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Endemic Fungal Infections in Solid Organ Transplant Recipients – Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abbreviations: AMB, amphotericin; ARDS, adult respiratory distress syndrome; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; CMV, cytomegalovirus; CNS, central nervous system; DTAC, Disease Transmission Advisory Committee; DNA, deoxyribose nucleic acid; EIA, enzyme immunoassay; GMS, Grocott methenamine-silver; IDSA, Infectious Diseases Society of America; IgG, immune reconstitution inflammatory syndrome, IRIS; immunoglobulin G; IgM, immunoglobulin M; KOH, potassium hydroxide; NPV, negative predictive value; OPTN, Organ Procurement and Transplantation Network; PAS, periodic acid-Schiff; PCR, polymerase chain reaction; PPV, positive predictive value

Conflict of Interest

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Abstract:

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention and management of blastomycosis, histoplasmosis and coccidioidomycosis in the pre- and post-transplant period. Though each of these endemic fungal infections has unique epidemiology and clinical manifestations, they all share a predilection for primary pulmonary infection and may cause disseminated infection, particularly in immunocompromised hosts. Culture remains the gold standard for definitive diagnosis, but more rapid diagnosis may be achieved with direct visualization of organisms from clinical specimens and antigen based EIA assays. Serology is of limited utility in transplant recipients. The mainstay of treatment for severe infections remains liposomal amphotericin followed by a step down azole therapy. Cases of mild to moderate severity with no CNS involvement may be treated with azole therapy alone. The newer generation azoles provide additional treatment options, but supported currently with limited clinical efficacy data. Azole therapy in transplant recipients presents a unique challenge owing to the drug-drug interactions with immunosuppressant agents. Therapeutic drug monitoring of azole levels is an essential component of effective and safe therapy. Infection prevention centers around minimizing epidemiological exposures, early clinical recognition, and azole prophylaxis in selected individuals.

Introduction

The endemic mycoses are fungal infections that localize to specific geographic regions with worldwide distribution. This guideline addresses the more commonly occurring endemic mycoses occurring in the United States: histoplasmosis, blastomycosis and coccidioidomycosis (cryptococcosis is addressed in a separate guideline). Although each infection has unique epidemiologic and clinical features, many characteristics are shared. Symptomatic disease occurs in both the immunocompetent and immunocompromised host, with the severity of infection typically correlating with underlying immune status. Cell mediated immunity plays an important role in the susceptibility to and control of these infections. 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. The geographic distribution of these organisms is a dynamic process as evidenced by the recent demonstration of shifting and expanding epidemiology of the infections they cause. Unique to transplantation, donor-derived transmission of endemic fungal infections to organ transplant recipients introduces an additional mode of transmission.

Although the true incidence of endemic fungal infections in the transplant population is unknown, estimates suggest it is <5% (1-3). The focal geographic distribution of these fungi and often indolent manifestations of clinical infection frequently lead to diagnostic delays and contribute to increased morbidity and mortality. Obtaining a detailed history regarding travel and/or residence in endemic areas is an important first step in prevention and early diagnosis of these infections. Knowledge of the epidemiology, clinical manifestations, diagnostic strategies, treatment, and preventive approaches will enable clinicians to more effectively identify and manage transplant recipients with endemic mycoses.

Blastomycosis

Etiology

Blastomycosis refers to disease caused by *Blastomyces dermatitidis*. The organism is a dimorphic fungus that is a mold in the environment, converting to a yeast phase at body temperature or in the laboratory at 35-37 degrees C. Yeast cells are 8 to 20 μm in diameter and morphologically demonstrate a doubly thick, refractile cell wall with distinctive broad-based budding, with the daughter cell often as large as the mother cell before detachment. These characteristic features are useful for laboratory identification of *B. dermatitidis.* Infection with *B. dermatitidis* results from inhalation of fungal spores into pulmonary alveoli or more rarely, direct cutaneous inoculation. Host cell-mediated immunity along with the neutrophilic response limits progression of infection from the site of inoculation. If impaired, disseminated infection can result concurrent with the primary infection or lead to reactivation infection (4).

Epidemiology and Risk Factors

Blastomycosis has a distinct geographic distribution as the majority of cases arise among individuals residing proximate to the Ohio and Mississippi Rivers Valleys, upper Midwest, and US states and Canadian provinces that border the Great Lakes and St. Lawrence Seaway. Within endemic areas, the specific environmental niche for *B. dermatitidis* is likely soil and decaying vegetation, especially in proximity to lakes and rivers (4). Historically, blastomycosis has been a disease that affects immunocompetent hosts, predominantly men with outdoor occupations or recreational activities involving soil exposure (5). The majority of reported cases of blastomycosis after organ transplantation have occurred in individuals residing in endemic areas (6, 7).

As compared to other endemic fungal infections, blastomycosis is uncommon in transplant recipients (2, 6, 7). In a case series from an endemic area, the cumulative incidence post-transplant was 0.14% over a 16 year period (6). Likewise, among 64 solid organ transplant recipients with endemic fungal infections enrolled in the Transplant-Associated Infection Surveillance Network (TRANSNET), which included centers within endemic regions, only 9 recipients had blastomycosis over the 5 year study period (2). The timing of cases is varied, ranging from 1 week to 20 years post-transplant, likely reflecting the balance of the timing of the epidemiologic exposure with the net

state of immunosuppression. CMV infection can also impair cellular immunity and, although the exact role is unclear, one study found that one-third of patients with post-transplant blastomycosis had concurrent CMV infection (6). To date, there are no reports of donor transmission of *B. dermatitidis*.

Clinical Manifestations

Pneumonia with or without extra-pulmonary dissemination is the most common presentation of blastomycosis in solid organ transplant recipients (2, 6-9). Although the time from transplantation to the development of infection is variable, most infections occur within the first 2 years (6). Median time from symptom onset to diagnosis is 14 days (range 3-90 days) (7).

Though nearly all transplant associated blastomycosis infections involve the lungs, the spectrum of pulmonary infection ranges from subclinical disease to acute or chronic pneumonia (7, 10). The most common presenting symptoms in organ transplant recipients are fever and cough (6). These symptoms are not specific for blastomycosis and, commonly patients may be misdiagnosed with bacterial pneumonia. This can lead to diagnostic delays and inappropriate treatment, resulting in progression of the infection. Radiographic findings in transplant patients include lobar or interstitial infiltrates, a reticulonodular pattern with mediastinal adenopathy or lung cavities (9). A subset of individuals with pulmonary blastomycosis develop fulminant multi-lobar pneumonia and rapid progression to ARDS and respiratory failure (11). Among solid organ transplant recipients, 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 (6).

Disseminated infection occurs in 33-50% of solid organ transplant recipients, with the skin being the most common site of involvement outside the lungs (6-9). Lesions are usually multiple and appear pustular or ulcerative (3, 4). Other sites of involvement include osteoarticular structures, genitourinary tract, the reticuloendothelial system and more rarely, the CNS, manifesting as meningitis or a mass lesion (7, 8, 12, 13). Fungemia is rare.

Diagnostic Strategies

A definitive diagnosis of blastomycosis is made by isolating *B. dermatitidis* in culture. Though culture yield is typically high from respiratory and tissue specimens, the mold form of the organism may require two to four weeks to grow. For that reason, a preliminary diagnosis is often made by direct visualization of yeast forms morphologically consistent with *B. dermatitidis* in sputum, BAL fluid, and tissue. Histopathology typically demonstrates micro-abscesses and noncaseating granulomas within which the yeast forms can be better visualized after application of PAS or methenamine silver stain. A wet preparation using KOH or calcofluor white can rapidly detect *B. dermatitidis* in respiratory specimens (4). Gastric lavage cultures may also be a useful diagnostic technique, particularly in pediatric patients, as it may avert the need for more invasive diagnostic testing (14).

An enzyme immunoassay (EIA) which detects the polysaccharide cell wall antigen of *B. dermatitidis*, provides an additional non-invasive tool for rapid diagnosis of blastomycosis. This assay may be performed on serum, urine, BAL fluid, and CSF (15-19). Reported test sensitivity is variable, ranging from 62-83%, depending on specimen tested and site of infection (20). Assay specificity is limited by the near uniform cross-reactivity with the *Histoplasma capsulatum* EIA, as the two organisms share cell wall galactomannans, requiring clinician interpretation in the context of an individual's

epidemiologic risks and clinical presentation. Serial *Blastomyces* antigen EIA monitoring in infected individuals may be valuable to monitor for response to therapy and/or relapsed infection (7, 12). The utility of this test has not been well established in solid organ transplant recipients.

Molecular diagnostic techniques are an emerging area of development (21). The development of DNA probes for *B. dermatitidis* that can be used to confirm organism identification of fungal culture isolates are now commercially available (http://ltd.aruplab.com/Tests/Pub/0062224). Currently available serologic antibody assays (complement fixation and immunodiffusion) lack sensitivity and are not useful for the diagnosis of blastomycosis (4, 22). Limited data suggest sera from patients with proven blastomycosis tests negative for (1-3)-β-D-glucan (23).

- Growth of *B. dermatitidis* from clinical specimens and/or direct visualization of morphologically consistent yeast forms in sputum, BAL fluid, and tissue specimens establishes the diagnosis (Strong, moderate).
- The *Blastomyces* antigen EIA, performed on serum, urine, BAL fluid and CSF, provides a non-invasive diagnostic tool for rapid diagnosis and monitoring treatment response (Strong, low). However, its utility is limited by variable sensitivity (62-83%) and high cross-reactivity with other endemic fungi.
- Serologic *Blastomyces* antibody assays and the (1-3)-β-D-glucan assay are not diagnostically useful (Strong, moderate).

Treatment

The management of blastomycosis in solid organ transplant recipients follows published guidelines (24). All immunocompromised individuals require treatment. For severe pulmonary and/or disseminated infections, amphotericin is recommended as first line therapy. A lipid formulation of amphotericin is preferred because of the reduced potential for nephrotoxicity. Amphotericin is recommended for a minimum of 1-2 weeks or until clinical improvement is demonstrated, at which time transition to oral itraconazole can be considered. Liposomal amphotericin is recommended for infection involving the CNS, but with a longer induction period, generally 4-6 weeks, before transitioning to azole therapy. Voriconazole is preferred over itraconazole for CNS infection, given the limited CNS penetration of itraconazole (<1%) (25-27). Fluconazole is regarded as less effective for blastomycosis and should only be used as a salvage regimen, including for prolonged therapy for CNS infection at high doses (24, 28). In selected patients with mild, localized infections, oral itraconazole may be given as initial therapy, but close clinical monitoring is warranted. Corticosteroids may be considered as adjunctive therapy in severe blastomycosis-induced ARDS (29). Echinocandins have intermediate to poor *in vitro* activity against *B. dermatitidis* and should not be prescribed (30, 31).

Though still limited, there is increasing experience with the use of voriconazole, posaconazole, and isavuconazole in the treatment of blastomycosis, beyond the singular use of voriconazole for CNS blastomycosis (12, 13, 32, 33). These newer agents provide treatment alternatives to itraconazole, with the potential advantages of improved tolerability, more reliable absorption, and more interpretable therapeutic drug levels. Regardless of the azole used, therapeutic monitoring of serum drug levels is strongly recommended to optimize therapy (24, 34).

The duration of treatment is generally 12 months if signs and symptoms of infection have resolved. Consideration may be given to a more prolonged treatment course as guided by the clinical response, though conclusive data are lacking to provide specific recommendations (24). As the *Blastomyces* antigen EIA is quantitative, serial urine antigen measurements have been used to follow treatment response over time for both adult and pediatric patients (7, 20, 35). Though this practice has not been validated conclusively in transplant recipients, a published transplant-associated blastomycosis case series found the median time from positive to negative urine antigen EIA was 22 months (range 10-48 months) (7). The benefit of concomitant serum antigen testing to assess treatment response if unknown. Data suggest that relapse of blastomycosis is uncommon after obtaining cure (6, 7). However, azole suppressive therapy may be considered in selected transplant recipients based on the intensity and accumulated immunosuppression (24). Recent data indicate this is a safe and effective approach (36).

- Azole monotherapy may be considered for mild, localized infections. Itraconazole (200 mg twice daily) remains first line (Strong, moderate).
- For moderate, severe, and/or disseminated infection, initial therapy with lipid formulation amphotericin is recommended for a minimum of 1-2 weeks or until clinical improvement is demonstrated, followed by stepdown azole therapy to complete 12 months of therapy (Strong, moderate).
- The preferred treatment of CNS blastomycosis is lipid formulation amphotericin for 4-6 weeks, followed by voriconazole (200-400 mg twice daily) for at least 12 months. Alternative stepdown therapy with fluconazole 800 mg daily is recommended in the setting of voriconazole intolerance (Strong, moderate).
- Therapeutic monitoring of azole serum drug levels is highly recommended during therapy (Strong, moderate).
- Limited data suggest that serial urine *Blastomyces* antigen EIA monitoring may be useful to follow response to therapy. Suppressive therapy following successful treatment may be considered (Weak, low).

Prevention

As there is no sensitive or specific serologic assay available to detect previous exposure to *Blastomyces* or active infection, pre-transplant evaluation involves screening with symptom assessment and chest radiography for those transplant candidates with potential exposure. Prevention of blastomycosis in the post-transplant setting generally centers on avoidance of at-risk environmental exposures, specifically activities involving exposure to soil and decaying vegetation within endemic areas. There have been no trials of targeted antifungal prophylaxis for prevention of blastomycosis in organ transplant recipients who reside in endemic areas. Primary antifungal prophylaxis for blastomycosis after solid organ transplantation is not recommended.

- Symptom assessment and chest radiography are the recommended screening for transplant candidates with potential *Blastomyces* exposure (Strong, low).
- Primary antifungal prophylaxis for blastomycosis after transplant is not recommended, but transplant recipients should avoid at-risk environmental exposures (Strong, low).

Coccidioidomycosis

Etiology

Coccidioidomycosis is a fungal infection caused by *Coccidioides immitis* and *C. posadasii*. These dimorphic, saprophytic fungi exist in the environment in the mycelial form where they survive well in arid climates and remain viable for long periods. Maturation leads to the development of thick-walled arthroconidia, which easily detach from adjacent cell remnants to disperse in the environment. The inoculum needed for infection can be small, even a few arthroconidia, which are typically introduced into an animal or human host via inhalation. Within the lung, the arthroconidia transform into spherules, which are large (up to 100 μm) structures containing hundreds of endospores. As the spherule matures, its outer wall thins and eventually ruptures, leading to propagation of infection. Individual control of disease greatly depends on the host immune response, with cell mediated immunity playing a central role (37).

Epidemiology and Risk Factors

Coccidioides sp. thrive in arid climates characterized by low annual rainfall, hot summers, few winter freezes and alkaline soils. As such, areas of endemicity include the southwestern United States, areas of Mexico adjacent to the US border, and parts of Central and South America. Infections within endemic regions occur most frequently during the dry summer months, with occasional epidemics after dust storms, earthquakes, and soil excavation which enhance the spread of spores (37). *Coccidioides* spores may also be carried from endemic areas to distant locations on fomites or other exported products (38). The incidence of coccidioidomycosis in the US has been increasing in recent years, in part due to recognition of infections in regions previously thought to be outside the areas of endemicity (39). The reasons for the overall increase are not fully clear, but have been attributed to changing environmental conditions, changing surveillance methods, increased numbers of immunosuppressed individuals, and improved awareness and diagnostics.

Coccidioidomycosis has been described after solid organ transplantation with an incidence of 1.4-6.9% in endemic regions (2, 40-45). The majority of these infections are diagnosed within the first year after transplant, and in most cases, result from primary or reactivation infection. Other risk factors for coccidioidomycosis in the transplant population include treatment of acute rejection, prior history of coccidioidomycosis and/or positive pre-transplant serologies, and African American race (41, 46). Donor *Coccidioides* transmission is also well described (47-51). Affected recipients typically present early post-transplant, usually within one month, with severe infections and a mortality rate approaching 30% (2, 47). Prompt identification of recipient infection and initiation of antifungal therapy in other common donor recipients leads to more favorable outcomes.

Clinical Manifestations

Coccidioidomycosis should be considered in the differential diagnosis of any solid organ transplant recipient with a fever and/or pneumonia who has traveled to or resides in an endemic area. This includes consideration for primary and/or reactivation infection depending on the timing of potential exposures. In the setting of reactivation infection, the exposure may have occurred months to years prior to the onset of symptoms. Clinical manifestations are highly variable and can range from asymptomatic seroconversion to disseminated infection associated with multi-organ failure and shock (44). However, in contrast to immunocompetent hosts in whom infections are

often mild and self-limited, organ transplant recipients are more likely to develop severe pneumonia and disseminated infection (44). The most common symptoms of pulmonary involvement are fever, chills, night sweats, cough, dyspnea, and pleurisy. Radiographic findings are varied and may consist of lobar consolidation, pulmonary nodules, mass-like lesions, interstitial infiltrates or cavities. Pulmonary coccidioidomycosis can progress to severe pneumonia with multilobar involvement, diffuse nodularity, ARDS and respiratory failure particularly in the setting of immunosuppression. Peripheral eosinophilia, while not diagnostic, is present in one-third to one-half of transplant recipients with coccidioidomycosis (40) and its presence should alert the clinician to the possibility of this infection.

In immunocompetent individuals with coccidioidomycosis, extrapulmonary infections occur in <1%. In case series of solid organ transplant recipients with coccidioidomycosis, the proportion of disseminated infections varies widely, involving nearly three quarters of cases in older literature, but significantly less in the era of routine post-transplant azole prophylaxis (42, 46, 52, 53). Extrapulmonary dissemination is often not associated with pulmonary complications as symptoms and radiographic findings may be minimal or absent. Manifestations typically involve the skin, osteoarticular system, and/or the CNS (54). Meningitis is the most serious form of disseminated infection, usually presenting with headache, vomiting and/or altered mentation(55). Due to the basilar location of meningeal involvement, hydrocephalus is a common complication. Coccidioides fungemia is uncommon, but is associated with a 30 day mortality of 62% (56). Coccidioidomycosis in children presents similarly to adults, though reactive rashes, including erythema multiforme are more common (57).

Diagnostic Strategies

The diagnosis of coccidioidomycosis requires a high index of suspicion, as symptoms can be nonspecific and initial diagnostic test results can be misleading. Positive cultures and histopathologic findings from infected specimens are definitive for diagnosis (58), but are less sensitive than other diagnostic methods. On direct microscopy or histopathologic exam, visualization of the characteristic spherule containing endospores is diagnostic of infection. *Coccidioides* sp. grow well on most mycologic and bacteriologic media in 5-7 days. *Coccidioides* reverts back to the high infectious mold 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 coccidioidomycosis is suspected.

Serologic testing can be a useful method of diagnosing coccidioidomycosis when cultures and histopathology are pending or negative. Several methodologies are available, including enzyme immunoassays (EIAs), immunodiffusion-based assays (ID), and complement-fixing anticoccidioidal antibodies (CF). Studies indicate that EIAs are approximately twice as sensitive in detecting early coccidioidal infections than ID and CF assays, thus, EIA is typically used for initial screening (59). The EIA is limited by false positive IgMs, though the extent depends on the pretest probability of infection (37). CF antibodies typically appear later in infection, but have the advantage of being quantitative, thus providing an assessment of the severity of infection and its resolution. ID assays are very specific and are useful for confirming the results of other serologic assays. The sensitivity of all of the serologic assays improves with serial testing. As with many infections, serologic responses may be low or absent in transplant recipients likely owing to the use of immunosuppressive medications (46). In a retrospective review of 27 solid organ transplant recipient with newly acquired coccidioidomycosis, the positivity of any single serologic test ranged from 21-56%,

compared with 77% seropositivity with a combination of serologic tests. With repeat testing one month later, 92% of patients had a positive test (60). In those individuals with symptoms concerning for coccidioidal meningitis, a lumbar puncture should be performed with testing to include both ID and CF coccidioidal antibodies and coccidioidal antigen EIA (see below) (59, 61).

An array of other nonculture based diagnostic methods for detecting coccidioidomycosis are also commercially available, but have not been extensively studied in organ transplant recipients. *Coccidioides* PCR testing of respiratory and CSF specimens demonstrate high sensitivity and specificity, with similar findings among immunocompetent and immunosuppressed individuals (62, 63) Molecular techniques for *Coccidioides* identification from fungal culture and tissue specimens are also available (64). *Coccidioides* antigen EIA to detect coccidioidal antigen (available from urine, serum, BAL, and CSF) can be useful in the rapid diagnosis of more severe forms of coccidioidomycosis. Like the *Blastomyces* and *Histoplasma* antigen EIA assays (discussed in other sections), this assay lacks specificity among individuals with other endemic mycoses (65). The utility of serum (1,3)-β-D-glucan assay in diagnosing coccidioidomycosis is limited as it demonstrates similar sensitivity, specificity, PPV, and NPV as is seen in other invasive mycoses (66, 67). Test interpretation is likewise challenged by defining a cutoff for a positive result, the prognostic value of serial testing, and numerous factors associated with a false positive result.

- Growth of *Coccidioides* sp. from clinical specimens and/or direct visualization of the characteristic spherule containing endospores are confirmatory of the diagnosis (Strong, moderate).
- Among the three available *Coccidioides* serologic assays (EIA, ID, CF), the EIA is recommended for initial screening. CF, though positive later in infection, is quantitative and provides prognostic information regarding severity and resolution of infection (Strong, moderate).
- Molecular diagnostic techniques are increasing in availability. *Coccidioides* PCR testing of respiratory and CSF specimens demonstrate high sensitivity and specificity (Strong, low).
- Multiple test modalities may be needed for diagnosis, with repeat studies over time to increase the likelihood of assay positivity in the setting of clinical infection (Strong, moderate).

Treatment

The treatment of coccidioidomycosis in solid organ transplant recipients follows published guidelines (59). For individuals with acute or chronic pulmonary coccidioidomycosis who are clinically stable, initiating treatment with fluconazole 400 mg daily (adjusted for renal function) is recommended. In the setting of severe and/or rapidly progressive acute pulmonary or disseminated coccidioidomycosis, amphotericin (lipid-associated amphotericin is preferred) is recommended until the patient has stabilized, followed by fluconazole. The lipid-associated amphotericin formulation is preferred based on tolerability. The decision to treat with oral versus intravenous therapy must be individualized, with assessment of symptom severity, respiratory status, extent of infection and the ability to take enteral therapy. A reduction in immunosuppression should be considered until the infection has begun to improve. A minimum treatment duration of 6-12 months is recommended, but this should be individualized based on response.

For meningeal coccidioidomycosis, fluconazole, 400-1200 mg daily is recommended as initial therapy owing to its excellent CSF penetration, although most clinicians use ≥800 mg daily**.** Serial lumbar punctures should be performed during treatment to document improvement. As azole therapy alone appears to suppress rather than cure coccidioidal meningeal disease, the treatment course should be followed by lifelong azole suppression. For solid organ transplant recipients with other forms of extrapulmonary coccidioidomycosis, treatment recommendations follow those outlined for non-transplant recipients (59).

There are multiple published case reports and small case series of relapsed or reactivated coccidioidomycosis following the discontinuation of antifungal therapy (45, 68-70). As such, similar to the recommendations for coccidioidal meningitis, treatment should be continued indefinitely or until withdrawal of immunosuppressive therapy (55, 71). Azoles are typically used for ongoing suppressive therapy, with fluconazole being acceptable for most. The optimal dosing of fluconazole in this setting is not established, with 200-400 mg daily recommended, factoring in medication efficacy, cost, and tolerability (59).

Favorable clinical responses have been demonstrated with voriconazole and posaconazole for treatment of refractory coccidioidomycosis or when toxicity develops to standard therapies (32, 72-75). Limited experience suggests isavuconazole can also be successfully used for treatment (13). Antifungal drug level monitoring should be performed with use of these agents to assure therapeutic levels (34). Echinocandins have variable *in vitro* activity against *Coccidioides* and sufficient clinical data are limited (31, 76-78).

- Azole monotherapy is recommended for clinically stable individuals with acute or chronic pulmonary coccidioidomycosis. Fluconazole (400 mg once daily) remains first line (Strong, low).
- For severe and/or rapidly progressing acute pulmonary or disseminated coccidioidomycosis, amphotericin (lipid formulation amphotericin is preferred) is recommended until the patient has stabilized, followed by fluconazole (Strong, low).
- Fluconazole, 400-1200 mg daily, is recommended as initial therapy for meningeal coccidioidomycosis (Strong, moderate).
- Recommended treatment duration for coccidioidomycosis in 6-12 months, but this should be individualized based on response (Strong, low).
- Due to the high risk of relapse or reactivation infection following the treatment course, solid organ transplant recipients with all forms of coccidioidomycosis should receive lifelong azole suppression (Strong, very low).

Prevention

Preventing *Coccidioides* infection in solid organ transplant recipients is imperative as infection is frequently severe and mortality is high (44, 47). During the pre-transplant evaluation, clinicians must determine if transplant candidates have a history, even remote, of residence in or travel to an endemic area. If so, the evaluation should include an assessment of previous or current symptoms consistent with coccidioidomycosis, chest x-ray, and serologic testing. Due to its higher sensitivity, the *Coccidioides* EIA is the preferred initial screening assay. 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 basis. When possible, organ transplantation should be deferred in

patients with active coccidioidomycosis until the infection is clinically, radiographically, and serologically quiescent (52, 71).

For all patients undergoing organ transplantation in endemic areas who do not have active coccidioidomycosis, oral azole prophylaxis is recommended (59). If seronegative pre-transplant, fluconazole 200 mg daily is deemed adequate. If seropositive pre-transplant, fluconazole 400 mg daily is recommended. As most post-transplant coccidioidomycosis cases occur during the first year, 6-12 months of prophylaxis is recommended, regardless of pre-transplant serostatus (59). Alternatively, some experts recommend lifelong fluconazole prophylaxis in seropositive transplant recipients, especially in the setting of lung transplantation (41, 53). Limited data suggest the newer generation azoles are also effective for prophylaxis (43, 53). Though antifungal therapy reduces the risk for post-transplant coccidioidomycosis, it does not eliminate it. Thus, post-transplant clinical monitoring of at-risk patients should be performed periodically to assess for evidence of new or reactivation infection, with consideration for adjunctive serologic monitoring for individuals deemed at high epidemiologic risk (71, 79).

Coccidioidomycosis transmission through transplantation is an uncommon, but serious event. In the United States, most cases involve donors from UNOS region 5, which includes states in the Southwest. Among healthy potential live doors within this endemic area, 2.1% were seropositive indicating recent infection and thus, potential for infection transmission (80). Published OPTN ad hoc DTAC experience identified 6 reports of proven or probable donor-derived coccidioidomycosis involving 21 recipients between 2005 and 2012 (47). Transmission occurred in 43% of recipients at a median of 30 days post-transplant with a mortality rate of 28.5%. In those individuals who received preemptive therapy, clinical infection was either prevented or mitigated. At this time, there are no recommendations for universal or targeted deceased donor screening for *Coccidioides* infection. Azole prophylaxis is efficacious for the prevention of donor-derived coccidioidomycosis in the transplant recipient, with fluconazole being the preferred agent. Individuals receiving a broader spectrum azole such as itraconazole, posaconazole or voriconazole for treatment or prophylaxis of other fungal organisms do not require additional fluconazole (81). The optimal duration of prophylaxis for donor-derived coccidioidomycosis has not been determined. For additional recommendations specifically addressing donor-derived coccidioidomycosis, we refer the reader to published guidelines (81).

- All transplant candidates should be assessed for travel to or residence in a *Coccidioides* endemic region. If deemed at risk, an additional evaluation for active coccidioidomycosis should be untaken with a symptom assessment, chest x-ray, and serologic testing (Strong, low).
- All transplant recipients in endemic areas, without active coccidioidomycosis and regardless of serostatus, should receive oral azole prophylaxis for a minimum of 6-12 months post-transplant (Strong, low).
- Transplant recipients who receive allografts from donors with prior or active *Coccidioides* infection should receive preemptive azole therapy to prevent or mitigate infection. Lifelong azole therapy (fluconazole 400 mg daily) is recommended for lung recipients. Non lung recipients should receive 6-12 months of preemptive azole therapy (fluconazole 400 mg daily), followed by the option of lifelong stepdown therapy (fluconazole 200 mg daily) or azole discontinuation with clinical and serologic monitoring for coccidioidomycosis (Strong, low).

Histoplasmosis

Etiology

Histoplasmosis is a fungal infection caused by the thermally dimorphic fungus, *Histoplasma capsulatum*. In the environment, the organism exists as a mold which produces two types of conidia. The larger, tuberculate conidia, are 8-15 μm in diameter with a distinct morphology. The smaller conidia, which measure 2-4 μm, can be effectively aerosolized and inhaled into the lungs where they are phagocytized by alveolar macrophages. Within the macrophages, the conidia convert to a yeast form and disseminate widely via the lymphatics and bloodstream (3). In the immunocompetent host, this dissemination rarely results in a clinically apparent infection as intact cellular immunity contains and eradicates the infection within the macrophage. In transplant recipients and other hosts with impaired cell-mediated immunity, the organism remains viable within macrophages, posing risk for further dissemination and clinical infection (82).

Epidemiology and Risk Factors

Histoplasmosis is the most common endemic mycosis in the United States as well as regions of Mexico and Central and South America (83). It is also found in many areas of the world, including Africa, China, Malaysia, Thailand, India, Bangladesh, and in the province of Quebec, Canada (84-87). In the United States, the organism is endemic to the Ohio and Mississippi River Valleys with evidence of broad population exposure based on *Histoplasma* skin testing dating back to the 1950's and 1960's (88). Based on disease surveillance data, additional cases have been more recently identified in areas believed to have a low level of endemicity, including Michigan, Minnesota, Texas, New York, Puerto Rico and others (88, 89). Whether these expanding areas of endemicity are due to improved detection of histoplasmosis cases, increasing populations of immunosuppressed individuals, environmental changes, and/or other factors is not known.

Exposure to disrupted soil around construction or remodeling sites, farming, caves where bats reside, chicken coops, or other buildings inhabited by birds or bats pose particular risk for infection (83, 88). Solid organ transplant recipients are at higher risk for significant infection due to impaired cellular immunity. Despite the higher risk, post-transplant histoplasmosis is rare, with an estimated incidence of <1%, even in endemic areas (7, 87, 90, 91). Among solid organ transplant recipients enrolled in the Transplant-Associated Infection Surveillance Network, which included several centers located in the endemic areas, 0.14% developed histoplasmosis over the study period with a 12 month cumulative incidence rate of 0.1% (2). Histoplasmosis in transplant recipients is acquired through primary infection, usually via inhalation through a pulmonary route (7). Previous infection can also reactivate in the setting of immunosuppression. Donor derived infection transmitted through the allograft is rare, with an estimated incidence of 1:10,000 transplants (2, 81, 92-95). Human to human transmission has not been reported.

Clinical Manifestations

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. Histoplasmosis has been described among all types of solid organ transplant recipients (7, 87, 90-92). The illness most commonly presents in an occult manner in the transplant

population, with the burden of disease often out of proportion to the severity of symptoms at initial presentation.

Although a spectrum of clinical manifestations has been reported in solid organ transplant recipients, the most common form is progressive disseminated infection, occurring in up to 81% of patients in the largest reported case series (92). It is characterized as a subacute febrile illness with radiographic and/or laboratory evidence of extrapulmonary infection (7, 87, 90-92). The typical period from onset of symptoms to diagnosis is 2-4 weeks. Most infections within the first 1-2 years after transplant, though individuals can present over a broad time range of months to several years post-transplant. As the infection progresses, associated clinical findings can include hepatosplenomegaly, pneumonia, gastrointestinal involvement, pancytopenia, weight loss, hepatic enzyme derangements, and elevated lactate dehydrogenase levels. Mucocutaneous manifestations are reported in up to 25% of transplant recipients (96). CNS histoplasmosis is also well described, mostly among immunocompromised individuals (97). Less common manifestations, typically in more severely ill patients, include thrombotic microangiopathy, hemophagocytic lymphohistiocytosis, adrenal hypofunction, as well as osteoarticular, peritoneal, and genitourinary tract infections (86, 98-104). Use of mycophenolate and the presence of fungemia are risk factors for more severe infection (92). Reports of histoplasmosis in transplanted children are few. However, in non-immunosuppressed children, symptoms of histoplasmosis are similar to those of adults, though meningitis accompanying progressive disseminated infection is more commonly seen in infants <2 years of age (105).

Diagnostic Strategies

Definitive diagnosis rests on direct visualization of yeast forms or growth of *H. capsulatum* from tissues and/or other specimens. Cultures may take up to 4 weeks to demonstrate growth. Thus, histopathologic examination of biopsy specimens from suspected sites of involvement, mostly commonly liver, lung, skin, lymph nodes and bone marrow, can expedite diagnosis. Typically yeast forms can be visualized with or with the presence of granulomas. Hematoxylin and eosin stains and Wright-Giemsa stains may aid in visualization of *Histoplasma* in blood or bone marrow, while GMS or PAS stains may enhance visualization in other tissues (106, 107).

The availability of newer generation antigen assays has improved early detection through increased sensitivity and specificity. In solid organ transplant recipients with histoplasmosis, the urine *Histoplasma* antigen EIA demonstrates the highest overall sensitivity, reported at 92%. However, within this patient group it is positive in only 73% of individuals with isolated pulmonary infection compared to 97% in those with disseminated disease (7, 90, 91, 108). Performed on serum, the sensitivity of the *Histoplasma* antigen EIA is 86%. Like its urinary counterpart, it is less likely to be positive in individuals with isolated pulmonary histoplasmosis (59%) versus disseminated infection (89%) (92). Combining both urine and serum testing increases the likelihood of antigen detection (109). Older case series indicate lower sensitivity which may reflect use of older generation assays in the reported cases. The level of antigenuria correlates with the severity of disseminated infection: concentration of $\geq$19 ng/ml occurs in 73% of severe cases, 39% of moderately severe cases, and 17% of mild cases (108). Antigen detection is similarly useful in children. Test specificity is limited by its cross reactivity with other endemic fungi, notably 90% with *Blastomyces*. Cross reactivity has also been reported with *Coccidioides* spp., *Paracoccidioides brasilensis*, *Talaromyces marneffei*, and *Sporothrix schenckii* (17, 108, 110).

For individuals with pulmonary histoplasmosis, performing *Histoplasma* antigen EIA testing of BAL fluid provides another option for rapid diagnosis, particularly in those where the infection is localized to the lungs. Among 31 patients with histoplasmosis (4 of whom were transplant recipients), test performance demonstrated a sensitivity of 93%, specificity 97%, PPV 69%, and NPV 99% (111). As with the urine and serum antigen EIA assays, cross reaction can be expected in most cases of pulmonary blastomycosis and a lower proportion of those with pulmonary coccidioidomycosis (112). False positive results approximate 10% in cases of pulmonary aspergillosis (111). Conversely, the *Aspergillus* galactomannan assay is positive in 50% of serum and BAL samples from individuals with histoplasmosis, which could lead to a false diagnosis of aspergillosis (113, 114). False positive serum and urine *Histoplasma* antigen results have not been reported in invasive aspergillosis cases with positive serum galactomannan assay results. *Histoplasma* antigen EIA testing of CSF is a useful adjunct in diagnosing CNS histoplasmosis, particularly in immunocompromised individuals and with those with severe infection (97).

Detection of *Histoplasma capsulatum* DNA by real-time PCR in the clinical setting is largely limited to fungal identification from culture isolates. The use of PCR to detect *Histoplasma* directly from human specimens is still under development and limited to case reports and small case series. Limited data on the diagnostic use of the (1-3)-β-D-glucan assay demonstrate a sensitivity of 87-89% and specificity of 68% in disseminated histoplasmosis cases (23, 115). Values also correlated with urine antigen levels (23). PET/CT imaging can also assist with diagnosis and management of histoplasmosis in the appropriate clinical context, particularly in the setting of adrenal involvement (116-119).

Regarding *Histoplasma* antibody detection, for both immunosuppressed and nonimmunosuppressed individuals from endemic areas, potential background seropositivity confounds test interpretation. In addition, antibodies require 4-8 weeks to become detectable in peripheral blood and are therefore largely unsuitable for the diagnosis of early infection. The diagnostic utility of serologic testing is variable in organ transplant recipients (120, 121), as the effects of immunosuppressive therapy on the humoral immune response may blunt the serologic response to infection, decreasing the sensitivity of the test in this setting (122). Among disseminated cases, antibodies are detected in up to 89% of immunocompetent individuals, but only 18-30% of solid organ transplant recipients (91, 108). Among individuals with acute pulmonary histoplasmosis, combined testing with the serum *Histoplasma* antibody EIA and urine/serum antigen EIA assays improves diagnostic sensitivity, however, this has not been validated in the transplant setting (123).

- Growth of *H. capsulatum* from clinical specimens is the definitive diagnostic test, but culture make take up to 4 weeks to demonstrate growth (Strong, moderate).
- Direct visualization of morphologically consistent yeast forms in blood, bone marrow, BAL, CSF and/or other tissue specimens can expedite the diagnosis (Strong, moderate).
- The *Histoplasma* antigen EIA should be performed on serum and urine if histoplasmosis is suspected as this assay provides a rapid, non-invasive method for diagnosis. *Histoplasma* antigen EIA can also be performed on BAL fluid and CSF as clinically indicated. Sensitivity is improved with combined testing from multiple sources and in the setting of disseminated infection. (Strong, moderate)
- *Histoplasma* antibody testing is of limited utility in solid organ transplant recipients due to poor sensitivity (Strong, moderate).

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 published guidelines (124). 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.

Mild to moderate infection may be treated effectively with itraconazole monotherapy (200 mg twice daily for at least 12 months). For moderately severe and severe infection, initial therapy with amphotericin is recommended (124). 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 stepdown therapy with itraconazole (200 mg twice daily) to complete a minimum 12 month total treatment course (124, 125). Concomitant reduction of immunosuppression, especially the calcineurin inhibitors, is an important treatment adjunct (92). Treatment recommendations for children with progressive disseminated histoplasmosis are similar to adults, though longer initial courses of amphotericin are recommended (124). Amphotericin-associated nephrotoxicity is generally less severe in infants and children than in adults (126).

The newer generation azole agents, including voriconazole, posaconazole, and isavuconazole, all demonstrate *in vitro* activity against *H. capsulatum*. Clinical efficacy data are limited to small series and case reports (7, 13, 32, 90, 91, 127-130). Though these data increasingly support treatment success with these agents, they are insufficient to establish new treatment recommendations. Fluconazole is currently the recommended second-line azole for histoplasmosis (124), but demonstrates a high relapse rate in non-HIV infected immunocompromised patients (131). Thus, for patients refractory or intolerant to the first line agents, the newer generation azoles provide treatment alternatives which may ultimately become first line with broader clinical experience.

Because of the marked intra- and interpatient variability in the pharmacokinetics and absorption of azoles, therapeutic monitoring of serum drug levels is strongly recommended to optimize therapy once steady state has been reached (34, 125, 132). Random itraconazole + the hydroxy-itraconazole metabolite serum concentrations of at least 1.0 µg/ml are recommended and correlate with clinical efficacy. While the newer generation azoles demonstrate more reliable absorption, therapeutic drug monitoring is also strongly recommended with their use (see section on specific issues related to azole therapy).

Urine and serum *Histoplasma* antigen EIA levels typically fall with effective therapy, thus can be used to follow treatment response and assess for relapse. Antigen levels should be measured at the time treatment is initiated, at 2 weeks, 1 month, then every 3 months during therapy. As *Histoplasma* antigenemia decreases more rapidly than antigenuria, the serum assay provides a more sensitive early marker for response to treatment (133). Solid organ transplant recipients clear urine and serum *Histoplasma* antigens slowly as 30% of individuals continue to demonstrate a positive test after 10 months of treatment (7). Persistent low level antigenuria may be observed in organ transplant recipients who received an appropriate duration of therapy with a complete clinical response. Limited experience suggests that antifungal therapy can be safely withdrawn in this setting with careful monitoring for relapse (7, 90, 91, 124). Nonetheless, relapse is more likely to

occur if the urine *Histoplasma* antigen EIA level is >2 ng/ml at the time of stopping therapy (92). Monitoring should continue for at least 6 months after discontinuing therapy (120).

Despite the severity of illness upon presentation, treatment efficacy among infected solid organ transplant recipients in the post-azole era ranges from 80-100% (7, 90, 91). Mortality in recent series ranges from 13-30%, with mortality attributable histoplasmosis of 10-13% (7, 92). Most deaths occur early, within a month of diagnosis. Older age and severe disease are significant risk factors for mortality (92). Immune reconstitution syndrome has also been described in transplant recipients with disseminated histoplasmosis, mainly associated with concomitant reduction of immunosuppression (134, 135).

- Recommended treatment for mild to moderate histoplasmosis is itraconazole, 200 mg twice daily for at least 12 months (Strong, moderate).
- For moderately severe and severe histoplasmosis, amphotericin (lipid formulation preferred) is recommended for 1-2 weeks or until there is stabilization of the infection, followed by stepdown therapy with itraconazole (200 mg twice daily) to complete a 12 month total treatment course (Strong, high).
- For individuals refractory or intolerant of first line agents, the newer generation azoles (voriconazole, posaconazole, and isavuconazole) should be used for treatment in preference to fluconazole (Strong, low).
- Concomitant reduction of immunosuppression, especially the calcineurin inhibitor regimen, is recommended to lessen the risk of relapse (Strong, low).
- Urine and serum *Histoplasma* antigen EIA levels typically fall with effective treatment and can be used to follow treatment response and assess for relapse. Relapse is more likely to occur if the urine *Histoplasma* antigen level is >2 ng/ml at the time of stopping therapy (Strong, low).

Prevention

Pre-transplant serologic and/or radiologic screening for prior histoplasmosis infection in endemic areas is not recommended based on the poor predictive value of a positive serology and low likelihood of subsequent infection (136). Primary prophylaxis for histoplasmosis in the post-transplant setting is not recommended. However, transplant recipients should be counseled to avoid at-risk exposures. Individuals who have recovered from active histoplasmosis during the two years before the initiation of immunosuppression may be considered for secondary azole prophylaxis, typically with itraconazole 200 mg daily (124). Voriconazole, posaconazole, and isavuconazole are also likely effective for prophylaxis. The optimal duration of secondary post-transplant prophylaxis is not established. Serial monitoring of the *Histoplasma* antigen EIA should be performed in solid organ transplant recipients with previous infection and during periods of intensive immunosuppression to assess for relapse. Management of individuals with incidental *H. capsulatum* detected 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 can be considered (91). For additional recommendations regarding donor-derived histoplasmosis, we refer the reader to the published guidelines (81).

- Screening for prior histoplasmosis in endemic areas is not recommended prior to organ transplant (Strong, moderate).
- Primary prophylaxis for histoplasmosis in the post-transplant setting is not recommended. However, transplant recipients should be counseled to avoid at-risk exposures (Strong, low). Individuals who have recovered from active histoplasmosis during the 2 years before the initiation of immunosuppression may be considered for azole prophylaxis, typically with itraconazole 200 mg daily (Weak, low).
- Serial monitoring of *Histoplasma* antigen EIA levels should be performed in solid organ transplant recipients with previous histoplasmosis and during periods of intensive immunosuppression to assess for relapse (Weak, low).

Specific Issues Related to Azole Therapy

Drug-drug interactions are an important consideration when prescribing azole antifungal agents for organ transplant recipients. Azoles interfere with the metabolism and transport of many drugs via inhibition of cytochrome p450 enzymes and/or drug transporter P-glycoprotein within the gastrointestinal tract and liver. Particularly relevant in transplantation, azoles increase serum concentrations of cyclosporine, tacrolimus, everolimus and sirolimus (137). The magnitude of azole inhibition of these enzymes is highly variable depending on the dose, potency and/or selectivity of individual azoles. Multiple enzymatic genetic polymorphisms have also been identified, resulting in further alterations in drug metabolism. Drug levels of the immunosuppressive agents must be closely monitored in individuals during the initiation and discontinuation of azole therapy to prevent inadvertent drug toxicity or allograft rejection. Preemptive dose adjustment is recommended (137).

Because of the marked intra- and interpatient variability in the pharmacokinetic and absorption of azole agents, therapeutic monitoring of serum drug levels is strongly recommended (34, 138). Pharmacokinetics of azole agents also differ between adults and children in that children have more rapid drug clearance, necessitating more frequent and higher dose administration (126). Therapeutic drug monitoring guides dose optimization for successful treatment and mitigation of drug toxicity. Recommendations for drug monitoring for each individual azole agent is beyond the scope of this guideline, but are discussed in detail by Stott (138).

Research and Future Areas of Investigation

There remain many unanswered questions surrounding the endemic mycoses in solid organ transplantation. There are many examples of identification of these infections occurring in individuals outside of the traditional endemic regions, suggesting an evolving epidemiology. While expanding patient populations at risk and transfer of organs between endemic regions likely account for some of these observations, there are likely other factors involved. Studying the role of climate change, animal and bird migration, and fungal organism adaptations will further our understanding of these endemic shifts, and may ultimately impact patient management.

New advances in fungal diagnostics, especially with the expanding molecular testing options, hold promise to allow for more precise and rapid identification of fungal pathogens as compared to currently available diagnostic methods. While not yet uniformly available nor validated in the transplant population, these techniques offer an area ripe for investigation.

The rarity of these infections in the transplant population limits the ability to perform randomized clinical trials to confirm and advise the current treatment recommendations. Azoles and polyenes remain the only therapeutic classes of antifungal agents available to treat endemic mycoses. Though there are several newer azole agents now available as options for prophylaxis and treatment, data are limited on their efficacy, particularly among transplant recipients. Further studies are needed to validate their use in this setting. Ultimately, the development of new antifungal drug classes would provide additional options for treatment.

Lastly, the host immune system plays a dynamic role throughout the time course of infection with the endemic mycoses by impacting the risk of acquisition, clinical manifestations, and resolution. In the transplant setting, iatrogenic immunosuppression is a modifiable component of the host immune response. In general, most experts recommend that reducing immunosuppression should be considered in the management of endemic fungal infections. However, the optimal timing and degree of such reductions are not established and they must be individualized for a given patient to balance the risk of allograft rejection. Although rarely reported, the immune reconstitution inflammatory syndrome (IRIS) may also result with reducing immunosuppression during treatment of blastomycosis, coccidioidomycosis, and histoplasmosis, potentially causing adverse clinical consequences (139-142). Additional investigation is needed to better understand the effects of immune modulation in the context of these infections, which will allow for development of more precise recommendations for immunosuppression management and prevention of the untoward pro-inflammatory consequences.

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Table 1. Summary of Recommendations

Infection	Predominant Geographic Distribution	Diagnostic Strategies	Treatment Regimen	Treatment Duration	Prevention
Blastomycosis	Upper Midwest US Ohio and Mississippi River valleys States and provinces bordering the Great Lakes	Culture Direct visualization Antigen EIA* DNA probe of culture isolates	Mild: Itraconazole 200 mg BID Moderate-Severe: AMB with stepdown to oral azole	Minimum of 12 mos	Primary post-transplant prophylaxis not recommended
Coccidioidomycosis	Southwest US Northern Mexico Areas of Central and South America	Culture Direct visualization Serology# BAL and CSF PCR Antigen EIA*	Acute or chronic pulmonary infection (stable): fluconazole 400 mg daily Severe or rapidly progressive infection: AMB with stepdown to fluconazole 400 mg daily Meningitis: fluconazole 400-1200 mg daily	Minimum of 6-12 mos, followed by lifelong azole suppression	All transplant recipients in endemic areas should receive azole prophylaxis for 6-12 mos after transplant Recipients of organs from donors with prior or active infection should receive azole prophylaxis
Histoplasmosis	Ohio and Mississippi River valleys Areas of Mexico, Central and South America	Culture Direct visualization Antigen EIA* Serology# DNA probe of culture isolates	Mild-moderate: Itraconazole 200 mg BID Moderately severe-severe: AMB with stepdown to Itraconazole 200 mg BID	Minimum of 12 mos	Primary post-transplant prophylaxis not recommended

* Commercially available for serum, urine, BAL fluid or CSF

EIA, ID and CF assays available