A Case Report of Culture-Negative Burkholderia Prosthetic Valve Endocarditis Identified by Metagenomic Next-Generation Sequencing (mNGS)

Lindsay N. Moy [1,*] and Alice Han [2]

[1] Department of Internal Medicine at Advocate Lutheran General Hospital (ALGH), 1775 Dempster Street, Park Ridge, IL 60068, USA
[2] Metro Infectious Disease Consultants
* Corresponding author: lindsaynmoy@gmail.com; Tel.: +1-(708)-955-2425

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Abstract: Burkholderia cepacia complex is a group of closely related opportunistic Gram-negative species that can be found in soil and water. Burkholderia cepacia complex is commonly associated with pulmonary infections in patients with cystic fibrosis, hospital-borne outbreaks related to contaminated medicines and devices, and, rarely, prosthetic valve endocarditis. The treatment of Burkholderia cepacia remains challenging because of the organism's intrinsic resistance to several antibiotics, and often requires combination therapy. Through this clinical vignette, we review an interesting case of culture-negative Burkholderia prosthetic valve endocarditis identified through metagenomic next-generation sequencing (mNGS) and the challenges associated with the diagnosis and selection of an appropriate treatment.

Keywords: endocarditis; culture-negative; prosthetic valve; Burkholderia cepacian; metagenomic next-generation sequencing; Karius

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Introduction

Infective endocarditis (IE) is defined as an infection of the endothelial layer of heart muscle. This condition leads to significant morbidity and mortality. In 2020, the incidence was estimated to be

between 3 and 9 per 100,000 people affected, with a mortality of up to 30% within one month of a diagnosis [1,2]. Over the years, there has been a notable increase in the incidence of healthcare-associated endocarditis due to advancements in medicine with implantable devices and heart valve replacements [2]. Other risk factors for IE include recent dental procedures, intravenous drug use, and immunosuppressed states, including poorly controlled diabetes, chronic renal disease requiring hemodialysis, chronic hepatic disease, congenital heart disease, and valvular disease [2,3]. Prosthetic valve endocarditis accounts for 7 to 25% of cases of infective endocarditis in most developed countries. Patients commonly present with fever, anorexia, night sweats, fatigue, and weight loss [2,3]. It is recommended that clinicians check three sets of blood cultures prior to starting treatment, as this allows for proper microbial identification in 90% of cases [2,3]. If a patient undergoes a valve replacement, culturing and a histopathologic study of the specimen can aid in finding the causative agent [3]. The most common pathogens responsible for IE are *Staphylococcus aureus*, *Streptococcus* spp., and *Enterococcus* spp. [1–3]. Other testing modalities for a diagnosis include serologic or polymerase chain reaction (PCR) testing [3]. The metagenomic next-generation sequencing (mNGS) of cell-free DNA has been shown to be a promising diagnostic tool [4]. The Karius test is an example of this, and is analyzed by a laboratory based in California. It works by extracting cell-free DNA from plasma, which is then sequenced and compared to control samples to discern which microbes are present. Approximately 10% of cases of infective endocarditis are culture-negative [3]. Culture-negative endocarditis typically occurs in cases where patients are treated with antimicrobials prior to diagnosis or with fastidious organisms [3]. Fastidious organisms include *Bartonella* spp., *Brucella* spp., *Coxiella burnetii,* HACEK bacteria (*Haemophilus aphrophilus*; *Actinobacillus actinomycetemcomitans*; *Cardiobacterium hominis*; *Eikenella corrodens*; and *Kingella kingae*), *Tropheryma whipplei*, and *Aspergillus* spp. [2,3]. Only five to seven percent of patients who have not received prior antibiotics and meet the strict criteria for IE will be culture-negative.

The diagnosis of IE is based off of the modified Duke criteria [1–3,5]. A transthoracic echocardiogram (TTE) is used to detect vegetations in patients with suspected IE [1–3]. A transesophageal echocardiogram (TEE) may be used to confirm the diagnosis when concern of IE remains [1–3].

Antimicrobial therapy is tailored to the causative organism, with the treatment duration generally ranging from two to six weeks depending on the causative organism and depending on if a native heart valve or a prosthetic heart valve is affected [1,2]. In instances of culture-negative endocarditis, treatment is typically at least six weeks [2]. In this report, we detail a unique and interesting case of culture-negative *Burkholderia cepacia* prosthetic valve endocarditis diagnosed by mNGS.

Case Report

A 56-year-old male presented to the hospital due to having a cough and fever for two weeks with a known positive COVID-19 home test result. He had been immunized with one dose of Janssen's Ad26.COV2.S vaccine nine months prior. In the emergency department, he was found to be hypoxic and required a six-liter nasal cannula. His past medical history was significant, having a bicuspid aortic valve and an ascending thoracic aortic aneurysm status post-bioprosthetic aortic valve replacement and aortic root replacement, both performed five years prior.

He was admitted to the hospital for the further management of COVID-19 pneumonia, and received standard therapy with 10 days of dexamethasone. Because his symptoms had started two weeks before admission, it was determined that he was likely outside the viral phase where remdesivir would have a significant benefit. His respiratory status continued to decline over the next few days, gradually requiring escalation to 60 liters of a 100% fraction of inspired oxygen (FiO2) via a high-flow nasal cannula. He received 800 mg of tocilizumab intravenously once. He was started on empiric ceftriaxone and doxycycline for possible superimposed bacterial pneumonia. The blood cultures collected upon admission were negative. The patient progressed and was transferred to the medical intensive care unit for inhaled nitric oxide therapy and continuous bilevel positive airway pressure

(BiPAP). His antibiotic coverage was broadened from ceftriaxone to cefepime. Doxycycline was stopped after the *Legionella* urine antigen test resulted in being negative. He developed worsening respiratory failure, requiring intubation, and renal failure, requiring continuous renal replacement therapy (CRRT). The antibiotics were broadened from cefepime to piperacillin–tazobactam after he had a gross episode of emesis during intubation. After a 10-day course of dexamethasone, the patient was started on a stress dose of steroids for septic shock. His course was complicated by high fevers, with a maximum temperature of 105.7 degrees Fahrenheit, and a leukocytosis as high as 90,100 cells/mcL. Hematology was consulted for the profound leukocytosis and ultimately determined that the patient had a reactive leukocytosis in response to the patient's infection combined with an underlying diagnosis of chronic lymphocytic leukemia (CLL). His condition worsened, requiring increasing vasopressor support. Another set of blood cultures were collected during this time and resulted in being negative. The antimicrobial treatment was broadened to meropenem, amphotericin B, daptomycin, and trimethoprim–sulfamethoxazole (TMP-SMX) (for *Pneumocystis jirovecii* pneumonia prophylaxis while on steroids). Daptomycin was switched to linezolid due to elevated creatinine kinase. The patient was noted to have gross bleeding from his orogastric tube and an ileus upon an abdominal X-ray. He developed ischemic changes to his bilateral feet related to increasing vasopressor requirements. A computed tomography (CT) scan of the chest, abdomen, and pelvis was unrevealing for any new sources of infection. Antibiotics were de-escalated to piperacillin–tazobactam, micafungin, and prophylactic TMP-SMX.

Over the next few days, the patient was noted to have new right-sided weakness and encephalopathy, despite being weaned off all sedatives. A CT scan of the head was negative for acute abnormalities. Osler nodes on his fingertips were noted on examination. Magnetic resonance imaging (MRI) of the brain revealed several punctate foci of acute infarction in the bilateral cerebral hemispheres and border zone hypoperfusion with areas of microbleeds, concerning for septic emboli. Blood cultures remained negative, but with this new suspicion for IE, another set was drawn. A TTE revealed a hazy, mobile, and echogenic density on his bioprosthetic valve. A subsequent TEE revealed a 29 mm St. Jude Medical porcine valve with a small mobile echodensity measuring 0.7 cm $\times$ 0.6 cm located on the aortic aspect of the aortic valve. Cardiothoracic surgery was consulted and recommended conservative management given the patient's unstable clinical status. The patient was transitioned to vancomycin and cefepime for culture-negative endocarditis, but continued to be febrile. A Karius microbial cell-free DNA sequencing (mNGS) test was ordered. The Karius test revealed *Burkholderia cepacia* complex, *Pseudomonas alcaligenes*, *Pseudomonas citronellosis*, *Staphylococcus epidermidis*, and *Lactobacillus rhamnosus*. Throughout his course, eight sets of blood cultures were collected in totality, and all resulted in being negative. The patient's antimicrobial regimen was modified to meropenem, levofloxacin, a treatment dose of TMP-SMX (to cover the *Burkholderia cepacia* complex), and intravenous vancomycin (to cover the *Staphylococcus epidermidis)*. He was weaned off vasopressor support but continued to spike fevers. Because of ongoing fevers, meropenem was switched to ceftazidime–avibactam. The patient was noted to have an immunoglobulin level of 124 mg/dL. He was replaced with 400 mg/kg of intravenous immune globulin once. The patient continued to clinically improve. The fevers resolved, his mental status improved, and he was successfully extubated. Unfortunately, shortly thereafter, he suffered from an acute gastrointestinal bleed with hemorrhagic shock. The patient's family opted to transition to comfort-focused care, and he expired.

Discussion

Case reports of *Burkholderia cepacia* complex prosthetic valve endocarditis have been published [5,6], but this is the first documented report of culture-negative *Burkholderia* prosthetic valve endocarditis diagnosed by mNGS. *Burkholderia cepacia* complex is a Gram-negative rod commonly associated with cystic fibrosis and chronic granulomatous disease [6–8]. Other risk factors for infection with this microorganism include immunosuppression, indwelling catheters, and the use of contaminated

medical products [8,9]. *Burkholderia cepacia* complex remains challenging to treat because of its intrinsic resistance to a vast array of antimicrobials; one study found that 55% of isolates were multidrug-resistant [10].

Our patient had several predisposing factors for IE, including a prosthetic heart valve and aortic root replacement, immunosuppression due to COVID-19 pneumonia, CLL, and renal disease requiring CRRT. He met one major (evidence of endocardial involvement) and three minor (predisposing heart condition, fever, and vascular phenomena) features of the modified Duke criteria. He had received broad-spectrum antimicrobials for sepsis, likely leading to negative blood cultures.

The mNGS Karius test was key to identifying the organisms responsible for disease in our patient. He was too critically unstable to undergo a valve replacement for both diagnostic and therapeutic reasons. The eight sets of blood cultures drawn throughout his hospital course remained negative. The Karius test proved to be highly valuable under these circumstances. One small prospective study, including 24 definite IE patients focusing on mNGS as compared to blood cultures in the diagnosis of IE, found that mNGS accurately identified causative organisms in all 20 of the culture-positive cases in addition to two of the four culture-negative cases [4]. The literature also promotes the use of mNGS as a rapid and simple way to identify pathogens, typically resulting within one day of receiving a single blood sample [11]. The timing of results can vary depending on institution and if a third party is involved for billing purposes. In our experience, the results of the Karius test took over 7 days. From a financial perspective, the Karius test may be favorable when other noninvasive tests have been nondiagnostic. In a study assessing the cost of using mNGS as an alternative to invasive procedures in the diagnosis of invasive fungal infections in immunocompromised patients, base case results showed savings of USD 2257 per patient based on diagnostic, administration, adverse event, and treatment cost savings [12]. The Karius test allowed physicians to avoid costs related to bronchoscopies and shortened hospitalizations.

This test has its limitations. As a novel diagnostic tool, its true clinical value remains to be seen on a broad scale. A retrospective cohort study reviewing 82 Karius tests found that only 11% of the results had a clinical impact [13]. Due to the nature of mNGS, it is difficult to distinguish which organisms are clinically relevant disease-causing agents versus colonizing species. In our case, we had several organisms identified. *Burkholderia cepacia* complex seemed the most likely cause of his culture-negative endocarditis. Our patient had multiple risk factors for harboring this microorganism, including the presence of indwelling venous catheters and an immunocompromised state. The other organisms detected on the Karius test (*Pseudomonas alcaligenes*, *Pseudomonas citronellosis*, *Staphylococcus epidermidis*, and *Lactobacillus rhamnosus*) were of unclear significance. We hypothesized the likely source of these other organisms to be the patient's gangrenous extremities. Due to our patient's inadequate clinical response with TMP-SMX, meropenem, and levofloxacin, meropenem was broadened to ceftazidime–avibactam. His insufficient response to the initial antibiotic therapies corroborated our suspicion that his endocarditis was likely due to the intrinsically resistant *Burkholderia* spp. This highlights another drawback of the mNGS Karius test: it lacks culture sensitivity data that can help guide antimicrobial therapy, which proved challenging in this particular case with an intrinsically resistant organism. Because tissue cultures of the valve were not performed, a definitive correlation between the *Burkholderia* on the Karius test and the culture-negative endocarditis could not be made.

Conclusions

Infectious endocarditis is a source of significant morbidity and mortality. A prompt diagnosis and treatment are key to survival. In cases where the causative organism is not easily cultured, other means of identification should be pursued. The Karius test can be a valuable noninvasive diagnostic tool, particularly in immunocompromised and critically ill patient populations, for whom further invasive testing is prohibitive, either medically or in terms of cost. To our knowledge, this is the first reported case of culture-negative *Burkholderia* endocarditis diagnosed by mNGS.

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References

1. Baddour, L.M.; Wilson, W.R.; Bayer, A.S.; Fowler, V.G., Jr.; Tleyjeh, I.M.; Rybak, M.J.; Barsic, B.; Lockhart, P.B.; Gewitz, M.H.; Levison, M.E.; et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications. *Circulation* **2015**, *132*, 1435–1486. [CrossRef] [PubMed]
2. Rajani, R.; Klein, J.L. Infective endocarditis: A contemporary update. *Clin. Med.* **2020**, *20*, 31–35. [CrossRef] [PubMed]
3. Hoen, B.; Duval, X. Infective endocarditis. *NEJM* **2013**, *368*, 1425–1433. [CrossRef] [PubMed]
4. Shah, P.; Ruffin, F.; Seng, H.; Hollemon, D.; Winn, L.; Drennan, C.; Chan, K.L.; Quach, H.; Blauwkamp, T.; Meshulam-Simon, G.; et al. 156. Direct Detection and Quantification of Bacterial Cell-free DNA in Patients with Infective Endocarditis (IE) Using the Karius Plasma Next Generation Sequencing (NGS) Test. *Open Forum Infect. Dis.* **2018**, *5*, S12. [CrossRef]
5. Li, J.S.; Sexton, D.J.; Mick, N.; Nettles, R.; Fowler, V.G., Jr.; Ryan, T.; Bashore, T.; Corey, G.R. Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis. *Clin. Infect. Dis.* **2000**, *30*, 633–638. [CrossRef] [PubMed]
6. Ki, H.K.; Kim, S.; Han, S.W.; Cheong, H.S. A case of native valve endocarditis caused by Burkholderia cepacia without predisposing factors. *BMC Infect. Dis.* **2011**, *11*, 114–114. [CrossRef] [PubMed]
7. Aggarwal, N.; Garg, S.; Pannu, H.S.; Kler, T.S. Fatal Burkholderia cepacia early prosthetic valve endocarditis: A very rare case and a review of the literature. *J. Hear. Valve Dis.* **2005**, *14*, 271–274.
8. Häfliger, E.; Atkinson, A.; Marschall, J. Systematic review of healthcare-associated Burkholderia cepacia complex outbreaks: presentation, causes and outbreak control. *Infect. Prev. Pr.* **2020**, *2*, 100082, Erratum in: *Infect Prev Pract.* **2021**, *3*, 100120. [CrossRef] [PubMed]
9. Kaitwatcharachai, C.; Silpapojakul, K.; Jitsurong, S.; Kalnauwakul, S. An outbreak of Burkholderia cepacia bacteremia in hemodialysis patients: An epidemiologic and molecular study. *Am. J. Kidney Dis.* **2000**, *36*, 199–204. [CrossRef] [PubMed]
10. Leitão, J.H.; A Sousa, S.; Cunha, M.V.; Salgado, M.J.; Cristino, J.M.; Barreto, M.C.; Sa-Correia, I. Variation of the antimicrobial susceptibility profiles of Burkholderia cepacia complex clonal isolates obtained from chronically infected cystic fibrosis patients: a five-year survey in the major Portuguese treatment center. *Eur. J. Clin. Microbiol.* **2008**, *27*, 1101–1111. [CrossRef] [PubMed]
11. Camargo, J.F.; Ahmed, A.A.; Lindner, M.S.; Morris, M.I.; Anjan, S.; Anderson, A.D.; Prado, C.E.; Dalai, S.C.; Martinez, O.V.; Komanduri, K.V. Next-generation sequencing of microbial cell-free DNA for rapid noninvasive diagnosis of infectious diseases in immunocompromised hosts [version 4; peer review: 3 approved]. *F1000Research* **2020**, *8*, 1194. [CrossRef] [PubMed]
12. MacIntyre, A.T.; Hirst, A.; Duttagupta, R.; Hollemon, D.; Hong, D.K.; Blauwkamp, T.A. Budget Impact of Microbial Cell-Free DNA Testing Using the Karius®Test as an Alternative to Invasive Procedures in Immunocompromised Patients with Suspected Invasive Fungal Infections. *Appl. Health Econ. Health Policy* **2020**, *19*, 231–241. [CrossRef] [PubMed]
13. A Hogan, C.; Yang, S.; Garner, O.B.; A Green, D.; A Gomez, C.; Bard, J.D.; A Pinsky, B.; Banaei, N. Clinical Impact of Metagenomic Next-Generation Sequencing of Plasma Cell-Free DNA for the Diagnosis of Infectious Diseases: A Multicenter Retrospective Cohort Study. *Clin. Infect. Dis.* **2020**, *72*, 239–245. [CrossRef] [PubMed]