Infections in Heart and Lung Transplant Recipients

Heather E. Clauss, M.D.,[1] Robert L. Bettiker, M.D.,[1] Rafik Samuel, M.D.,[1] Allan L. Truant, Ph.D.,[2] Donald Jungkind, Ph.D.,[3] and Byungse Suh, M.D., Ph.D., Section of Infectious Diseases, Temple University School of Medicine,[1] and Clinical Microbiology, Immunology, and Virology Laboratories, Department of Pathology and Laboratory Medicine, Temple University Hospital and School of Medicine,[2] Jefferson University Hospital and School of Medicine,[3] Philadelphia, Pennsylvania

Abstract

Patients undergoing thoracic organ transplantation procedures involving the heart or lung are at increased risk for developing a wide variety of infections due to their underlying immunosuppression and/or other factors. Lung transplant recipients are at high risk for developing infections caused by bacteria, viruses, and opportunistic fungi, whereas heart transplant recipients are at risk for developing infections caused by these same microorganisms, as well as parasitic infections, including toxoplasmosis and New World trypanosomiasis. This review will highlight the various infections that thoracic organ transplant recipients may develop following their procedures.

Lung Transplant

Lung transplantation is a viable treatment option for patients with end-stage emphysema and other poorly treated lung diseases. Through 2009, some 20,000 lung and heart-lung transplants were performed in the United States. Compared with other solid-organ transplant (SOT) recipients, lung transplant (LT) recipients have a shorter survival time. LT patients typically have a 1- and 3-year survival of 77% and 59%, respectively. Infections are the major cause of death often linked to rejection, most commonly manifested as bronchiolitis obliterans (BO). Certain infections may trigger BO, and BO increases the risk of opportunistic infections. Pneumonia is perhaps the most common infection in lung recipients and is the leading cause of death in the first year (1).

Infection risk in LT recipients is similar to risks in other SOT recipients and is related to immunosuppression, rejection, the infection status of the donor and recipient, prophylaxis, and the time interval since transplant (2). The lung, however, has several unique infection risks: constant exposure to the environment, limited vascularization of the bronchial anastomotic site, disrupted lymphatics, compromised cough reflex, impaired mucociliary function, and exposure to colonizing pathogens in the native lung (1).

Four out of five infections in LT recipients occur in the mediastinum, pleural space, or lung. Pneumonia accounts for one- to two-thirds of these. Bloodstream infections occur in approximately 25% of LT recipients, and 38% of these arise from the lung itself (2). Perhaps because of heavy bacterial colonization in the native lung, cystic fibrosis patients appear to have a higher rate of bacteremia.

Bronchial anastomotic site infections are infrequent but can be serious. One chart review of some 280 heart-lung and LT recipients showed 15 (5.3%) anastomotic site infections; 6 *Aspergillus*, 8 *Candida*, and 1 *Staphylococcus aureus* (1). In this series, no patient had dehiscence, but others had anastomotic rupture.

Infections in the brain and central nervous system (CNS) occur in 1% of LT recipients, mostly due to *Aspergillus* and *Nocardia*. Due to arterial invasion by *Aspergillus*, hemorrhage and infarcts can occur. Mortality is high for CNS *Aspergillus* infections (3).

Bacterial infections

Bacteria account for the majority of all infections in LT recipients, with bacterial bronchitis and pneumonia occurring in up to 60% of patients. Many patient cases of pneumonia occur within the first month post-transplantation, but bacterial infection may also complicate BO. Many transplant centers culture tracheal aspirates of both the recipient and the donor and provide specific antibiotic prophylaxis against the bacteria that grow (1).

Corresponding Author: Allan L. Truant, Ph.D., Clinical Microbiology Laboratories, Department of Pathology and Laboratory Medicine, Temple University School of Medicine, 3401 N. Broad St., Philadelphia, PA 19140. Tel.: 215-707-3210. Fax: 215-707-2053. E-mail: allan.truant@tuhs.temple.edu

Burkholderia cepacia and *Pseudomonas aeruginosa* are of particular concern, since they often colonize the native lung and can be resistant to multiple antibiotics. A few transplant programs will not perform transplants on patients colonized with resistant *Burkholderia* or *Pseudomonas*. For instance, it has been shown that patients colonized with *Burkholderia cenocepacia* (genovar III) have a much lower survival rate than patients colonized with other species of the *B. cepacia* complex (4). For this reason, many transplant programs may refuse to perform transplants on patients colonized with *B. cenocepacia*. Surgeons who do perform transplants on patients colonized with these bacteria often use broad-spectrum antibiotic prophylaxis in the peri- and post-operative periods. Cystic fibrosis patients with a single LT may be at greater risk of pneumonia, as the native lung functions as a reservoir for these resistant pathogens (5). Laboratory diagnosis of the most commonly encountered bacterial infections requires the use of only routine culture media along with manual or automated identification and antimicrobial susceptibility methods. Most organisms can be fully identified, with antibiotic susceptibility results available within 48 h. However, fastidious and/or uncommon organisms may need the use of special media and incubation conditions, requiring additional time for isolation and complete identification (6).

Although *Legionella*, the causative agent of Legionnaire's disease, commonly afflicts immunocompromised patients, it is rarely reported as a pathogen in LT patients. Diagnosis is usually made by culture or urinary antigen testing. Occasionally, PCR or *Legionella* antibody testing with a single acute-phase serum or paired sera may be used. *Nocardia* spp. can cause soft tissue infections, lung infections, and brain abscesses in lung and heart-lung transplants (7), most commonly a year after transplant, with a 1 to 2% incidence**.** CNS infections may require surgery for diagnosis and management (see "Heart Transplant" below for laboratory diagnosis of *Nocardia* spp.).

Mycobacterium tuberculosis has been reported in 0.8 to 6.5% of LT recipients. One Spanish study (8) of 187 LT patients found 12 (6.4%) cases of active tuberculosis. Six were diagnosed via histologic examination of the explanted lung and underwent therapy. Five of the remaining 6 patients developed evidence of subclinical disease after 3 months, and 4 of the 6 eventually developed symptoms. The 2 patients without symptoms had positive *M. tuberculosis* cultures from broncho-alveolar lavage (see "Heart Transplant" below for laboratory diagnosis of *M. tuberculosis*). Half of the patients died by the end of the study, but in all cases, it was attributed to BO. Interestingly, the 3 patients who were PPD positive at the time of transplantation and did not receive prophylaxis developed active tuberculosis. Tuberculosis therapy in transplant patients is complicated by the severe drug interaction between rifampin and calcineurin inhibitors.

Approximately two dozen cases of nontuberculous mycobacterial (NTM) infections have been reported in LT recipients. These include the *Mycobacterium avium* complex, *Mycobacterium haemophilum, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium asiaticum, Mycobacterium fortuitum, Mycobacterium abscessus,* and *Mycobacterium chelonae*. The incidence rate of NTM infection in LT recipients is 0.46 to 8.0%. LT recipients with chronic rejection have an increased risk of NTM infections (9). Most infections occur in the lung or pleura. These organisms are present in the environment and can innocuously colonize the bronchial tree, making diagnosis difficult. Therapy often lasts for months and is guided by culture and susceptibility test results.

Viral infections

The beta-herpes virus cytomegalovirus (CMV) is the most common opportunistic pathogen in LT patients after bacteria. Compared with other SOTs, lung and heart-lung transplant patients have more CMV disease, with an incidence of 38 to 75% in individuals who do not receive prophylaxis (1). This may be due to the higher degree of immunosuppressive therapy used in these patients compared to other transplant recipients. Besides life-threatening pneumonitis, CMV can cause hepatitis, enteritis, and colitis after transplantation. CMV may also predispose individuals to bacteremia, *Aspergillus* infection, and Epstein-Barr virus (EBV)-related post-transplant lymphoproliferative disease (PTLD). Most worrisome, CMV disease is associated with BO. Different strategies are employed to prevent CMV disease after LT (see "Heart Transplant" below for laboratory diagnosis of CMV). Most commonly, prophylaxis with valganciclovir is used due to ease of administration. In lung transplantation, longer courses (6 months or greater) of antiviral therapy may be used (10). Ganciclovir resistance may occur, requiring treatment with higher doses of ganciclovir or foscarnet. These high doses increase the side effect of bone marrow suppression, specifically, leukopenia.

The alpha-herpesviruses herpes simplex (HSV) and varicella zoster virus (VZV) often complicate the post-transplant period. One study showed 14% of heart-lung transplant patients developed mucocutaneous herpes infection. HSV pneumonitis occurs in 5 to 10% of heart-lung recipients. Zoster afflicts some 8 to 15% of LT recipients (11). Initial VZV infection may cause visceral disease in 14 to 33% of cases but rarely

causes meningoencephalitis ([3]). In contrast, EBV, a gamma-herpesvirus, infects 90% of people by age 35. One in 5 heart-lung transplant patients will have some form of EBV reactivation, with half experiencing sore throat, fever, and malaise. EBV is also associated with PTLD. Although estimates vary, the 8% incidence of PTLD in LT recipients may exceed rates in other solid organ transplants ([1]). Mortality from PTLD is 69 to 81%.

Reactivation of the beta-herpesvirus human herpes virus 6 (HHV-6), infection causes no distinct clinical syndrome in LT recipients other than meningo-encephalitis ([12]), but in some cases, HHV-6 may trigger BO. One study showed 20 of 30 lung and heart-lung transplant recipients had evidence of HHV-6 reactivation approximately 18 days post-transplant. Seven of these patients died within 3 months.

Community-acquired respiratory viruses, such as respiratory syncytial virus (RSV), parainfluenza virus, influenza virus, adenovirus, rhinovirus, coronavirus, human metapneumovirus, and enterovirus, infect both immunocompromised and immunocompetent patients. LT recipients may present with atypical symptoms, such as a subtle decrease in pulmonary function. Viral shedding is often prolonged. In addition, respiratory viral infections are a risk factor for both acute and chronic rejection ([13]). In a comparison of 50 LT recipients with respiratory viral infections and 50 without infections, 8 of the infected patients developed BO 3 months post-infection compared with none in the uninfected cohort patient population ([14]). Laboratory diagnosis of viral infections may require the use of routine cell cultures, shell vial cell cultures, immunofluorescence techniques, rapid immunoblot or enzyme immunoassay (EIA) testing, or molecular analysis. Due to the relatively low sensitivity and specificity of many of the rapid tests, confirmatory testing by other methods is usually required, and the use of molecular analysis is becoming more commonplace. Specifically, multiplex molecular testing is detecting increases in mixed viral infections, which were not previously detected using traditional viral culture methods. The significance of mixed viral infections is not fully known, but preliminary findings show increased severity of disease in some cases, which may impact the care and treatment of the patient.

Fungal infections

Fungal infections occur in 15 to 35% of LT recipients ([15]), with *Candida* spp. currently the third most common cause of bloodstream infection. Isolation of *Candida* spp. from the respiratory tract typically indicates colonization, not invasive candidiasis, and is not usually treated. However, in immunocompromised transplant patients, candidemia may lead to metastatic infections half of the time compared to only 5% in immunocompetent persons. In addition, *Candida* spp. may cause anastomotic infections, which are usually diagnosed by bronchoscopy.

Perhaps the most feared pathogens in LT recipients are *Aspergillus* spp., which can cause asymptomatic colonization, isolated tracheobronchial infection, invasive pneumonia, and systemic infection. Airway colonization rates of 20 to 56% have been reported, with an estimated 5% of these progressing to disease. *Aspergillus* tracheobronchitis with ulcerations, pseudomembranes, eschar, bronchial suture line dehiscence, anastomotic infections or bronchial stenosis may occur within 6 months in 4 to 6% of LT patients. Less than 10% of patients develop invasive aspergillosis, usually within the first 6-month post-transplant period, though infection can occur after 3 years ([15]).

The overall incidence of invasive aspergillosis ranges from 4 to 23.3% in LT recipients ([16]). Invasive aspergillosis and tracheobronchitis carry mortality of 50 to 78% and 14 to 18%, respectively ([15],17). Besides the lung, *Aspergillus* may invade the CNS. One retrospective study of 598 lung, heart-lung, and heart transplant (HT) recipients found 4 *Aspergillus* brain abscesses over a 14-year period. All 4 died ([12]). *Aspergillus* disease may precede or follow rejection. Detection of this mold should prompt a search for rejection, and patients with BO may need surveillance for *Aspergillus* ([15]). Lipid formulation amphotericin B, caspofungin, and voriconazole have been used successfully for treatment.

The third most common invasive fungus among all transplant recipients is *Cryptococcus neoformans*. It can cause pneumonia or disseminated disease. LT patients have a 1 to 2.3% incidence of meningitis, perhaps a bit less than other SOT recipients ([18]). It can also cause primary cellulitis and skin nodules.

Pneumocystis jirovecii pneumonia may afflict 10 to 40% of LT recipients who receive no trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis, which represents a higher incidence of disease than any other SOT recipients. With preventive therapy, the incidence of infection is low.

Other fungal infections are also increasing in LT patients. Disease from *Fusarium* spp. may be on the rise, causing lung nodules, endocarditis, and skin lesions in heart-lung transplant and LT patients. Although *Scedosporium* infections may be rare in LT recipients, they, too, may be becoming more common. At one transplant center, *Scedosporium apiospermum* was isolated from respiratory cultures in 5 lung transplant recipients from 1989 to 2006. Three of the recipients had cystic fibrosis and had positive cultures for *S. apiospermum* prior to transplantation (see "Heart Transplant" below for fungal laboratory diagnosis). In the post-transplant infections, 2 patients appeared to be colonized; in 3 patients, disseminated disease developed. The 3 patients who developed disseminated disease died. The median time from transplant to onset of infection was 14 months (range, 1 to 18 months) ([19]).

Heart Transplant

HT has been performed for over 4 decades, with more than 2,000 completed yearly in the U.S. Over 80% of patients survive the first year after transplant ([20]). Even though rejection is the most common cause of death in the first year after transplant, infections are the most common cause of death later in the post-transplant period. The infections occurring after transplant are commonly organized by time period since the transplant (0 to 1 months, 1 to 6 months, and greater than 6 months) based on risks of net immunosuppression and epidemiologic exposure ([3]). Although HT recipients are susceptible to all infections, a few infections are unique to this population. These include infections related to ventricular assist devices (VADs) present prior to transplant, toxoplasmosis, and New World

trypanosomiasis. Here, we review, by organism, infections that may present in the HT recipient.

Bacterial infections

HT recipients, particularly in the early post-operative period, are at risk for hospital-acquired infections, including bacterial pneumonia in 25% of patients and bacteremia in approximately 15% (21,22). The causative pathogens are the usual bacterial agents that cause hospital-related infections, including *S. aureus*, coagulase-negative staphylococci, *P. aeruginosa,* and members of the *Enterobacteriaceae*. Multidrug resistant gram-negative bacteria, which are increasing in frequency worldwide, are present in post-transplant patients, as well.

Patients with bacteremia can develop the complication of endocarditis in the transplanted heart (23). HT recipients are also at risk for developing mediastinitis (24) at a higher rate than those undergoing thoracotomies for other procedures. Patients who require a VAD prior to transplant are at higher risk for infection than patients who do not have VADs. These individuals are susceptible to bacteremias, VAD endocarditis, pocket infections, drive line infections, and mediastinitis (25).

Clostridium difficile-associated diarrhea occurs in up to 4% of HT recipients. Presentation is similar to normal hosts, but the disease may often be more severe. More recent studies suggest that oral vancomycin is the preferred therapy for severe *C. difficile*-associated diarrhea, (26). Diagnosis can be made by the use of latex agglutination assays for toxins A and B concurrently with glutamate dehydrogenase common-antigen testing, by EIA, by culture, by cytoxicity assay, or by a molecular gene amplication assay.

HT recipients are also at risk for opportunistic bacterial infections, such as listeriosis and nocardiosis. *Listeria monocytogenes* and *Nocardia* sp. infections usually occur within the first 6 months after transplant or in patients who have recently undergone treatment for rejection due to their impaired cell-mediated immunity. The use of TMP/SMX for preventing *P. jirovecii* infection is also useful for preventing infection caused by both of these organisms. Listeriosis is quite uncommon in SOT recipients. The disease usually begins

with gastrointestinal symptoms that can progress to bacteremia. This bacterium has a predilection for the CNS and can cause meningitis, as well.

A 2007 review showed that *Nocardia* infections occurred in 2.5% of HT recipients. Nocardiosis usually presents with pulmonary disease, which progresses to CNS involvement. Diagnosis can be made by biopsy or culture of the infected site, but the laboratory must be specifically notified to look for *Nocardia* spp. The organism grows slowly and may be overgrown by routine bacteria; however, fungal culture typically allows the extra incubation time required to isolate the organism. Gram stain examination of clinical material may demonstrate gram-positive, filamentous, branching, beaded rods that have a weakly acid-fast appearance with a beaded morphology. Tests that are useful for the identification of *Nocardia* spp. include (i) hydrolysis of gelatin, casein, xanthine, and tyrosine; (ii) growth at 45°C; (iii) acid production from rhamnose; (iv) antibiotic susceptibility pattern; and (v) various molecular technologies, such as nucleic acid sequencing and mass spectrometry.

Mycobacterial infections are also a concern in HT recipients. Reactivation of *M. tuberculosis* can occur in up to 2% of patients. It usually occurs in the first 6 months after transplantation and is more likely in those who develop rejection. Presentation and treatment can be similar to disease in non-transplant recipients; however, one-third to one-half of all cases of active tuberculosis after transplantation are disseminated or occur at extra-pulmonary sites compared to only 15% of cases in healthy hosts (27). Caution should be exercised when treating either latent or active tuberculosis in transplant recipients, due to the rifamycins' interactions with some immunosuppressive agents. The cultural laboratory diagnosis of *M. tuberculosis* infection relies on the use of broth and/or solid media. Newer automated broth methods can detect mycobacterial species within days or 1 to 2 weeks of incubation, while solid agar methods may take up to 6 weeks. Positive broth or agar cultures may be supplemented with molecular probes, which can identify specific species. In recent years, rapid molecular methods have been successfully used, but they rely on early clinical suspicion. DNA

probe assays based on two sequence databases have been reported (28). One is used for species identification and the other for *M. tuberculosis* rifampin resistance. Special media and conditions may be required for culture of non-*M. tuberculosis* strains, such as *M. haemophilum* and *Mycobacterium genavense*.

Viral infections

Both CMV and EBV can cause significant disease in HT recipients. If either the donor or the recipient has latent CMV infection, CMV usually reactivates within the first 3 months after transplantation without some form of preventive therapy. The highest risk occurs when the donor is seropositive for CMV but the recipient is seronegative — a CMV mismatch. The risk of the recipient developing primary CMV infection in this situation is as high as 85% (29).

CMV disease usually presents with fever, malaise, myalgias, and bone marrow suppression. End-organ disease can occur and may involve the gastrointestinal tract, lungs, heart, liver, or brain. CMV also has an immunomodulatory effect. Active CMV infection has been found to be an independent risk factor for the development of other infections, such as invasive fungal disease and EBV-related PTLD. CMV has also been implicated as a cause of acute and chronic allograft injury, such as accelerated coronary artery disease in HT recipients (30).

Two strategies are commonly used to prevent both the direct and indirect effects of CMV infection: preemptive therapy and universal prophylaxis. In preemptive therapy, patients are monitored at regular intervals for the development of CMV viremia. Patients with viral replication are then treated with antiviral therapies, such as ganciclovir, to prevent CMV disease. Universal CMV prophylaxis, on the other hand, gives all "at risk" patients antiviral therapy for a defined duration to prevent the development of the disease. Isolation and identification of CMV from blood and other clinical specimens using traditional cell culture technologies or by shell vial culture lack sufficient sensitivity and do not provide quantitation of the viral load. CMV antigenemia testing, detecting the pp65 protein of CMV within polymorphonuclear leukocytes in blood, provides a semi-quantitative result and

is a specific marker for active and early infection. Newer molecular tests are increasingly being used for CMV due to increased sensitivity and earlier detection of viremia. Standardization is now available for these and other molecular tests from the World Health Organization (WHO) and National Institute for Science and Technology standards for CMV.

EBV is associated with most cases of PTLD. The highest rate of PTLD is seen in the first year after transplantation. However, these cases represent only one-fifth of the cumulative 10-year PTLD burden. When PTLD develops within the first year after transplantation, it can present as a mononucleosis-like syndrome and later develop into a fulminant malignant disease with over 75% mortality. After the first year, late-onset PTLD presents as a non-Hodgkins lymphoma. Treatment includes chemotherapy and reduction in immunosuppression (31).

Since EBV replication usually precedes the onset of clinical symptoms, there is growing interest in the use of sensitive molecular EBV tests to detect early EBV-associated PTLD. These methods need standardization, as no WHO standard is available. When quantitative PCR assays are used, there is consistently a 3- to 4-order-of-magnitude difference between normal peripheral blood viral load of a healthy carrier and the viral load detected in a PTLD patient. Testing EBV viral loads may assist in (i) early detection, (ii) preemptive therapeutic intervention, and (iii) evaluating therapeutic effectiveness.

Finally, as with LT patients, many common respiratory viruses can cause morbidity and mortality in the HT population, including influenza virus, RSV, parainfluenza virus, and human metapneumovirus (32). The seasonality of these viruses appears to be the same as in the general population. The viruses cause a range of disease severity from rhinorrhea to pneumonia. Transplant recipients are at higher risk of complications from the viruses.

Fungal infections

As with all SOT recipients, fungi play an important role in causing infections in HT patients. These include *Candida* spp., *C. neoformans*, *P. jirovecii*, the dimorphic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*), and the filamentous molds, including *Aspergillus* spp. *Candida* spp. are the most common cause of invasive fungal infections among SOT recipients (33).

Candida infections can vary in severity from mucosal involvement to fungemia to disseminated disease. The less serious mucosal infections can occur at any time after transplantation, while the more severe infections usually occur as a complication of hospitalization. Candidemia usually results from indwelling catheters and the use of broad-spectrum antimicrobial agents. Candidemia can result in disseminated disease involving the liver, spleen, kidneys, heart, and eyes. Invasive candidiasis generally occurs within 3 months after transplantation (34). Diagnosis can be made via scrapings or biopsy of mucosal surfaces, by positive culture of a sterile site, or by histological staining of the involved organ. Diagnosis is commonly established by culture, since *Candida* spp. are easily grown on routine media used in mycology laboratories and are readily identified by commercially available systems (35). Treatment of these infections in transplant recipients is similar to treatment of non-transplant recipients, based on the 2009 Infectious Diseases Society of America guidelines (36).

Cryptococcosis is the third most common fungal infection following an HT procedure. The overall incidence in HT recipients is 2.8%, ranging from 0.3 to 5% (37). Cryptococcal disease usually develops after inhalation of the organism. The syndrome begins with pulmonary disease and is followed by dissemination. The organism has a propensity to cause meningitis, osteomyelitis, and cellulitis. In one report, 61% of HT recipients had disseminated disease, 54% had pulmonary disease, and 8.1% had skin, soft tissue, or bone involvement. All patients with suspected cryptococcosis should have a lumbar puncture and blood and urine cultures to determine the extent of the disease. The diagnosis is usually made by detecting the cryptococcal polysaccharide capsular antigen in serum and/or cerebrospinal fluid (CSF), by recovery of the organism by culture, or by histologic detection of the organism in tissue using the mucicarmine capsule stain. Treatment includes amphotericin B with flucytosine, followed by fluconazole. Recent data suggest that the lipid formulations of amphotericin B significantly improve outcome in HT recipients with CNS cryptococcosis.

P. jirovecii pneumonia (PJP) occurred in up to 10% of HT recipients prior to the introduction of effective prophylaxis. It usually occurs in the first 6 months following transplantation without this prophylaxis. The incidence has decreased due to prophylaxis, as well as the reduction in corticosteroid use in organ transplantation. Clinical presentation of PJP is usually subacute with dyspnea, non-productive cough, and hypoxemia. The diagnosis can be made with methenamine silver staining and other stains of induced sputum or bronchioalveolar lavage specimens. Specific immunofluorescence stains have also been used with success. Treatment with high-dose TMP/SMX is recommended. In patients with hypoxemia, adjunctive corticosteroids should be administered as well. Because of the high incidence of PCP, prophylaxis with TMP/SMX for 6 to 12 months after HT is recommended (38). Dapsone is often used as a second-line agent.

Mycotic infections caused by the dimorphic fungi also occur in HT recipients. They can be a result of reactivation of previously dormant infection or a result of new exposure. *Histoplasma* infection is rare post-transplantation, with an estimated incidence of <1% in areas of endemicity. This infection occurs after inhalation of the organism and frequently results in pulmonary disease. If the infection is not cleared, the transplant recipient can develop disseminated disease involving the liver, spleen, bone marrow, mucosa, and skin. Symptoms include fever, chills, malaise, and fatigue. The diagnosis is made by culturing the affected tissue or by histologic examination. Other methods of diagnosis include *H. capsulatum* capsular polysaccharide antigen testing of blood and urine by EIA or in situ hybridization. Treatment with amphotericin B followed by itraconazole is recommended (39).

Coccidioidomycosis incidence following HT is 3 to 9% in areas of endemicity (40). It usually occurs after inhalation of the organism or reactivation of previously contained disease. *C. immitis* usually disseminates quickly in transplant recipients and can cause

meningitis or osteomyelitis. Transplant recipients can develop fevers, headaches, nuchal rigidity, and altered mentation; CNS coccidioidomycosis can be fatal in these patients. The diagnosis can be made histologically by visualizing the unique spherules of *C. immitis*. *C. immitis* may easily infect laboratory personnel, so appropriate safety precautions must be instituted when growth of a mold colony suggests the possibility of this organism. Bronchoalveolar lavage fluid, CSF, and tissue are the preferred specimens for diagnosis. Sputum may also be cultured; however, in some cases, sputum production may be scant. Treatment of coccidioidomycosis with amphotericin B followed by fluconazole is recommended.

Blastomycosis has been infrequently described as an opportunistic infection following HT. The disease can result in pneumonia followed by extra-pulmonary dissemination, often to the skin. The diagnosis of blastomycosis can be made by culture or histology. Dimorphic mold safety precautions are warranted for suspect colonies. Treatment with amphotericin B, as first-line therapy, followed by itraconazole is recommended.

The incidence of invasive aspergillosis in HT recipients ranges from 1 to 14%. *Aspergillus* is usually inhaled from the environment, causing pneumonitis or sinusitis. The organism can then quickly disseminate, causing significant morbidity and mortality. In one study, the mortality rate for HT recipients with invasive aspergillosis was 66.7% (1). *Aspergillus* frequently causes CNS infection, but any organ can be involved. Independent poor prognostic factors among SOT patients include hepatic insufficiency, malnutrition, and CNS disease.

Making a diagnosis of *Aspergillus* infection is difficult. The definitive method of diagnosis includes both microbiologic and histological confirmation. Cultures of the respiratory tract lack sensitivity, and a positive culture does not necessarily indicate invasive disease. In HT recipients, the positive predictive value of a positive *Aspergillus* culture from the respiratory tract was 60 to 70% (41). Therefore, other methods that can be used to aid in diagnosis include galactomannan testing, 1-3, β-D-glucan testing, radiographic findings consistent with pulmonary disease, such

as the halo sign, or cultural recovery of the mold from a normally sterile site. Treatment of invasive aspergillosis usually includes the prompt initiation of voriconazole or lipid formulations of amphotericin B. Voriconazole is now the drug of choice for treatment of invasive aspergillosis in all patients, including SOT recipients. The echinocandins may also play an adjunctive role.

There have been other mold infections reported in the HT recipient, including zygomycosis, fusariosis, and phaeohyphomycosis (42). Culture is usually relied upon to establish the diagnosis of these infections. Although more "home brew" molecular testing is in development for the detection of these fungi, the methods are poorly standardized.

Parasitic infections

Two parasitic infections are worth noting in HT recipients because they cause more problems in this population than in other SOT recipients. The first is *Trypansoma cruzi*, the cause of American trypanosomiasis. The second is *Toxoplasma gondii*, which causes toxoplasmosis. These two parasites play an important role because they specifically infect the heart and can be transmitted via the donor organ.

T. cruzi occurs in Central and South America and, in these areas of endemicity, chagasic cardiomyopathy is the third leading cause of HT infections (21.9% of all heart transplants) (43). Reactivation after transplantation occurred in 26.5% of recipients. Two reports of acute Chagas infection by organ transplantation from unscreened donors have been published in the U.S. All transplant candidates who have lived in regions of endemicity should be serologically tested for *T. cruzi* infection. If either the donor or the recipient is seropositive, parasitemia can occur in up to 70% of the recipients (44). The recipient should receive benznidazole for 2 months. In addition, they should have close monitoring during the first 16 weeks and then monthly thereafter to make sure no reactivation occurs.

T. gondii serological testing should be done on all cardiac donors and recipients because the organism can persist latently in the myocardium. The most common presentation of toxoplasmosis is myocarditis and dissemination as opposed to encephalitis (45). Diagnosis of the infection should be performed

by histology; serology is not adequate to diagnosis reactivation of *T. gondii* infection (46). Treatment of *T. gondii* infection includes pyrimethamine and sulfadiazine with folate rescue with leucovorin. If serologic testing is positive, the HT recipient should receive prophylaxis with TMP/SMX or with pyrimethamine. Without prophylaxis, up to 75% of seropositive patients develop symptomatic infection, usually within 3 months after transplantation. The routine use of TMP/SMX for PCP prophylaxis has decreased the risk of post-transplant toxoplasmosis (47).

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