Clinical Infectious Diseases

IDSA GUIDELINES

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

Sandra R. Arnold,[1,2,a] Andrej Spec,[3,a,©] John W. Baddley,[4] Peter Pappas,[5] Robert J. Lentz,[6,©] Joshua Wolf,[7,©] Carol A. Kauffman,[8] Monica I. Ardura,[9,10] Nevert Badreldin,[11] Nathan C. Bahr,[12,13] Karen Bloch,[14] Rachel A. Miller,[15] Satish Mocherla,[16] Michael Saccente,[17] Ilan Schwartz,[15] Kayla R. Stover,[18] Nathan P. Wiederhold,[19] and Jennifer Loveless[20]

[1]Department of Pediatrics, Le Bonheur Children's Hospital, Memphis, Tennessee, USA; [2]University of Tennessee Health Science Center, Memphis, Tennessee, USA; [3]Division of Infectious Diseases, Washington University in St Louis, St Louis, Missouri, USA; [4]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [5]Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA; [6]Division of Allergy, Pulmonary & Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [7]Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, Tennessee, USA; [8]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA; [9]Pediatric Infectious Diseases & Host Defense, Nationwide Children's Hospital, Columbus, Ohio, USA; [10]Department of Pediatrics, The Ohio State University, Columbus, Ohio, USA; [11]Department of Obstetrics & Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [12]Division of Infectious Diseases, Department of Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA; [13]Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA; [14]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [15]Division of Infectious Diseases, Duke University, Durham, North Carolina, USA; [16]Division of Infectious Diseases, Houston Methodist Hospital, Houston, Texas, USA; [17]Division of Infectious Diseases, Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; [18]Department of Pharmacy Practice, University of Mississippi, Jackson, Mississippi, USA; [19]Department of Pathology and Laboratory Medicine, Fungus Testing Laboratory, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA; and [20]Clinical Affairs and Practice Guidelines, Infectious Diseases Society of America, Arlington, Virginia, USA

As the first part of an update to the clinical practice guideline on the management of histoplasmosis in adults, children, and pregnant people, developed by the Infectious Diseases Society of America, we present 4 updated recommendations. These recommendations span treatment of asymptomatic *Histoplasma* pulmonary nodules (histoplasmomas), mild acute pulmonary histoplasmosis, and moderate acute pulmonary histoplasmosis. The panel's recommendations are based 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.

Keywords. histoplasmosis; histoplasmoma; asymptomatic pulmonary nodules; guideline.

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

Guideline Scope

The scope of this guideline update includes treatment of asymptomatic *Histoplasma* pulmonary nodules (histoplasmomas) and mild or moderate acute pulmonary histoplasmosis. Available evidence for children, adults, and pregnant people was reviewed. For the purposes of this guideline, newborns and patients with African histoplasmosis or possible ocular histoplasmosis syndrome were excluded.

This guideline is intended for use by healthcare professionals who care for patients with histoplasmosis, including but not limited to primary care clinicians, infectious diseases physicians, pulmonologists, specialists prescribing biologic response

Received 20 March 2025; editorial decision 27 March 2025; published online 16 July 2025

[a]S. R. A. and A. S. contributed equally to this work.

Correspondence: S. R. Arnold, Le Bonheur Children's Hospital, 49 N Dunlap St, Room 293, Memphis, TN 38105 (practiceguidelines@idsociety.org).

Clinical Infectious Diseases® 2025;81(9):i27–32

https://doi.org/10.1093/cid/ciaf256

Table 1. Severity of Acute Pulmonary Histoplasmosis. These definitions are offered as guidance but are not intended to be prescriptive. Clinical assessment should drive care decisions.

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

modifiers and other immunosuppressive agents, and cardiothoracic surgeons.

Publication Scope

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

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

METHODS

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

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

RESULTS: RECOMMENDATIONS AND *REMARKS*

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

Recommendation: In adults and children with asymptomatic 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 2), closely monitor for clinical/radiological change or consider treatment.
- Patients with only calcified pulmonary nodules should not be treated.
- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits 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.

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

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

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

High	Moderate	Low[a]
Receiving corticosteroids: [11] ≥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: [11] 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: [11] <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, Nuclear factor-kappaB Essential Modulator [NEMO] deficiency, chronic mucocutaneous candidiasis, X-linked hyper IgM syndrome, autosomal recessive HIES)	
Advanced or untreated HIV/AIDS (CD4 <200 cells/mm^3)[b] [8]	HIV (CD4 200–300 cells/mm^3) [8, 12–21]	HIV (CD4 ≥300 cells/mm^3); VL undetectable [8]
Hematopoietic stem cell transplant within 100 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 [22]	CAR T-cell therapy >90 d and resolved cytopenias [22]	
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 [18, 23–28]		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 [11].

[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).

enlarging hilar or mediastinal adenopathy. In a large outbreak study, >75% of persons affected were ill for 1 week or less, and all recovered completely within 2 months without treatment [29].

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

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.
- The goals of treatment are to decrease the duration of illness and mitigate risk of dissemination, though treatment effectiveness in this patient population is unknown.
- When treatment is indicated, itraconazole is preferred [1].
- 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 maximum 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 [4–7]. 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 [30, 31]. A goal trough concentration of itraconazole component >1 mg/L and <3–4 mg/L (as measured by chromatographic assay) is associated with efficacy and a lower risk of toxicity [4–7, 30, 32–34]. Due to the long half-life of itraconazole, non-trough/random levels of itraconazole can also be used to monitor serum concentrations. Hydroxy-itraconazole is an active metabolite; however, a cutoff for combined hydroxy-itraconazole and itraconazole levels has not been established [33, 35, 36]. Patients with a combined hydroxy-itraconazole and itraconazole level >2 mg/L may respond similarly to patients with itraconazole levels >1 mg/L [37].
- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits 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 2) may not warrant treatment.
- When treatment is indicated, itraconazole is preferred [1].
- 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 maximum 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.
- Therapeutic drug monitoring (TDM) should be performed for patients receiving itraconazole [4–7]. In recent studies, approximately 20% of patients required dose adjustments due to sub- or super-therapeutic levels of itraconazole, and approximately 28% experienced side effects [30, 31]. A goal trough concentration of itraconazole component of >1 mg/L and <3–4 mg/L (as measured by chromatographic assay) is associated with efficacy and a lower risk of toxicity [4–7, 30, 32–34]. Due to the long half-life of itraconazole, non-trough/random levels of itraconazole can also be used to monitor serum concentrations. Hydroxy-itraconazole is an active metabolite; however, a cutoff for combined hydroxy-itraconazole and itraconazole levels has not been established [33, 35, 36]. Patients with a combined hydroxy-itraconazole and itraconazole level >2 mg/L may respond similarly to patients with itraconazole levels >1 mg/L [37].
- Treatment of pregnant individuals should only be considered after carefully weighing the potential benefits 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.

RESEARCH NEEDS

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

Notes

Acknowledgments. The panel acknowledges the work of the previous panel, under the leadership of L. Joseph Wheat, for their work on the previous iteration of this larger guideline, and the contributions of Elizabeth Kiscaden and Mary Beth McAteer, medical librarians, for the creation and execution of question-specific literature searches. Rebecca Goldwater and Imani Amponsah provided project coordination. The panel also acknowledges the following organizations and selected external reviewers for their review of the draft manuscript: the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists; Drs. David Andes, John Christenson, and Marisa Miceli; and Drs. Robin Colgrove and Clinton White on behalf of the Standards & Practice Guidelines Subcommittee.

S. R. A. and A. S. are chair and vice-chair, respectively, of the expert panel. J. W. B., R. J. L., P. P., and J. W. served as clinical leads for the questions addressed in this article. K. R. S. and N. P. W. led the development of remarks on therapeutic drug monitoring for itraconazole. Remaining panelists assisted with the 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. J. L., methodologist, was responsible for general project management, synthesizing and presenting the data, and leading the panel according to the GRADE process.

Disclaimer. It is important to recognize that guidelines cannot always account for individual variation among patients. They are assessments of current scientific and clinical information provided as an educational

service; are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is drafted and when it is published or read); should not be considered inclusive of all proper methods of care or as a statement of the standard of care; do not mandate any course of medical care; and are not intended to supplant clinician judgment with respect to particular patients or situations. Whether to follow guidelines and to what extent is voluntary, with the ultimate determination regarding their application to be made by the clinician in the light of each patient's individual circumstances. While IDSA makes every effort to present accurate, complete, and reliable information, these guidelines are presented "as is" without any warranty, either express or implied. IDSA (and its officers, directors, members, employees, and agents) assume no responsibility for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with these guidelines or reliance on the information presented.

Financial support. This work was supported by the Infectious Diseases Society of America.

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. R. S. with Cidara Therapeutics (concluded), and N. P. W. with F2G (concluded). C. A. K. is editor-in-chief for UpToDate's Infectious Diseases sections, and J. W. 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; P. P. with Mayne; R. A. M. with Scynexis and F2G; and N. P. W. with F2G, Scynexis, Mycovia (concluded), and Sfunga (concluded). No disclosures were reported for all other authors (the majority of panelists), including the 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.

References

1. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guideline for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis **2007**; 45:807–25.
2. Baddley JW, Wolf J, Ardura MI, et al. 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. Clin Infect Dis.
3. Lentz RJ, Pappas P, Ardura MI, et al. 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. Clin Infect Dis.
4. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother **2014**; 69:1162–76.
5. Chau MM, Daveson K, Alffenaar J-WC, et al. Consensus guidelines for optimizing antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy and haemopoietic stem cell transplant recipients, 2021. Intern Med J **2021**; 51 Suppl 7:37–66.
6. Laverdiere M, Bow EJ, Rotstein C, et al. Therapeutic drug monitoring for triazoles: a needs assessment review and recommendations from a Canadian perspective. Can J Infect Dis Med Microbiol **2014**; 25:327–43.
7. McCreary EK, Davis MR, Narayanan N, et al. Utility of triazole antifungal therapeutic drug monitoring: insights from the Society of Infectious Diseases Pharmacists: endorsed by the Mycoses Study Group Education and Research Consortium. Pharmacotherapy **2023**; 43:1043–50.
8. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines. Accessed 16 June 2024.
9. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ **2008**; 336:924–6.
10. Infectious Diseases Society of America. IDSA handbook on clinical practice guideline development. Available at: https://www.idsociety.org/practice-guideline/clinical-practice-guidelines-development-training-and-resources/. Accessed 3 January 2024.
11. Kroger A, Bahta L, Long S, et al. General best practice guidelines for immunization: altered immunocompetence. Available at: https://www.cdc.gov/vaccines/hcp/imz-best-practices/altered-immunocompetence.html. Accessed 16 June 2024.
12. Antinori S, Magni C, Nebuloni M, et al. Histoplasmosis among human immunodeficiency virus-infected people in Europe: report of 4 cases and review of the literature. Medicine **2006**; 85:22–36.
13. Anderson AM, Mehta AK, Wang YF, et al. HIV-associated histoplasmosis in a nonendemic area of the United States during the HAART era: role of migration from endemic areas and lack of antiretroviral therapy. J Int Assoc Physicians AIDS Care **2010**; 9:296–300.
14. Ashbee HR, Evans EGV, Viviani MA, et al. Histoplasmosis in Europe: report on an epidemiological survey from the European Confederation of Medical Mycology Working Group. Med Mycol **2008**; 46:57–65.
15. Bourgeois N, Douard-Enault C, Reynes J, et al. Seven imported histoplasmosis cases due to *Histoplasma capsulatum* var. *capsulatum*: from few weeks to more than three decades asymptomatic period. J Mycol Med **2011**; 21:19–23.
16. Buitrago MJ, Bernal-Martinez L, Castelli MV, et al. Histoplasmosis and paracoccidioidomycosis in a non-endemic area: a review of cases and diagnosis. J Travel Med **2011**; 18:26–33.
17. Choi J, Nikoomanesh K, Uppal J, Wang S. Progressive disseminated histoplasmosis with concomitant disseminated nontuberculous mycobacterial infection in a patient with AIDS from a nonendemic region (California). BMC Pulm Med **2019**; 19:46.
18. Gandhi V, Ulyanovskiy P, Epelbaum O. Update on the spectrum of histoplasmosis among Hispanic patients presenting to a New York City municipal hospital: a contemporary case series. Respir Med Case Rep **2015**; 16:60–4.
19. Peigne V, Dromer F, Elie C, et al. Imported acquired immunodeficiency syndrome-related histoplasmosis in metropolitan France: a comparison of pre-highly active anti-retroviral therapy and highly active anti-retroviral therapy eras. Am J Trop Med Hyg **2011**; 85:934–41.
20. Martin-Iguacel R, Kurtzhals J, Jouvion G, Nielsen SD, Llibre JM. Progressive disseminated histoplasmosis in the HIV population in Europe in the HAART era: case report and literature review. Infection **2014**; 42:611–20.
21. Norman FF, Martin-Davila P, Fortun J, et al. Imported histoplasmosis: two distinct profiles in travelers and immigrants. J Travel Med **2009**; 16:258–62.
22. Shahid Z, Jain T, Dioverti V, et al. Best practice considerations by the American Society of Transplant and Cellular Therapy: infection prevention and management after chimeric antigen receptor T cell therapy for hematological malignancies. Transplant Cell Ther **2024**; 30:955–69.
23. Hage CA, Bowyer S, Tarvin SE, Helper D, Kleiman MB, Wheat LJ. Recognition, diagnosis, and treatment of histoplasmosis complicating tumor necrosis factor blocker therapy. Clin Infect Dis **2010**; 50:85–92.
24. Jain VV, Evans T, Peterson MW. Reactivation histoplasmosis after treatment with anti-tumor necrosis factor alpha in a patient from a nonendemic area. Respir Med **2006**; 100:1291–3.

25. Lucey O, Carroll I, Bjorn T, Millar M. Reactivation of latent *Histoplasma* and disseminated cytomegalovirus in a returning traveller with ulcerative colitis. JMM Case Rep **2018**; 5:e005170.
26. Prakash K, Richman D. A case report of disseminated histoplasmosis and concurrent cryptococcal meningitis in a patient treated with ruxolitinib. BMC Infect Dis **2019**; 19:287.
27. Sani S, Bilal J, Varma E, et al. Not your typical Arizona granuloma: a case report of disseminated histoplasmosis. Am J Med **2018**; 131:e375–6.
28. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis **2004**; 38:1261–5.
29. Brodsky AL, Gregg MB, Loewenstein MS, Kaufman L, Mallison GF. Outbreak of histoplasmosis associated with the 1970 earth day activities. Am J Med **1973**; 54: 333–42.
30. Osborn MR, Zuniga-Moya JC, Mazi PB, Rauseo AM, Spec A. Side effects associated with itraconazole therapy. J Antimicrob Chemother **2025**; 80:503–8.
31. Spec A, Thompson GR, Miceli MH, et al. MSG-15: super-bioavailability itraconazole versus conventional itraconazole in the treatment of endemic mycoses—a multicenter, open-label, randomized comparative trial. Open Forum Infect Dis **2024**; 11:ofae010.
32. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother **2009**; 53: 24–34.
33. Cartledge JD, Midgely J, Gazzard BG. Itraconazole solution: higher serum drug concentrations and better clinical response rates than the capsule formulation in acquired immunodeficiency syndrome patients with candidosis. J Clin Pathol **1997**; 50:477–80.
34. Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, Hope WW. Toxicodynamics of itraconazole: implications for therapeutic drug monitoring. Clin Infect Dis **2009**; 49:928–30.
35. Firkus D, Saleh A, Enzler OM, et al. Does metabolite matter? Defining target itraconazole and hydoxy-itraconazole serum concentrations for blastomycosis. Mycoses **2023**; 66:412–9.
36. Khurana A, Agarwal A, Singh A, et al. Predicting a therapeutic cut-off serum level of itraconazole in recalcitrant tinea corporis and cruris—a prospective trial. Mycoses **2021**; 64:1480–8.
37. Wiederhold NP, Schwartz IS, Patterson TF, Thompson III GR. Variability of hydroxy-itraconazole in relation to itraconazole bloodstream concentrations. Antimicrob Agents Chemother **2021**; 65:e02353-20.