Histoplasmosis

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KEYWORDS

• Histoplasmosis • *Histoplasma capsulatum* • Endemic mycosis • Dimorphic fungi • Itraconazole

KEY POINTS

- *Histoplasmosis* is one of the most common endemic mycoses in North America and South America.
- Infection occurs through inhalation of aerosolized microconidia in the environment.
- Pulmonary infection is the most common disease manifestation, but patients may present with a spectrum of disease ranging from asymptomatic disease to disseminated infection.

INTRODUCTION

Histoplasmosis is one of the most common endemic mycoses in North and South America. Infection results from inhalation of aerosolized microconidia in the environment. It causes a spectrum of disease ranging from asymptomatic pulmonary infection to severe disseminated infection with central nervous system (CNS) involvement. This review will provide an update on histoplasmosis with emphasis on the changing epidemiology, pathogenesis, disease manifestations, diagnostic strategies, and management considerations for immunocompetent and immunocompromised populations.

EPIDEMIOLOGY

Human infections due to *Histoplasma* are caused primarily by *Histoplasma capsulatum var. capsulatum* and *H capsulatum var. duboisii*. The third variety—*H capsulatum*

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var. farciminosum—does not typically infect humans.[1] Several major changes to our perception of this organism have recently come to light. First, while *Histoplasma* varieties within *H capsulatum* genus have historically been delineated by geographic and clinical manifestations, recent population genetic and phylogenetic analyses have identified new cryptic species and will continue to impact the taxonomy.[2] In addition, though histoplasmosis has traditionally been thought of as an endemic fungal infection, specific to certain geographic regions, evolving data have demonstrated broader distributions of these dimorphic fungi than previously known, likely owing to changes in climate and increasing numbers of immunocompromised hosts.[3–5] *H capsulatum* is globally distributed and has been identified on every continent including Antarctica, while *Histoplasma duboisii* is primarily concentrated in Africa.[1,3,6,7]

Despite the wide geographic distribution of *Histoplasma*, significant geographic variability exists with hyperendemic regions with exceedingly high prevalence of disease.[8] Outbreaks can also occur within and outside of these highly endemic areas.[9] Furthermore, with shifts in global commerce, migration, and tourism, identifying autochthonous cases versus those related to external exposures remains challenging.[1] Finally, seroprevalence assessments using histoplasmin skin antigen testing are of limited reliability and are no longer available, making efforts at characterizing epidemiology more challenging.[10] Nonetheless, North America as well as Central America and South America have high endemicity, while Europe continues to have few reports of endemic infection, concentrated primarily in Italy.[3,11] In Central America and South America, seroprevalence varies across countries but is greater than 20% in most countries other than Chile, Paraguay, Peru, and Uruguay, and ranges up to 57% in Guatemala.[12] One study in Brazil estimated a seroprevalence of 93% in one region of Rio de Janeiro.[13] In North America, histoplasmosis has historically been considered most prevalent in the regions surrounding the Ohio and Mississippi river valleys, though a recent publication has significantly expanded these high prevalence areas using Medicare claims data.[4,14] Asia and Africa also report moderate levels of seropositivity depending on the region, though variability in access to diagnostic testing may lead to underdiagnosis.[1,15]

PATHOGENESIS

Histoplasma is a dimorphic fungus, existing in either a mycelial or a yeast form, depending on temperature and nutritional conditions. At 37°C or in humans, the yeast form predominates. Yeast cells have thin walls and are oval with diameters of 2 to 5 μm. In the environment and at ambient temperatures, *Histoplasma* exists in the mycelial phase. Hyphal elements are 1.25 to 2.0 μm in diameter, and they produce 2 types of conidia: thick-walled macroconidia ranging from 8 to 15 μm in diameter and microconidia ranging in size from 2 to 5 μm. *Histoplasma* microconidia are believed to be the infectious form as their size is most suited for aerosolization and inhalation.

Innate and cellular immune responses are necessary for control of histoplasmosis. Neutrophils are considered the primary responders to *Histoplasma* in the lung and inhibit the fungus.[16] Experimental studies support that $CD8^+$ T cells are helpful in initial clearance of *Histoplasma* yeast cells, whereas $CD4^+$ T cells are required for survival.[17] When cellular immunity is compromised, infection can disseminate, or reactivation can occur in latently infected individuals with controlled infection.[17,18]

Several cytokines, including interleukin-12 and interleukin-17, tumor necrosis factor-alpha (TNF-α), granulocyte-macrophage colony-stimulating factor, and interferon-γ are important in protective immunity to *Histoplasma.*[17] The critical role of

lymphocytes and production of TNF is better understood after reporting of increased incidence of disseminated histoplasmosis in patients receiving TNF inhibitors.[19]

CLINICAL MANIFESTATIONS

Histoplasmosis can cause significant clinical disease in both immunocompetent and immunocompromised individuals.[20] Despite its ability to cause severe and life-threatening disease, the majority (approximately 90%) of infections are asymptomatic or subclinical.[5,21]

Acute and Subacute Pulmonary Histoplasmosis

Among patients who develop symptomatic infection, pulmonary histoplasmosis is the most common clinical manifestation.[22,23] Acute infection typically occurs 1 to 3 weeks after inhalation of fungal conidia and is most often self-limited.[20] Severe, prolonged pneumonia or pneumonitis with associated acute respiratory distress syndrome can develop rarely, primarily in patients with a high inoculum or deficits in immunity.[23] Common presenting symptoms of pulmonary histoplasmosis include cough, dyspnea, chest pain, fever, or chills. Chest radiography frequently shows patchy bilateral opacities, at times with hilar or mediastinal lymphadenopathy.[21] Given the vague nature of the symptoms and imaging findings, pulmonary histoplasmosis is frequently confused with community-acquired pneumonia, leading to delays in diagnosis. The presence of hilar/mediastinal lymphadenopathy and/or failure to respond to standard antimicrobial therapy can raise the clinical suspicion for histoplasmosis.[21,24] Nonpulmonary manifestations of histoplasmosis such as pericarditis, arthritis/arthralgias, and dermatologic conditions including erythema nodosum or erythema multiforme can arise concomitantly with the pulmonary syndrome in a small number of patients.[25,26] Subacute pulmonary histoplasmosis is similar to the acute disease but is thought to be related to reduced exposure to fungal conidia.[22] It typically presents with milder symptoms that progress over weeks to months and more focal opacities visualized on imaging.[21,27]

Chronic Cavitary Pulmonary Histoplasmosis

Chronic cavitary pulmonary histoplasmosis is an unusual manifestation of pulmonary histoplasmosis that occurs in 2% to 8% of patients, with symptoms that often progress over years.[27] Patients affected by this form of histoplasmosis tend to be older with underlying lung disease.[9] Clinical symptoms are similar to those seen in pulmonary tuberculosis including fatigue, anorexia, weight loss, chronic cough with sputum production and/or hemoptysis, night sweats, and occasionally fevers.[23] Classic radiographic features consist of thick-walled cavitations, located most often in upper lobes including bilateral apices, often with associated pleural thickening.[28,29]

Pulmonary Nodules

Pulmonary nodules can arise following *Histoplasma* infection and can be the primary radiographic presentation of symptomatic chronic histoplasmosis in a subset of patients.[28,30] Asymptomatic pulmonary nodules may be indistinguishable from malignancy, often prompting invasive biopsies.[22] At this point, novel imaging modalities including nuclear medicine studies have not been able to reliably distinguish between nodules related to histoplasmosis and those associated with malignancy.

Mediastinal Histoplasmosis

Mediastinal histoplasmosis presents in multiple forms and ranges from asymptomatic lymphadenopathy to life-threatening mediastinal fibrosis affecting vital structures.[31]

Mediastinal adenitis is typically identified radiographically and occurs early after acute infection. It is most often self-resolving and seen as homogenous lymph nodes or mediastinal mass on imaging, typically without evidence of necrosis or calcification.[23] Occasionally this can progress to granulomatous mediastinitis with caseation and necrosis of the lymph nodes, demonstrated by heterogenous or necrotic mediastinal masses on imaging.[21] Mediastinal adenitis or granulomas are frequently asymptomatic but both can lead to complications via structural obstruction or impingement of the adjacent structures including the airways or esophagus.[27] This is an increased risk in children with less rigid airways.[21] Fibrosing mediastinitis is a rare but highly morbid complication that occurs late after infection and is characterized by an exuberant fibrotic reaction to histoplasmosis involving the mediastinal structures and, at times, the great vessels.[32,33] Patients may present with hemoptysis, pleuritic chest pain, dyspnea, or dysphagia related to encasement of mediastinal structures, as well as sequelae of the vascular obstruction including thrombosis or superior vena cava syndrome.[23] Dense calcifications are often seen on imaging.[21]

Disseminated Histoplasmosis

Hematogenous dissemination is most frequently seen in immunocompromised hosts with deficits in cell-mediated immunity and can lead to severe extrapulmonary manifestations of histoplasmosis.[20,23] Traditionally, patients with advanced human immunodeficiency virus (HIV) and low CD4 T-cell counts have been the most prevalent population in which this syndrome is described, but infection in other risk groups is increasing, including patients with hematologic malignancy, recipients of solid organ transplantation, and those receiving immunotherapy such as TNF-alpha-targeted monoclonal antibodies.[19,34–41] Patients may present with systemic symptoms including fever, night sweats, weight loss, and fatigue. Illness can progress to shock, respiratory failure, disseminated intravascular coagulation, adrenal insufficiency, and hemophagocytic lymphohistiocytosis.[27,41] On laboratory evaluation, patients may have pancytopenia, liver function abnormalities, and hyperferritinemia.[42–44] Imaging may reveal hepatosplenomegaly, multistation lymphadenopathy, and diffuse pulmonary infiltrates, miliary pattern of involvement (**Fig. 1**), or cavitary nodular lesions.[41] Hepatic, splenic, lymphatic, gastrointestinal, and bone marrow involvement are most common; though other sites including skin, bone, endocardium, adrenal glands, peritoneal space, or the CNS may be involved.[25,45–49] In contrast to the rapidly progressive acute disseminated histoplasmosis that occurs in immunocompromised hosts as described, chronic progressive disseminated histoplasmosis is a frequently fatal presentation of disseminated disease that progresses in a more indolent manner, typically in older patients without known immunocompromising conditions.[42,50]

DIAGNOSIS

Culture

The gold standard for diagnosing *Histoplasma* infection is isolation of the mold in culture from clinical specimens.[51] Because *Histoplasma* grows poorly on standard laboratory culture media, specimens should be plated onto Sabouraud dextrose agar and incubated at 25°C to allow for growth of the mycelial phase. Growth typically occurs within 2 to 4 weeks but may require up to 6 to 8 weeks, rendering culture a less practical method for timely diagnosis and treatment of disease.[51]

Mold colonies appear tan or white with cotton like texture (**Fig. 2**). The lactophenol cotton blue test can assist in microscopic examination of *Histoplasma*, revealing septate hyphae that produce 2 types of conidia: macroconidia measuring 8 to

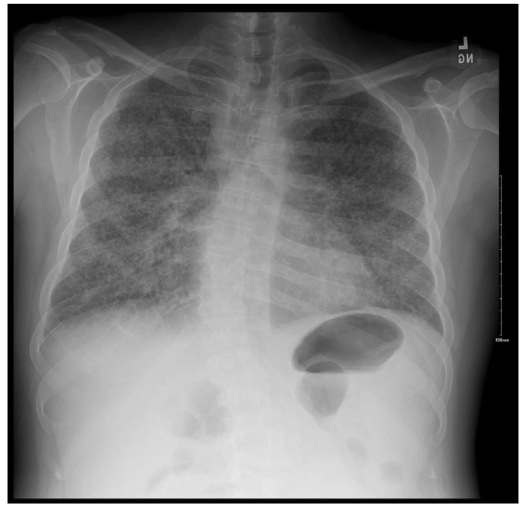

Fig. 1. Miliary pulmonary histoplasmosis.

15 μm in diameter with spiny projections on their surface, and smooth-walled microconidia that measure 2 to 4 μm (Fig. 3). Confirmatory testing with chemiluminescent DNA probe or matrix-assisted laser desorption/ionization-time of flight mass spectrometry may confirm the identification of *H capsulatum* from culture.[52,53]

Histoplasma can also be cultured from blood using the BACTEC Mycolytic/F (Becton Dickinson, Sparks, MD) blood culture system or lysis-centrifugation system.[54] When blood cultures are incubated at 37°C, the organism converts to a yeast form. Microscopic examination reveals narrow, budding yeast that are ovoid shaped measuring 2 to 4 μm in diameter with thin cell walls. Because *Histoplasma* is frequently intracellular, it is rarely detected on routine Gram staining.

The sensitivity of cultures depends on the clinical manifestation, the specimen used for culture, the patient's net state of immunosuppression, and the overall burden of disease. Culture yield is higher in patients with immunocompromising conditions

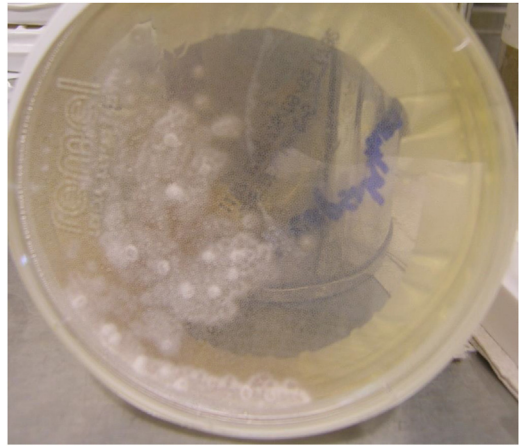

Fig. 2. Colonies on Sabouraud dextrose agar.

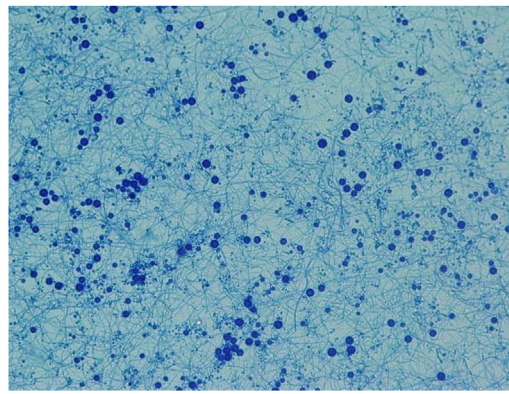

Fig. 3. Lactophenol cotton blue mount showing conidia with tuberculate projections.

and disseminated disease.[51,55] There are several significant limitations to culture. These include the lengthy incubation time required, limited sensitivity, and need for handling specimens in a biohazard safety level 3 laboratory due to the risk of pulmonary infections in laboratory workers handling mold cultures.[56]

Histopathology and Cytopathology

Histoplasma may also be identified on histopathology. Infected tissue may demonstrate caseating or noncaseating granulomatous inflammation. Identification is possible by visualizing narrow budding, ovoid yeast cells in tissue or fluid specimens. *H capsulatum* var. *capsulatum* yeast cells typically measure 2 to 4 μm in diameter whereas *H capsulatum* var. *duboisii* typically measure 6 to 12 μm in diameter. *Histoplasma*, predominantly an intracellular pathogen, can be seen within macrophages and monocytes, although it may be extracellular in some preparations. For accurate visualization of the yeast, tissue samples should be stained with Gomori methenamine silver (**Fig. 4**) or periodic acid-Schiff stains, as routine hemotoxylin and eosin stains may not effectively reveal the organisms.[42,51]

As with culture, sensitivity of histopathology and cytopathology varies with disease burden, extent of infection, and type of clinical specimen.[27,42] When combined with

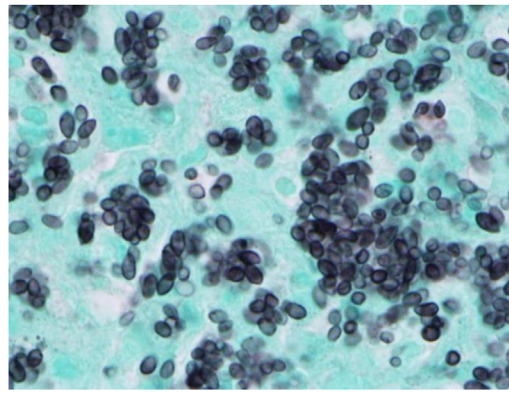

Fig. 4. Gomori methenamine silver stain.

additional diagnostics such as antigen testing as described in later discussions, the sensitivity is significantly improved.[57]

Antigen Testing

Histoplasma antigen testing detects *Histoplasma* galactomannan, the major polysaccharide antigen within the *Histoplasma* cell wall.[58] This test can be performed on blood, urine, and other body fluids. It exhibits the highest sensitivity in cases of disseminated disease.[59] Antigen testing demonstrates good sensitivity in acute pulmonary histoplasmosis (83.3% for urine antigen) and chronic pulmonary histoplasmosis (88% for urine antigen). It has lower sensitivity for the diagnosis of subacute pulmonary histoplasmosis (33% for urine antigen), and mediastinal granuloma or fibrosis,[60] although this can vary depending on the assay used.[61] When conducted on bronchoalveolar lavage specimens, the antigen test demonstrates a sensitivity of up to 93.5%.[57] In CNS disease, *Histoplasma* antigen sent from the cerebrospinal fluid (CSF) is 78% sensitive, and improves to 98% sensitive when combined with CSF antibody by enzyme immunoassay (EIA).[62] It is the recommended test for diagnosing histoplasmosis in persons living with HIV (PLWH).[63] Important limitations to the antigen test are its cross-reactivity with other fungi including *Blastomyces*, *Talaromyces* (formerly *Penicilliosis*) *marneffei*, *Paracoccidioides*, and occasionally *Coccidioides* and *Aspergillosis*, and its lack of availability in many areas outside of the United States.[57,60,61,64,65]

Antibody Testing

There are 3 main antibody tests used for the diagnosis of *Histoplasma* infection including immunodiffusion (ID), complement fixation (CF), and immunoglobulin G and immunoglobulin M EIA. ID detects antibodies against the H and M antigens. The M antibody is present in up to 75% to 80% of patients with histoplasmosis and remains positive for many years. The M antibody is unable to discriminate between active versus prior resolved infection. The H antigen is present in less than 25% of patients and only remains positive for approximately 6 months after infection, indicating acute infection.[43,45]

The CF test uses 2 antigens: a yeast antigen and a mycelial antigen (histoplasmin). A 4 fold increase in the CF antibody titer obtained 2 weeks apart is diagnostic for an acute infection. A single titer of 1:32 or greater is suggestive of infection but not diagnostic.[42] The EIA is more sensitive than either the CF or ID test.[66]

Antibodies take anywhere between 4 and 8 weeks to develop and are, therefore, negative early in infection.[9] Antibodies may also be negative in immunocompromised patients. The overall sensitivity of CF or ID is approximately 36% for solid organ transplant (SOT) recipients, and ranges from 38% to 63% in PLWH.[59,67,68] Antibody testing is best suited for diagnosis in immunocompetent patients with chronic histoplasmosis and patients with symptoms lasting longer than 4 weeks who are stable enough to await confirmatory CF testing.[42] Combining serology testing with antigen testing can improve the sensitivity for acute pulmonary histoplasmosis[66] and CNS histoplasmosis.[62]

False-positive results with CF testing may occur, with notable cross reactivity to other endemic fungi like *Blastomyces* and *Coccidioides*.[69] False-positive serologies have also been identified in cases of sarcoidosis, tuberculosis, and lymphoma, which may similarly present with mediastinal lymphadenopathy and pulmonary nodules.[42]

Next-Generation Sequencing Assays

Next-generation sequencing assays may have a role in difficult-to-diagnose infections including histoplasmosis. Fungal sequencing assays targeting 18S rRNA, 28S rRNA,

and 5.8S rRNA have demonstrated high sensitivity for the identification of fungi from tissue and fluid specimens,[70] though there is a paucity of data for *Histoplasma* specifically. Sequencing of microbial cell-free DNA (mcfDNA) from peripheral blood samples can also detect fungi. The sensitivity of the mcfDNA testing for *Histoplasma* has not been explored, but success has been described on a case-report level.[71]

Other Fungal Assays

The Fungitell assay (Associates of Cape Cod, Inc., USA) detects *(1→3)-ß-D-glucan* in the cell wall of many fungi including *H capsulatum.* This test is positive in up to 87% of patients with histoplasmosis[58] and can aid in the workup of suspected invasive fungal infection, though it is not specific for histoplasmosis. There are other fungal tests that have high rates of cross reactivity with *Histoplasma*, including the *Blastomyces* urine antigen test, which is positive in up to 79% of patients with *Histoplasma*, and serum aspergillus galactomannan, which is positive in up to 73% of patients with *Histoplasma*.[61,72]

MANAGEMENT

The mainstay of treatment of histoplasmosis is itraconazole for mild-to-moderate infection and liposomal amphotericin B induction therapy for severe disease or immunocompromised hosts (**Table 1**). Liposomal amphotericin B (LAmB) is preferred over deoxycholate amphotericin B given improved tolerability and safety as well as efficacy in immunocompromised patients.[73,74] Therapeutic drug monitoring with itraconazole levels is recommended owing to variable pharmacokinetics, drug–drug interactions, and absorption.[73] It is also recommended that *Histoplasma* antigen levels are monitored every 3 to 4 months during treatment. An antigen increase of 4 or greater is concerning for relapse.[30]

Acute Pulmonary Histoplasmosis

Immunocompetent patients infected with *Histoplasma* who present with mild or moderate symptoms often have self-limited courses and typically do not require treatment. However, if symptoms persist for 4 or more weeks, guidelines recommend treatment with itraconazole for 6 to 12 weeks. Severe disease requires treatment with (LAmB) dosed at 3 to 5 mg/kg daily for 1 to 2 weeks followed by itraconazole 200 mg twice daily for 12 weeks. Systemic corticosteroids should be considered in cases of severe acute pulmonary histoplasmosis.[30]

Chronic Pulmonary Histoplasmosis

Chronic histoplasmosis is typically treated with 12 months of itraconazole, though because disease relapse occurs in approximately 15% of cases, some clinicians elect to prolong therapy for up to 2 years to theoretically offset the risk of relapse.[30] Because tobacco smoking and chronic obstructive pulmonary disease are notable risk factors for the development of cavitary disease, tobacco cessation plays a critical role in treatment.[29]

Mediastinal Lymphadenitis, Granuloma, or Fibrosis

In cases of mild mediastinal lymphadenitis in which symptoms have been present for under 4 weeks, treatment is not recommended. Patients with moderate-to-severe symptoms or patients with symptoms lasting 4 weeks or greater may benefit from treatment with itraconazole for 12 weeks with the option of adding prednisone to reduce inflammation. Fibrosing mediastinitis does not require treatment with antifungals, and mediastinal granuloma typically only necessitates treatment if symptoms are

Table 1
Management[3,30]

Syndrome	Management
Acute pulmonary histoplasmosis (mild-to-moderate symptoms)	Symptoms <4 wk: No treatment Symptoms ≥4 wk: Itraconazole once to twice daily × 6–12 wk
Acute pulmonary histoplasmosis (moderately severe or severe)	LAmB 3–5 mg/kg daily × 1–2 wk followed by itraconazole 200 mg twice daily × 12 wk[a]
Chronic pulmonary histoplasmosis	Itraconazole 200 mg once-twice daily for ≥12 mo
Mediastinal lymphadenitis	Mild symptoms <4 wk: no treatment indicated Symptoms ≥4 wk: itraconazole 200 mg once or twice daily for 12 wk + prednisone
Mediastinal granuloma	Asymptomatic: no treatment Symptomatic: itraconazole 200 mg once or twice daily for 6–12 wk
Mediastinal fibrosis	Antifungals not indicated. Stenting obstructive vessels may be indicated
Pulmonary nodule	Antifungals not indicated
Disseminated histoplasmosis (mild to moderate)	Itraconazole 200 mg twice daily ≥12 mo
Disseminated histoplasmosis (moderately severe to severe)	LAmB 3 mg/kg/d × 1–2 wk followed by itraconazole 200 mg twice daily ≥12 mo
CNS histoplasmosis	LAmB 5 mg/kg daily × 4–6 wk followed by itraconazole 200 mg 2–3 times daily for ≥12 mo

Abbreviation: LAMB, liposomal amphotericin B.
[a] Can consider addition of methylprednisolone 0.5 to 1 mg/kg daily IV × 1–2 wk.

present. In this scenario, treatment consists of 6 to 12 weeks of itraconazole with possible surgery relieve any obstruction that may be present.[30]

Disseminated Histoplasmosis

Patients with severe disseminated histoplasmosis are treated with LAmB induction therapy for 2 weeks followed by consolidation with itraconazole for a minimum of 12 months. Patients with mild-to-moderate disseminated histoplasmosis may not require induction LAmB therapy and instead may be treated with itraconazole monotherapy for at least 12 months.[30]

Central Nervous System Histoplasmosis

Patients with CNS histoplasmosis require a minimum of 4 to 6 weeks of LAmB induction followed by consolidation and maintenance with itraconazole for at least 12 months. CSF analysis should be repeated at the completion of therapy to ensure full resolution of CSF abnormalities, including a CSF *Histoplasma* antigen.[30]

Treatment of Histoplasmosis in Special Populations

Persons living with human immunodeficiency virus

PLWH who have moderately severe or severe disseminated histoplasmosis are recommended to receive LAmB induction for 2 weeks followed by itraconazole for at least 12 weeks.[34,75] A recent prospective multicenter randomized phase II noninferiority

open label trial found that induction therapy with a single dose of 10 mg/kg of LAmB was noninferior and had lower rates of nephrotoxicity at day 14 relative to a standard 2 week induction of 3 mg/kg of LAmB daily in PLWH with disseminated histoplasmosis.[76] Both arms were treated with maintenance itraconazole. A confirmatory phase III trial is planned.

Immune reconstitution syndrome is uncommon in PLWH during treatment with disseminated histoplasmosis and initiation of antiretroviral therapy.[77] For that reason, guidelines recommend prompt initiation of ART for PLWH with disseminated histoplasmosis when CNS involvement is not suspected or identified.[75]

Solid organ transplant recipients

SOT recipients with moderately severe to severe histoplasmosis should receive 1 to 2 weeks of LAmB followed by at least 12 months of itraconazole, while those with mild-to-moderate disease do not require LAmB induction.[78] SOT recipients requiring high-level immunosuppression, those with CNS involvement, or relapsed disease may require indefinite therapy.[73] As with immunocompetent patients, serum or urine antigen monitoring is recommended. On occasion, antigenemia and/or antigenuria may not fully clear in SOT recipients. Provided that symptoms have fully resolved at the completion of therapy, data indicate that persistent antigenemia or antigenuria is not associated with the risk of relapse in SOT.[79,80]

A careful reduction of immunosuppression in SOT recipients with histoplasmosis is recommended by the current American Society of Transplantation guidelines.[78] A large multicenter study of SOT recipients with histoplasmosis identified mycophenolate use to be a risk factor for severe disease, and failure to reduce calcineurin inhibitors to be associated with relapse.[59] As with PLWH, the risk of immune reconstitution syndrome during histoplasmosis is uncommon and should not prevent lowering of immunosuppression in non-CNS disease.[73] Unfortunately, even with treatment, mortality remains high in SOT recipients with histoplasmosis.[40]

Children with histoplasmosis

Children should receive similar regimens for treatment as for adults but note 2 major differences. First, amphotericin B deoxycholate is generally well tolerated in children and preferred over LAMB for pediatric patients. Second, children with disseminated histoplasmosis are recommended to receive amphotericin B deoxycholate for 4 to 6 weeks as opposed to the 2 weeks in adults.[30]

Alternative Antifungal Agents

Tri-azoles

Voriconazole and newer generation azoles including posaconazole and isavuconazole have been explored as treatment of *Histoplasma* in small studies and limited case series.[81–85] Voriconazole is appealing for the treatment of CNS histoplasmosis given its enhanced CNS penetration relative to itraconazole; however, a single-center retrospective study found significantly higher mortality in patients receiving voriconazole relative to itraconazole for histoplasmosis.[82] A recent systematic review of patients with CNS histoplasmosis reported a nonstatistically significant mortality difference among patients treated with voriconazole versus itraconazole (12% vs 20%).[86] Isavuconazole was studied in the VITAL study, an open-label nonrandomized phase 3 trial evaluating the efficacy and safety of isavuconazole for endemic mycoses. Isavuconazole was well tolerated and effective for the treatment of 7 patients with histoplasmosis, and it demonstrated favorable minimum inhibitory concentrations (MICs) to histoplasmosis.[87] Additionally, isavuconazole may have clinical activity for CNS infections though additional data are needed.[85] Posaconazole has also been reported as

effective salvage therapy for histoplasmosis[88] and has demonstrated greater in vitro activity against histoplasmosis relative to isavuconazole.[89] Notable limitations of posaconazole include is its low CNS penetration and, as with the other tri-azoles mentioned, limited data. Fluconazole is not recommended for use given its limited activity against *Histoplasma*.[90]

Super-bioavailability itraconazole

An open label randomized controlled trial recently evaluated a novel antifungal super-bioavailability itraconazole (SUBA-itra) compared to conventional itraconazole in patients with endemic mycoses, including *Histoplasma*. SUBA-itra given at one-third the dose of conventional itraconazole was well tolerated, associated with fewer adverse events, achieved similar levels and was noninferior to conventional itraconazole.[91]

Prophylaxis

Prophylaxis for *Histoplasma* with itraconazole is recommended in patients PLWH with CD4 count less than 150 cells/m^3 in areas of hyperendemicity.[30] For patients undergoing pretransplant evaluation, current data do not support screening or antifungal prophylaxis of pretransplant candidates for *Histoplasma*, even in for those in endemic areas[3,58,92]; however, candidates with *Histoplasma* infection in the preceding 2 years are thought to potentially benefit from antifungal prophylaxis at the time of transplant,[73] though data supporting this practice are limited.

SUMMARY

With evolving geographic epidemiology and an expanding immunocompromised host population, histoplasmosis remains an important yet underdiagnosed infection. Effective management hinges on timely recognition of its clinical manifestations, rapid and accurate diagnosis, and implementation of appropriate antifungal therapy. Continued research and education are necessary to ensure that clinicians remain vigilant against this endemic mycosis.

CLINICS CARE POINTS

- Hematogenous dissemination of histoplasmosis is most frequently seen in immunocompromised hosts with deficits in cell-mediated immunity.
- While culture remains the gold standard for diagnosis, *Histoplasma* antigen testing offers greater sensitivity, faster results and is noninvasive.
- Itraconazole is the standard treatment for mild-to-moderate pulmonary histoplasmosis; liposomal amphotericin B is used for induction therapy in moderately severe and severe disease.
- Serum itraconazole levels and *Histoplasma* antigen testing should be monitored during treatment.

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DISCLOSURE

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