



Endemic Mycosis in HIV Infected Individuals

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Learning Objectives

- Upon completion of this activity, participants should be able to:
 - Describe the epidemiology of Histoplasmosis and Coccidioidomycosis in the USA
 - Enumerate the clinical manifestation of Histoplasmosis and Coccidioidomycosis in HIV infected patients
 - Discuss laboratory test utilized in the diagnosis of Histoplasmosis and Coccidioidomycosis
 - Apply current guidelines to prevent and treat Histoplasmosis and Coccidioidomycosis in the setting of HIV

Disclosure of Financial Relationships

This speaker has no significant financial relationships with commercial entities to disclose.

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

Case 1

- A 35 yr old AAM with history of AIDS non-adherent to ART presented with fever, cough, SOB and diarrhea. Last CD4 count was 85(8%) and HIV-VL log 5.
- On physical exam T 38.5, PR 112/m, BP 90/60, RR 20/m. He has ulcers in the buccal mucosa, crackles on lung exam as well as hepatosplenomegaly
- Laboratory tests include WBC 3, 000/mm³, HgB 7 gm, urine and serum Histoplasma Ag were positive and peripheral smear revealed budding yeast forms confirming disseminated Histoplasmosis

Which one of the following is the preferred initial treatment for this patient

- A. Fluconazole 400 mg IV daily
- B. Fluconazole 800 mg IV daily
- C. Itraconazole 200 mg PO TID for 3 days then 200 mg BID for 12 months
- D. Amphotericin B deoxycholate 0.5mg/kg IV daily plus Flucytosine
- E. Liposomal Amphotericin B 3mg/kg daily

Case 1 continuation

After completing Liposomal Amphotericin induction treatment for two weeks, he was started on itraconazole for maintenance treatment which he has been taking for the last 15 months. Current medications include DTG/ABC/3TC 1 tab daily, Bactrim DS daily, itraconazole 200 mg BID. Six months after starting ART, his CD4 count is 250 (20%) and HIV-VL is undetected. Blood culture is negative for Histoplasma and urine Histoplasma Ag is also negative.

Which of the following is the appropriate next step regarding itraconazole maintenance therapy?

- A. Decrease dose of Itraconazole to 200 mg daily
- B. Switch itraconazole to Fluconazole to reduce DDI
- C. Stop Itraconazole
- D. Continue Itraconazole current dose until CD4 count increases to 300

Histoplasmosis

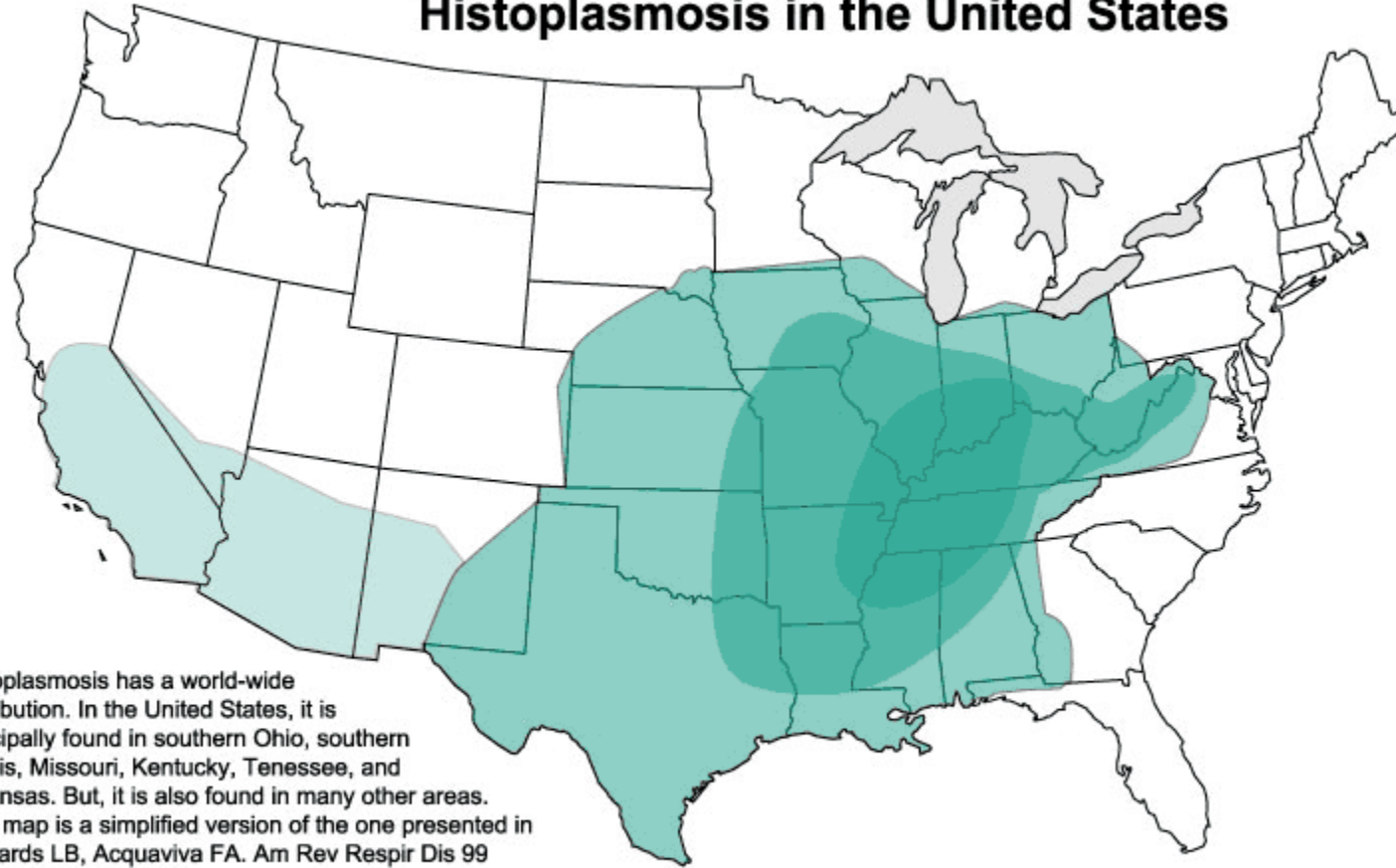
- Etiology: *Histoplasma capsulatum*
- Natural reservoir: soil, bat and avian habitat
- The lungs provide portal of entry when spore or mycelia are inhaled
- The vast majority of primary infections (>90%) go unrecognized medically.
- Extent of exposure and host immunity determines disease progression.

Epidemiology

- Distribution-worldwide
- It is the most prevalent endemic mycosis in the United States
- Most endemic region is found in the Ohio and Mississippi River valleys.
- Up to 50 million people in the United States have been infected and up to 500,000 new infections every year

Distribution of Histoplasmosis in the USA

Simplified Map of the Distribution of Histoplasmosis in the United States



Histoplasmosis has a world-wide distribution. In the United States, it is principally found in southern Ohio, southern Illinois, Missouri, Kentucky, Tennessee, and Arkansas. But, it is also found in many other areas. This map is a simplified version of the one presented in Edwards LB, Acquaviva FA. Am Rev Respir Dis 99 (Suppl.): 1-132, 1969

Clinical features

- Vary based on host immunity and the degree of exposure to the fungus.
- Acute infection
 - Flu like symptoms with pulmonary complaints, bronchopneumonia or an interstitial pneumonitis

Progressive disseminated histoplasmosis

- Progressive disseminated histoplasmosis occurs in two forms:
 - Acute PDH mostly seen in infants and heavily immunocompromised hosts. Patients present with fever, fatigue, hepatosplenomegaly, pancytopenia. AIDS patients and or those receiving immunosuppressive medications can present with overwhelming infection manifested by shock, respiratory distress, hepatic and renal failure, obtundation, and coagulopathy. The mortality in spite of amphotericin B treatment approaches 50% in such cases
 - Chronic PDH is noted mostly in elderly patients and in men more often. Patients present with pancytopenia, hepatosplenomegaly, elevated liver enzymes, oropharyngeal or GI ulcers. Other sites include skin, brain and adrenal glands

Histoplasmosis Skin lesions



Histoplasmosis Skin lesions



RISK FACTORS FOR PROGRESSIVE DISSEMINATED HISTOPLASMOSIS

- HIV/AIDS and other immunosuppressive disorders
- Immunosuppressive medications: steroids, methotrexate, TNF-blocking therapies, other immunosuppressant
- Extremes of age
- Idiopathic CD4 lymphocytopenia

A Patient with AIDS and Disseminated Histoplasmosis

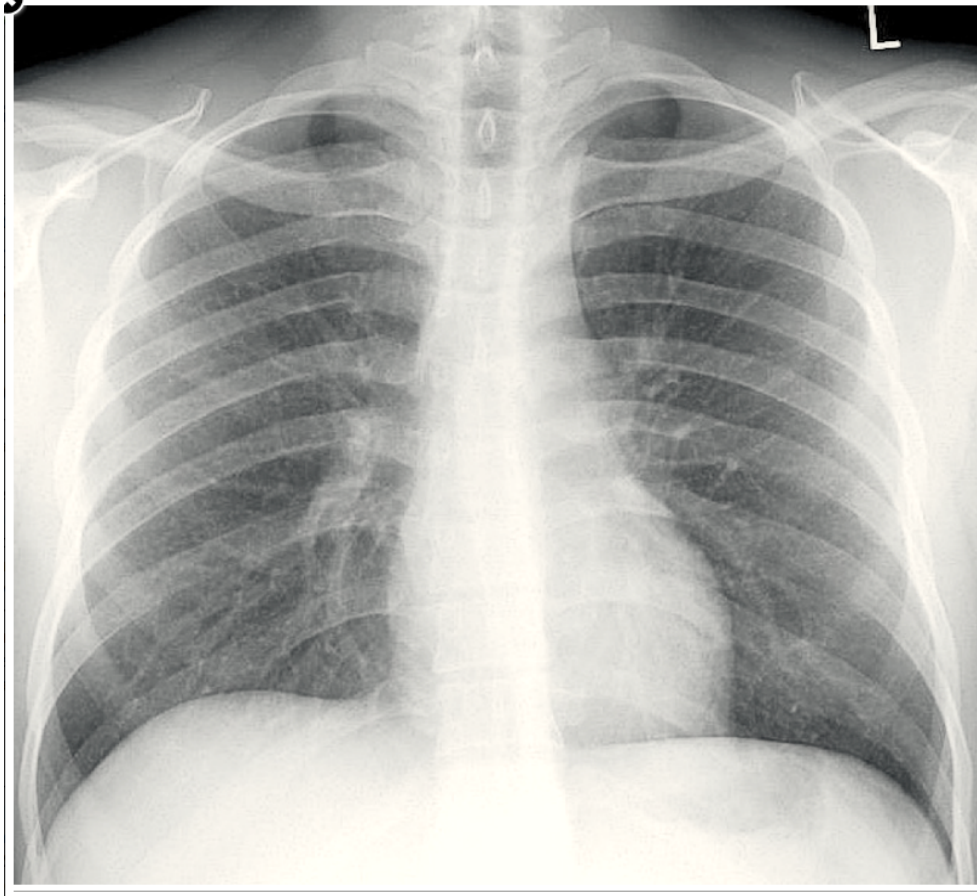


Figure 19 - Chest Radiograph of a Patient with AIDS and Disseminated Histoplasmosis

This chest radiograph in a patient with AIDS and disseminated histoplasmosis shows subtle diffuse ground-glass pulmonary infiltrates.

Diagnosis

- Samples: sputum, tissue, bone marrow, CSF, blood (lyses centrifugation)
- Direct examination: Geimisa/ Wright stain intra/extra cellular yeast cells
- Culture: mold at 25° c conversion to yeast in enriched medium at 37° c
- Serology : CF, ID and Histoplasma antigen from blood and urine

Peripheral blood smear Disseminated Histo

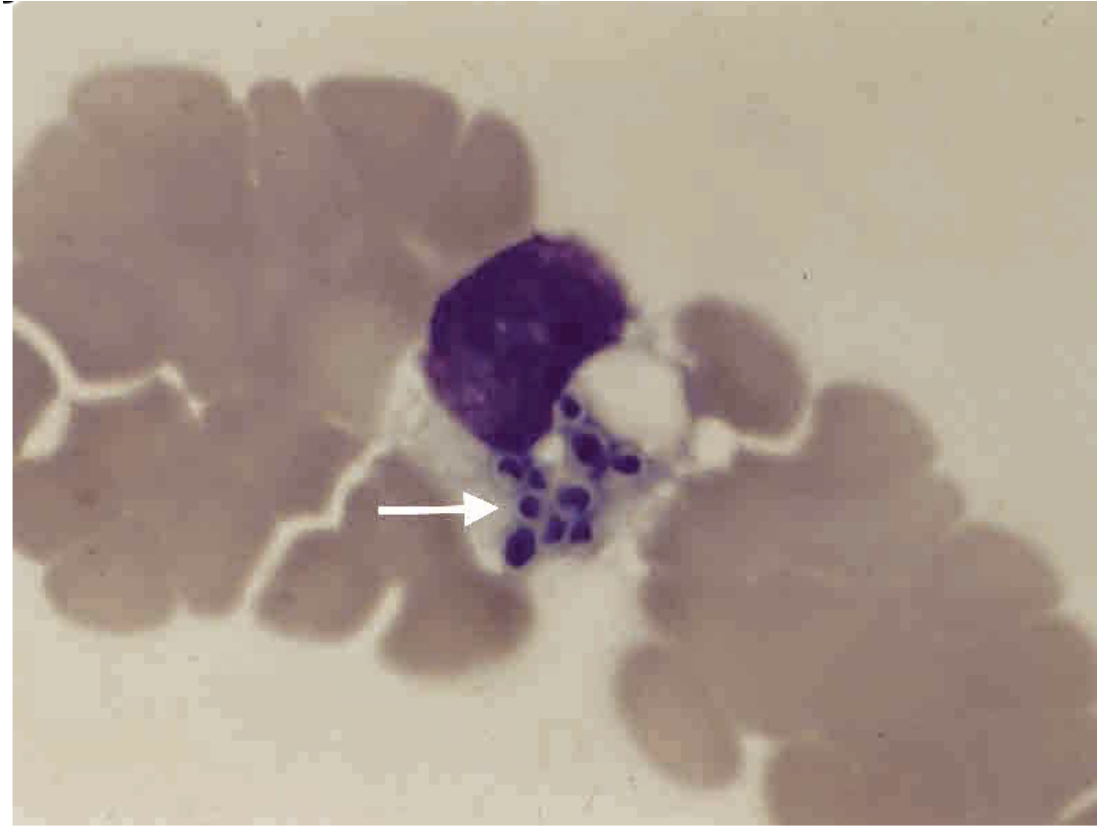
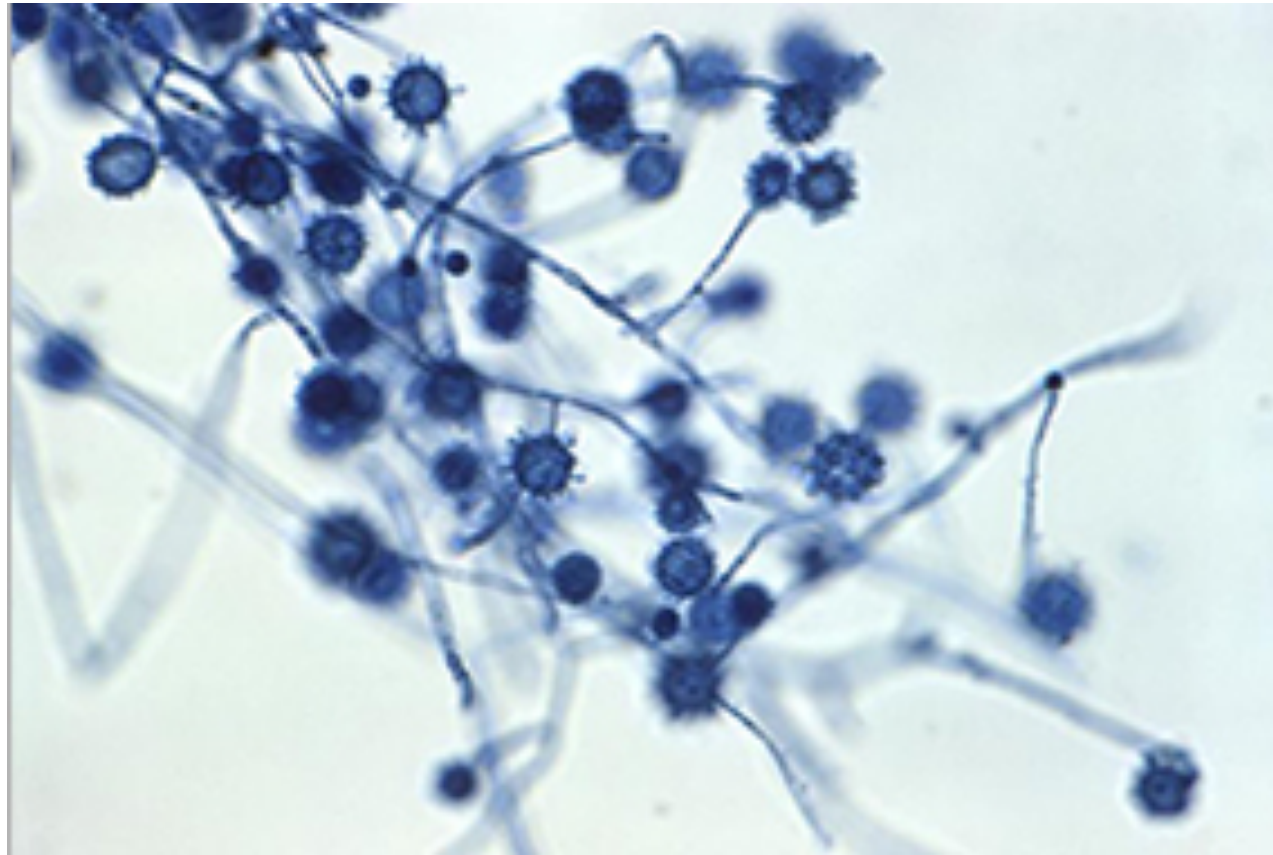


Figure 21 - Disseminated Histoplasmosis and Peripheral Blood Smear

This peripheral blood smear from a patient with AIDS shows a cluster of intracellular *Histoplasma capsulatum* organisms (white arrow). Blood cultures subsequently grew *Histoplasma capsulatum*.

Histoplasmosis



Estimated Sensitivity of Diagnostic Tests for Disseminated Histoplasmosis in patients with AIDS

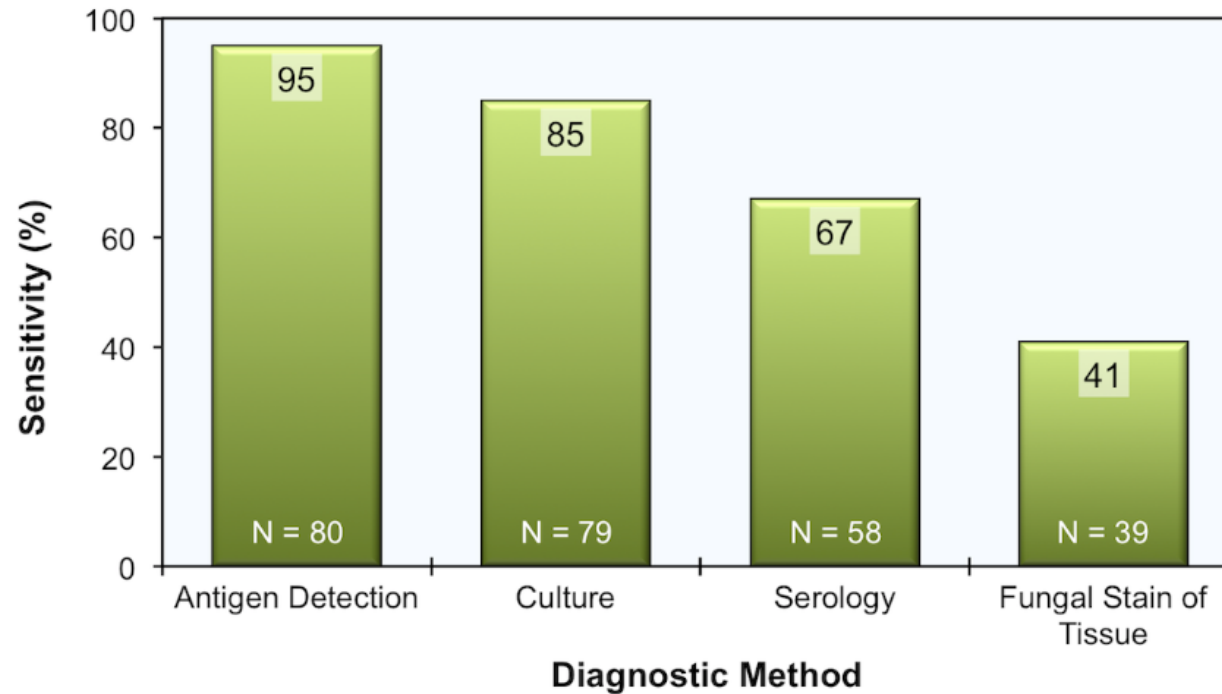


Figure 20 - Estimated Sensitivity of Diagnostic Tests for Disseminated Histoplasmosis in Patients with AIDS

These data reflect the sensitivity of four different tests used to diagnose histoplasmosis in patients with AIDS who have disseminated histoplasmosis. These data include samples from blood, bone marrow, respiratory secretions, or localized skin lesions.

Source: Wheat J. Endemic mycoses in AIDS: a clinical review. Clin Microbiol Rev. 1995;8:146-59.

Treatment of Less severe Disease

Treating Less Severe Disseminated Disease

Induction and Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID for ≥ 12 months (**AII**), with dosage adjustment based on interactions with ARV and itraconazole serum concentration

Alternative Therapy:

Note: These recommendations are based on limited clinical data (for patients intolerant to itraconazole who are only moderately ill).

- Posaconazole 400 mg PO BID (**BIII**)
- Voriconazole 400 mg PO BID for 1 day, then 200 mg PO BID (**BIII**)
- Fluconazole 800 mg PO daily (**CII**)

Treatment of Disseminated Histoplasmosis

Table 11. Guidelines for the Prevention and Treatment of Opportunistic Infections

Treatment of Disseminated Histoplasmosis

Treating Moderately Severe to Severe Disseminated Disease

Induction Therapy

Preferred Therapy:

- Liposomal amphotericin B at 3 mg/kg IV daily (**AI**)

Alternative Therapy:

- Amphotericin B lipid complex or amphotericin B cholesteryl sulfate complex 3 mg/kg IV daily (**AIII**)

Duration:

- For at least 2 weeks or until clinically improved

Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months (**AII**), with dosage adjustment based on interactions with ARV and itraconazole serum concentration

Treating Histoplasma Meningitis

Treating *Histoplasma* Meningitis

Induction Therapy (4-6 weeks)

- Liposomal amphotericin B: 5 mg/kg IV daily (**AIII**)

Maintenance Therapy:

- Itraconazole 200 mg PO BID (TID for at least 12 months and until resolution of abnormal CSF findings) with dosage adjustment based on interactions with ARV and itraconazole serum concentration (**AIII**)

Monitoring Response

- Antigen concentrations fall with effective therapy and increase at the time of relapse
- Antigen concentrations in urine or serum rise by at least 2 units in 90 percent of patients at the time of relapse

Discontinuing Long-Term Suppressive Therapy

- Secondary prophylaxis can be discontinued when the patient meets the following criteria:
- Received azole therapy for longer than 1 year, and
- Has negative fungal blood cultures, and
- Serum *Histoplasma* antigen is less than 2 ng/mL, and
- CD4 count has been higher than 150 cells/mm³ for at least 6 months due to antiretroviral therapy.

Histoplasmosis

- **Restarting Long-Term Suppressive Therapy**

- Long-term suppressive therapy should be restarted if the patient's CD4 count decreases to less than 150 cells/mm³

- **Timing of Initiating Antiretroviral Therapy**

- Patients diagnosed with histoplasmosis should be started on antiretroviral therapy as soon as possible after starting antifungal treatment for histoplasmosis

Case 2

- 35 y/o male with AIDS and a recent CD4 count of 100 cells/mm³ presents with cough and dyspnea. He was lost to follow up and did not take HIV medications for five years. He is from Mexico but he denies travelling outside GA since he came 10 years ago. Physical examination shows a temperature of 38.6°C, crackles in the lung fields, axillary and inguinal lymphadenopathy, hepatosplenomegaly, and a 2 by 3 cm ulcerated lesion on his face.

Case 2 continue

- Labs: CD4 100(5%), HIV-VL log 6, WBC 10K/mm³, neutrophils 50%, Eosinophils 10%, CXR Diffuse bilateral infiltrates, serum Cryptococcus Ag neg, a skin biopsy of the facial lesion demonstrates numerous spherules (10 to 80 microns in diameter), many of which contain multiple smaller endospores (daughter cysts).
- BAL culture stain also showed spherules confirming diagnosis of severe Coccidioidomycosis.
- What is the preferred initial treatment for this patient?
- A. Itraconazole 200 mg PO TID for 3 days followed by 200 mg BID
- B. Fluconazole 800 mg IV daily
- C. Amphotericin B
- D. Amphotericin B and Flucysoine

Case 2 cont..

- The patient has been taking Fluconazole for maintenance treatment for the past six months. He is also on DTG plus TAF/FTC for about 5 months and currently his CD4 is 250/mm³ (16%) and HIV-VL is undetected but CF AB is positive. He is feeling great and would like to know if he still needs to be on Fluconazole.
- What is your recommendation at this time?
- A. Yes he needs to continue maintenance treatment until his CD4 count is >500 for 6 months
- B. He can stop Fluconazole now
- C. He can stop Fluconazole after six months if he remains asymptomatic and serum CF Ab is negative
- D. He should continue maintenance treatment with Fluconazole indefinitely because relapse is common.

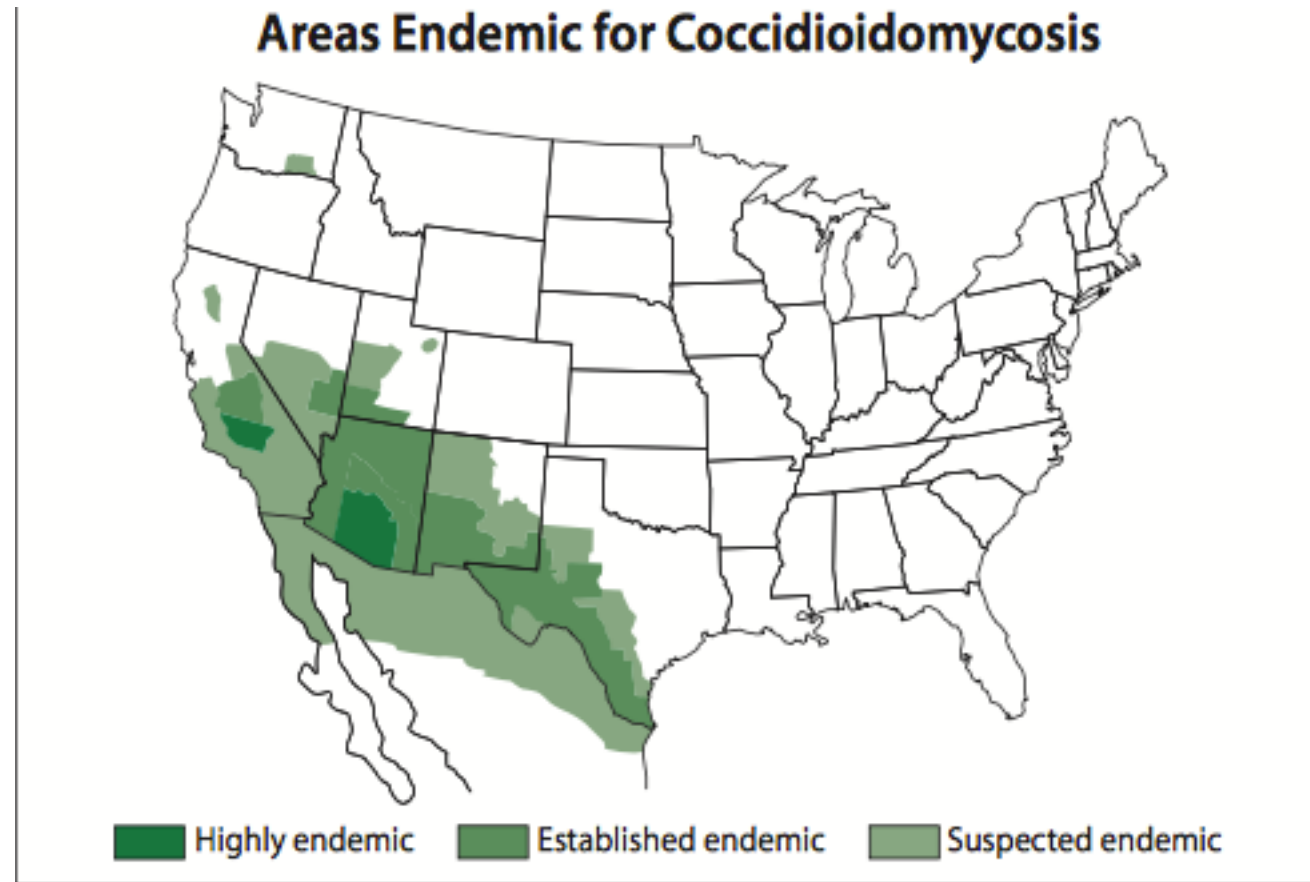
Coccidioidomycosis

- Etiology: *coccidioides immitis*
- Location: Endemic to southern Arizona, central California, southwestern New Mexico, and west Texas, Mexico, Central, and South America
- Micro: tissue 37° c spherules filled with endospores, 25° c hyphae, arthroconidia

Coccidioidomycosis

- Coccidioidomycosis is caused by a soil-dwelling fungus, *Coccidioides immitis*, and encompasses a wide spectrum of clinical diseases among individuals with HIV infection.
- The incidence of coccidioidomycosis has decreased in the era of potent antiretroviral therapy, but when infection does occur, a lower CD4 count (<250/mm³) predicts more severe disease

Coccidioidomycosis



Clinical Manifestation Primary Infection

- Most infections are asymptomatic
- Coccidial Pneumonia (fever, cough and chest pain)
- Hemoptysis occurs mainly in patients with a pulmonary cavity
- Arthralgias, Erythema nodosum

Desert bumps



HOST RISK FACTORS FOR COMPLICATIONS AND DISEASE SEVERITY

- Major suppression of cellular immunity (HIV, organ transplant, steroids, Chemotherapy anti- TNF)
- Diabetes mellitus
- Pregnancy (especially third trimester)

- Individuals of African or Philippine descent may also have an increased risk of extra pulmonary complications.

CLINICAL MANIFESTATIONS

- In the setting of HIV infection, the risk of developing symptomatic coccidioidomycosis is significantly increased in those who have a CD4 count less than 250 cells/mm³ and live (or previously lived) in a region endemic for coccidioidomycosis.
- Persons at higher risk of acquiring disseminated disease include black and Filipino men, Native Americans, and pregnant women in their second or third trimester.
- Patients with CD4 cell count greater than 250 cells/mm³ typically present with localized pulmonary infection that mimics community-acquired pneumonia. Patients with lower CD4 counts may develop diffuse pneumonia with infiltrates (that may resemble *Pneumocystis* pneumonia) or disseminated extrapulmonary infection that may include cutaneous, lymph node, hepatic, or central nervous system manifestations

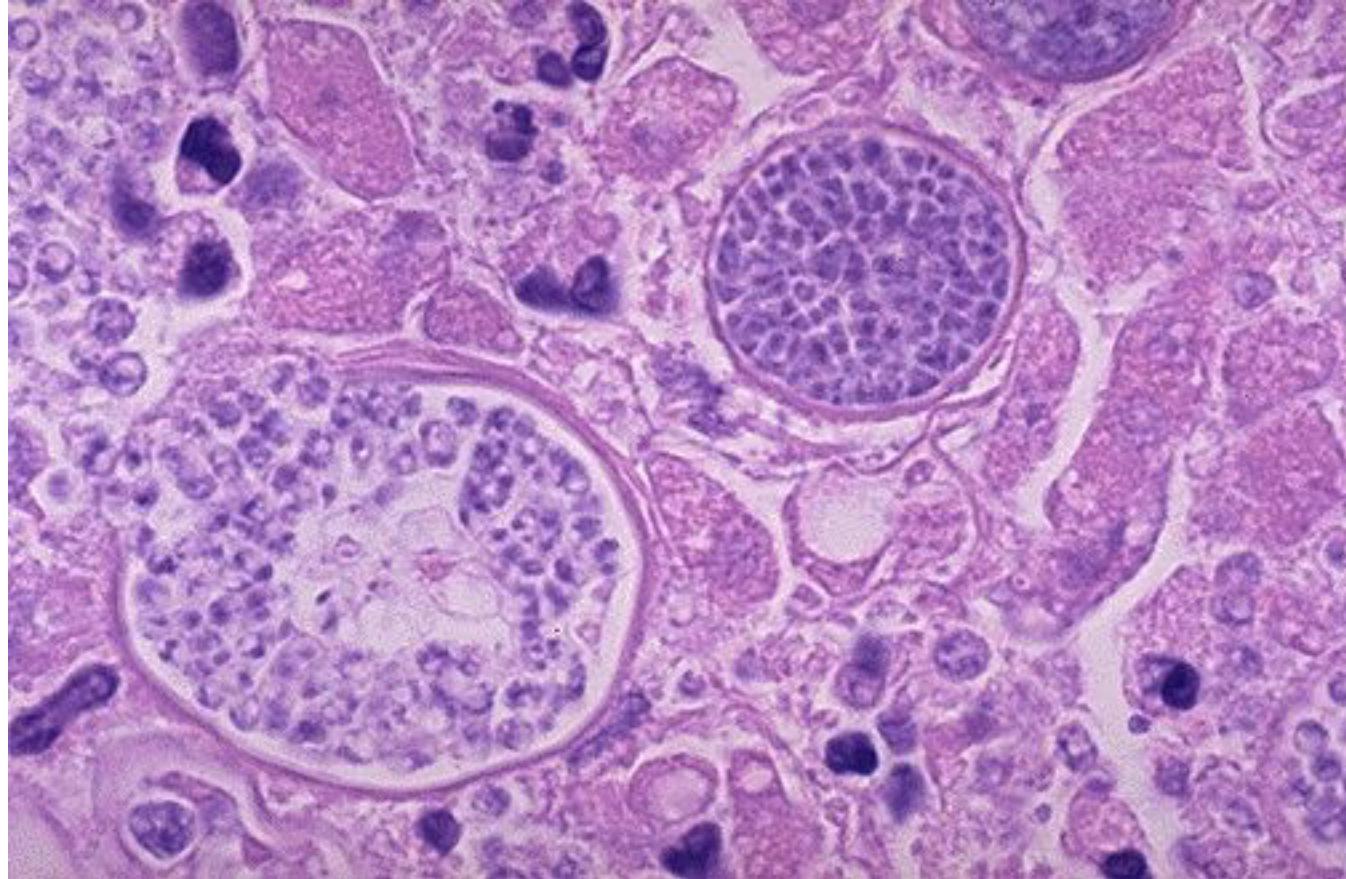
Cavitary lung disease Coccidioidomycosis



DIAGNOSIS

- The diagnosis of coccidioidomycosis can be confirmed by identifying the characteristic spherules that contain multiple endospores on a wet mount, potassium hydroxide (KOH) preparation, culture, or on a histopathology specimen.
- A positive serology test (usually using complement fixation) suggests and supports the diagnosis of coccidioidomycosis, though serology testing is less reliable in immunosuppressed patients.

Coccidioidomycosis spherules



Coccidioides immitis arthroconidia and hyphae



Serologic tests

- Immunodiffusion kit that measures IgM and IgG antibodies directed against the organism is the most common test ordered currently
- CF generally reserved for specimens other than serum, especially cerebrospinal fluid
- EIA highly sensitive but false positive results can be seen.

Serologic tests

- Very specific but they are relatively insensitive, especially early in an initial infection.
- Most patients lose serologic reactivity within months of an infection unless residual lesions are evident or infection is active.
- Repeating tests, if a first serologic test is negative, will improve diagnostic sensitivity

TREATMENT OF MILD INFECTIONS

Table 12. Guidelines for the Prevention and Treatment of Opportunistic Infections

Initial Treatment of Coccidioidomycosis

Treating Mild Infections (Such As Focal Pneumonia or Asymptomatic Patients with Positive Serology and CD4 count <250 cells/mm³)

Preferred Therapy:

- Fluconazole 400 mg PO once daily (**BII**)*, *or*
- Itraconazole 200 mg PO twice daily (**BII**)*

Alternative Therapy for Patients Who Failed to Respond to Fluconazole or Itraconazole):

- Voriconazole 200 mg PO twice daily after a loading dose of 400 mg twice on first day (**BIII**)*, *or*
- Posaconazole (delayed release tablet) 300 mg PO daily after a loading dose of 300 mg twice daily for one day, then 300 mg once daily* (**BIII**)* *or*
- Posaconazole (oral suspension) 400 mg PO twice daily (**BII**)*

Treating Bone or Joint Infections

Preferred Therapy:

- Itraconazole 200 mg PO twice daily (**AI**)*

Alternative Therapy:

- Fluconazole 400 mg PO once daily (**BI**)*

Treating Severe, Non-Meningeal Infection

Treating Severe, Non-Meningeal Infection (Diffuse Pulmonary or Severely Ill Patients with Extrathoracic Disseminated Disease)—Acute Phase

Preferred Therapy:

- Lipid formulation amphotericin B 3–5 mg/kg IV daily (**AIII**), or
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (**AII**)
- Use until clinical improvement, then switch to triazole (**BIII**)

Alternative Therapy:

- Some specialists add a triazole (either fluconazole 400 mg daily or itraconazole 200 mg twice daily, with itraconazole preferred for bone or joint disease) to amphotericin B therapy and continue the triazole once amphotericin B is stopped (**BIII**)

Treatment of Meningeal Infection

Treatment For Meningeal Infections (Consultation With A Specialist Is Advised)

Preferred Therapy:

- Fluconazole 400–800 mg PO daily (**AII**); IV if patient unable to take orally.

Alternative Therapy:

- Itraconazole 200 mg PO twice to three-times daily* (**BII**), or
- Voriconazole 200–400 mg PO twice daily after loading dose* (**BIII**), or
- Posaconazole (delayed release tablet) loading dose of 300 mg twice twice on first day, then 300 mg once daily* (**CIII**), or
- Posaconazole (oral suspension) 400 mg PO twice daily* (**CIII**), or
- Intrathecal amphotericin B (**AIII**) when triazole antifungals are not effective. Use in consultation with a specialist and should be administered by a clinician experienced in this technique.

Other Considerations

- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy.

Duration of Maintenance Therapy for Coccidioidomycosis

Table 13. Guidelines for the Prevention and Treatment of Opportunistic Infections

Duration of Maintenance Therapy for Coccidioidomycosis

Focal Pneumonia or Asymptomatic Patients with Positive Serology and CD4 count <250 cells/mm³

Therapy can be stopped if (All):

- Clinically responded to ≥ 6 months of antifungal therapy (for patients with focal pneumonia), and
- CD4 count ≥ 250 cells/mm³, and
- Receiving effective antiretroviral therapy with virologic suppression, and
- Continued monitoring for recurrence should be performed using serial chest radiograph and coccidioidal serology every 6-12 months.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis

- Relapse can occur in 25% to 33% of HIV-seronegative patients, and can occur in HIV patients with CD4 count >250 cells/mm³
- Therapy is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts (BIII).

Coccidioidal Meningitis

- Relapse has been reported in 80% of patients after stopping triazoles; therefore, suppressive therapy should be lifelong (All)

References

- Uptodate. Com
- National HIV curriculum <https://www.hiv.uw.edu>
- WWW.cdc.gov/fungal