Update on Therapy for Histoplasmosis

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Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*, which is endemic to the Ohio and Mississippi river valleys. It is associated with a variety of manifestations, and its severity ranges from asymptomatic infection to severe disseminated illness.

**Key words:** Histoplasmosis, Amphotericin B, Itraconazole

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*, which is endemic to the Ohio and Mississippi river valleys. It is associated with a variety of manifestations, and its severity ranges from asymptomatic infection to severe disseminated illness. Treatment is often based on the severity and site of the disease. Updated guidelines for the treatment of histoplasmosis have been published by the Infectious Diseases Society of America.\(^1\) In the treatment of histoplasmosis, the first-line agents are amphotericin B (AmB) and itraconazole (Table A, B). AmB is commonly used for severe disease, at least during initial treatment. Lipid formulations are preferred. These include liposomal AmB and AmB lipid complex. The deoxycholate formulation can be used if the risk of nephrotoxicity is low. For CNS disease and disseminated disease in patients with HIV/AIDS, liposomal AmB is preferred.\(^1,2\) Treatment can be switched to oral itraconazole once clinical response is seen. This usually occurs within 1 to 2 weeks. Itraconazole is the mainstay of therapy for most forms of histoplasmosis, either as initial therapy in milder disease or as follow-on therapy after treatment with AmB in severe disease. It is available in both capsule and liquid forms. Higher blood concentrations are achieved with the liquid, which
should be given on an empty stomach. However, adverse GI effects occur more frequently with the liquid formulation than with the capsule. Itraconazole capsules should be given with food or cola to help increase absorption. Because antacids, histamine-2 blockers, and proton pump inhibitors will decrease absorption, they should not be given concurrently with itraconazole. Hepatotoxicity can occur; therefore, monitoring of hepatic enzyme levels at baseline and intermittently during therapy is recommended. Serum itraconazole levels should be assessed after 2 weeks of therapy. Drug levels should also be assessed after dose adjustments and the addition of new medications that may interact with itraconazole as well as in the setting of treatment failure. Random concentrations should be at least 1.0 µg/mL. \(^1\) Levels greater than 10 µg/mL should raise concern about toxicity, and the dose should be lowered.

Fluconazole is not preferred for treatment of histoplasmosis; it is less active in vitro and has been associated with higher relapse rates and the development of resistance. \(^3,4\) Its use as a second-line agent is indicated in cases in which itraconazole is not tolerated.

Newer antifungal agents include posaconazole, voriconazole, and echinocandins. Posaconazole appears to be active against \(H\) capsulatum in vitro, \(^5\) and it shows promise in the setting of salvage therapy in experimental models. \(^6\) Voriconazole also has been used successfully in some case studies. \(^7\) Echinocandins have little activity in vitro and in murine models and should not be used for the treatment of histoplasmosis. \(^8\)

**Pulmonary histoplasmosis**

Although pulmonary histoplasmosis is commonly asymptomatic, patients can present with acute, severe respiratory disease. In addition, chronic cavitary disease can develop, particularly in patients with underlying structural lung disease, resulting in significant loss of lung function over time. In cases of acute disease with only mild to moderate symptoms, treatment is not recommended; more than 95% of patients improve without therapy within 3 weeks. \(^9\) If symptoms do not improve after 1 month, it is reasonable to treat the patient with a 6- to 12-week course of itraconazole.

For acute, severe pulmonary disease, treatment should begin immediately. A lipid formulation of AmB is preferred and should be given for the initial 1 to 2 weeks of treatment, followed by itraconazole to complete a 3-month course of therapy. If patients have acute respiratory distress symptoms, methylprednisolone is indicated as well for the first 1 to 2 weeks of therapy. \(^1\) Treatment is indicated for chronic cavitary disease. It usually is effective, although relapse occurs in up to 15% of patients. \(^10\) Generally, itraconazole should be used for at least 1 year. Some experts recommend 18 to 24 months of treatment. \(^1\) Response to therapy can be monitored by chest imaging. Patients should be followed up for several years after treatment because of the risk of relapse.

Complications of pulmonary histoplasmosis include mediastinal lymphadenitis, mediastinal granulomas, fibrosing mediastinitis, broncholithiasis, pulmonary nodules or histoplasmosomas, pericarditis, and rheumatological symptoms. Patients with mediastinal lymphadenitis can present with chest pain, cough, atelectasis, or dysphagia. Treatment is not usually necessary, although corticosteroids can help relieve compressive symptoms. If corticosteroids are used or if symptoms are prolonged, itraconazole should be given for 6 to 12 weeks. \(^1\)

A mediastinal granuloma is a large coalesced mass of lymph nodes that develops as a complication of histoplasmosis. It is frequently found incidentally during chest imaging. Asymptomatic patients do not require treatment. Compression can sometimes cause symptoms. Itraconazole therapy for 6 to
12 weeks is reasonable for symptomatic patients, and surgery is an option for patients who do not respond to pharmacological treatment.\(^1\)

Fibrosing mediastinitis, a rare but serious complication of pulmonary histoplasmosis, causes progressive fibrosis of lymph nodes and can result in compression of airways or blood vessels.\(^1\)

Antifungal and anti-inflammatory agents are unlikely to influence the disease course. If vascular obstruction is present, intravascular stenting can be pursued. Airway stenting should be used only as a last resort because granulation tissue formation often results in further obstruction. Surgery is a consideration, but operative mortality rates are high.\(^1\)

Broncholithiasis occurs when calcified lymph nodes erode into adjacent bronchi. Surgical or bronchoscopic removal may be necessary. Antifungal therapy does not play a role in the treatment of this condition.

Pulmonary nodules or histoplasmomas occur at sites previously affected by *Histoplasma* and commonly enlarge or cavitate slowly. They are often asymptomatic. Active infection is usually not present in isolated nodules, and antifungal therapy is not indicated. If patients are symptomatic and have multiple nodules, acute pulmonary histoplasmosis should be suspected and treated.\(^1\)

Pericarditis is an inflammatory complication of acute pulmonary histoplasmosis and is not related to active infection of the pericardium. NSAIDs are often sufficient for treatment, although corticosteroids should be used for treatment of severe disease.\(^1\)

Effusion drainage may be necessary if hemodynamic compromise occurs. Antifungal agents are necessary only if corticosteroids are used, in which case itraconazole can be given for 6 to 12 weeks.

Finally, arthritis and arthralgias may present as an inflammatory complication of acute pulmonary histoplasmosis.\(^1\)

Erythema nodosum can occur as well. NSAIDs will aid in recovery, although corticosteroids may be required in the setting of severe disease, in which case itraconazole should be given as well.

**Progressive disseminated histoplasmosis**

Hematogenous dissemination probably occurs in many patients with acute histoplasmosis but is eventually controlled by cell-mediated immunity. Progressive disseminated disease develops in 0.05% of patients, particularly in those who are immunosuppressed. Disseminated histoplasmosis can affect multiple organ systems, including the bone marrow, liver, CNS, GI tract, lymph nodes, adrenal glands, mucosa, and skin. The disease is nearly always fatal if untreated. In patients who are ill and require hospitalization, initial treatment with AmB to eradicate fungemia is preferred.\(^1\)

Liposomal AmB is the drug of choice in patients with HIV/AIDS. Its use has been associated with higher response rates and lower mortality compared with use of AmB deoxycholate in this patient population.\(^2\)

Although previous guidelines recommended treating with liposomal AmB for the entire course, the current recommendation is to switch to oral itraconazole after an initial 1 to 2 weeks of treatment.\(^1\)

In patients who have mild to moderate illness, itraconazole can be used as first-line therapy. It should be continued for at least 1 year, with monitoring of drug levels during therapy. In addition, response should be assessed with serum and urine antigen monitoring. Antigen levels should be assessed at 2 weeks and 1 month before treatment and then every 3 months during therapy and for 6 months after treatment is discontinued.\(^1\)

Prolonged suppression (secondary prophylaxis) with once-daily itraconazole is recommended for patients who experience relapse or are in irreversible immunosuppression. Itraconazole can be discontinued in patients with HIV/AIDS after 1 year if blood cultures are negative for *Histoplasma*, serum and urine *Histoplasma* antigen levels are less than 2 ng/mL (4 U/mL), and the CD4\(^+\) cell count is greater than 150/µL while they are receiving highly active antiretroviral therapy.\(^1\)

Prophylaxis for disseminated histoplasmosis with once-daily itraconazole is recommended for HIV-infected patients with CD4\(^+\) cell counts of less than 150/µL who are living in areas in which *H. capsulatum* is highly endemic (more than 10 cases per 100 patient-years).\(^1\)

**CNS histoplasmosis**

CNS histoplasmosis can present as meningitis as well as parenchymal lesions. Response to therapy is often not as good as is seen in other forms of the disease, and the relapse rate tends to be higher. Liposomal AmB at a dosage of 5 mg/kg/d is recommended for CNS histoplasmosis because higher levels of drug in the brain are thought to be achieved with this formulation than with other formulations of AmB.\(^1\)

A 4- to 6-week course of liposomal AmB is preferred, followed by itraconazole given 2 or 3 times daily for at least a year. Itraconazole levels and *Histoplasma* antigen levels should be monitored. Abnormal findings from cerebrospinal fluid analysis or on radiographic imaging or abnormal antigen levels should be resolved before discontinuation of therapy.

**Conclusions**

- Antigen levels should be resolved before discontinuation of therapy.
- Abnormal findings from cerebrospinal fluid analysis or on radiographic imaging should be monitored.
- Itraconazole levels and formulations of AmB should be considered.
- Liposomal AmB at a dosage of 5 mg/kg/d is recommended for CNS histoplasmosis.
- Response to therapy should be assessed with serum and urine antigen monitoring.
- Antigen levels should be continued for at least 1 year, with monitoring of drug levels during therapy.
- In addition, response should be assessed with serum and urine antigen monitoring.
- Prolonged suppression (secondary prophylaxis) with once-daily itraconazole is recommended for patients who experience relapse or are in irreversible immunosuppression.
- Prophylaxis for disseminated histoplasmosis with once-daily itraconazole is recommended for HIV-infected patients with CD4\(^+\) cell counts of less than 150/µL who are living in areas in which *H. capsulatum* is highly endemic.
Histoplasmosis is a disease with many manifestations. Multiple antifungal agents are available, but AmB and itraconazole are the mainstays of therapy.

References:
REFERENCES

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