2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on Histoplasmosis: Treatment of Asymptomatic *Histoplasma* Pulmonary Nodules (Histoplasmomas) and Mild or Moderate Acute Pulmonary Histoplasmosis in Adults, Children, and Pregnant People

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ABSTRACT. As the first part of an update to the clinical practice guideline on the management of histoplasmosis in adults, children, and pregnant people, developed by the Infectious Diseases Society of America, we present four updated recommendations. These recommendations span treatment of asymptomatic *Histoplasma* pulmonary nodules (histoplasmomas), mild acute pulmonary histoplasmosis, and moderate acute pulmonary histoplasmosis. The panel's recommendations are based upon evidence derived from systematic literature reviews and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach (Supplementary Figure 1).

Key words. histoplasmosis; histoplasmoma; asymptomatic pulmonary nodules; itraconazole; treatment; guideline

BACKGROUND

Histoplasmosis is caused by infection with the thermally dimorphic fungus *Histoplasma capsulatum.* Histoplasmosis occurs through inhalation of *H. capsulatum* which has a worldwide distribution but is hyperendemic in specific areas such as the midwestern United States. Histoplasmosis syndromes include pulmonary and disseminated disease, the spectrum of which varies from asymptomatic to severe disease depending on inoculum and cell-mediated immune function. Asymptomatic pulmonary histoplasmosis, and mild, moderate, and severe acute pulmonary histoplasmosis are defined in Table 1.

Table 1. Severity of Acute Pulmonary Histoplasmosis

These definitions are offered as guidance but are not intended to be prescriptive. Clinical assessment should drive care decisions.

Severity	**Definition**
Asymptomatic pulmonary histoplasmosis	Asymptomatic but with evidence of recent onset or active infection (based on review of recent, prior imaging indicating new or progressive radiographic abnormality, detection of urine or serum *Histoplasma* antigen, detection of *Histoplasma* antibodies by complement fixation with high titer (≥1:32) or rising titer on sequential testing, or presence of H-band by immunodiffusion)
Mild acute pulmonary histoplasmosis	Mild symptoms (e.g., cough, fever, dyspnea, chest discomfort) that do not interfere with normal activities
Moderate acute pulmonary histoplasmosis	Symptoms (e.g., cough, fever, dyspnea, chest discomfort) significant enough to interfere with normal activities; may require low-flow oxygen supplementation; may require hospitalization
Severe acute pulmonary histoplasmosis	Respiratory failure requiring substantial supplemental oxygen; significant weight loss and/or malaise; requires hospitalization, may require intensive care

Guideline Scope

The scope of this guideline update includes treatment of asymptomatic *Histoplasma* pulmonary nodules (histoplasmomas) and mild or moderate acute pulmonary histoplasmosis. Available evidence for children,

adults, and pregnant people was reviewed. For the purposes of this guideline, newborns and patients with African histoplasmosis or possible ocular histoplasmosis syndrome were excluded.

This guideline is intended for use by healthcare professionals who care for patients with histoplasmosis, including but not limited to primary care clinicians, infectious diseases physicians, pulmonologists, specialists prescribing biologic response modifiers and other immunosuppressive agents, and cardiothoracic surgeons.

Publication Scope

The last iteration of the guideline was published in 2007 [1]. The goals of this guideline update were to incorporate contemporary evidence and apply the GRADE approach for the evidence appraisal process. Two manuscripts and their corresponding supplementary materials comprise this guideline update [2,3]. Additional sections of this guideline update are planned and include: alternative treatment options for patients who fail to improve, absorb, or are unable to tolerate first-line therapy; antifungal treatment for patients with severe/disseminated acute pulmonary histoplasmosis and chronic cavitary pulmonary histoplasmosis; as well as whether and in what circumstances to add steroids and/or NSAIDs to an antifungal treatment regimen.

Several existing guidelines from other organizations related to this topic were reviewed during the guideline development process [4-8].

METHODS

The panel included clinicians with expertise in infectious diseases, pediatric infectious diseases, pulmonology, maternal-fetal medicine, and pharmacology. Selected reviewers included clinicians with expertise in infectious diseases and pediatric infectious diseases. Relevant recommendations have been reviewed and endorsed by the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists.

The panel's recommendations are based on evidence derived from systematic literature reviews and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE approach [9,10]. Strong recommendations, indicated by "the panel recommends," are made when the recommended course of action would apply to most people with few exceptions. Conditional recommendations, indicated by "the panel suggests," are made when the suggested course of action would apply to the majority of people with many exceptions and shared decision making is important. Details of the systematic review and guideline development processes are available in the supplementary materials for each manuscript.

RECOMMENDATIONS AND REMARKS

In patients with asymptomatic, previously untreated *Histoplasma* pulmonary nodules (histoplasmomas), for which patients should antifungal treatment be initiated?

Recommendation: In adults and children with asymptomatic non-calcified pulmonary nodules related to histoplasmosis with no evidence of other active sites, or asymptomatic patients with known untreated prior infection, the panel suggests against routinely providing treatment for histoplasmosis to prevent reactivation *(conditional recommendation, very low certainty of evidence)*.

Remark(s):

- In patients with elevated risk for disseminated/severe histoplasmosis (especially those with immunocompromising conditions that confer high and moderate risk according to Table 2), closely monitor for clinical/radiological change or consider treatment.
- Patients with only calcified pulmonary nodules should not be treated.
- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits vs. harms of treatment, ideally in consultation with a maternal fetal medicine specialist and an infectious diseases specialist, as these cases are rare, complex, and highly variable. If treatment is necessary, azoles should be avoided in the first trimester when possible and liposomal amphotericin B used instead.

In patients presenting with mild or moderate acute pulmonary histoplasmosis, should antifungal treatment be given for resolution of symptoms?

Recommendation: In immunocompetent adults and children presenting with mild acute pulmonary histoplasmosis, the panel suggests against routinely providing antifungal treatment *(conditional recommendation, very low certainty of evidence)*.

Remark(s):

- Treatment may be considered in immunocompetent patients with mild acute pulmonary histoplasmosis and prolonged duration of illness, progression of pulmonary infiltrates, or enlarging hilar or mediastinal adenopathy. In a large outbreak study, >75% of persons affected were ill for 1 week or less, and all recovered completely within 2 months without treatment [29].

Recommendation: In immunocompetent adults and children presenting with moderate acute pulmonary histoplasmosis, the panel suggests either antifungal treatment or no antifungal treatment, considering the severity and duration of signs/symptoms, as well as potential harms of antifungal treatment *(conditional recommendation, very low certainty of evidence)*.

Remark(s):

- Moderate acute pulmonary histoplasmosis includes a heterogeneous group of patients. Prolonged duration of illness, worsening symptoms, progression of pulmonary infiltrates, enlarging hilar or mediastinal adenopathy, and more severe signs or symptoms favor treatment.
- Consider drug-drug interactions and other potential harms vs. benefits of antifungal treatment when deciding whether to treat. Potential financial burden should be discussed with the patient as well.
- The goals of treatment are to decrease the duration of illness and mitigate risk of dissemination, though treatment effectiveness in this patient population is unknown.

- When treatment is indicated, itraconazole is preferred [1].
- Dosing for original itraconazole capsules or oral solution: (adults: 200 mg 3 times daily for 3 days and then 200 mg twice daily for 6-12 weeks; children: 5 mg/kg/dose [up to a max of 200 mg/dose] three times daily for 3 days and then 5 mg/kg/dose twice daily [not to exceed 400 mg daily] for 6-12 weeks). Super-Bioavailable (SUBA) itraconazole (only available as capsules and currently approved for use in adults): 130 mg 3 times daily for 3 days, then 130 mg twice daily for 6-12 weeks. In consultation with a pharmacist, similar dosing for SUBA itraconazole based on the child's weight may be considered in children old enough to swallow capsules (as off-label use). For additional information on the various itraconazole formulations, see Implementation Considerations section.
- Therapeutic drug monitoring (TDM) should be performed for patients receiving itraconazole [4-7]. In recent studies, ~20% of patients required dose adjustments due to sub- or super-therapeutic levels of itraconazole, and ~28% of patients experienced side effects [30,31]. A goal trough concentration of itraconazole component >1 mg/L and <3-4 mg/L (as measured by chromatographic assay) is associated with efficacy and a lower risk of toxicity [4-7,30,32-34]. Due to the long half-life of itraconazole, non-trough/random levels of itraconazole can also be used to monitor serum concentrations. Hydroxy-itraconazole is an active metabolite; however, a cutoff for combined hydroxy-itraconazole and itraconazole levels has not been established [33,35,36]. Patients with a combined hydroxy-itraconazole and itraconazole level >2 mg/L may respond similarly to patients with itraconazole levels >1 mg/L [37].
- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits vs. harms of treatment, ideally in consultation with a maternal fetal medicine specialist and an infectious diseases specialist, as these cases are rare, complex, and highly variable. If treatment is necessary, azoles should be avoided in the first trimester when possible and liposomal amphotericin B used instead.

Recommendation: In immunocompromised adults and children presenting with mild or moderate acute pulmonary histoplasmosis who are at moderate to high risk of progression to disseminated disease, the panel suggests antifungal treatment *(conditional recommendation, very low certainty of evidence)*.

Remark(s):

- Patients with asymptomatic or mild acute pulmonary histoplasmosis and a lesser degree of immunocompromise (see Table 2) may not warrant treatment.
- When treatment is indicated, itraconazole is preferred [1].
- Dosing for original itraconazole capsules or oral solution: (adults: 200 mg 3 times daily for 3 days and then 200 mg twice daily for 6-12 weeks; children: 5 mg/kg/dose [up to a max of 200 mg/dose] three times daily for 3 days and then 5 mg/kg/dose twice daily [not to exceed 400 mg daily] for 6-12 weeks). Super-Bioavailable (SUBA) itraconazole (only available as capsules and currently approved for use in adults): 130 mg 3 times daily for 3 days, then 130 mg twice daily for 6-12 weeks. In consultation with a pharmacist, similar dosing for SUBA itraconazole based on the child's weight may be considered in children old enough to swallow capsules (as off-label use). For additional information on the various itraconazole formulations, see Implementation Considerations section.
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- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits vs. harms of treatment, ideally in consultation with a maternal fetal medicine specialist and an infectious diseases specialist, as these cases are rare, complex, and highly variable. If treatment is necessary, azoles should be avoided in the first trimester when possible and liposomal amphotericin B used instead.

Table 2. Categories of Immunocompromise and Risk for Disseminated/Severe Histoplasmosis

Categories of immunocompromise represent a continuum rather than distinct categories. Conditions are categorized here as a guide; given limited evidence, this table is **not** exhaustive or exact.

High	Moderate	Low*
Receiving corticosteroids: [11] ≥2 mg/kg/day of prednisone (or equivalent) for persons ≤10 kg or ≥20 mg/day of prednisone (or equivalent) for persons >10 kg for at least 2 weeks	Receiving corticosteroids: [11] 0.5-2 mg/kg/day of prednisone (or equivalent) for persons <10 kg or 5-20 mg/day of prednisone (or equivalent) for persons >10 kg for at least 4 weeks	Receiving corticosteroids: [11] <0.5 mg/kg/day of prednisone (or equivalent) for persons <10 kg or ≤5 mg/day of prednisone (or equivalent) for persons >10 kg for at least 4 weeks
Primary cellular immunodeficiency (e.g., SCID, autosomal dominant hyperIgE syndrome [AD HIES], interferon-gamma receptor/IL-12 pathway defects)	Primary immunodeficiency (e.g., common variable immunodeficiency, NF-kappaB pathway defects [NEMO], chronic mucocutaneous candidiasis, X-linked hyper IgM syndrome, autosomal recessive HIES)	
Advanced or untreated HIV/AIDS (CD4 <200 cells/mm^3)† [8]	HIV (CD4 200-300 cells/mm^3) [8,12-21]	HIV (CD4 ≥300 cells/mm^3); VL undetectable [8]
Hematopoietic stem cell transplant within 100 days or receiving immunosuppressive therapy for graft vs. host disease	Hematopoietic stem cell transplant >100 days prior and no evidence of graft vs. host disease	
	Hematologic malignancy	
Chimeric antigen receptor (CAR) T-cell therapy within 90 days [22]	Chimeric antigen receptor (CAR) T-cell therapy >90 days and resolved cytopenias [22]	
Solid organ transplant and treatment of rejection‡	Solid organ transplant recipient on maintenance immunosuppressive regimen‡	
Autoimmune and rheumatic diseases requiring treatment with biologic agents§, especially		Autoimmune and rheumatic diseases not requiring treatment

those that interfere with T cell function and granuloma formation [18,23-28]		
		General medical frailty, including but not limited to: Liver, kidney, lung disease, diabetes, malnutrition

*The following conditions confer no known increased risk: sickle cell disease and other asplenia syndromes; antibody, complement, or neutrophil deficiencies.

†Severe immunocompromise in children ≤5 years of age is defined as CD4+T lymphocyte [CD4+] percentage <15%, and in individuals ≥6 years, CD4+percentage <15% and CD4+ >200 lymphocytes/mm^3 [11].

‡Carefully consider drug-drug interactions (e.g., tacrolimus for Graft-versus-host disease [GVHD] prophylaxis).

§There are a variety of biologic agents with varying levels of immunosuppression. Serious infections have happened in patients receiving biologic response modifiers, including tuberculosis and disseminated infections caused by viruses, fungi, or bacteria. Frequently reported biologics associated with disseminated/severe histoplasmosis include: Tumor necrosis factor-alpha inhibitors (TNF-alpha inhibitors, e.g., infliximab, etanercept, adalimumab); IL12/IL23 blockade (ustekinumab, risankizumab, guselkumab).

RESEARCH NEEDS

Additional studies are needed on the incidence and timing of reactivation with and without antifungal treatment in various populations, especially in pregnant persons and children. Studies evaluating outcomes of treatment versus no treatment in patients with asymptomatic pulmonary nodules, mild acute pulmonary histoplasmosis, and moderate acute pulmonary histoplasmosis would also be helpful.

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