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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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 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.

Key words. 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)*.

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 [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)*.

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 [2].

- Initial 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 [3-6]. 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 [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 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 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 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). 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 (similar dosing may be considered in children old enough to swallow capsules).
- Therapeutic drug monitoring (TDM) should be performed for patients receiving itraconazole [3-6]. 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 [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 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: [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 ≥300 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].

‡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 [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.

Mild acute pulmonary histoplasmosis refers to mild symptoms (e.g., 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 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) [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 1-2). 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 both 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 (e.g., 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 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 non-severe 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 (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 one 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 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.

In the context of most immunocompetent patients with mild to moderate acute pulmonary histoplasmosis recovering without specific treatment while 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 (e.g., >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 which 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, and patients improve spontaneously without specific intervention with antifungal therapy. 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 (e.g., 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 (e.g., 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 enhance 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 three, 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 ~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 start or stop, 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.

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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 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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