Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America

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Evidence-based guidelines for the management of patients with histoplasmosis were prepared by an Expert Panel of the Infectious Diseases Society of America. These updated guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 30:688–95). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. Since 2000, several new antifungal agents have become available, and clinical trials and case series have increased our understanding of the management of histoplasmosis. Advances in immunosuppressive treatment for inflammatory disorders have created new questions about the approach to prevention and treatment of histoplasmosis. New information, based on publications from the period 1999–2006, are incorporated into this guideline document. In addition, the panel added recommendations for management of histoplasmosis in children for those aspects that differ from aspects in adults.

EXECUTIVE SUMMARY

Background

Histoplasma capsulatum variety *capsulatum* infection is endemic in certain areas of North, Central, and South America, Africa, and Asia, but cases have also been reported from Europe. In the United States, most cases have occurred within the Ohio and Mississippi River valleys. Precise reasons for this distribution pattern of endemicity are unknown but are thought to include moderate climate, humidity, and soil characteristics. Bird and bat excrement enhances the growth of the organism in soil by accelerating sporulation. These unique growth requirements explain, in part, the localization of histoplasmosis into so-called microfoci. Activities that disturb such sites are associated with exposure to *H. capsulatum*. Air currents carry the conidia for miles, exposing individuals who were unaware of contact with the contaminated site. Furthermore, environmental sites that are not visibly contaminated with droppings may harbor the organism, making it difficult to suspect histoplasmosis in most cases.

Certain forms of histoplasmosis cause life-threatening illnesses and result in considerable morbidity, whereas other manifestations cause no symptoms or minor self-limited illnesses.

The objective of this guideline is to update recommendations for treating patients with histoplasmosis.

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These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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Treatment of Acute and Chronic Pulmonary Histoplasmosis

Moderately Severe to Severe Acute Pulmonary Histoplasmosis

1. Lipid formulation of amphotericin B (3.0–5.0 mg/kg daily intravenously for 1–2 weeks) followed by itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks) is recommended (A-III).

2. The deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily intravenously) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

3. Methylprednisolone (0.5–1.0 mg/kg daily intravenously) during the first 1–2 weeks of antifungal therapy is recommended for patients who develop respiratory complications, including hypoxemia or significant respiratory distress (B-III).

Mild-to-Moderate Acute Pulmonary Histoplasmosis

4. Treatment is usually unnecessary (A-III). Itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for >1 month (B-III).

Chronic Cavitary Pulmonary Histoplasmosis

5. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for at least 1 year) is recommended, but some prefer 18–24 months in view of the risk for relapse (A-II).

6. Blood levels of itraconazole should be obtained after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).

Complications

Pericarditis

7. Nonsteroidal anti-inflammatory therapy is recommended in mild cases (B-III).

8. Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended for patients with evidence of hemodynamic compromise or unremitting symptoms after several days of therapy with nonsteroidal anti-inflammatory therapy (B-III).

9. Pericardial fluid removal is indicated for patients with hemodynamic compromise (A-III).

10. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended if corticosteroids are administered (B-III).

Rheumatologic Syndromes

11. Nonsteroidal anti-inflammatory therapy is recommended in mild cases (B-III).

12. Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended in severe cases (B-III).

13. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended only if corticosteroids are administered (B-III).

Mediastinal Lymphadenitis

14. Treatment is usually unnecessary (A-III).

15. Itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended in patients who have symptoms that warrant treatment with corticosteroids and in those who continue to have symptoms for >1 month (B-III).

16. Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended in severe cases with obstruction or compression of contiguous structures (B-III).

Mediastinal Granuloma

17. Treatment is usually unnecessary (A-III)

18. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended for symptomatic cases (B-III).

Mediastinal Fibrosis

19. Antifungal treatment is not recommended (A-III).

20. The placement of intravascular stents is recommended for selected patients with pulmonary vessel obstruction (B-III).

21. Itraconazole (200 mg once or twice daily for 12 weeks) is recommended if clinical findings cannot differentiate mediastinal fibrosis from mediastinal granuloma (C-III).

Broncholithiasis

22. Antifungal treatment is not recommended (A-III).

23. Bronchoscopic or surgical removal of the broncholith is recommended (A-III).

Pulmonary Nodules (Histoplasmomas)

24. Antifungal treatment is not recommended (A-III).

Progressive Disseminated Histoplasmosis

25. For moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg daily) is recommended for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months) (A-I).

26. Substitution of another lipid formulation at a dosage of 5.0 mg/kg daily may be preferred in some patients because of cost or tolerability (A-III).

27. The deoxycholate formulation of amphotericin B

(0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

28. For mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) is recommended (A-II).

29. Lifelong suppressive therapy with itraconazole (200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed (A-II) and in patients who relapse despite receipt of appropriate therapy (C-III).

30. Blood levels of itraconazole should be obtained to ensure adequate drug exposure (B-III).

31. Antigen levels should be measured during therapy and for 12 months after therapy is ended to monitor for relapse (B-III). Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence of active infection.

Prophylaxis for Immunosuppressed Patients

32. Prophylaxis with itraconazole (200 mg daily) is recommended in patients with HIV infection with CD4 cell counts <150 cells/mm^3 in specific areas of endemicity where the incidence of histoplasmosis is >10 cases per 100 patient-years (A-I).

33. Prophylaxis with itraconazole (200 mg daily) may be appropriate in specific circumstances in other immunosuppressed patients (C-III).

CNS Histoplasmosis

34. Liposomal amphotericin B (5.0 mg/kg daily for a total of 175 mg/kg given over 4–6 weeks) followed by itraconazole (200 mg 2 or 3 times daily) for at least 1 year and until resolution of CSF abnormalities, including *Histoplasma* antigen levels, is recommended (B-III).

35. Blood levels of itraconazole should be obtained to ensure adequate drug exposure (B-III).

Histoplasmosis in Pregnancy

36. Lipid formulation amphotericin B (3.0–5.0 mg/kg daily for 4–6 weeks) is recommended (A-III).

37. The deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

38. If the newborn shows evidence for infection, treatment is recommended with amphotericin B deoxycholate (1.0 mg/kg daily for 4 weeks) (A-III).

Histoplasmosis in Children

Acute Pulmonary Histoplasmosis

39. Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate (1.0 mg/kg daily) is usually well tolerated, and the lipid preparations are not preferred (A-III).

40. Itraconazole dosage in children is 5.0–10.0 mg/kg daily in 2 divided doses (not to exceed 400 mg daily), generally using the solution formulation (A-III).

Progressive Disseminated Histoplasmosis

41. Amphotericin B deoxycholate (1.0 mg/kg daily for 4–6 weeks) is recommended (A-III).

42. Amphotericin B deoxycholate (1.0 mg/kg daily for 2–4 weeks) followed by itraconazole (5.0–10.0 mg/kg daily in 2 divided doses) to complete 3 months of therapy is an alternative (A-III).

43. Longer therapy may be needed for patients with severe disease, immunosuppression, or primary immunodeficiency syndromes (A-III).

44. Lifelong suppressive therapy with itraconazole (5.0 mg/kg daily, up to 200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed (A-II) and in patients who experience relapse despite receipt of appropriate therapy (C-III).

45. Blood levels of itraconazole should be obtained to ensure adequate drug exposure (B-III).

46. Antigen levels should be monitored during therapy and for 12 months after therapy is ended to monitor for relapse (B-III). Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence of active infection.

INTRODUCTION

In 2000, the Infectious Diseases Society of America (IDSA) published a clinical practice guideline on the management of patients with histoplasmosis [1]. The IDSA updates its guidelines when new data or publications might change a prior recommendation or when the panel feels clarification or additional guidance is warranted.

For the 2007 update, the indications for treatment and agents of choice from the 2000 guideline were reviewed [1]. The previous document is a source for a more detailed review of earlier studies.

Areas related to several newer antifungal agents and immunosuppressive regimens for chronic inflammatory disorders were not previously covered, because there was limited information at the time. Therefore, the panel decided to include them in this update. The panel addressed the following clinical questions in the 2007 update.

1. What is the treatment for acute and chronic pulmonary histoplasmosis?
2. What is the treatment for complications of pulmonary

Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from Canadian Task Force on the Periodic Health Examination [3].

histoplasmosis (e.g., pericarditis, arthritis/erythema nodosum, mediastinal lymphadenitis, mediastinal granuloma, mediastinal fibrosis, broncholithiasis, and pulmonary nodule)?

3. What is the treatment for progressive disseminated histoplasmosis?
4. Is prophylaxis recommended for immunocompromised patients?
5. What is the treatment for CNS histoplasmosis?
6. What is the treatment for histoplasmosis in pregnancy?
7. What treatment is recommended for histoplasmosis in children?

PRACTICE GUIDELINES

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [2]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [2].

UPDATE METHODOLOGY

Panel Composition

The IDSA Standards and Practice Guidelines Committee (SPGC) convened experts in the management of patients with histoplasmosis. The panel members are listed in Appendix A.

Literature Review and Analysis

For the 2007 update, the expert panel completed the review and analysis of data published since 1999. Computerized literature searches of the PubMed database were performed. The searches of the English-language literature published from 1999 through July 2006 used the terms "histoplasmosis" and "*Histoplasma*" and focused on human studies but included a few studies from experimental models of histoplasmosis.

Process Overview

In evaluating the evidence regarding the management of histoplasmosis, the panel followed a process used in the development of other IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (table 1) [3].

Consensus Development Based on Evidence

The panel met on 6 occasions via teleconference to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions to be addressed, make writing assignments, and discuss recommendations. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee (SPGC) and the Board of Directors prior to dissemination.

Guidelines and Conflicts of Interest

All members of the expert panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the expert panel were provided IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether

an individual's role should be limited as a result of a conflict. Potential conflicts are listed in the Acknowledgements section.

Revision Dates

At annual intervals, the Panel Chair, the SPGC liaison advisor, and the Chair of the SPGC will determine the need for revisions to the guideline on the basis of an examination of current literature. If necessary, the entire panel will be reconvened to discuss potential changes. When appropriate, the panel will recommend revision of the guideline to the SPGC and the IDSA Board for review and approval.

RESULTS

Literature Search

The literature search identified 858 potential articles. A few abstracts from national meetings were included. The types of studies included randomized, clinical trials; open-label clinical trials; retrospective case series; case reports; reports of in vitro studies; and animal model experiments. Because of the limited nature of the data in many areas, the panel decided also to retain high-quality reviews or background papers. Panel members were assigned sections of the guideline and reviewed the relevant literature.

Limitations in the Literature

Review of the literature revealed a paucity of clinical trials evaluating the newer agents in histoplasmosis. Most data came from cohort studies; case series; small, nonrandomized clinical trials; or case reports.

Literature Search Results

Clinical manifestations. Severity of illness and disease manifestations after primary inhalation exposure to *H. capsulatum* vary, depending on the intensity of exposure and the immunity of the host. Acute exposure causes a spectrum of disease ranging from asymptomatic infection to severe pneumonitis with respiratory compromise. In most cases, illness resolves without therapy within 1 month [4]. Some patients, however, may experience protracted pulmonary complaints caused by persistent inflammation of the lung or mediastinal lymph nodes.

Acute pulmonary histoplasmosis also may be associated with other inflammatory manifestations, including pericarditis and arthritis or arthralgia with erythema nodosum. Complications of pulmonary histoplasmosis include mediastinal lymphadenitis, mediastinal granuloma, chronic cavitary disease in patients with underlying emphysema, fibrosing mediastinitis, and broncholithiasis [4].

Hematogenous dissemination occurs in most patients during the first few weeks after acute infection, but it is rarely progressive, resolving with the development of cell-mediated immunity to *H. capsulatum.* Progressive disseminated histoplasmosis occurs in individuals who are unable to mount a cell-mediated immune response to the organism and is fatal if untreated. Progressive disseminated histoplasmosis is defined as a clinical illness that does not improve after at least 3 weeks of observation and that is associated with physical or radiographic findings and/or laboratory evidence of involvement of extrapulmonary tissues. Hepatosplenomegaly, mucosal ulcers and skin lesions, gastrointestinal involvement, pancytopenia, progressive elevation of hepatic enzyme levels, increased lactate dehydrogenase level, and increased serum ferritin level may provide clues to the diagnosis. Laboratory evidence of dissemination includes demonstration of granulomas with yeasts resembling *H. capsulatum* in extrapulmonary tissues, growth in culture of *H. capsulatum,* and persistent antigenuria and/or antigenemia.

Chronic chorioretinitis, referred to as "presumed ocular histoplasmosis syndrome," is commonly diagnosed in areas of endemicity [5], but it is not clearly caused by *H. capsulatum.* In one report, presumed ocular histoplasmosis was not responsive to amphotericin B treatment [6].

Treatment is clearly indicated in severe or moderately severe acute pulmonary, chronic pulmonary, disseminated, and CNS histoplasmosis (table 2). In other manifestations, the role of therapy is uncertain, and efficacy has not been assessed with clinical trials. Treatment is not indicated in asymptomatic patients with certain noninfectious complications or residue of healed histoplasmosis, such as asymptomatic pulmonary nodules, mediastinal lymphadenopathy, and splenic lesions, especially when calcified.

Antifungal agents. The antifungal agents that have been proven to be effective and that are preferred for treatment of histoplasmosis include amphotericin B [7], liposomal amphotericin B [8], amphotericin B lipid complex [9], and itracon-

Table 2. Indications for antifungal therapy.

Definite indication, proven or probable efficacy
Acute diffuse pulmonary infection, moderately severe symptoms, or severe symptoms
Chronic cavitary pulmonary infection
Progressive disseminated infection
CNS infection
Uncertain indication, unknown efficacy
Acute focal pulmonary infection, asymptomatic case, or mild symptoms that persist for >1 month
Mediastinal lymphadenitis
Mediastinal granuloma
Inflammatory syndromes, treated with corticosteroids
Not recommended, unknown efficacy or ineffective
Mediastinal fibrosis
Pulmonary nodule
Broncholithiasis
Presumed ocular histoplasmosis syndrome

azole [10, 11]. There is no evidence to recommend the echinocandins as treatment for histoplasmosis; in vitro susceptibility studies and animal experiments have shown conflicting results [12–14], and there is no published experience regarding treatment of humans who have histoplasmosis with echinocandins. Amphotericin B formulations are used for patients who have severe pulmonary or disseminated forms of histoplasmosis. A multicenter, randomized, blinded clinical trial demonstrated a higher response rate (88% vs. 64%) and lower mortality rate (2% vs. 13%) in patients who had AIDS and progressive disseminated histoplasmosis and who were treated with liposomal amphotericin B than among recipients of amphotericin B deoxycholate, respectively [8]. Amphotericin B lipid complex has also been used successfully for treatment of histoplasmosis [9] and may be preferred by some because of lower cost. Amphotericin B deoxycholate is the least expensive formulation and is a reasonable alternative to the lipid formulations for patients who are at a low risk for nephrotoxicity. Presently, except for children, for whom a 1-month course of amphotericin B deoxycholate is usually curative, it is rare to see amphotericin B given for the entire course of therapy, as was recommended in the 2000 guidelines. However, amphotericin B, as sole therapy, is effective and may be preferred in situations precluding treatment with itraconazole or other oral azoles. Generally, amphotericin B is used initially until the patient has shown a favorable response and can take an oral antifungal agent; then, itraconazole is given for the remainder of the treatment course.

Itraconazole given orally is preferred for patients who have mild-to-moderate histoplasmosis and, as noted above, as step-down therapy after the initial response to amphotericin B. The response rate for primary therapy with itraconazole in early studies was 100% for disseminated histoplasmosis and 80% for pulmonary histoplasmosis [10]. The oral capsule formulation or the solution can be used. Itraconazole capsules should be taken in the setting of high gastric acidity (concomitant consumption of food or a cola drink is recommended), to maximize absorption. In patients who are receiving antacids, H_2 blockers, or proton pump inhibitors, the capsules should not be used because of decreased absorption. Itraconazole concentrations are higher with use of the solution given on an empty stomach than with capsules; thus, the solution should be used whenever possible. However, some patients dislike its taste or experience unacceptable gastrointestinal side effects, reducing adherence to therapy.

Some patients are intolerant of itraconazole, are unable to achieve adequate blood levels with either preparation, or are receiving concomitant medications that lead to serious drug interactions with itraconazole. Thus, there is a need for alternative therapies. Fluconazole has been used successfully for treatment of histoplasmosis, but it appears to be less effective than itraconazole. In patients with disseminated histoplasmosis who did not have AIDS, fluconazole (200–800 mg daily) was effective in 70% of cases [15]. Fluconazole (800 mg daily for 12 weeks as induction therapy, followed by 400 mg daily) [16] was less effective than itraconazole [11] for treatment of histoplasmosis in patients who had AIDS, and fluconazole resistance developed in patients who failed therapy [17].

Ketoconazole is seldom used for histoplasmosis in the United States because of the increased number of adverse effects, compared with itraconazole. However, it is effective and much less expensive than itraconazole, justifying its use in some cases involving mild manifestations of histoplasmosis, but not in cases of disseminated or CNS disease.

The newer azoles, posaconazole and voriconazole, also demonstrate in vitro activity against *H. capsulatum* [18]. Posaconazole appears to be more active in vitro [18] and in experimental infection [19]. Isolates that were noted to have become resistant to fluconazole when patients with AIDS were treated with the agent were also noted to show increased MICs to voriconazole [18], suggesting that resistance may develop during treatment with voriconazole, as well as with fluconazole [17]. Both voriconazole [20–24] and posaconazole [25–27] have been used successfully in a small number of patients with a variety of different forms of histoplasmosis. Data are inadequate to make an evidence-based recommendation, and all 4 of the other available azoles (i.e., fluconazole, ketoconazole, voriconazole, and posaconazole) are second-line alternatives to itraconazole.

The azoles exert their antifungal activity by inhibition of the fungal cytochrome P450 3A4-dependent enzyme lanosterol 14-α-demethylase. The azoles vary in their ability to inhibit mammalian cytochrome P450 metabolism of other drugs, and several azoles (itraconazole and voriconazole) are extensively metabolized by hepatic cytochrome P450 enzymes. Thus, drug-drug interactions mediated through cytochrome P450 pathways are common and vary with each azole. In addition, posaconazole and itraconazole are both inhibitors and substrates of p-glycoprotein, and posaconazole is eliminated through glucuronidation, leading to other important drug-drug interactions. Up-to-date prescribing information should be reviewed before initiating azole therapy in patients who are taking other medications.

The azoles may be hepatotoxic. Hepatic enzyme levels should be measured before therapy is started and at least at 1, 2, and 4 weeks and then every 3 months during therapy.

Therapeutic drug monitoring. Optimization of itraconazole therapy for treatment of life-threatening systemic fungal infections is strongly recommended [28]. Blood concentrations vary widely in patients receiving itraconazole for treatment of histoplasmosis [11, 29]. Blood concentrations are ~30% higher

using the solution formulation than the capsule formulation, but wide intersubject variability persists [30]. Itraconazole concentrations in serum should be determined only after steady-state has been reached, which takes ~2 weeks. Serum levels should be obtained to ensure adequate absorption, to monitor changes in the dosage of itraconazole or the addition of interacting medications, to determine the cause of treatment failure, and to assess adherence. Because of its long half-life (~24 h), blood concentrations of itraconazole vary little during a 24-h dosing interval. Thus, the timing of collection of the blood specimen in relationship to the most recent dose of itraconazole is not important. *Histoplasma* yeasts are highly susceptible to itraconazole, with MICs of <0.01 μg/mL in all strains tested. Although a blood concentration associated with treatment failure in histoplasmosis has not been identified, random concentrations of at least 1.0 μg/mL are recommended. Although the concentration associated with an increased risk for toxicity has not been defined, concentrations of >10 μg/mL are unnecessary for treatment of histoplasmosis, are likely to be associated with toxicity, and should prompt dosage reduction. When measured by high-pressure liquid chromatography, both itraconazole and its bioactve hydroxy-itraconazole metabolite are reported, the sum of which should be considered in assessing drug levels.

Drug level monitoring is not recommended when using fluconazole, because of its excellent drug exposure, even in patients with AIDS [16]. Although less information is available, therapeutic drug monitoring also appears to be appropriate when administering voriconazole [31] and posaconazole. Both agents demonstrate considerable subject-to-subject variability [32–34] related to differences in absorption and/or metabolism. Furthermore, drug-drug interactions can lead to major changes in the serum concentrations of voriconazole [35]. Voriconazole's half-life is 6–8 h, and blood levels vary 2-fold over a 12-h dosing interval [32]. Accordingly, timing of obtainment of the blood specimen in relationship to the most recent dose of the medication is essential in assessing voriconazole drug exposure. For voriconazole, the trough concentrations should be at least 0.5 μg/mL, and the peak concentration should be at least 2.0 μg/mL. Posaconazole's half-life is ~12 h [33], and concentrations vary only slightly during a 12–24-h dosing interval [33, 34]. Random concentrations of at least 0.5 μg/mL may be adequate. Voriconazole and posaconazole metabolites are not bioactive; thus, they are not reported by laboratories using high-pressure liquid chromatography.

Azole blood levels are available in most of the large reference laboratories and several laboratories specializing in fungal diagnostics (e.g., Fungus Testing Laboratory [San Antonio, TX] and Mira Vista Diagnostics [Indianapolis, IN]).

Use of antigen testing to monitor therapy for progressive disseminated histoplasmosis. *Histoplasma* antigen can be detected in the urine in >90% of patients and in the serum in 80% of patients who have disseminated histoplasmosis, and this measurement is commonly used as an aid to early diagnosis (MiraVista Diagnostics) [36]. The sensitivity and specificity are increased in newer generations of the test [37, 38], but cross-reactions occur in patients with other endemic mycoses [36, 39]. In patients with antigenuria and/or antigenemia, levels decrease during therapy [40] and increase in 90% of those who relapse [41]. Furthermore, failure of the antigen concentration to decrease may indicate treatment failure. Accordingly, changes in antigen levels can be used as indicators for response to therapy. Antigen levels should be measured before treatment is initiated, at 2 weeks, at 1 month, and then approximately every 3 months during therapy and for at least 6 months after treatment is stopped. Antigen levels also should be measured if treatment failure or relapse is suspected.

In the experience of the panel, some patients have done well after receiving appropriate therapy when treatment was discontinued, despite having persistent low-level antigenuria. Also, in a study of withdrawal of suppressive therapy in patients with AIDS following immune reconstitution, none had relapse, even though ~20% of patients had an antigen level of 1–3 U [42]. Considering the complexity of issues involved in decisions about discontinuation of therapy, the panel recommends that expert opinion be sought if the physician is uncertain whether to stop treatment because of persistent antigenuria. More specific guidance for use of antigen detection to monitor therapy is discussed in a recent review [36].

Salvage therapy in patients who fail standard therapy. The approach to therapy in patients who fail amphotericin B or itraconazole therapy is complex, and there are very limited data on which to make evidence-based recommendations. One study reported response to posaconazole in 3 patients who failed treatment with multiple drugs, including amphotericin B, itraconazole, and voriconazole, and in a fourth patient who failed itraconazole treatment [25]. Whether combining amphotericin B with an azole would be effective in refractory cases has not been reported. In animal models, however, the combination of amphotericin B and an azole was no more effective than amphotericin B alone [43, 44]; in fact, fluconazole was antagonistic to amphotericin B.

The role of immune modulator therapy in patients who fail antifungal therapy for histoplasmosis is unknown. Granulocyte-macrophage colony-stimulating factor [45], IFN-γ [46], and antibodies to *H. capsulatum* cell surface proteins [47] have demonstrated marginal benefit in murine models but have not been studied in patients. A patient who had a specific defect in the IL-12/IFN-γ pathway appeared to benefit from IFN-γ after antifungal therapy failed on several occasions [48]. The

panel recommends that expert opinion be sought in refractory cases.

GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF HISTOPLASMOSIS

The guideline recommendations are also summarized in table 3.

WHAT IS THE TREATMENT FOR ACUTE AND CHRONIC PULMONARY HISTOPLASMOSIS?

Moderately Severe to Severe Acute Pulmonary Histoplasmosis

Recommendations

1. Lipid formulation of amphotericin B (3.0–5.0 mg/kg daily intravenously for 1–2 weeks) followed by itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks) is recommended (A-III).

2. The deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily intravenously) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

3. Methylprednisolone (0.5–1.0 mg/kg daily intravenously) during the first 1–2 weeks of antifungal therapy is recommended for patients who develop respiratory complications, including hypoxemia or significant respiratory distress (B-III).

Evidence summary. The effectiveness of therapy in patients with acute pulmonary histoplasmosis is based on anecdotal case reports, as recently summarized elsewhere [36], and clinical experience. In severe cases, cases accompanied by respiratory insufficiency, or hypoxemia, anecdotal reports [49] suggest that corticosteroid therapy may hasten recovery. In most patients for whom corticosteroids are considered, hospitalization is appropriate. The optimal duration of therapy is unknown, but presumably a relatively short course of 12 weeks may suffice, because cell-mediated immunity to *Histoplasma* usually develops within the first month of infection. The pulmonary infiltrates should be resolved on the chest radiograph before antifungal therapy is stopped.

Mild-to-Moderate Acute Pulmonary Histoplasmosis

Recommendation

4. Treatment is usually unnecessary (A-III). Itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for >1 month (B-III).

Evidence summary. Antifungal treatment is unnecessary in patients with mild symptoms caused by acute pulmonary histoplasmosis. In an outbreak in a junior high school [50], illness resolved within 3 weeks in >95% of cases, and only 1% of patients were hospitalized. In a more recent outbreak at a high school, only 3.7% of patients received antifungal therapy, and only 2.5% of children, several of whom were immunocompromised, were hospitalized [51]. However, whether therapy could hasten recovery in such cases is unknown, because clinical trials of treatment for acute pulmonary histoplasmosis have not been conducted.

Antifungal treatment has been recommended in patients whose symptoms do not improve within 1 month [52], but no clinical trials have been performed to prove efficacy in this situation. In such cases, persistent fever, fatigue, or weight loss raises concern about the development of progressive disseminated histoplasmosis, providing an additional reason for the initiation of antifungal therapy. If treatment is administered, a 6–12-week course of itraconazole (200 mg once or twice daily) is recommended. In an open-label clinical trial, a small number of patients who had persistent symptomatic pulmonary histoplasmosis were shown to respond to itraconazole (200 mg once or twice daily, given for at least 6 months) [10].

Chronic Cavitary Pulmonary Histoplasmosis

Recommendations

5. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for at least 1 year) is recommended, but some prefer 18–24 months in view of the risk for relapse (A-II).

6. Blood levels of itraconazole should be obtained after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure (A-III).

Evidence summary. Patients with underlying emphysema often develop progressive pulmonary disease, which is characterized by cavities with surrounding inflammation, after infection with *H. capsulatum* [4]. The effectiveness of therapy with either amphotericin B or itraconazole for chronic pulmonary histoplasmosis has been established by clinical trials and cohort studies [10, 53–57]. Relapses have occurred in 9%–15% of those treated with these agents. Treatment should be continued until pulmonary imaging shows no further improvement when monitored at 4–6-month intervals. In most cases, chest radiographs provide sufficient information for monitoring response to therapy. Patients should continue to be monitored for relapse for at least 1 year after they stop itraconazole treatment. Results of tests for detection of antigen are usually negative in patients with chronic pulmonary histoplasmosis and play a limited role in an assessment of response to treatment. Furthermore, although antibody levels generally decrease with recovery, insufficient data are available to support measurement of antibody levels for assessment of response to treatment.

WHAT IS THE TREATMENT FOR THE COMPLICATIONS FROM PULMONARY HISTOPLASMOSIS (E.G., PERICARDITIS, ARTHRITIS/ERYTHEMA NODOSUM, MEDIASTINAL LYMPHADENITIS, MEDIASTINAL GRANULOMA, MEDIASTINAL FIBROSIS, BRONCHOLITHIASIS, AND PULMONARY NODULE)?

Pericarditis

Recommendations

7. Nonsteroidal anti-inflammatory therapy is recommended in mild cases (B-III).

8. Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended for patients with evidence of hemodynamic compromise or unremitting symptoms after several days of therapy with nonsteroidal anti-inflammatory therapy (B-III).

9. Pericardial fluid removal is indicated for patients with hemodynamic compromise (A-III).

10. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended if corticosteroids are administered (B-III).

Evidence summary. Pericarditis occurs as a complication of inflammation in adjacent mediastinal lymph nodes in patients with acute pulmonary histoplasmosis. It represents an inflammatory condition rather than infection of the pericardium. Pericardial infection is a very rare complication of disseminated disease. Patients respond to nonsteroidal anti-inflammatory agents without antifungal therapy, often improving after only a few days of therapy [58, 59]. Large pericardial effusions may impair cardiac output, however, and thus require drainage [59]. Pericardial constriction is rare and is not a basis for prophylactic therapy or surgical removal of the pericardium. If corticosteroids are used, concurrent itraconazole treatment is recommended to reduce the risk of progressive infection. If the patient has symptomatic acute pulmonary histoplasmosis with features for which treatment is recommended, in addition to pericarditis, itraconazole therapy is appropriate

Rheumatologic Syndromes

Recommendations

11. Nonsteroidal anti-inflammatory therapy is recommended in mild cases (B-III).

12. Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended in severe cases (B-III).

13. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended only if corticosteroids are administered (B-III).

Evidence summary. Arthritis or arthralgia with erythema nodosum occurs in 5%–10% of cases as a systemic inflammatory response to acute pulmonary histoplasmosis [60, 61]. These manifestations do not represent infection, and they respond to nonsteroidal anti-inflammatory agents without antifungal therapy. In some cases, the manifestations are moderately severe, requiring treatment with corticosteroids [60]. If corticosteroids are used, concurrent itraconazole treatment is recommended to reduce the risk of progressive infection. Bone or joint involvement is very rare in progressive disseminated histoplasmosis, but it should not be overlooked.

Mediastinal Lymphadenitis

Recommendations

14. Treatment is usually unnecessary (A-III).

15. Itraconazole (200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended in patients who have symptoms that warrant treatment with corticosteroids and in those who continue to have symptoms for >1 month (B-III).

16. Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) is recommended in severe cases with obstruction or compression of contiguous structures (B-III).

Evidence summary. Antifungal treatment is unnecessary in most patients with symptoms due to mediastinal lymphadenitis. The symptoms that occur most frequently are chest pain, cough and/or atelectasis due to bronchial compression, or dysphagia resulting from esophageal compression. Children are more likely than adults to present with airway obstruction. In patients with symptoms of compression of the airways or esophagus, administration of prednisone in tapering doses over 1–2 weeks may result in prompt relief by reducing the size of the inflamed lymph nodes [62]. Itraconazole is recommended for 6–12 weeks to reduce the risk of progressive disseminated disease caused by corticosteroid-induced immunosuppression in patients who are given corticosteroids and in patients whose symptoms last longer than 1 month.

Mediastinal Granuloma

Recommendations

17. Treatment is usually unnecessary (A-III)

18. Itraconazole (200 mg 3 times daily for 3 days and then once or twice daily for 6–12 weeks) is recommended for symptomatic cases (B-III).

Evidence summary. The term mediastinal granuloma describes a large (3–10 cm in adults but smaller in children), mostly caseous mass of mediastinal lymph nodes that coalesce into a single encapsulated lesion, which is usually located in

Table 3. Recommendations for the treatment of histoplasmosis.

Manifestation	Treatment	Class	Comments
Acute pulmonary histoplasmosis			
Moderately severe or severe	Lipid AmB[a] (3.0–5.0 mg/kg daily) or deoxycholate AmB (0.7–1.0 mg/kg daily) for 1–2 weeks, followed by Itra[b] (200 mg twice daily for a total of 12 weeks)	A-III	Usually follows easily identifiable heavy exposure and is accompanied by diffuse infiltrates and hypoxemia
	Methylprednisolone (0.5–1.0 mg/kg daily intravenously for 1–2 weeks)	B-III	Effectiveness is not well documented
Mild to moderate	For symptoms of <4 weeks, none	A-III	Whether treatment shortens the duration of illness is unknown
	For symptoms of >4 weeks, Itra (200 mg once or twice daily for 6–12 weeks)	B-III	
Chronic cavitary pulmonary histoplasmosis	Itra[b] (200 mg once or twice daily for at least 12 months)	A-II	Relapse occurs in ~15% of cases
Pericarditis			
Moderately severe to severe	Itra (200 mg once or twice daily for 6–12 weeks) only if prednisone used	B-III	Tamponade requires drainage of pericardial fluid; antifungal therapy is given to reduce possible dissemination caused by prednisone-induced immunosuppression
	Prednisone (0.5–1.0 mg/kg daily in tapering doses over 1–2 weeks)	B-III	
Mild	Nonsteroidal anti-inflammatory agents	B-III	Usually rapidly effective at reducing symptoms and pericardial effusion
Rheumatologic histoplasmosis	Nonsteroidal anti-inflammatory agents	B-III	Corticosteroids are rarely needed
Mediastinal lymphadenitis	Mild symptoms of <4 weeks, none	A-III	Nonsteroidal anti-inflammatory agents may be given, but the effectiveness is unknown; corticosteroids are rarely needed but have been used in severe cases involving airway obstruction
	Symptoms warranting treatment with prednisone, prednisone (0.5–1.0 mg/kg daily in tapering doses over 1–2 weeks) and Itra (200 mg once or twice daily for 6–12 weeks)	B-III	
	Symptoms of >4 weeks, Itra (200 mg once or twice daily for 6–12 weeks)	B-III	
Mediastinal granuloma	Asymptomatic, none	B-III	Surgery may be required to relieve obstruction
	Symptomatic, Itra (200 mg once or twice daily for 6–12 weeks)	B-III	
Mediastinal fibrosis	Antifungal treatment not indicated	A-III	Surgery should be avoided
	Stenting of obstructed vessels can be useful	B-III	Surgery should be avoided
	Itra (200 mg once or twice daily for 6–12 weeks)	C-III	Treatment given only if clinical findings cannot differentiate mediastinal fibrosis from mediastinal granuloma

Broncholithiasis	None	A-III	Removal of stones by bronchoscopy or surgery may be indicated
Pulmonary nodule	None	A-III	Must be differentiated from malignancy
Progressive disseminated histoplasmosis			
Moderately severe to severe	Liposomal AmB[a] (3.0 mg/kg daily), AmB lipid complex[a] (5.0 mg/kg daily), or deoxycholate AmB[a] (0.7–1.0 mg/kg daily) for 1–2 weeks, followed by Itra[a] (200 mg twice daily for at least 12 months)	A-I	Longer treatment may be required in patients with persistent immunodeficiency[c]
Mild to moderate	Itra (200 mg twice daily for at least 12 months)	A-II	Longer treatment may be required in patients with persistent immunodeficiency[c]
CNS histoplasmosis	Liposomal AmB[a] (5.0 mg/kg daily for 4–6 weeks), followed by Itra[b] (200 mg 2–3 times daily for at least 12 months)	B-III	High failure and relapse rates support aggressive therapy, but whether less intensive therapy would suffice is unknown; longer treatment may be required for patients with persistent immunodeficiency[c]

NOTE. AmB, amphotericin B; Itra, itraconazole.

With regard to prophylaxis, there are few studies on which to make evidence-based recommendations on the role of prophylaxis to prevent histoplasmosis in immunosuppressed patients. Prophylaxis is not used routinely but is reserved for situations in which the rate of development of infection exceeds 10 cases per 100 patient-years. The optimal duration for prophylaxis is unknown, but health care providers should consider the incidence of histoplasmosis in the community and the severity of immunosuppression. Itra (200 mg daily) is recommended when prophylaxis is prescribed.

With regard to pregnancy, all azoles are contraindicated because of the risk of teratogenicity. Otherwise, the indications for treatment are not different in pregnancy, and lipid formulations of AmB are preferred.

AmB deoxycholate is preferred for use in children, because it is effective, well tolerated, and less costly. The dosage of Itra for children is 5.0–10.0 mg/kg daily in 2 divided doses, not to exceed 400 mg daily. The dosage of methyl-prednisolone is 2.0 mg/kg daily given intravenously, and the dosage of prednisone is 2.0 mg/kg daily given orally. Indomethacin (1.0–3.0 mg/kg daily, divided 3 times) is the nonsteroidal anti-inflammatory agent of choice for pericarditis in children.

[a] Liposomal AmB (3.0 mg/kg daily) or AmB lipid complex (5.0 mg/kg daily) are recommended for 1–2 weeks, except in patients with meningitis, for whom the dosage of liposomal AmB is 5.0 mg/kg daily for 4–6 weeks. The deoxycholate formulation of AmB (0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity.

[b] Itra should be given as a loading dose of 200 mg 3 times daily for the first 3 days, followed by 200 mg twice daily thereafter. Itra (200 mg once daily) may be sufficient in patients with less severe manifestations of histoplasmosis. If used for prophylaxis, a dosage of 200 mg daily is recommended. Concentrations of Itra in serum should be monitored in patients being treated for chronic pulmonary, disseminated, or CNS histoplasmosis; a random serum concentration >1.0 μg/mL should be sought. Drug monitoring is infrequently needed for patients receiving shorter courses of therapy for acute pulmonary histoplasmosis and its complications.

[c] Chronic, potentially lifelong suppressive therapy with Itra is required for patients with AIDS who do not achieve immune reconstitution in response to antiretroviral therapy. Lifelong suppressive therapy may be useful in patients with other immunosuppressive disorders in whom immunosuppression cannot be substantially reduced and in patients who experience relapse despite receipt of appropriate therapy.

the right paratracheal region or the subcarinal area [52, 63]. Most patients are asymptomatic, and mediastinal granuloma is found incidentally by imaging studies, but symptoms related to compression of adjacent structures can occur. The caseous center can spontaneously drain via a fistula or sinus tract to the bronchus, skin, or esophagus; bacterial superinfection occasionally develops when fistulae or sinus tracts are present [64].

Itraconazole is appropriate for symptomatic cases, but there are no controlled trials to prove its efficacy. The capsule is thin (2–3 mm) and adherent, but it is not invasive, so surgical removal or decompression with removal of the free wall and contents is possible when involvement of the superior vena cava or esophagus causes persistent symptoms (despite administration of antifungal therapy). There is no evidence that mediastinal granuloma evolves into mediastinal fibrosis. Thus, treatment with either surgery or itraconazole should not be used to prevent the development of mediastinal fibrosis [63, 64].

Mediastinal Fibrosis

Recommendations

19. Antifungal treatment is not recommended (A-III).
20. The placement of intravascular stents is recommended for selected patients with pulmonary vessel obstruction (B-III).
21. Itraconazole (200 mg once or twice daily for 12 weeks) is recommended if clinical findings cannot differentiate mediastinal fibrosis from mediastinal granuloma (C-III).

Evidence summary. Mediastinal fibrosis is characterized by invasive fibrosis that encases mediastinal or hilar nodes and that is defined by occlusion of central vessels and airways [65–68]. Occlusion of airways or vessels of both lungs occurs in only a small proportion of cases (~20%) but is usually fatal [69]. Most patients have occlusion of the superior vena cava or loss of function of only 1 lung, which may have significant morbidity with chest pain or hemoptysis, but long-term survival is generally favorable [69].

Most authorities believe that neither antifungal nor anti-inflammatory treatment ameliorates the outcome of mediastinal fibrosis [65, 66], but others have reported improvement after antifungal therapy [70]. If the clinical findings are consistent with a more inflammatory process rather than a chronic fibrotic process, especially if complement fixation antibodies for *H. capsulatum* are present and the erythrocyte sedimentation rate is elevated, treatment should be considered. A 12-week course of itraconazole (200 mg once or twice daily) is suggested if clinical and CT findings do not differentiate mediastinal fibrosis from mediastinal granuloma. Patients who truly have mediastinal fibrosis are not expected to respond to antifungal therapy. Corticosteroid therapy has not been helpful when tried [66, 71, 72] and is discouraged.

Placement of intravascular stents has been helpful in some patients with superior vena cava, pulmonary artery, or pulmonary vein obstruction [73] and should be considered especially for patients who are at highest risk because of involvement of both lungs. The placement of stents in obstructed airways is not recommended because of the high risk of growth of granulation tissue, leading to recurrent obstruction, but it may be necessary in selected patients in whom interventional airway experts find that no other treatment alternative is feasible.

Surgery should be approached with great caution in patients with mediastinal fibrosis and should be performed only for those who are expected to die of the condition without intervention. Surgeons experienced in the management of this condition should be consulted [72].

Broncholithiasis

Recommendations

22. Antifungal treatment is not recommended (A-III).
23. Bronchoscopic or surgical removal of the broncholith is recommended (A-III).

Evidence summary. Broncholithiasis is the erosion of calcified lymph nodes into a bronchus, often causing hemoptysis and inflammation. Spitting of small pieces of white chalk-like material, termed "lithoptysis," may occur [52]. When stones of substantial size are extruded, they may cause prolonged periods of intense cough and hemoptysis, with localized wheeze and distal obstructive pneumonitis. Diagnosis is made bronchoscopically. Removal of the stones bronchoscopically or surgically is recommended.

Pulmonary Nodules (Histoplasmomas)

Recommendation

24. Antifungal treatment is not recommended (A-III).

Evidence summary. Lung parenchymal sites of infection may contract and then persist indefinitely as lung nodules or histoplasmomas [74]. Calcification is usually found in the center of a histoplasmoma or in concentric rings and is generally diagnostic, although it may require years to develop and is not always present. Histoplasmomas may enlarge slowly and even cavitate [74]. Pulmonary nodules cause no symptoms, usually are identified as incidental findings on chest radiographs or CTs, and are frequently removed surgically to exclude malignancy. There is no evidence that antifungal agents have any effect on histoplasmomas or that histoplasmomas contain viable organisms. This recommendation applies to patients who are asymptomatic and who have 1 or a few isolated nodules.

This recommendation does not apply to symptomatic patients who have multiple or diffuse nodules, which may represent acute pulmonary histoplasmosis.

WHAT IS THE TREATMENT FOR PROGRESSIVE DISSEMINATED HISTOPLASMOSIS?

Recommendations

25. For moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg daily) is recommended for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months) (A-I).

26. Substitution of another lipid formulation at a dosage of 5.0 mg/kg daily may be preferred in some patients because of cost or tolerability (A-III).

27. The deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

28. For mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) is recommended (A-II).

29. Lifelong suppressive therapy with itraconazole (200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed (A-II) and in patients who relapse despite receipt of appropriate therapy (C-III).

30. Blood levels of itraconazole should be obtained to ensure adequate drug exposure (B-III).

31. Antigen levels should be measured during therapy and for 12 months after therapy is ended to monitor for relapse (B-III). Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence of active infection.

Evidence summary. Progressive disseminated histoplasmosis is fatal without therapy [54], and treatment with either amphotericin B [7, 8, 54] or itraconazole [10, 11] is highly effective. Among patients with AIDS and moderately severe to severe disseminated histoplasmosis, the rate of response was higher (88% vs. 64%) and the mortality rate was lower (2% vs. 13%) among recipients of liposomal amphotericin B (3 mg/kg daily for 1–2 weeks) than among recipients of the deoxycholate formulation [8].

In patients with severe disease, renal impairment is common as a consequence of multiple-organ failure caused by severe histoplasmosis or amphotericin B nephrotoxicity. Often, physicians consider switching to an azole in such cases, to avoid further renal impairment. The panel recommends continued treatment with liposomal amphotericin B. The poor prognosis justifies using the most effective therapy, despite nephrotoxicity. In many cases, renal impairment improves despite continued receipt of amphotericin B as a result of improvement in the patient's overall condition.

Although it was recommended in the 2000 guidelines on the basis of the results of earlier studies [7, 54], therapy with amphotericin B for the entire therapeutic course (typically 35 mg/kg given over 4–8 weeks) is now uncommon. "Step-down therapy" to oral itraconazole has become the standard of practice and is supported by studies of patients with AIDS [8].

Response rates of 80%–100% were reported using itraconazole for treatment of disseminated histoplasmosis in patients who were not severely ill and who did not have CNS involvement [10, 11]. Itraconazole is administered at 200 mg 3 times daily for 3 days as a loading dose, followed by 200 mg twice daily [10, 11], as guided by determination of the blood concentration of itraconazole, for at least 1 year. In immunosuppressed patients, an even longer course of therapy should be considered. Treatment should be continued until clinical and laboratory findings have returned to normal. Ten percent to 15% of patients experience relapse [10, 11], which may be a basis for long-term maintenance therapy.

In patients with AIDS, the timing of antiretroviral therapy poses an interesting dilemma. Antiretroviral therapy causes improvement in cellular immunity, the key defense against *H. capsulatum*. Not surprisingly, the outcome of disseminated histoplasmosis is better in patients receiving antiretroviral therapy. In a recent report, the response rate was 100% among patients receiving antiretroviral therapy, compared with 47% among those who were not treated with antiretroviral therapy [75]. Initiation of antiretroviral therapy may unmask undiagnosed histoplasmosis through immune reconstitution–induced inflammation [76, 77]. Immune reconstitution inflammatory syndrome during treatment for histoplasmosis is rare, however, and the clinical manifestations are usually not severe [76]. Accordingly, antiretroviral therapy should not be withheld on the basis of concern about the possible development of immune reconstitution inflammatory syndrome.

Long-term suppressive therapy with itraconazole [29] was recommended previously for patients with AIDS [1]. Subsequently, studies have shown that itraconazole can be safely discontinued in patients who have a good immunologic response to antiretroviral therapy [42]. For consideration of discontinuation of suppressive therapy, data suggest that patients should have received at least 1 year of itraconazole therapy, should have negative results of blood cultures, should have a *Histoplasma* serum and urine antigen level <2 ng/mL (comparable to 4 U/mL in the original assay) and a CD4 T cell count >150 cells/mm^3, and should be receiving HAART [42]. Although the practice of discontinuation of suppressive therapy in patients with AIDS who have good immunologic recovery is widespread, the number of published trials evaluating this strategy is small.

Suppressive therapy should be resumed if patients become nonadherent with antiretroviral therapy, if antiretroviral therapy is failing, or if the CD4 T cell count decreases to <150 cells/mm^3. Suppressive therapy also may be warranted in patients with other immunodeficient states that cannot be reversed, but there are no data and minimal clinical experience on which to base this recommendation.

IS PROPHYLAXIS RECOMMENDED FOR IMMUNOSUPPRESSED PATIENTS?

Recommendations

32. Prophylaxis with itraconazole (200 mg daily) is recommended in patients with HIV infection with CD4 cell counts <150 cells/mm^3 in specific areas of endemicity where the incidence of histoplasmosis is >10 cases per 100 patient-years (A-I).

33. Prophylaxis with itraconazole (200 mg daily) may be appropriate in specific circumstances in other immunosuppressed patients (C-III).

Evidence summary. There are few studies on which to make evidence-based recommendations on the role of prophylaxis to prevent histoplasmosis in immunosuppressed patients: a single study has addressed this issue in patients with AIDS. Itraconazole (200 mg daily) prevented histoplasmosis in patients with HIV infection who had CD4 cell counts <150 cells/mm^3 and who lived in an area of hyperendemicity [78]. Prophylaxis had no impact on survival, however. Accordingly, prophylaxis is not used routinely but is reserved for situations in which the rate of development of infection exceeds 10 cases per 100 patient-years. The duration of prophylaxis has not been studied. On the basis of studies showing that suppressive therapy for disseminated histoplasmosis in AIDS can be stopped in patients whose CD4 cell count increases to ⩾150 cells/mm^3 [42], continuation of itraconazole as long as the incidence of histoplasmosis exceeds the threshold noted above and the CD4 count is <150 cells/mm^3 seems to be prudent. The optimal duration for prophylaxis in patients with immunosuppressive conditions other than AIDS is unknown, and health care providers should consider the incidence of histoplasmosis in the community and the severity of immunosuppression.

Today, a more common question is the need for prophylaxis in a patient who is receiving immunosuppressive therapy for malignancy, organ transplantation, or chronic inflammatory disease and who exhibits radiographic or serologic evidence of past histoplasmosis. The utility of prophylaxis in these patients has not been studied, but the risk of histoplasmosis appears to be low. Histoplasmosis was not observed after a mean of 16 months of follow-up in >500 patients who received immunosuppressive therapy for solid organ or bone marrow transplantation in an area of hyperendemicity [79]. Included in this study were persons with radiographic (calcified lung or spleen lesions) or serologic (complement fixation titers of 1:8 or 1:16 or M band by immunodiffusion) evidence of old histoplasmosis, none of whom developed active histoplasmosis. On the other hand, therapy with TNF antagonists has been noted to be a risk factor for the development of disseminated histoplasmosis; in fact, histoplasmosis is the most common fungal infection associated with TNF antagonist therapy [80].

Active histoplasmosis during the past 2 years may be a basis for itraconazole prophylaxis during immunosuppression. Evidence of recent histoplasmosis includes a history of pulmonary infection, with radiographic findings showing infiltrates, nodules, or lymphadenopathy without a clear etiology; *Histoplasma* antigenuria; or anti-*Histoplasma* complement fixation antibody titers ⩾1:32. The appropriate duration of prophylaxis is unknown.

In patients who have finished treatment for histoplasmosis and who are about to receive a transplant or to commence new immunosuppressive therapies, a urinary antigen level should be obtained before the new intervention and then every 2–3 months during the intensive course of immunosuppression. An increase in urinary antigen levels should be assessed with a more thorough investigation for active histoplasmosis, including chest CT and bronchoscopy (if infiltrates are identified), blood cultures using methods suitable for isolation of *Histoplasma* species, and a careful search for disseminated histoplasmosis. A consistent elevation of the urinary *Histoplasma* antigen level should prompt initiation of antifungal therapy empirically in the context of ongoing immunosuppression.

WHAT IS THE TREATMENT FOR CNS HISTOPLASMOSIS?

Recommendations

34. Liposomal amphotericin B (5.0 mg/kg daily for a total of 175 mg/kg given over 4–6 weeks) followed by itraconazole (200 mg 2 or 3 times daily) for at least 1 year and until resolution of CSF abnormalities, including *Histoplasma* antigen levels, is recommended (B-III).

35. Blood levels of itraconazole should be obtained to ensure adequate drug exposure (B-III).

Evidence summary. CNS histoplasmosis includes meningitis, parenchymal lesions of the brain and/or spinal cord, or both. The response to therapy is inferior to that in other types of histoplasmosis [81]; thus, an aggressive approach is recommended [82]. In a recent review of experience in one medical center, 4 of 5 patients treated with amphotericin B (40 mg/kg over 8 weeks) followed by fluconazole (200–400 mg daily for 12 months) made a full recovery, and the fifth had minor sequelae [83]. The panel preferred a high dose (5 mg/kg daily) of liposomal amphotericin B rather than amphotericin B lipid

complex in adults, in part because liposomal amphotericin B achieves the highest concentrations in brain tissue [84]. However, they also noted that there are no data to specifically support this recommendation for CNS *Histoplasma* infection. Of note is the fact that none of the amphotericin B formulations achieve detectable concentrations in CSF. Some have reported success with a shorter course of amphotericin B (2–3 weeks) followed by an azole [85–89], but the panel recommended a longer course of liposomal amphotericin B therapy.

After completion of 4–6 weeks of treatment with liposomal amphotericin B, itraconazole is recommended for at least 1 year. Although itraconazole does not achieve detectable levels in CSF, it was more effective than fluconazole in an animal model of CNS histoplasmosis [43]. The role of combination therapy has not been studied in humans. In the animal model, however, fluconazole was antagonistic to amphotericin B, and the addition of itraconazole to the amphotericin B regimen failed to improve the outcome noted with amphotericin B alone [43]. Therefore, combination treatment is not recommended.

Whether an azole alone would be effective treatment is not known. Itraconazole was as effective as amphotericin B in an animal model of CNS histoplasmosis [43]. Also, individual cases have been reported in which patients responded to azoles without having received prior amphotericin B treatment; these azoles include ketoconazole [90], itraconazole [83, 91], fluconazole [83, 92], fluconazole combined with itraconazole [83], and voriconazole [24]. Another report described a patient for whom multiple prior regimens had failed but who had responded to posaconazole treatment [25]. However, the panel felt that the evidence was insufficient to recommend azole therapy alone for CNS histoplasmosis.

Although resection of brain or spinal cord lesions has been reported, surgery is rarely needed and should be performed only with progressive clinical findings despite receipt of antifungal therapy.

WHAT IS THE TREATMENT FOR HISTOPLASMOSIS IN PREGNANCY?

Recommendations

36. Lipid formulation amphotericin B (3.0–5.0 mg/kg daily for 4–6 weeks) is recommended (A-III).

37. The deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

38. If the newborn shows evidence for infection, treatment is recommended with amphotericin B deoxycholate (1.0 mg/kg daily for 4 weeks) (A-III).

Evidence summary. Unique issues in pregnancy include the risk of teratogenic complications of azole therapy [93] and of transplacental transmission of *H. capsulatum* to the fetus [94]. Transplacental transmission may be prevented by administration of antifungal therapy before delivery, but the evidence is not adequate to make a recommendation. The placenta should be examined histopathologically for granuloma and for organisms resembling *H. capsulatum.* Furthermore, the baby should be monitored for clinical and laboratory findings suggestive of histoplasmosis, in which case treatment with amphotericin B deoxycholate is recommended.

Amphotericin B remains the treatment of choice in pregnancy, and the lipid formulations are safe [93]. The azoles are teratogenic and embryotoxic in animals and should be avoided during pregnancy. Long-term administration of fluconazole during pregnancy has been associated with congenital anomalies [95]. Women of childbearing age who receive azole antifungal agents should use effective contraception during therapy and for 2 months after it is stopped. Reports suggesting that fetal risk is not increased [96–98] focused on low-dose, short-duration therapy and should not be used as a basis for azole treatment for histoplasmosis. Theoretically, the risk for toxicity during the third trimester may be low, but there are no data available to assess the safety of prolonged treatment for histoplasmosis.

WHAT TREATMENT IS RECOMMENDED FOR HISTOPLASMOSIS IN CHILDREN?

Symptoms of histoplasmosis in children are similar to those that occur in adults, with some exceptions. Acute pulmonary manifestations are common; however, chronic pulmonary infection has not been described. Airway obstruction caused by mediastinal lymphadenitis is more common in children than in adults because of greater airway pliability in children. Lithoptysis and broncholithiasis are rarely seen. Rheumatologic complications are similar, although erythema nodosum is unusual and is almost never associated with arthritis or arthralgia. Mediastinal fibrosis rarely occurs during childhood. Meningitis is common in progressive disseminated histoplasmosis of infancy [99], but the subacute meningitis and parenchymal lesions characteristic of CNS infections in adults are rarely seen in children. The recommendations for management of progressive disseminated histoplasmosis—the most common reason for treatment in children—will be reviewed in more detail.

Acute Pulmonary Histoplasmosis

Recommendations

39. Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate (1.0 mg/kg daily) is usually well tolerated, and the lipid preparations are not preferred (A-III).

40. Itraconazole dosage in children is 5.0–10.0 mg/kg daily

in 2 divided doses (not to exceed 400 mg daily), generally using the solution formulation (A-III).

Progressive Disseminated Histoplasmosis

Recommendations

41. Amphotericin B deoxycholate (1.0 mg/kg daily for 4–6 weeks) is recommended (A-III).

42. Amphotericin B deoxycholate (1.0 mg/kg daily for 2–4 weeks) followed by itraconazole (5.0–10.0 mg/kg daily in 2 divided doses) to complete 3 months of therapy is an alternative (A-III).

43. Longer therapy may be needed for patients with severe disease, immunosuppression, or primary immunodeficiency syndromes (A-III).

44. Lifelong suppressive therapy with itraconazole (5.0 mg/kg daily, up to 200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed (A-II) and in patients who experience relapse despite receipt of appropriate therapy (C-III).

45. Blood levels of itraconazole should be obtained to ensure adequate drug exposure (B-III).

46. Antigen levels should be monitored during therapy and for 12 months after therapy is ended to monitor for relapse (B-III). Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence of active infection.

Evidence summary. Progressive disseminated infection, often accompanied by meningitis [99], may occur in otherwise healthy infants aged <2 years, presumably resulting from relatively immature cellular immunity. Most are ultimately found to be immunologically healthy. Additional risk factors for disseminated histoplasmosis at any age include large inoculum exposure and acquired immunodeficiency resulting from use of immunosuppressive agents, malnutrition, or HIV infection. Primary immunodeficiency disorders that impair the function of T cells, monocytes, and macrophages also predispose to disseminated histoplasmosis.

Progressive disseminated histoplasmosis in children is fatal if untreated [100]. Amphotericin B deoxycholate (1 mg/kg daily) given for 4 weeks has been used successfully [100–103] and with minimal toxicity. A lipid formulation of amphotericin B (3–5 mg/kg daily) may be substituted if the patient is intolerant of amphotericin B deoxycholate. A shorter course of amphotericin B followed by an azole was effective in 74% of cases [101] and is an alternative to a prolonged course of amphotericin B treatment.

In contrast to cases in adults, meningitis that accompanies progressive disseminated histoplasmosis of infancy responds to amphotericin B deoxycholate (given for 4–6 weeks) without a high rate of relapse [99]. Treatment recommended for progressive disseminated histoplasmosis of infancy does not need to be modified in patients found to have CNS involvement. In a single report, amphotericin B (1 mg/kg daily for 40 days) followed by ketoconazole for 3 months was successful in 88% of cases [99]. The panel favored itraconazole (10 mg/kg daily) in place of ketoconazole, however.

Prolonged treatment with amphotericin B may be needed for patients with large fungal burdens, particularly infants who present with prolonged failure to thrive, pancytopenia, coagulopathy, gastrointestinal ulceration, and meningitis and in severely affected patients who have received TNF antagonist therapy or who have congenital immunodeficiencies that cannot be reversed. Less severe infection can be treated with a 2–4-week course of amphotericin B followed by itraconazole for a total duration of therapy of 3 months in families judged to be compliant with oral therapy.

Experience using itraconazole as sole treatment for progressive disseminated histoplasmosis in infants and older children is limited. In a report of seven children (mean age, 4.6 years) with disseminated histoplasmosis treated with only itraconazole for 3–12 months, 5 were markedly improved at the conclusion of 3–6 months of treatment, and none experienced relapse [104]. One child died 1 month after treatment was stopped. The use of itraconazole as sole treatment of disseminated histoplasmosis is not recommended. However, in infrequent situations, in which the child has only mild-to-moderate symptoms, itraconazole may be considered as primary therapy if the clinical course and laboratory findings are closely monitored. Candidates for oral itraconazole should include those in whom compliance is expected and absorption of the drug is assured.

Children with disseminated histoplasmosis and HIV infection can be treated with the protocol recommended for adults, using dosages appropriate for children. Children with disseminated histoplasmosis should be screened for HIV infection. Low CD4 cell counts are common during the acute phase of disseminated histoplasmosis in infancy [99, 105], and assessment of cellular immunity later in the course is needed to exclude primary immunodeficiency. Antigen testing, as described in the section on adults, should be used to monitor the effectiveness of therapy. The blood antigen level decreases rapidly (within 2 weeks), whereas the urine antigen level may decrease more slowly and may persist in low concentrations for several months before antigenuria fully resolves [102].

PERFORMANCE MEASURES

1. Itraconazole is the preferred azole for initial therapy for patients with mild-to-moderate histoplasmosis and as step-down therapy after receipt of amphotericin B. When other azole agents are used, the medical record should document the specific reasons that itraconazole was not used and why other azoles were used.

2. Patients with severe or moderately severe histoplasmosis should be treated with an amphotericin B formulation initially. When amphotericin B is used, the patient's electrolyte level, renal function, and blood cell count should be monitored several times per week and documented in the medical record.

3. Itraconazole drug levels should be measured during the first month in patients with disseminated or chronic pulmonary histoplasmosis, and these levels should be documented in the medical record, as well as the physician's response to levels that are too low.

4. Itraconazole should not be given to patients receiving contraindicated medications (i.e., pimozide, quinidine, dofetilide, lovastatin, simvastatin, midazolam, and triazolam). Reasons for deviation from this practice should be documented in the medical record.

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Potential conflicts of interest. L.J.W. is President of MiraVista Diagnostics and MiraBella Technologies; he has research contracts with Astellas, Basilea, Schering-Plough, and Bio-Rad Laboratories and serves as a consultant to Bio-Rad Laboratories; L.J.W. is also a speaker for Bio-Rad and Enzon. J.W.B. has received research grants from Merck and Astellas and is on the speakers' bureaus for Merck, Pfizer, and Enzon. A.G.F. serves as a consultant for Enzon and as a speaker for Pfizer, Merck, and Schering. C.A.K. has received research grants from Merck, Astellas, and Schering-Plough and is on the speakers' bureaus for Merck, Pfizer, Astellas, and Schering-Plough. D.S.M. is on the speakers' bureaus of Merck and Pfizer. M.B.K. and J.E.L.: no conflicts.

APPENDIX A.

EXPERT PANEL

Infectious diseases: L. Joseph Wheat (MiraVista Diagnostics, Indianapolis, IN), John W. Baddley (University of Alabama at Birmingham and Birmingham Veterans Affairs Medical Center), Alison G. Freifeld (University of Nebraska Medical Center, Omaha), Carol A. Kauffman (University of Michigan and Veterans Affairs Healthcare System, Ann Arbor), and David S. McKinsey (ID Associates of Kansas City, Kansas City, MO). Pediatric infectious diseases: Martin B. Kleiman (Indiana University School of Medicine, Indianapolis). Pulmonology: James E. Loyd (Vanderbilt University Medical Center, Nashville, TN)

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