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Case Reports

Nontuberculous Mycobacterial Infections Associated With Left Ventricular Assist Devices in 3 Patients

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Durable left ventricular assist devices (LVADs) provide circulatory support in patients with end-stage heart failure; however, complications include infection of the driveline exit site. Nontuberculous mycobacterial infections are rare in patients with LVADs, but they should be considered in those who have undergone device exchanges and have bacterial infections with driveline exit-site discharge but no fever or leukocytosis.

We reviewed the charts of patients who had an LVAD implanted at our institution from January 2009 through December 2019, to identify those with a device-related nontuberculous mycobacterial infection. Collected data included patient demographics, premorbid conditions, infection type, previous device complications, treatment, and outcomes. We identified infections in 3 patients (mean age, 41 yr): Mycobacterium abscessus *in 2 and* M. chimaera *in 1. All had a HeartMate II device and had undergone device exchanges for pump thrombosis or for driveline fault or infections. All presented with driveline exit-site discharge without fever or leukocytosis. The mean time between initial device implantation and diagnosis of a nontuberculous mycobacterial infection was 55 months. All 3 patients were treated with antibiotics and underwent localized surgical débridement; one underwent an additional device exchange. The* M. abscessus *infections disseminated, and both patients died; the patient with* M. chimaera *infection continued to take suppressive antibiotics.*

Nontuberculous mycobacterial infections are associated with high morbidity and mortality rates, warranting prompt diagnosis and treatment. ***(Tex Heart Inst J 2022;49(4):e207498)***

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Durable left ventricular assist device (LVAD) therapy provides circulatory support for patients with advanced heart failure and has become a standard of care. This therapy is used as a bridge to recovery, a bridge to cardiac transplantation, or as destination therapy. Compared with medical management alone, destination therapy improves survival[1-3] and quality of life[4,5] for patients with severe heart failure. However, complications include catastrophic events, such as stroke, hemorrhage, or infection; a slow decline in health, such as from right-sided heart failure, a concurrent life-limiting malignancy, or other illness; or progression of other comorbid conditions, such as dementia.[6]

Infection can also complicate the clinical course of patients who have an LVAD. Percutaneous driveline infections (DLIs) often occur in these patients.[7] Although most DLIs are caused by staphylococcal species and gram-negative bacteria,[8] nontuberculous mycobacterial (NTM) species have been reported as causative agents.[9-12]

We present a case series of NTM infections identified at our center, with the goals of illuminating the incidence of these infections in LVAD-supported patients and describing the clinical courses and outcomes. Table I summarizes the patients' clinical details, and Table II shows their antibiotic regimens.

Patients and Methods

We searched our LVAD database to identify LVAD recipients who were diagnosed with a culture-positive NTM infection from January 2009 through December 2019. We collected the following data from electronic medical records: patient demographics, premorbid conditions, infection site, previous LVAD-associated complications, treatment, and outcomes. Institutional review board approval was waived because so few patients were identified (Tables I and II).

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We identified 3 LVAD recipients who had a culture-positive NTM infection during the search period.

Patient 1

A 30-year-old woman with congenital human immunodeficiency virus (HIV) infection (treated with antiretroviral therapy) developed HIV cardiomyopathy that led to end-stage heart failure. She initially underwent implantation of a HeartMate II LVAD (Abbott) as destination therapy and had 2 subsequent pump exchanges. The first exchange was to another HeartMate II after pump thrombosis. The second exchange was to a HeartMate 3 LVAD (Abbott) after diagnosis of mediastinitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and a DLI caused by MRSA and *Citrobacter freundii*. The DLI recurred with MRSA and multidrug-resistant *Klebsiella pneumoniae*, and the patient was maintained on a long-term antibiotic regimen of oral tedizolid and minocycline.

The patient presented at our emergency department with chest pain. At admission, she was afebrile (body temperature, 36.7 °C) and had a normal white blood cell (WBC) count of 5,500/μL; however, the discharge from a driveline exit site (DLES) wound had recently increased. Blood and superficial-wound cultures were obtained. A computed tomographic (CT) scan showed no mediastinal fluid collection; however, persistent fat-stranding and skin-thickening around the DLES were noted in the right abdominal wall. Because of the patient's history of multidrug-resistant DLIs, she was prescribed an empiric regimen of antibiotics. She underwent débridement of the DLES, and wound samples were sent for culture. Her blood cultures were positive for acid-fast bacilli (AFB), which were identified as *Mycobacterium abscessus*, and the wound culture grew *Pseudomonas aeruginosa*. We changed her antibiotic regimen to intravenous linezolid, eravacycline, and azithromycin for the *M. abscessus* infection and to intravenous cefepime for the *P. aeruginosa* infection, according to susceptibility data from the cultures. After multidisciplinary discussions, we decided that the patient's comorbidities and history of multiple pump exchanges made the risk of death too high for another device exchange. Although her blood cultures initially showed clearing of infection, *M. abscessus* bacteremia recurred, possibly because of the LVAD infection and her intolerance to intravenous antibiotic therapy. Adverse effects of the therapy (including thrombocytopenia, transaminitis, and lactic acidosis) had led to interruptions in antibiotic delivery. Multiorgan failure and shock secondary to disseminated *M. abscessus* infection eventually developed, and the patient died after a long hospital stay.

Patient 2

A 48-year-old woman with nonischemic cardiomyopathy and end-stage heart failure had undergone implantation of a HeartMate II and 2 subsequent device exchanges. Both exchanges were to a HeartMate II, the first after an electrical issue and the second after pump thrombosis. The patient presented at our hospital with purulent drainage from the DLES. On admission, she was afebrile (body temperature, 37 °C) and had a normal WBC count (7,700/μL). A CT scan showed a focal area of fluid collection superficial to the driveline along with fat-stranding around the driveline. Blood cultures were obtained; however, to increase the yield of intraoperative cultures, an empiric antibiotic regimen was not initiated. The patient underwent débridement of the DLES, surgical tissue was sent for culture, and she was prescribed intravenous vancomycin. The tissue culture grew *Staphylococcus* species, so the patient was discharged from the hospital on a 4-week regimen of intravenous vancomycin, with close outpatient follow-up of cultures.

Two weeks after débridement, the wound cultures grew AFB, which were identified as *M. abscessus* by DNA probe. An outpatient abdominopelvic CT showed persistent fat-stranding around the DLES. The patient was readmitted and underwent another débridement, from which surgical tissue cultures were obtained. She was discharged from the hospital with instructions to take oral azithromycin and intravenous imipenem; oral linezolid was added to the regimen because the tissue culture was positive for vancomycin-resistant enterococci. Because *M. abscessus* infection persisted in the DLES, the patient underwent multiple débridement procedures, and the antibiotic regimen was changed to intravenous amikacin and imipenem on the basis of susceptibility data. Although *M. abscessus* was susceptible to tigecycline, a national shortage prevented us from prescribing this drug. After several months of suppressive intravenous antibiotic therapy, she was admitted to the hospital because of elevated lactate dehydrogenase levels and concerns about pump thrombosis despite adequate anticoagulation; infection-related thrombosis was suspected. Medical therapy did not resolve the pump thrombosis, so the patient's device was replaced with a HeartWare LVAD (Medtronic). Surgical

tissue cultures were positive for AFB, so she was prescribed at minimum a 6-month intravenous regimen of amikacin, tigecycline, and cefoxitin. Despite the device exchange, *M. abscessus* was isolated from DLES cultures. Approximately 3 months after the exchange, the *M. abscessus* infection disseminated, and she died of multiorgan failure.

Patient 3

A 45-year-old man with a history of end-stage systolic heart failure due to nonischemic cardiomyopathy underwent placement of a HeartMate II. The device was exchanged twice, first to another HeartMate II because of pump thrombosis and then to a HeartMate 3 because of short-to-shield phenomenon. The patient presented at the hospital with fever, night sweats, myalgias, and discomfort around the DLES but no increased drainage. On admission, he was afebrile (body temperature, 37.2 °C) and had a normal WBC count (5,400/μL). A CT scan showed a focal area of fluid collection around the driveline in the anterior abdominal wall. Wound and blood cultures were obtained; however, to increase their yield, empiric antibiotics were not initiated. The patient underwent incision and drainage along with débridement of the DLES, and tissue was sent for culture. At 5 days, the surgical cultures were negative, and he was discharged from the hospital with prescribed long-term doxycycline therapy because of his history of coagulase-negative staphylococci infection.

Two weeks after the drainage procedure, the tissue cultures grew *M. avium* complex, which was further identified as *M. chimaera*. The patient was prescribed oral rifabutin, ethambutol, and azithromycin and intravenous amikacin. A repeat CT showed residual fluid collection around the driveline. The antibiotic regimen was adjusted to intravenous amikacin, azithromycin, and moxifloxacin, in accordance with susceptibility data. He tolerated the combination regimen, and repeat wound-culture results were negative. The planned treatment time was 6 months, to be followed by oral azithromycin therapy; however, the intravenous amikacin became nephrotoxic after 4 months of therapy despite adequate serum amikacin levels, so it was stopped. The patient continued taking azithromycin and moxifloxacin for 2 months to complete the 6-month regimen of combination antibiotic therapy. At last follow-up, he was still taking azithromycin for the *M. chimaera* infection and was doing well, with no driveline drainage.

Discussion

Infections associated with an LVAD have high morbidity and mortality rates.[13-15] According to the International Society for Heart and Lung Transplantation classification,[16] VAD-related infections include endocarditis, bloodstream infection, and mediastinitis. Infections classified as VAD-specific include those of the driveline, the pump pocket, and the cannula. Driveline infections are further subdivided into superficial and deep. Superficial DLIs spare the fascia and muscle layers, whereas deep DLIs involve these tissues and are more frequently associated with fever or systemic signs of infection.[16] Early diagnosis is important for initiating appropriate antimicrobial therapy (with or without surgical débridement) to prevent disease progression. Coagulase-negative staphylococci and *S. aureus* account for almost half of LVAD infections; however, *P. aeruginosa* and Enterobacteriaceae have also been identified as causative organisms.[16,17]

Nontubercular mycobacterial LVAD infections are rare. Breton and colleagues[9] reported 2 cases of DLIs caused by *M. abscessus*. In the context of a worldwide outbreak of infected heater-cooler units, *M. chimaera* was reported in 2 patients who had DLIs.[10] Roest and

TABLE I. Nontuberculous Mycobacterial Infections in Three Patients With Left Ventricular Assist Devices

Pt.	Age (yr), Sex	NTM Species	Time from Initial LVAD Implant* to Infection (mo)	Pump Exchanges (n)	Infection Type	Surgical Treatment	Outcome
1	30, F	*Mycobacterium abscessus*	34	2	Disseminated	Débridement of driveline exit site	Died (infection)
2	48, F	*M. abscessus*	64	3	Driveline	Débridement, driveline exit site revision, and device exchange	Died (infection)
3	45, M	*M. chimaera*	69	2	Driveline	Débridement, incision, and drainage of driveline exit site	Ongoing antibiotic therapy

F = female; LVAD = left ventricular assist device; M = male; NTM = nontuberculous mycobacterial; Pt. = patient

*The initial LVAD in all patients was a HeartMate II.

TABLE II. Antimycobacterial Treatment Regimens for Left Ventricular Assist Device Infections

Pt.	Antimycobacterial Regimen	Therapy Duration (mo)	Monitoring of Response and Toxicity
1	Linezolid, eravacycline, and azithromycin until death	6	Driveline drainage; weekly CBC, kidney panel, and liver panel
2	Amikacin, imipenem, and tigecycline (12 mo); amikacin and imipenem (8 mo); then amikacin, tigecycline, and cefoxitin (17 mo) until death	37	Driveline drainage; weekly CBC, kidney panel, and liver panel; weekly amikacin trough level and monthly audiology evaluation while taking amikacin
3	Amikacin, azithromycin, and moxifloxacin (4 mo); azithromycin and moxifloxacin (2 mo) after amikacin became nephrotoxic; then ongoing azithromycin monotherapy	6 (ongoing)	Driveline drainage; weekly CBC, kidney panel, and liver panel; weekly amikacin trough level and monthly audiology evaluation while taking amikacin

CBC = complete blood count; Pt. = patient

colleagues[10] reported DLIs caused by *M. chelonae*, and Radcliffe and associates[18] reported DLIs caused by *M. fortuitum*.

Our 3 cases of DLI included two with *M. abscessus* and one with *M. chimaera*. The DLI with *M. chimaera* is, to our knowledge, only the third such case ever reported. Of our 2 patients with *M. abscessus* LVAD infection, one had a DLI that disseminated, and the other had disseminated infection from the outset. All 3 patients had undergone device exchanges that were complicated by initial bacterial infection, and they had presented with mild symptoms, without fever or leukocytosis, despite severe, deep-seated infections. All were treated with use of intravenous antibiotics and DLES surgical débridement, and one underwent another device exchange.

Investigators have identified predisposing factors for LVAD infection. The most frequent independent predictor of infection is high body mass index,[19] followed by history of trauma to the driveline site,[20] young age,[21] and duration of LVAD support.[20,22] Our patients were younger (mean age, 41 yr) and had been undergoing LVAD therapy for a long time (range, 34–69 mo). These factors increase the risk for all types of LVAD infections, including NTM infections. Conflicting data have been reported for the association of LVAD infections and diabetes, renal disease, history of depression, vitamin D deficiency, and low albumin (as a surrogate marker of malnutrition). Our report shows that a history of DLIs and pump exchanges may increase the risk of NTM infections, possibly because frequent hospitalizations increase the risk of hospital-acquired infections.

Nontuberculous mycobacterial species are found throughout the environment; healthcare venues, heater-cooler units, and water have been reported as sources of NTM infections.[11,23] These mycobacteria can be divided into slow-growing and rapidly growing organisms. Slow-growing NTM usually need more than 7 days to grow in culture; faster-growing NTM usually need less time. The *M. abscessus* complex, *M. fortuitum*, and *M. chelonae* are the most clinically relevant species among rapidly growing NTM. Slow-growing mycobacteria like *M. chimaera* can take as long as 6 to 8 weeks to grow in culture,[24] and they have a long incubation period after exposure before causing symptoms (median, 17 mo) and an even longer time to diagnosis (median, 26 mo after open-chest cardiac surgery).[25] Species identification is crucial, because susceptibility and optimal treatment approaches differ between infections caused by rapidly growing and slow-growing NTM.

In patients with LVAD infection who have negative cultures, specimens should be sent for AFB culture. If mycobacteria are isolated from LVAD cultures, empiric antibiotic therapy should be started promptly, because culture and susceptibility data may not be available for weeks. In general, prolonged administration of a combination of antibiotic agents is eventually needed. Effective empiric antimicrobial treatment should cover the rapidly growing mycobacteria most often isolated: *M. mucogenicum*, *M. fortuitum* (complex), *M. abscessus*, *M. chelonae*, and *M. neoaurum*. Almost all species are susceptible to amikacin. *Mycobacterium abscessus* is usually macrolide-susceptible but quinolone-resistant. *Mycobacterium fortuitum* and *M. neoaurum* are usually quinolone-susceptible but are resistant to macrolides, whereas *M. mucogenicum* is often susceptible to both quinolones and macrolides. Therefore, an initial antimycobacterial combination should ideally include intravenous amikacin, a quinolone, and a macrolide.[26] When the identification and susceptibility data become available from the cultures, the empiric regimen should be tailored accordingly and consist of at least 2 active drugs. If the patient is considered hemodynamically unstable and has no side effects from or contraindications for amikacin, continuing this drug, along with a quinolone or macrolide, is reasonable. However, treating NTM

infections associated with LVADs can be challenging because of the long culture time necessary to identify the species and because all NTM can produce biofilms, which increase virulence, aid bacterial migration along the driveline,[27] provide protection from host immune responses, and facilitate the transfer of antibiotic resistance genes. Patients with NTM infections may need extended periods of combined antibiotic therapy, which places them at risk of antibiotic side effects or toxicity, drug resistance, and *Clostridium difficile* infections.[8] Because NTM infections are unlikely to resolve even with surgical treatment because of their propensity to form biofilms, they are often considered incurable.[26,28] The usefulness of device exchange as an adjunct to medical therapy in cases of NTM infections of an LVAD is unknown. Despite optimal management of these infections, mortality rates are high. Nevertheless, in each case, a multidisciplinary approach to treating NTM infections of an LVAD is recommended.

Conclusion

Nontuberculous mycobacterial infections are rare in patients with durable LVADs; however, they should be considered when culture-negative LVAD driveline infections occur in patients who have a history of DLIs and pump exchanges. These infections can result in superficial and deep driveline, mediastinal, and pump pocket involvement and may progress or disseminate. Nontuberculous mycobacterial infections are associated with high morbidity and mortality rates and warrant a multidisciplinary approach to prompt diagnosis and treatment.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

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