

Endemic Mycoses in Solid Organ Transplant Recipients



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KEYWORDS

- Solid organ transplant • Endemic mycoses • Histoplasmosis • Blastomycosis
- Coccidioidomycosis

KEY POINTS

- Endemic mycoses are thermally dimorphic fungal pathogens occupying a specific geographic range.
- Histoplasmosis, coccidioidomycosis, and blastomycosis are the chief endemic mycoses in North America.
- Infections with endemic mycoses are uncommon, but can cause serious infection in solid organ transplant recipients.

INTRODUCTION

The endemic mycoses are a group of thermally dimorphic fungal pathogens occupying a specific geographic range. This geographic restriction occurs as a result of the unique environmental requirements that best promote sporulation for each species. In North America, the chief endemic mycoses are histoplasmosis, coccidioidomycosis, and blastomycosis.

GENERAL PRINCIPLES

Although they can cause serious infections, all 3 endemic mycoses are surprisingly rare in solid organ transplant (SOT) recipients ([Table 1](#)).^{1,2} A prospective study

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Table 1
Endemic mycoses in SOT recipients

| | Histoplasmosis | Blastomycosis | Coccidioidomycosis |
|--|---|---|---|
| Principle North American areas of endemicity | Ohio and Mississippi River Valley areas | Ohio, Mississippi and Tennessee River Valley areas, Great Lakes region | Southwest USA and Northern Mexico |
| Cases acquired through infected allograft | Yes | No | Yes |
| Typical clinical presentation | Disseminated disease typically involving lungs, bone marrow, liver and spleen | Severe pulmonary disease \pm dissemination often involving skin | Disseminated disease typically involving lungs, skin, bone, joints, meninges |
| Severity of illness compared to immunocompetent patients | Increased | Increased | Increased |
| Typical histologic appearance | Small yeast, 2-5 μ m in size, with narrow-based budding, often clustered within macrophages | Large yeast, 8-15 μ m in size, with broad-based budding and a thick, refractile cell wall | Large (10-100 μ m) unique structures called spherules, containing numerous endospores. |
| Role of antibody detection | Limited role, test insensitive | Insensitive, limited clinical usefulness | Moderately sensitive, but if positive generally indicates current or recent infection. EIA more sensitive but less specific than immunodiffusion tests. |
| Role of urine antigen detection | Highly sensitive test ($\geq 93\%$) | Moderately sensitive test (76%-93%) | Relatively insensitive test ($\leq 71\%$) |
| Mortality | ~ 10% | ~ 25-38% | ~ 43-62% |

Abbreviations: EIA, enzyme-linked immunoassay; SOT, solid organ transplantation.

performed in 15 transplant centers throughout the United States, including in high incidence areas, found only 33 cases of endemic mycoses among 16,806 patients who received a SOT during the 5-year study period; 23 were histoplasmosis, 6 were coccidioidomycosis, and 4 were blastomycosis.¹ By way of contrast, the incidence of invasive candidiasis in SOT recipients is approximately an order of magnitude higher.³ The incidence of the endemic mycoses is typically greatest in the 12 months after transplant, but the risk period extends for years thereafter.^{1,4-7}

Histoplasmosis, coccidioidomycosis, and blastomycosis are all caused by environmental, soil-based fungi that are acquired chiefly, although not exclusively, through inhalation of conidia that have been aerosolized as a result of disturbance of the soil in which they are produced.⁸ The causative fungi are all thermally dimorphic, existing initially as a mold in the environment and then once in the body transforming themselves into either yeasts or, in the case of coccidioidomycosis, specialized structures called spherules.^{8,9} The fungi typically establish themselves initially in the lung, although whether this is clinically apparent or not depends on a balance between the burden of disease and the state of the host immune system. Clinical disease can also occur when immunosuppression causes a loss of containment of a previously controlled infection, such as occurs from antirejection medication.^{10,11} Dissemination of the fungus can occur throughout the body if the immune system is unable to control the infection within the lungs. In the case of histoplasmosis and coccidioidomycosis, rare cases of disease acquired by an infected allograft have also been described; there are no reports of this with blastomycosis to date.^{1,12-15} There is typically a median of 2 weeks from symptoms onset until the diagnosis is ultimately made.^{5,7} In general, SOT recipients have been found to have more severe disease and a higher disease-related mortality from the endemic mycoses than immunocompetent patients.²⁻⁶

Currently, no single diagnostic test has optimal sensitivity and specificity to reliably diagnose any of the endemic mycoses. Thus, in situations where histoplasmosis, blastomycosis, or coccidioidomycosis are considered, multiple different tests should be used. In general, microscopy, culture, antigen detection, and antibody assays are well-established for all the endemic mycoses, although with important differences in their limitations that vary by species. Polymerase chain reaction testing is less well-established and often not commercially available, but offers the potential to complement the existing diagnostic armamentarium.

The agents used for treatment of the endemic mycoses are the polyenes (with liposomal amphotericin B now preferred) and the azoles (chiefly itraconazole or fluconazole). In general, mild infections can be treated with an azole alone, but more severe and/or disseminated disease (as occurs frequently in SOT recipients) requires initial therapy with amphotericin B and transition to an azole once clinical improvement occurs.¹⁶⁻¹⁸ Most SOT recipients with histoplasmosis, blastomycosis, and coccidioidomycosis generally require at least 12 months of treatment along with a temporary decrease in immunosuppressive regimens if possible. A risk of recrudescence or relapse exists for all of the endemic mycoses. However, the role and benefit of secondary prophylaxis is unclear and much debated.

HISTOPLASMOSIS

Epidemiology

Mycelial growth in histoplasmosis is favored in soil in climates with moderate temperatures (between 15°C and 40°C), high relative humidity and a soil pH of greater than 5.5, although spores can survive for many years in less favorable environmental

conditions.¹⁹ Bird and bat guano provides a high nitrogen, phosphorus, and organic matter content that is especially advantageous for histoplasmosis' sporulation, allowing for mycelial growth even in the absence of soil.²⁰ Typical risk factors for histoplasmosis acquisition in endemic areas include spelunking, farming, cleaning up bird droppings, refurbishing buildings that have been inhabited by birds or bats, such as barns, or other activities that disturb the soil.^{19,21}

In the United States, studies from the 1950s to the 1970s identified areas of endemicity on the basis of positive histoplasmin skin test reactivity. Within North America, these areas are centered around the Mississippi and Ohio River valleys (**Fig. 1**). Outside the United States, areas in Central and South America, and large parts of Africa and Australasia, are also considered endemic.^{21,22} However, it is likely that histoplasmosis can at least occasionally be acquired from a much wider range of environments than previously thought, especially in immunocompromised hosts.^{23,24}

Pathogenesis

Infection with *Histoplasma capsulatum* is typically acquired when aerosolized microconidia are inhaled, because these infectious particles are small enough to reach the alveoli.^{10,21} Once in the lung, the microconidia transform into yeasts and are phagocytosed by macrophages, within which they initially proliferate and may be transported throughout the reticuloendothelial system. Approximately 1 to 2 weeks are required before sufficient Th1 cell-mediated immune response is generated to either kill or control the fungi in a quiescent state, driven by cytokines including interleukin-12, tumor necrosis factor- α , and interferon- γ .²⁵ This process may be impaired in SOT recipients. In addition, previous immunologic control of the fungus can be lost in patients who later receive immunosuppressant medication.¹⁰

Histoplasmosis in SOT recipients can thus be acquired in 1 of 2 main ways: as a new (primary) infection or via reactivation of a previously controlled infection. A surprisingly low baseline incidence in endemic areas (usually <0.5%) combined with dramatic

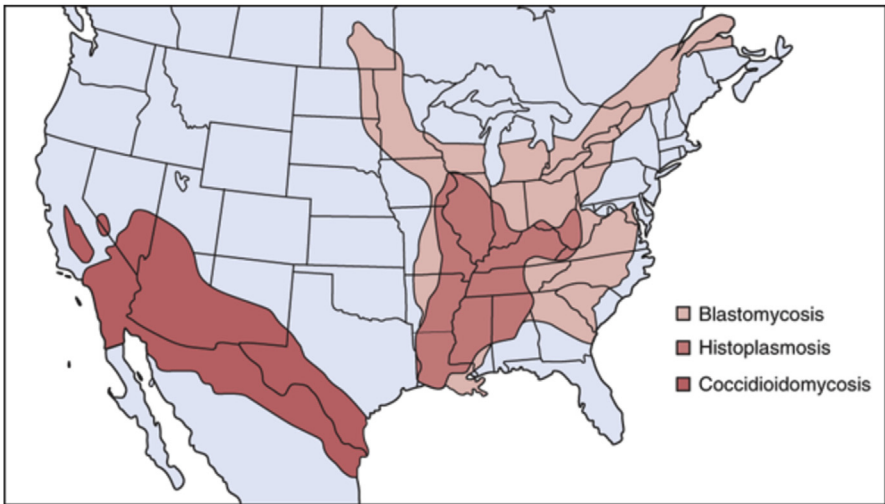


Fig. 1. Geographic distribution of endemic fungal infections in the North America. (From Ryan KJ. The systemic fungal pathogens: cryptococcus, histoplasma, blastomyces, coccidioides, paracoccidioides. In: Ryan KJ, editor. Sherris medical microbiology. 7th edition. New York: McGraw-Hill; 2018. p. 750; with permission.)

increases seen during community outbreaks argue that primary infection may be the dominant mode of acquisition.^{5,26–28} Rarely, histoplasmosis can also rarely be transmitted via an infected allograft, although only a handful of confirmed cases of this have been published to date.^{12,13}

Clinical Presentation

In hosts with intact immunity, histoplasmosis is usually confined to the lungs, with a diverse array of presentations, including acute and chronic pneumonias, isolated pulmonary nodules, fibrosing mediastinitis, and broncholithiasis. In SOT recipients, however, presentation is mostly that of progressive disseminated disease.^{5,6,28} As may be expected from the pathogenesis of histoplasmosis, pulmonary involvement is extremely common (>80%, although this may be subclinical and detectable only on chest computed tomography scans), and thereafter the sites most likely to be involved are lymphoid-rich tissues: bone marrow, liver, spleen, and gastrointestinal tract.^{5,28} Typical symptoms include fever, fatigue, nonproductive cough, and diarrhea, and typical signs include hepatomegaly, splenomegaly, lymphadenopathy, and sometimes oral ulcers. Central nervous system (CNS) disease (<10%) and skin (<5%) involvement seem to be relatively uncommon. Almost any site can ultimately be involved however; rare cases of histoplasmosis in SOT recipients are reported involving the adipose tissue and tonsils.^{5,29} Patients can also present with an undifferentiated sepsis picture.

Diagnosis

No single test is sufficiently sensitive to reliably diagnose histoplasmosis in SOT recipients, so a strategy using multiple diagnostic modalities simultaneously is recommended (Table 2). The single most sensitive test is a urine *Histoplasma* antigen test, which is positive in approximately 93% of cases when the newer generation assays are used. The test’s sensitivity correlates positively with disease severity.^{6,30} However, the assay’s specificity is limited by cross-reactions to antigens from *Blastomyces*, *Paracoccidioides*, and *Penicillium* species.^{30–32} Blood, bone marrow, and bronchoalveolar lavage cultures are all moderately sensitive in disseminated disease, but typically take several weeks to become positive.³³ A bronchoscopic lung biopsy or cytology is positive in approximately three-quarters of cases.⁶ *Histoplasma capsulatum*’s distinctive histologic appearance is that of a yeast, 2 to 5 μm in size, with narrow-based budding, often clustered within macrophages.³⁴ The least sensitive test seems to be serum antibodies, with an overall sensitivity in SOT recipients of just 36% in 1 large series.⁶ Of note, false-positive *Aspergillus galactomannan* results have been

| Table 2 Approximate sensitivities of histoplasmosis diagnostic tests in solid-organ transplant recipients | |
|--|-----------------------------|
| Test | Approximate Sensitivity (%) |
| Urine antigen | ≥93 |
| Serum antigen | 80 |
| Antibody | 35 |
| Blood culture | 50–70 |
| Bronchoalveolar lavage culture | 60–72 |
| Lung biopsy or cytology | 77 |

Data from Refs. 2,5,6,28,86

reported in SOT recipients who had histoplasmosis.³⁵ This finding should be borne in mind in SOT patients from histoplasmosis-endemic areas.

Treatment

Even without clear evidence of dissemination, SOT recipients with histoplasmosis should generally be treated as if they have disseminated disease.²¹ Liposomal amphotericin B is preferred over both itraconazole and amphotericin B deoxycholate for initial treatment in moderate and severe cases of disseminated disease.^{16,36,37} Liposomal amphotericin B has a lower rate of associated toxicities than the deoxycholate form, and is also possibly more potent in disseminated histoplasmosis.³⁶ Liposomal amphotericin B should even be considered in cases complicated by renal disease despite the potential for additional nephrotoxicity; in many cases, as the disease comes under control, renal function improves rather than worsens.²¹ Liposomal amphotericin B is generally given for 1 to 2 weeks, followed by oral itraconazole for at least a year (Table 3). All azoles have some activity in histoplasmosis, although posaconazole is possibly the best alternative to itraconazole in cases of drug intolerance or clinical failure.²¹ Rising minimum inhibitory concentrations to both fluconazole and voriconazole have been observed while on therapy (whereas this has not been demonstrated with posaconazole), and there is limited clinical experience with isavuconazole.³⁸ There is no role for echinocandin therapy in histoplasmosis.³¹

Once the diagnosis of histoplasmosis is made, immunosuppressive medication should be reduced, although the optimal timing and strategy in this regard is unknown. Azole treatment can probably be stopped after 12 months if there is no evidence of active infection. Ideally, the urine and blood antigen tests should be negative by that point, although they may remain positive at a low level for years after clinical

| Table 3 Typical therapeutic regimens for endemic fungi in SOT recipients | | | |
|---|---|--|--|
| | Mild Disease | Severe Disease | CNS Disease |
| Histoplasmosis | Itraconazole 200 mg every 8 hours for 3 d and then twice daily for 12 mo | Liposomal amphotericin B (3 mg/kg) for 1–2 wk then itraconazole 200 mg twice daily for 12 mo | Liposomal amphotericin B (5 mg/kg) for 4–6 wk then itraconazole 200 mg twice daily for 12 mo |
| Blastomycosis | Itraconazole 200 mg every 8 hours for 3 d and then twice daily for 12 mo (but consider treating as for severe disease in all immunosuppressed patients) | Liposomal amphotericin B (3 mg/kg) for 1–2 wk then itraconazole 200 mg twice daily for 12 mo | Liposomal amphotericin B (5 mg/kg) for 4–6 wk then a triazole for 12 mo (optimal triazole unclear) |
| Coccidioidomycosis | Fluconazole 400 mg/d for at least 12 mo | Liposomal amphotericin B (5 mg/kg) for 1–2 wk then fluconazole 400 mg/d for at least 12 mo | Fluconazole 400–1200 mg/d, continued indefinitely |

Abbreviations: CNS, central nervous system; SOT, solid organ transplantation.

resolution of disease. Therapy should not be prolonged merely because of this low-level antigenemia. After completion of treatment, long-term suppressive azole therapy in SOT recipients may be considered, but there is little evidence to endorse this practice, and the risk of disease relapse after completion of therapy is less than 5% when adequate initial therapy is given.⁶ In addition, in high-risk patients (eg, patients in whom no significant reduction of immunosuppression was possible), relapses can be screened for by serial urine antigen testing.¹⁶ Thus, chronic suppressive therapy may be unnecessary for the majority of SOT recipients.

Prognosis

The mortality from histoplasmosis acquired after SOT is approximately 10%.^{1,6,28} In the largest study, 72% of the deaths occurred within 1 month after diagnosis, and on multivariate analysis those who died from histoplasmosis were statistically more likely to be older and to have had severe disease, as might be expected.⁶

BLASTOMYCOSIS

Epidemiology

A recent phylogenetic analysis has revealed that *Blastomyces dermatitidis*, the sole cause of blastomycosis, is in fact 2 distinct species, *B dermatitidis* and *Blastomyces gilchristii*.³⁹ The natural habitat of *Blastomyces* is largely unknown, partly because, unlike other dimorphic fungi, it is extremely difficult to culture the organism from soil samples. Interesting new phylogeographic work has found a strong association of blastomycosis with freshwater basins, which complements earlier findings that suggested that *Blastomyces* conidiophores required exposure to water before their conidia could be dispersed by air currents.^{40,41} In North America, endemic regions seem to be the US and Canadian areas bordering the Mississippi, Ohio, Tennessee, and Nelson River drainage basins, and a small area in the northeast surrounding the St Lawrence River (see Fig. 1). A detailed history usually reveals occupational or recreational activities that have disrupted the soil in these regions, such as construction, boating, fishing, cutting trees, or clearing brush. As with all endemic mycoses, however, cases can occasionally be seen outside these endemic regions (see Table 1).⁴²

Pathogenesis

In a similar manner to other endemic fungi, *Blastomyces* conidia must generally be inhaled to acquire the infection. Once inside the lung, the conidia transform into the yeast phase, and can survive within macrophages. Both innate and cell-mediated immunity play vital roles in controlling blastomycosis, whereas the humoral immune system plays no clear role.⁴³ Unlike histoplasmosis and coccidiomycosis, no cases of blastomycosis acquired via infected allograft have been reported.¹

Clinical Presentation

In immunocompetent individuals, approximately one-half of blastomycosis infections are asymptomatic and, of the symptomatic cases, pulmonary infection occurs in approximately 80% and disseminated disease occurs in 25% to 40%—a far higher rate than seen with other endemic mycoses.^{17,44} Interestingly, from the limited number of cases published to date, the chief difference in presentation among SOT recipients is not necessarily a greater propensity for disseminated disease, but rather more severe pulmonary disease, with a higher consequent mortality.^{2,3,7} Lung involvement in SOT recipients more frequently progresses to acute respiratory distress syndrome and respiratory failure. In disseminated cases, the same typical sites are involved as with immunocompetent individuals. The skin is the most frequently involved

extrapulmonary site, although multiple pustules or ulcers are more common than the classic verrucous lesions seen in immunocompetent patients.^{45,46} Bone (lytic lesions), genitourinary (prostatitis or epididymitis), and CNS (meningitis or abscess) involvement are the next most common manifestations.

Diagnosis

Blastomycosis has a distinctive appearance on histologic specimens, namely that of a large yeast, 8 to 15 μm in size, with broad-based budding and a thick refractile cell wall.³⁴ This characteristic appearance permits a rapid diagnosis to be provisionally made directly from sputum, bronchoalveolar lavage specimens, and tissue biopsies. This property is especially useful considering the frequent involvement of the skin, which provides an easily accessible biopsy site. A definitive diagnosis requires culturing the organism, but like the other endemic fungi this usually takes 1 to 4 weeks. Blastomycosis antigen enzyme-linked immunoassay tests can be performed on urine, blood, and cerebrospinal fluid samples, with urine having the greatest sensitivity (76%–93%).^{47,48} Like the urine histoplasmosis antigen test, this also suffers from a lack of specificity, principally owing to cross-reaction with other endemic fungi.^{43,47} Unlike histoplasmosis and coccidiomycosis, commercially available serologic testing in blastomycosis has poor sensitivity and therefore little clinical usefulness.⁴⁹

Treatment

In immunocompetent patients, milder non-CNS forms of blastomycosis may be treated entirely with an azole, typically itraconazole. However, because of the greater propensity for severe disease, it is recommended that blastomycosis cases in SOT recipients generally be treated with amphotericin B for 1 to 2 weeks initially, or until improvement is noted.^{17,43} Thereafter, as with histoplasmosis, approximately 12 months of oral itraconazole should be given. Itraconazole is probably more efficacious than fluconazole, and considerably more clinical experience exists with itraconazole than with any other of the azoles in the treatment of blastomycosis (see [Table 3](#)).⁵⁰

Prognosis

The limited numbers of cases of blastomycosis in SOT recipients reported in the literature makes assessing outcomes with any precision difficult, but mortality in SOT recipients with blastomycosis seems to be in the 35% to 38% range (although the rate directly attributable to blastomycosis itself is likely closer to 25%).^{2,7} This mortality rate is higher than that seen in immunocompetent patients, though lower than seen in patients with malignancies or AIDS.⁷

COCCIDIOMYCOSIS

Epidemiology

Coccidiomycosis is caused by 1 of 2 species: *Coccidioides immitis* or *Coccidioides posadasii*.⁵¹ Unlike *Histoplasma* and *Blastomyces*, *Coccidioides* is found exclusively within in hot, dry climates, in arid and semiarid soil.⁵² Specifically, *Coccidioides* is found in the southwestern United States, in the San Joaquin Valley, southern California, Texas, Arizona, and New Mexico, together with northern Mexico and noncontiguous areas in South America (see [Fig. 1](#)).^{53,54} *C immitis* is found predominantly within California and *C posadasii* is found in the remainder of the endemic areas in the Western hemisphere. Drought conditions are associated with a higher incidence of reported coccidiomycosis the following year, possibly because *Coccidioides* is relatively more tolerant of such conditions than competing organisms, and because dry

conditions favor spore distribution.⁵⁴ In endemic areas, sandstorms, military exercises, and outdoor construction work are recognized risk factors for disease acquisition.⁵⁵

Pathogenesis

Maturing mycelial cells develop within the soil into arthroconidia, which are prone to be aerosolized by air currents or other disruptions of the soil. When inhaled, the arthroconidia form unique structures called spherules. Each of these develops to contain viable spores that can form further spherules when the original spherule ruptures, thereby quickly generating an exponential increase in fungal burden if unchecked. T-cell immunity is the principal form of control required for coccidioidomycosis, which may otherwise spread to extrapulmonary locations. Disseminated coccidioidomycosis is associated with a failure to generate an interferon- γ -led delayed-type hypersensitivity response to coccidioidal antigens.⁵⁶ In a similar manner to histoplasmosis and blastomycosis, coccidioidomycosis can either be acquired de novo or be reactivate from a dormant state if the patient loses prior immunologic control of the organism owing to immunosuppression.¹¹ Rarely, coccidioidomycosis can be transmitted via infected allograft.^{14,15}

Clinical Manifestations

In immunocompetent hosts, approximately 60% of disease is asymptomatic and the vast majority of the remainder manifests as isolated pulmonary disease, with only less than 0.5% of patients having disseminated infection.⁵⁵ In immunocompromised hosts, such as SOT recipients, the rates of disease dissemination increase markedly, causing an increase in mortality and morbidity. Pulmonary disease mimics community-acquired pneumonia and can range from minimally symptomatic to fulminant disease. Apart from the lung, common sites for dissemination are the CNS, liver, spleen, kidney, skin, and joints.^{4,57}

Diagnosis

The spherule is pathognomonic for coccidioidomycosis, and thus identification of it from any sample establishes the diagnosis. *Coccidioides* cultures readily on most media in approximately 1 week.⁴ Laboratory personnel should be warned that coccidioidomycosis is suspected, because biocontainment procedures are required for safety when working with cultures. In tissue samples, spherules may be surrounded by either a granulomatous or a suppurative inflammatory response.⁴ The sensitivity of serologic tests is lessened in SOT recipients, who may not mount as robust an antibody response.^{4,58} Furthermore, a detectable serologic response may take 3 or more weeks to develop, causing false-negative results in early infection. However, because antibody levels generally decrease to undetectable levels with successful clearance of infection, a positive result typically represents either recent or active infection.⁵⁹ Overall, enzyme-linked immunoassays are more sensitive but less specific than immunodiffusion tests; thus, the immunodiffusion tests are often used as confirmation tests for positive enzyme-linked immunoassay results. Urine or serum antigen testing is insensitive but most likely to be positive in disseminated disease. Cross-reaction with *Histoplasma* antigen test occurs.^{60,61}

Treatment

As with the treatment of other endemic fungi in SOT recipients, mild pulmonary forms of the disease can be treated with azoles alone, but severe or disseminated cases generally require intravenous amphotericin B therapy initially, followed by azole

therapy for approximately 12 months (see [Table 3](#)). Fluconazole and itraconazole are the most commonly used azoles, with fluconazole generally being preferred on the basis of more reliable absorption and less severe drug–drug interactions. A randomized, controlled trial comparing the 2 azoles failed to find a statistically significant difference in clinical response or relapse rate between them, although there was a trend toward itraconazole superiority.⁶²

Fluconazole is the recommended first-line treatment for CNS infections, in contrast with histoplasmosis and blastomycosis, where the initial treatment for infections involving the CNS should be with amphotericin B. Immunosuppression should be lessened when possible, at least until the infection has begun to improve.⁵⁹ The risk of recrudescence in SOT recipients with evidence of prior coccidioidomycosis may be substantial, and is far higher than seen with the other endemic mycoses.^{4,57,59} Thus, patients with a history of coccidioidomycosis should receive preemptive therapy after transplantation. Many experts also tend to preemptively treat all SOT recipients in endemic areas, regardless of the evidence for prior coccidioidomycosis.⁵⁹ In either case, the usual duration of therapy is 6 to 12 months. Furthermore, after successful treatment of SOT recipients, indefinite secondary prophylaxis with fluconazole is often necessary for as long as the patient takes immunosuppressive medications, because the rate of relapse is otherwise unacceptably high.

Prognosis

Although heterogeneous, the mortality rate in SOT recipients who develop coccidioidomycosis is substantial, and higher than seen with the other endemic mycoses. Early reports from the 1980s showed mortality rates of up to 62%, and a large-scale study 2 decades later highlighted a 43% mortality attributable to coccidioidomycosis.^{1,4} Mortality rates are higher with disseminated disease than localized pulmonary disease.

TREATMENT ISSUES IN SOLID ORGAN TRANSPLANT RECIPIENTS

The primary agents available to treat the endemic mycoses are amphotericin B and the triazole antifungals. The echinocandins have poor *in vitro* activity against the dimorphic fungi and should not be considered as treatment options for them.^{16,17,59,63} Amphotericin B is only available intravenously, in either a deoxycholate or a liposomal form. When the drug is required, the liposomal formulation is preferred owing to its lower toxicity, particularly nephrotoxicity. In a randomized controlled trial of disseminated histoplasmosis in patients with AIDS, there was also a trend toward a higher clinical success rate and a lower mortality rate with the liposomal amphotericin B.³⁶ Common side effects include nephrotoxicity, hypokalemia, and hypomagnesemia, as well as infusion-related chills. Severe disease from the endemic mycoses is often accompanied by a degree of renal impairment, but renal dysfunction should not necessarily dissuade clinicians from using amphotericin B, because it is preferred over the azoles in most cases of severe disease.^{16–18,21} Although the CNS penetration of amphotericin B is poor (<3%), amphotericin B has demonstrable efficacy and is recommended first-line therapy for meningitis in both histoplasmosis and blastomycosis, although not coccidioidomycosis.^{16–18}

Of the triazoles, the bulk of clinical experience lies with the first-generation agents, itraconazole and fluconazole. Voriconazole, posaconazole, and isavuconazole are less well-studied despite their demonstrable *in vitro* activity, and their clinical evidence base primarily consists of small case series, often as salvage therapy, and with varying degrees of success.^{28,64–67} Fluconazole has oral bioavailability of more than 90%, and absorption is not significantly affected by food or gastric acidity.⁶⁸ The reliability of its

absorption precludes the need to check plasma levels routinely. Fluconazole has the best CNS penetration of any of the available antifungal drugs (approximately 75%) and is used as an agent of first choice for coccidioidomycosis meningitis.^{18,69}

Itraconazole is available both as a capsule or a solution. The solution formulation is preferred because of greater bioavailability, although gastrointestinal tolerability can be more problematic. Importantly, instructions to maximize bioavailability are opposite depending on the formulation. Food and an acidic gastric pH improve absorption of the capsule form of the drug (and so proton pump inhibitors, H₂-antagonists, and antacids are contraindicated, whereas acidic cola beverages can improve absorption).^{70,71} By contrast, the oral solution is best absorbed on an empty stomach, and gastric pH has no effect.⁷² The erratic absorption of either form of the drug makes checking blood levels mandatory.⁷³ A further important limitation of itraconazole is its poor CNS penetration, although successful treatment of meningitis is nonetheless achievable.⁶⁹ Despite these disadvantages, itraconazole seems to be more efficacious than fluconazole in histoplasmosis and possibly in blastomycosis as well, accounting for its preference as the azole of choice for these conditions.^{50,74}

Drug–drug interactions between commonly used immunosuppressive medications in SOT recipients and the antifungal medications discussed are essentially limited to the triazole class. These agents all target the fungal cytochrome P450-dependent enzyme lanosterol 14- α -demethylase, thereby inhibiting fungal ergosterol production.⁷⁵ However, all the azoles have varying degrees of affinity for various human cytochrome P450 enzyme system isoforms as well, and this property accounts for the bulk of the drug–drug interactions witnessed.⁷⁶ In general, fluconazole has the least potent inhibition of cytochrome P450, and thus the fewest drug–drug interactions. The other mechanism of drug–drug interactions is via P-glycoprotein, an efflux pump for xenobiotics, which the triazoles similarly can inhibit and/or be a substrate of.^{76,77}

It takes approximately 1 week after starting a triazole antifungal for the full effect of the enzyme inhibition to be felt. Conversely, when the triazole therapy is discontinued, the enzyme inhibition can last for up to a month thereafter.⁷⁶ Close attention to azoles and immunosuppressive drug levels and dosage adjustments should be taken, particularly around these times. The effects of the antifungal drugs on commonly used immunosuppressive medications are summarized in [Table 4](#). In general, drug levels of the calcineurin inhibitors (eg, tacrolimus) and mammalian target of rapamycin inhibitors (eg, sirolimus) almost always require dose reduction when triazoles are used. Of the listed antifungals, only isavuconazole has been documented to alter mycophenolate levels. The data for increased prednisone exposure with azoles that are strong CYP3A4 inhibitors (itraconazole, voriconazole, posaconazole, and ketoconazole) are contradictory, and so monitoring for steroid side effects is recommended.^{78–81} There is no evidence of significant drug–drug interactions with prednisone and any of the other antifungals.

Reductions in immunosuppressive drug exposure can cause an immune reconstitution syndrome (IRS) with any of the endemic fungi. This syndrome is manifest by an immunologically mediated worsening of the symptoms and signs of the infection, and may be hard to distinguish from treatment failure.⁸² Clues to IRS include clinical deterioration despite adequate antifungal therapy, a failure to culture viable organisms from involved body sites, and stable or decreasing antigen levels for the endemic mycoses despite the clinical worsening.⁸³ Management is on a case-by-case basis, and depends on delicately navigating the trade-off between the need to control the infection and to maintain an adequate level of immunosuppression to prevent organ rejection. Mild cases of IRS usually settle without intensifying immunosuppression, but IRS

Table 4
Therapeutic agents for the treatment of endemic mycoses

| Drug | Common Side Effects | CSF Penetration | Tacrolimus Dose Requirement | Cyclosporine Dose Requirement | Mycophenolate Dose Requirement | Sirolimus Dose Requirement | Prednisone Dose Requirement |
|--------------------------|---|--|---|---------------------------------------|--------------------------------------|---------------------------------------|-----------------------------------|
| Liposomal amphotericin B | Nephrotoxicity, hypokalemia, hypomagnesemia, infusion-related chills. | Poor (<3%) but often clinically effective nonetheless ⁶⁹ | No significant change | No significant change | No significant change | No significant change | No significant change |
| Fluconazole | Generally well-tolerated. Can cause transaminitis occasionally. | Good (50%–94%) ⁶⁹ | Decreased by 40%–60% ^{87,88} | Decreased by 21%–50% ^{76,89} | No significant change | No significant change | No significant change |
| Itraconazole | Nausea, vomiting. Can cause transaminitis occasionally. | Poor (<10%), but clinical efficacy may be achieved nonetheless ⁶⁹ | Decreased by 40%–60% in general, but highly variable ^{76,90} | Decreased by 50%–66% ^{76,91} | No significant change | Decreased by 50%–90% ^{92,93} | Unclear; monitor for side effects |
| Voriconazole | Visual disturbances, occasional transaminitis | Moderate (38%–68%) ⁶⁹ | Decreased by 66% ^{94,95} | Decreased by 50% ⁹⁶ | No significant change | Decreased by 66%–90% ⁹³ | Unclear; monitor for side effects |
| Posaconazole | Generally well-tolerated. Can cause transaminitis occasionally. | Poor, but clinical efficacy may be achieved nonetheless ⁹⁷ | Decreased by 66% ^{98,99} | Decreased by 25%–29% ⁹⁸ | No significant change | Decreased by 90% ¹⁰⁰ | Unclear; monitor for side effects |
| Isavuconazole | Headache, nausea, vomiting, shortened QTc, transaminitis | Unclear | Decreased by 23% ¹⁰¹ | Decreased, mildly ¹⁰² | Decreased, moderately ¹⁰² | Decreased, moderately ¹⁰² | No significant change |

Abbreviation: CSF, cerebrospinal fluid.

reactions can be life threatening, especially if they occur in sites such as the CNS, and these more severe instances usually mandate temporarily increasing the level of immunosuppression again.

PROPHYLAXIS REGIMENS IN SOLID ORGAN TRANSPLANT RECIPIENTS: AN UNRESOLVED ISSUE

A donor known with active disease with any of the endemic fungi is not considered a suitable candidate until (in the case of living donors) several months of therapy have controlled the infection.⁸⁴ Nonetheless, active donor infection is sometimes only discovered after transplantation has occurred, in which case primary prophylaxis of the recipient is indicated (Table 5). The other definite indication for peritransplant prophylaxis is in SOT recipients with evidence of prior coccidioidomycosis. This evidence may include positive serologic tests or thin-walled cavities seen on chest radiographs or computed tomography scans. Equivocal cases required specialist assessment, although many experts give prophylaxis to all SOT recipients if they reside in a coccidioidomycosis-endemic area, regardless of prior coccidioidomycosis or not.⁵⁹ There is only limited evidence for this practice, however. Primary prophylaxis in patients living in areas endemic for histoplasmosis or blastomycosis, and secondary

Table 5

Suggested prophylactic regimens for endemic fungi in SOT recipients

| | Recipient Peritransplant Prophylaxis | Secondary Prophylaxis for Recipients After Completion of Treatment Course |
|--------------------|--|--|
| Histoplasmosis | Donor with localized pulmonary disease: itraconazole 200 mg once or twice daily for 3–6 mo Donor with disseminated disease: itraconazole 200 mg once or twice daily for 12 mo ⁸⁴ | Not routinely indicated. Can monitor urine antigen level every 3 mo to determine need. If required, consider itraconazole 200 mg/d. ^{16,84} |
| Blastomycosis | Donor with localized pulmonary disease: itraconazole 200 mg once or twice daily for 3–6 mo Donor with disseminated disease: itraconazole 200 mg once or twice daily for 12 mo | Not routinely indicated. If required, consider itraconazole 200 mg/d. ¹⁷ |
| Coccidioidomycosis | Donor with isolated pulmonary disease: fluconazole 400 mg/d for 3–12 mo (non-lung recipients) or lifelong (lung recipients). Donor with positive serology or extrapulmonary disease: fluconazole 400 mg/d lifelong. ⁸⁴ Recipient with positive serology or history of coccidioidomycosis: fluconazole 200 mg/d for 6–12 mo. Recipient living in a Coccidioides-endemic area: fluconazole 200 mg/d for 6–12 mo. ⁵⁹ | Fluconazole 400 mg/d indefinitely. ⁵⁹ |

Abbreviation: SOT, solid organ transplantation.

prophylaxis in patients with a history of prior histoplasmosis or blastomycosis is probably unnecessary. This probably includes patients living in endemic areas who have computed tomography evidence of calcified granulomas in lungs, liver, spleen, lymph nodes, or other organs, because the risk of reinfection in this case seems low to nonexistent.^{16,26,85}

There is a similar lack of definitive evidence to guide secondary prophylaxis in SOT recipients after completion of a treatment course. The relapse rate after treatment completion in coccidioidomycosis is particularly high in SOT recipients, and so consensus opinion is that all such patients should receive life-long secondary prophylaxis.⁵⁹ The role of secondary prophylaxis for histoplasmosis and blastomycosis is less clear, and should probably be limited to cases at high risk of relapse only (see [Table 5](#)).^{16,84} These high-risk scenarios would include patients in whom immunosuppression was not able to be lessened.

SUMMARY

Histoplasmosis, blastomycosis, and coccidioidomycosis are all relatively rare in SOT recipients, even those from endemic areas. However, they are more difficult to diagnose than many other infections that plague this population and can cause significant morbidity and mortality if they are not identified early. Therapy for the endemic mycoses is typically given for at least a year and is frequently complicated by drug–drug interactions between the triazoles and antirejection medications that requires close monitoring of immunosuppressive drug levels both when the triazoles are started and when they are stopped again after treatment completion.

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