbiota [5]. This patient's transient bacteremia and lead wire infection were felt possibly related to his tooth extraction procedures performed without prophylaxis and about three weeks prior to onset of his illness [6]. We could not discount his gastrointestinal tract as a source given his long-standing dysphagia secondary to anoxic brain injury, though he had no signs or symptoms of a new gastrointestinal illness. Dermatologic sources of this organism are less common, but his extensive onychomycosis rendered this a possibility; there are cases of skin and soft tissue infections with *S. intermedius* as the sole pathogen or a component of a polymicrobial necrotizing infection [7, 8]. Given that a 2D echo performed about three weeks prior to onset of his illness had not revealed lead wire vegetations, it was conceivable that his illness developed only a few weeks before presentation. However, it remained unclear whether his significant weight loss over a longer timeframe may have been a manifestation of this infection, especially since he regained weight during treatment. His neurologic status and significant pre-existing dysphagia, as well as additional nutritional support provided during his hospitalization, were confounding features.

S. intermedius is a well-recognized cause of endocarditis [9, 10], and the majority of these isolates are susceptible to vancomycin and ceftriaxone [11]. The patient improved from both clinical and laboratory standpoints while receiving both agents during his hospitalization, followed by an additional 4–5 weeks

of ceftriaxone monotherapy. In addition to antibiotic therapy, the best outcomes for device infections are generally achieved with device and wire removal [12–14]. The duration of antibiotic therapy, and timing of device re-implantation, depend on the involvement of lead wires. If leads are involved, the general recommendation is wait at least two weeks after the device and wire(s) are removed prior to re-implantation [15, 16]. An alternative strategy involves device retention and six weeks of IV antibiotics [17, 18]. Published failure rates are higher with the latter approach, especially if a device had been placed more remotely [19–21]. Our patient was doing well at follow-up two months after hospital discharge, with plans for device retention pending additional longitudinal evaluation.

The Karius test detects degraded microbial cell-free DNA (mcfDNA) in plasma. mcfDNA is amplified and sequenced for microbial pathogens by matching it to a library of DNA sequences for > 1400 pathogens. One study validated this assay in a series of patients with definite or possible endocarditis using Duke criteria. Detection of mcfDNA exhibited similar sensitivity to routine blood cultures (about 87%) with good pathogen identification agreement. Moreover, levels of mcfDNA for specific pathogens remained detectable for 38 days from the date of antibiotic initiation and/or surgical source control. In contrast, blood cultures exhibited microbial growth over only 3–4 days after antibiotic initiation. Additionally, mcfDNA levels declined during therapy, further validating the utility of the assay as a diagnostic tool in these cases [22]. Whether the *S. intermedius* mcfDNA concentration in our case reflected a somewhat lower bacterial inoculum, with vegetations noted only on ICD lead wires but not valves, was not clear. Correlations between mcfDNA concentrations in peripheral blood and clinical presentations have not been established. Of note, Karius testing has successfully identified organisms associated with ICD lead wire infection [22] and has identified *S. intermedius* as the etiologic agent responsible for invasive infections [23]. Additionally, as in our case, results may lead to effective de-escalation of antibiotic therapy, vancomycin in particular [24]. The value of NGS technology for the evaluation of infective endocarditis was highlighted within recent guidelines, with positive results representing a “minor” Duke criterion [25].

CONCLUSION

To our knowledge, this is the first reported case of successful application of NGS (and specifically Karius testing) for identifying Streptococcal infection of ICD lead wires in the absence of heart valve involvement or growth of the organism in standard blood cultures. It also adds to the body of literature supporting the value of NGS in cases of culture-negative endocarditis for both etiologic diagnosis and appropriate antibiotic selection.

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Author Contributions

Chris Parsons – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy

or integrity of any part of the work are appropriately investigated and resolved

Stephen Vickery – Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Aaron Timins – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Adam Parsons – Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ashley Reyes – Acquisition of data, Drafting the work, Revising the work critically for important intellectual

content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

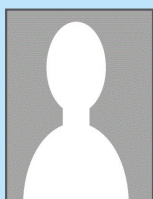
All relevant data are within the paper and its Supporting Information files.

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Article citation: Parsons C, Vickery S, Timins A, Gowe I, Parsons A, Reyes A. Implantable cardioverter-defibrillator infection by *Streptococcus intermedius* identified by next-generation sequencing. J Case Rep Images Infect Dis 2025;8(1):1–7.



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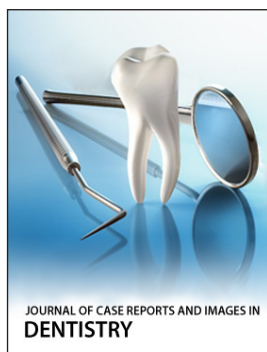
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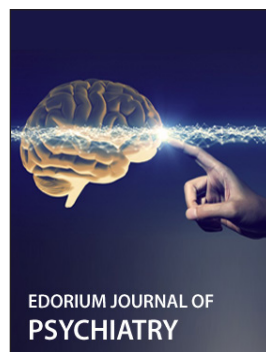
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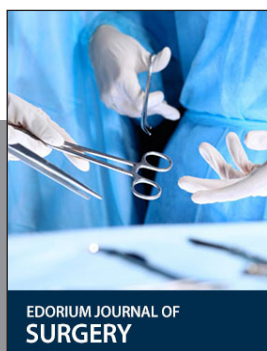
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