Practice Guidelines for the Management of Patients with Histoplasmosis

Joe Wheat,1,2,3 George Sarosi,1,3 David McKinsey,4 Richard Hamill,5 Robert Bradsher,7 Philip Johnson,6 James Loyd,6 and Carol Kauffman9

Executive Summary

Objective. The objective of this guideline is to provide recommendations for treating patients with the more common forms of histoplasmosis.

Participants and consensus process. A working group of 8 experts in this field was convened to develop this guideline. The working group developed and refined the guideline through a series of conference calls.

Outcomes. The goal of treatment is to eradicate the infection when possible, although chronic suppression may be adequate for patients with AIDS and other serious immunosuppressive disorders. Other important outcomes are resolution of clinical abnormalities and prevention of relapse.

Evidence. The published literature on the management of histoplasmosis was reviewed. Controlled trials have been conducted that address the treatment of chronic pulmonary and disseminated histoplasmosis, but clinical experience and descriptive studies provide the basis for recommendations for other forms of histoplasmosis.

Value. Value was assigned on the basis of the strength of the evidence supporting treatment recommendations, with the highest value assigned to controlled trials, according to conventions established for developing practice guidelines.

Benefits and costs. 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 nonprogressive forms of histoplasmosis, however, may reduce functional capacity, affecting work capacity and quality of life for several months. Treatment is clearly beneficial and cost-effective for patients with progressive forms of histoplasmosis, such as chronic pulmonary or disseminated infection. It remains unknown whether treatment improves the outcome for patients with the self-limited manifestations, since this patient population has not been studied. Other chronic progressive forms of histoplasmosis are not responsive to pharmacologic treatment.

Treatment options. Options for therapy for histoplasmosis include ketoconazole, itraconazole, fluconazole, amphotericin B (Fungizone; Bristol-Meyer Squibb, Princeton, NJ), liposomal amphotericin B (AmBisome; Fujisawa, Deerfield, IL), amphotericin B colloidal suspension (ABCD, or Amphotec; Seques, Menlo Park, CA), and amphotericin B lipid complex (ABLC, or Abelcet; Liposome, Princeton, NJ).

Introduction

*Histoplasma capsulatum* is endemic in certain areas of North and Latin America, but cases have also been reported from Europe and Asia. In the United States, most cases have occurred within the Ohio and Mississippi River valleys. Precise reasons for this endemic distribution pattern 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 spores 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.

Severity of illness after inhalation exposure to *H. capsulatum* varies, depending on the intensity of exposure and the immunity of the host. Asymptomatic infection or mild pulmonary disease follows low-intensity exposures in healthy individuals, whereas heavy exposure may cause severe diffuse pulmonary infection. Hematogenous dissemination from the lungs to other tissues probably occurs in all infected individuals during the first 2 weeks of infection before specific immunity has developed, but
is nonprogressive in the majority of cases, which leads to the development of calcified granulomas in the liver and/or spleen. Progressive dissemination occurs primarily in those with underlying immunosuppressive disorders or those at the extremes of age. Progressive pulmonary infection is common in patients with underlying centrilobular emphysema. A variety of acute and chronic manifestations of histoplasmosis appear to result from unusual inflammatory or fibrotic responses to the infection, including rheumatologic syndromes and pericarditis during the first year after exposure, and chronic mediastinal inflammation or fibrosis, broncholithiasis, and enlarging parenchymal granulomas occurring later. A variety of treatment options are available, but first the decision must be made to treat or to observe, since most patients with histoplasmosis recover without therapy (table 1).

Table 1. Indications for antifungal treatment in patients with histoplasmosis.

<table>
<thead>
<tr>
<th>Treatment indicated</th>
<th>Treatment not indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pulmonary histoplasmosis with hypoxemia</td>
<td>Acute self-limited syndromes</td>
</tr>
<tr>
<td>Acute pulmonary histoplasmosis for &gt;1 month</td>
<td>Acute pulmonary histoplasmosis, mildly ill</td>
</tr>
<tr>
<td>Chronic pulmonary histoplasmosis</td>
<td>Rheumatologic</td>
</tr>
<tr>
<td>Esophageal compression and/or ulceration</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Granulomatous mediastinitis with obstruction and/or invasion of tissue</td>
<td>Histoplasmosa</td>
</tr>
<tr>
<td>Disseminated histoplasmosis</td>
<td>Broncholithiasis</td>
</tr>
<tr>
<td></td>
<td>Fibrosing mediastinitis*</td>
</tr>
</tbody>
</table>

* Antifungal therapy has not been proven to be effective for this form of histoplasmosis but should be considered, especially in patients with elevated erythrocyte sedimentation rates or complement fixation titers ≥1 : 32.

Specific Treatment Recommendations

Specific treatment recommendations for the more common types of histoplasmosis are reviewed below and in table 2.

Acute Pulmonary Histoplasmosis

Fever, chills, headache, myalgia, anorexia, cough, and chest pain characterize this form of histoplasmosis and are seen in 85%–100% of cases. Patients may experience pleuritic pain. The findings on examination are usually unremarkable, except for fever, but may include rales or pleural friction rubs.

The course after low-level exposure is benign in immunocompetent patients. Symptoms usually abate within a few weeks of onset [1]. Therapy may be helpful in symptomatic patients whose conditions have not improved during the first month of infection. Fever persisting for >3 weeks in acute histoplasmosis may indicate that the patient is developing progressive disseminated disease, which may be aborted by therapy. Whether antifungal therapy hastens recovery or prevents complications is unknown, since it has never been studied in prospective trials.

Patients with diffuse radiographic involvement following more intense exposure often experience more severe disease. They may become hypoxemic and even require ventilatory support. Without treatment, recovery is usually slow and the outcome may be fatal.

Localized pulmonary histoplasmosis. Treatment is not indicated in the typical patient with acute pulmonary histoplasmosis because the illness is self-limited and associated with minimal morbidity (EIII; see article by Sobel [2] for definitions of categories reflecting the strength of each recommendation for or against its use and grades reflecting the quality of evidence on which recommendations are based).

Treatment with itraconazole, 200 mg once daily for 6–12 weeks, should be considered for patients who have shown no clinical improvement after 1 month of observation (BIII). Blood concentrations of itraconazole obtained 2–4 h after administration of a dose could be monitored in selected situations: suspected treatment failure, concern about compliance or absorption, use of medications that may reduce the solubility of itraconazole or accelerate its metabolism, and desire to reduce the dose from 200 mg twice daily to 200 mg once daily. Although the “therapeutic” concentration has not been defined, the MIC90 of itraconazole for *H. capsulatum* is .02 µg/mL, which suggests that serum concentrations of 1 µg/mL measured by bioassay should be therapeutic. Among AIDS patients, the median plasma concentration was about 6 µg/mL for patients receiving a dosage of 200 mg twice daily and ~3 µg/mL for those receiving 200 mg once daily [3].

Diffuse pulmonary histoplasmosis in an immunocompetent host. Amphotericin B, 0.7 mg/kg/d (or 1 of the lipid preparations at a dose of 3 mg/kg/d for patients with renal impairment) should be used initially in those patients with more severe manifestations who require ventilatory supportive therapy (AIII). If amphotericin B is used exclusively because the patient cannot be treated with oral medications, a total course of ≈35 mg/kg is recommended, but this situation is expected to be rare (AIII).

The inflammatory response may contribute to the pathogenesis of the respiratory compromise; thus, corticosteroids may be helpful, and prednisone could be administered at a dosage of 60 mg daily for 2 weeks [4] (CIII). The role of corticosteroids for treating extensive pulmonary histoplasmosis in the immunocompromised host is less clear. Patients with AIDS and concurrent disseminated histoplasmosis and *Pneumocystis carinii* pneumonia who received corticosteroids in conjunction with treatment for both microbial pathogens did not appear to do more poorly than other patients treated with antifungal therapy only.
After discharge from the hospital, itraconazole, 200 mg once or twice daily, should be used to complete a 12-week course (BIII).

Itraconazole alone, 200 mg once or twice daily for 6–12 weeks, could be used for patients who are not sufficiently ill to require hospitalization (BIII).

**Chronic Pulmonary Histoplasmosis**

Patients with underlying lung disease may develop chronic pulmonary infection after exposure to *H. capsulatum*. The clinical and radiographic findings resemble those seen in reactivation tuberculosis [5]. Without treatment, the illness is progressive, causing loss of pulmonary function in most patients and death in up to half [5, 6]. In 1 study, although only 30% of cases progressed after 1 year, 79% progressed with longer observation [5]. Although some patients improve spontaneously, they remain at risk for recrudescence.

Treatment is indicated in all patients with chronic pulmonary histoplasmosis. Studies have shown amphotericin B to be effective in 59%–100% of cases [6–14] (table 3). Ketoconazole and itraconazole are effective in 75%–85% of case patients, but their use is also complicated by high relapse rates [11–13]. Fluconazole, 200–400 mg daily, appears to be less effective (64% response) than ketoconazole or itraconazole [14].

Itraconazole, 200 mg once or twice daily for 12–24 months, is the treatment of choice for chronic pulmonary histoplasmosis (AII).

Amphotericin B, 50 mg daily, or about 0.7 mg/kg/d, is recommended for patients who are judged to require hospitalization because of ventilatory insufficiency or general debilitation, inability to take itraconazole because of drug interactions or allergies, inability to absorb itraconazole, inability to achieve detectable concentrations of itraconazole in the blood, or failure to improve clinically after at least 12 weeks of itraconazole therapy (AII). Some patients may not be able to tolerate that dosage of amphotericin B, which justifies reducing the dosage to 0.5–0.6 mg/kg/d or to use of 1 of the lipid formulations. If amphotericin B is administered for the full course of therapy, at least 35 mg/kg should be given at doses of 50 mg 3 times weekly, if tolerated. In most patients, however, treatment can be changed to itraconazole, 200 mg once or twice daily.

Fluconazole, 200–400 mg daily, is less effective than amphotericin B or itraconazole and yielded a response rate of 64% in 1 study [14]. Fluconazole could be used in patients who cannot receive itraconazole or are unable to achieve detectable blood concentrations with itraconazole, but the dose should be increased to 400–800 mg daily (BIII). In a study of patients with AIDS who had disseminated histoplasmosis, 800 mg daily was used for histoplasmosis [15].

Ketoconazole (200 mg, 400 mg, or 800 mg daily) is reasonably effective but less well-tolerated than itraconazole or fluconazole [12, 13]. Toxicity is more common in patients receiving the 800 mg daily dosage, which is discouraged.

**Disseminated Histoplasmosis**

Underlying immunosuppressive conditions and extremes of age are risk factors for dissemination, and illness is more severe in immunocompromised individuals. Fever and weight loss are the most common symptoms, and hepatomegaly or splenomegaly are common physical findings of disseminated histoplasmosis. Other frequent sites of dissemination include the oropharyngeal or gastrointestinal mucosa, the skin, and the adrenal glands. Shock, respiratory distress, hepatic and renal failure, and coagulopathy may complicate severe cases [16]. CNS involvement occurs in 5%–20% of cases, presenting as chronic meningitis or focal brain lesions. *Histoplasma* rarely...
infects the spinal cord. The mortality without treatment is 80% but can be reduced to <25% with antifungal therapy [6, 11–22] (table 4). Treatment is indicated for all patients with progressive disseminated histoplasmosis.

In studies that mostly included immunocompetent hosts and specifically excluded those with AIDS, amphotericin B was effective in 68%–92% of patients [6, 17, 18], itraconazole (200–400 mg daily) in 100% (only 10 patients studied) [11], ketoconazole (200–400 mg daily) in 56%–70% [12, 13], and fluconazole (200–400 mg daily) in 86% [14] (table 4).

Among patients with AIDS, therapy with amphotericin B was effective in 74%–88% of patients [19, 20], itraconazole (400 mg daily for 12 weeks) in 85% [21], ketoconazole (200-400 mg daily) in 9% (only 11 cases) [16], and fluconazole (800 mg daily for 12 weeks) in 74% [15] (table 4). Of note, patients with severe or moderately severe clinical manifestations were excluded from the prospective studies that used itraconazole [21] and fluconazole [15] but not from the retrospective reviews of patients treated with amphotericin B. Of patients with severe disease, nearly half died despite treatment with amphotericin B, whereas 98% of those with less severe illness responded to therapy [20].

There are no published reports about the use of the newer lipid preparations of amphotericin B for treating histoplasmosis [16]. Most patients respond to therapy rapidly, with resolution of fever in 1–2 weeks. Therapy is not curative for patients with AIDS. Lifelong maintenance therapy is needed to prevent relapse in patients with AIDS and disseminated histoplasmosis. Amphotericin B, 50 mg given weekly or twice weekly, is highly effective (81%–97%) but inconvenient and not well-tolerated [16, 23]. Itraconazole, 200–400 mg daily, was effective in at least 90% of cases [22]. Fluconazole, 100–400 mg daily was effective maintenance therapy in 88% of patients with AIDS who received amphotericin B induction therapy [24]. However, in a prospective study, relapse occurred in nearly one-third of patients who received fluconazole, 400 mg daily, after successful induction therapy with fluconazole, 800 mg a day [15]. In vitro resistance to fluconazole developed in isolates from about half of those patients who relapsed [15].

**Immunocompetent hosts and immunocompromised hosts with-out AIDS.** Amphotericin B, 0.7–1.0 mg/kg/d is recommended for patients who are sufficiently ill to require hospitalization (table 2) (AII). Experience using the lipid formulations of amphotericin B for treating histoplasmosis has not been reported. Most patients respond quickly to amphotericin B and can then be treated with itraconazole. The transition from amphotericin B to itraconazole therapy could occur after the patient becomes afebrile, no longer requires blood pressure or ventilatory support or iv fluids or nutrition, and is able to take oral medications. If amphotericin B is to be used for the full course, the total dosage should be 35 mg/kg given over 2–4 months.

Itraconazole, 200 mg once or twice daily for 6–18 months, is the treatment of choice for patients with mild or only moderately severe symptoms who do not require hospitalization, and for continuation of therapy in those whose condition has improved in response to amphotericin B (AII).

Fluconazole should be used only in patients who cannot take itraconazole (BII). The fluconazole dosage should be at least 400 mg daily in nonimmunocompromised individuals and 800 mg daily in those with severe immunosuppressive conditions. *H. capsulatum* may develop resistance to fluconazole during therapy, leading to relapse [25] and thus necessitating careful follow-up assessment, including measurement of *H. capsulatum* antigen concentration in blood and urine (BIII).

Ketoconazole, 200 mg once or twice daily, is also reasonably effective (56%–70% response rate) but less well-tolerated than itraconazole or fluconazole [12, 13]. Ketoconazole could be used in some situations where itraconazole is contraindicated (BII).

Antigen testing may be useful for monitoring therapy in patients with disseminated histoplasmosis. Most of the data on the use of the antigen test for monitoring therapy are derived from studies of patients with AIDS. Antigen concentrations decrease with therapy [16, 22] and increase with relapse [3, 26]. Some investigators recommend that treatment should be continued until antigen concentrations revert to negative or at least reach low levels of <4 units. If treatment is stopped before antigen concentrations in urine and serum revert to negative, patients should be followed closely for relapse, and antigen levels should be monitored every 3–6 months until they become negative (BIII).

**Patients with AIDS as the cause of immunosuppression.** Therapy is divided into an initial 12-week intensive phase to induce a remission in the clinical illness and then followed by a chronic maintenance phase to prevent relapse. A similar approach may be appropriate in other patients without AIDS who have relapsed after appropriate courses of therapy.

For induction therapy, amphotericin B is recommended for patients who are sufficiently ill to require hospitalization (table 2) (AII). Amphotericin B can be replaced with itraconazole, 200 mg twice daily (when the patient no longer requires hospitalization or iv therapy), to complete a 12-week total course of induction therapy.

### Table 3. Outcome of antifungal therapy for patients with chronic pulmonary histoplasmosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antifungal agent</th>
<th>No. of patients treated</th>
<th>Treatment outcome, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putnam [9]</td>
<td>Amphotericin B</td>
<td>32</td>
<td>100 NR NR</td>
</tr>
<tr>
<td>Sulfitt [8]</td>
<td>Amphotericin B</td>
<td>16</td>
<td>81 12 6</td>
</tr>
<tr>
<td>Baum [10]</td>
<td>Amphotericin B</td>
<td>56</td>
<td>96 9 NR</td>
</tr>
<tr>
<td>Dismukes [12]</td>
<td>Ketoconazole</td>
<td>23</td>
<td>74 4 NR</td>
</tr>
<tr>
<td>Slama [13]</td>
<td>Ketoconazole</td>
<td>7</td>
<td>86 NR NR</td>
</tr>
<tr>
<td>McKinsey [14]</td>
<td>Fluconazole</td>
<td>11</td>
<td>64 29 NR</td>
</tr>
</tbody>
</table>

**NOTE.** NR, not reported.
Table 4. Outcome of antifungal therapy for patients with disseminated histoplasmosis.

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Antifungal agent</th>
<th>No. of patients treated</th>
<th>Treatment outcome, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Responded</td>
</tr>
<tr>
<td>Sathapatayavongs [19]</td>
<td>Amphotericin B</td>
<td>43</td>
<td>74</td>
</tr>
<tr>
<td>Reddy [17]</td>
<td>Amphotericin B</td>
<td>17</td>
<td>76</td>
</tr>
<tr>
<td>Sarosi [18]</td>
<td>Amphotericin B</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>Wheat [16, 20]a</td>
<td>Amphotericin B</td>
<td>73</td>
<td>88</td>
</tr>
<tr>
<td>Dismukes [11]</td>
<td>Itraconazole</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Wheat [21, 22]</td>
<td>Itraconazole</td>
<td>59</td>
<td>85</td>
</tr>
<tr>
<td>Dismukes [12]</td>
<td>Ketoconazole</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>Slama [13]</td>
<td>Ketoconazole</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>Wheat [16]b</td>
<td>Ketoconazole</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Wheat [15]</td>
<td>Fluconazole</td>
<td>49</td>
<td>74</td>
</tr>
</tbody>
</table>

NOTE: NR, not reported.
a These studies were done in patients with AIDS.
b Relapses occurred in patients who responded to induction therapy and continued the medication chronically for maintenance, although some of the relapses occurred in patients who were not compliant with therapy or in those who were receiving rifampin.

Itraconazole, 200 mg 3 times daily for 3 days and then twice daily for 12 weeks is the treatment of choice for patients who have mild or moderately severe symptoms who do not require hospitalization (AII).

Fluconazole, 800 mg daily, is an alternative for patients who cannot take itraconazole (BIi). Patients who are receiving fluconazole should be followed closely clinically for relapse, and antigen concentrations in urine and blood should be monitored quarterly and at the time of suspected relapse (BIII).

For maintenance therapy, the treatment of choice is itraconazole 200 mg once or twice daily for life (AII). Antigen concentrations in serum and urine should be monitored every 3–6 months to provide evidence that maintenance therapy is continuing to suppress the progression of infection (BIII).

Amphotericin B, 50 mg iv once weekly, is an alternative but is not as well-tolerated or accepted by patients and should be reserved for patients who cannot take itraconazole (BIi).

Fluconazole, 400–800 mg daily, could be used for patients who cannot tolerate or do not absorb itraconazole and prefer not to be treated with amphotericin B, but fluconazole therapy is discouraged because of its reduced efficacy as chronic maintenance therapy for histoplasmosis (DII). Patients receiving fluconazole should be followed closely clinically for relapse, and antigen concentrations in urine and blood should be monitored quarterly and at the time of suspected relapse.

For prophylaxis in immunocompromised subjects, itraconazole is recommended. A trial comparing itraconazole, 200 mg daily, versus placebo in patients with CD4+ counts <150/μL showed a 2-fold reduction in the incidence of histoplasmosis in the itraconazole group, compared with the placebo group (6.8%–2.7%) during a median follow-up period of 1 year [27].

In regions experiencing high rates of histoplasmosis (>5 cases/100 patient-years), prophylaxis with itraconazole is recommended (200 mg once daily) (BI). Fluconazole is not an acceptable alternative because of its inferior activity against *H. capsulatum*, and lower efficacy for treatment of histoplasmosis [15].

CNS Histoplasmosis

Manifestations include meningitis, focal brain or spinal cord lesions, cerebrovascular accident caused by vascular involvement or cerebral emboli, and diffuse encephalitis [28]. Symptoms usually have been present for months to years before diagnosis. Fever, headache, confusion, mental status changes, seizures, or focal neurological deficits may be seen. CSF abnormalities include lymphocytic pleocytosis, protein elevation, and hypoglycorrhachia in patients with meningitis. Single or multiple enhancing lesions may be seen by CT scan or MRI in the brain or spinal cord of those with parenchymal involvement [28].

The course of the disease is progressive and fatal if not treated, although the speed of clinical deterioration is highly variable [28]. The response to therapy is inferior to that in other types of histoplasmosis: 20%–40% of patients with meningitis succumb to the infection, despite treatment with amphotericin B, and up to half of responders relapse after therapy is discontinued [28].

The optimal treatment for *Histoplasma* meningitis is unknown, but an aggressive approach is recommended because of the poor outcome.

Amphotericin B, 0.7–1 mg/kg/d to complete a 35 mg/kg total dose over 3–4 months has been used most often (BIII). Fluconazole, 800 mg daily, might be continued for another 9–12 months after completion of amphotericin B, to reduce the risk for relapse (BIII).

Liposomal amphotericin B (AmBisome), 3–5 mg/kg/d or every other day given over a 3–4 month period might be considered for patients who have failed therapy with amphotericin B followed by fluconazole (CIII). In animal studies, liposomal
amphotericin B achieved higher concentrations in the blood and brain than did amphotericin B or the other lipid formulations [29], which provides a theoretical basis for its use in meningitis. However, neither the lipid preparation nor amphotericin B achieve detectable concentrations in CSF [29–31], and none have been evaluated in cases of Histoplasma meningitis.

Chronic fluconazole maintenance therapy, 800 mg daily, should be considered for patients who relapse, despite full courses of therapy, as described elsewhere (CIII).

Itraconazole, although more active than fluconazole against H. capsulatum, does not enter the CSF, which makes it a less appealing choice for treatment of meningitis and discourages its use for this indication (DIII). Of note, however, the role of CSF concentrations of antifungal agents in the outcome of treatment of fungal meningitis is unclear.

Patients who relapse despite chronic maintenance therapy are candidates for administration of amphotericin B directly into the ventricles, cisterna magna, or lumbar arachnoid space. Experience using intrathecal or intraventricular therapy, however, has not been encouraging; this approach to therapy is discouraged except for patients for whom all other approaches to therapy have failed [28] (DIII).

Focal involvement of the brain or spinal cord in the absence of meningitis may be more responsive to antifungal therapy. Of 6 such cases in persons without AIDS, all responded to amphotericin B therapy, but 2 relapsed [28]. Amphotericin B is recommended for the initial therapy (BIII). Penetration of the CSF may not be required for successful therapy of parenchymal lesions; thus itraconazole, 200 mg 2 or 3 times daily, may be appropriate after the patients’ conditions have improved with amphotericin B (CIII).

Parenchymal lesions rarely require surgical excision [28] (DIII).

Granulomatous Mediastinitis

Symptoms that include chest pain, cough, hemoptysis, and dyspnea may be caused by compression of the airways, superior vena cava, or pulmonary vessels in patients with granulomatous mediastinitis. These syndromes represent active inflammation of the mediastinal lymph nodes rather than fibrotic reactions to past infection. Although symptoms are often mild and resolve over a few months, they may be more severe and protracted. Antifungal therapy has been helpful in some cases [32, 33]. Adjunctive treatment with corticosteroids appeared to have been beneficial in 1 patient who had airway obstruction [34]. Resection of obstructive masses is another approach that has been helpful for patients with granulomatous mediastinitis [35–38].

Amphotericin B, 0.7–1.0 mg/kg/d, should be considered as initial therapy for patients with severe obstructive complications of mediastinal histoplasmosis (BIII). Therapy could be changed to itraconazole, 200 mg once or twice daily, after improvement is sufficient for outpatient treatment.

Itraconazole, 200 mg once or twice daily for 6–12 months, is recommended for patients with milder manifestations that persist for >1 month (table 3) (BIII).

Prednisone, 40–80 mg daily for 2 weeks, could be considered in those with major airway obstruction (CIII).

Surgical resection of the mediastinal mass should be reserved for patients who remain symptomatic and continue to demonstrate obstruction of major mediastinal structures, despite a trial of antifungal therapy (BIII).

Fibrosing Mediastinitis

Fibrosing mediastinitis is a late complication of histoplasmosis arising from nodal regions and ultimately invasion and obstruction of the central vessels and airways. Patients often report symptoms of several years’ duration at the time of diagnosis. The course is progressive and often fatal [39, 40]. Although most authorities believe that neither antifungal nor anti-inflammatory treatment ameliorates the outcome of fibrosing mediastinitis [39, 40], others have reported improvement after antifungal therapy [41].

Information is inadequate on which to make firm treatment recommendations. The progressive course of this syndrome, however, makes it difficult to withhold antifungal therapy. If the clinical findings are consistent with a more acute inflammatory process rather than a chronic fibrotic process, especially if complement fixation titers and the erythrocyte sedimentation rate are elevated, treatment may be helpful.

A 12-week trial of itraconazole, 200 mg once or twice daily, is suggested if clinical findings do not differentiate fibrosing mediastinitis from granulomatous mediastinitis (CIII). Patients who truly have fibrosing mediastinitis are not expected to respond to antifungal therapy. The only basis to prolong therapy beyond 12 weeks would be clearcut radiographic demonstration of abatement of obstruction, in which case therapy could be continued for 1 year.

Corticosteroid therapy has not been helpful when tried [39, 42, 43] and is discouraged (DIII).

Surgery should be approached with great caution in patients with severe complications of fibrosing mediastinitis and only in those who are expected to succumb from the condition without intervention. Surgeons experienced in the management of fibrosing mediastinitis should be consulted (CIII).

Placement of intravascular stents has been helpful in some patients with superior vena cava, pulmonary artery, or pulmonary vein obstruction, and might be tried in patients with severe manifestations (CIII).

Pericarditis

Pericarditis occurs in 5%–10% of patients with acute histoplasmosis and appears to be caused by the inflammatory response to the infection rather than the infection per se. These manifestations rarely may be a complication of disseminated
Histoplasmosis [44]. Patients with pericarditis respond to nonsteroidal anti-inflammatory agents without antifungal therapy, but those with pericardial tamponade often require percutaneous or surgical drainage of the pericardial fluid [44]. Long-term outcome is excellent, with only rare progression to constrictive pericarditis [44].

Antifungal therapy is not recommended (DIII).

Therapy with nonsteroidal anti-inflammatory agents is recommended for 2–12 weeks, on the basis of clinical resolution of the symptoms and physical findings of pericarditis (BIII). Corticosteroids might be tried for 1–2 weeks in patients with hemodynamic compromise, followed by continued treatment with nonsteroidal anti-inflammatory agents, until the clinical findings and radiographic evidence of cardiomegaly resolved (CIII). Concurrent itraconazole, 200 mg once or twice daily for 12 weeks, could be given along with corticosteroids, to reduce the concern that corticosteroids might promote progression of the infection (CIII).

Percutaneous or surgical drainage is recommended for patients with more severe findings of pericardial tamponade or with moderately severe evidence of hemodynamic compromise that does not respond to corticosteroids (AIII). There is no evidence that antifungal, anti-inflammatory, or surgical therapy prevents constrictive pericarditis (DIII).

Rheumatologic Syndromes

The arthritis is polyarticular and symmetrical in half of cases and involves joints of the upper and lower extremities with similar frequency. Nearly half of patients with rheumatologic manifestations exhibit erythema nodosum and/or erythema multiforme [45, 46]. The joint symptoms usually resolve in response to treatment with nonsteroidal anti-inflammatory agents.

Antifungal therapy is not recommended (DIII).

Therapy with nonsteroidal anti-inflammatory agents is recommended for 2–12 weeks, on the basis of resolution of the symptoms and physical findings of arthritis and erythema nodosum (BIII). Relapse may occur after anti-inflammatory therapy is stopped, thus requiring reinstallation for another 4–8 weeks.

Histoplasmosis During Pregnancy

Pregnant women with histoplasmosis should not be treated with azole antifungal agents because of the potential of this class of drugs to cause teratogenic complications. Amphotericin B, however, is safe during pregnancy and is the treatment of choice for such cases. The safety of the lipid preparations of amphotericin B during pregnancy is unknown. There is no evidence that histoplasmosis is more severe during pregnancy or that dissemination occurs to the fetus.

References


