

Clinical Perspectives in the Diagnosis and Management of Histoplasmosis

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KEYWORDS

• Histoplasmosis • Endemic • Diagnosis • Treatment

KEY POINTS

- Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum*, is endemic to certain regions within the United States, as well as other parts of the world.
- Pneumonia is the most common disease presentation but extrapulmonary dissemination can occur, especially in immunocompromised patients.
- A multipronged approach is recommended for diagnosis, including laboratory, radiographic, histopathologic, microbiologic, and serologic evaluation.
- Manifestations that are always treated include moderate-to-severe acute pulmonary histoplasmosis, disseminated disease, and histoplasmosis in immunocompromised individuals.
- Amphotericin B is the drug of choice for moderate-to-severe and disseminated presentations, whereas itraconazole is appropriate for mild disease and as step-down therapy.

INTRODUCTION

Histoplasma capsulatum, the etiologic agent of histoplasmosis, is a dimorphic fungus highly endemic to the Mississippi and Ohio River valleys of North America. In an increasingly interconnected continent, in which millions of travelers migrate through high-prevalence areas, the Ohio River Valley fever has become a disease of international extent, much farther-reaching than the simple geographic confines of its endemicity. Moreover, with increasing numbers of patients receiving immunosuppressive therapies, including solid-organ and bone marrow transplantation and tumor-necrosis-factor inhibitors, the population at risk for histoplasmosis, including severe

disseminated forms, will continue to grow. In terms of disease cadence (acute, subacute, and chronic), onset (primary or reactivation disease), distribution (pulmonary, mediastinal, disseminated, and isolated extrapulmonary) and severity (asymptomatic, mild, and moderate-severe), the clinical spectrum of histoplasmosis is very wide, often contributing to delays in diagnosis. The advent of *Histoplasma* antigen testing has revolutionized the diagnosis of histoplasmosis by providing a convenient and highly sensitive test; however, a multipronged approach is recommended for the diagnosis of histoplasmosis, including laboratory, radiographic, histopathologic, microbiologic, and serologic evaluation. Treatment of

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histoplasmosis is contingent on the severity and specific manifestation of the disease, but immunocompromised patients and disseminated disease should always be treated. This article details the current concepts in the diagnosis and management of this protean disease.

RISK FACTORS FOR HISTOPLASMOSIS

The primary risk factor for the acquisition of histoplasmosis is living in or traveling to an area endemic for the fungus. The most highly endemic regions of North America have long been known to be the Ohio River and Mississippi River basins.¹ However, based on data from animal infections,²⁻⁴ skin testing for histoplasmin sensitivity,⁵ and case reports,⁶ areas of previously unrecognized endemicity continue to be elucidated. Since 1938, outbreaks of histoplasmosis have been reported in more than 26 states,⁷ widening the presumed geographic distribution of the fungus. Outside of mainland United States, the island of Puerto Rico has been associated with multiple cases of histoplasmosis.⁸ *H capsulatum var capsulatum* is now understood to be endemic to parts of Central and South America, Southern Europe, Southeast Asia, and Oceania,⁹ whereas African histoplasmosis caused by *H capsulatum var duboisii* is prevalent in central and western regions of the continent.¹⁰

Bird and bat guano are strongly associated with the presence of *H capsulatum* and their presence is commonly implicated in outbreaks of infection among humans. Disruption of nests and roosting sites, spelunking, and other activities that afford exposure to these animals or their dwellings increase the risk of inhaling fungal spores.¹¹ In an epidemiologic survey of 105 outbreaks recorded from 1983 to 2013, exposure to birds, bats, or their

droppings was reported in 77% of cases.⁷ Construction, landscaping, excavation, strong winds, and other natural or anthropogenic phenomena that result in soil aerosolization are other risk factors for acquiring histoplasmosis. Persons involved in work-related or recreational activities that involve the outdoors are, in turn, more likely to be infected.

In addition to epidemiology, host factors play an important role in the susceptibility to histoplasmosis. Immunocompromised patients, particularly those with deficiencies of the cellular immune system, have decreased capacity to contain a burgeoning infection. Such patients are at greater likelihood of developing progressive disseminated disease, even when exposed to smaller fungal inocula.¹² Patients at extremes of age; those infected with human immunodeficiency virus, acquired immune deficiency syndrome (HIV/AIDS); solid-organ transplant recipients¹³; and patients receiving tumor necrosis factor (TNF) inhibitors¹⁴ are populations identified to be at increased risk.¹⁵ However, histoplasmosis may be heterogeneous in different populations of immunosuppressed individuals. After solid-organ transplantation, donor-related infection and reactivation of asymptomatic latent histoplasmosis are the most common mechanisms of infection and occur in a bimodal fashion: within 6 months and after 2 years of transplantation,¹⁶ respectively. On the other hand, almost all patients with HIV/AIDS develop progressive disseminated histoplasmosis secondary to de novo infection.¹⁷ A summary of risk factors for histoplasmosis is found in [Table 1](#).

Over the last decade, new at-risk populations have emerged. In a 2001 to 2012 survey of hospitalizations due to histoplasmosis, significant increases in hospital admissions over time were seen with the use of biologic agents, a history of

Table 1
Risk factors for histoplasmosis

Epidemiologic Factor	Host Factors	Pathogen Factors
Endemic area <ul style="list-style-type: none"> • Ohio and Mississippi River basins (US) • Puerto Rico & Caribbean • Central and South America • Southeast Asia • Oceania • Africa (<i>H var duboisii</i>) Bird and Bat guano exposure <ul style="list-style-type: none"> • Spelunking Aerosolized soil exposure <ul style="list-style-type: none"> • Construction • Landscaping • Strong winds 	HIV/AIDS (especially CD4 count <150 cells/mm ³) TNF-alpha inhibitors Solid organ transplantation Bone marrow transplantation Extremes of age (<2 or >50 y) Other causes of cellular immune suppression or dysfunction	Size of inoculum Inherent virulence

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