Darling's Disease: A Review

Nachiket S Dighe[*1], Shashikant R Pattan[1], Sanjay B Bhawar[2], Vinayak M Gaware[1], Mangesh B Hole[1], Prerana A Chavan[1], Smita K Parjane[1]

[1]*Department of Medicinal Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, M.S, India*
[2]*Department of Pharmacology, Pravara Rural College of Pharmacy, Pravaranagar, M.S, India*

Abstract

Histoplasmosis is primarily a pulmonary disease caused by the fungus *Histoplasma capsulatum* with varying symptoms.The fungus is found in high concentrations in soil contaminated with bird or bat excreta while transmission occurs via inhalation of H. capsulatum spores from the soil. The fungal infection either is cleared or the organism continues to reproduce intracellularly and disseminates throughout the body via lymphatic and hematogenous circulation. Darling, a world-leading pathologist discovered Histoplasmosis to be a fungal infection in 1905 therefore it is also called as Darling's disease. Transmission occurs in areas like caves containing bat or bird droppings, chicken coops, birdhouses, bird roosts, or soil contaminated with such droppings. *H. capsulatum* can survive in soil for years and if the soil becomes airborne, it may cause Histoplasmosis. In patients that are immunosuppressed, complications are mouth ulcers, fevers, headaches, confusion, seizures, encephalopathy and infrequently, death.

Keywords: Histoplasmosis, *Histoplasma capsulatum*, Ketoconazole, Miconazole,

Introduction:

Histoplasmosis, also known as Darling's disease,[1]] is a disease caused by the fungus *Histoplasma capsulatum*. Symptoms of this infection vary greatly, but the disease primarily affects the lungs. Occasionally, other organs are affected; this is called disseminated histoplasmosis and it can be fatal if untreated. Histoplasmosis is common among AIDS patients because of their lowered immune system.[2]

History: [3, 4]

Table 1: History of Histoplasmosis

1905	Samuel Taylor Darling a world-leading pathologist discovered Histoplasmosis to be a fungal infection in 1905. Darling studied smears and slides made from tissues of a carpenter with an unknown infection and observed defense cells that resembled Plasmodium organisms.
1906	Darling found in Panama, in the spleens of three patients who had suffered over a long period from symptoms similar to those of kala-azar, a somewhat similar parasite which he designated the Histoplasma capsulatum.
1934	Other studies made in 1934, & '45, disclosed that the disease was a good deal less deadly than had been universally thought and a good deal less than hertofore supposed.
1972	Jun 29, 1972 between 125000 and 150.000 Americans will be infected by a disease that very few have ever heard of and even fewer could spell The disease is 'histoplasmosis' and the source of the figures is Dr Fred Tosh of the National Communicable Disease Center in Atlanta.
1985	The fungus transmitted by birds In the Ohio Valley.
1994	Typically, the histoplasmosis organism grows as a mold in soil that's been undisturbed for several years. Bird, bat or poultry droppings, The disease is histoplasmosis, which recently caused at least 30 inmates and employees at Powhatan Correctional Center to become ill.
1997	Dylan spokesman Elliot Mintz said that the singer, to the best of Mintz's knowledge, does not have a history of heart problems. He declined to reveal Dylan's prognosis or where the legendary songwriter is hospitalized. Histoplasmosis is an infection caused by a soil fungus.
2001	Diffuse nodular or linear densities in the chest radiographs of AIDS patients with a history of residence in endemic areas suggests the possibility of disseminated histoplasmosis. Disseminated histoplasmosis is usually fatal if not diagnosed early and treated rapidly.
2003	Disseminated histoplasmosis is a serious disease that affects the skin, lungs and internal organs. A month before admission, the patient developed focal joint pain and lower extremity edema that made walking.
2004	Unusual case of a hemodialysis-dependent end-stage renal disease patient who presented with isolated gastrointestinal histoplasmosis. He had no history of human immunodeficiency virus (HIV) disease or being on immunosuppressive medications.

Epidemology:

Histoplasmosis is found in temperate zones worldwide; specific endemic areas include the Mississippi, Ohio and St. Lawrence River valleys, the Caribbean, southern Mexico and certain parts of Central and South America, Africa and Asia. In these regions, the fungus is found in high concentrations in soil contaminated with bird or bat excreta. Transmission occurs via inhalation of H. capsulatum spores from the soil. [5]

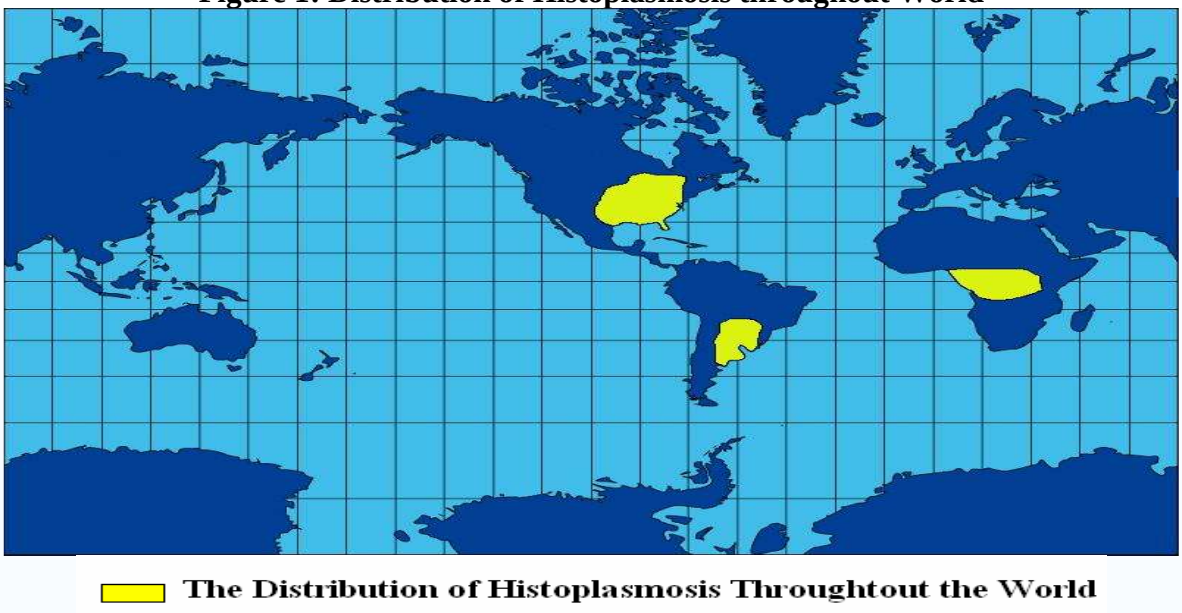
Distribution:

Histoplasma capsulatum is found throughout the world.It is endemic in certain areas of the United States, particularly in states bordering the Ohio River valley and the lower Mississippi River. It also common in caves in southern and East Africa. Positive histoplasmin skin tests occur in as many as 80% of the people living in areas where *H. capsulatum* is common, such as the eastern and central United States.[6]

United States

An estimated 50 million individuals have been infected with *H capsulatum.* Nationwide, approximately 22% of the population have positive skin-test results for histoplasmin, though the rate may be as high as 80% in endemic areas in the central United States, specifically the Ohio and Mississippi River Valleys . Of the 500,000 individuals who are exposed annually, 50,000-200,000 develops symptoms and 1500-4000 requires hospitalization. [7]

Figure 1: Distribution of Histoplasmosis throughout World



Life Cycle:

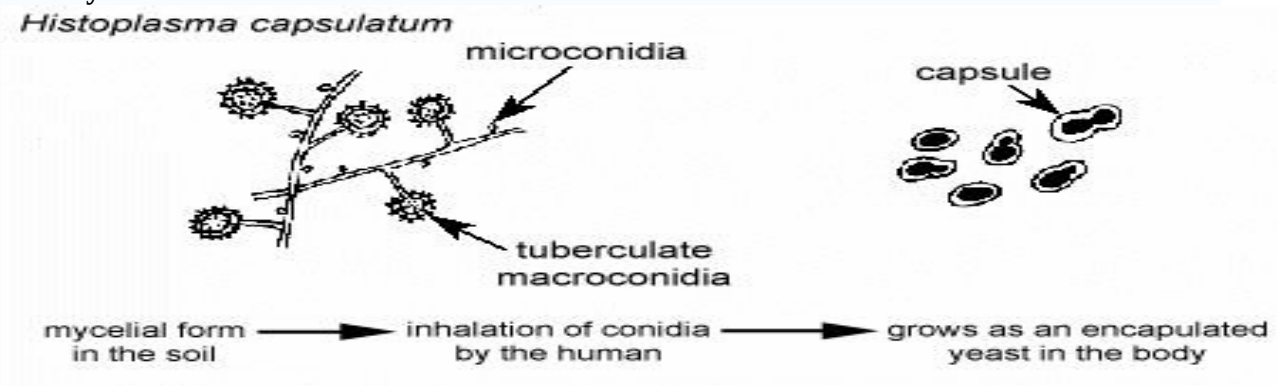


Figure 2: Life Cycle of Histoplasmosis

H. capsulatum is a dimorphic fungus, which resides in the soil or decaying organic matter during the free living mycelial stages. It produces fruiting bodies in the form of micronidia (2-5 µm) and macronidia (5-18 µm). Infection occurs via inhalation of micronidia, which can reach the lower respiratory tract. [8] It is also thought that primary fungal infection also can occur by ingestion of the organism, but this has not been demonstrated experimentally. The incubation period is 12 to 16 days during which the micronidia convert to the yeast phase and replicate by budding. These yeasts are subsequently phagocytosed by macrophages. The fungal infection either is cleared or the organism continues to reproduce intracellularly and disseminates throughout the body via lymphatic and hematogenous circulation. [9]

Transmission:

Histoplasmosis is not transmitted person to person except for a few rare instances when a transplant patient has contracted histoplasmosis from a transplanted organ. [10] The large majority of cases occur when people inhale fungal mycelia and spores, usually from a source where the fungus growth is enhanced. Such sources or areas are in caves containing bat or bird droppings, chicken coops, birdhouses, bird roosts, or soil contaminated with such droppings. Unfortunately, *H. capsulatum* can survive in soil for years and if the soil becomes airborne (dust), inhalation of *H. capsulatum*-contaminated dust may lead to histoplasmosis. [11]

Genomic Structure:

Sre1p specifically bound DNA containing the 5′-(G/A) ATC (T/A)GATAA-3′ sequence, and that binding was both iron- and zinc-dependent. Metal analysis indicated that a substoichiometric amount of iron, predominately Fe^{3+}, was bound to the purified protein. About 0.5−1 equiv of Fe^{3+} per monomer was necessary for full DNA-binding activity. Mutations in the conserved cysteine residues in the cysteine-rich region led to a decrease in bound iron. The loss of iron led to a ~2.5-fold decrease in DNA-binding affinity, indicating that iron was directly involved in *SRE1* regulation of iron-uptake genes. [13, 14]

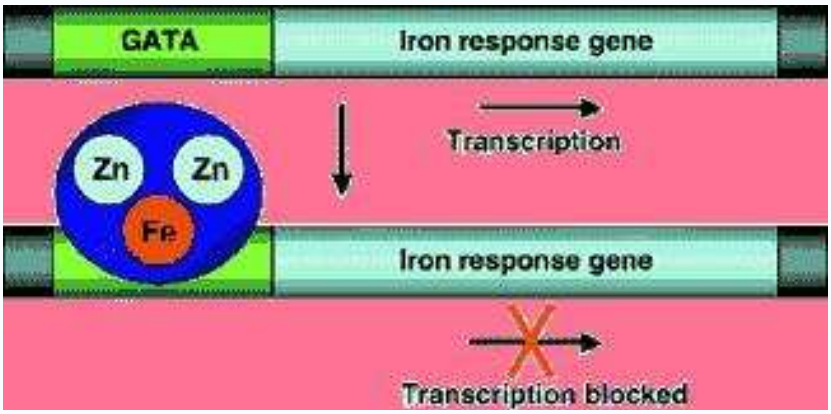


Figure 3: Genomic Structure of Histoplasma capsulatum

Pathophysiology:

Five serotypes of *capsulatum* are known, including some avirulent strains. *Histoplasma* species have a mycelial form at ambient temperatures. The spores of *H capsulatum* (microconidia) become airborne when soil is disturbed. The initial neutrophil response is ineffective against the yeast form. Macrophages ingest the yeast, but they continue to proliferate. Specific immunity,

which occurs 10-21 days after infection, is needed to kill the organisms. [15] Specific helper T cells are able to activate macrophages to form the granulomas that are characteristic of the disease. Natural killer cells mediate extracellular killing, which antibodies enhance. Pneumonitis, with a predominant mononuclear infiltrate, peaks 2 weeks after infection. Granulomas can form in the pulmonary parenchyma and in the hilar and mediastinal lymph nodes. [16] These lesions can be caseating and may develop calcification and fibrosis over time. In most infections, fungemia likely occurs at some point because splenic granulomas have been observed after asymptomatic infection. In individuals with impaired T cell–mediated immunity, other sites of infection include the bone marrow, liver, adrenal glands, CNS, joint spaces, heart valves and blood vessels.[17] Reports describe infectious complications in almost every tissue. Reactivation of infection may occur in individuals who become immunosuppressed long after a primary infection; this reactivation accounts for many of the cases observed in nonendemic areas. Reinfection can occur in the setting of heavy conidial burdens but is generally mild because of specific immunity. Recent animal studies have revealed that interleukin (IL)-1, tumor necrosis factor (TNF)-alpha and GR 1(+) cells are important in localizing and controlling *Histoplasma* infection. *YPS3* and cell wall alpha-(1, 3)-glucan of *Histoplasma* are also associated with virulence. [18]

Disease Mechanism:

H. capsulatum grows in soil and material contaminated with bird or bat droppings (guano). The fungus has been found in poultry house litter, caves, areas harboring bats and in bird roosts (particularly those of starlings). The fungus is thermally dimorphic: in the environment it grows as a brownish mycelium, whereas at body temperature (37°C in humans) it morphs into a yeast.[19] The inoculum is represented principally by microconidia that, once inhaled into the alveolar spaces, germinate and then transform into budding yeast cells. Histoplasmosis is not contagious, but is contracted by inhalation of the spores from disturbed soil or guano.[20]

Incubation:

If symptoms occur, they will start within 3 to 17 days after exposure; the average is 10 days. [20]

Mortality/Morbidity:

The overall mortality rate of histoplasmosis is low; most cases spontaneously resolve. In individuals with immunosuppressant, progressive disseminated disease has a high mortality rate of 7-23%. Without treatment, disseminated disease is usually fatal. Disseminated infection can localize in any tissue, leading to various complications. Pericarditis and obstruction of mediastinal structures are the principal complications in individuals who are immunocompetent. [21, 22]

Race:

No racial predilection to infection or to disease presentation is apparent. [23]

Sex:

Among adults, histoplasmosis is described more commonly in men than in women. However, certain clinical manifestations, such as erythema nodosum, are described most commonly in women. These sex differences in infection and disease are not observed in children. [23]

Age:
Histoplasmosis occurs at any age. Disseminated disease is more likely to occur in individuals at the extremes of life, unless a person has immunodeficiency. The incidence of disseminated histoplasmosis in children appears to have decreased in the last 30 years. The sex-related differences observed in infection and disease among adults is not observed in children. [24, 25]

Signs and Symptoms:
About 90% of infections caused by *H. capsulatum* are asymptomatic (produce no symptoms). Occasionally, a few asymptomatic patients will show small scars in lung X-rays. Symptomatic people often develop fever, chills, dry cough, malaise, sweats and abdominal pains about three to 14 days after exposure. If the disease progresses, symptoms such as weight loss, fatigue, dyspnea, chest pain and reduced or loss of vision may occur. A sign of progression are patchy infiltrates seen on chest X-rays, usually in the lower lung fields. Other symptoms that can occur, especially in patients that are immunosuppressed, are mouth ulcers, fevers, headaches, confusion, seizures, encephalopathy and infrequently, death. [26]

Presumed ocular histoplasmosis syndrome (POHS) is characterized by the triad of:

1. Disseminated midperipheral choroiditis, consisting of infiltrates and scarring which appears as yellow-white punched-out lesions.
2. A macular or parafoveal subretinal neovascular membrane which appears as a grayish-green patch beneath the retina in the peripapillary and foveal areas, with or without subretinal blood, exudate or disciform scarring.
3. Atrophy or scarring adjacent to the optic disc, which appears as a flat, whitish-brown lesion; the presentation varies depending on the amount of retinal pigmentary epithelial hyperplasia next to the optic disc.

POHS occurs bilaterally in 60 percent of cases. Patients are usually age 20-50. The eye remains remarkably quiet with virtually no aqueous or vitreous cells and minimal flare. In fact, most patients are asymptomatic until a choroiditis or subretinal neovascular membrane develops around the fovea. Optic disc edema is an occasional finding in active disease. [27, 28]

Diagnosis: *[29-34]*

Table 2: Diagnosis of Histoplasmosis

General considerations in histoplasmosis	• The laboratory diagnoses of fungal disease and histoplasmosis are particularly challenging because of the nonspecific clinical findings, the difficulty of culturing organisms and the confusing array of tests available. MiraVista Diagnostics has established a Web site to assist clinicians. • General laboratory findings in disseminated disease include pancytopenia, elevated liver enzyme levels, hyperbilirubinemia and elevated serum lactate dehydrogenase (LDH) levels. • Silver stain of tissue sections or Wright stain of smears of peripheral blood or bone marrow aspirates are useful for diagnosing acute disseminated infection or severe pulmonary infection.
Culturing	• The criterion standard of diagnosis is culture of the fungus from clinical

	specimens. • *H capsulatum* can be recovered from sputum, bronchoalveolar lavage (BAL), skin lesions, blood, or bone marrow on routine fungal cultures, but the organism grows slowly and plates must be kept as long as 12 weeks. A DNA probe for *H capsulatum* permits rapid identification. • Blood culture by using the lysis-centrifugation system is somewhat more rapid and increases sensitivity. • Cultures are positive in as many as 85% of patients with progressive disseminated histoplasmosis (PDH) or chronic pulmonary histoplasmosis (CPH), but they can be falsely negative in about 20% of disseminated cases. • The combination of blood and bone marrow cultures increases the likelihood of positive cultures. • Bronchoscopy is an important diagnostic tool, especially for PDH, with a diagnostic yield of 60% in patients from endemic areas with pulmonary infiltrates and 88% for chronic cavitary histoplasmosis. • Use of several specimens may increase the yield.
Skin testing	• Histoplasmin skin testing is not recommended for diagnostic purposes because of the high rate of positive reactions in endemic areas, because of the variable duration of responses to the skin test and because of skin testing can affect the results of subsequent serologic tests. • Skin testing has been useful as an epidemiologic tool.
Serologic testing	• A number of tests have been developed to detect *H capsulatum* antigen or host antibodies to infection. Tests to detect host antibodies are those more commonly used in the clinical setting. However, test results for antibodies can be falsely negative in patients with disseminated disease because of underlying immunosuppression. On the other hand, patients with disseminated disease have a high fungal burden that enables rapid diagnosis by means of antigen detection. Because of the low fungal burden in patients with mild manifestations, the yield of antigen detection is low. • Antibody levels peak 6 weeks after exposure and decline over 2-5 years. Elevated antihistoplasmal antibody levels might result from a previous infection or after other types of fungal infections.
Antibody testing	• The standard serologic tests for histoplasmosis are the immunodiffusion (ID) test and the complement fixation (CF) test. • Histoplasmin, a filtrate of mycelial cultures, is the antigen used in the ID test. Two possible precipitin bands are observed: The H band reflects antibodies formed during active infection and becomes undetectable within 6 months. The M band is present in acute and chronic acute and chronic infection and remains elevated for years. This test is less sensitive than CF and should not be used for screening. M precipitins can be detected in 50-75% of patients with acute histoplasmosis and in almost 80-100% of patients with chronic pulmonary infections. • The CF test uses both mycelial and yeast phase antigens. An antibody to

	a yeast-phase CF titer of more than 1:32 is consistent with active infection in an endemic area, though an acute titer of more than 1:8 suggests infection, especially in nonendemic areas. CF has higher sensitivity than ID. In acute pulmonary histoplasmosis, the CF result is positive in 90% of patients, whereas the sensitivity of ID is as much as 75%. • A 4-fold rise in titer between acute and convalescent paired sera is diagnostic. Antibodies may clear within months after a brief exposure but might persist for years after a prolonged exposure. • Although CF and ID both are fairly specific, some cross-reactivity with other mycoses occurs. • Radioimmunoassay (RIA) and subsequent enzyme immunoassay (EIA) have been reported to be more sensitive than CF; however, higher background seropositivity in endemic areas and recent studies questioning the sensitivity of these assays compared with CF limit their usefulness. • Antibody responses can also be measured with enzyme immunoassay or Western blot assay. Although antibodies can be detected faster with these methods than with standard tests, these methods are difficult to standardize and their results are hard to quantitate and interpret.
Antigen testing	• Detection of polysaccharide antigen in serum, urine, or BAL of patients with disseminated and acute pulmonary histoplasmosis is a rapid and specific diagnostic method. Urine specimens have high sensitivity, as much as 90% in immunocompetent patients with disseminated or acute pulmonary disease. BAL fluid antigen levels can be higher than those in blood or urine and matched BAL, urine and serum specimens have the highest yield. Heat and ethylenediaminetetraacetic acid treatment of serum specimens significantly increases sensitivity without compromising specificity. • The recommended approach is first to perform antigen testing with blood and urine from a patient with suspected histoplasmosis. Then, the focus in testing depends on the symptoms. For example, in patients with respiratory symptoms, obtain BAL samples; in those with CNS symptoms, obtain CSF. • Cross-reactivity with other endemic mycoses occurs. • If initial results are positive, the antigen test can be used to monitor the treatment response. Antigen levels decrease with treatment, eventually reaching undetectable levels in patients who are cured or in patients undergoing chronic maintenance treatment. Persistent antigenemia or antigenuria indicates an ongoing infection and supports the continuation of antifungal therapy. Antigen levels rise during relapse, enabling detection in patients whose antifungal treatment has been discontinued. • Recently, *Histoplasma* antigen detection by means of enzyme-linked immunosorbent assay (ELISA) has become available for different specimens, including serum, urine and BAL and CSF samples. The sensitivity of this test is reported to be as high as 92% in urine specimens

	and 82% in serum specimens from patients with disseminated histoplasmosis.Although the sensitivity is low in self-limited and CPH; the specificity is as much as 98%.
Molecular diagnostic testing	• Preliminary data suggest that polymerase chain reaction (PCR) might improve the accuracy of identifying *H capsulatum* in tissue specimens.DNA probes are also commercially available and are used for definitive identification of positive cultures. DNA probes are also commercially available and are used for confirmation of positive cultures. • A retrospective review of pediatric patients with cancer at St Jude Children's Research Hospital demonstrated that the most rapid and specific tests for histoplasmosis were histopathologic examination of lung biopsy specimens in patients with localized pulmonary infection and *Histoplasma* -specific antigen detection in the urine of patients with disseminated histoplasmosis.
Other Tests	• Pulmonary function testing may demonstrate fixed or variable airway obstructive patterns in mediastinal obstructive syndromes. • Acute pulmonary disease is most likely to demonstrate a restrictive pattern. • A recent small study found that testing of fecal mucus for *Histoplasma* was helpful in diagnosing disseminated histoplasmosis in children.

Treatment: *[35-43]*

Most acute forms of histoplasmosis in immunocompetent hosts resolve without specific treatment. Systemic antifungal treatment is indicated for severe acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis (CPH), progressive disseminated histoplasmosis (PDH) and any manifestation in an immunocompromised patient. Specific therapy recommendations vary with the presenting syndrome.

Table 3: Treatment of Histoplasmosis

Syndromes in immunocompetent hosts	• Localized disease: Antifungal therapy is unnecessary in patients with localized disease. However, oral itraconazole is recommended for 6-12 weeks in patients whose symptoms have not improved after 3-4 weeks of observation. • Severe acute pulmonary syndrome: Antifungal therapy (amphotericin B) is indicated for patients presenting with clinically significant dyspnea or hypoxemia. After discharge from the hospital, itraconazole should be used to complete a 12-week course of antifungal therapy. Patients with relatively mild manifestations can be treated with only itraconazole and treatment should be continued for 3 months. Corticosteroids have also been used for short-term therapy (tapered over 2 wk); however, these agents always should be used with caution in fungal infections because of the risk of impaired cell-mediated immunity with prolonged use. • Mediastinal obstructive syndromes: For patients with clinically significant, symptomatic obstructive symptoms, antifungal treatment should be started. Reports describe successful treatment

	with oral (eg, itraconazole, ketoconazole) and systemic (amphotericin B) antifungal agents. Surgical resection should be considered for life-threatening obstruction or if a patient's condition fails to improve after 4-6 weeks of antifungal treatment. Surgical interventions do not prevent progression to fibrosing mediastinitis. Although reports mention successful surgical management of fibrosing mediastinitis, the surgical mortality rate is high and surgeons inexperienced in managing this disorder should not attempt such interventions. Medical management with antifungal agents should be attempted first unless the obstruction is life threatening. • Pericarditis: Anti-inflammatory treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids is the mainstay of management. Progression to constrictive pericarditis is described but rare. • Rheumatologic syndrome: Rheumatologic syndrome often resolves without treatment or with a brief course of NSAIDs.
Syndromes in hosts with an underlying illness or immunodeficiency	• CPH: Without antifungal treatment, CPH is progressive, causing loss of pulmonary function in most patients and death in up to half. Amphotericin B has been used most successfully and is effective in 59-100% of cases, but most patients can be treated with itraconazole or ketoconazole for at least 3 months. Relapse rates are 10-15% with the last 2 agents; fluconazole is less effective. The preferred treatment is amphotericin B followed by itraconazole for 12-24 months. • Local manifestations of disseminated disease: Endocarditis is very difficult to treat and may require resection of the affected valve and systemic antifungal treatment.
Surgical Care	• Surgical consultation is indicated for patients with infections complicated by fistulas, hemoptysis, or broncholithiasis. The surgical management of mediastinal obstructive syndromes is somewhat controversial because they may improve with observation or medical therapy. Severe obstruction of the airways or large blood vessels may be life threatening and immediate intervention may be required. • In general, unroofing and debridement of large granulomas is preferable to excision. Fibrosing mediastinitis is especially difficult to manage because normal structures are encased in collagenous connective tissue. Surgeons in endemic areas often are well versed in the management of these surgically challenging problems.
Activity	• Bed rest has been recommended for systemic syndromes.
Antifungal agents	• Systemic antifungal treatment is indicated for severe acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis (CPH), progressive disseminated histoplasmosis (PDH) and any manifestation in an immunocompromised patient .Amphotericin B

	is the mainstay of therapy for most systemic fungal infections. It is highly effective but has potential adverse effects. New lipid formulations of amphotericin B reduce renal toxicity; however, they are expensive and their improvements in efficacy are not proven. A double-blind randomized trial performed to compare liposomal amphotericin B (L-AMB) with the standard formulation (AmB) in patients with AIDS showed that L-AMB was at least as effective as AmB, with marked reduction in renal toxicity.Echinocandins (eg, caspofungin) should not be used.
Antifungal agents, azoles	• The azole antifungal agents are divided into 2 groups: imidazoles and triazoles. The imidazoles are an older group and include miconazole, ketoconazole and clotrimazole. The triazoles consist of fluconazole; itraconazole; and the new second-generation azoles ravuconazole (investigational in the United States), voriconazole and posaconazole. Itraconazole is more effective than ketoconazole or fluconazole for treatment of histoplasmosis. It is also effective for long-term suppression of histoplasmosis in patients with AIDS.Voriconazole and posaconazole may be useful in patients who are intolerant of or who fail treatment with AmB or itraconazole. In vitro studies with voriconazole and posaconazole have shown the activity of these agents against *H capsulatum, Blastomyces dermatitidis and Coccidioides immitis.* Data from a few animal studies have verified their efficacy in vivo.Posaconazole is reported to be effective for histoplasmosis in a small number of patients. In a case series, 6 of 7 patients were successfully treated with posaconazole.Four of these 6 patients had disseminated infection and, in all, other therapy failed or was intolerable.Phase 3 clinical trials for the treatment of invasive fungal infections have been completed and the US Food and Drug Administration recently approved posaconazole for the prophylaxis of invasive *Aspergillus* and *Candida* infections in high-risk, severely immunocompromised patients aged 13 years or older.
NSAIDs	• NSAIDs have analgesic, anti-inflammatory and antipyretic activities. Their mechanism of action is not known, but they may inhibit cyclooxygenase activity and prostaglandin synthesis. Other mechanisms may include inhibition of leukotriene synthesis, lysosomal enzyme release, lipoxygenase activity, neutrophil aggregation and various cell-membrane functions. A brief course of NSAIDs may be required for patients who develop rheumatologic symptoms e.g Naproxen (Aleve, Naprosyn), Ibuprofen (Motrin, Advil, Ibuprin)
Nutrition and Dietary Supplements	• Vitamin C, 500 - 1,000 mg one to three times daily, as an antioxidant and for immune support. • Grapefruit seed extract (*Citrus paradisi)*, 100 mg capsule or 5 - 10 drops (in favorite beverage) three times daily when needed, for

	antibacterial, antifungal and antiviral activity and for immunity. • N-acetyl cysteine, 200 mg daily, for antioxidant effects. • Probiotic supplement (containing *Lactobacillus acidophilus*), 5 - 10 billion CFUs(colony forming units) a day, when needed for maintenance of gastrointestinal and immune health. You should refrigerate your probiotic supplements for best results. • Coenzyme Q10, 100 - 200 mg at bedtime, for antioxidant and immune activity.
Herbs	• Cat's claw (*Uncaria tomentosa*) standardized extract, 20 mg three times per day, for inflammation and antifungal activity. • Garlic *(Allium sativum)*, standardized extract, 400 mg two to three times per day, for antifungal and immune activity. • Cranberry (*Vaccinium macrocarpon)*, 300 - 1,800 mg two times per day, for antifungal activity. • Reishi mushroom (*Ganoderma lucidum*), 150 - 300 mg two to three times per day, for inflammation and for immunity. You may also take a tincture of this mushroom extract, 30 - 60 drops two to three times a day. • Olive leaf (*Olea europaea*) standardized extract, 250 - 500 mg one to three times per day, for antifungal activity and immunity. You may also prepare teas from the leaf of this herb.

Management:

People living in endemic areas like the Ohio River Valley are likely to be exposed to histoplasmosis no matter what they do, since the fungus is likely in the dust in the air. However, if they are healthy, most people that get exposed or infected with *H. capsulatum* will be asymptomatic. Immunosuppressed (those with HIV or cancer or who are receiving chemotherapy for cancer) might reduce their chances of exposure if they live in endemic areas by avoiding high dust areas like construction sites.[44] Soil can be decontaminated with 3% formalin under special circumstances. If people need to work in potential high exposure areas like caves, bridges, construction sites, chicken coops, or other areas where bird and bat droppings could be concentrated, the National Institute for Occupational Safety and Health (NIOSH) recommends using a Part 84 particulate respirator certified by NIOSH. Some investigators suggest that simply watering down soil will help prevent dust formation and reduce the chance of exposure. There is no vaccine for histoplasmosis. In some cases, *H. capsulatum* becomes dormant and may reactivate if the person becomes stressed or immunodepressed. Although people develop an immune response to histoplasmosis and recover with no complications, the response is not completely protective and the person can become reinfected with *H. capsulatum*. [45]

Prognosis:

- Most cases of histoplasmosis spontaneously resolve and do not recur.
- Reinfection is possible, as is reactivation in individuals from endemic areas who become immunosuppressed.
- The mortality rate of disseminated disease even with appropriate treatment is high (7-23%); without treatment it is as high as 80%.

- Poor clinical response or relapse may indicate insufficient total dose of antifungal agent, unrecognized immuno suppression, or occult localized infection, such as endocarditis or meningitis.
- Relapse occurs in 10-20% of patients with disseminated infection and in as many as 80% of those with AIDS.[45]

Conclusion

Histoplasmosis primarily being a pulmonary fungal disease, after progression shows symptoms such as weight loss, fatigue, dyspnea, chest pain and reduced or loss of vision .Although commonly not a fatal disease, death can occur if untreated or in immunocompromised patients. Diagnosis is made with signs and symptoms X-ray and microscopically.Treatment is with antifungal agents like miconazole and ketoconazole while some herbal drugs are also useful synergistically.

References

1. ST Darling , *J Am Med Assoc* **1906**, 46, 1283–5.
2. Histoplasma capsulatum, cause of histoplasmosis in humans and other animals, Tom Volk's Fungus of the Month for January **2000**".
3. P Silberberg , *Biochemistry***, 2007**,14, 154-158.
4. P Tong, WC Tan, M Pang, *Br Med J (Clin Res Ed)* **1983**, 287 (6395), 822–3.
5. JF Murray, J Mills, Part II. *Am Rev Respir Dis* **1990**; 141, 1582.
6. T Gari, P Marty, Y Le Fichoux, R Loubière, *Bull Soc Fr Mycol Med* **1987,**16 (1): 87–90.
7. CA Kauffman, *Clinical Microbiology Reviews* **2007**,20 (1), 115–132.
8. EC Hawkins, DB DeNicola, *J Am Vet Med Assoc,* **1990**, 197, 79-82.
9. AM Wolf, Systemic mycosis. *J Am Vet Med Assoc*, **1989** 194, 1192-1196.
10. SY Wong, DM Allen, *Clin Infect Dis* **1992**, 14, 232-4.
11. N Campbell, C Charlotte. G H Hil, *Science* **1962***;* 136, 1050–1051.
12. R. J Britten, D. E. Graham and B. R. Neufeld, *Enzymol.* **1974**, 29, 363-418.
13. Y, Lily Chao, A Michael, R Jasper, *Biochemistry*, **2008**, *47* (27), 7274–7283.
14. J Rady and G. Shearer, *J. Med. Vet. Mycol*. **1997**, 35:159-166.
15. LJ Wheat, CA Kauffman, *Infect Dis Clin North Am*. **2003**; 17(1), 1-19.
16. J Rosenthal, KD Brandt, LJ Wheat, *Arthritis Rheum*. **1983**, 26(9), 1065-70.
17. AETC. Clinical Manual for Management of the HIV-Infected Adult. AETC National Resource Center Accessed **January 11, 2007**.
18. GL Mandell, JE Bennett, R Dolin. Histoplasmosis, Oxford, England: Churchill Livingstone; *Principles and Practice of Infectious Diseases***, 2004,** 6, 121-126.
19. R James, D William, V Berger, et al, **2006** ,ISBN 0-7216-2921-0.
20. MA Barron and NE Madinger, *Infections in Medicine,* **2008**, 3, 147-151.
21. R Kurowski, M Ostapchuk, *Am Fam Physician*, **2002**; 66(12), 2247-52.
22. SM Levitz, *Clin Infect Dis*, **1992**; 14 Suppl 1, and S37-42.
23. DJ Mathisen, HC Grillo, *Ann Thorac Surg*, 1992; 54(6), 1053-7; discussion 1057-8.
24. S Mocherla, LJ Wheat. *Semin Respir Infect*. **Jun 2001**; 16(2), 141-8.
25. JF Murray, JA Nadel, Histoplasmosis, In: Textbook of Respiratory Medicine, 4th ed **, 2005**:1045-55.

26. E Ledezma, R Apitz-Castro, *Rev Iberoam Micol*. **2006**; 23(2), 75-80.
27. GL Mandell, et al. *Mandell*, Douglas and Bennett's Principles and Practice of Infectious Diseases, 5th ed Philadelphia, Pa, Churchill Livingstone; **2004,** 235-241.
28. PR Murray, et al. Medical Microbiology. 5th ed. St. Louis, Mo: Mosby; **2005,** 148-156.
29. LJ Wheat, T Garringer, E Brizendine, *Diagn Microbiol Infect Dis*. **May 2002**; 43(1), 29-37.
30. EM O'Shaughnessy, YM Shea, FG Witebsky. Laboratory diagnosis of invasive mycoses. *Infect Dis Clin North Am*, **2003**; 17(1), 135-58.
31. D Maubon, S Simon, C Aznar, *Diagn Microbiol Infect Dis*. **2007**; 11, 177-179.
32. LJ Wheat, CE Musial, E Jenny-Avital, *Clin Infect Dis*, 2005; 40(6), 844-52.
33. LJ Wheat., *Transpl Infect Dis*. **2006**; 8(3), 128-39.
34. AJ Guimaraes, AJ Pizzini, , et al, *J Med Microbiol*. **2004**; 53 (6), 509-14.
35. PC Johnson, LJ Wheat, GA Cloud, et al., *Ann Intern Med*. **2002**; 137(2), 105-9.
36. P Pitisuttithum, R Negroni, JR Graybill, et al., *J Antimicrob Chemother*, **2005**; 56(4), 745-55.
37. II Raad, JR Graybill, AB Bustamante, et al., *Clin Infect Dis*, **2006**; 42(12), 1726-34.
38. A Restrepo, A Tobon, B Clark, et al., *J Infect*, **2007**; 54(4), 319-27.
39. LB Edwards, FA Acquaviva, VT Livesay, *Am Rev Respir Dis*. **1969**; 99(4), Suppl 1-132.
40. GM Keating, *Drugs*, **2005**; 65(11), 1553-67.
41. S Mocherla, LJ Wheat, *Semin Respir Infect*, 2001; 16(2), 141-8.
42. LM Tierney Jr, et al. *Current Medical Diagnosis and Treatment*, **2008**, 23, 85-89.
43. S Doron, SL Gorbach, *Expert Rev Anti Infect Ther*. **2006**; 4(2), 261-75.
44. J Wheat, G Sarosi, D McKinsey, et al., *Clin Infect Dis*, **2000;** 30(4), 688-95.
45. BL Wiedermann. Histoplasmosis, Textbook of Pediatric Infectious Diseases. WB Saunders; 7th eds **1998**, 2337-50.