

CASE REPORTS

Fungemia Associated with Left Ventricular Assist Device Support

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ABSTRACT ***Objective:*** **Infections remain an important complication of left ventricular assist device (LVAD) support. While relatively uncommon, fungal infections present a serious concern given a high association with adverse events including death. We sought to further characterize the epidemiology of fungemias during LVAD support.** ***Methods:*** **Retrospective review of 292 patients receiving LVAD support from October 1996 to April 2009 at the University of Michigan Health System was done.** ***Results:*** **Seven cases of LVAD-associated fungemia were observed during the study period (0.1 infections/1000 days of device support). Five patients had infection with *Candida* species and two with *Aspergillus* species. The two patients with *Aspergillus* infection presented with disseminated disease, quickly dying of multiorgan failure, and sepsis. All five patients with *Candida* infections were successfully treated with systemic antifungal therapy along with transplantation in four of five patients. The fifth patient is receiving mechanical support as destination therapy. He remains on long-term suppression with high-dose fluconazole.** ***Conclusions:*** **Fungal infections appear to be a rare but serious complication of LVAD support. Future studies should aim to improve our understanding of risk factors for fungal infection during mechanical support, especially disseminated *Aspergillus*. Short-term perioperative antifungal prophylaxis with fluconazole appears to be an effective and reasonable approach to prevention.** doi: 10.1111/j.1540-8191.2009.00919.x *(J Card Surg 2009;24: 763-765)*

As the use of left ventricular assist devices (LVAD) continues to burgeon, infectious complications remain a vital concern. Several investigators have reported their experiences with infections and LVAD support, noting that treatment of an established infection is both difficult and expensive.[1-4] Risk factors for infection include extended duration of LVAD support, prolonged intensive care unit stay with invasive monitoring, poor preoperative nutritional status, and hemodialysis.[2-4]

Among infectious complications, fungemia represents a serious concern due to the high association with adverse events including death.[5-7] The ability of fungal pathogens, especially *Candida* species, to adhere to foreign surfaces is well established, making fungemia in the setting of a large prosthetic device particularly problematic in terms of management and treatment.[8] Candidemia has been reported in 1.3-9.7% of ventricular assist device recipients.[5] In 1995, universal, short-term fluconazole prophylaxis was recommended based on limited early data suggesting a high incidence of fungal infections during LVAD support.[7] This practice has continued at many centers, including ours. We sought to further characterize the epidemiology of fungemias during LVAD support by reviewing our experience from 1996 to 2009.

METHODS

The University of Michigan Health System is an 850-bed tertiary care center with an active transplantation and cardiothoracic surgery services. In 2008, 37 LVAD implantations and 34 heart transplantations were performed. Medical records of all patients who received LVAD support from October 1996 to April 2009 were reviewed. Fungemia was defined as any positive blood or catheter tip culture for a fungal pathogen with an appropriate clinical presentation. An attending

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TABLE 1
Clinical and Microbiological Characteristics of Left Ventricular Assist Device (LVAD)-Associated Fungemia among Seven Patients

Age, Gender	Device Type	ICU Days Prior to Infection	Need for Dialysis	Delayed Sternal Wound Closure	LVAD Support Days until Infection	Culture Site	Organism	Antifungal Therapy	Outcome
21/F	HeartMate® IP-1000 (Thermo Cardiosystems Inc., Woburn, MA, USA)	14	Yes	Yes	2	Catheter tip	*Candida krusei*	Amphotericin B	Transplanted
34/F	HeartMate® vented electric	10	No	No	2	Catheter tip	*Candida albicans*	Fluconazole	Transplanted
63/F	MicroMed Debakey VAD® (MicroMed Cardiovascular, Inc., Houston, TX, USA)	3	No	No	3	Catheter tip	*Candida glabrata*	Fluconazole Caspofungin	Transplanted
68/M	HeartMate® vented electric	14	Yes	Yes	14	Catheter tip	*Candida albicans*	Fluconazole	Transplanted
65/M	HeartMate® II	—	No	Yes	674*	Blood	*Candida parapsilosis*	Fluconazole Caspofungin	Remains on high dose fluconazole for long-term suppression.
21/F	Thoratec® PVAD (Thoratec Corporation, Pleasanton, CA, USA)	123	No	Yes	123	Aortic thrombus	*Aspergillus fumigatus*	Voriconazole Caspofungin	Death—support day 160
50/M	HeartMate® XVE	22	No	No	182	Blood	*Aspergillus versicolor*	†None	Death—support day 188

F = female; M = male.
Device type: IP-1000 = HeartMate implantable pneumatic; PVAD = paracorporeal ventricular assist device.
*Patient receiving LVAD support as destination therapy. Fungemia identified 674 days after implantation of his second device.
†Results of blood cultures final after the patient's death.

infectious diseases physician established the presence or absence of fungemia after review of each patient's medical record. These cases were further corroborated by review with the attending cardiac surgeon (FDP). The Institutional Review Board of the University of Michigan Health System approved this study.

RESULTS

Two hundred and ninety-two patients underwent LVAD placement during the 12 and a half year study period; 231 were male (79.1%) with a mean age of 53.9 ± 13.1 years. Device use ranged from 1 to 1984 days (mean 233.1 ± 297.6 days, median 142 days). Patients had an average intensive care unit (ICU) stay of 10.7 ± 13.9 days (median 7 days). Fifty-nine (20.2%) patients died during support; 172 (58.9%) were transplanted, six (2.1%) were weaned from support. The other 55 (18.8%) patients remained on support at the time of evaluation, either awaiting transplant or as destination therapy.

Seven of 292 (2.6%) patients developed fungemia during LVAD support (Table 1). Five patients had infection with *Candida* species, and two with *Aspergillus* species. All patients received perioperative antimicrobial prophylaxis including fluconazole. Infections were identified on LVAD support days 2–674.

Among the five patients with *Candida* species infections, all received systemic antifungal therapy as treatment. Four of the five were eventually successfully transplanted. The fifth patient remains on long-term mechanical support as destination therapy. His initial device was placed in March 2006, later removed and replaced in May 2007 due to a refractory *Pseudomonas aeroginosa* drive line infection. In March 2009, he presented with fevers and was found to have high-grade *C. parapsilosis* fungemia. In addition to systemic antifungal therapy with fluconazole and caspofungin, the patient eventually underwent removal of his automatic implantable cardioverter defibrillator (AICD). After 15 days of persistently positive blood cultures, he cleared the fungemia. The patient remains well on chronic fluconazole 400 mg a day for suppressive treatment.

Both patients with *Aspergillus* infection died of multiorgan failure and sepsis despite aggressive supportive therapy including antimicrobials. The patient with *A. fumigatus* had a very complicated postoperative course notable for disseminated intravascular coagulation, intracranial hemorrhage, and aortic thrombosis requiring stent placement and thrombectomy. Thrombus cultures demonstrated *A. fumigatus*. The patient with *A. versicolor* had a clinical picture suggestive of sepsis along with persistent drive line drainage. He also developed intracranial hemorrhage felt to be related to blockage of his LVAD outflow tract. Subsequently, *A. versicolor* grew in multiple blood cultures postmortem.

DISCUSSION

In our experience, fungemia during LVAD support was extremely uncommon with a rate of 0.10 infections/1000 days of device support. This low rate

is somewhat unexpected given that LVAD support is frequently associated with many established risk factors for fungemia, including extended ICU stay, presence of indwelling catheters, need for hemodialysis, receipt of broad spectrum antimicrobial therapy, and transfusion of blood products.[9]

Although the small number of infections observed limits our ability to draw firm conclusions, fluconazole has likely provided some benefit given the low rate of fungemia. We note that two of five *Candida* isolates were species with relative fluconazole resistance (*C. krusei* and *C. glabrata*). We also note that only one of five patients had persistent high-grade candidemia such as that seen in association with other indwelling devices like central catheters. This patient was different than the usual "bridge-to-transplant" LVAD patient given the extended duration of support for destination therapy, the removal of his initial device due to infection, as well as the presence of an additional device (AICD). We believe that removal of his AICD was essential to his eventual clearance of *C. parapsilosis* infection. The current plan is to maintain him on life-long suppression with oral fluconazole 400 mg daily.

In general, the development of a serious candida infection (especially persistent fungemia and/or device infection) during LVAD support would result in an urgent 1A transplant listing. The only patient in this small series that developed persistent candidemia was receiving support as destination therapy and therefore was not a candidate for transplantation. Ultimately, removal of his AICD proved critical to control of infection and permitted retention of his LVAD. This scenario is not typical since eradication of persistent fungemia in the setting of a prosthetic device, especially an LVAD, is nearly impossible without removal. Over time, the risk of serious sequelae including endopthalmitis or endocarditis is significant, thus the timing of device removal and transplantation is often the key to clinical success.

Disseminated *Aspergillus* infection is extremely uncommon. When it does occur it is almost always in the setting of a host who is highly immunocompromised, such as patients with hematologic malignancies with prolonged neutropenia. Review of earlier case series of LVAD infection does not identify filamentous fungi as a pathogen frequently associated with device infection. In general, there was nothing specific in either patient's history that suggests an increased risk for invasive filamentous fungal infection, neither was otherwise immunocompromised. However, both patients did experience intracranial hemorrhage requiring craniotomy and had clinical evidence of outflow tract obstruction related to overwhelming device infection. We speculate that there may be some factors related to the actual device that allowed these filamentous organisms to sporulate and cause fatal infection. Animal models may be useful in exploring this possibility given the rarity of such infection.

Although our understanding of this unusual process in nonimmunocompromised populations is limited, we believe that disseminated aspergillosis would preclude successful transplantation. Even if *Aspergillus* disease were diagnosed earlier with more limited involvement, we do not believe that transplantation would be prudent given the need for high-dose immunosuppression. Improved understanding of this uniformly fatal infection may help define an approach to prevention.

Although uncommon, fungal infections carry significant mortality and are difficult to treat, especially in the setting of retained device. Risk factors for the development of fungemia during LVAD support remain incompletely understood. Besides established factors (ICU stay, broad spectrum antimicrobials, indwelling catheters, etc.), the possibility that LVAD implantation may itself be associated with the development of defects in host immunity must also be considered.[10] The use of perioperative fluconazole prophylaxis appears to be a reasonable approach to the prevention of candidal infection. Our current protocol consists of fluconazole 400 mg once daily for 48 hours. Questions surrounding optimal timing and duration of antifungal prophylaxis should be considered in future investigations, particularly if the overall epidemiology of fungemia continues to shift toward more fluconazole-resistant, non-albicans species.[11]

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