Hey Clinical Problem Solvers! My name's T.J. La, a 6th year MD/JD/LLM student at Baylor College of Medicine and the University of Houston Law Center, and I am so excited to talk to you about histoplasmosis.

Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum*, is a pulmonary and hematogenous disease that can affect both immunocompetent and immunocompromised patients. More specifically, Histoplasmosis is part of the family of endemic mycoses, including Blastomycosis, Coccidioidomycosis, and Sporotrichosis. These are dimorphic fungal species that are present in the soil in specific geographic regions. Dimorphic means that they are molds in the environment (when temps are < 35 C), and in yeast form in human tissue (when temps are > 37 C).

For instance, Histoplasmosis is commonly seen in the eastern and midwestern U.S., particularly along the Ohio and Mississippi river valley, but can also be found worldwide in Central and South America, Africa, Asia and Australia. *Histoplasma* grows best in soil and dust that are contaminated with bird or bat droppings. Individuals most at risk are farmers, construction workers, and cave explorers.

Most people who come down with *Histoplasma* do not develop symptoms, but severe illness can develop if a large number of spores are inhaled and if the patient is immunocompromised, especially for someone with T cell abnormalities such as advanced HIV, steroids, TNF-alpha inhibitors, and transplantation.

Histoplasmosis comes in 3 flavors.

Acute pulmonary histoplasmosis is the initial form of the infection and occurs in the lungs, causing a flu-like illness (fever, cough, myalgias, chest pain, and malaise that could persist for months). However, it is usually asymptomatic and a self-limited illness. Sometimes, pneumonia and ARDS can occur in severe cases.

Chronic cavitary histoplasmosis, which is associated with emphysema, develops when one or more cavitary lesions form in the lung over a period of weeks. These pulmonary lesions often resemble that of cavitary tuberculosis, and these patients experience progressive cough and dyspnea. Of note, there is no dissemination of disease with either the acute or chronic forms of pulmonary histoplasmosis, and complications include granulomatous mediastinitis, mediastinal fibrosis that can cause compression of the pulmonary circulation and SVC, and broncholithiasis (a condition where calcified nodes or ossified material can erode into a bronchial lumen, causing obstruction, cough and/or hemoptysis).

The worst disease manifestation is disseminated histoplasmosis where *Histoplasma* infects macrophages and forms granulomas, which can reactivate and cause systemic disease akin to reactivated TB. I once had a 24-year-old HIV-infected patient who came to the ER with

progressive fatigue, weight loss, fevers, and several ecchymoses on his arms and legs. Labs revealed a CD4 count of 40 and DIC, and the peripheral blood smear showed intracellular yeasts, leading to the diagnosis of disseminated histoplasmosis, an AIDS-defining illness. A year later, the patient was seen in the ED for severe sepsis and altered mental status and was found to have reactivated Histoplasmosis, despite treatment for the initial episode.

Advanced HIV is thus one of the risk factors for disseminated histo, along with hematologic malignancies, transplantation, steroids, treatment with TNF-a inhibitors, and older age. Clues that raise suspicion for disseminated histoplasmosis are fever, cytopenias, hepatosplenomegaly, lymphadenopathy, and colitis. It is also known to cause oral or GI ulcers and can affect the adrenal glands causing Addison's disease. But keep in mind, disseminated histoplasmosis can affect any organ.

To diagnosis a patient with histoplasmosis, you can get a blood smear that would show intracellular yeasts, a fungal culture, a urine or serum antigen test (which is best for disseminated disease), PCR, and sometimes serologic testing for chronic infections. You should also order chest imaging if you suspect pulmonary involvement. It should be noted that a test for the *Histoplasma* antigen is both sensitive and specific, but there can be cross-reactivity with blastomycosis. Also, getting a serum beta-d-glucan, serum galactomannan, and BAL galactomannan, can aid in the diagnosis of histoplasmosis.

Now looking at the treatment options, for mild-mod infection, treatment is usually unnecessary as the infection is self-limiting. You can consider treating pulmonary histoplasmosis if symptoms do not improve after one month or if disseminated disease. For a mild to moderate infection >1 month, itraconazole is the agent of choice. For severe infection like disseminated histo or severe pneumonia, more aggressive therapy is required in the form of amphotericin B. Remember that amphotericin B is "amphoterrible" and has a lot of side effects including infusion reactions (fevers, chills, phlebitis, hypotension, bronchospasm) and others including nephrotoxicity, electrolyte wasting, anemia, nausea/vomiting, and abnormal liver chemistry tests.

To recap, histoplasmosis is a common fungal infection acquired by inhaling spores and is endemic to the Ohio-Mississippi River valleys, but can be seen worldwide. It can cause an acute primary pulmonary infection, a chronic cavitary pulmonary infection, or disseminated infection. To diagnose, look to histopathology, cultures, and antigen testing. An acute infection is almost always self-limited, but may need itraconazole for mild/mod disease or amphotericin B if severe.

We hope you enjoyed this schema!