Candidemia in Patients with Ventricular Assist Devices

Shmuel Shoham, Rebecca Shaffer, Leslie Sweet, Richard Cooke, Nancy Donegan, and Steven Boyce

Departments of 1Infectious Diseases, 2Cardiovascular Surgery, 3Cardiology, and 4Infection Control, Washington Hospital Center, Washington, D.C.

During the period 1998–2004, candidemia developed in 7 of 117 ventricular assist device recipients at our hospital, and the associated mortality rate was 71%. Five cases of candidemia were due to Candida parapsilosis, and 2 were due to Candida albicans. Three of the 7 patients with ventricular assist device–associated Candida bloodstream infections were cured, and the device was retained in 2 of the 3 patients.

Ventricular assist devices (VAD) are increasingly used for management of advanced heart failure. These mechanical pumps take over the function of damaged ventricles to improve cardiac hemodynamics and end-organ blood flow [1]. Such devices are used in patients with ventricular dysfunction to support the heart while the patient awaits cardiac recovery or transplantation and, increasingly, as long-term therapy for patients who are not candidates for transplantation [1, 2]. Invasive nosocomial and device-related infections are a significant cause of morbidity and mortality among VAD recipients [2–7]. Candida species are a leading cause of invasive infection and are associated with poor outcomes in patients with VADs [5, 8]. The objectives of this study were to determine the incidence of and risk factors for candidemia, the distribution of species, and the impact of infection in patients who underwent VAD implantation at our institution.

Methods. This was a retrospective case-control study. The institutional review board of Washington Hospital Center (Washington, DC) approved the study, and the requirement for informed consent was waived. Patients were identified by review of infection-control and VAD program databases.

All patients who underwent VAD placement at the Washington Hospital Center (a 907-bed tertiary care hospital) during the period from 1 January 1998 through 31 December 2004 were evaluated. Fungal isolates recovered from blood cultures were identified to the species level by use of the germ tube test and either the ID YST Vitek 2 test (bioMérieux) or the API 20C test (bioMérieux). Candida colonization was defined as presence of Candida species in normally nonsterile sites or specimens (i.e., respiratory tract, stool, urine, and skin) without evidence for invasive disease.

Case patients were defined as persons who had developed candidemia while a VAD was in place. Patients were included only once during their hospitalization if they developed candidemia, and any subsequent cultures positive for the same species were considered to be part of the same episode of bloodstream infection. For each case patient, 2 control subjects were chosen. Control subjects were noncandidemic VAD recipients whose devices had been in place for >14 days. Control subjects were matched with case patients by age, but they were otherwise selected at random from a database of VAD recipients. Medical records were abstracted for demographic characteristics, VAD type, duration of VAD placement, echocardiographic findings, underlying illnesses, surgery, receipt of immunosuppressive medications or antibiotics, and microbiological data. Crude mortality was assessed at the end of hospitalization.

Statistical analyses were performed using EpiInfo, version 6 (Centers for Disease Control and Prevention). Categorical variables were compared using Fisher’s exact test, and continuous variables were compared using Student’s t test.

Results. During the study period, 117 patients underwent VAD implantation. Candidemia developed in 7 patients (overall attack rate, 6%). Five patients had a left VAD implanted, 1 had a right VAD implanted, and 1 had a bilateral VAD implanted. All 7 candidemic and 14 noncandidemic VAD recipients (control subjects) were included in the study. VAD patients with and patients without invasive candidiasis were similar with regard to demographic characteristics and associated conditions. No host factor was identified as significantly associated with the development of VAD-associated candidemia. The median duration of VAD placement before the onset of candidemia was 25 days (range, 11–72 days). The median total duration of VAD placement in case patients was 57 days (range, 17–171 days), and it was 72.5 days (range, 18–811 days) for noncandidemic control subjects. The median ages of case patients and control subjects were 59 and 57 years, respectively. Seventy-one percent of case patients and 86% of control subjects were male. None

CID 2007:44 (15 January) • e9

© 2006 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2007/4402-00E3$15.00
of the patients in this study received perioperative antifungal prophylaxis.

Five of 7 case patients and 7 of 14 control subjects had evidence of Candida colonization. Colonization was not significantly associated with bloodstream infection (OR, 2.14; 95% CI, 0.21–24.44), and in patients with candidemia, the colonizing species did not reliably predict the identities of the infecting species. Two patients were colonized with Candida albicans but developed Candida parapsilosis bloodstream infection. All fungal bloodstream infections were due to either C. parapsilosis (in 5 case patients) or C. albicans (in 2 case patients).

The clinical courses and outcomes of patients with candidemia are shown in table 1. All patients were evaluated using 2-dimensional echocardiography, and 2 patients were also evaluated by transesophageal echocardiography; none had evidence of device infection. Five of 7 case patients and 9 of 14 control subjects died before discharge from hospital (OR for death, 1.39; 95% CI, 0.14–15.6). In 4 patients, death was attributed to fungal sepsis. The VAD was exchanged in 3 patients after the onset of candidemia; all 3 of these patients died, 2 of whom died of fungal sepsis. Both patients with C. albicans fungemia died. Bloodstream infection resolved despite retention of the device in 2 patients and did not recur after transplantation. Pathological examination of the heart and VAD from those patients did not reveal fungal infection. One patient with C. albicans infection developed progressive decline in left VAD function, with abnormal inflow and altered hemodynamics. That patient underwent removal of the device and transplantation, but soon thereafter, the patient died of multisystem organ failure. Pathological examination revealed fungal vegetations on the device.

**Discussion.** Candidemia developed in 7 (6%) of 117 patients who underwent placement of a VAD at our hospital. Invasive candidiasis is an important complication in VAD recipients, and candidemia has been reported in 1.3%–9.7% of such patients [3, 5, 8–12]. In a study of 140 episodes of nosocomial bloodstream infection among 236 VAD recipients, Candida species (13.6% of cases) were second only to Staphylococcus species as a cause of bloodstream infection [5]. Univariate analysis did not reveal statistically significant differences between case patients and control subjects with regard to the prevalence of diabetes mellitus, corticosteroid use, antibiotic exposure, acute or chronic renal failure, dialysis use, central venous catheterization, or abdominal surgery. However, given the small number of case patients and control subjects, these findings do not preclude the possibility that meaningful differences existed with regards to these variables.

The significance of positive results of fungal cultures of samples from normally nonsterile sites is unclear. Known colonization of skin, urine, respiratory tract, or stool with Candida

### Table 1. Clinical courses for and outcomes of patients with ventricular assist device–associated candidemia.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Device</th>
<th>Organism</th>
<th>Persistent candidemia</th>
<th>Candidemia cured without device removal</th>
<th>Therapy* (duration, days)</th>
<th>Findings of pathologic examination of heart and/or device</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LVAD</td>
<td>Candida albicans</td>
<td>No</td>
<td>No</td>
<td>Flu (7)</td>
<td>Not performed</td>
<td>Patient died with device in place</td>
</tr>
<tr>
<td>2</td>
<td>LVAD</td>
<td>Candida parapsilosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Flu (3), L-AmB (22)</td>
<td>No infection identified</td>
<td>Patient survived to transplantation and was alive at discharge</td>
</tr>
<tr>
<td>3</td>
<td>LVAD</td>
<td>C. albicans</td>
<td>Yes</td>
<td>No</td>
<td>Flu (1), ABLC (10), Flu (50), ABLC (6), Flu (5), ABLC (10), L-AmB (8)^b</td>
<td>Vegetations found on device</td>
<td>Patient died 1 day after transplantation</td>
</tr>
<tr>
<td>4</td>
<td>RVAD</td>
<td>C. parapsilosis</td>
<td>No</td>
<td>Unknown^b</td>
<td>Flu (10), ABLC (1), L-AmB (1)</td>
<td>No infection identified</td>
<td>Patient survived to transplantation but died after transplantation</td>
</tr>
<tr>
<td>5</td>
<td>RVAD/LVAD</td>
<td>C. parapsilosis</td>
<td>Yes</td>
<td>No</td>
<td>Flu (10)^b</td>
<td>Not performed</td>
<td>Patient died with new device in place</td>
</tr>
<tr>
<td>6</td>
<td>LVAD</td>
<td>C. parapsilosis</td>
<td>Yes</td>
<td>Yes</td>
<td>ABLC (24), ABLC plus Flu (11), Flu (5)</td>
<td>No infection identified</td>
<td>Patient survived to transplantation and was alive at discharge</td>
</tr>
<tr>
<td>7</td>
<td>LVAD</td>
<td>C. parapsilosis</td>
<td>Yes</td>
<td>No</td>
<td>Flu (3), Cas (6)</td>
<td>Not performed</td>
<td>Patient died with device in place</td>
</tr>
</tbody>
</table>

**NOTE.** ABLC, amphotericin B lipid complex; Cas, caspofungin acetate; Flu, fluconazole; L-AmB, liposomal amphotericin B; LVAD, left ventricular assist device; RVAD, right ventricular assist device.

* Antifungal agents are listed in the order that they were given to patients.

^b Device was removed during therapy.
species was present in 71% of VAD recipients who went on to develop candidemia, but compared with control subjects, fungal growth at these sites was not significantly associated with an increased rate of invasive infection (OR, 2.14; 95% CI, 0.21–24.44). This study may have underestimated the rate of Candida colonization, because assessment of nonsterile sites for fungi was not routinely performed in all VAD recipients. Colonization often precedes infection, and blood cultures may fail to yield Candida species, despite the presence of invasive disease [13]. Thus, empirical antifungal therapy may be warranted for colonized patients who remain febrile despite receiving antibacterial therapy [14]. Our data suggest that the administration of routine systemic antifungal therapy solely on the basis of isolation of Candida species from cutaneous, respiratory, stool, or urine specimen is probably not indicated.

Although nearly all instances of culture-proven colonization involved C. albicans, only 2 of the bloodstream infections were due to this organism; the other 5 cases were due to C. parapsilosis. This finding is not surprising, given the propensity for C. parapsilosis to adhere to and infect prosthetic devices, including artificial heart valves and intravascular catheters [15, 16]. C. parapsilosis is frequently recovered from cutaneous surfaces and is often carried on the hands of health care workers [17]. Thus, careful attention to caregiver hand hygiene is important to reduce transmission of this pathogen and subsequent infection.

Although the overall survival rate for candidemic patients with VADs was poor (29%), infection cleared in 3 patients, all of whom were infected with C. parapsilosis. In 2 of these patients, the infections were successfully treated without device removal. VADs may become infected via percutaneous lines leading directly to the devices or secondary to seeding from distant foci. It is unclear whether antifungal therapy prevented infection of the devices with the yeast or whether the infected VAD was sterilized by therapy. In both cases, candidemia persisted over several days, providing an opportunity for the VAD to become infected. When the devices were ultimately explanted at the time of heart transplantation, there was no evidence of device-associated infection. Fungemia due to C. parapsilosis at the time of heart transplantation, there was no evidence of colonization, because assessment of nonsterile sites for fungi was not routinely performed in all VAD recipients. Colonization often precedes infection, and blood cultures may fail to yield Candida species, despite the presence of invasive disease [13]. Thus, empirical antifungal therapy may be warranted for colonized patients who remain febrile despite receiving antibacterial therapy [14]. Our data suggest that the administration of routine systemic antifungal therapy solely on the basis of isolation of Candida species from cutaneous, respiratory, stool, or urine specimen is probably not indicated.

Although nearly all instances of culture-proven colonization involved C. albicans, only 2 of the bloodstream infections were due to this organism; the other 5 cases were due to C. parapsilosis. This finding is not surprising, given the propensity for C. parapsilosis to adhere to and infect prosthetic devices, including artificial heart valves and intravascular catheters [15, 16]. C. parapsilosis is frequently recovered from cutaneous surfaces and is often carried on the hands of health care workers [17]. Thus, careful attention to caregiver hand hygiene is important to reduce transmission of this pathogen and subsequent infection.

Although the overall survival rate for candidemic patients with VADs was poor (29%), infection cleared in 3 patients, all of whom were infected with C. parapsilosis. In 2 of these patients, the infections were successfully treated without device removal. VADs may become infected via percutaneous lines leading directly to the devices or secondary to seeding from distant foci. It is unclear whether antifungal therapy prevented infection of the devices with the yeast or whether the infected VAD was sterilized by therapy. In both cases, candidemia persisted over several days, providing an opportunity for the VAD to become infected. When the devices were ultimately explanted at the time of heart transplantation, there was no evidence of device-associated infection. Fungemia due to C. parapsilosis at the time of heart transplantation, there was no evidence of colonization, because assessment of nonsterile sites for fungi was not routinely performed in all VAD recipients. Colonization often precedes infection, and blood cultures may fail to yield Candida species, despite the presence of invasive disease [13]. Thus, empirical antifungal therapy may be warranted for colonized patients who remain febrile despite receiving antibacterial therapy [14]. Our data suggest that the administration of routine systemic antifungal therapy solely on the basis of isolation of Candida species from cutaneous, respiratory, stool, or urine specimen is probably not indicated.

Although nearly all instances of culture-proven colonization involved C. albicans, only 2 of the bloodstream infections were due to this organism; the other 5 cases were due to C. parapsilosis. This finding is not surprising, given the propensity for C. parapsilosis to adhere to and infect prosthetic devices, including artificial heart valves and intravascular catheters [15, 16]. C. parapsilosis is frequently recovered from cutaneous surfaces and is often carried on the hands of health care workers [17]. Thus, careful attention to caregiver hand hygiene is important to reduce transmission of this pathogen and subsequent infection.

Although the overall survival rate for candidemic patients with VADs was poor (29%), infection cleared in 3 patients, all of whom were infected with C. parapsilosis. In 2 of these patients, the infections were successfully treated without device removal. VADs may become infected via percutaneous lines leading directly to the devices or secondary to seeding from distant foci. It is unclear whether antifungal therapy prevented infection of the devices with the yeast or whether the infected VAD was sterilized by therapy. In both cases, candidemia persisted over several days, providing an opportunity for the VAD to become infected. When the devices were ultimately explanted at the time of heart transplantation, there was no evidence of device-associated infection. Fungemia due to C. parapsilosis at the time of heart transplantation, there was no evidence of colonization, because assessment of nonsterile sites for fungi was not routinely performed in all VAD recipients. Colonization often precedes infection, and blood cultures may fail to yield Candida species, despite the presence of invasive disease [13]. Thus, empirical antifungal therapy may be warranted for colonized patients who remain febrile despite receiving antibacterial therapy [14]. Our data suggest that the administration of routine systemic antifungal therapy solely on the basis of isolation of Candida species from cutaneous, respiratory, stool, or urine specimen is probably not indicated.

Although nearly all instances of culture-proven colonization involved C. albicans, only 2 of the bloodstream infections were due to this organism; the other 5 cases were due to C. parapsilosis. This finding is not surprising, given the propensity for C. parapsilosis to adhere to and infect prosthetic devices, including artificial heart valves and intravascular catheters [15, 16]. C. parapsilosis is frequently recovered from cutaneous surfaces and is often carried on the hands of health care workers [17]. Thus, careful attention to caregiver hand hygiene is important to reduce transmission of this pathogen and subsequent infection.

Although the overall survival rate for candidemic patients with VADs was poor (29%), infection cleared in 3 patients, all of whom were infected with C. parapsilosis. In 2 of these patients, the infections were successfully treated without device removal. VADs may become infected via percutaneous lines leading directly to the devices or secondary to seeding from distant foci. It is unclear whether antifungal therapy prevented infection of the devices with the yeast or whether the infected VAD was sterilized by therapy. In both cases, candidemia persisted over several days, providing an opportunity for the VAD to become infected. When the devices were ultimately explanted at the time of heart transplantation, there was no evidence of device-associated infection. Fungemia due to C. parapsilosis is associated with a lower mortality rate than infection due to other species of Candida. C. parapsilosis infection is often associated with medical devices. When feasible, removal of all intravascular catheters is recommended for most patients with candidemia. In a patient with a VAD, however, removal of the device may not be a viable option. Our data indicate that antifungal therapy alone can eradicate invasive candidiasis in some patients with VADs.

The optimal antifungal regimen for treatment of VAD-associated candidemia is not known. Patients in our study were treated with multiple antifungal agents, including fluconazole, caspofungin, and lipid formulations of amphotericin B. One patient was treated with caspofungin, but infection progressed despite the administration of antifungal therapy. Compared with other common Candida species, C. parapsilosis tends to have reduced in vitro susceptibility to echinocandin antifungal agents and possibly a diminished clinical response [18]; this may have contributed to treatment failure in the patient.

In conclusion, candidemia—in particular, candidemia due to C. parapsilosis or C. albicans—may complicate the clinical course in VAD recipients. The mortality rate is high, despite the administration of aggressive antifungal therapy. In instances in which device removal is not a viable option, cure of the infection (with salvage of the VAD) and long-term survival are sometimes possible with antifungal therapy alone.

Acknowledgments

Potential conflicts of interest. S.S. has received recent research funding from Astellas Pharma, has served as a consultant for Pfizer and Enzon, and has been a member of the speakers’ bureau for Pfizer, Enzon, and Astellas Pharma. All other authors: no conflicts.

References