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

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ABSTRACT. This paper is part of a larger clinical practice guideline on the management of histoplasmosis in adults, children, and pregnant people, developed by the Infectious Diseases Society of America. In this paper, the panel provides a recommendation for treatment of asymptomatic pulmonary nodules. The panel's recommendation is based upon evidence derived from systematic literature reviews and adheres 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.

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

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 1), 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.

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).

INTRODUCTION

This paper is part of a clinical practice guideline update on the treatment of pulmonary histoplasmosis in adults, children, and pregnant people, developed by the Infectious Diseases Society of America [20,21]. This recommendation replaces the previous recommendation on treatment of pulmonary nodules (histoplasmomas) [22]. The primary audience for this recommendation is clinicians seeing patients with asymptomatic *Histoplasma* pulmonary nodules, including primary care clinicians, infectious diseases physicians, pulmonologists, specialists prescribing biologic response modifiers and other immunosuppressive agents, and cardiothoracic surgeons.

Asymptomatic pulmonary histoplasmosis refers to 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). The presence of calcifications in lymph nodes or pulmonary nodules almost always indicates residual healed disease.

METHODS

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) [23]. The recommendation has been endorsed by the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists.

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.

A comprehensive literature search (through January 2024) was conducted as part of a systematic review. Key eligibility criteria at both the topic and clinical question levels guided the search and selection of studies for inclusion (Supplementary Figure 2). Eligibility criteria were expanded to include case series and case reports due to a lack of evidence. Included studies were summarized narratively and critically appraised according to the GRADE approach. An assessment of benefits and harms of care options informed the recommendations [23,24]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

SUMMARY OF EVIDENCE

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 (Supplementary Table 1) [3-12,14-19,25-28]. Included studies reported on the outcomes of progression to disseminated disease or significant pulmonary disease, reactivation of latent disease, and possible predisposing factors (Supplementary Table 2). We did not find any studies addressing this question in pregnant people.

In a single-center study, Demkowicz, et al. retrospectively evaluated short-term (up to 12 months) outcomes for 62 patients with pulmonary granulomas diagnosed as histoplasmomas presenting in a *Histoplasma* endemic area [27]. Most (39/62) of these patients did not receive antifungal therapy and did not have reactivation identified at that institution within 12 months after diagnosis. This suggests that for many patients with incidentally diagnosed histoplasmomas, antifungal therapy is not required for prevention of short-term reactivation. However, there are important limitations to this study that leave areas of uncertainty: 1. Highly immunocompromised patients typically received antifungal therapy with the goal of preventing reactivation, so it is unclear whether these patients could safely be managed without therapy; 2. Long-term clinical follow-up was not performed, so patients who developed reactivation disease more than 1 year after diagnosis, with or without being immunocompromised, would

not have been identified; 3. The investigators only identified illnesses diagnosed at that institution, so reactivation presenting at another hospital would have been missed.

Nineteen studies provided evidence of possible or probable reactivation of latent disease in at least 275 patients [3-12,15-19,25,26,28,29]. In these studies, similar limitations as noted for the Demkowicz study above apply.

Several studies noted various immunocompromising conditions as possible predisposing factors for reactivation [Table 2].

Table 2. Evidence for reactivation of latent histoplasmosis in immunocompromising conditions

Study	Study type	Exposure	No. with likely reactivation	Age (years)	Reactivation of latent infection [30]	Comments
HIV infection						
Antinori 2006	Case series	HIV	4	Adult	Probable	Presentation in lower incidence area (Milan, Italy); median 24 months since last travel to higher incidence area (range 1-144 months)
Anderson 2010	Case series	HIV	27	27-55	Possible	Presentation in lower incidence area (Atlanta, USA); Insufficient data for recent travel to higher incidence area to determine whether likely reactivation or acute/subacute presentation
Ashbee 2008*	Survey-based case series	HIV	43	Mostly adults	Probable	Presentation in lower incidence area (Europe); no recent travel (25% >5 years since last likely exposure)
Bourgeois 2011**	Case series	HIV	4	42-70	Probable	Presentation in lower incidence area (Montpellier and Nîmes, France); no recent travel (>4 years) in 4/7 cases
Buitrago 2011*	Case series	HIV	29	22-54	Possible	Presentation in lower incidence area (Spain); insufficient data for recent travel to higher incidence area to determine whether likely reactivation or acute/subacute presentation
Choi 2019	Case report	HIV	1	50	Probable	Presentation in lower incidence area (California, USA); no travel to higher incidence area in >30 years
Gandhi 2015*	Case series	HIV	1	27-77	Possible	Presentation in lower incidence area (Pittsburgh, PA and New York, New York, USA); recent travel not specified

Study	Study type	Exposure	No. with likely reactivation	Age (years)	Reactivation of latent infection [30]	Comments
Peigne 2011**	Case series	HIV	104	~39 with SD~9	Probable	Presentation in lower incidence area (France); no recent travel in >59% of cases
Martin-Iguacel 2014	Case report	HIV	1	30	Probable	Presentation in lower incidence area (Copenhagen, Denmark); no recent travel
Norman 2009	Case series	HIV	5	Adult	Probable	Presentation in lower incidence area (Madrid, Spain); 3/5 no travel within 5 years
Immunomodulatory agents						
Ashbee 2008	Survey-based case series	Corticosteroids	7	Mostly adults	Probable	Presentation in lower incidence area (Europe); no recent travel (25% >5 years since last likely exposure)
Gandhi 2015	Case series	Corticosteroids/ Azathioprine	1	27-77	Probable	Presentation in lower incidence area (Pittsburgh, PA and New York, New York, USA); recent travel not specified
Hage 2010	Case series	TNF blockers and other immunosuppressive agents	9	8-66	Probable	Presentation in IN, with 9 of 19 cases having documented exposure to *Histoplasma capsulatum*
Jain 2006	Case report	Infliximab	1	40	Probable	Presentation in lower incidence area (Fresno, CA, USA); no recent travel (5 years)
Lucey 2018	Case report	Corticosteroids/ Azathioprine	1	62	Possible	Presentation in lower incidence area (London, United Kingdom); most recent travel to higher incidence area 5 months prior
Prakash 2019	Case report	Ruxolitinib	1	51	Possible	Presentation in lower incidence area (San Diego, CA, USA); insufficient data for recent travel to higher incidence area to determine whether likely reactivation or acute/subacute presentation
Sani 2018	Case report	Infliximab (plus azathioprine)	1	44 years	Probable	Presentation in lower incidence area (Tucson, AZ, USA); no recent travel (> 1 year)
Wallis 2004	Case series from AERS database	TNF antagonists (Etanercept and Infliximab) plus other immunomodulatory agents	42 (39 infliximab; 3 etanercept)	Not provided	Possible	Insufficient data to determine whether acute/subacute infection or reactivation
Other immunocompromising conditions						
Alamri 2021	Case report	Heart transplant	1	68	Possible	Presentation in lower incidence area (Riyadh, Saudi Arabia); no recent travel (> 2 years) but

Study	Study type	Exposure	No. with likely reactivation	Age (years)	Reactivation of latent infection [30]	Comments
						heart donor from higher incidence area
Ashbee 2008	Survey-based case series	Malignancy	2	Mostly adults	Probable	Presentation in lower incidence area (Europe); no recent travel (25% >5 years since last likely exposure)
Buitrago 2011	Case series	Malignancy	1	22-54	Possible	Presentation in lower incidence area (Spain); insufficient data for recent travel to higher incidence area to determine whether likely reactivation or acute/subacute presentation
Carmans 2020	Case report	Renal transplantation	1	63	Probable	Presentation in lower incidence area (Belgium); no recent travel (> 20 years)
Garcia-Marron 2008	Case report	Excessive alcohol use	1	46	Probable	Presentation in lower incidence area (Asturias, Spain); no recent travel (>10 years)

*Some studies provided data for multiple categories of immunocompromise; participant age range was typically not provided for each category, so the overall range is provided.
**Two studies report data from overlapping regions and time periods, so some participants might appear in both studies.

The overall certainty of evidence for all outcomes assessed is very low due to risk of bias concerns (Supplementary Table 3), as well as imprecision due to small sample sizes and limited number of events [30-32]. Refer to the Supplementary Material for exact judgments affecting certainty of evidence for each outcome.

RATIONALE FOR RECOMMENDATION

Most patients who have asymptomatic pulmonary nodules (histoplasmomas) do not require therapy. In many cases, histoplasmomas represent past or dormant infection. However, there is the possibility of reactivation of infection, worsening pulmonary disease or disseminated disease. Based on published reports, it is unclear which underlying host conditions or other factors may lead to reactivation (Table 1). This literature review supports that many reported patients with likely reactivation were immunocompromised. Moreover, the time to reactivation varies greatly and may occur decades after initial infection. In some patients, the risk of reactivation may be higher and treatment to prevent reactivation should be discussed thoroughly with the patient or caregivers. Although itraconazole is

typically safe, it is important to consider potential adverse effects, drug-drug interactions or other associated issues (costs) related to prolonged therapy. The panel agrees that the overall balance of benefits and harms favors avoiding routine treatment of asymptomatic histoplasmomas.

IMPLEMENTATION CONSIDERATIONS

We did not identify any specific data on treatment of asymptomatic histoplasmomas in pregnant or pediatric patients, but it would be reasonable to apply these recommendations to these populations. Due to the potential prolonged time in which reactivation of histoplasmomas may occur, the potential effects of months or years of antifungal therapy, including toxicities, drug-drug interactions and costs must be thoroughly considered.

RESEARCH NEEDS

Additional studies are needed on the incidence and timing of reactivation with and without antifungal treatment (including itraconazole and newer azoles) in various populations, especially in pregnant persons and children. To date, there are no studies available that compare treatment versus no treatment in patients with asymptomatic pulmonary nodules (histoplasmomas). The most relevant study, by Demkowicz and colleagues, evaluated 12-month outcomes for 62 patients with pulmonary granulomas diagnosed as histoplasmomas presenting in a *Histoplasma* endemic area [27]. Most of these patients did not receive antifungal therapy and did not develop reactivation disease within 12 months after diagnosis. Highly immunocompromised patients typically received antifungal therapy with the goal of preventing reactivation, so it is unclear whether these patients could safely be managed without therapy.

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Sandra Arnold and Andrej Spec are chair and vice chair, respectively, of the expert panel. John Baddley and Joshua Wolf served as clinical leads for the question addressed in this manuscript. Remaining panelists assisted with conception and design of the analysis, interpretation of data, drafting and revising the recommendation and manuscript, and final approval of the recommendation and manuscript to be published. Jennifer Loveless, methodologist, was responsible for general project management, organizing and presenting the data, and leading the panel according to the GRADE process.

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Additional Information: More detailed information on the analysis and development of recommendations is available in the Supplementary Material.

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