

A PEER-REVIEWED ARTICLE

Histoplasmosis can be severe for HIV-infected persons in endemic areas

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Histoplasma capsulatum is a fungal organism endemic to the Ohio and Mississippi river basin areas of the United States, as well as parts of Central and South America, Europe, Africa, and Asia. This organism is found in the soil, typically in moist areas where the soil is enriched with organic material such as bird and bat droppings. It is a dimorphic fungus, existing as a mold in the environment and as a yeast at body temperature. Primary infection occurs when infectious microconidia are inhaled from the soil in an endemic area. Most cases occur sporadically, although large outbreaks have occurred in association with construction or demolition projects. There is a spectrum of disease, ranging from asymptomatic or mild, self-limited infections in immunocompetent patients, to disseminated, severe infections in the immunocompromised such as persons with the Acquired Immune Deficiency Syndrome (AIDS). Infection can be primary, from direct exposure to the organism, or reactivation of a latent focus that may have been acquired years before.

Clinical manifestations

Histoplasmosis is common in endemic areas, but most infections are asymptomatic, or manifest as a mild subclinical illness. Public Health Service studies from the 1960s demonstrated that 80% of young adults in the states bordering the Ohio and Mississippi Rivers had evidence of previous infection with *H. capsulatum*. Of the relatively small number of symptomatic persons, pulmonary infections predominate in those with normal immune systems or those only mildly immunosuppressed. Immunocompromised persons may have only pulmonary symptoms but are more likely to develop severe, disseminated disease.

Pulmonary infections range from a self-limited, acute pneumonia to severe, life-threatening acute respiratory distress syndrome (ARDS). Acute pulmonary histoplasmosis is associated with fever, chills, malaise, chest discomfort, and dry cough. Chest radiographs may show a patchy infiltrate in one or more lobes and hilar lymphadenopathy. Immunocompromised persons or those who inhale a large amount of *H. capsulatum* may develop a severe infection with acute onset of fever, chills, dyspnea, and chest pain. Chest radiographs may show diffuse, multilobar infiltrates. Progression to ARDS may occur over the course of several days. Cavitory lesions are chronic and almost always occur in the setting of pre-existing lung disease. The presentations of pulmonary histoplasmosis may be indistinguishable from pulmonary blastomycosis or tuberculosis.

Hematologic dissemination of *H. capsulatum* throughout the reticuloendothelial

system may occur in all infections. Proliferation of histoplasma-specific T-lymphocytes activate macrophages to control the infection. In persons with defects in cell-mediated immunity, the organism proliferates, resulting in disseminated disease. Persons with AIDS or hematologic malignancies, transplant recipients, and those on immunosuppressive medications such as chronic steroids and tumor necrosis factor antagonists are particularly at risk.

In endemic areas, histoplasmosis is frequently the first manifestation of HIV infection and AIDS. Patients with absolute CD4 counts less than 150 cells/ μ L are most at risk for developing disseminated disease. Symptoms include fevers, chills, nightsweats, anorexia, malaise, and weight loss and typically develop insidiously over the course of days to weeks. Dyspnea and cough are not uncommon. GI symptoms including nausea, vomiting, diarrhea, or GI bleeding may occur in up to 45% of patients. On physical exam, hepatosplenomegaly and lymphadenopathy may be seen. Pancytopenia may present with petechiae and pallor. Oral ulcerations may be seen on the lips, tongue, palate, or buccal mucosa and should prompt the consideration of histoplasmosis in persons with AIDS. A sepsis syndrome may be seen with hypotension, renal failure, disseminated intravascular coagulation, and ARDS. A few cases of Hemophagocytic Syndrome have been reported with disseminated histoplasmosis in HIV patients.

Disseminated histoplasmosis in AIDS patients can involve any organ system. Lesions may be seen on GI endoscopy with the colon being most commonly involved, followed by the small bowel. Biopsy may reveal the characteristic yeast forms on pathology examination. Adrenal involvement may occur with destruction of the glands leading to adrenal insufficiency, presenting with hypotension, nausea, vomiting, fever, and malaise. Central nervous system (CNS) involvement occurs in up to 10% of patients with disseminated histoplasmosis. Chronic lymphocytic meningitis is the most common manifestation; however, parenchymal mass lesions, cerebral vasculitis, and encephalitis may also occur.

Laboratory findings in patients with disseminated histoplasmosis are nonspecific. Elevated levels of transaminases, alkaline phosphatase, lactate dehydrogenase (LDH), ferritin, and C-reactive protein may be seen, along with pancytopenia and prolonged erythrocyte sedimentation rates. In our experience in Arkansas, transaminase elevations are common, especially in patients with CD4 counts less than 75 cells/ μ L, and resolve with appropriate therapy, indicating the elevations are due to the infection.

Mortality in AIDS patients with histoplasmosis may be as high as 50%, due to disseminated and severe disease resulting in sepsis and multi-organ failure. Several studies have evaluated prognostic factors in HIV patients with histoplasmosis and found renal failure, hypoalbuminemia, thrombocytopenia, anemia, and elevated LDH to be associated with poor outcomes. A recent study by Baddley *et al* reported a mortality of 39% within three months of diagnosis of histoplasmosis in 46 HIV patients in Montgomery County, Alabama, during the era of highly active antiretroviral therapy (HAART). In this study, fungemia, renal failure, and age were associated with increased mortality. Only 21.7% of their patients were on HAART at the time of histoplasmosis diagnosis, and all had viral loads greater than 9000 copies. Nacher *et al* showed that the

diagnosis of disseminated histoplasmosis increased within two months after starting HAART, likely due to immune reconstitution unmasking latent infection. Patients on HAART for six months or more were less likely to manifest histoplasmosis.

Diagnosis

Culture of *H. capsulatum* from clinical specimens remains the gold standard for diagnosis. For patients with acute pulmonary or chronic cavitary histoplasmosis, culture of respiratory samples may secure the diagnosis. In our experience, blood cultures may be positive in up to 80% of patients with AIDS and disseminated histoplasmosis. Unfortunately, the organism grows slowly, usually taking several weeks for growth to become apparent. The Isolator tube, a lysis-centrifugation method, has been shown to increase the yield of blood cultures. Direct examination of clinical specimens stained with methenamine silver or periodic acid-Schiff may show the characteristic ovoid yeasts with narrow-based budding inside macrophages and provide for rapid presumptive diagnosis. In AIDS patients with disseminated disease, routine blood smears may reveal the yeast forms in neutrophils if carefully examined.

Serology is not helpful in the diagnosis of histoplasmosis. In endemic areas, many people will be positive from prior asymptomatic exposure by either complement fixation (CF) or immunodiffusion (ID) assays. A four-fold rise in CF titers could confirm recent exposure to histoplasmosis, although it may take several weeks for antibodies to develop. For patients with suspected CNS histoplasmosis, cerebrospinal fluid (CSF) could be sent for serologic testing, as the presence of either CF or ID antibodies confirms the diagnosis.

Antigen testing has better utility for the detection of *H. capsulatum*. Up to 90% of patients with progressive disseminated histoplasmosis will have antigen detectable in the urine. In AIDS patients, the rate of urine antigen positivity increases to 95%. Urine antigen testing is less sensitive for patients who have only pulmonary disease. In this setting, antigen testing of broncho-alveolar lavage fluid may be helpful with reported sensitivity of 84%. Serum antigen testing is less sensitive than in the urine. CSF antigen testing may be useful in diagnosing CNS disease. Urine antigen levels can be followed to assess the efficacy of antifungal therapy. Antigenuria should fall below the level of detection with successful therapy, while a return of antigenuria may reflect relapse.

Treatment

Updated guidelines for the treatment of histoplasmosis are available from the Infectious Diseases Society of America. Immunocompetent patients who have acute pulmonary histoplasmosis for less than one month duration may not require treatment. For those with pulmonary symptoms for more than one month or of moderate severity, itraconazole is recommended for three months. Patients with chronic cavitary histoplasmosis will require longer courses. In general, all immunocompromised patients, including patients with HIV, should be treated.

Patients with disseminated histoplasmosis may be treated initially with itraconazole or amphotericin B, depending on the severity of symptoms. Liposomal preparations of amphotericin B are preferred due to improved side effect profiles. Patients treated with

amphotericin B may be switched to itraconazole once clinical response is obtained, typically in one to two weeks. Itraconazole therapy should continue for at least six months if immunosuppression resolves, or longer if it does not. In patients with AIDS, itraconazole therapy should continue until the patient has been on antifungal therapy for at least one year, is receiving HAART, has a CD4 count greater than 150 cells/ μ L, and has negative blood cultures for *H. capsulatum*, as well as negative serum and urine antigen assays.

Patients with CNS histoplasmosis should receive a lipid formulation of amphotericin B for four to six weeks and be switched to oral azole therapy if there has been good clinical response. Duration of therapy should be at least one year and indefinitely if immunosuppression is not reversed. Antifungal therapy can be stopped after at least a year, if immunosuppression is reversed, and all CSF abnormalities have resolved, including CSF *Histoplasma* antigen levels.

Itraconazole remains the oral antifungal of choice for the treatment of histoplasmosis. Drug levels should be monitored while on therapy. Ketoconazole, fluconazole, voriconazole, and posaconazole have also been used for this disease. Ketoconazole and fluconazole are associated with higher rates of treatment failure compared to itraconazole. Patients who failed fluconazole therapy were found to have isolates with increased MICs to voriconazole as well, raising the concern for failure with this agent. Voriconazole and posaconazole have been used successfully in a limited number of cases, but experience with these agents is less than with itraconazole.

HIV clinicians should be aware of the drug interactions that itraconazole can have with antiretroviral agents. Protease inhibitors may increase the levels of itraconazole when administered together. Itraconazole dosing should be limited to 200mg daily when administered with lopinavir/ritonavir, darunavir/ritonavir, or tipranavir/ritonavir. The interaction with atazanavir/ritonavir is less significant and no dose adjustment is necessary. Efavirenz may decrease the serum concentration of itraconazole. Concomitant use of these agents should be avoided, or itraconazole levels monitored. Itraconazole capsules should not be used if the patient is also on a proton pump inhibitor or H₂ blockers as gastric acid is required for proper absorption. Itraconazole solution may be used if acid-blocking agents are essential.

Summary

Histoplasmosis is a common and often severe infection in HIV-infected individuals in endemic areas. It may be the first manifestation of HIV infection and AIDS. Providers need to maintain a high index of suspicion for the disease, especially in non-endemic areas where immunosuppressed patients may present with reactivation of *H. capsulatum* acquired years before in an endemic area. While direct identification of the organism, either in pathology specimens or culture, remains the mainstay of diagnosis, antigen testing is useful and may provide for rapid, sensitive diagnosis in AIDS patients with disseminated disease. Amphotericin B should be used for initial treatment of severe pulmonary or disseminated disease with transition to oral itraconazole therapy once there is improvement. Therapy should continue for prolonged periods, including indefinitely for

patients who continue to have immunosuppression.❖

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