Recommendation: Treatment of Asymptomatic Histoplasma Pulmonary Nodules (Histoplasmomas) and Mild or Moderate Acute Pulmonary Histoplasmosis in Adults, Children, and Pregnant People

Background

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

Recommendation: Treatment of Asymptomatic *Histoplasma* Pulmonary Nodules (Histoplasmomas)

Table 1. 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: [1] ≥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: [1] 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: [1] <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)† [2]	HIV (CD4 200-300 cells/mm^3) [3-12]	HIV (CD4 ≥300 cells/mm^3); VL undetectable [2]
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 [13]	Chimeric antigen receptor (CAR) T-cell therapy >90 days and resolved cytopenias [13]	
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 those that interfere with T cell function and granuloma formation [9,14-19]		Autoimmune and rheumatic diseases not requiring treatment

		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 [1].

‡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).

Results

Twenty-one studies (including case series and case reports) that addressed efficacy of antifungal therapy of asymptomatic pulmonary nodules in adults and children were identified [3-12,15-25]. Included studies reported on the outcomes of progression to disseminated disease or significant pulmonary disease, reactivation of latent disease, and possible predisposing factors. We did not find any studies addressing this question in pregnant people.

Outcome	No. studies; No. patients	Results	Certainty of evidence
Progression to disseminated disease/significant pulmonary disease	2 observational studies [22,24]; 64 patients	In Demkowicz 2021, 39/62 patients with pulmonary granulomas did not receive antifungal treatment and did not have reactivation within 12 months. In Hess 2017, 2 patients with pulmonary nodules who were treated with itraconazole showed improvement on follow-up testing.	⊕◯◯◯ Very low
Reactivation of latent disease	20 studies [3-12,15-19,20,21,23-25]; at least 276 patients	Provided evidence of possible or probable latent reactivation of infection.	⊕◯◯◯ Very low
Possible predisposing factors	19 studies [3-12, 15-21,23,25]; at least 276 patients	19 studies noted various immunocompromising conditions are possible predisposing factors	⊕◯◯◯ Very low

		for reactivation, including HIV infection and immunomodulatory agents. Add'l case reports also named malignancy, heart transplant, renal transplant, and excessive alcohol use as possible predisposing factors.	

Recommendation: Treatment of Mild or Moderate Acute Pulmonary Histoplasmosis

Table 1. 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: [15] ≥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: [15] 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: [15] <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)† [16]	HIV (CD4 200-300 cells/mm^3) [16-26]	HIV (CD4 ³300 cells/mm^3); VL undetectable [16]
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 [27]	Chimeric antigen receptor (CAR) T-cell therapy >90 days and resolved cytopenias [27]	
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 those that interfere with T cell function and granuloma formation [23,28-33]		Autoimmune and rheumatic diseases not requiring treatment

		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 [15].

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Results

Limited evidence was identified for the outcomes of mortality (9 studies [1,34-41]), symptom resolution/radiographic regression (9 studies [1,34-37,39-42]), and toxicity (1 study [35]).

Outcome	No. studies; No. patients	Results	Certainty of evidence
Resolution of symptoms	9 observational studies [1,34-37,39-4,2] 1606 patients	In one outbreak study, 353 people were symptomatic but received no treatment, and >75% were ill for 1 week or less, all recovering within 2 months. In another outbreak study, only 13/682 participants with serologic evidence of infection received an antifungal. In the largest outbreak, of over 100,000 presumed infected, only 43 received treatment. Several studies reported treatment of individuals with immunocompromising conditions.	⊕◯◯◯ Very low
Toxicity	1 observational study [35]; 37 patients	37 patients were treated with itraconazole 200-400 mg/day for a median 9 months, and itraconazole was stopped in 1/37 patients due to toxicity.	⊕◯◯◯ Very low

Mortality	9 observational studies [1, 34-41]; 1201 patients	No deaths attributable to histoplasmosis in any study regardless of whether patients were treated.	⊕◯◯◯ Very low