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IDSA GUIDELINES

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

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This article 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 article, the panel provides recommendations for treatment of mild 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.

Keywords. histoplasmosis; itraconazole; treatment; antifungals; guideline.

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)*.

Remarks:

- 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 [1].

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)*.

Remarks:

- 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 versus benefits of antifungal treatment when deciding whether to treat. Potential financial burden should be discussed with the patient as well.

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- 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 [2].
- Initial dosing for original itraconazole capsules or oral solution: (adults: 200 mg three 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 three 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 the Implementation Considerations section.
- Therapeutic drug monitoring (TDM) should be performed for patients receiving itraconazole [3–6]. In recent studies, approximately 20% of patients required dose adjustments due to sub- or super-therapeutic levels of itraconazole, and approximately 28% of patients experienced side effects [7, 8]. 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 [3–7, 9–11]. 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 [10, 12, 13]. Patients with a combined hydroxy-itraconazole and itraconazole level >2 mg/L may respond similarly to patients with itraconazole levels >1 mg/L [14].
- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits versus 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)*.

Remarks:

- Patients with asymptomatic or mild acute pulmonary histoplasmosis and a lesser degree of immunocompromise (see Table 1) may not warrant treatment.
- When treatment is indicated, itraconazole is preferred [2].
- Initial dosing for original itraconazole capsules or oral solution: (adults: 200 mg three 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). SUBA itraconazole (only available as capsules and currently approved for use in adults): 130 mg three 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 the Implementation Considerations section.
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- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits versus 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.

This article 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 [34, 35]. These recommendations replace part of the previous recommendation on treatment of mild-to-moderate acute pulmonary histoplasmosis [2]. Alternative treatment options for patients who fail to improve, absorb, or are unable to tolerate first-line therapy will be addressed in a future, planned update. The primary audience for this recommendation is clinicians seeing patients with mild or moderate acute pulmonary histoplasmosis, including primary care clinicians, infectious diseases physicians, pulmonologists, specialists prescribing biologic response modifiers and other immunosuppressive agents, and cardiothoracic surgeons.

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[a]
Receiving corticosteroids: [15] ≥2 mg/kg/d of prednisone (or equivalent) for persons ≤10 kg or ≥20 mg/d of prednisone (or equivalent) for persons >10 kg for at least 2 wks	Receiving corticosteroids: [15] 0.5–2 mg/kg/d of prednisone (or equivalent) for persons <10 kg or 5–20 mg/d of prednisone (or equivalent) for persons >10 kg for at least 4 wks	Receiving corticosteroids: [15] <0.5 mg/kg/d of prednisone (or equivalent) for persons <10 kg or ≤5 mg/d of prednisone (or equivalent) for persons >10 kg for at least 4 wks
Primary cellular immunodeficiency (eg, SCID, autosomal dominant hyperIgE syndrome [AD HIES], interferon-gamma receptor/IL-12 pathway defects)	Primary immunodeficiency (eg, 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)[b] [16]	HIV (CD4 200–300 cells/mm^3) [16–26]	HIV (CD4 ≥300 cells/mm^3); VL undetectable [16]
Hematopoietic stem cell transplant within 100 d or receiving immunosuppressive therapy for graft versus host disease	Hematopoietic stem cell transplant >100 d prior and no evidence of graft versus host disease	
	Hematologic malignancy	
CAR T-cell therapy within 90 d [27]	CAR T-cell therapy >90 d and resolved cytopenias [27]	
Solid organ transplant and treatment of rejection[c]	Solid organ transplant recipient on maintenance immunosuppressive regimen[c]	
Autoimmune and rheumatic diseases requiring treatment with biologic agents[d], 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

Abbreviations: CAR, chimeric antigen receptor; HIV, human immunodeficiency virus; IL-12, interleukin 12; IgM, immunoglobulin M; VL, viral load.

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

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

[c]Carefully consider drug-drug interactions (eg, tacrolimus for Graft-vs-host disease [GVHD] prophylaxis).

[d]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, eg, infliximab, etanercept, adalimumab); IL-12/IL-23 blockade (ustekinumab, risankizumab, guselkumab).

Mild acute pulmonary histoplasmosis refers to mild symptoms (eg, cough, fever, dyspnea, chest discomfort) that do not interfere with normal activities. Moderate acute pulmonary histoplasmosis refers to moderate symptoms significant enough to interfere with normal activities; patients with moderate disease may require low-flow oxygen supplementation and/or hospitalization.

METHODS

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 (Grading of Recommendations Assessment, Development, and Evaluation) approach (Supplementary Figure 1) [36]. The recommendations have been endorsed by the Pediatric Infectious Diseases Society, the Society of Infectious Diseases Pharmacists, and the Mycoses Study Group Education and Research Consortium.

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). For this question, a larger search on treatment of histoplasmosis was conducted. A critical appraisal of the evidence according to the GRADE approach, along with an assessment of the benefits and harms of care options informed the recommendations [36, 37]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

SUMMARY OF EVIDENCE

Limited evidence was identified for the outcomes of mortality (9 studies [1, 38–45]), symptom resolution/radiographic

regression (9 studies [1, 38–41, 43–46]), and toxicity (1 study [39]) (Supplementary Tables 1 and 2). For the outcome of mortality, there were no deaths attributable to histoplasmosis in any study regardless of whether patients were treated. Five of 9 studies were retrospective reviews (including 2 school outbreak reports of 876 affected people, 708 of whom were symptomatic), 3 were case reports, and 1 was a prospective, nonrandomized trial. Many of the same studies reported on symptomatic resolution and/or radiographic regression. In one of the outbreak studies, 353 people (mostly adolescents) were symptomatic but received no treatment, and >75% were ill for 1 week or less, with all recovering within 2 months [1]. In another outbreak study, 523/682 study participants had serologic evidence of infection, 355 of whom developed symptoms, with only 13 receiving an antifungal agent [38]. In the largest outbreak, of over 100 000 presumed infected, 435 presented to a hospital (285 with acute respiratory histoplasmosis), with only 43 receiving treatment [47]. In this study, 7 immunocompromised individuals with disseminated histoplasmosis recovered without treatment. Only 1 study addressed toxicity within the context of this clinical question [39]. In this study, 37 patients with confirmed histoplasmosis were treated with itraconazole 200–400 mg/day for a median 9 months, and itraconazole was stopped in 1/37 patients due to toxicity.

In one of the outbreak cohorts [38], 4 people were receiving immunocompromising medications, and 3 of the 4 were hospitalized. A case report of a pediatric oncology patient with acute pulmonary histoplasmosis who received treatment with itraconazole reported improvement [40]. A retrospective review of 52 children with histoplasmosis (7 immunocompromised) reported longer duration of antigenuria, antigenemia, and duration of therapy in immunocompromised patients, with no recurrence within 2 years for those treated with antifungals [43].

For all recommendations, the certainty of evidence is very low according to the GRADE approach due to study risk of bias (Supplementary Table 3), inconsistency amongst studies (eg, patients in an outbreak study have a higher inoculum, heterogeneous populations in terms of histoplasmosis severity and type), and imprecision (small number of events) [48–50]. Refer to the Supplementary Material for more information on each study and exact judgments affecting the certainty of evidence for each outcome.

RATIONALE FOR RECOMMENDATIONS

The studies demonstrate that most cases of mild-to-moderate acute pulmonary histoplasmosis will resolve without treatment. Data on the prevalence of *Histoplasma capsulatum* exposure, rate at which significant illness develops, and prognosis of nonsevere acute pulmonary disease largely derive from population-level histoplasmin sensitivity studies and large outbreak reports, most dating from the 1950s–80s. These indicate that exposure to *H. capsulatum* is widespread in endemic areas, with over half of children by age 8 [51] and more than 80% of long-term residing adults [52] demonstrating an immunologic response to *Histoplasma* antigen. Most infections are subclinical with an estimated fewer than 5% of exposed individuals developing even mild symptoms [46]. In a large urban outbreak study involving an estimated 120 000 individuals, only 435 cases (0.36%) were identified in a hospital setting (and therefore likely to meet current criteria for moderate or severe disease) [47]. At most, 4 of 285 individuals with acute respiratory disease required treatment, with all others recovering without treatment. In another large outbreak involving 383 junior high school students and some adult staff, only 1 patient required hospitalization, and all recovered without treatment, most within 2 weeks of symptom onset [1].

Treatment decisions also require an assessment of the potential harms of treatment. Itraconazole is associated with several common undesirable effects, including nausea and vomiting, rash, and peripheral edema. More serious complications, including hepatotoxicity and heart failure, are rare but have been reported. Itraconazole is a strong CYP3A4 inhibitor with many significant drug-drug interactions and is known to have highly variable oral absorption requiring monitoring of drug levels. Its use is contraindicated in the first trimester of pregnancy, necessitating involvement of maternal fetal medicine and infectious diseases specialists and use of alternative agents such as amphotericin B with potentially greater undesirable effects. Treatment duration of 6–12 weeks also imposes a large pill burden, most notably for children. Overall, the panel assesses the burden of undesirable effects to be typically small in children, moderate in adults, and large in pregnant people. Treatment courses may also be associated with significant cost with variable insurance coverage.

Since most immunocompetent patients with mild to moderate acute pulmonary histoplasmosis recover without specific treatment, and several potential harms of treatment are apparent, the panel agrees that the overall balance of benefits versus harms favors not treating with an antifungal medication in most cases. Greater consideration to treatment may be appropriate in cases with more prolonged symptom duration (eg, >1 month), progressive symptoms or radiographic abnormalities, or more severe initial symptoms. Treatment in these scenarios would be intended to shorten duration of symptoms, prevent progression to more severe disease, and/or prevent late sequalae of pulmonary histoplasmosis such as mediastinal granuloma or fibrosing mediastinitis. However, there are no data demonstrating treatment is associated with any of these potentially improved clinical outcomes.

Progression to severe acute pulmonary histoplasmosis or disseminated disease appears rare in immunocompetent patients in large outbreak studies. However, immunocompromise has been identified as a clear risk factor for more severe disease

in these and other reports [53]. For this reason, the panel agrees that the overall balance of benefits to harms favors antifungal treatment in patients with acute pulmonary histoplasmosis and an underlying immunocompromise that places them at significant risk for disease progression.

IMPLEMENTATION CONSIDERATIONS

Proper implementation of the approaches suggested above has two major limitations [54]. First, acute mild to moderate histoplasmosis is vastly underdiagnosed, including cases that occur within immunocompromised patients, because of the non-specificity of symptoms and the high rate of spontaneous resolution. As such, most cases of acute histoplasmosis remain undetected. The second limitation to implementation is related to the first, that is, lack of recognition. The remedy to this involves creating greater awareness of histoplasmosis as a frequent cause of community-acquired pneumonia, especially in highly endemic regions. Current efforts by the Centers for Disease Control and Prevention (eg, Fungal Disease Awareness Week) and other groups such as the Mycoses Study Group, aim to increase awareness of histoplasmosis and other endemic mycoses through programs which encourage a lower threshold for rapid testing (eg, urine *Histoplasma* antigen) and an overall greater awareness of this pathogen as a cause of non-specific community-acquired pneumonia. In the absence of specific laboratory testing, greater emphasis must be placed on patient history, including travel, occupation, hobbies, and detailed history of any significant comorbidities which might increase the risk of more aggressive disease.

There are currently three available oral formulations of itraconazole that are not interchangeable, as there are differences in dosing, administration, and cost. The original capsule formulation has limited and variable oral bioavailability, and it must be taken with food containing high fat content [55]. Its bioavailability may be increased with a low stomach pH and longer gastric retention time. Although slightly more costly than the capsule formulation, the oral solution of itraconazole has better bioavailability [10, 56]. However, this formulation must be taken on an empty stomach and is associated with gastrointestinal side effects such as osmotic diarrhea due to the presence of hydroxypropyl-β-cyclodextrin, used to solubilize the drug. A newer oral capsule formulation of itraconazole, SUBA itraconazole, is now available. Currently the most expensive of the 3, this formulation contains itraconazole in a polymeric matrix that enhances its bioavailability compared the original capsule formulation and lessens the impact of gastric pH (and pH-altering medications) on absorption [57–59]. Similar to the original capsule formulation, it is recommended to take SUBA itraconazole with food.

Therapeutic drug monitoring should be performed for patients receiving itraconazole [3–6]. In general, blood concentrations should be checked after approximately 5–7 days when loading doses are used, and 10–14 days without a loading dose [6]. Levels should also be checked when interacting drugs are started or stopped, there are concerns for patient adherence or gastrointestinal absorption, and/or the patient has symptoms of toxicities. 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 [3–6, 9–11]. 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 [10, 12, 13]. Patients with a combined hydroxy-itraconazole and itraconazole level >2 mg/L may respond similarly to patients with itraconazole levels >1 mg/L [14].

RESEARCH NEEDS

Randomized controlled trials or large cohort studies evaluating outcomes of antifungal treatment (including itraconazole and alternative azoles) versus no antifungal treatment in patients with mild-to-moderate acute pulmonary histoplasmosis would be very helpful. However, studies of this sort are extraordinarily difficult to conduct, largely due to the difficulty in diagnosing acute disease and identifying subgroups who might benefit from therapeutic intervention. Clinical trials of this sort involving older, generic antifungals are likely to require sponsorship and/or coordination by a federal agency, such as the Centers for Disease Control and Prevention or the National Institute of Allergy and Infectious Diseases, on the basis of public health needs. At present, there are no randomized controlled trials involving treatment of mild or moderate pulmonary histoplasmosis. As a result, the impact of treatment on symptom duration, progression to severe pulmonary histoplasmosis or disseminated disease, or development of late sequelae of pulmonary histoplasmosis is largely unknown, and the above recommendations are largely based on expert interpretation of observational studies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Sandra Arnold and Andrej Spec are chair and vice chair, respectively, of the expert panel. Robert Lentz and Peter Pappas served as clinical leads for the question addressed in this manuscript. Kayla Stover and Nathan Wiederhold led the development of remarks on therapeutic drug monitoring for itraconazole. Remaining panelists assisted with conception and design of the analysis, interpretation of data, drafting and revising the recommendations and manuscript, and final approval of the recommendations and manuscript to be published. Jennifer Loveless, methodologist, was responsible for general project management, synthesizing and presenting the data, and leading the panel according to the GRADE process.

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

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Potential conflicts of interest. Evaluation of relationships as potential conflicts of interest (COIs) is determined by a review process. The assessment of disclosed relationships for possible COIs is based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The following panelists have scientific advisory/consultant roles related to the topic (ie, manageable conflicts of interest): A. S. (vice chair) with Mayne and Scynexis, C. A. K. with Cidara Therapeutics (concluded) and Laboratoires SMB (concluded), K. S. with Cidara Therapeutics (concluded), and N. W. with F2G (concluded). C. A. K. is Editor-in-Chief for UpToDate's Infectious Diseases sections, and J. B. is an editor for UpToDate's Fungal Infections sections. The following panelists have research relationships related to the topic: A. S. (vice chair) with Astellas; R. M. with Scynexis and F2G; P. P. with Mayne; and N. W. with F2G, Scynexis, Mycovia (concluded), and Sfunga (concluded). No disclosures were reported for all other authors (the majority of panelists) including chair. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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IDSA GUIDELINES

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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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.

Keywords. histoplasmosis; histoplasmoma; asymptomatic pulmonary nodules; 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 noncalcified 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)*.

***Remarks*:**

- 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 versus 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.

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

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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[a]
Receiving corticosteroids: [1] ≥2 mg/kg/d of prednisone (or equivalent) for persons ≤10 kg or ≥20 mg/d of prednisone (or equivalent) for persons >10 kg for at least 2 wks	Receiving corticosteroids: [1] 0.5–2 mg/kg/d of prednisone (or equivalent) for persons <10 kg or 5–20 mg/d of prednisone (or equivalent) for persons >10 kg for at least 4 wks	Receiving corticosteroids: [1] <0.5 mg/kg/d of prednisone (or equivalent) for persons <10 kg or ≤5 mg/d of prednisone (or equivalent) for persons >10 kg for at least 4 wks
Primary cellular immunodeficiency (eg, SCID, autosomal dominant hyperIgE syndrome [AD HIES], interferon-gamma receptor/IL-12 pathway defects)	Primary immunodeficiency (eg, 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)[b] [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 d or receiving immunosuppressive therapy for graft versus host disease	Hematopoietic stem cell transplant >100 d prior and no evidence of graft versus host disease	
	Hematologic malignancy	
Chimeric antigen receptor (CAR) T-cell therapy within 90 d [13]	CAR T-cell therapy >90 d and resolved cytopenias [13]	
Solid organ transplant and treatment of rejection[c]	Solid organ transplant recipient on maintenance immunosuppressive regimen[c]	
Autoimmune and rheumatic diseases requiring treatment with biologic agents[d], 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

Abbreviations: HIV, human immunodeficiency virus; IgE, immunoglobulin E; IL, interleukin; NF, nuclear factor; SCID, severe combined immunodeficiency; VL, viral load.

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

[b]Severe immunocompromise in children ≤5 y of age is defined as CD4+ T lymphocyte [CD4+] percentage <15%, and in individuals ≥6 y, CD4+ percentage <15% and CD4+ >200 lymphocytes/mm^3 [1].

[c]Carefully consider drug-drug interactions (eg, tacrolimus for graft-vs-host disease prophylaxis).

[d]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 [eg, infliximab, etanercept, adalimumab]); IL-12/IL-23 blockade (ustekinumab, risankizumab, guselkumab).

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, the Society of Infectious Diseases Pharmacists, and the Mycoses Study Group Education and Research Consortium.

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

Table 2. Evidence for Reactivation of Latent Histoplasmosis in Immunocompromising Conditions

Study	Study Type	Exposure	No. With Likely Reactivation	Age (y)	Reactivation of Latent Infection [31]	Comments
HIV infection						
Antinori et al [3]	Case series	HIV	4	Adult	Probable	Presentation in lower incidence area (Milan, Italy); median 24 mo since last travel to higher incidence area (range 1–144 mo)
Anderson et al [4]	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 et al [5][a]	Survey-based case series	HIV	43	Mostly adults	Probable	Presentation in lower incidence area (Europe); no recent travel (25% >5 y since last likely exposure)
Bourgeois et al [6][b]	Case series	HIV	4	42–70	Probable	Presentation in lower incidence area (Montpellier and Nîmes, France); no recent travel (>4 y) in 4/7 cases
Buitrago et al [7][a]	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 et al [8]	Case report	HIV	1	50	Probable	Presentation in lower incidence area (California, USA); no travel to higher incidence area in >30 y
Gandhi et al [9][a]	Case series	HIV	1	27–77	Possible	Presentation in lower incidence area (Pittsburgh, Pennsylvania, and New York, New York, USA); recent travel not specified
Peigne et al [10][b]	Case series	HIV	104	~39 with SD ~9	Probable	Presentation in lower incidence area (France); no recent travel in >59% of cases
Martin-Iguacel et al [11]	Case report	HIV	1	30	Probable	Presentation in lower incidence area (Copenhagen, Denmark); no recent travel
Norman et al [12]	Case series	HIV	5	Adult	Probable	Presentation in lower incidence area (Madrid, Spain); 3/5 no travel within 5 y
Immunomodulatory agents						
Ashbee et al [5]	Survey-based case series	Corticosteroids	7	Mostly adults	Probable	Presentation in lower incidence area (Europe); no recent travel (25% >5 y since last likely exposure)
Gandhi et al [9]	Case series	Corticosteroids/azathioprine	1	27–77	Probable	Presentation in lower incidence area (Pittsburgh, Pennsylvania, and New York, New York, USA); recent travel not specified
Jain et al [15]	Case report	Infliximab	1	40	Probable	Presentation in lower incidence area (Fresno, California, USA); no recent travel (5 y)
Lucey et al [16]	Case report	Corticosteroids/azathioprine	1	62	Possible	Presentation in lower incidence area (London, United Kingdom); most recent travel to higher incidence area 5 mo prior
Prakash and Richman [17]	Case report	Ruxolitinib	1	51	Possible	Presentation in lower incidence area (San Diego, California, USA); insufficient data for recent travel to higher incidence area to determine whether likely reactivation or acute/subacute presentation
Sani et al [18]	Case report	Infliximab (plus azathioprine)	1	44 y	Probable	Presentation in lower incidence area (Tucson, Arizona, USA); no recent travel (>1 y)
Wallis et al [19]	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

Table 2. Continued

Study	Study Type	Exposure	No. With Likely Reactivation	Age (y)	Reactivation of Latent Infection [31]	Comments
Other immunocompromising conditions						
Alamri et al [25]	Case report	Heart transplant	1	68	Possible	Presentation in lower incidence area (Riyadh, Saudi Arabia); no recent travel (>2 y) but heart donor from higher incidence area
Ashbee et al [5]	Survey-based case series	Malignancy	2	Mostly adults	Probable	Presentation in lower incidence area (Europe); no recent travel (25% >5 y since last likely exposure)
Buitrago et al [7]	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 et al [26]	Case report	Renal transplantation	1	63	Probable	Presentation in lower incidence area (Belgium); no recent travel (>20 y)
Chang et al [30]	Case report	Renal transplantation	1	16	Possible	Presentation in lower incidence area (Southern California); possible exposure in New York City 6 y prior
Garcia-Marron et al [28]	Case report	Excessive alcohol use	1	46	Probable	Presentation in lower incidence area (Asturias, Spain); no recent travel (>10 y)

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation; TNF, tumor necrosis factor.

[a]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.

[b]Two studies report data from overlapping regions and time periods, so some participants might appear in both studies.

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 for asymptomatic pulmonary nodules in adults and children were identified (Supplementary Table 1) [3–12, 15–19, 25–30]. 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 in a patient presenting to another hospital would have been missed.

Twenty studies provided evidence of possible or probable reactivation of latent disease in at least 275 patients [3–12, 15–19, 25, 26, 28–30]. In these studies, similar limitations as noted for the Demkowicz study apply.

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

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 [32, 33]. 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

The panel did not identify any specific data on treatment of asymptomatic histoplasmomas in pregnant or pediatric patients, but it would be reasonable to apply the recommendation 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 et al, 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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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, synthesizing and presenting the data, and leading the panel according to the GRADE process.

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Possible conflicts of interest. Evaluation of relationships as potential conflicts of interest (COIs) is determined by a review process. The assessment of disclosed relationships for possible COIs is based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The following panelists have scientific advisory/consultant roles related to the topic (ie, manageable conflicts of interest): A. S. (vice chair) with Mayne and Scynexis, C. A. K. with Cidara Therapeutics (concluded) and Laboratoires SMB S. A. (concluded), K. S. with Cidara Therapeutics (concluded), and N. W. with F2G (concluded). C. A. K. is Editor-in-Chief for UpToDate's Infectious Diseases sections, and J. B. is an editor for UpToDate's Fungal Infections sections. The following panelists have research relationships related to the topic: A. S. (vice chair) with Astellas; R. M. with Scynexis and F2G; P. P. with Mayne;

N. W. with F2G, Scynexis, Mycovia (concluded), and Sfunga (concluded). No disclosures were reported for all other authors (the majority of panelists) including chair. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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

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