

HISTOPLASMOSIS

by Bill Wojciechowski, MS, RRT



Histoplasmosis is an infectious disease caused by the inhalation of the dimorphic fungus *Histoplasma capsulatum*. It is the most common pulmonary and systemic mycosis in humans. Histoplasmosis caused by *H. capsulatum* is also known as North American histoplasmosis, which is contrasted with African histoplasmosis resulting from inhaling fungal spores of *Histoplasma duboisii*. *H. capsulatum*, first identified as a lethal fungal pathogen in 1906, is endemic to the temperate zones of the world. In the United States, the endemic areas include the Ohio, Mississippi, and St. Lawrence River valleys.

Microbiology

As a dimorphic fungus, *H. capsulatum* can grow in two forms. These two morphologies correlate with the saprophytic and parasitic modes of growth undertaken by the fungus. As a saprophyte, *H. capsulatum* develops in the soil in a filamentous, or mycelial, form. The mycelial form is characterized by long, branched tubular filaments. These filaments constitute the vegetative body of many fungi. The filaments produce spores, or conidia. Both these spores and mycelial fragments can aerosolize, and be inhaled.

Once introduced into the host via inhalation, *H. capsulatum* becomes a parasite, and converts to a budding yeast form. The conversion from the mycelial form to the pathogenic yeast form occurs within the alveolar macrophages, which phagocytose the conidia. Furthermore, the mycelial-yeast transition is induced by a tempera-

ture change from 25° C to 37° C. The ability of *H. capsulatum* to grow in both a mycelial form in the environment, and a yeast form in the host is critical for the establishment and progression of disease.

Etiology

H. capsulatum is found in the mycelial form in the soil which is typically contaminated with bird or bat excreta. These avian droppings, rich in nitrogen, provide nutrients essential for fungal growth. When the contaminated soil is disturbed, either by wind, farming, or excavation, fungal spores or mycelial fragments become airborne, and can enter the lungs of mammals. Air currents transport this material for miles, exposing people who are unaware of such exposure. Contaminated areas commonly include starling roosts, chicken houses, and caves harboring bats. Birds can carry *H. capsulatum* on their feet, wings, and beaks. However, birds themselves are not infected with this fungus because their body temperatures generally range from 38° to 42°C, non-supportive of the mycelial-yeast transition. Bats, on the other hand, have lower body temperatures, and often are infected with *H. capsulatum*.

Epidemiology

Approximately, 40 million people in the United States have been infected by *H. capsulatum*. The annual infection rate is estimated at 500,000. However, less than 5% of people infected with *H. capsulatum* demonstrate clinical manifestations of histoplasmosis. Males have a predilection for histoplasmosis four times that of females. All ages are susceptible to this infection; however, infants and the elderly are more symptomatic than other age groups. Persons who are immunocompromised are at greater risk for contracting this infection.

Pathogenesis

After spores deposit in the alveoli, *H. capsulatum* enters, and grows within macrophages. Macrophages kill most microbes; however, *H. capsulatum* interferes with the microbicidal powers of macrophages. Current research has identified 30 *H. capsulatum* genes that are induced when the fungus is inside a macrophage. These genes likely contribute to the subversion of the macrophages. After phagocytosis by macrophages, yeast replicates in approximately 15 to 18 hours. As the immune response of the host strengthens during the first two weeks following exposure, yeast replication terminates. T lymphocytes produce a specific cell-mediated immunity within two weeks following the initial infection. During this time macrophages and neutrophils become "programmed" to destroy *H. capsulatum* throughout the body. In regions where yeast is heavily concentrated, *H. capsulatum* is not destroyed, but is contained by fibrotic granulomas, which eventually calcify. This process occurs over months or years, depending on the size of the inoculum. Within the lungs, these granulomas frequently form in the pulmonary parenchyma and in hilar and mediastinal lymph nodes. As cell-mediated immunity continues to strengthen, about 90% of infected persons demonstrate a positive skin test for *Histoplasma* species 3 to 6 weeks post-exposure.

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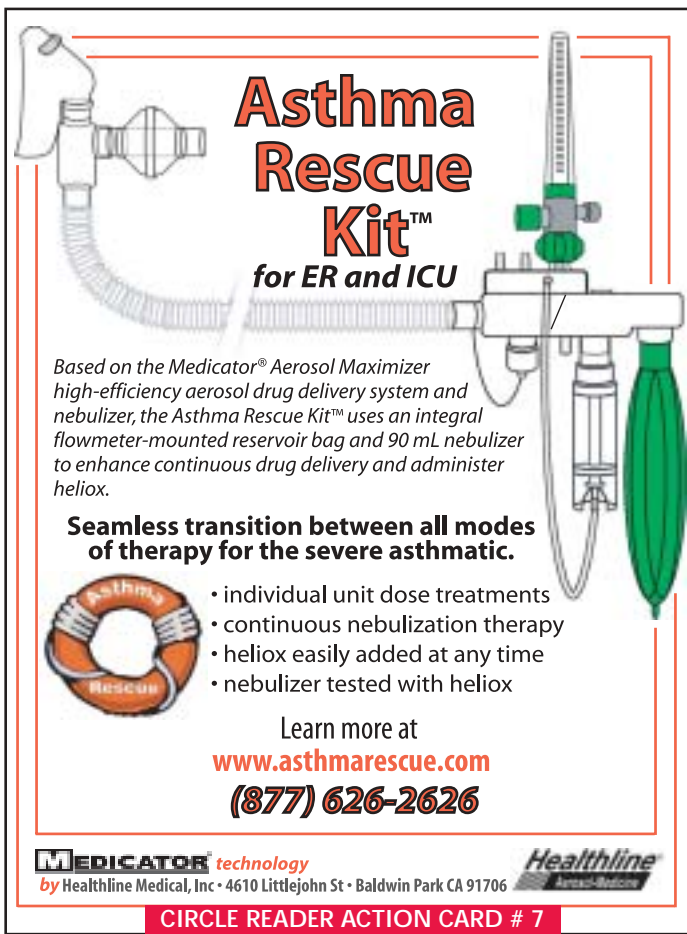
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Acute Pulmonary Histoplasmosis

Approximately, 90% of such persons are asymptomatic. When symptoms occur, they include fever, chills, severe asthenia, headaches, and digestive tract involvement. Cough, dyspnea, and hepatic involvement may also occur. Pulmonary nodules and mediastinal adenopathies are sometimes observed on chest radiography or computed tomography, but ordinarily abnormalities are absent. The physical exam is also generally unremarkable. Recovery occurs in about two weeks.

Persons experiencing a large inoculum of spores may present with dyspnea and hypoxemia. A massive inoculum, perhaps, inhaled by a spelunker disturbing a bat lair, can produce symptoms resembling adult respiratory distress syndrome. Depending on the severity of symptoms, patients with acute pulmonary histoplasmosis may receive amphotericin B for two weeks, followed by itraconazole for about 12 weeks.

Chronic Pulmonary Histoplasmosis

This form of histoplasmosis typically occurs at a rate of about 1 per 100,000 in patients having underlying pulmonary disease, e.g., pulmonary emphysema. The symptoms associated with this form of histoplasmosis resemble those of tuberculosis, i.e., malaise, weight loss, productive cough, fever, and night sweats. Cavities along with hemoptysis develop. Chest radiography demonstrates scattered infiltrates, bilateral hilar adenopathy with fibronodular shadows in the upper lobes. These patients tend to experience cor pulmonale and recurrent bacterial infections, which eventually lead to their demise. Destruction and necrosis of lung tissue accompanies the progression of this disease. Itraconazole, when administered for 1 to 2 years, is 75% to 85% effective for this form of histoplasmosis. If itraconazole is ineffective after 12 weeks, amphotericin B can be given for 2 to 4 months. Once the yeast population is reduced with amphotericin B, itraconazole is sometimes resumed, and amphotericin B terminated. Treatment is generally maintained as long as clinical manifestations persist. Pulmonary resection of the infected cavity often cures this condition.

Progressive Disseminated Histoplasmosis

This condition is characterized by involvement of other organs in addition to the lungs, e.g., lymph nodes, bone marrow, heart, adrenal glands, central nervous system, gastrointestinal tract, eyes, skin, and genitourinary tract. This form of histoplasmosis is uncommon in immunocompetent persons, but develops in almost up to 30% of those who are immunocompromised. These patients are unable to develop cellular immunity responsible for neutralizing the yeast. For some immunocompromised hosts, death occurs abruptly. For others, a deteriorating course over months or years leads to demise.

Prognosis

Acute pulmonary histoplasmosis has a good prognosis. Chronic pulmonary histoplasmosis has a re-activation rate of about 20%. When untreated, progressive disseminated histoplasmosis has a mortality rate exceeding 90%. Otherwise, this condition has a protracted course with lengthy asymptomatic periods.

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Hematogenous spread from the lungs to other tissues likely occurs in all infected persons during the first 2 weeks following infection before specific immunity develops, but this dissemination is not progressive in the majority of cases. Persons who are immunocompromised do not acquire cell-mediated immunity, and develop progressive disseminated histoplasmosis.

Reactivation of infection may occur if hosts become immunosuppressed years after a primary infection. Such reactivation accounts for many cases observed in non-endemic areas.

Diagnosis

A number of diagnostic tests can determine the presence of *H. capsulatum* infection. These tests include culture, fungal stains, serologic tests for antibodies, and antigen detection tests. The sensitivity of these tests varies, and differs among the forms of histoplasmosis. The gold standard is the culture, which has 85% sensitivity for chronic pulmonary and progressive disseminated types. Its sensitivity for acute pulmonary histoplasmosis is only 15%. The fungal stain has a low sensitivity for all forms of histoplasmosis. Serologic testing for antibodies is 98% and 100% sensitive for acute and chronic forms, respectively, and 71% for the disseminated variety. Antigen detection tests are only useful for disseminated histoplasmosis (92% sensitivity).

Clinical Presentations of Histoplasmosis

Histoplasmosis manifests itself differently depending on factors such as magnitude and duration of exposure, and various host characteristics.