

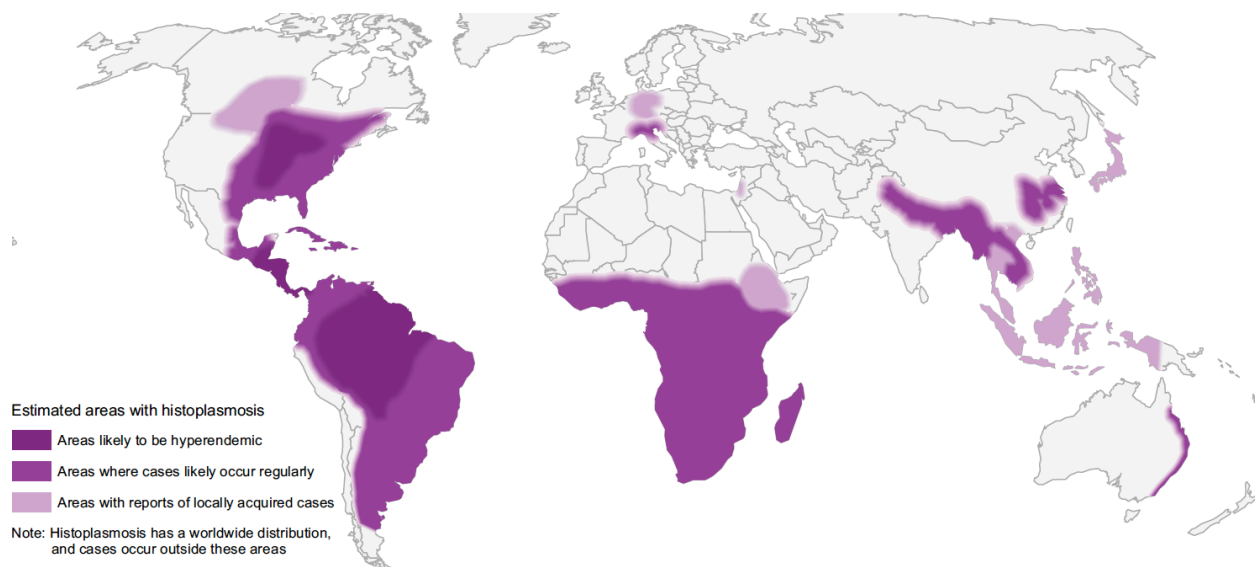
## Histoplasmosis

Disseminated histoplasmosis is a sub-acute infection that may be diagnosed in patients with impaired T-cell immunity especially those with AIDS and solid organ transplant recipients<sup>1,2</sup>. 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.

Histoplasmosis can also manifest as an acute or chronic pulmonary disease<sup>3</sup>. Acute infection follows a significant exposure, usually in caves or tunnels where bats reside or chicken coops. Chronic pulmonary histoplasmosis is related to prior lung damage, notably smoking and can present with cavities or nodules on imaging.

*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.

It is acquired from inhalation of dust contaminated with *H. capsulatum* in endemic areas as USA, Central and South America<sup>4</sup>, as well as in some regions from eastern Asia (especially India, Malaysia Myanmar and Indonesia<sup>5</sup>), Africa<sup>6</sup> and Australia<sup>7</sup>.



*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*.

### 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, French Guiana and Guatemala) and patients with CD4 counts of <150 cells/ $\mu$ L are at highest risk. The global burden of histoplasmosis is not known and under-estimated. A recent modelling study in Latin America, 6710 to 15,657 HIV-associated cases of disseminated histoplasmosis each year<sup>8</sup>. In Guatemala, disseminated histoplasmosis is more common than TB as the presenting opportunistic infection in advanced HIV disease<sup>9</sup>.

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 being well documented as an AIDS-defining illnesses, this systemic mycosis is mostly undiagnosed or ignored by a substantial number of clinicians in endemic areas when faced with a febrile patient with weight loss as it is similar to TB. Two recent country experiences are illustrative<sup>10</sup>. In French Guinea diagnosis by dermatology and microscopy found 40 cases in 1992-1997, compared to 118 cases culture and PCR in 2005-2011. In Colombia, investigators showed a jump in the diagnosis of histoplasmosis from 30-45 cases per year in 2006-2009 but introduction of an antigen test and clinical training increased case detection to 120-140 cases a year in 2012-2014. Deaths also fell dramatically in French Guinea.

Over the course of days to weeks, patients develop fevers, chills, night sweats, fatigue, weight loss and eventually respiratory and gastrointestinal symptoms. Lung involvement is common, typically manifest as bilateral reticulonodular infiltrates. Clinical suspicion is usually facilitated by the coexistence of mucocutaneous lesions with hepatosplenomegaly and lymphadenopathy. Of note,



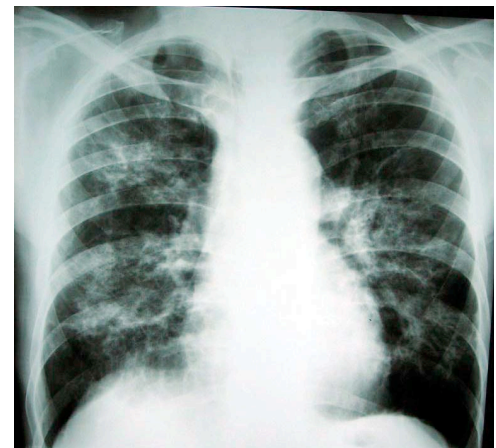
Diffuse micronodular pattern of lung lesions in a case of disseminated histoplasmosis in AIDS.

skin lesions are frequently found in cases reported in Latin America (30-80%), but they are uncommon in US cases (<10%). 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.

### Chronic pulmonary histoplasmosis (CPH)

Chronic pulmonary histoplasmosis is a condition mostly present in patients with emphysema and can mimic TB with cavities or nodules, often with mediastinal lymphadenopathy<sup>11</sup>. Subacute or chronic symptoms occur in the majority of patients, but asymptomatic disease also occurs. Both the constitutional and pulmonary symptoms of chronic pulmonary histoplasmosis are identical to those of pulmonary TB, although usually less severe. The most significant symptoms are chronic cough without hemoptysis and considerable weight loss, with ~40% of patients having fever. Chest pain tends to be a deep aching pain, as opposed to the pleuritic chest pain found in pulmonary TB. Smoking and the presence of chronic lung disease are risk conditions for CPH. A minority of cases may spontaneously improve or resolve, most patients require prolonged periods of antifungal therapy and sometimes surgery to control this fungal infection.



Chronic pulmonary histoplasmosis.

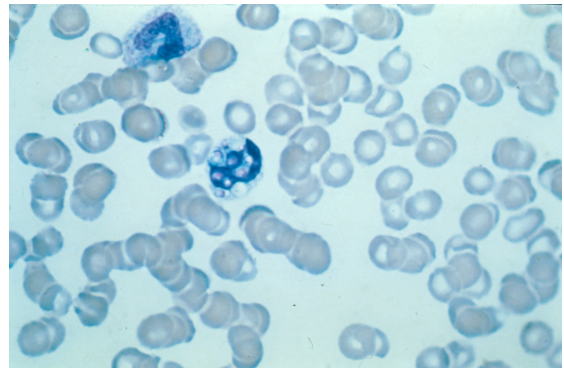
### Diagnosis

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. In Latin America there has been a 60% increase in culture negative tuberculosis compared to culture positive tuberculosis. The large proportion of culture negative tuberculosis among AIDS patients may be related to other causes, including fungal infections<sup>9</sup>.

The best approach in the diagnosis of disseminated histoplasmosis in HIV/AIDS is the detection of histoplasma antigen in urine, which is positive in over 70% of cases<sup>12</sup>. This test is now a WHO recommended Essential Diagnostic, although no commercial tests are pre-qualified by the WHO. Antigen is also detectable in serum, but overall is slightly less

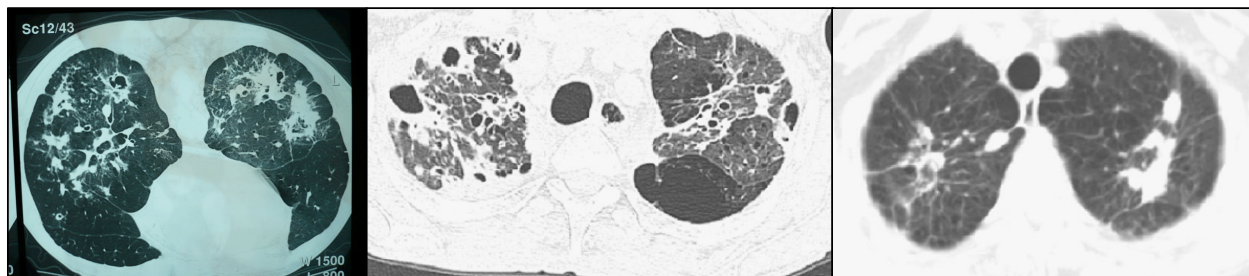
sensitive. The first of 3 lateral flow devices to detect *Histoplasma* antigen is now commercialized<sup>13</sup>. Systematic testing on all ill HIV positive patients may be considered in areas of high prevalence<sup>14</sup>.

A Wright's stain on blood film – peripheral buffy coat 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.



Histoplasma yeasts inside phagocytes in a buffy coat treated by Wright's stain

Cultures may be positive in disseminated histoplasmosis (up to 75%), especially for blood and bone marrow cultures, but are slow (14-21 days and occasionally longer) and requires adequate laboratory infrastructure for handling class 3 pathogens. PCR on blood is used in reference centres in Latin America and is more sensitive than culture and complements antigen detection. Unfortunately, there are no commercial *Histoplasma* PCR assays. The sensitivity of diagnostic testing is greatest in patients with disseminated clinical manifestations, and impaired immune status, reflecting a higher tissue fungal burden<sup>15</sup>.



Chronic pulmonary histoplasmosis. Right hand images from Kennedy<sup>3</sup>.

Serology for detecting specific anti-*H. capsulatum* antibodies may be helpful in the diagnosis of acute and chronic pulmonary histoplasmosis (sensitivity >80%)<sup>16</sup>. In Colombia, 31% of all 641 histoplasmosis diagnoses were made using antibody testing<sup>17</sup>, although which forms of disease they were is not documented as it was a laboratory-based study. A serious limitation for detecting specific anti-*H. capsulatum* antibodies is the limited availability of good antigen preparations in most routine laboratories in endemic areas, and the likely substantial inter-laboratory variability of results.

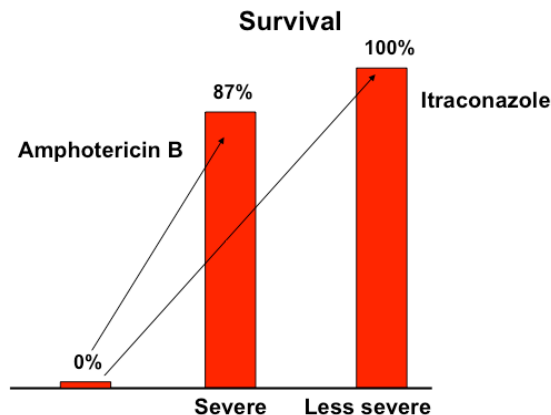
## Treatment

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<sup>18,19</sup>. If liposomal amphotericin B is not available or affordable,



deoxycholate amphotericin 0.7-1.0 mg/K is recommended. 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. Itraconazole is on the WHO Essential Medicines List.

#### Impact of therapy on **disseminated histoplasmosis** in AIDS



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 advanced HIV disease, 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 PAHO and IDSA guidelines provide more detail<sup>18,20</sup>.

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)<sup>20</sup>. Due to the high rates of relapses, some authors suggest at least 18–24 months of antifungal therapy.

#### Other 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.

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.

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.
- The frequency and latency of histoplasmosis in HIV infected patients is not completely known. The proportion of patients with community acquired pneumonia caused by *H. capsulatum* in endemic areas needs to be documented.
- Point-of-care test tests for *Histoplasma* antigen need to be made readily available to detect histoplasmosis early in risk populations in endemic areas.
- It is mandatory to include chronic histoplasmosis and other fungal pulmonary diseases in the differential diagnosis of patients with negative-ACB treated empirically for pulmonary tuberculosis.
- Interlaboratory studies of *Histoplasma* antibody testing are required.
- Shorter, and possibly higher dose, liposomal amphotericin B regimens need to be trialled to shorten the current standard of 2 weeks, if possible.

Arnaldo Lopes Colombo  
August 2020

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