Histoplasmosis

Epidemiology

TRANSMISSION
- From the inhalation of conidia
- NOT Person-to-person secretions

Incubation
1 to 3 weeks

Among those infected: 95%
Asymptomatic.
Positive histoplasmin skin tests occur in as many as 90% of the people living in areas where *H. capsulatum* is common, such as the eastern and central United States

Not transmissible person-to-person

Once inside the host, **conidia** are phagocytosed by alveolar macrophages. The conidia subsequently germinate and produce a budding yeast-like form that colonizes host macrophages and can disseminate throughout host organs and tissues

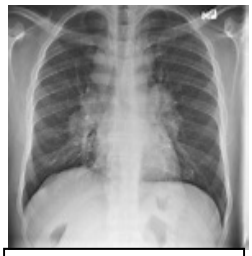
Histoplasma
Conidia

Primary or reactivation
Pulmonary acute or progressively disseminated

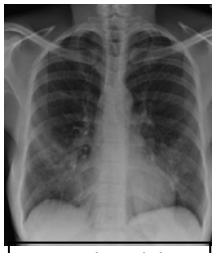
Clinical presentation includes either:
- **At least two** of the following clinical findings:

ofever, chest pain, cough, myalgia, shortness of breath, headache, or erythema nodosum/erythema multiforme rash; OR
- **At least one** of the following clinical findings:

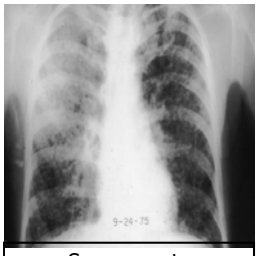
o Abnormal chest imaging (e.g., pulmonary infiltrates, cavitation, enlarged hilar or mediastinal lymph nodes, pleural effusion);
o Clinical evidence of disseminated disease:
- gastrointestinal ulcerations or masses;
- skin or mucosal lesions;
- peripheral lymphadenopathy;
- pancytopenia, as evidence of bone marrow involvement;
- enlargement of the liver, spleen, or abdominal lymph nodes; or
- meningitis, encephalitis, or focal brain lesion



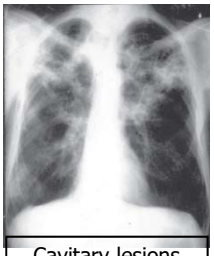
Hilar adenopathy



Reticulonodular infiltrates



Severe acute pulmonary disease



Cavitary lesions

SUSCEPTIBILITY TO INFECTION /DISEASE
- Very few people will develop symptomatic disease after a low-level exposure.
- Longer durations of exposure and exposure to higher concentrations of airborne contaminated material increase risk of developing disease
- Children <2 years of age, persons with compromised immune systems, and older persons, in particular those with underlying illnesses such as diabetes and chronic lung disease, are at increased risk for developing disease

PREVENTION MESSAGE
If someone who engages in these activities develops flu-like symptoms days or even weeks after disturbing material that might be contaminated with H. capsulatum, and the illness worsens rather than subsides after a few days, medical care should be sought and the health care provider informed about the exposure.

Environmental Issues

ENVIRONMENTAL SOURCE:
- Endemic in certain areas of the US (states bordering Ohio River valley and the lower Mississippi River.
- Soil humidity and acidity patterns associated with endemicity.
- Bird and bat droppings in soil promote growth of *Histoplasma*.
- Contact with such soil aerosolizes the microconidia, which can infect humans.
- Common in caves, tree holes, piles of decaying vegetation
- The fungus seems to grow best in soils having a high nitrogen content, especially those enriched with bird droppings or bat guano.
- **Histo contamination** common in:
  - Active and inactive roosts of blackbirds (e.g., starlings, grackles, red-winged blackbirds, and cowbirds)
  - Soil in a stand of trees where blackbirds have roosted for 3 or more years should be suspected of being.
  - Habitats of pigeons, bats and poultry houses with dirt floors

BIRD DROPPINGS
- Fresh bird droppings on surfaces (sidewalks/windowsills) ➔NO health risk for Histo because birds themselves are not infected.
- Bird manure is primarily a nutrient source for the growth of Histo already present in soil.
- Bats can become infected with Histo can excrete the organism in their droppings.

HIGH RISK ACTIVITIES /JOBS
- Bridge inspector or painter
- Chimney cleaner
- Construction, Demolition worker
- Farmer, Gardener
- Heating and air-conditioning system installer or service person
- Microbiology laboratory worker
- Pest control worker
- Restorer of historic or abandoned buildings
- Roofer
- Spelunker (cave explorer)

REDUCING ENVIRONMENTAL EXPOSURES
- Clean up any accumulation of bird droppings (Buildings)
- Exclude colonies of birds /bats from buildings (Block entry & exit points)
- Post health risk warnings
- Explain risks to workers
- Control aerosolization of dust: wet the area, add wetting agent to water
- Disinfect contaminated material: formaldehyde (irritant to humans)
- Dispose of waste
- Respirators (N95), Powered Air Purification respirators (PAPR)
- Disposable clothing and shoe covers

Diagnosis

DIFFERENTIAL DIAGNOSIS
- Atypical pneumonia:
  - Legionella
  - Mycoplasma
- Sarcoidosis
- Tuberculosis

Confirmatory laboratory criteria:
- Culture of *H. capsulatum* from a clinical specimen,
- Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by histopathology,
- ≥ 4-fold rise in *H. capsulatum* serum complement fixation antibody titers taken at least 2 weeks apart,
- Detection in serum of H band by *H. capsulatum* immunodiffusion antibody test,
- Detection in serum of M band by *H. capsulatum* immunodiffusion antibody test after a documented lack of M band on a previous test
- Demonstration of *H. capsulatum*-specific nucleic acid in a clinical specimen using a validated assay (i.e., PCR).

Non-confirmatory laboratory criteria:
- Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by cytopathology,
- Detection in serum or cerebrospinal fluid (CSF) of *H. capsulatum* antibodies by single complement fixation titer of 1:32 or greater (e.g., 1:64),
- Detection in serum or cerebrospinal fluid (CSF) of M band by *H. capsulatum* immunodiffusion antibody test without a previous negative test,
- Detection of *H. capsulatum* antigen in serum, urine, or other body fluid by an enzyme immunoassay test.

- Test characteristics and performance vary with the different clinical syndromes
- Histoplasmin skin testing is no longer available.
- **Fungal culture** =gold standard but lengthy
- **Complement Fixation Immuno-diffusion:** *H. capsulatum* serum antibody (complement fixation - CF, immunodiffusion - ID) more helpful in immunocompetent individuals (4-fold increase in titers) and among patients with chronic cavitary and chronic disseminated histoplasmosis.
- False positive tests in patients with lymphoma, tuberculosis, sarcoidosis, blastomycosis, and coccidioidomycosis.
- **Histoplasma urine antigen** by enzyme immuno-assay (EIA). False positives in patients with other fungal infections (the endemic area of blastomycosis overlaps with the one for histoplasmosis). Cross-reactivity does not occur with aspergillosis, candidiasis, or cryptococcosis.
- **Histopathological exam and culture of fluids and tissues** reserved for critically ill patients or in cases of clinical uncertainty. The 2-4 micrometer oval budding yeasts seen in silver or periodic acid-Schiff staining are characteristic.

ACUTE PULMONARY INFECTION.
- In localized disease, antibody present in over 90% if both complement fixation and immunodiffusion are used.
- Serum or urine antigen detection may be as low as 40%.
- The organism may grow in culture on some lung samples, and sensitivity is improved with antigen testing of bronchoalveolar lavage (BAL) fluid.
- Histology demonstrates caseating and non-caseating granulomas, with few yeast and giant cells.

CHRONIC CAVITARY PULMONARY INFECTION.
- Most cases have positive antibody serology, often with high titers.
- Sputum cultures or bronchoscopy specimens positive in 65-85%,
- Urine antigen sensitivity has been estimated at 87.5%.

DISSEMINATED HISTOPLASMOSIS.
- Antibody present in 70-90%,
- Urine antigen is positive in 75% of immunocompetent and 95% of immunocompromised patients.
- Serum antigen sensitivity 100%.
- Grows in 50% of lung samples, and histology demonstrates diffuse and significant macrophage infiltration and giant cells (the lymphocytic response is limited).
- Lactate Dehydrogenase (LDH) and ferritin are often markedly elevated in disseminated disease, and other laboratory tests (ex. cytopenias, increased transaminases) can suggest specific organ involvement.

MENINGITIS.
- Cultures of cerebrospinal fluid (CSF) positive only 50%
- Fungal stains are rarely positive.
- Antigen testing on CSF, difficult and is not excluded by a negative CSF test.

Treatment

ACUTE PULMONARY INFECTION

Mild to moderate - No treatment if symptom duration is less than 4 weeks.
If symptoms persist after 4 weeks, itraconazole load (200 milligrams [mg] every 8 hours for 3 days) is recommended followed by 200 mg once to twice daily for 6-12 weeks.

Severe or diffuse disease - intravenous antifungal therapy for 1-2 weeks followed by itraconazole load and 200 mg twice daily for 12 weeks.
--Intravenous antifungal options include: Liposomal amphotericin B 3 mg/kg/day,
--amphotericin B lipid complex 5 mg/kg/day,
--amphotericin B deoxycholate 0.7-1 mg/kg/day.
AND methylprednisolone, 0.5-1 mg/kg/day, 1-2 weeks for respiratory complications, such as hypoxemia.

CHRONIC CAVITARY PULMONARY INFECTION:

Itraconazole load, followed by 200 mg once to twice daily for at least 12 months.

PROGRESSIVE DISSEMINATED HISTOPLASMOSIS

Mild to moderate - itraconazole 200 mg twice daily for at least 12 months.
Severe disease - intravenous antifungal therapy (Liposomal amphotericin B 3 mg/kg/day, amphotericin B lipid complex 5 mg/kg/day, or amphotericin B deoxycholate 0.7-1 mg/kg/day for 1-2 weeks) followed by itraconazole load and 200 mg twice daily for at least 12 months.

CENTRAL NERVOUS SYSTEM

Treatment is similar to disseminated disease, but a higher dose and duration of intravenous antifungal therapy (Lipsomal amphotericin B 5 mg/kg/day for 4-6 weeks) is recommended.
Fluconazole is a second line agent (responses lower than itraconazole). *Ketoconazole should not be used*.