Open Access

OBM Transplantation

Review

Endemic Mycoses and Cryptococcus in Solid Organ Transplant Recipients

Omer Eugene Beaird *, Deepa Nanayakkara, Pryce Gaynor, Joanna Schaenman

David Geffen School of Medicine at UCLA, 200 UCLA Medical Plaza Suite 365-C, Los Angeles, CA 90095, United States; E-Mails: obeaird@mednet.ucla.edu; dnanayakkara@mednet.ucla.edu; pgaynor@mednet.ucla.edu; jschaenman@mednet.ucla.edu

* **Correspondence:** Omer Eugene Beaird; E-Mail: obeaird@mednet.ucla.edu

Academic Editor: Maricar Malinis

Special Issue: Diagnosis and Management of Infections in Solid Organ Transplant Recipients

OBM Transplantation
2019, volume 3, issue 3
doi:10.21926/obm.transplant.1903075

Received: April 05, 2019
Accepted: June 27, 2019
Published: July 26, 2019

Abstract

The endemic mycoses are an important cause of morbidity and mortality in transplant recipients. These fungal infections are notable for their dimorphic life cycle, specific geographic distributions, and typical infection via environmental exposure. Their nonspecific presentation can make diagnosis challenging. Because of their geographic associations, assessment of both donor and recipient history is critical in making an accurate and timely diagnosis. *Coccidioides* spp. are endemic to the southwestern United States and can cause severe pneumonia, meningitis, as well as bone and joint infection. Coccidioidomycosis is unique in its likelihood to reactivate following immunosuppression compared with the other endemic fungal infections. For this reason, recipients with even remote history of infection benefit from secondary prophylaxis to prevent reactivation. Histoplasmosis in North America typically occurs in the Mississippi and Ohio River valleys, however is distributed worldwide. Histoplasmosis presents as pneumonia and frequently with disseminated disease. Blastomycosis has an overlapping geographic distribution with Histoplasmosis but is less commonly seen in transplant recipients. Cryptococcus does not have a dimorphic form. However, it is an environmental fungus and has a presentation similar to the endemic fungi, and is therefore discussed in this review. Amphotericin B and the azole antifungals are

commonly used to treat or prevent these infections. However, despite the availability of effective therapy delays in diagnosis can result in adverse clinical outcomes.

Keywords
Endemic mycosis; fungal infection; cryptococcus; coccidioidomycosis; histoplasmosis; blastomycosis

1. Introduction

The endemic mycoses encompass a group of environmental, temperature dimorphic fungi with distinct geographic distributions (see Figure 1). Infection usually results after inhalation of conidia from the mold form of the fungi, which are present in the environment and exist as yeast or spherules at body temperature. In North America, endemic fungal infections include blastomycosis, coccidioidomycosis and histoplasmosis, while paracoccidioidomycosis is seen in South America. The endemic mycoses are particularly problematic in solid organ transplantation (SOT) due to the potential for atypical presentations as well as risk of disseminated and more severe infection when compared to immunocompetent individuals. In addition to primary exposure and infection, there are transplant specific concerns including donor transmission and reactivation of previously latent disease after the start of immune suppression. This review will focus on the dimorphic endemic fungi and will also discuss *Cryptococcus*, an endemic yeast with a similar spectrum of infection as the dimorphic fungi.

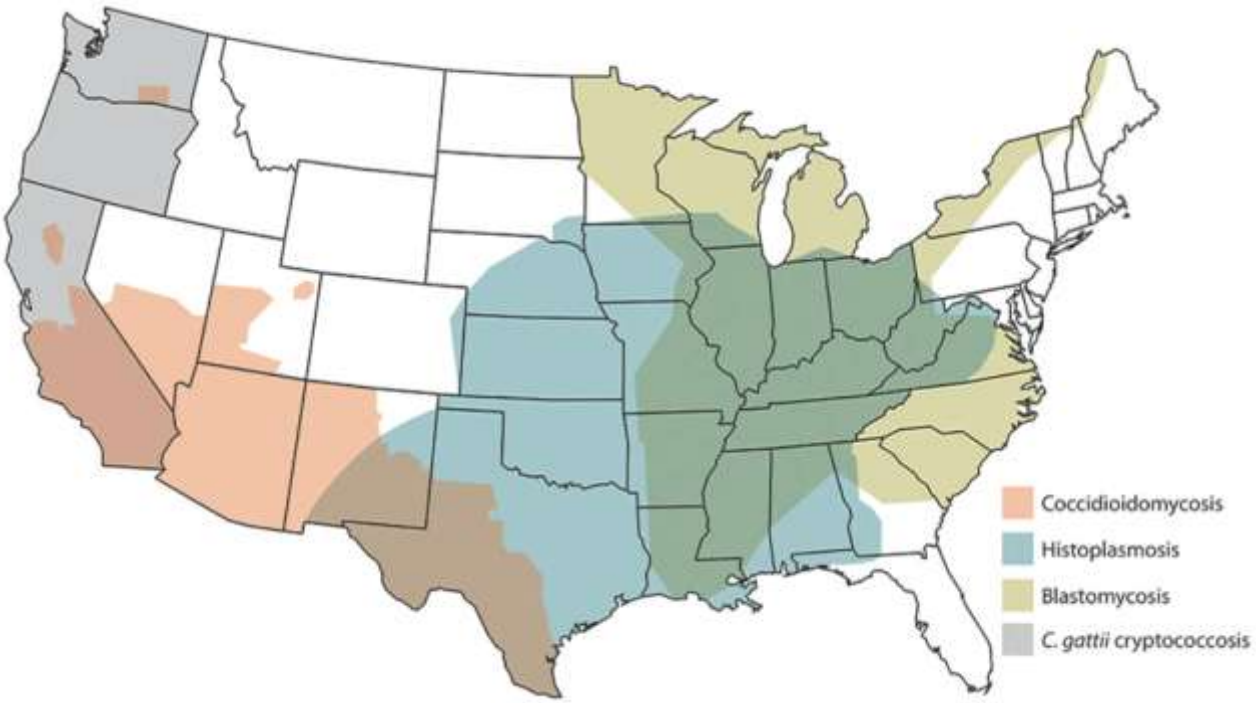

Figure 1 Geographic distribution of endemic fungal infections in the United States. [From CDC https://www.cdc.gov/features/fungalinfections/index.html]

2. Coccidioidomycosis

2.1 Background & Epidemiology

Coccidioidomycosis or "valley fever", results from infection by *Coccidioides immitis* or *Coccidioides posadasii*. *Coccidioides* spp. are endemic to the hot and dry climates of the southwestern United States and northern Mexico. *Coccidioides immitis* is associated with infection in California and is particularly prevalent in the southern California central valley (aka San Joaquin Valley) and Sonoran Desert. *Coccidioides posadasii* is present in southern Arizona, New Mexico, Texas, and northern Mexico [1]. Infection occurs after inhalation of arthroconidia present within soil or dust. The infectious dose required to cause illness is small; inhalation of a single spore can result in disease [2]. Rates of coccidioidomycosis have been rising consistently over the past two decades and the geographic range has also expanded over this time to include central and eastern Oregon and Washington state, although cases in these regions are still rare [3, 4]. This geographic spread has been ascribed to the impact of global warming. The spread of development into previously uninhabited areas may be another factor.

2.2 Clinical Manifestations & Pathogenesis

A majority of patients have subclinical seroconversion after exposure, however, illness ranges from asymptomatic to severe disseminated disease even in non-immunocompromised patients [5]. The classical clinical presentation is one of acute or subacute pneumonia. Coccidioidomycosis in SOT recipients is more likely to result in severe pulmonary or disseminated disease. Notable extrapulmonary manifestations include central nervous system (CNS) infection (meningitis, arachnoiditis), osteomyelitis, cutaneous disease, and involvement of the transplanted organ [2, 6]. Risk factors for disease in SOT include treatment for acute rejection, prior history of coccidioidomycosis or positive pre-transplant serology. Risk factors in the general population for severe infection include heritage (Filipino, African American ancestry), pregnancy, and other forms of immunosuppression particularly that which impairs cell mediated immunity. Behavioral factors that may increase risk for exposure include occupations such as landscaping or construction, and travel to or residence in an endemic area, including prisoners who may be incarcerated in endemic areas such as the California central valley [2, 7].

Patients with pulmonary coccidioidomycosis frequently present with fever, cough, night sweats, and fatigue. Illness is often protracted and many patients suffer from non-specific musculoskeletal complaints and arthralgias. Secondary cutaneous manifestations resulting from the immune response to infection are common and include erythema nodosum and erythema multiforme; primary skin involvement from dissemination also occurs [8]. Eosinophilia is a common laboratory abnormality, particularly in transplant recipients. The presence of pneumonia in conjunction with eosinophilia should prompt consideration of coccidioidomycosis [9, 10]. Radiographic findings may include pulmonary nodules, consolidative or cavitary lesions [2].

Coccidioidal meningitis is a severe complication that occurs in cases of disseminated infection; the presentation is often subacute or chronic with headache the predominant complaint. Potential complications include arachnoiditis and CNS vasculitis with resulting myelopathy or strokes. In SOT recipients with disseminated disease, CNS is the most commonly involved extrapulmonary site, followed by the transplant graft, spleen, liver and then skin/soft tissue and bone (including spinal

vertebrae) [6]. Positron-emission tomography (PET) may be helpful in identifying foci of non-pulmonary, non-CNS disease.

Coccidioidomycosis after transplantation can occur via de novo infection or by reactivation, even with remote exposure occurring decades prior [6, 11, 12]. Infection in this population is frequently severe, with extrapulmonary infection occurring in as many as 75% of SOT recipients [13]. For this reason, it is important to obtain a thorough social history to determine if there has been residence in or travel to endemic regions when evaluating SOT candidates and organ donors. The majority of disease occurs within the first year after transplantation, although there is also increased risk following treatment for acute rejection [2, 6]. Donor transmission has been described in all types of organ transplantation. In these cases, disease typically manifests early (within 60 days from transplant), and is usually severe with dissemination and high mortality [6, 14].

2.3 Pre-Transplant Screening & Diagnosis

The risk of coccidioidomycosis after SOT is highest in patients with a prior history of infection or serologic evidence of past infection. Available serologic tests include an enzyme-linked immunoassay (EIA) for detection of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, immunodiffusion (ID) for IgM and IgG antibodies, and antibody detection by complement fixation (CF). In general EIA is the most sensitive method, and is therefore recommended for use as a screening test, while ID and CF antibodies have higher specificity, and are more appropriate for confirming a suspected diagnosis. CF provides a quantitative value which can be used as a surrogate for disease burden and provides prognostic information as well as a useful measure for tracking disease status [2, 9]. Patients with a CF titer greater than 1:16 are at increased risk for disseminated disease [15, 16].

Limitations of serological diagnosis include lower sensitivity in transplant recipients when compared to immunocompetent patients [9, 13]. Additionally, due to the delay in seroconversion, patients presenting with acute illness may initially have negative serologic testing (incubation period after exposure 1-4 weeks) [15]. This can partially be addressed by serial testing as well as utilizing combination serologic testing to increase sensitivity in cases of suspected disease [9]. Definitive diagnosis is made by demonstration of *Coccidioides* either by culture or histopathology. The pathognomonic histopathological finding of coccidioidomycosis is the presence of a spherule, and *Coccidioides* spp. grow readily in multiple types of culture media as mold. Due to high risk of exposure and infection, it is critical to notify laboratory personnel about cases of suspected coccidioidomycosis to ensure that proper safety precautions are taken when isolating the fungus in culture.

Because of the relatively low sensitivity of serological and microbiological tests, there has been interest in the utility of a *Coccidioides* antigen test; a commercially available *Coccidioides* specific antigen assay demonstrated 71% sensitivity in cases of severe coccidioidomycosis (antigenuria); the majority of these patients were immunosuppressed, including SOT recipients [17]. Additionally, antigen testing was demonstrated to have a sensitivity of 93% and specificity of 100% for diagnosis of coccidioidal meningitis [15, 18].

Pre-transplant screening with EIA antibodies is recommended for all individuals with current or prior residence in endemic areas [2]. Studies examining rates of pre-transplant seropositivity from transplant centers in endemic regions range from 1.4%–5.6% [19-21]. Interpretation of EIA results,

particularly isolated IgM in an otherwise asymptomatic patient, can pose difficulty. While isolated IgM may represent early infection, there are high false positive rates [15, 22-24]. Follow-up testing 4-6 weeks later is recommended to determine if there is subsequent IgG seroconversion. Interpretation of negative serologies requires caution, as persistence of anti-coccidioidal antibodies is not lifelong, and remote infection with negative serology is possible [19]. Additionally, infection without a serological response can occur, and negative serology does not exclude coccidioidomycosis, particularly in immunocompromised patients [13, 15]. The impact of pre-transplant conditions such as end-stage renal disease and cirrhosis on serologic testing is unknown.

2.4 Prophylaxis & Treatment

As noted above, all patients undergoing evaluation for transplantation within endemic areas should undergo serologic screening to evaluate for prior infection. Patients with positive screening tests should undergo testing with ID and CF antibody tests, in addition to a thorough clinical and radiographic assessment to evaluate for the presence of active disease. Many centers located in endemic areas have adopted a universal prophylaxis strategy with administration of fluconazole to all patients who reside within highly endemic areas [2, 15]. In addition, patients with a history of pre-transplant seropositivity or history of coccidioidomycosis are recommended to receive targeted therapy. Prophylaxis and treatment regimens are noted in Table 1. The recommended dose of fluconazole for seropositive or recently infected patients is 400 mg per day (qday) for 12 months post-transplant with subsequent conversion to dose of 200-400 mg qday indefinitely, adjusted for renal insufficiency if needed. For patients who are seronegative but reside in highly endemic areas, fluconazole at a dose of 200 mg qday is recommended for at least 6-12 months, although at our center prophylaxis is continued indefinitely as long as they live within the endemic area [2, 15, 19, 25].

All transplant patients who develop coccidioidomycosis should be treated, regardless of severity. Lumbar puncture (LP) with cerebrospinal fluid (CSF) evaluation should be performed for immunocompromised patients with elevated CF titers, even in the absence of neurologic symptoms. LP should be performed for patients with unusual or persistent headache, unexplained nausea, vomiting, altered mental status or new focal neurologic deficits [15].

Treatment regimens are summarized in Table 1. Fluconazole is the treatment of choice for acute or chronic pulmonary coccidioidomycosis, at a dose of 400 mg qday for uncomplicated infection. In cases with bone involvement the recommended dose of fluconazole is 800 mg qday. If there is extensive bone or spinal involvement initial treatment should include lipid amphotericin B; azole therapy and amphotericin can be administered concurrently [15]. For meningitis, the recommended dose of fluconazole is 800 – 1200 mg qday; in severe cases consideration can be given to addition of liposomal amphotericin B [15]. Lifelong secondary prophylaxis with fluconazole 200-400 mg is recommended for all transplant recipients with a history of coccidioidomycosis given the high risk for relapse [2].

Table 1 Endemic fungal infections in solid organ transplant.

	Geographic range U.S.	Pre-transplant Screening	Diagnosis	Prophylaxis	Treatment
Coccidioidomycosis	Southern Arizona, California central valley, SW United States	Recommended if residence in endemic area; *Coccidioides* IgM/IgG EIA	Serologic: *Coccidioides* IgM/IgG EIA, confirmatory with cocci CF, ID Ab[1]; role for cocci antigen particularly CNS Culture Histopathology: Spherule	Seropositive or clinical history: FLUC 400 mg x 12 months → 200-400 mg indefinitely Residence in endemic area[2]: FLUC 200 mg for at least 6-12 months or indefinitely	- Evaluate for CNS involvement if elevated CF titer, consider bone scan - Monitor CF titers to trend treatment response Pulmonary: FLUC 400 mg qday x 6 months Bone: FLUC 800 mg qday x 36 months +/- lipid AMB for extensive/spinal involvement CNS: FLUC 800-1200 mg qday +/- lipid AMB - After treatment secondary prophylaxis recommended for life FLUC 200-400 mg qday
Histoplasmosis	Mississippi & Ohio river Valleys, Texas	Not routinely recommended	Serologic: Urine + serum antigen testing, increased sensitivity in disseminated disease[3] Culture Histopathology: Intracellular yeast	Recent histoplasmosis (2 years): ITRA 200 mg qday or BID + serial antigen x 6-12 mo	Mild: consider ITRA 200 mg BID x 12 mos Mod-severe disease: lipid AMB x 1-2 weeks followed by ITRA 200 mg BID x 12 mo - Monitor antigen baseline, 2 weeks, 1 month, q3months; continue 6-12 months after treatment discontinuation
Blastomycosis	SE, south central US, Mississippi & Ohio river basins, Midwest states	Not routinely recommended	Serologic studies limited due to high cross-reactivity Culture	Not recommended	AMB x 1-2 weeks followed by ITRA 200 mg BID x 12 mo CNS disease: A<=MB x 4-5 weeks followed by FLUC 800 mg qday or VORI 200-400 mg

	bordering Great Lakes		Histopathology: Broad based, budding yeast		qday or ITRA 200 mg BID-TID x 12 mo
Cryptococcosis	Ubiquitous; *Cryptococcus gattii* epidemic strain in PNW and non-epidemic strain along Pacific coast and SE	Not routinely recommended	Serologic: Serum and CSF cryptococcal antigen Culture Histopathology Yeast, thick capsule + mucicarmine, india-ink stain	Not recommended, although consider if prior history and receiving augmented IS	LP recommended in all SOT, obtain opening pressure Pulmonary disease: FLUC 400 mg qday x 6-12 mo Severe pulmonary, CNS, disseminated: - Induction: Lipid AMB + flucytosine (100 mg/kg/day divided q6h) x 2 wk - Consolidation: FLUC 400-800 mg qday x 8 wk - Maintenance: FLUC 200 – 400 mg qday x 6-12 mo Monitor for IRIS
Paracoccidioidomycosis	Brazil, Venezuela, Ecuador, Columbia, Argentina	Not routinely recommended	Serologic: Quantitative ID is most widely available in endemic regions Culture Histopathology: “Pilot’s wheel”, large yeas with multiple budding daughter cells	Not recommended	Mild-mod: ITRA 200 mg qday x 9-18 mo, TMP/SMX second line Severe or disseminated: AMB x 2-4 weeks followed by transition to azole

EIA = enzyme-linked immunoassay, CF = complement fixation, ID = immunodiffusion, FLUC = fluconazole, AMB = amphotericin B, ITRA = itraconazole, VORI = voriconazole

[1]serial testing required if acute infection, combination serologic assays increases sensitivity

[2]see Figure 1 (map)

[3]combination urine + serum antigen increases sensitivity

The extended spectrum triazoles (voriconazole, posaconazole, isavuconazole) appear to have good in vitro activity against *Coccidioides* spp, and have a role in treatment of refractory cases [2, 15]. Despite the availability of effective therapies, the mortality in transplant recipients with coccidioidomycosis remains high, around 30% [25].

3. Histoplasmosis

3.1 Background & Epidemiology

Histoplasma capsulatum is a thermally dimorphic fungus that exists as a mold in the environment and yeast in the infected host. It often causes asymptomatic infection in the immunocompetent population but can cause severe, often disseminated, life-threatening infection in immunocompromised patients. Though rare, histoplasmosis in transplant recipients can be fatal if not promptly recognized. In SOT recipients, histoplasmosis may result from reactivation of latent infection, donor-derived infection, and de novo post-transplant acquisition [26, 27]. Most infections occur due to inhalation of microconidia released from the mold. The majority of post-transplant histoplasmosis is reported to occur within the first two years following transplantation [28, 29]. This is likely due to reactivation of undiagnosed occult infection pre-transplantation or donor-derived infection. Periodic cases can continue to manifest years later. With appropriate treatment, mortality of post-transplant histoplasmosis is about 10% [30]. Most post-transplant histoplasmosis cases have been reported in kidney transplant recipients, owing to the large number of kidney transplantations being performed [28].

The incidence of histoplasmosis following solid organ transplantation is uncommon and is less than1% [28, 30, 31]. There are two varieties that cause illness in humans – *Histoplasma capsulatum* var. *capsulatum* and *H. capsulatum* var*. duboisii. H. capsulatum* var. *capsulatum* has a global distribution, whereas *H. capsulatum* var. *duboisii* is found in Africa. In the United States, histoplasmosis is highly endemic in the Mississippi and Ohio river valleys, namely the “Histo Belt” [28]. More than half of the population residing in the Histo Belt are exposed to *H. capsulatum*. *Histoplasma* infection in North America can also be found in patients from Asia or South America [32].

3.2 Clinical Manifestations & Pathogenesis

Clinical features of post-transplant histoplasmosis may initially be nonspecific, which can delay diagnosis [28-30]. It may take 2-3 weeks between onset of symptoms and diagnosis, and some indolent cases can present with vague symptoms lasting for several weeks to months [28, 30, 33]. There is no significant difference in disease presentation and severity between various types of organ transplants. In contrast to immunocompetent patients, most SOT recipients have disseminated disease and extra-pulmonary involvement at the time of diagnosis [28, 29, 34, 35]. Lungs are the most commonly effected organ (81%), followed by bone marrow (26%), liver (18%), spleen (13%), gastrointestinal (11%), central nervous system (7%), and skin (3%) [30].

Fever and fever of unknown origin are the most common presentation. Other nonspecific symptoms include cough, dyspnea, pleuritic chest pain, diaphoresis, headache, diarrhea, and weight loss. Cutaneous lesions can be solitary or multiple and can present as subcutaneous nodules, ulcers, cellulitis, and erythema nodosum. Unusual presentations reported in the literature include chest wall mass, necrotizing fasciitis, septic arthritis, and genitourinary disease

[28, 30]. There are a few reported cases of hemophagocytic lymphohistiocytosis secondary to histoplasmosis.

Associated laboratory abnormalities include pancytopenia, with leukopenia and anemia being most common, and elevated lactate dehydrogenase and ferritin levels [30]. Computed tomography (CT) of the chest may be more sensitive than chest x-ray (CXR) findings in detecting pulmonary involvement early on. Radiologic findings are nonspecific and include pulmonary nodules, cavitary lesions, diffuse bilateral infiltrates, and mediastinal and perihilar lymphadenopathy [28, 30, 33]. CT of the abdomen may reveal splenomegaly and lymphadenopathy in disseminated disease.

3.3 Diagnosis

Diagnosis of post-transplant histoplasmosis is made by histopathological or cytological examination, fungal culture, and *histoplasma* antigen assays. Intracellular yeasts 2-4 micrometers in size can be seen in biopsy specimens of affected tissue. *Talaromyces marneffei* and *Leishmania* are intracellular organisms that can resemble *H. capsulatum*, hence the importance of interpreting biopsy results in the appropriate clinical and epidemiological context. In disseminated and severe disease, intracellular yeast may be seen on Wright's stained peripheral blood smear. A positive fungal culture of either tissue or body fluid provides definitive proof of post-transplant histoplasmosis.

Compared to older generation urinary antigen assays, modern assays have improved sensitivity [28, 33]. The urine antigen has increased diagnostic yield in immunocompromised patients and is more likely to be positive in severe disseminated disease. The diagnostic yield of urinary antigen is reported to be low in patients with isolated pulmonary disease [30, 36]. There are no large studies analyzing the utility of bronchoalveolar lavage *Histoplasma* antigen testing in solid organ transplant recipients, however, experience from other patient populations show that it is highly sensitive and specific in cases of pulmonary histoplasmosis [37]. Combining urine and serum antigen tests can increase diagnostic yield [30]. *Histoplasma* antigen tests have significant cross-reactions with other fungi, such as *Blastomyces* dermatitidis, *Coccidioides* spp., *Paracoccidioides brasilenses*, and *T. marneffei* [38-40]. False-positive Aspergillus galactomannan assays can occur in patients with histoplasmosis [36, 39].

Histoplasma antibody testing is generally not reliable in post-transplant patients due to their dysfunctional immune system and inability to mount an effective immune response. A positive *Histoplasma* antibody test should be interpreted in the correct clinical and epidemiological setting [2]. Real-time polymerase chain reaction amplification of the ITS2 and D2 regions of the fungal RNA locus is sometimes used in identifying fungal elements in formalin-fixed, paraffin-embedded tissue [41]. The histoplasmin skin test is not used for diagnostic purposes and is mainly used to assess seroprevalence.

3.4 Pre-Transplant Screening & Prophylaxis

Routine pre-transplant screening of donors and recipients is not currently recommended even in endemic areas, because of the low incidence of post-transplant histoplasmosis [2]. A diagnosis of histoplasmosis within 2 years of transplantation warrants serial *Histoplasma* antigen monitoring as well as consideration for secondary prophylaxis with itraconazole 200 mg once or twice daily

post-transplant. In patients with a remote history of histoplasmosis but with persistent antigenuria or antigenemia, it is recommended to start prophylaxis at the time of transplantation [30]. The optimal duration of post-transplant prophylaxis is not well-defined but experts suggest that it be continued for 6-12 months along with monitoring of *Histoplasma* antigen [30].

Incidental findings of calcified granulomas on chest imaging that could be consistent with prior *H. capsulatum* infection do not warrant post-transplant prophylaxis in patients who are otherwise asymptomatic [30]. Lesions suspicious for granulomas on explanted organs of donors or recipients should be cultured and undergo histopathological examination as well as antigen and serologic testing if possible [42]. Positive histopathology in the setting of negative cultures suggests non-viable organisms. The utility of prophylaxis is not clearly defined in this setting however urine and serum antigen should be monitored every 3 months for one year in the recipient. If serology is positive with CF >1:32, treatment for 3-6 months is recommended with itraconazole 200 mg once or twice daily. If cultures or antigen are positive, the recipient should be treated for 12 months with serial antigen monitoring [42].

3.5 Treatment

Randomized controlled trials assessing optimal therapy in SOT recipients are currently lacking, hence, the treatment recommendations are similar to those for non-transplant patients. Recommendations are summarized in Table 1. For moderate to severe disease, a lipid formulation of amphotericin B (liposomal amphotericin B at 3 mg/kg daily or amphotericin B lipid complex at 5 mg/kg daily) is the recommended first-line therapy for the first 1-2 weeks followed by oral itraconazole 200 mg twice daily (BID) [43]. In mild to moderate disease, oral itraconazole 200 mg BID can be used. The bioavailability of itraconazole suspension is shown to be better than capsules and tablets and is not dependent on gastric pH. An itraconazole serum concentration should be checked after 2 weeks of therapy to assess both compliance and absorption [43]. Itraconazole, similar to other azoles, has interactions with immunosuppressive medications namely calcineurin inhibitors. It can increase serum concentrations of tacrolimus, sirolimus, and cyclosporine [2]. Fluconazole has been shown to be less efficacious and should not be used as first-line therapy. There is limited clinical data on the use of voriconazole, posaconazole and isavuconazole although all demonstrate good in vitro activity [44-46].

AST guidelines recommend at least 12 months of treatment in post-transplant histoplasmosis. Some studies have reported cure with shorter courses of therapy [2, 33]. Further, relapse following treatment for a median duration of 12 months is documented in a small percentage of patients [28]. Any reduction in immunosuppression should be weighed against the risk of allograft rejection. Both urine and serum antigen levels decrease with successful treatment; therefore, monitoring antigen levels can gauge treatment response. The recommended time interval for monitoring of antigen levels are pre-treatment, 2 weeks post-treatment, 1 month, and every 3 months for up to 6-12 months after treatment is discontinued [2, 43]. Additionally, for SOT patients with prior infection, antigen levels should be monitored during periods of augmented immunosuppression [2].

4. Blastomycosis

4.1 Background & Epidemiology

Blastomycosis is caused by the dimorphic fungi *Blastomyces dermatitidis* and *Blastomyces gilchristii* [47]. *Blastomyces* exists in nature in mold or mycelial form, but when inhaled into the host's lungs converts to the yeast form at body temperatures [48, 49]. Although *Blastomyces* is one of three dimorphic fungi that are known to cause disease in North America, the frequency of blastomycosis in SOT recipients is rare in comparison to Histoplasmosis and Coccidioidomycosis. From the Transplant-Associated Infection Surveillance Network (TRANSNET), a total of 70 patients were diagnosed with endemic mycosis between the years 2001-2006, 9 of which were due to blastomycosis [31]. In a retrospective multicenter study of histoplasmosis and blastomycosis after solid organ transplantation from three Midwestern transplant institutions, 30 patients were identified as having endemic fungal infections, 8 of which were blastomycosis [29].

The endemic area in North America includes the states bordering the Mississippi and Ohio Rivers, the Midwestern states, and the Canadian provinces that border the Great Lakes. Blastomycosis has also been reported in New York and Canada along the St. Lawrence River. There was recently a reported outbreak in the Albany, NY, where it was previously not considered to be endemic [50]. Most cases have been identified in Kentucky, Arkansas, Mississippi, North Carolina, Tennessee, Louisiana, Illinois, and Wisconsin. In 2012, an epidemiologic review of cases in Illinois and Wisconsin found an annual incidence of 0.4-2.6 cases per 100,000 population [50]. The previously described geographic areas may not entirely represent the distribution of *Blastomyces* as reporting is only required in 6 states; additionally, subclinical cases may also be missed due to the poor sensitivity of diagnostic testing and historical absence of a valid skin test [48, 49]. Although most patients diagnosed with blastomycosis have a history of exposure to soil, wooded areas, or lakes and rivers, the exact natural habitat has been difficult to identify.

There is a newly re-classified emerging species of dimorphic fungus within the genus *Blastomyces* in North America. Recently re-classified on the basis of phylogenetic analyses, *Blastomyces helicus* (formerly *Emmonsia helica*) has been identified as the pathogen in several cases resulting in severe pulmonary and disseminated infection and primarily occurring in immunocompromised hosts; infection resulted in high rates of mortality. The geographic range appears to include western Canada (Alberta, Saskatchewan) and the mountain west region of the United States [51].

4.2 Clinical Manifestations & Pathogenesis

The clinical manifestations of blastomycosis can vary widely, ranging from an asymptomatic infection to pulmonary disease progressing to acute respiratory distress syndrome (ARDS). Symptom onset after inhalation of conidia ranges between 3 weeks to 3.5 months [52]. 25%-40% of patients with blastomycosis have extrapulmonary dissemination, most commonly to the skin and bone [47, 52]. In comparison to immunocompetent patients, the rate of disseminated disease is similar amongst SOT patients and immunocompetent patients, however presentation differs in the severity of pulmonary disease, which can often progress to ARDS [49, 52, 53]. Disseminated disease can also involve osteoarticular structures, the genitourinary tract, and the CNS. Pulmonary blastomycosis can present in a similar manner to bacterial community acquired pneumonia with

fevers, chills, headache, productive or non-productive cough, dyspnea, and with a consolidation on chest imaging. Chest imaging can also show nodules, masses, cavitation, or have a miliary pattern. The skin is the most common site of extrapulmonary involvement. Lesions are typically pustular or ulcerative in transplant patients, whereas lesions in immunocompetent patients are typically verrucous. The most common areas of skin involvement are exposed areas, such as the head and extremities. Blastomycosis can also form a cutaneous sinus tract from underlying osteomyelitis [53]. After skin, bone is the most common site of disseminated disease. Genitourinary cases can present in men as prostatitis, epididymitis, and in women as tubo-ovarian abscesses, endometritis, and salpingitis. Lastly, patients with CNS blastomycosis can present with headaches, focal neurological defects, and seizure. Patients may have a meningitis presentation and will have either a lymphocytic or neutrophilic CSF pleocytosis. Neurologic involvement can also present as a mass lesion and can progress to hydrocephalus, mass effect from edema, herniation, and seizures [53]. However, CNS disease is uncommon in SOT patients [49].

4.3 Pre-Transplant Screening & Diagnosis

Each donor and recipient should be assessed individually. As mentioned previously, the incidence of blastomycosis in SOT patients is low, even amongst those who receive transplants in endemic areas. Routine pre-transplant screening is not recommended, but testing should be considered in donors and recipients from endemic areas that have lung and skin lesions of unclear etiology [54]. In contrast to the other major North American endemic fungi, there have been no documented cases of *Blastomyces* transmission through an infected allograft [2, 52].

Culture of *B. dermatitidis* from respiratory secretions or other clinical specimens in the laboratory is the most sensitive form of diagnosis and will grow as a mold at 30 C. Growth usually occurs after 1-3 weeks, but colonies can be observed as early as 5-10 days of incubation. The mycelial form will appear as branching, septate hyphae with right angled conidiophores, often described as having a lollipop appearance [48]. When grown at 37 C, the yeast can be observed under light microscope and are round, have a double cell wall, and bud with a broad base. The daughter cell will become as large as the mother cell prior to detaching, giving it the well-recognized broad-based budding appearance associated with *B. dermatitidis*. Once there is growth, a DNA probe is used to rapidly identify *B. dermatitidis* from culture [49]. There are no commercially available polymerase chain reaction (PCR) assays for blastomycosis.

Direct observation of the typical yeast form can confirm the diagnosis, and has been the most commonly used method for rapid diagnosis [54]. However, microscopy has a diagnostic yield of only up to 40% [52]. Histopathologic examination of tissue with methenamine silver or PAS stain is usually the diagnostic method for extrapulmonary disease [54].

Serologic tests are of limited utility due to the cross reactivity with other endemic fungi and low sensitivity. Complement fixation, immunodiffusion, and EIA can be used for epidemiologic studies, but at this time have limited utility in diagnosis due to low sensitivity and cross reactivity with other endemic fungi, in particular with *H. capsulatum* [54]. *Blastomyces* downregulates the amount of 1, 3-beta-d-glucan in its cell wall when it undergoes phase transition, limiting the utility of assays that detect this component of the cell wall [47].

4.4 Prophylaxis & Treatment

Because the incidence in SOT recipients is low, prophylaxis is not recommended for patients who live in endemic regions. The rates of disseminated disease are similar when comparing immunocompetent patients and SOT patients (25%-50%), although immunocompromised patients are at greater risk for severe pulmonary disease, and progression to respiratory failure and ARDS [2, 52, 55] Infectious Disease Society of America (IDSA) guidelines for management of blastomycosis state that prolonged suppressive azole therapy in immunocompromised patients may be necessary if immunosuppression cannot be reversed; this is primarily based on extrapolation from HIV/AIDS patients. However, in more recent AST guidelines the recommended duration of treatment is generally 12 months, assuming resolution of signs/symptoms of infection; consideration can be given for more prolonged treatment although data are lacking for this approach, and it seems that the risk of relapse is low [2, 54].

Based on 2008 IDSA treatment guidelines and 2013 AST guidelines, all SOT recipients diagnosed with blastomycosis require treatment which is summarized in Table 1 [2, 54]. In immunocompromised patients, amphotericin B as a lipid formulation at 3-5 mg/kg per day or amphotericin B deoxycholate at 0.7-1 mg/kg per day is recommended for 1-2 weeks or until clinical improvement is demonstrated. While there is more clinical experience with amphotericin B deoxycholate for treatment of severe blastomycosis, lipid formulations appear to be equally efficacious with lower toxicity and are preferred in SOT patients [2, 54]. Itraconazole is recommended as step down therapy after clinical response has been observed. Itraconazole is dosed at 200 mg 3 times daily for 3 days, and then 200 mg bid afterwards to complete at least 12 months of therapy [2].

For mild isolated pulmonary infection, treatment with oral itraconazole at a dose of 200 mg BID alone could be considered although this approach would require close clinical monitoring [2, 54]. Serum levels of itraconazole should be checked after two weeks of therapy to ensure therapeutic drug levels. In SOT recipients the recommended duration of treatment is at least 12 months assuming resolution of symptoms and signs of infection; data regarding benefit of longer treatment is lacking.

For patients with CNS involvement, liposomal amphotericin B dosed at 5 mg/kg/day is recommended for a longer duration of 4-6 weeks before transition to an azole. For CNS infection stepdown therapy to high dose fluconazole 800 mg per day or voriconazole 200-400 mg BID is preferred over itraconazole. The duration of treatment for CNS disease is at least 12 months and assumes resolution of CSF abnormalities [2, 54].

Echinocandins have no activity against *Blastomyces* because of the decrease in cell wall content of 1,3-beta-d-glucan [47]. In general, fluconazole seems to be less efficacious when compared to itraconazole with the exception of CNS disease; the newer extended-spectrum triazoles appear to have good in vitro activity against *B. dermatiditis* [2].

5. Cryptococcosis

5.1 Background/Epidemiology

Cryptococcus is the third most common cause of invasive fungal disease in SOT recipients, and is a major cause of morbidity and mortality in this population [34, 56]. Infection is primarily caused

by two species within the genus; *Cryptococcus neoformans* and *Cryptococcus gattii*. While *Cryptococcus* is present globally there is some geographic variability. In North America the majority of infections are caused by *Cryptococcus neoformans* serotype A (var. *grubii*), however *Cryptococcus gattii* (VII) has recently been recognized as an emerging pathogen in the Pacific northwestern United States and Vancouver Island in British Columbia, Canada; prior to this there had been sporadically reported cases of *Cryptococcus gattii* mostly occurring along the Pacific coast and in the southeastern United States [57].

Infection occurs by inhalation of the yeast or basidiospores of the organism from soil. C. neoformans in particular has an association with soil contaminated by bird droppings and has also been isolated from bird nests and guano directly [58]. Given this association, many experts recommend that transplant recipients avoid direct contact with birds and bird droppings. *C. gattii* is found in rotting vegetation or wood of certain trees such as eucalyptus, coniferous trees, and mopane [58].

5.2 Clinical Manifestations/Pathophysiology

The majority of cryptococcal infections in SOT recipients are felt to represent reactivation of latent infection, although primary infection and donor transmission have also been documented [59, 60]. Disease usually occurs as late-onset infection (median 16-21 months), with the exception of lung and liver transplant recipients where disease is more likely to develop within the first 12 months after transplantation. Cases with very early onset post-transplant are more likely to occur with donor transmission or unrecognized active pre-transplant infection [60].

Cryptococcosis most commonly presents as pulmonary or CNS disease. Pulmonary disease can range from asymptomatic involvement to severe pneumonia. 50%-75% of SOT recipients have extrapulmonary or CNS involvement and risk of dissemination is particularly high in liver transplant recipients [56, 61-63]. CNS involvement is typically characterized by meningitis, frequently with high opening pressure. The epidemic strain of *C. gattii* more commonly presents with pulmonary or CNS mass lesions in non-immunocompromised patients, however this finding was not observed in SOT recipients from a case series of *C. gattii* cases in Oregon which noted high rates of dissemination and mortality among transplant recipients infected with this species [64]. Skin involvement in SOT occurs with relative frequency; presentation can be variable with nodular, maculopapular, ulcerative/pustular disease, and cellulitis most commonly involving the lower extremities. Cutaneous involvement usually indicates disseminated infection although primary skin infection is possible [65].

The risk of cryptococcal disease in patients with advanced cirrhosis, including in pre-transplant patients should be noted. Cirrhotic patients are at substantially increased risk for disseminated cryptococcosis, and frequently present with fungemia as well as peritonitis. It is crucial to have a high clinical index of suspicion in cirrhotic patients presenting with sepsis, as the clinical course is typically fulminant with high rates of mortality [66].

5.3 Pre-Transplant Screening & Diagnosis

Serum cryptococcal antigen can be detectable in blood weeks to months before onset of disease, and current WHO guidelines recommend use of cryptococcal antigen screening with pre-emptive prophylaxis in HIV-infected patients with CD4 counts below 100/uL [67]. While the

incidence of *cryptococcus* in SOT is relatively high (0.2%–5%), there are currently no recommendations for screening in solid organ transplant recipients and more study is needed on this subject [56].

Cryptococcus infection should be considered in any transplant recipient presenting with pneumonia or pulmonary nodules, as well as in patients presenting with subacute or chronic headache and meningeal symptoms. Cultures should be obtained from any sites of suspected involvement including respiratory, blood, CSF and urine. A high proportion of SOT recipients with cryptococcal meningitis have detectable fungemia [68]. Serum cryptococcal antigen has high sensitivity in transplant recipients, particularly in disseminated infection; sensitivity for cryptococcal antigen is lower in isolated pulmonary disease [68]. Patients with *C. gattii* typically have detectable cryptococcal antigen although at lower titers than with C. neoformans and infection with other species e.g. *C. albidus*, *C. laurentis* will frequently have negative cryptococcal antigen [56, 69]. On histopathology, *cryptococcus* appears as a yeast with thick capsule that stains positive by mucicarmine staining [56].

Due to high rates of CNS involvement, lumbar puncture should be performed in all transplant recipients with suspected cryptococcal disease, with routine studies including culture, cryptococcal antigen; it is important to measure opening pressure as elevated pressures impact management.

5.4 Prophylaxis & Treatment

There are no guidelines regarding prophylaxis for *Cryptococcus* in SOT recipients. For patients with a history of Cryptococcus undergoing transplant or enhanced immunosuppression, the decision to utilize secondary prophylaxis with fluconazole should be made on a case-by-case basis. The duration of secondary prophylaxis if used is for at least 1 year [56].

Treatment in SOT recipients is consistent with current IDSA guidelines (Table 1). It is critical to determine the site and extent of disease and to evaluate for CNS involvement with lumbar puncture. For patients with CNS involvement and elevated CSF opening pressure above 25 mmHg, daily LPs are recommended until the opening pressure is consistently below 20 mmHg [70].

For uncomplicated pulmonary disease, recommended treatment is fluconazole 400 mg qday for 6-12 months. In cases of severe pulmonary disease, disseminated infection or meningitis, initial treatment should include lipid formulations of amphotericin B plus flucytosine; induction with this regimen should be continued for a minimum of 2 weeks, and in cases of CNS involvement until CSF sterilization has occurred. Induction should be followed by an 8-week consolidation phase with fluconazole at doses of 400-800 mg qday. After induction and consolidation, maintenance with fluconazole at doses of 200-400 mg qday is recommended for at least 6-12 months [56, 70].

Antifungal susceptibility testing for C. neoformans has been standardized by CLSI however the clinical relevance of MICs in relation to clinical outcomes is not clearly established. The epidemic strain of *C. gattii* has been noted to have elevated fluconazole MICs. The extended spectrum azoles including posaconazole, voriconazole, and isavuconazole have excellent in vitro MICs even for isolates with elevated fluconazole MICs, and could be considered as an alternative for oral phase of treatment [46, 56, 71].

A potential complication when treating *Cryptococcus* in SOT recipients is the development of immune reconstitution syndrome (IRIS). In one series IRIS occurred in 14% of SOT recipients being

treated for cryptococcal disease [72]. IRIS occurs with rapid reduction in immunosuppression (in particular discontinuation of calcineurin inhibitors) coupled with initiation of antifungal therapy, and can manifest with clinical worsening including lymphadenitis, cellulitis, aseptic meningitis or enlarging/new CNS lesions. Onset is typically 4-6 weeks after initiation of antifungal therapy [56]. Distinguishing IRIS from relapsed/persistent infection can pose difficulty and requires repeat microbiological assessment in order to ensure negative cultures. There is no proven treatment for IRIS, although there may be a role for corticosteroids in select cases of CNS disease or with severe pulmonary/extrapulmonary involvement [56].

Although useful for diagnosis, serial testing of cryptococcal antigen has not been demonstrated to have a clear role in monitoring response to therapy. An exception is in SOT recipients with cryptococcosis who require re-transplantation. In these patients the cryptococcal antigen titer should ideally be stable or declining prior to re-transplantation [56].

6. Paracoccidioidomycosis

6.1 Background & Epidemiology

Paracoccidioidomycosis is caused by the endemic fungi *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii*. It is endemic to South and Central America, and typically affects men who work in agriculture [73]. Like the North American endemic mycoses, *Paracoccidioides* is dimorphic, growing as mold at 28C and yeast at 35-37C. The majority of clinical experience with Paracoccidioidomycosis is from immunocompetent hosts, with less available data for disease in SOT patients.

Paracoccidioidomycosis was once referred to as “South American blastomycosis”. Approximately 80% of cases of Paracoccidioidomycosis have been identified in Brazil, in particular the states of Sao Paulo, Parana, Rio Grande do Sul, Goias, Rio De Janiero, and Rondonia. Cases have also been identified in Venezuela, Ecuador, Columbia, and Argentina. There have been no documented cases in Chile, Surinam, Nicaragua, or Belize [74].

It is believed that paracoccidioidomycosis is found in soil, however it is only sporadically isolated from the environment and the true natural habitat has been difficult to identify [74]. Incidence rates of 0.7-3 cases/100,000 people in endemic regions and 9-40 cases/100,000 people in hyperendemic regions have been reported [75, 76]. The prevalence of paracoccidioidomycosis is thought to be around 10 million in Latin America, but only 1%-2% of those infected will develop disease. The incidence, prevalence, and mortality data may not be a true representation of the burden of disease in Latin America, as paracoccidioidomycosis is not reportable. Among SOT recipients, chronic paracoccidioidomycosis has been identified predominantly in renal transplant recipients, and has a low incidence [76]. In a review assessing paracoccidioidomycosis in various immunocompromised populations, nine cases of paracoccidioidomycosis in renal transplant recipients were identified with one case in a liver transplant recipient [76].

6.2 Clinical Manifestations

Paracoccidioidomycosis can affect any organ system and presents in a variety of ways. It is classified into acute and chronic forms. The acute form most commonly affects children and young adults, while the chronic form typically occurs in adults [76]. Acute paracoccidioidomycosis

accounts for 5%-25% of cases with equal incidence between males and females [75, 76]. Manifestations include fevers, weight loss, anorexia and it can also present with suppurative lymphadenopathy, hepatosplenomegaly, mucocutaneous lesions, osteoarticular involvement, and less commonly pulmonary involvement. The acute form of disease is also associated with severe intraabdominal lymphadenopathy that can coalesce, forming large masses and resulting intestinal and biliary obstruction. It is frequently associated with peripheral eosinophilia, occurring in 30%-50% of cases [76].

Chronic paracoccidioidomycosis accounts for the majority of cases and typically occurs in adults. In contrast to acute paracoccidioidomycosis, the chronic form is more common in men, with a male to female ratio of 22:1 [76]. Symptoms develop slowly, often persisting for months prior to development of symptoms serious enough to necessitate medical attention. Pulmonary disease is common, with skin and mucosal involvement being the most common extrapulmonary sites of involvement. Disease often presents with mucosal lesions and alveolar-interstitial infiltrates, followed by skin lesions, and progression to pulmonary fibrosis [76]. Skin lesions can present as ulcerations, vegetation, nodules, or plaques. One of the more serious sequelae of the fibrotic disease associated with paracoccidioidomycosis is adrenal involvement, which can result in Addison's disease and may necessitate lifelong hormonal replacement therapy [76].

In the small number of cases of SOT patients with paracoccidioidomycosis, most had pulmonary involvement, with presentations varying between bilateral pulmonary nodules, pulmonary cavitation, or bronchopneumonic infiltrates. Lymphatic involvement was uncommon [76].

6.3 Pre-Transplant Screening & Diagnosis

In a review for screening of infectious diseases, *Paracoccidioides brasiliensis* was determined to have a risk that was not assessable for risk of transmission. As a result, routine screening is not recommended prior to transplantation with the exception of screening donors and recipients from known endemic areas that have pulmonary disease and skin lesions of unclear etiology [77].

A proven diagnosis of paracoccidioidomycosis can be made when the characteristic yeast form is found in clinical specimens under direct microscopy [78]. Microscopically, the yeast form has a characteristic multiple budding formation, referred to as a pilot's wheel, characterized by large yeast cells surrounded by multipolar budding daughter cells [73, 78]. At 35-37C the fungus will grow in about 10 days, however culture can take up to one month to grow, and the ideal means of diagnosis should always be through direct observation of the organism in a tissue sample.

Serological methods are available in endemic regions, but there are no standardized serological assays and results may vary between different laboratories. There are no validated serologic assays for the diagnosis of *P. lutzii* [78]. Serological tests may also not be reliable in diagnosis of acute disease in the solid organ transplant population due to a delayed immune response in the setting of immunosuppression.

6.4 Prophylaxis & Treatment

While there are no specific recommendations for prophylaxis against *P. brasiliensis* after transplantation, trimethoprim-sulfamethoxazole has been found to have activity against *Paracoccidioides*, and may account for the low incidence among SOT recipients [75, 79]. In a

review of paracoccidioidomycosis in transplant recipients, the majority of cases occurred after the first year of transplantation when trimethoprim-sulfamethoxazole had been stopped [75].

P brasiliensis and *P lutzii* are susceptible to most systemic antifungal agents as well as sulfonamide derivatives, and both species have similar susceptibility patterns [76]. In patients with mild to moderate disease, the treatment of choice is itraconazole 200 mg daily for 9 to 18 months, based on clinical response. Although only used on a small number of patients, voriconazole, posaconazole, and isavuconazole are potential substitutes [76]. Trimethoprim/sulfamethoxazole is considered the second line treatment for patients with mild to moderate disease. Severe or disseminated disease should be treated with Amphotericin B in deoxycholate or a lipid formulation of Amphotericin B. The duration of IV amphotericin is typically around 2-4 weeks with observed clinical improvement, followed by transition to oral antifungal agents such as itraconazole [76].

7. Discussion

Endemic fungi have a varied number of geographic distributions, covering much of the United States. Given this diversity, it is imperative to assess potential exposures in transplant candidates and recipients, as well as in organ donors. This issue is of special note given the rise of organ exchange either between UNOS regions, or as part of paired living donor exchange for kidney transplantation. In addition to a careful geographic history, an occupational history can also provide important clues to increased risk of endemic fungi exposure.

Another important aspect of endemic fungi and *Cryptococcus* is the fact that infection can occur in one of three ways: reactivation of previous infection, donor derived infection, or primary infection occurring after transplantation. Given these three possibilities, when both donor and recipient share similar geographic exposures it can be challenging to establish when infectious exposure occurred. Clinical clues that may shed light on distinguishing between these possibilities include geographic history and life style factors as described above, pre-transplant serologic or antigen testing results, and pre-transplant imaging studies. Another indication of time of infection may be the timing and anatomical location of infection. For example, as primary fungal infections are derived from breathing an environmental source, the sudden development of disseminated disease without evidence of lung involvement, especially in the first month after transplant, would suggest a potential donor-derived infection. In contrast, development of a focal lung infection in a patient with previous normal radiographic studies would suggest primary infection.

Endemic fungal infections lack a characteristic presentation. Given their ability to involve a variety of anatomic areas including the lungs, CNS, skin, bone, and joints as well as cause disseminated disease, it is often difficult to establish the correct diagnosis early in the course of infection, which likely increases the risk of poor response to therapy when the correct diagnosis is made. In addition, immunocompromised patients may present in an atypical manner, often with extrapulmonary manifestations or with more severe disease than is commonly encountered. This highlights the importance of entertaining the diagnosis of endemic fungal infection early in the course of disease. In addition, the development of more sensitive and specific testing modalities would be a great improvement to the current state of fungal diagnostics. Traditional testing has relied on antibody testing, which is often blunted during immune suppression and may not be reliable in transplant recipients; these tests may also become negative over time if exposure was

remote. Newer methods are often antigen based, offering an improvement over serologic testing. However, these tests still require the physician to consider the correct diagnosis. Future non-targeted testing, such as molecular testing of cell-free DNA, may be an attractive option to provide earlier diagnosis before a specific fungal infection has been considered, however, data is limited regarding the sensitivity of this approach.

Given the large geographic distributions of the endemic fungi and *Cryptococcus*, it is perhaps surprising that these infections are not encountered more frequently. In both immunocompromised and non-immunocompromised patients, a spectrum of severity of presentation occurs, with some presumably exposed patients never developing disease despite an absence of specific antifungal prophylaxis. This raises several possible explanations including strain variation in organism pathogenicity, as well as differences in genetic susceptibility to fungal infection despite similar levels of immune suppression. Reaching a better understanding of host vulnerability to infection and factors that predispose to severe disease would improve the ability to provide targeted prophylaxis or monitoring for patients at increased risk.

Antifungal treatment or prophylaxis with azole drugs is a common refrain in the prevention of infection due to *Coccidioides*, *Histoplasma*, *Blastomyces*, and *Cryptococcus*. This may mean exposure to azoles, often fluconazole, for months or even years after transplantation. Although fluconazole and itraconazole tend to be well tolerated even with chronic use, some patients do experience side effects including dry skin, gastrointestinal upset, dry mouth, and hair loss. These symptoms are sometimes alleviated with lower drug doses. Another challenge inherent in transplant recipients is the typical concurrent lifetime use of calcineurin inhibitors (CNI) such as tacrolimus. Given the drug-drug interaction with azoles, CNI dosing typically needs to be decreased after azole medications are started and regular monitoring CNI levels is critical; it is imperative to appropriately counsel patients regarding the important of medication compliance. Patients who fail to refill or stop taking their azole medication may develop sub-therapeutic tacrolimus levels, leading to increased risk for antibody development and rejection.

8. Conclusions

The endemic fungi and *Cryptococcus* are important causes of morbidity and mortality in transplant recipients. Therefore, it is crucial that transplant specialists and ID consultants be familiar with the geographic distribution of these endemic fungi in order to consider these organisms as possibilities when diagnosing patients with a wide spectrum of clinical presentations. Improvements in diagnostic modalities should speed diagnosis and improve clinical outcomes in transplant patients with fungal infections.

Author Contributions

O.E.B. performed literature review, wrote, and edited the manuscript; D.N. and P.G. performed literature and wrote the manuscript, and J.S. wrote and edited the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Fisher MC, Koenig GL, White TJ, Taylor JW. Molecular and phenotypic description of coccidioides posadasii sp. nov., previously recognized as the non-california population of coccidioides immitis. Mycologia. 2002; 94: 73-84.
2. Miller R, Assi M. Endemic fungal infections in solid organ transplantation. Am J Transplant. 2013; 13: 250-261.
3. Marsden-Haug N, Goldoft M, Ralston C, Limaye AP, Chua J, Hill H, et al. Coccidioidomycosis acquired in washington state. Clin Infect Dis. 2013; 56: 847-850.
4. Coates SJ, Fox LP. Disseminated coccidioidomycosis as a harbinger of climate change. JAAD Case Rep. 2018; 4: 424-425.
5. Brown J, Benedict K, Park BJ, Thompson GR. Coccidioidomycosis: Epidemiology. Clin Epidemiol. 2013; 5: 185-197.
6. Blair JE, Logan JL. Coccidioidomycosis in solid organ transplantation. Clin Infect Dis. 2001; 33: 1536-1544.
7. de Perio MA, Niemeier RT, Burr GA. Coccidioides exposure and coccidioidomycosis among prison employees, california, united states. Emerg Infect Dis. 2015; 21: 1031-1033.
8. DiCaudo DJ. Coccidioidomycosis: A review and update. J Am Acad Dermatol. 2006; 55: 929-942.
9. Mendoza N, Blair JE. The utility of diagnostic testing for active coccidioidomycosis in solid organ transplant recipients. Am J Transplant. 2013; 13: 1034-1039.
10. Braddy CM, Heilman RL, Blair JE. Coccidioidomycosis after renal transplantation in an endemic area. Am J Transplant. 2006; 6: 340-345.
11. Hernández JL, Echevarría S, García-Valtuille A, Mazorra F, Salesa R. Atypical coccidioidomycosis in an AIDS patient successfully treated with fluconazole. Eur J Clin Microbiol Infect Dis. 1997; 16: 592-594.
12. Vartivarian SE, Coudron PE, Markowitz SM. Disseminated coccidioidomycosis. Unusual manifestations in a cardiac transplantation patient. Am J Med. 1987; 83: 949-952.
13. Blair JE. Approach to the solid organ transplant patient with latent infection and disease caused by coccidioides species. Curr Opin Infect Dis. 2008; 21: 415-420.
14. Kusne S, Taranto S, Covington S, Kaul DR, Blumberg EA, Wolfe C, et al. Coccidioidomycosis transmission through organ transplantation: A report of the OPTN *Ad Hoc* disease transmission advisory committee. Am J Transplant. 2016; 16: 3562-3567.
15. Galgiani JN, Ampel NM, Blair JE, Catanzaroet A, Geertsma F, Hoover SE, et al. Executive summary: 2016 infectious diseases society of america (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016; 63: 717-722.
16. Blair JE, Coakley B, Santelli AC, Hentz JG, Wengenack NL. Serologic testing for symptomatic coccidioidomycosis in immunocompetent and immunosuppressed hosts. Mycopathologia. 2006; 162: 317-324.
17. Durkin M, Connolly P, Kuberski T, Myers R, Kubak BM, Bruckner D, et al. Diagnosis of coccidioidomycosis with use of the coccidioides antigen enzyme immunoassay. Clin Infect Dis. 2008; 47: e69-e73.
18. Kassis C, Zaidi S, Kuberski T, Moran A, Gonzalez O, Hussainet S, et al. Role of coccidioides antigen testing in the cerebrospinal fluid for the diagnosis of coccidioidal meningitis. Clin Infect Dis. 2015; 61: 1521-1526.

19. Phonphok K, Beaird O, Duong T, Datta N, Schaenman J, Bunnapradist S. Screening coccidioides serology in kidney transplant recipients: A 10-year cross-sectional analysis. Transpl Infect Dis. 2018; 20: e12932.
20. Blair JE, Kusne S, Carey EJ, Heilman RL. The prevention of recrudescent coccidioidomycosis after solid organ transplantation. Transplantation. 2007; 83: 1182-1187.
21. Blair JE, Balan V, Douglas DD, Hentz JG. Incidence and prevalence of coccidioidomycosis in patients with end-stage liver disease. Liver Transpl. 2003; 9: 843-850.
22. Lindsley MD, Ahn Y, McCotter O, Gade L, Hurst SF, Brandt ME, et al. Evaluation of the specificity of two enzyme immunoassays for coccidioidomycosis by using sera from a region of endemicity and a region of nonendemicity. Clin Vaccine Immunol. 2015; 22: 1090-1095.
23. Blair JE, Mendoza N, Force S, Chang YH, Grys TE. Clinical specificity of the enzyme immunoassay test for coccidioidomycosis varies according to the reason for its performance. Clin Vaccine Immunol. 2013; 20: 95-98.
24. Kuberski T, Herrig J, Pappagianis D. False-positive IgM serology in coccidioidomycosis. J Clin Microbiol. 2010; 48: 2047-2049.
25. Vikram HR, Blair JE. Coccidioidomycosis in transplant recipients: A primer for clinicians in nonendemic areas. Curr Opin Organ Transplant. 2009; 14: 606-612.
26. Brunet K, Alanio A, Lortholary O, Rammaert B. Reactivation of dormant/latent fungal infection. J Infect. 2018; 77: 463-468.
27. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. Am J Transplant. 2011; 11: 1123-1130.
28. Assi M, Martin S, Wheat LJ, Hage C, Freifeld A, Avery R, et al. Histoplasmosis after solid organ transplant. Clin Infect Dis. 2013; 57: 1542-1549.
29. Grim SA, Proia L, Miller R, Alhyraba M, Costas‐Chavarri A, Oberholzer J, et al. A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. Transpl Infect Dis. 2012; 14: 17-23.
30. Gajurel K, Dhakal R, Deresinski S. Histoplasmosis in transplant recipients. Clin Transplant. 2017; 31: e13087.
31. Kauffman CA, Freifeld AG, Andes DR, Baddley JW, Herwaldt L, Walker RC, et al. Endemic fungal infections in solid organ and hematopoietic cell transplant recipients enrolled in the Transplant-Associated Infection Surveillance Network (TRANSNET). Transpl Infect Dis. 2014; 16: 213-224.
32. Adenis AA, Valdes A, Cropet C, McCotter OZ, Derado G, Couppie P, et al. Burden of HIV-associated histoplasmosis compared with tuberculosis in Latin America: A modelling study. Lancet Infect Dis. 2018; 18: 1150-1159.
33. Cuellar-Rodriguez J, Avery RK, Lard M, Budev M, Gordon SM, Shrestha NK, et al. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. Clin Infect Dis. 2009; 49: 710-716.
34. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: Results of the transplant-associated infection surveillance network (TRANSNET). Clin Infect Dis. 2010; 50: 1101-1111.
35. Freifeld AG, Wheat LJ, Kaul DR. Histoplasmosis in solid organ transplant recipients: Early diagnosis and treatment. Curr Opin Organ Transplant. 2009; 14: 601-605.

36. Gajurel K, Dhakal R, Deresinski S. Diagnosis and treatment of histoplasmosis in solid organ transplant patients. Curr Opin Infect Dis. 2018; 31: 301-308.
37. Hage CA, Davis TE, Fuller D, Egan L, Witt JR, Wheat LJ, et al. Diagnosis of histoplasmosis by antigen detection in BAL fluid. Chest. 2010; 137: 623-628.
38. Hage C, Kleiman MB, Wheat LJ. Histoplasmosis in solid organ transplant recipients. Clin Infect Dis. 2010; 50: 122-123.
39. Vergidis P, Walker RC, Kaul DR, Kauffman CA, Freifeld AG, Slagle DC, et al. False-positive aspergillus galactomannan assay in solid organ transplant recipients with histoplasmosis. Transpl Infect Dis. 2012; 14: 213-217.
40. Theel ES, Ramanan P. Clinical significance of low-positive histoplasma urine antigen results. J Clin Microbiol. 2014; 52: 3444-3446.
41. Moncada PA, Budvytiene I, Ho DY, Deresinski SC, Montoya JG, Banaei N. Utility of DNA sequencing for direct identification of invasive fungi from fresh and formalin-fixed specimens. Am J Clin Pathol. 2013; 140: 203-208.
42. Singh N, Huprikar S, Burdette SD, Morris MI, Blair JE, Wheat LJ, et al. Donor-derived fungal infections in organ transplant recipients: Guidelines of the american society of transplantation, infectious diseases community of practice. Am J Transplant. 2012; 12: 2414-2428.
43. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the infectious diseases society of america. Clin Infect Dis. 2007; 45: 807-825.
44. Freifeld A, Proia L, Andes D, Baddour LM, Blair J, Spellberg B, et al. Voriconazole use for endemic fungal infections. Antimicrob Agents Chemother. 2009; 53: 1648-1651.
45. Restrepo A, Tobón A, Clark B, Graham DR, Corcoran G, Bradsher RW, et al. Salvage treatment of histoplasmosis with posaconazole. J Infect. 2007; 54: 319-327.
46. Thompson GR, Rendon A, Ribeiro Dos Santos RR, Queiroz-Telles F, Ostrosky-Zeichner L, Azie N, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. Clin Infect Dis. 2016; 63: 356-362.
47. McBride JA, Gauthier GM, Klein BS. Turning on virulence: Mechanisms that underpin the morphologic transition and pathogenicity of blastomyces. Virulence. 2018; 1-9.
48. Bradsher RW. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, updated edition. 8th ed. Philadelphia: Saunders; 2015; 2963-2973.
49. Castillo CG, Kauffman CA, Miceli MH. Blastomycosis. Infect Dis Clin North Am. 2016; 30: 247-264.
50. McDonald R, Dufort E, Jackson BR, Tobin EH, Newman A, Benedict K, et al. Notes from the field: Blastomycosis cases occurring outside of regions with known endemicity-new york, 2007-2017. MMWR Morb Mortal Wkly Rep. 2018; 67: 1077-1078.
51. Schwartz IS, Wiederhold NP, Hanson KE, Patterson TF, Sigler L. Blastomyces helicus, a new dimorphic fungus causing fatal pulmonary and systemic disease in humans and animals in western canada and the united states. Clin Infect Dis. 2019; 68: 188-195.
52. McBride JA, Gauthier GM, Klein BS. Clinical manifestations and treatment of blastomycosis. Clin Chest Med. 2017; 38: 435-449.
53. Kauffman CA, Miceli MH. Histoplasmosis and blastomycosis in solid organ transplant recipients. J Fungi (Basel). 2015; 1: 94-106.

54. Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the infectious diseases society of america. Clin Infect Dis. 2008; 46: 1801-1812.
55. Gauthier GM, Safdar N, Klein BS, Andes DR. Blastomycosis in solid organ transplant recipients. Transpl Infect Dis. 2007; 9: 310-317.
56. Baddley JW, Forrest GN, Practice AIDCo. Cryptococcosis in solid organ transplantation. Am J Transplant. 2013; 13: 242-249.
57. Espinel-Ingroff A, Kidd SE. Current trends in the prevalence of cryptococcus gattii in the united states and canada. Infect Drug Resist. 2015; 8: 89-97.
58. Perfect JR. Mandell, douglas, and bennett's principles and practice of infectious diseases, updated edition. 8th ed. Philadelphia: Saunders; 2015; 2933-2948.
59. Baddley JW, Schain DC, Gupte AA, Lodhi SA, Kayler LK, Frade JP, et al. Transmission of cryptococcus neoformans by organ transplantation. Clin Infect Dis. 2011; 52: e94-e98.
60. Sun HY, Alexander BD, Lortholary O, Dromer F, Forrest GN, Marshall Lyon G, et al. Unrecognized pretransplant and donor‐derived cryptococcal disease in organ transplant recipients. Clin Infect Dis. 2010; 51: 1062-1069.
61. Husain S, Wagener MM, Singh N. Cryptococcus neoformans infection in organ transplant recipients: Variables influencing clinical characteristics and outcome. Emerg Infect Dis. 2001; 7: 375-381.
62. Vilchez RA, Fung J, Kusne S. Cryptococcosis in organ transplant recipients: An overview. Am J Transplant. 2002; 2: 575-580.
63. Baddley JW, Perfect JR, Oster RA, Larsen RA, Pankey GA, Henderson H, et al. Pulmonary cryptococcosis in patients without HIV infection: Factors associated with disseminated disease. Eur J Clin Microbiol Infect Dis. 2008; 27: 937-943.
64. Forrest GN, Bhalla P, DeBess EE, Winthrop KL, Lockhart SR, Mohammadi J, et al. Cryptococcus gattii infection in solid organ transplant recipients: Description of oregon outbreak cases. Transpl Infect Dis. 2015; 17: 467.
65. Sun HY, Alexander BD, Lortholary O, Dromer F, Forrest GN, Marshall Lyon G, et al. Cutaneous cryptococcosis in solid organ transplant recipients. Med Mycol. 2010; 48: 785-791.
66. Singh N, Husain S, De Vera M, Gayowski T, Cacciarelli TV. Cryptococcus neoformans infection in patients with cirrhosis, including liver transplant candidates. Med Mycol. 2004; 83: 188-192.
67. Temfack E, Bigna JJ, Luma HN, Spijker R, Meintjes G, Jarvis JN, et al. Impact of routine cryptococcal antigen screening and targeted preemptive fluconazole therapy in antiretroviral-naive human immunodeficiency virus-infected adults with CD4 cell counts <100/μL: A systematic review and meta-analysis. Clin Infect Dis. 2019; 68: 688-698.
68. Singh N, Lortholary O, Dromer F, Alexander BD, Gupta KL, John GT, et al. Central nervous system cryptococcosis in solid organ transplant recipients: Clinical relevance of abnormal neuroimaging findings. Transplantation. 2008; 86: 647-651.
69. Harris JR, Lockhart SR, Debess E, Marsden-Haug N, Goldoft M, Wohrle R, et al. Cryptococcus gattii in the united states: Clinical aspects of infection with an emerging pathogen. Clin Infect Dis. 2011; 53: 1188-1195.

70. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010; 50: 291-322.
71. Thompson GR, Wiederhold NP, Fothergill AW, Vallor AC, Wickes BL, Patterson TF. Antifungal susceptibilities among different serotypes of cryptococcus gattii and cryptococcus neoformans. Antimicrob Agents Chemother. 2009; 53: 309-311.
72. Sun HY, Alexander BD, Huprikar S, Forrest GN, Bruno D, Marshall Lyon G, et al. Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: Implications for the management of immunosuppression. Clin Infect Dis. 2015; 60: 36-44.
73. Restrepo A, Tobon AM, Cano LE. Mandell, douglas, and bennett's principles and practice of iInfectious diseases, updated edition. 8th ed. Philadelphia: Saunders; 2015; 2995-3002.
74. Colombo AL, Tobón A, Restrepo A, Queiroz-Telles F, Nucci M. Epidemiology of endemic systemic fungal infections in latin america. Med Mycol. 2011; 49: 785-798.
75. De Almeida JN, Peçanha PM, Colombo AL. Paracoccidioidomycosis in immunocompromised patients: A literature review. J Fung. 2018; 5: 2.
76. Shikanai-Yasuda MA, Mendes RP, Colombo AL, de Queiroz-Telles F, Gonçalves Kono AS, M Paniago AM, et al. Brazilian guidelines for the clinical management of paracoccidioidomycosis. Rev Soc Bras Med Trop. 2017; 50: 715-740.
77. Len O, Garzoni C, Lumbreras C, Molina I, Meije Y, Pahissa A, et al. Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor-derived infections. Clin Microbiol Infect. 2014; 20: 10-18.
78. Salzer HJF, Burchard G, Cornely OA, Lange C, Rolling T, Schmiedel S, et al. Diagnosis and management of systemic endemic mycoses causing pulmonary disease. Respiration. 2018; 96: 283-301.
79. Borges SRC, da Silva GMS, Chambela MC, de Oliveira RVC, Braga Costa RL, Wanke B, et al. Itraconazole vs. trimethoprim-sulfamethoxazole: A comparative cohort study of 200 patients with paracoccidioidomycosis. Med Mycol. 2014; 52: 303-310.