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Special Article

Endemic Fungal Infections in Solid Organ Transplantation

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Abbreviations: AIDS, acquired immune deficiency syndrome; ARDS, adult respiratory distress syndrome; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; DNA, deoxyribonucleic acid; EIA, enzyme immunoassay; GMS, Grocott methenamine-silver; HIV, human immunodeficiency virus; HPLC, high performance liquid chromatography; IDSA, Infectious Diseases Society of America; IgG, immunoglobulin G; IgM, immunoglobulin M; KOH, potassium hydroxide; PAS, periodic acid-Schiff; PCR, polymerase chain reaction.

Introduction

The endemic mycoses, histoplasmosis, blastomycosis and coccidioidomycosis, are fungal diseases prevalent in specific geographic regions. The environment is the main source for exposure to these fungi, with the respiratory tract serving as the primary portal of entry into the human body. Although the epidemiologic and clinical features of each infection are unique, some characteristics are shared. Symptomatic disease occurs in both the immunocompetent and immunocompromised host with the severity of infection correlating with underlying immune status. Cell mediated immunity plays an important role in the susceptibility to and control of these infections. Recently reports of endemic fungal infections occurring in organ transplant recipients have been increasing (1,2). In addition, increased recognition of donor-derived fungal infections in recipients prompted the recent development of guidelines discussing the unique characteristics, evaluation and approach to their management (3). Although the true incidence of these infections among this population is unknown, estimates suggest it is <5% (4–6). The focal geographic distribution of the endemic fungi and indolent symptoms of infection frequently lead to diagnostic delays and contribute to increased morbidity and mortality (5,7). Knowledge of the epidemiology, pathogenesis, clinical manifestations, diagnostic methodologies and therapy will enable clinicians to more effectively identify and manage transplant recipients with endemic mycoses.

Blastomycosis

Epidemiology and pathogenesis

Blastomycosis refers to disease caused by the fungus, *Blastomyces dermatitidis*, which occurs more often in persons living in the midwestern, southeastern and south central United States, particularly along the Ohio-Mississippi River Valley (8). *B. dermatitidis* is also found in the soil of northern New York and Canadian provinces that border the Great Lakes and St. Lawrence Seaway. Recent studies have shown an increase in the incidence of blastomycosis in some of these endemic regions (6,9,10). The majority of reported cases of blastomycosis after organ transplantation have occurred in patients residing in endemic areas (1,11).

Historically blastomycosis has been a disease that affects immunocompetent hosts, predominantly men with outdoor occupations or recreational activities involving soil exposure, although many individuals have no apparent source for infection (8,12). In the immunocompromised host, it may be associated with severe pneumonia or disseminated infection, particularly in patients with diabetes, HIV or those receiving chronic corticosteroids or cytotoxic chemotherapy (13). Unlike coccidioidomycosis or histoplasmosis, blastomycosis has been described infrequently as an opportunistic pathogen after solid organ transplantation (1,6,11). In one review, the cumulative incidence posttransplant was only 0.14% during a 16-year period (1). Reports of blastomycosis after renal, cardiac, hepatic and lung transplantation have been published with disease onset ranging from 1 week to 20 years posttransplant (1,6,11,13,14). Blastomycosis in this population may result from primary infection, reactivation of latent disease or conversion of subclinical infection to symptomatic disease after organ transplantation (1).

To date, there are no reports of donor transmission of *B. dermatitidis*.

Infection with *B. dermatitidis* results from inhalation of fungal spores into pulmonary alveoli. Cell-mediated immunity limits progression of *B. dermatitidis* infection in the lungs. If impaired, pneumonia or extrapulmonary dissemination may develop. As such, the majority of transplant recipients who develop blastomycosis are concurrently taking two or more immunosuppressive agents (1,11,13,14). Cytomegalovirus (CMV) infection can also impair cellular immune defenses and, although its exact role is unclear, in one study one-third of patients with posttransplant blastomycosis were co-infected with CMV (1). There are no data to suggest that acute rejection increases the risk for blastomycosis (1). Though less common, blastomycosis arising from primary cutaneous inoculation is also described (15).

Clinical presentation

Pneumonia with or without extra-pulmonary dissemination is the most common presentation of blastomycosis in solid organ transplant recipients (1,6,11,13,14). Although the time from transplantation to development of blastomycosis is variable, the median time ranges from 1 to 2 years posttransplant (1,11). Median time from symptom onset to diagnosis is 14 days (range 3–90 days; Ref.11).

Though nearly all transplant associated blastomycosis infections involve the lungs, the spectrum of pulmonary infection ranges from subclinical disease to acute or chronic pneumonia (11,16). Acute pulmonary blastomycosis is a flu-like illness which develops 30–45 days after initial infection. Typical symptoms include fever, chills, arthralgias and productive cough with an accompanying alveolar or lobar infiltrate on chest radiography. In solid organ transplant recipients the most common presenting symptoms are fever and cough (1). These symptoms are not specific for blastomycosis and, not uncommonly, patients may be misdiagnosed with bacterial pneumonia. Radiographic findings in transplant patients include lobar or interstitial infiltrates, a reticulonodular pattern with mediastinal adenopathy or lung cavities (14). A subset of individuals with pulmonary blastomycosis develop fulminant multi-lobar pneumonia and rapid progression to the adult respiratory distress syndrome (ARDS) and respiratory failure (17). In patients who underwent solid organ transplantation, diffuse bilateral pneumonia was the most common radiographic finding; 78% developed respiratory failure and ARDS complicated 67% of cases. The majority of patients that developed ARDS died (1).

Chronic pulmonary blastomycosis may follow acute infection with more prolonged symptoms such as fever, night sweats, anorexia, weight loss, productive cough, pleurisy and occasional hemoptysis. Chest radiography or a computed tomography (CT) scan may show a mass-like infiltrate or cavitary pneumonia mimicking tuberculosis or malignancy (8). Although blastomycosis usually remains localized to the lungs, 25–40% of those infected will develop extra-pulmonary dissemination manifested by cutaneous, osteo-articular, genitourinary or central nervous system (CNS) disease (8). In solid organ transplant patients, disseminated disease was observed in 36–50%, with skin being the most common site of involvement outside the lungs (1,11,13,14). CNS blastomycosis is rare in the setting of organ transplantation; though has been reported (11,13). Fungemia is rare.

Diagnosis

A presumptive diagnosis of blastomycosis is made by identifying the organism in sputum, bronchoalveolar lavage (BAL) fluid or tissue specimens; growth in culture confirms the diagnosis (16). In one study of solid organ transplant patients, culture of sputum or BAL fluid was 100% sensitive for diagnosing pulmonary blastomycosis (1). Alternatively other sites of involvement, such as skin, bone, synovial fluid, brain tissue or cerebrospinal fluid (CSF) may be sampled for histopathologic examination and culture. Gastric lavage cultures may also be a useful diagnostic technique, particularly in pediatric patients, as it may avert the need for more invasive diagnostic techniques (18). The characteristic fungal forms seen on direct examination are large (8–15 μm), broad-based budding yeast. A potassium hydroxide (KOH) wet mount or special fungal stains, may enhance visualization of *B. dermatitidis* in body fluids or tissue. Micro-abscesses and noncaseating granulomas are often observed on histopathology since the initial inflammatory response to *B. dermatitidis* is both neutrophilic and cell-mediated.

A second generation assay for detection of *Blastomyces* antigen in urine, blood and BAL fluid is available and can often lead to more rapid diagnosis than culture (19–21). In patients with blastomycosis, sensitivity of this assay is over 90%. Specificity is 99% in individuals with nonfungal infections and healthy subjects, however, cross-reactivity occurs in 96% of patients with histoplasmosis (19–21). The utility of this test has not been well established in solid organ transplant recipients. Limited data suggest sera from patients with proven blastomycosis tests negative for (1–3)-β-D-glucan (Fungitell®; Ref.22). Currently available serologic tests lack sensitivity and are not useful for diagnosis of blastomycosis.

Treatment

The management of blastomycosis in solid organ transplant recipients follows published guidelines (23). All immunocompromised individuals require treatment and since these patients are more likely to present with severe pulmonary or disseminated infection, amphotericin B is

recommended as first line therapy (III). A lipid formulation, such as liposomal amphotericin B or amphotericin B lipid complex, is preferred because of the reduced potential for nephrotoxicity (23). Amphotericin B is administered for the first 1–2 weeks until clinical improvement is demonstrated at which time transition to oral itraconazole may be acceptable (III) (23). Liposomal amphotericin B is recommended for infection involving the CNS but more prolonged therapy is given, generally 4–6 weeks, before transitioning to azole therapy (III) (23). In some patients with mild pulmonary infection, oral itraconazole may be given as initial therapy but close clinical monitoring is warranted (III). Corticosteroids may be considered as adjunctive therapy in severe blastomycosis-induced ARDS (24).

Fluconazole appears to be less effective for blastomycosis (II-1) and should only be used as second line therapy or in high doses for prolonged treatment of CNS infection (III) (23,25). Oral voriconazole has good CNS penetration and excellent *in vitro* activity against *B. dermatitidis*, thus another option for prolonged therapy of CNS blastomycosis (1,23,26–28). Voriconazole and fluconazole are preferred over itraconazole for CNS infection, given the limited CNS penetration (<1%) and *in vitro* susceptibilities of itraconazole. Data are lacking for posaconazole use in CNS infection. Echinocandins have intermediate to poor *in vitro* activity against *B. dermatitidis* and should not be prescribed (27,28).

The duration of treatment is generally 12 months with resolution of symptoms and signs of infection (III). Consideration may be given to more prolonged treatment courses for organ transplant recipients, although conclusive data are lacking (III) (23). As the *Blastomyces* antigen assay is quantitative, serial measurements can be used to follow treatment response over time both for adult and pediatric patients (11,29). However, using the antigen assay to guide treatment duration, is not well established. In a recent series of 8 transplant associated blastomycosis cases, median time to urine antigen negativity was 22 months (range 10–48 months; Ref.11). Data suggest that relapse of blastomycosis is uncommon after therapy and evidence of cure (1,11).

Pretransplant evaluation

There is no sensitive or specific serologic assay available to diagnose previous exposure to *Blastomyces* or active disease. Careful screening for active infection, including symptom assessment and chest radiography, should be a part of the pretransplant evaluation of patients who live in *Blastomyces* endemic areas. There have been no trials of targeted antifungal prophylaxis for prevention of blastomycosis in organ transplant recipients who reside in endemic regions. At this time primary or secondary antifungal prophylaxis for blastomycosis after solid organ transplantation is not recommended (III).

Coccidioidomycosis

Epidemiology and pathogenesis

Coccidioides species are fungi that thrive in the arid, desert soil of the southwestern United States, particularly the San Joaquin Valley and Sonoran desert of southern California, Arizona and northern Mexico (30,31). Other regions of endemicity include New Mexico, western Texas and parts of Central and South America. Coccidioidomycosis, whether primary or reactivation disease, may also develop in individuals after return from an endemic location or in those without a history of travel to an endemic area. In some cases, exposure to *Coccidioides* occurs when spores are carried to distant locations on fomites or on the surfaces of produce or textiles exported from endemic regions (32). Two species of *Coccidioides* have been identified: *C. immitis* is associated with infection acquired in California and *C. posadasii* with infection acquired outside of California, such as Arizona and New Mexico (33).

Coccidioides spores gain entry into the body when aerosolized from soil and inhaled into the lungs. Increased infection rates have been observed after rainy seasons, dust storms or earthquakes which disrupt soil and enhance the spread of spores. *Coccidioides* is highly infectious; a single inhaled spore may produce infection. Resolution of infection depends ultimately on T cell immune responses (30,34).

Coccidioidomycosis has been described after lung, kidney, heart and liver transplantation with an incidence of 1.4–6.9% in endemic regions (35–40). The majority of these infections are diagnosed within the first year posttransplant, and in most cases, result from primary or reactivation infection. Other risk factors for *Coccidioides* infection in the transplant population include treatment of acute rejection, prior history of coccidioidomycosis and/or positive pretransplant serologies and African American race (37,41). It is unclear whether concomitant immunosuppressing conditions such as diabetes or CMV infection further increase the risk for posttransplant coccidioidomycosis. Donor transmission of *Coccidioides*, has also been described (42–45). In these cases, recipients presented with symptoms within 1 month after transplantation, most with severe infections. Prompt identification of recipient infection and initiation of antifungal prophylaxis in other common donor recipients has led to more favorable outcomes in recent transmission events (41,42).

Clinical presentation

Coccidioidomycosis should be considered in the differential diagnosis of any solid organ transplant recipient with a febrile illness who has traveled to or resides in an endemic area. Clinical manifestations of *Coccidioides* infection in solid organ transplant recipients range from asymptomatic seroconversion to widespread dissemination with multi-organ failure and shock (39). However, unlike

immunocompetent hosts in whom infection is often mild and self-limited, organ transplant patients are more likely to develop severe pneumonia and disseminated infection (39,41). The most common symptoms of pulmonary coccidioidomycosis are fever, chills, night sweats, cough, dyspnea and pleurisy (39). Radiographic findings are varied and may consist of lobar consolidation, pulmonary nodules, mass-like lesions, interstitial infiltrates or cavitary disease (39,41). Pulmonary coccidioidomycosis can progress to severe pneumonia with multilobar involvement, diffuse nodularity, ARDS and respiratory failure, particularly in the setting of immunosuppression (39).

In individuals with coccidioidomycosis, extrapulmonary infection occurs in 1–5%. Risk factors include male gender, African, Filipino or Native American ancestry, pregnancy and other forms of immunosuppression (46). It is unclear whether these factors pose any additional risk for dissemination of *Coccidioides* in solid organ transplant recipients. Extrapulmonary infection usually manifests as cutaneous, osteo-articular or meningeal disease. Widespread dissemination with multi-organ involvement, including graft infection, is common in patients with coccidioidomycosis after organ transplantation (38–41). CNS *Coccidioides* infection, usually presenting as meningitis with headache and/or altered mentation, has been reported in organ transplant recipients and may be fatal (40,47). *Coccidioides* fungemia is an uncommon manifestation of disseminated infection, but is associated with 30 day mortality of 62% (48). Coccidioidomycosis in children presents similarly as in adults, though reactive rashes, including erythema multiforme are more common (49).

Diagnosis

Culture of sputum, BAL fluid or tissue is the gold standard for diagnosis of coccidioidomycosis. Blood, CSF and pleural or peritoneal fluids are less likely to be culture positive. *Coccidioides* may also be diagnosed by histopathologic examination, although this is less sensitive than culture. On direct examination, visualization of the characteristic spherule containing endospores is diagnostic of infection (45). Spherules are not detected by Gram stain, but microscopic identification may be aided by a variety of fungal stains. *Coccidioides* reverts back to the highly infectious mould form when cultured and care must be taken to prevent aerosolization and accidental inhalation in the laboratory. Thus it is imperative to notify laboratory personnel when *Coccidioides* is suspected.

Serologic testing can be useful for diagnosing *Coccidioides* infection when histopathology or cultures are negative. Serologic testing is based on the identification of IgM or IgG antibodies. IgM appears first and can be detected in serum by a tube precipitin method, immunodiffusion, latex agglutination and enzyme immunoassay (EIA) within 1–3 weeks of acute *Coccidioides* infection. IgG follows the IgM response and can also be detected by several methods. Complement-fixing IgG antibodies, which typically appear 2 weeks after infection, can be quantitated to assess the severity of infection; high or rising IgG antibody levels may be seen with worsening pulmonary infection or disseminated disease (46). Conversely, IgG antibody titers should decrease with effective therapy. Diagnosis and management of meningeal coccidioidomycosis requires lumbar puncture for CSF analysis. Because CSF cultures are positive in only 15% of patients with coccidioidal meningitis (50), CSF complement-fixing IgG antibodies are the primary method for diagnosis (47). Immunosuppression can lead to diminished immunoglobulin responses in serum and CSF, and false negative serologic results have been observed in solid organ transplant recipients, complicating test interpretation and diagnosis (40,41,50,51).

Other nonculture based diagnostic methods for detecting coccidioidomycosis include a *Coccidioides* antigen EIA and *Coccidioides* polymerase chain reaction (PCR) testing. The *Coccidioides* antigen EIA (available for urine, serum, BAL and CSF) can be useful in the rapid diagnosis of more severe forms of coccidioidomycosis. Like the *Blastomyces* and *Histoplasma* antigen assays (discussed in other sections), this assay lacks specificity among individuals with other endemic mycoses (52). *Coccidioides* PCR testing of respiratory specimens and CSF is available in some centers and recent reports indicate its promise as a rapid diagnostic method (53,54). The utility of these assays has not been studied extensively in organ transplant recipients.

Treatment

Acute pulmonary coccidioidomycosis may be mild and self-limited in the immunocompetent host and antifungal therapy may be withheld with close clinical monitoring (III) (55). However all patients with underlying immune impairment, including organ transplant recipients, must be treated regardless of the severity of infection (III).

As for blastomycosis, treatment of coccidioidomycosis in the setting of solid organ transplantation follows published guidelines (55). Treatment options for mild to moderate coccidioidomycosis include oral fluconazole or itraconazole (I) (55,56). Amphotericin B, or preferably a less toxic lipid formulation, is generally reserved for severe pneumonia or disseminated infection (III). The decision to treat with oral versus intravenous therapy must be individualized, but symptom severity, respiratory status, extent of infection and the ability to take enteral therapy must be considered.

Alternatively, meningeal coccidioidomycosis may be treated with high dose fluconazole (II-1), which has excellent CSF penetration, but lifelong therapy is necessary to prevent relapse (III). Repeat lumbar puncture during therapy to document improvement in CSF parameters and

a decline in CSF complement-fixing antibodies is recommended (III).

Favorable clinical responses have been demonstrated with voriconazole and posaconazole for treatment of refractory coccidioidomycosis or when toxicity develops to standard therapies (57–59). The echinocandins have variable *in vitro* activity against *Coccidioides* and sufficient clinical data are limited (28,60,61). Lifelong antifungal prophylaxis is recommended for organ transplant recipients once active coccidioidomycosis has been controlled to prevent relapse (46).

Pretransplant evaluation and posttransplant interventions

Preventing *Coccidioides* infection in solid organ transplant recipients is imperative because infection is frequently severe and mortality is high (39,41). The risk of developing coccidioidomycosis after organ transplantation is greater in persons with a past history of infection or positive antibodies for *Coccidioides* before surgery (46,62). During the pretransplant evaluation, clinicians must determine if transplant candidates have a history, even remote, of residence in or travel to an endemic area given the risk for reactivation of latent infection posttransplant. The evaluation should include an assessment of previous or current symptoms consistent with coccidioidomycosis, a chest x-ray and serologic testing. Any evidence of prior or active infection requires evaluation by an infectious diseases specialist, with ultimate clearance for transplant listing determined on a case by case base (III) (46). When possible, organ transplantation should be deferred in patients with active coccidioidomycosis until the infection is clinically, serologically and radiographically quiescent (III) (46,63).

Prophylactic antifungal therapy with fluconazole is recommended for all transplant recipients with a past or recent history of coccidioidomycosis or positive *Coccidioides* serologies before surgery (II-1) (38,46,51). The recommended fluconazole dose (200–400 mg) and duration (6–12 months or lifelong) varies based on the extent of prior/current infection and serology results (38,46). Based on a large retrospective review, universal antifungal prophylaxis for liver transplant recipients who reside in endemic areas for 6–12 months posttransplant is recommended (38). Lifelong antifungal prophylaxis is also recommended for recipients who receive organs from donors with active coccidioidomycosis or positive serologies (III) (46,62). For recommendations specifically addressing donor-derived coccidioidomycosis, we refer the reader to recently published guidelines (3). Though antifungal prophylaxis reduces the risk for posttransplant coccidioidomycosis, it does not eliminate it. Among 100 patients in an endemic area who underwent solid organ transplantation with prior coccidioidomycosis, 94% received antifungal prophylaxis, of whom five experienced reactivated infection. Conversely, of the six patients who did not receive antifungal prophylaxis, none developed reactivation infection (37). Further characterization of risk factors for recrudescent infection requires additional study.

Posttransplant clinical and serologic monitoring of at-risk patients should be performed periodically to assess for evidence of reactivation infection. Because reactivation infection occurs most commonly in the first year after transplantation, an evaluation should be performed every 3–4 months initially, then once or twice yearly thereafter (III) (46).

Histoplasmosis

Epidemiology and pathogenesis

Histoplasmosis is an opportunistic fungal infection caused by the dimorphic fungus, *Histoplasma capsulatum.* Although found in many areas of the world such as South America, India and Bangladesh (64–66), the organism is endemic in the Ohio and the Mississippi River valleys in the United States. The clinical spectrum of infection ranges from a self limited febrile illness to severe multi-organ dysfunction, depending on the size of the host inoculum and immune status of the infected individual. Posttransplantation histoplasmosis is rare, with an estimated incidence of $<1\%$, even in endemic areas (2,11,66,67).

Primary infection occurs via inhalation of *H. capsulatum* mycelia, typically found in high concentrations in excavated soil, avian or bat droppings in endemic areas. Exposure to disrupted soil around construction or agricultural areas, caves where bats reside or buildings inhabited by birds or bats pose particular risk. Intact cellular immunity is critical to containing and eradicating *Histoplasma* infection, thus solid organ transplant recipients are at particular risk for significant infection. Histoplasmosis in transplant recipients can result from a primary infection, reactivation of previous infection, or rarely, transmitted via an infected allograft (11,68–70). Human to human transmission has not been reported.

Clinical presentation

Histoplasmosis was initially described among liver and kidney transplant recipients (71–73), however more recent case series also include heart, lung and kidney-pancreas transplant recipients (2,11,66,67). The illness most commonly presents in an occult manner among transplant recipients, with the burden of disease often out of proportion to the severity of symptoms at initial presentation. Although a spectrum of clinical manifestations have been reported in solid organ transplant recipients, the most common form is progressive disseminated infection, characterized as a subacute febrile illness with radiographic and/or laboratory evidence of extrapulmonary infection. The typical period from onset of symptoms to diagnosis is 2–4 weeks (2,11,66,67). As the infection progresses,

associated clinical findings include hepatosplenomegaly, pneumonia, gastrointestinal involvement, pancytopenia, weight loss, hepatic enzyme elevations, mucosal/skin findings and increased lactate dehydrogenase levels. Any organ can be involved with *Histoplasma* as cases of septic arthritis and prostatitis have been described in transplant recipients (64,74). Unusual presentations in more severely ill patients have also been reported as part of the clinical picture, such as thrombotic microangiopathy and hemophagocytic lymphohistiocytosis (75–77). Most infections occur within the first 1–2 years after transplantation, though patients can present over a broad time range from months to several years posttransplant (2,11,66,67). Reports of histoplasmosis in transplanted children are few. However, in nonimmunosuppressed children, symptoms of histoplasmosis are similar to those that occur in adults, though meningitis accompanying progressive disseminated infection is more commonly seen in infants <2 years (78).

Diagnosis

Confirmation of the diagnosis rests on direct visualization of *H. capsulatum* yeast forms with or without granulomas in involved tissues, culture growth of *H. capsulatum* and/or antigenuria/antigenemia. The availability of newer generation antigen assays has improved early detection through increased sensitivity and specificity, as blood and tissue cultures may take up to 4 weeks to demonstrate growth (79,80). The sensitivity of antigen detection in disseminated histoplasmosis is higher in immunocompromised patients (92%) and in patients with more severe illness than in immunocompetent patients (73%). Though not specifically studied in organ transplant recipients, recent case series suggest the sensitivity is comparable for patients with disseminated disease (2,11,67,81). The sensitivity for detection of antigenemia is similar to that for antigenuria (100% vs. 97%) in disseminated infection (81). The specificity of antigen detection is 99%, however, cross-reactive antigen is detected in 90% of patients with blastomycosis, and has also been reported in the setting of other endemic fungal infections such as sporotrichosis (79,81–83). The degree of antigenuria correlates with the severity of disseminated infection: concentrations of ≥19 ng/mL occurs in 73% of severe cases, 39% of moderately severe cases and 17% of mild cases (81). Antigen detection is similarly useful in children.

For patients with pulmonary histoplasmosis, the diagnostic utility of *Histoplasma* antigen detection in BAL fluid carries a sensitivity of 93%, specificity 97%, a positive predictive value 69%, and negative predictive value 99% (84). False-positive results approximate 10% in cases of pulmonary aspergillosis. Cross reactions can be expected in most cases of pulmonary blastomycosis and a lower proportion of those with pulmonary coccidioidomycosis (85). Conversely, the *Aspergillus* galactomannan test (Platelia™, Bio-Rad Laboratories Inc., Hercules, CA, USA, *Aspergillus* enzyme immunoassay [EIA]) is positive in 50% of serum and BAL samples from patients with histo-plasmosis, which could lead to a false diagnosis of aspergillosis (86,87).

Detection of *Histoplasma* capsulatum DNA in human samples by real-time PCR is under investigation (88,89). Case reports have detailed the use of PCR on whole blood and synovial fluid for detection of histoplasmosis (74,90,91). The use of the (1–3)-β-D-glucan (Fungitell®) test in the diagnosis of histoplasmosis is still under investigation. Limited data suggests a sensitivity of the test is 87–89% in disseminated histoplasmosis cases and a specificity of 68% with controls (22,92). Values also correlated with *Histoplasma* antigenuria levels (22).

Histopathologic examination of biopsy specimens from suspected sites of involvement, including liver, lung, skin, lymph nodes and bone marrow can also expedite diagnosis. Special stains such as hematoxylin and eosin and Wright-Giemsa may aid in visualization of *Histoplasma* in blood or bone marrow while GMS or PAS may enhance visualization in tissue.

Although serologic testing is beneficial for the diagnosis of histoplasmosis in the normal host, the diagnostic utility of serologic testing is variable in organ transplant recipients (80,93). For both immunosuppressed and nonimmunosuppressed individuals from endemic areas, potential background seropositivity confounds test interpretation. In healthy individuals with acute histoplasmosis, *Histoplasma* serology by immunodiffusion and complement fixation become positive in the majority of patients by 6 weeks. Seroconversion or fourfold increase in titers strongly suggests the diagnosis of histoplasmosis. However, the effects of immunosuppressive agents on the humoral immune response may blunt the serologic response to infection, decreasing the sensitivity of the test in this setting (94). Among disseminated cases, antibodies are detected in up to 89% of immunocompetent patients but only 18–30% of solid organ transplant recipients (67,81).

Treatment

As the most common manifestation of histoplasmosis in solid organ transplant recipients is progressive disseminated infection, treatment recommendations will be limited to this form. For more detailed treatment recommendations for other forms of histoplasmosis, the reader is referred to the published 2007 IDSA clinical practice guidelines (95). Antifungal agents with proven efficacy in the treatment of progressive disseminated histoplasmosis include amphotericin B deoxycholate, liposomal amphotericin B (96), amphotericin B lipid complex (96) and itraconazole (97). Echinocandins have no established efficacy (28,98,99). Mild to moderate infection may be treated effectively with itraconazole monotherapy (200 mg twice daily for at least 12 months), (II-2). For moderately severe and severe infection, initial therapy with amphotericin is

recommended, (I) (95). As there are no randomized studies of comparative efficacy in organ transplant recipients, the choice of amphotericin formulation is usually dictated by availability, cost and potential for nephrotoxicity. Amphotericin therapy should be continued for 1–2 weeks or until there is stabilization of the infection, followed by "step-down" therapy with itraconazole (200 mg twice daily) to complete a 12 month total treatment course (95,97). In most instances antigen levels correlate with response to therapy over time, though the use of antigen levels to guide duration of therapy has not been established. Case series suggest antifungal therapy can be successfully discontinued after a prolonged course in some individuals despite a persistently positive antigen assay (11,59,67). Concomitant reduction of immunosuppression, especially calcineurin inhibitors, is also an important treatment adjuvant if possible. Criteria for characterizing mild, moderate and severe illness is not well defined in the literature, but rather rest on clinical impression based on factors such as need for hospitalization, hemodynamic stability, respiratory status, extent of infection and ability to take oral medication. Mortality in solid organ transplant recipients with histoplasmosis ranges from 0% to 13% (11,59,67).

Treatment recommendations for children with progressive disseminated histoplasmosis are similar to adults, though longer initial courses of amphotericin are recommended based on published treatment experience (95). Amphotericin-associated nephrotoxicity is generally less severe in infants and children than adults (100).

Other azole agents, specifically voriconazole (59), posaconazole (101,102), fluconazole (103) and ketoconazole, all demonstrate *in vitro* susceptibility against *H. capsulatum*. Clinical efficacy data are limited to small series and case reports, thus inadequate to establish treatment recommendations. Consequently, these agents are considered second line treatment options for those individuals intolerant of itraconazole (III) (95).

Urine and serum antigen levels typically fall with effective therapy and can be used to follow treatment response and assess for relapse. Antigen levels should be measured before treatment is initiated, at 2 weeks and 1 month, then every 3 months during therapy (II-2). In AIDS patients with disseminated histoplasmosis receiving amphotericin B, antigen levels decline most rapidly during the first 2 weeks of treatment. Whereas in similar AIDS patients treated with itraconazole alone, the decline in antigenuria is slower, occurring later during treatment compared to those treated with amphotericin B. With effective therapy, *Histoplasma* antigenemia decreases more rapidly than antigenuria, providing a more sensitive early laboratory marker for response to treatment (104). In a recent series it was observed that 70% of solid organ recipients with positive *Histoplasma* antigen assays had a negative test by 10 months of treatment (11). Monitoring should continue at least 6 months after therapy is discontinued (80). Persistent low level antigenuria may be observed in organ transplant recipients treated for histoplasmosis, despite complete clinical response and an appropriate duration of therapy. Limited experience suggests that antifungal therapy can be safely withdrawn in this situation with careful monitoring for relapse (2,11,62,67,95). Despite the severity of illness upon presentation, treatment efficacy among infected solid organ transplant recipients in the post-azole era ranges from 80–100% (2,11,67). Mortality in one transplant series was 30%, with mortality attributable to histoplasmosis of 13% (11). Immune reconstitution syndrome has also been described in transplant recipients with disseminated histoplasmosis, mainly related to concomitant reduction of immunosuppression (105,106; Table 1).

Pretransplant evaluation

Pretransplant serologic and/or radiologic screening for prior histoplasmosis infection in endemic areas is not recommended based on the low likelihood of subsequent infection (107). Patients who have recovered from active histoplasmosis infection, with or without treatment, during the 2 years before the initiation of immunosuppression may be considered for itraconazole prophylaxis (200 mg daily), although the efficacy and appropriate duration of prophylaxis is unknown. Serial monitoring of urinary antigen levels in individuals with previous infection should also be performed during periods of intensive immunosuppression to monitor for relapse (III) (95). Management of individuals with incidental *H. capsulatum* detection in the explanted organ or donor tissue is not well established. This scenario occurs primarily in lung transplant recipients, and based on one center's experience, antifungal prophylaxis could be considered (67). For additional recommendations regarding donor-derived histoplasmosis we refer the reader to recently published guidelines (3).

Specific issues related to azole therapy

Drug–drug interactions are an important consideration when prescribing azole antifungal agents to organ transplant recipients. Azoles inhibit hepatic cytochrome P450 enzymes and modify the pharmacokinetics of the many drugs metabolized by this route. Azoles increase serum concentrations of cyclosporine, tacrolimus and sirolimus (108–110), thus drug levels of these immunosuppressive agents must be closely monitored in individuals during the initiation and discontinuation of azole therapy to prevent inadvertent drug toxicity or allograft rejection (Table 2). Preemptive dose adjustment is recommended (I). Other immunosuppressive drugs such as mycophenolate, antithymocyte globulin, prednisone and alemtuzumab have no known drug–drug interactions with azoles (108). Pharmacokinetics of azole agents differ between adults and children in that children have more rapid drug clearance, necessitating more frequent and higher dose administration (100). Because of the potential hepatotoxic effects of azole use, hepatic enzymes should be

Table 1: Summary of recommendations

Infection	Geographic distribution	Diagnosis	Treatment	Suggested duration	Strength of recommendation
Blastomycosis	Midwest, Southeast & South central US	Culture, direct visualization, urine/serum antigen	Mild to Moderate: itraconazole 200 mg BID	Minimum of 6–12 months.	II-1
			Moderately severe or severe: AMB[1]	Minimum of 2 weeks of AMB until clinical improvement, then transition to oral azole.	
Coccidioidomycosis	Southwest US	Culture, direct visualization, serology (serum & CSF), urine/serum/BAL/CSF antigen, PCR	Mild to Moderate: fluconazole 400–800 mg daily (preferred) OR itraconazole 200 mg BID	Minimum of 6–12 months followed by chronic suppressive therapy.	I
			Meningeal disease: AMB[1] or fluconazole 800 mg daily	Lifelong suppression for meningitis	II-1
			Moderately severe or severe: AMB[1]	Minimum of 2 weeks of AMB until clinical improvement then transition to oral azole.	
			Pretransplant or donor infection: fluconazole 200–400 mg daily	Minimum of 6–12 months	II-1 III II-1
Histoplasmosis	Mississippi & Ohio River valleys	Culture, direct visualization, urine/serum/BAL antigen, PCR	Mild to Moderate: itraconazole 200 mg BID	Minimum of 12 months.	II-2
			Moderately severe or severe: AMB[1] for 1–2 weeks or until favorable response, followed by itraconazole 200 mg BID		I

[1]There are no established data to recommend a specific amphotericin B (43) preparation. Lipid formulations are generally preferred for patients at high risk for nephrotoxicity.

Table 2: Summary of azole-immunosuppressant drug interactions

Antifungal	Immunosuppressant	Severity of interaction	Interaction	Suggested actions	Evidence
Ketoconazole	CsA, Tac, Sir	+++	↑ Imm level	Avoid	A
Voriconazole	CsA, Tac, **Sir**	+++	↑ Imm level	↓ CsA by 1/2, ↓ Tac by 2/3	A
Itraconazole	CsA, Tac, Sir	++	↑ Imm level	Monitor Imm level	A
Posaconazole	CsA, Tac, Sir	+++	↑ Imm level	↓ CsA by 1/4, ↓ Tac by 2/3	A
Fluconazole	CsA, Tac, **Sir**	++	↑ Imm level	Dose dependent↓ CsA and Tac by 1/2	A

Drugs in bold are contraindicated.
CsA = cyclosporine; Tac = tacrolimus; Imm = immunosuppressant; Sir = sirolimus. +++ = severe interaction, use alternative drug if possible, otherwise monitor levels of immunosuppressant or potential toxic effects and modify dose accordingly; ++ = moderate interaction, requires monitoring levels or potential toxicity, and may require modification of immunosuppressant dosing.

monitored in all individuals before therapy is started, at 1, 2 and 4 weeks, followed by every 3 months during therapy (95).

Issues related to itraconazole therapy deserve special consideration given the variable absorption among patients and among available drug formulations. The lipophilic composition of itraconazole limits its solubility and consequent gastrointestinal absorption. The bioavailability of oral itraconazole is dependent on the dosage formulation and the presence or absence of food. Food enhances the dissolution and absorption of itraconazole capsules, thus the dose should be taken with a full meal. As absorption is reduced with decreased gastric acidity, itraconazole capsules should not be co-administered with medications that lower gastric pH, such as antacids, H2 blockers or proton pump

inhibitors (111–113). Conversely, capsule absorption can be enhanced when taken with an acidic or carbonated beverage such as Coca Cola (114). Itraconazole suspension is preferred over the capsule formulation owing to enhanced gastric absorption (115). Blood concentrations are ~30% higher using the suspension rather than the capsule formulation (115). Itraconazole suspension does not require food or gastric acidity for absorption and is best taken on an empty stomach but the higher cost might be prohibitive in some patients.

Because of the marked intra- and interpatient variability in the pharmacokinetics and absorption of itraconazole, therapeutic monitoring of serum drug levels is strongly recommended to optimize therapy once steady-state has been reached (~2 weeks) (III) (23,116). Random itraconazole serum concentrations of at least 1.0 ug/mL (by HPLC) are recommended and correlate with clinical efficacy. Therapeutic drug monitoring of itraconazole may also be useful for assessing a poor treatment response, managing drug–drug interactions or interpreting an adverse effect (117). Monitoring of voriconazole levels is also suggested in certain clinical scenarios such as in patients with poor clinical response, or with the addition of an interacting medication. Levels of 0.5–2.0 g/mL are to be achieved for efficacy. For posaconazole, conditions that might hinder gastrointestinal absorption would also prompt measurement of drug concentration. The trough goal should be 0.5–1.5 ug/mL for patients with invasive fungal infection (118).

Additional information regarding drug–drug interactions relevant to treating transplant-associated infections can be found in the Drug Interactions section of these guidelines.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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