Disseminated histoplasmosis

Disseminated histoplasmosis is a sub-acute infection that may be diagnosed in patients with impaired T-cell immunity including mostly solid organ transplant recipients and AIDS. In addition, it may also be found among infants, elderly and, rarely in apparently healthy people. Infection usually involves lungs, reticulo-endothelial system, skin, mucous membranes, adrenals and less frequently the central nervous system. Consequently, clinical presentation is very polymorphic and 100% of patients will die if untreated. It is acquired from inhalation of dust contaminated with *H. capsulatum* in endemic areas as USA, Central and South America, as well as in some regions from eastern Asia (specially India and Malaysia), Africa and Australia.

*Histoplasma capsulatum*, the causative organism, grows very slowly, so diagnosis is often delayed, or requires biopsy. A highly sensitive antigen test (ELISA format) is available enabling same day diagnosis in a few laboratories. There is a 90% survival if diagnosed and treated with liposomal amphotericin B or itraconazole.

Disseminated histoplasmosis in AIDS patients

In endemic areas, attack rates of disseminated histoplasmosis in AIDS patients usually range from 5% to 40% (top rates documented in Fortaleza, Brazil and French Guiana) and patients with CD4 counts of <150 cells/µL are at highest risk. The global burden of histoplasmosis is not known, but a recent cohort study conducted in French Guiana found an incidence rate of 1.5 per 100 persons-year. If we extrapolate this rate to the 1,600,000 HIV patients living in the Americas, ~24,000 histoplasmosis are anticipated there each year.

Disseminated histoplasmosis in an AIDS patient: multiple skin lesions (papules and macules), some of them resembling Kaposi sarcoma. Skin lesions are seen in more than 50% of AIDS patients with histoplasmosis in Latin America, but are uncommon in US patients.

More than 90% of HIV-infected persons with histoplasmosis develop the disseminated form of the disease and it is often an AIDS-defining illness. Despite well documented as an AIDS-defining illnesses, this systemic mycosis is mostly undiagnosed or ignored by a substantial number of clinicians when faced with a febrile patient with weight loss (similar
to TB) in endemic regions. The recent experience reported by Colombian investigators, showed a jump in the diagnosis of histoplasmosis from 27 to 44 cases per year in 17 health departments after providing to the clinicians better diagnostic tools and a program of medical education focused on the epidemiology, diagnosis and treatment of histoplasmosis.

Over the course of days to weeks, patients develop fevers, chills, night sweats, fatigue, weight loss and eventually respiratory and gastrointestinal symptoms. Clinical suspicion is usually facilitated by the coexistence of mucocutaneous lesions with hepatosplenomegaly and lymphadenopathy. Of note, skin lesions are frequently found in cases reported in Latin America (30-80%), but they are uncommon in US cases (<10%). Lung involvement is common, typically manifest as bilateral reticulonodular infiltrates. A sepsis syndrome occurs in 10-20% of patients who develop hypotension, renal and hepatic failure, respiratory distress syndrome and coagulopathy. Laboratory abnormalities frequently include anemia, leukopenia, thrombocytopenia, hepatic enzyme elevation, increased ferritin, and/or adrenal insufficiency. Mortality rates during hospital admission range from 10 to 40%, and higher rates have been reported in Brazilian and Guatemalan patients than in US patients.

If clinicians seeing AIDS patients with prolonged fever in endemic areas don’t consider the diagnosis, clinical hesitation and delays in starting appropriate antifungal therapy greatly increase the chance of death. Patients with comorbidities associated with immunosuppression such as cancer, organ transplant recipients, and those exposed to corticosteroids and TNF-alpha antagonists may also develop disseminated histoplasmosis.

**Diagnosis**

A relevant aspect to be considered is that a substantial number of patients with histoplasmosis are initially misdiagnosed as tuberculosis. In fact, in regions with limited access to diagnostic tools for histoplasmosis this infection is clearly inflating the statistics of tuberculosis. Of note, data from Latin America showed a 60% increase in culture negative relative to culture positive tuberculosis. The large proportion of culture negative tuberculosis among AIDS patients may be related to other causes, including fungal infections (Sterling T el al, 2015).

The best approach in the diagnosis of disseminated histoplasmosis is the detection of histoplasma antigen in urine, which is positive in over 90% of cases. Unfortunately this test is not readily available and only one test is approved by the FDA, and none pre-qualified by the WHO. Systematic testing on all ill HIV positive patients is the best approach in areas of
high prevalence. A Wright’s stain on a blood film or bone marrow aspiration may demonstrate intracellular yeast-like organisms. Skin, mucosal or lymph node biopsies will also reveal characteristic intracellular yeasts visible with fungal stains. Positive cultures are usual in disseminated histoplasmosis (>70%), especially for blood and bone marrow cultures, but are slow (10-20 days and occasionally longer) and requires adequate laboratory infrastructure for handling class 3 pathogens. The sensitivity of diagnostic testing is greatest in patients with clinical manifestations, and impaired immune status, reflecting a higher tissue fungal burden.

Treatment

Induction therapy with intravenous liposomal amphotericin B (Ambisome) in daily doses of 3mg/Kg, for 2 weeks, is the treatment of choice for patients with moderate to severe disseminated histoplasmosis. Patients who respond to induction therapy with liposomal amphotericin B may be changed to consolidation therapy with oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily), which should be continued for a total of 12 months, until recovery of CD4 cell counts on antiretroviral therapy.

Therapeutic drug monitoring is desirable for itraconazole but frequently difficult to perform in endemic areas such as in Latin America. Early antiretroviral therapy in new AIDS cases is helpful and recommended. Furthermore, in AIDS patients, secondary prophylaxis with itraconazole should be used to avoid relapses. For clinically stable patients with mild-to-moderate disease (without CNS involvement), therapy may be initiated with itraconazole, 200 mg 3 times daily for 3 days and then twice daily for at least 12 months, as long as the patient is not also treated with rifampicin for possible tuberculosis, with which histoplasmosis may be confused. The IDSA guidelines provide more detail.
**Histoplasma capsulatum**

*Histoplasma capsulatum* has two varieties with medical relevance: *H. capsulatum* var *capsulatum*, exhibiting 8 clades with a worldwide distribution, and *H. capsulatum* var *duboisii* that circulates exclusively in Africa. Here we focus on diseases caused by *H. capsulatum var capsulatum*, soon to be called *H. capsulatum*.

*Histoplasma capsulatum* usually grows in soils enriched with organic nitrogen sources, especially bird or bat excrement. Consequently, exposure of human hosts to the fungi usually occurs during cleaning accumulated animal excrements, attics or barns as well as caving or participating in construction projects in contaminated areas, especially during remodeling or demolition of old buildings. The large majority of normal hosts who are exposed to *H. capsulatum* (>95%) remain asymptomatic, or develop only mild symptoms, that are never recognized as being due to histoplasmosis. Skin test surveys in populations reveal the extent of ‘natural’ exposure without disease, and serves to identify hyperendemic regions.

A small number of hosts infected in endemic areas will develop one of the clinical forms of histoplasmosis. There is a large spectrum of clinical presentations, which are strongly influenced by the extent of exposure and possibly virulence of different *H. capsulatum* strains, age and immunological status of the host, as well as the presence of chronic pulmonary disease prior to fungal infection. Outbreaks of histoplasmosis involving a large number of patients have been reported worldwide.

**Other clinical forms of histoplasmosis**

People newly exposed to *H. capsulatum* may become symptomatic and develop **Acute Pulmonary Histoplasmosis**, presenting with fever, chills, cough, dyspnea and pulmonary nodular infiltrates or consolidation on chest imaging. In the case of heavy exposure, diffuse pulmonary disease and respiratory failure may occur. Antifungal therapy should be used only in patients who are highly symptomatic or have moderate to severe clinical presentations. Methylprednisolone (0.5–1.0 mg/kg daily intravenously) during the first 1–2 weeks of antifungal therapy may be required for patients who develop hypoxemia and respiratory failure.

Elderly normal hosts with underlying structural lung disease such as emphysema may develop **Chronic Pulmonary Histoplasmosis** exhibiting signs and symptoms resembling tuberculosis or chronic pulmonary aspergillosis with cavitary lesions and fibrosis. Unfortunately, most cases of chronic histoplasmosis are misdiagnosed as tuberculosis. Serology for detecting specific anti-*H. capsulatum* antibodies may be helpful in the diagnosis of acute and chronic pulmonary histoplasmosis (sensitivity >80%). Patients with chronic pulmonary histoplasmosis should receive at least 12 months of oral itraconazole (200 mg 3 times daily for 3 days and then once or twice daily). Due to the high rates of relapses, some authors suggest at least 18–24 months of antifungal therapy.
After disseminated histoplasmosis, the most severe clinical manifestation of this endemic mycosis is **Progressive (Subacute) Disseminated Histoplasmosis** that occurs in patients at extremes of ages, who have subtle immunosuppression. Adrenal or intestinal masses or lymphadenopathy are the commonest manifestations of subacute disseminated histoplasmosis, but CNS involvement and endocarditis may occur. Itraconazole or liposomal amphotericin B are the treatments of choice.

Sequelae are frequently documented in patients with CNS and adrenal involvement, as well as in patients with chronic pulmonary histoplasmosis.

Research needs for disseminated histoplasmosis:

- **Areas of hyperendemicity** are not well defined, especially in Africa. Skin test surveys are required to develop a much more detailed geographical understanding of the distribution of disease. No maps have been drawn for Asia or Australasia to define the areas infected with *H. capsulatum*.
- The frequency and latency of pulmonary histoplasmosis in HIV infected patients is not known. The proportion of patients with community acquired pneumonia caused by *H. capsulatum* in endemic areas needs to be documented.
- The histoplasma antigen test needs be better studied in multicenter studies to ascertain its comparative performance.
- A simpler lateral flow like device for histoplasma antigen on urine needs to be developed and tested in multiple locations.
- Shorter, and possibly higher dose, liposomal amphotericin B regimens need to be trialled to shorten the current standard of 2 weeks, if possible.

**References**


Karimi K et al. Differences in histoplasmosis in patients with acquired immunodeficiency syndrome in the United States and Brazil. J Infect Dis 2002; 186:1655–60


The neglected histoplasmosis in Latin America Group. Disseminated histoplasmosis in Central and South America, the invisible elephant: the lethal blind spot of international health organizations AIDS 2016 30:167-170

Sterling T et al. Culture negative TB is associated with increased mortality in HIV-infected persons. In CROI 2015 Seattle, Washington, USA

Arnaldo Lopes Colombo
March 2016