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Updates on Histoplasmosis in Solid Organ Transplantation

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Abstract

Purpose of Review Histoplasmosis remains a challenging infection in solid organ transplantation. This review provides a topic update with emphasis on the changing *Histoplasma* epidemiology, along with new diagnostic and treatment innovations.

Recent Findings Recent years have observed expanding *Histoplasma* geographic distribution due to climate change, environmental disruption, and host factors. Early clinical experience also suggests a relationship between COVID-19 infection and histoplasmosis, particularly among immunocompromised individuals. Advances in diagnostic methods, such as newer enzyme immunoassays and molecular techniques, have broadened the capability for expedient and highly specific pathogen identification. Novel drug innovations, including the development of new formulations of existing antifungal agents, extended-spectrum azoles and new antifungal drug classes have expanded therapeutic options.

Summary Advances in organ transplantation have largely outpaced those for histoplasmosis. However, these emerging insights enhance our understanding of this pathogen and management of clinical infection, particularly for transplant recipients with a higher incidence and severity of disease.

Keywords Histoplasmosis · Solid organ transplantation · Infection · Endemic mycoses · Antifungal therapy · Immunocompromised · COVID-19

Introduction

Histoplasmosis is a common endemic mycosis caused by the thermally dimorphic fungus *Histoplasma capsulatum* which exists as a mold in the environment with conversion to a yeast at body temperature within the human host. Most infections result from inhalation of aerosolized microconidia from the environment, most commonly affecting the lung. Solid organ transplant (SOT) recipients and other immunocompromised hosts have a propensity for severe infection inclusive of extrapulmonary and disseminated disease given their inability to contain the infection, with significant associated morbidity and mortality. This review provides a general topic update, with emphasis on (1) the expanding geographic distribution of histoplasmosis; (2) the relationship between coronavirus disease 2019 (COVID-19) infection and histoplasmosis; (3) advances in fungal diagnostics; and (4) novel antifungal therapies, approved or in the pipeline.

Epidemiology and Risk Factors

Histoplasmosis is the most common endemic mycosis reported in the SOT population and is among the most common endemic mycoses in the United States (US) and throughout the world [1, 2•]. Three varieties of *Histoplasma* have been identified, though *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* predominate among humans. The former variety is most common with the widest geographic distribution, whereas the latter is localized to Africa [3••, 4].

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Importantly, genomic sequencing and phylogenetic analyses demonstrate marked diversity within the *Histoplasma* genus. The identification of multiple cryptic species with varying geography and virulence has led to modifications of *Histoplasma* taxonomy [5, 6].

The geographic distribution and overall burden of disease worldwide is grossly underestimated due to lack of access to available diagnostics and infection recognition, as well as insufficient surveillance and reporting [2•]. For example, histoplasmosis is not a nationally notifiable disease in the US. Prior to 2016, it was reportable in only 12 states and lacked a standardized case definition [7]. In addition, maps detailing the geographic distribution of histoplasmosis date as far back as the 1940s based on skin testing surveillance studies [2•]. Figure 1 reflects ongoing efforts to detail the expansion of histoplasmosis beyond previously defined high endemicity regions such as the Ohio and Mississippi River Valleys in the US, Central and South America, areas of Africa and Asia [3••]. The revised maps draw from many sources including autochthonous case reports and series, skin testing surveillance, and environmental sampling. Explanations proposed for the geographic expansion of histoplasmosis include improved diagnostics and clinical recognition, climate change, environmental disruption, and expanding at-risk hosts [2•, 3••].

Histoplasmosis is uncommon among SOT recipients despite their increased susceptibility to infection. Prospective epidemiologic data from 23 transplant centers in the Transplant-Associated Infection Surveillance Network (TRANSNET) reported a 1-year cumulative incidence of histoplasmosis of 0.1% [1]. Transplant-associated histoplasmosis may occur de novo after environmental exposure, from reactivation of latent infection, or rarely via transmission from the donor. Although lung transplant recipients are at greater risk for acquiring other opportunistic fungi from the environment via the respiratory tract, such as *Aspergillus* spp., case series describe histoplasmosis most commonly after renal transplantation, likely as it reflects the largest transplant group worldwide [1, 8, 9].

Risks for post-transplant histoplasmosis include applied immunosuppression and environmental exposure. Human-to-human transmission has not been described. *Histoplasma* is commonly found in soil with high nitrogen content due to bird and bat droppings from nearby trees, coops, or caves [10]. Outdoor recreational activities, particularly spelunking, are a known risk. A review of 105 outbreaks of histoplasmosis in the US spanning 1938 to 2013 demonstrated that nearly one-third were work-related involving occupations in construction, demolition, or maintenance. Exposure to birds, bats, or "droppings" were reported in 86% [11]. Enhanced histoplasmosis surveillance in nine US states also identified handling of plants and trees and digging soil to be common potential exposures [12], though no obvious geographic or other exposure was identified in 22% of the cases. This point highlights the pitfalls of relying on a lack of relevant exposures to exclude histoplasmosis, as doing

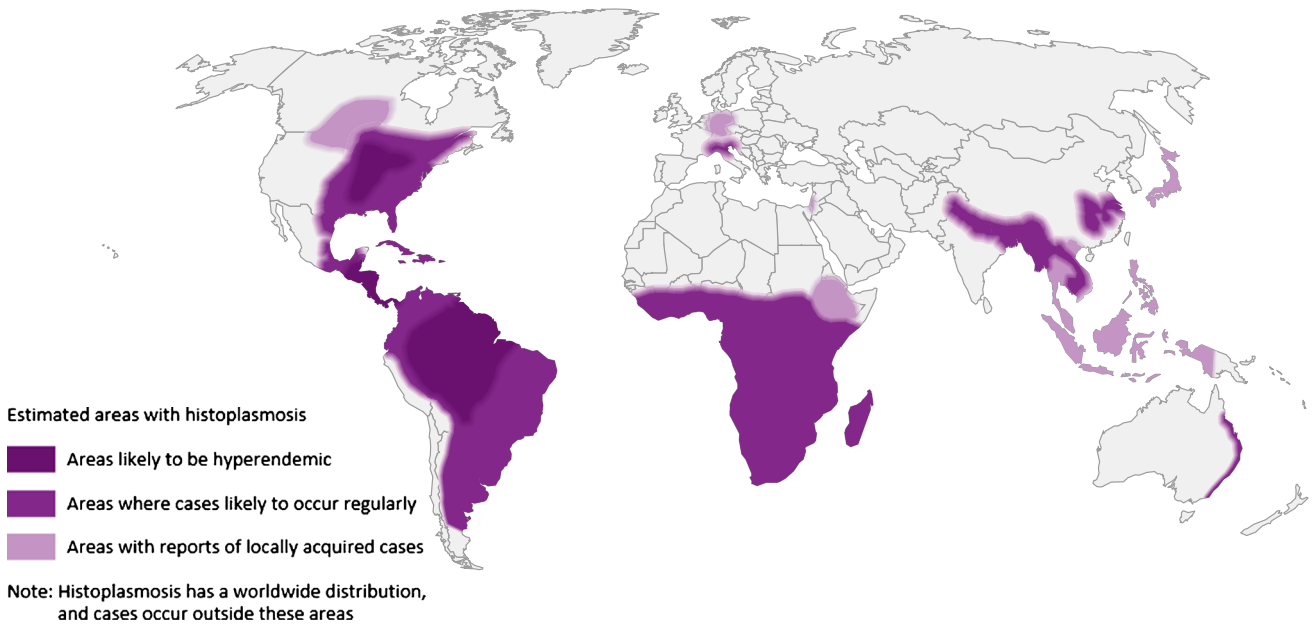

Fig. 1 Estimated areas of histoplasmosis worldwide. Legend: from reference [3••] under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

so could risk delayed or even missed diagnoses resulting in poor outcomes [13].

Clinical Manifestations

Clinical manifestations of histoplasmosis are highly variable and often non-specific making diagnosis challenging. Infection is often reported within the first 2 years following transplant, presumably due to higher levels of immunosuppression in this earlier transplant period. However, histoplasmosis can occur at any interval after transplant, having been reported as late as 20 to 30 years post-transplant [1, 8, 14••, 15, 16]. Infections occurring in the immediate post-transplant period, particularly the first month, should signal an investigation for donor-derived infection [8, 17••].

Signs and symptoms are dependent on the organ(s) involved and disease severity. Most infections present subacutely, with progressive disseminated infection representing the most common manifestation among SOT recipients, ranging from 64 to 81% in large multicenter evaluations [1, 8, 15]. Fevers, night sweats, malaise, cough, dyspnea, weight loss, hepatosplenomegaly, and other gastrointestinal symptoms are often present [10, 18, 19]. The most common sites of dissemination include bone marrow, lymph nodes, spleen, liver, gastrointestinal tract, skin, and central nervous system (CNS). Fungemia is common [8, 15, 20]. In the largest series of CNS histoplasmosis ($n=77$), the most common findings included headaches (60%), altered mental status (42%), and focal neurologic deficits (30%) [21].

Common laboratory findings include pancytopenia, transaminitis, hyperbilirubinemia, elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, and ferritin), and hypercalcemia [10, 20, 22]. Histoplasmosis-associated hemophagocytic lymphohistiocytosis has also been rarely described in the SOT population [23]. Findings on chest imaging are varied, including isolated nodules, miliary infiltrates, multifocal consolidation, and cavitary lesions [10, 24]. Additional common radiologic abnormalities include intra-thoracic and abdominal lymphadenopathy, and hepatosplenomegaly [10, 18]. Computed tomography or magnetic resonance imaging in CNS disease often reveal mass lesions, meningeal enhancement, and/or infarcts though may be normal [21].

Diagnostic Strategies

Establishing the diagnosis of histoplasmosis in transplant recipients typically requires a multifaceted approach. The first step is suspecting the diagnosis by recognizing the various manifestations of progressive disseminated histoplasmosis, the most common presentation in SOT recipients. Table 1 summarizes available diagnostics for histoplasmosis.

The diagnostic gold standard is growth of *Histoplasma* from clinical specimens. While definitive, cultures from blood and tissue may take up to 4 to 6 weeks to demonstrate growth, which may delay actionable clinical intervention [25]. Direct visualization of yeast forms with morphologic features consistent with *Histoplasma* from suspected sites of involvement is more timely and, unlike culture, can impact clinical decision making in real time. Though morphologic features may overlap with other fungi, careful attention to differences in yeast size, shape, budding, and capsular characteristics highly support the diagnosis of histoplasmosis in the right clinical context. Positive biopsy specimens are most commonly obtained from liver, lung, lymph nodes, bone marrow, and skin. Associated granuloma formation may also be seen, though less consistently in immunosuppressed hosts owing to the less robust host response to infection. With a high burden of infection, fungal forms within neutrophils may be identified on peripheral blood smear [26]. Cytopathologic examination of fine needle aspirate specimens from involved tissues may also be positive and provide a non-invasive, economical, and expedient diagnostic approach [27•]. The sensitivity of culture and direct visualization from histopathologic and cytopathic specimens is variable and dependent on the organism burden, site of involvement, and host factors [28•].

Prior to the development of more rapid diagnostic assays for histoplasmosis, acute and convalescent antibody detection was used to establish the diagnosis. The two available methods, testing by immunodiffusion and complement fixation, have differing sensitivity and specificity characteristics and are most useful in subacute and chronic forms of histoplasmosis [29]. However, in addition to the 4 to 8 weeks lag in antibody detection after acute infection, background seropositivity in individuals with prior exposure to endemic areas or past infection confound test interpretation. Serologic testing in immunosuppressed individuals is even more challenging as the effects of immunosuppressive therapy or underlying disease may blunt the antibody response to infection and decrease test sensitivity. Data demonstrate that only 25–30% of SOT recipients develop a serum antibody response [19]. However, CSF anti-*Histoplasma* antibody detection was found to be a useful adjunct to CSF antigen detection in diagnosing *Histoplasma* meningitis, even in immunosuppressed individuals [21, 30].

Owing to the challenges of culture identification and serologic testing, which are particularly problematic in transplant recipients and other immunocompromised hosts, antigen testing has become the primary modality for diagnosing histoplasmosis. The first antigen assay was introduced in 1986, with the development of newer iterations of enzyme immunoassays (EIAs) over time with quantitative capabilities and improved performance. Currently there are two commercially available EIAs. Most published data

Table 1 Laboratory diagnosis for histoplasmosis [19, 21, 25, 26, 27•, 28•, 29–34, 36, 37, 44•, 45, 47, 48••]

Diagnostic assay	Methodology	Specimen sources	Advantages	Limitations
Fungal culture	Selective fungal media: brain heart infusion agar, Sabouraud dextrose agar Lysis centrifugation for blood cultures	• Blood • Other body fluids • Tissue	Gold standard	• Prolonged incubation required for growth (4–6 weeks) • Variable sensitivity, limited by infection burden
Histopathology	PAS staining GMS staining	Tissue biopsy	• Timely results • Supports tissue invasive infection	• Variable sensitivity, limited by infection burden • Fungal morphology not confirmatory • Reviewer dependent
Cytopathology		• Tissue aspirate • BAL fluid • Peripheral blood smear	• Timely results • Minimally invasive • Economical	
Serology	Complement fixation Immunodiffusion	• Serum • CSF	• Minimally invasive • Positive CSF result sufficient to diagnose meningitis • Economical	• Less useful for acute infection due to 4–8-week lag for seroconversion • Poor sensitivity in immunocompromised hosts • Background seropositivity in endemic areas • Hard to delineate past versus active infection • Cross-reactivity with other fungal infections, TB, and sarcoidosis
Antigen testing	Enzyme immunoassay	• Urine • Serum • Other body fluids	• High sensitivity for disseminated infection • Minimally invasive • Faster turnaround time than culture • Quantitative • Serial monitoring capability for treatment response	• Cross-reactivity with other fungal infections • Less sensitivity with localized infection
	Lateral flow assay	Urine	• High sensitivity for disseminated infection • Minimally invasive • Rapid result at POC • Economical	• Cross-reactivity with other fungal infections • Less sensitivity with localized infection • Qualitative only
Molecular testing	Chemiluminescence-labeled DNA probe directed at *H. capsulatum* ribosomal RNA MALDI-ToF MS	Culture isolates	• High specificity • Streamlined isolate identification	• Requires culture growth, delaying results • Limited availability
	Fungal RNA sequencing		• Streamlined isolate identification to the species level	• Requires culture growth, delaying results • Available only through a reference laboratory
	Tissue-based PCR testing Broad-range PCR of fungal 28S ribosome	• Fresh tissue • Formalin-fixed, paraffin-embedded tissue blocks • Blood • Other body fluids	• Provides an alternative diagnostic option when other testing is inconclusive	• Heterogeneous assay methodology limits test interpretation • Variable sensitivity, generally low for tissue specimens • Available only through a reference laboratory • Expensive

BAL, bronchoalveolar lavage; *CSF*, cerebrospinal fluid; *DNA*, deoxyribonucleic acid; *GMS*, Gomori methenamine silver; *MALDI-ToF MS*, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; *PAS*, periodic acid-Schiff; *PCR*, polymerase chain reaction; *POC*, point-of-care; *RNA*, ribonucleic acid; *TB*, tuberculosis

and clinical experience stems from use of the MiraVista® (MiraVista Diagnostics, Indianapolis, IN, USA) assay, which was the first assay developed, now in its third generation. The IMMY® (Immuno-Mycologics [IMMY], Norman, OK, USA) ALPHA EIA assay, now replaced with the subsequently developed IMMY® clarus *Histoplasma*

galactomannan monoclonal EIA assay, has the advantage of the ability to be processed in local facilities rather than requiring shipment to a reference laboratory. These EIA assays demonstrate reasonable concordance, with overall sensitivity dependent on the type of specimen sent, the underlying burden of infection, and clinical manifestation [31–34].

Owing to the concentration of antigen in urine, urine testing is marginally more sensitive than serum antigen testing, with some data suggesting enhanced sensitivity with combined testing [35]. Antigen testing may also be performed on other body fluids, including bronchoalveolar lavage (BAL), CSF, and pleural fluid, though result interpretation is less established. The development of the quantitative component allows for serial monitoring to assess antigen clearance as a response to therapy, best supported in people living with human immunodeficiency virus (PLWH) [36].

Cross-reactivity with other fungal antigens is well demonstrated and limits EIA test interpretation, emphasizing the importance of interpreting the assay in the appropriate clinical context [32, 37]. False-positive BAL *Histoplasma* antigen results were found in 8% (5/60 patients) of pulmonary aspergillosis cases with high concentrations of *Aspergillus* galactomannan, though notably at low concentrations [38]. Conversely, the *Aspergillus* galactomannan assay was positive in 50% of serum and BAL samples from individuals with histoplasmosis, typically in those specimens with very high *Histoplasma* antigen concentrations. In this setting, the results could incorrectly lead to the conclusion there is co-infection and potentially impact treatment [39, 40]. The (1–3)-β-D-glucan assay as a screening tool for invasive fungal infection is widely used in clinical settings, but notably the assay does not have a US Food and Drug Administration (FDA)-approved indication for the diagnosis of histoplasmosis. Limited data demonstrate a sensitivity of serum (1–3)-β-D-glucan assay of 87 to 89% and specificity of 68% in disseminated histoplasmosis cases, with quantitative values correlating with urine antigen EIA concentrations [41, 42]. CSF (1–3)-β-D-glucan assay test performance was poor in *Histoplasma* meningitis cases [43].

While the development and broad availability of the *Histoplasma* antigen EIA assays have advanced the timely identification of histoplasmosis infections, logistical barriers related to the requirement of specialized laboratories, equipment, and personnel present challenges, particularly in resource limited areas. This recognition has led to the recent development of a qualitative lateral flow assay (LFA) for *Histoplasma* antigen detection. This assay has the advantage of using urine specimens at the point of care and providing results within 40 min of specimen collection without the need for specialized equipment. Direct cross comparison of results from urine specimens between the LFA and EIA assay has demonstrated high concordance between the two assays, with high test sensitivity in immunosuppressed individuals with a higher burden of infection [44•, 45]. However, both assays are limited by positive results due to cross-reactions with other fungal pathogens.

Currently, molecular detection of *Histoplasma* in the clinical setting is largely limited to fungal identification from culture isolates [46]. Matrix-assisted laser desorption ionization time-of-flight is increasingly applied in clinical microbiology laboratories for pathogen identification from culture isolates including both fungal morphologic stages of *H. capsulatum* [47]. While these approaches offer the advantage of rapid identification from primary cultures without needing a more prolonged and laborious method, they still require culture growth, which may require weeks to occur. Wide availability and applicability of molecular detection methods for *H. capsulatum* directly from clinical specimens remains elusive. Currently, there are no FDA-approved assays for detecting *Histoplasma* species directly from human specimens. Tissue-based polymerase chain reaction (PCR) testing and sequencing, along with broad-range PCR of fungal 28S ribosome, are available at reference laboratories, but are largely cost prohibitive for routine use. Available data are largely limited to case reports and small case series. Cross comparisons of studies are challenging due to the use of heterogeneous molecular assays using different molecular targets, multiple specimen sources, and various comparison assays [48••]. As with other diagnostic assays, the overall sensitivity of molecular techniques is superior with higher organism burden [49]. Performance evaluation and clinical validation of these assays require further refinement, but emerging data suggest molecular methods will play an increasing future role in our diagnostic armamentarium for histoplasmosis.

Management of Histoplasmosis

Most *Histoplasma* infections in immunocompetent individuals do not necessitate directed therapy [50••]. In contrast, SOT recipients can develop severe and disseminated infection warranting timely initiation of antifungal therapy and reduction of immunosuppression [14••]. While infections in SOT recipients are best categorized as mild, moderate, or severe, well-defined characteristics of severity in this population are lacking as are randomized controlled trials comparing the efficacy of antifungal therapies.

Available antifungal therapies used to treat histoplasmosis are detailed in Table 2; however, the mainstays of therapy have historically been amphotericin B (AmB) and/or itraconazole (ITZ). Intravenous AmB remains the initial drug of choice for severe infection. Liposomal AmB is preferred over conventional AmB deoxycholate (AmB-d) due to its more favorable safety and tolerability profile and

improved efficacy as demonstrated in other immunocompromised populations such as PLWH [51]. The American Society of Transplantation (AST) guidelines recommend step down to oral ITZ therapy following at least 1 to 2 weeks of AmB alongside evidence of clinical stabilization [14••]. For patients with CNS disease, longer courses of AmB therapy (i.e., 4 to 6 weeks) are recommended [50••, 52•]. Mild to moderate disease can be treated with ITZ monotherapy. In general, antifungal therapy should be continued for a minimum of 12 months irrespective of initial disease severity. Indefinite therapy may be considered in patients necessitating continued high-level immunosuppression or after relapsed disease, particularly with CNS involvement [53].

Conventional ITZ (C-ITZ) is available as both an oral capsule and solution [54, 55]. C-ITZ capsules have variable bioavailability, which is particularly poor when administered with concomitant acid-suppressive therapies. Absorption can be optimized when C-ITZ is taken with a fatty meal and/or acidic drink. Conversely C-ITZ solution is minimally impacted by acid-suppressive therapies but requires administration on an empty stomach. C-ITZ solution has generally been preferred owing to its superior bioavailability though palatability can be problematic. Therapeutic drug monitoring is essential with both formulations to ensure adequate exposure [56]. Super bioavailable itraconazole (SUBA-ITZ) is a novel formulation of ITZ developed to address issues of tolerability and bioavailability observed with C-ITZ formulations [57]. It is available as an oral capsule formulation and applies a solid dispersion of ITZ in a polymetric matrix. Studies of SUBA-ITZ in healthy adults demonstrated no significant reductions in bioavailability in the presence of acid-suppressive therapies or in fed versus fasted states [58]. A compilation of seven crossover studies in healthy adults receiving SUBA-ITZ and C-ITZ capsules demonstrated improved bioavailability of SUBA-ITZ (173%) compared to C-ITZ capsules with less variability in ITZ exposure [59]. In addition, steady-state findings from an open-label crossover pharmacokinetic analysis of SUBA-ITZ and C-ITZ capsules showed greater attainment of therapeutic ITZ trough values (i.e., > 1000 ng/mL) in the SUBA-ITZ than C-ITZ group (81 versus 44%, respectively) [60]. SUBA-ITZ was approved by the FDA in 2018 for the treatment of specific fungal infections including histoplasmosis. Published results from a Mycosis Study Group-sponsored phase 3 multicenter, randomized, open-label study of invasive endemic fungal infections evaluating the pharmacokinetics, safety, efficacy, tolerability, and health economics of oral SUBA-ITZ compared to C-ITZ capsules are highly anticipated (NCT03572049).

Echinocandins are not currently recommended for histoplasmosis treatment due to a lack of supportive clinical data. However, fluconazole (FCZ) has been used as an alternative to ITZ in settings such as intolerance. Concerns with application of FCZ for *Histoplasma* include reduced in vitro activity, delayed fungemia clearance, and resistance emergence [50••, 61, 62]. Newer-generation extended-spectrum azoles including voriconazole (VCZ), posaconazole (PCZ), and isavuconazole (ISZ) may be suitable alternatives to ITZ though data are limited to case reports and series [63–66]. A particular advantage may exist in CNS infection, as VCZ has improved CNS penetration compared to ITZ but necessitates further study. Hendrix et al. published the only data to date comparing outcomes with VCZ and ITZ for histoplasmosis in a single-center, retrospective evaluation in 194 cases that included 21 (10.8%) transplant recipients [67••]. Survival analysis in patients receiving ITZ (90.2%) and VCZ (9.8%), either as primary or step-down therapy following AmB, demonstrated a statistically significant association of VCZ therapy with early mortality during the first 6 weeks (hazard ratio, 4.3; 95% confidence interval, 1.3–13.9; $P = 0.015$). Results of therapeutic drug monitoring were not reported and only one case with CNS disease was treated with VCZ. Potential explanations for poorer survival with VCZ include suboptimal drug exposure and resistance emergence. As previously mentioned, resistance has been demonstrated with FCZ and is due to a point mutation in cytochrome P450 enzyme 14α-demethylase (CYP51p) [68]. This mutation results in increased minimal inhibitor concentrations (MIC) for both FCZ and VCZ but does not appear to impact the MIC for the other extended-spectrum azoles [68, 69]. Despite the limitations of this retrospective evaluation, caution is advised when utilizing VCZ for histoplasmosis, particularly in the setting of preceding FCZ exposure. In situations of ITZ intolerance, the authors prefer PCZ based on resistance concerns and improved tolerability despite the limited clinical data. Prospective controlled trials are necessary to determine whether VCZ and other extended-spectrum azoles are effective therapeutic options for histoplasmosis, including CNS disease, and to further understand the potential for resistance emergence.

There are additional important considerations when managing histoplasmosis in the SOT recipient. Drug toxicities and drug interactions, especially those related to the cytochrome P450 isoenzyme system, remain a significant issue with azole therapies (see Table 2). Polypharmacy is common in the transplanted host and often includes other narrow therapeutic index agents such as calcineurin inhibitors (CNIs) impacting the CYP450 isoenzyme system. Thus, azole use necessitates careful dose adjustment of relevant medications and close monitoring. Reducing immunosuppression during acute infection is also paramount. However, an optimal strategy is lacking, with decisions typically individualized to the transplant recipient based on the transplant type and timeline, status of allograft rejection, and net state of immunosuppression. Mycophenolate has been identified as a risk factor for severe disease and failure to reduce CNI exposure has been associated with relapsed disease; hence,

Table 2 Antifungal therapy for histoplasmosis [50••, 54, 55, 57, 67••, 92–100]

Antifungal agents[a]	Usual dosage	Common adverse reactions[b]	Therapeutic drug monitoring	Major drug interactions[b,c]	Additional comments
Polyenes					
AmB-d (Fungizone) (IV only) Liposomal AmB (AmBisome)* (IV only) AmB Lipid Complex (ABLC, Abelcet)* (IV only) *Lipid-based AmB formulations	0.7–1 mg/kg/day 3–5 mg/kg/day 5 mg/kg/day	• Acute infusion reactions (e.g. fever, chills, hypotension, nausea, vomiting, headache) • Anemia • Electrolyte imbalance (low potassium, magnesium, calcium, and sodium) • GI effects • Hepatotoxicity • Nephrotoxicity	Not recommended	• Digitalis glycosides, skeletal muscle relaxants, and antiarrhythmic agents (possible increased toxicity due to AmB-mediated hypokalemia) • Nephrotoxic medications (possible increased drug-induced nephrotoxicity) • Leukocyte transfusions (acute pulmonary toxicity reported when given concomitant to AmB; should not be given concurrently)	• Infusion-related reactions can be reduced with pre-infusion acetaminophen and diphenhydramine; meperidine may be used for rigors • Nephrotoxicity can be minimized with pre- and post-infusion hydration and lipid-based AmB formulations • Close monitoring of electrolytes and renal function required
Azoles					
ITZ (PO only) C-ITZ (Sporanox) Capsule/tablets and oral solution SUBA-ITZ (Tolsura) Capsule	Loading dose: 200 mg TID × 3 days Maintenance dose: 200 mg BID Initial dose: 130 mg daily (max dose 130 mg BID)	• Adrenal insufficiency (long-term use, rare) • CHF (avoid use if ventricular dysfunction/CHF) • GI effects • Headache • Hearing loss • Hepatotoxicity • Neuropathy • Peripheral edema • QT prolongation • Rash	• Random concentration after ≥ 2 weeks of therapy; goal ≥ 1.0 µg/mL (via HPLC) • For HPLC, the goal concentration is sum of ITZ and active metabolite hydroxy-ITZ	• ITZ is an inhibitor of CYP3A4 and p-glycoprotein • Potentiation of QT prolongation when used with other QT prolonging drugs	For C-ITZ • Capsules: take with food and acidic beverage (e.g., cola); avoid proton pump inhibitors and H-2 blockers which reduce absorption • Solution: take on empty stomach For SUBA-ITZ • Take with food • Has not been adequately studied in *Histoplasma* CNS infections
FCZ (Diflucan) IV/PO	Recommendations vary based on site of infection	• Alopecia (with prolonged therapy) • Exfoliative skin disorders • GI effects • Hepatotoxicity • Headaches • QT prolongation	Not recommended	• FCZ is an inhibitor of CYP2C9 and CYP3A4 • Potentiation of QT prolongation when used with other QT prolonging drugs	Concerns with use for histoplasmosis include reduced in vitro activity, delayed fungemia clearance, and resistance emergence (see text)

Table 2 (continued)

Antifungal agents[a]	Usual dosage	Common adverse reactions[b]	Therapeutic drug monitoring	Major drug interactions[b,c]	Additional comments
VCZ (Vfend) IV/PO	IV: 6 mg/kg BID × 2 doses then 4 mg/kg BID PO: 400 mg BID × 2 doses then 200 mg BID	• Fluorosis and periostitis • GI effects • Headache • Hepatotoxicity • QT prolongation • Skin rash, photosensitivity • Visual disturbances (e.g., photopsia, color vision change, photophobia, other visual hallucinations), rare optic neuritis, and papilledema • Long-term use associated with skin cancer	• Trough concentration ≥ day 5 of therapy; goal trough ≥ 1.0 to 5.5 μg/mL • Recommendations extrapolated from IFIs such as aspergillosis; target trough values for histoplasmosis have not been defined	• VCZ is metabolized by, and an inhibitor of CYP2C19, CYP2C9, and CYP3A4 • Potentiation of QT prolongation when used with other QT-prolonging drugs	• Take 1 h before or after a meal • IV formulation contains SBECD and typically avoided when CrCl < 50 mL/min unless risk:benefit assessed • Caution is advised when utilizing VCZ for histoplasmosis given increased early mortality demonstrated in comparison to ITZ (see text)
PCZ (Noxafil) IV/PO	Loading dose: 300 mg BID × 2 doses Maintenance dose: 300 mg daily	• GI effects • Headache • Hepatotoxicity • QT prolongation	• Trough concentration > 1.0 μg/mL; measured after 7 days of therapy • Recommendations extrapolated from IFIs such as aspergillosis; target trough values for histoplasmosis have not been defined	• PCZ is a substrate of p-glycoprotein and an inhibitor of CYP3A4 • Potentiation of QT prolongation when used with other QT-prolonging drugs	• PCZ suspension—take with high-fat meal, acidic beverage (e.g., cola, ginger ale), and avoid proton pump inhibitors • PCZ delayed-release tablet—take with food • IV formulation contains SBECD and typically avoided when CrCl < 50 mL/min unless risk:benefit assessed
ISZ (Cresemba) IV/PO	Loading dose: 372 mg Q8h for 6 doses Maintenance dose: 372 mg daily	• GI effects • Headache • Hypokalemia • Peripheral edema • Hepatotoxicity • Cardiac effects: shortening of the QT interval; contraindicated in familial short QT syndrome	Not routinely recommended	• ISZ is a substrate of CYP3A4 and inhibitor of CYP3A4, p-glycoprotein, and organic cation transporter 2	• IV formulation does not contain SBECD

Table 2 adapted with permissions from [100]

ABLC, amphotericin B lipid complex; *AmB*, amphotericin B; *AmB-d*, amphotericin B deoxycholate; *BID*, twice daily; *C-ITZ*, conventional itraconazole; *CHF*, congestive heart failure; *CNS*, central nervous system; *CrCl*, creatinine clearance; *CYP*, cytochrome P450 enzyme system; *FCZ*, fluconazole; *GI*, gastrointestinal; *H2*, histamine-2 receptor; *HPLC*, high-performance liquid chromatography; *ISZ*, isavuconazole; *IFI*, invasive fungal infections; *ITZ*, itraconazole; *IV*, intravenous; *MIC*, minimal inhibitory concentration; *LAmB*, liposomal amphotericin B; *PO*, by mouth; *PCZ*, posaconazole; *spp*, species; *SBECD*, sulfobutyl ether beta-cyclodextrin sodium; *SUBA-ITZ*, super bioavailable itraconazole; *TID*, three times daily; *VCZ*, voriconazole

[a]AmB and C-ITZ are recommended first-line therapies (see the "Management of Histoplasmosis" section). Data with other extended-spectrum azoles is limited to case series and reports

[b]This is not an all-inclusive list

[c]Critical to assess for drug interactions with concomitant medications that either share or modify the activity of involved metabolic pathways. See package insert and drug interactions screening databases for important drug interactions

reductions in these agents should be prioritized [8]. While immune reconstitution syndrome has been described during treatment of disseminated histoplasmosis, it is uncommon in SOT and other immunocompromised populations such as PLWH [70, 71]. Finally, monitoring of urine and serum *Histoplasma* antigen levels during and after therapy is recommended to assess response to infection and monitor for relapse. The Infectious Diseases Society of America (IDSA) and AST guidelines recommend monitoring antigen levels at regular intervals, including at therapy initiation, 2 weeks, 1 month, and approximately every 3 months thereafter during therapy and for at least 6 to 12 months post-cessation [14••, 50••]. Additional testing should be performed as clinically indicated, such as scenarios when there is concern for relapse or with marked augmentation of immunosuppressive therapy (e.g., re-transplantation and severe allograft rejection). Not all SOT recipients will completely clear antigenemia and/or antigenuria at the end of appropriate therapy; however, most can still safely stop antifungal therapy without relapse, assuming all other indicators support clinical response [15, 72]. Of note, quantitative antigen values may vary depending on the specific EIA assay applied; hence, a consistent laboratory should be utilized for serial monitoring when feasible.

Novel Fungal Therapies for Histoplasmosis

There are additional drugs either in the antifungal pipeline or FDA-approved for other indications that have *Histoplasma* activity. These agents may ultimately supplement the limited fungal armamentarium for histoplasmosis and other endemic mycoses. For example, new polyene formulations in development include encochleated amphotericin B deoxycholate (MAT2203; Matinas BioPharma Nanotechnologies, Bedminster, NJ) which utilizes a novel lipid nanocrystal to allow for oral administration. This therapy lacks many of the adverse effects associated with intravenous AmB including infusion reactions, nephrotoxicity, and electrolyte disarray [73, 74]. Tetrazoles are next-generation azoles in development to abrogate management issues such as drug interactions given their greater selectivity for fungal Cyp51 compared with the mammalian cytochrome P450 enzyme system [75, 76]. Among these, VT-1598 (Viamet Pharmaceuticals, Durham, NC) has a broad spectrum of activity including *Histoplasma* and was granted orphan drug designation for the treatment of coccidioidomycosis. Ibrexafungerp is an oral triterpenoid antifungal with a mechanism of action similar to echinocandins, inhibiting 1,3-β-D-glucan synthase [75, 77, 78]. It received FDA approval in 2021 for treatment of vulvovaginal candidiasis. An ongoing phase 3 multicenter, open-label study evaluating the efficacy and safety of ibrexafungerp in patients with fungal diseases refractory to or intolerant of standard treatment was expanded to include histoplasmosis (FURI, NCT03059992) [77]. Other novel agents with *Histoplasma* activity include olorofim, fosmanogepix, and nikkomycin Z [76, 78, 79•, 80–83]. Both olorofim and fosmanogepix have activity against *Histoplasma*, are available in oral and intravenous formulations, and are actively being pursued for multiple fungal applications. Olorofim, an antifungal in the orotomide class, inhibits dihydroorotate dehydrogenase in the pyrimidine biosynthesis pathway [81]. Fosmanogepix, the oral prodrug of manogepix, inhibits the fungal enzyme Gwt1 important for mannoprotein adherence to the cell wall during establishment of infection [79•]. Finally, nikkomycin Z is a chitin synthase inhibitor and impacts chitin production, an important structural component of fungal cell walls. It demonstrates activity against histoplasmosis both as monotherapy and in combination with FCZ [83]. Renewed interest in nikkomycin Z for coccidioidomycosis treatment alongside the development of an extended-release formulation to offset its short half-life may hold promise in future application for endemic mycoses including histoplasmosis [84].

COVID-19 and Histoplasmosis

Emerging reports have described a temporal relationship between COVID-19 infection and invasive fungal infections, including histoplasmosis [85•]. Reports of histoplasmosis developing during and after COVID-19 infection are limited to small series and case reports, occurring among both immunocompromised and immunocompetent individuals [86–90]. Only one such case has been reported in a kidney transplant recipient, though additional anecdotal cases in SOT recipients have occurred (author personal communication) [90].

There are two main proposed mechanisms to explain an association between histoplasmosis and COVID-19 infection. First, parenchymal lung injury related to COVID-19 infection may predispose individuals to developing acute pulmonary histoplasmosis after an inhalation of environmental *Histoplasma* conidia. Second, SARS-CoV-2-associated immune modulation or that related to corticosteroid therapy used for COVID-19 infection management may lead to reactivation of latent *Histoplasma* infection in those individuals previously infected. Further, these factors may act synergistically in an infected individual. In many of the reported cases, interpretation of the diagnostic testing in the clinical context is challenging such that firm conclusions regarding a true link between *Histoplasma* and COVID-19 infections are lacking. More data are needed, but these early cases suggest clinicians should maintain heightened clinical suspicion for histoplasmosis, especially in endemic areas, among patients with concurrent or recent COVID-19 infection.

Peri-transplant Donor and Recipient Considerations

Recipient Evaluation

General consensus based on data compiled over 2 decades support that pre-transplant screening for histoplasmosis in transplant candidates is not indicated, even for those in endemic areas. Early support for this approach came from a retrospective review of 449 SOT recipients from a hyperendemic region, where approximately one quarter of SOT candidates had either a positive *Histoplasma* serology or chest radiograph evidence of prior infection [91]. None developed post-transplant histoplasmosis despite no antifungal prophylaxis, suggesting the risk for reactivation infection is negligible in this setting. Transplant candidates with active histoplasmosis should be deferred at least until there is significant clinical improvement, or if feasible, until therapy is completed. Active histoplasmosis within the prior 2 years may be a basis for antifungal prophylaxis after transplantation, though the duration is not established [50••]. Subsequent case series have further supported this approach, with targeted post-transplant antifungal prophylaxis for other selected recipients [8, 15, 19, 72].

Donor Evaluation

Given the low incidence of histoplasmosis in healthy donors and rarity of reported donor transmission events, even in endemic areas, routine donor screening is not indicated. However, if the donor demonstrates clinical findings such as non-hemorrhagic neurological disease, unexplained fever, and/or pneumonia, histoplasmosis should be considered and testing performed. Though procurement may proceed before tests result, organs should be carefully inspected for findings suspicious for histoplasmosis, such as hepatosplenomegaly, granuloma formation, and lymphadenopathy. In addition to obtaining tissue specimens for histopathology and culture, serology and antigen EIA testing should be performed. The collective results will inform recipient management following allograft implantation. Potential living donors with active histoplasmosis should be deferred and treated with antifungal therapy at least 3–6 months prior to consideration for organ donation [17••].

Management Recommendations

The optimal management approach for clinical scenarios where is there is concern for possible donor *Histoplasma* transmission and pre-existing recipient infection remain undefined. Accordingly, there exists significant practice variability among individual transplant centers, geographic regions, and organ transplanted. Recognizing the paucity of data, in 2012, the AST published guidance [17••]. Per these recommendations, azole prophylaxis should be offered if the donor tissue fungal stains are positive but cultures and antigen assays are negative and/or the donor complement fixation serology is $\geq$ 1:32. The recommended prophylaxis duration is 3 to 6 months. For lower risk scenarios, observation without azole prophylaxis with antigen EIA monitoring every 3 months is a reasonable approach. If active histoplasmosis is confirmed in the donor after allograft implantation, the recipient should be treated with azole therapy for at least 1-year post-transplant.

While appreciating the attempt to provide a construct for uniform practice across the transplant community, these recommendations were based largely on expert opinion and now date back a decade, leaving leeway for alternative present day approaches. Without updated data, testing and management of donors and recipients remain variable and individualized based on the infection burden and underlying recipient risk. Lung transplant recipients are considered higher risk for developing active histoplasmosis based on requirements for relatively higher baseline immunosuppression compared to other transplant groups as well as the pulmonary reservoir of latent or active *Histoplasma* organisms. Newer, extended-spectrum azoles with improved tolerability also introduce expanded options for prophylaxis and treatment. It is important to recognize that histoplasmosis remains a rare infection (< 1%) in the post-transplant setting, even in endemic areas [1].

Conclusions

Though an uncommon infection in the SOT population, histoplasmosis has significant clinical implications. Given the myriad of clinical manifestations associated with infection in SOT recipients and the expanding worldwide distribution, histoplasmosis should increasingly be suspected in the appropriate clinical context. Laboratory testing continues to evolve to optimize timely diagnosis and monitoring and the antifungal armamentarium is growing. With diligent monitoring for active infection and targeted post-transplant antifungal prophylaxis, serious infection can largely be averted in the highest risk transplant recipients.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Jennifer L. Saullo declares that she has no conflicts of interest. Rachel A. Miller receives research support from Scynexis (institutional principal investigator in the FURI clinical trial, NCT03059992) and has no other conflicts of interest to disclose.

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•• Of major importance

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