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Histoplasmosis in children

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SUMMARY

Histoplamosis is the most common primary systemic mycosis in the USA and is becoming more common as an opportunistic infection in HIV patients worldwide. In children the rate of asymptomatic infection is high. However, in infants with an immature immunological system, disseminated disease may occur. The clinical picture is variable depending on the immunological status. At the onset of the infection clinical manifestations are non specific (headache, fever, cough and nausea). Usually, these symptoms are self-limited and improve without treatment. However, patients with disseminated diseases present with prolonged fever, malaise, cough and weight loss. Hepatosplenomegaly is frequent in infants. Chest radiographs may be normal in 40 to 50% of patients with disseminated disease but findings such as lobar or diffuse infiltrates, cavitations, hilar adenopathy, or any combination of these may be found. Frequently, the clinical presentation is misdiagnosed as tuberculosis. Skin tests, serological reaction and specific cultures are used for diagnosis confirmation. Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate is usually well tolerated in children.

INTRODUCTION

Histoplasmosis is caused by *Histoplasma capsulatum,* a fungal organism which usually infects an individual by way of the respiratory tract. The first description of *H. capsulatum* was done by a pathologist from Ancon Hospital - Panama Canal Zone, Samuel Taylor Darling, in 1906 at the autopsy of a patient from Martinique with a disseminating disease described as a general protozoan infection[1]. In 1912, Rocha-Lima, a Brazilian studying in Hamburg, was the first to suggest that the microorganism described by Darling was a yeast, rather than a protozoa. Since then, the disease has been diagnosed with increasing frequency. However, the diagnosis had always been made post mortem until 1934, when Dodd and Tompkins diagnosed histoplasmosis in a living infant[2]. The fungal culture from this case was isolated and studied by De Monbreun at Vanderbilt University. De Monbreun described the fungal aetiology and discovered the dimorphism of *H. capsulatum*[3]

H. capsulatum has recently emerged as an important opportunistic infection among patients presenting with immunosuppression (HIV mainly) living in endemic areas for this fungus[4]. In normal children this condition is usually self-limiting, rarely requiring treatment. Immunocompromised children are prone to develop more severe disease.

EPIDEMIOLOGY

H. capsulatum is a dimorphic fungus which is endemic in certain areas of North, Central, and South America, Africa, and Asia. However, cases have also been reported in Europe. Outbreaks have been found in pigeon or chicken breeders, in places where bats are common (caves) and in old demolition sites.

The real incidence of histoplasmosis is unknown because the majority of the studies done on this subject were restricted to regions which were affected by outbreaks of histoplasmosis and based on skin tests. Furthermore, some studies were done in selected groups such as hospitalized patients or on recruits[4,5,6].

The first isolation from the environment was in 1948 from soil contaminated with chicken excreta[6]. The natural habitat of *H. capsulatum* is soil; particularly that contaminated by bat or bird droppings, which creates an environment with a high nitrogen content. Other environmental requirements include high concentrations of carbohydrates, cationic salts, acidic pH, soil temperature ranging from -18 °C to 37 °C and 12% moisture[6].

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H. capsulatum normally lives in soil that is contaminated with guano from bats or birds. Once contaminated the soil yields the fungus for many years. Caves can be highly contaminated by *Histoplasma* thriving on the bat guano.

Infection is endemic and occurs through the inhalation of spores. Following inhalation of the infecting particles, a small area of pneumonitis develops. Only a minority of patients become symptomatic, and only a small fraction of symptomatic individuals visit a physician or require treatment. The incubation period is variable but is usually no more than a few weeks from exposure[6].

Considering age groups, histoplasmosis affects mainly young adults who are infected in outbreaks. Children have a high rate of asymptomatic or mild infections even when exposed in outbreaks[7]. However, infants are at risk of developing more severe disease or disseminated infections[6]. Additional risk factors for disseminated histoplasmosis at any age include large inoculum exposure and acquired immunodeficiency resulting from the use of immunosuppressive agents, malnutrition or HIV infection. Primary immunodeficiency disorders that impair the function of T cells, monocytes, and macrophages also predispose to disseminated histoplasmosis.[8]

Despite the fact that immunosuppressed hosts are more susceptible to histoplasmosis, reports of pulmonary disease as well as central nervous system manifestations in immunocompetent patients have been described[9]. Person-to-person or animal to person transmission does not occur, and no isolation precautions are needed.

DISEASE MECHANISMS

The extent of disease is determined by the inoculum of conidia inhaled into the lungs and the immune response of the host.

Once the microconidia or mycelial fragments of *H. capsulatum* are inhaled, they undergo transition to a yeast phase in the lower respiratory tract. The ability of the organism to cause clinical symptoms depends on the host's immune status and the size of the inhaled inoculum. T cell immunity plays an important role in this process[6].

Decreased lymphocyte activity or numbers can enhance dissemination in immunocompromised patients. T cell activity develops 10 to 21 days after infection. The number of T-suppressor cells decreases, whereas the number of T-helper cells rises, resulting in a delayed-type hypersensitivity reaction. *H. capsulatum* yeast cells are phagocytosed by human macrophages, but killing does not occur. The yeast cells replicate inside macrophages and spread via the lymphatic or haematogenous route. New foci of infection develop at these sites. These lesions eventually develop caseating necrosis or heal with fibrosis and calcification[6].

The initial polymorpholeukocytic response to the inhaled organism is ineffective in killing it and lymphocytes and macrophages are recruited. Early in the disease, spread to lymph nodes is common and extra-thoracic spread is frequent. Healing with formation of a fibrous capsule around the inflammatory focus frequently occurs with calcification.

CLINICAL MANIFESTATIONS

Almost all persons infected with *H capsulatum* have asymptomatic hematogenous dissemination, but only rarely does this lead to symptomatic disease. Exposure to a heavy inoculum of *H capsulatum* can also lead to reinfection in an immune host. In an immunosuppressed host who has waning cell-mediated immunity, reinfection can occur with exposure to even a small inoculum from the environment. In most patients, histoplasmosis is asymptomatic, and the infection is self-limited. When symptoms do occur, they are generally nonspecific and include fever, cough, and malaise[5,6,7,8,10].

Symptomatic patients often present with respiratory problems, pulmonary opacities, hilar lymphadenopathy, and possibly, organomegaly. In severe cases, the organism may cause overwhelming infection with haemoptysis, pericarditis, acute respiratory distress syndrome, and death[7].

Vascular compromise: The superior vena cava, the pulmonary arteries, and the pulmonary veins can be severely compromised by the fibrotic process secondary to Histoplasmosis. When the latter are involved the patient's symptoms may mimic those of the mitral stenosis[6].

Clinical forms of Histoplasmosis

Infection is so common in endemic area that most persons have been infected before adulthood without their knowledge.

1. Pulmonary histoplasmosis- Most patients who have pulmonary histoplasmosis have a self-limited illness or show a good response to therapy. Nonetheless, a small number develop complications related to mediastinal involvement[9]. Complications of pulmonary histoplasmosis include mediastinal lymphadenitis, mediastinal granuloma, chronic cavitary disease in patients with underlying emphysema, fibrosing mediastinitis, and broncholithiasis[7,11]. Granulomatous mediastinitis presents as persistently enlarged mediastinal and hilar lymph nodes. The nodes may cause compression on adjacent structures (bronchi and Oesophageal). Esophogeal traction diverticula and tracheoesophageal fistula can occur. Resolution may take months to years.[5]. In heavy exposure focal necrosis or dissemination may occur.
2. Chronic pulmonary histoplasmosis is rarely seen in children. It may present with upper lobe linear opacities and fibrocavitary consolidation which is similar to post primary tuberculosis
3. Acute disseminated histoplasmosis- Haematogenous dissemination occurs in most patients during the first few weeks after acute infection, but it is rarely progressive[8]. The disseminated form of histoplasmosis usually occurs in very young children or in severely immunocompromised individuals, such as patients who have AIDS or in transplant recipients[12]. Young infants cannot handle primary infection with *H capsulatum* and develop overwhelming disseminated infection[5]. Symptoms include chills, fever, malaise, anorexia, weight loss, and dyspnoea. The radiographic appearance is a miliary pattern that can affect extrathoracic organs.
4. Progressive disseminated histoplasmosis is defined as a clinical illness that does not improve after at least 3 weeks of observation and is associated with physical or radiographic findings and/or laboratory evidence of involvement of extrapulmonary tissues[8].

   Fibrosing mediastinitis- Mediastinal fibrosis is rarely seen in children as a complication of pulmonary histoplasmosis and does not seem to be related to granulomatous mediastinitis[8]. Infection of mediastinal lymph nodes can result in necrosis and fibrosis of the affected lymph nodes—"fibrosing mediastinitis"—with subsequent venous obstruction, bronchial stenosis, and narrowing of the pulmonary arteries. Fibrosing mediastinitis probably occurs most often in a genetically susceptible population[12].

   Patients experience dyspnoea, cough, wheezing, and sometimes haemoptysis. Superior vena cava syndrome, heart failure, and pulmonary emboli can ensue and the outcome is death after several years[5].

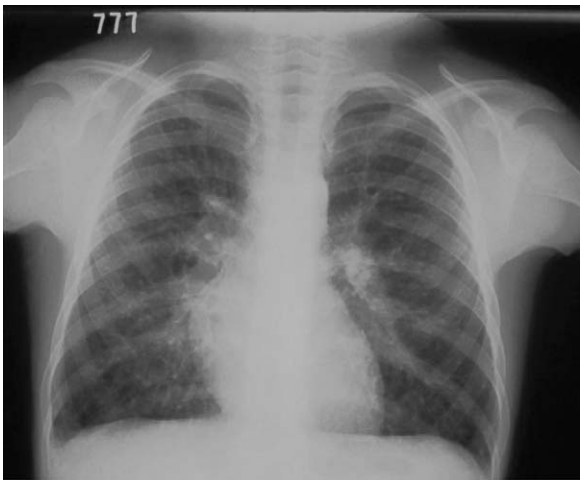

Figure 1. X-ray of a 8y child with acute pulmonary histoplasmosis showing hilar enlargement with bilateral infiltrates.

5. Chronic disseminated histoplasmosis- Patients often experience symptoms for months before being diagnosed. Symptoms include fever, night sweats, weight loss, and fatigue. Presentation with fever of unknown origin is common[5]. Hepatosplenomegaly is found in 89% of infants. Chest radiographs are characterized by lobar or diffuse infiltrates, cavitation, hilar adenopathy, or any combination thereof. However, 40% to 50% of immunocompromised patients with disseminated histoplasmosis have been reported to have a normal chest radiograph[13] (Fig. 1).
6. Rarer clinical presentations- Other focal involvement with *H capsulatum* is rare. Epididymitis, prostatitis, and osteoarticular infection have been reported, and reflect hematogenous dissemination of the organism during initial infection[8,10,13]

To illustrate our experience in different regions of Brazil we have included a series of 14 cases of histoplasmosis in children, published in Brazil in 2005[11] (Table 1).

DIAGNOSIS

Radiological Findings

Chest x-ray

Chest radiography in acute pulmonary histoplasmosis is characterized by enlarged hilar or mediastinal lymphadenopathy and lobar infiltrates. These findings usually resolve over several weeks or months. Pleural effusion occurs in about 10% of adults and less than 5% of children with acute histoplasmosis. Mediastinal granuloma, mediastinal fibrosis, and pericarditis are rare, late sequelae of mediastinal histoplasmosis. However, 40% to 50% of immunocompromised patients with disseminated histoplasmosis have been reported to have a normal chest radiograph[1,15].

X-Ray: Histoplasmosis can present a diagnostic dilemma if unusually large masses of lymph nodes, invasive mediastinal fibrosis, or pericarditis result from the infection[14–16].

The radiographic manifestations of histoplasmosis are very similar to tuberculosis.

1. Mediastinal
   a. Mediastinal granuloma- is an uncommon complication of primary histoplasmosis and consists of a lobulated mass of lymph nodes several centimeters in thickness, surrounded by a thin capsule and occasionally calcification is present. The involvement of adjacent structures is minimal and compression, if present, is minor[16]. In children it is frequently identified on chest radiographs obtained for unrelated reasons[14].
   b. Mediastinal fibrosis - Mediastinal fibrosis it is a much more severe complication of histoplasmosis than mediastinal granuloma, but occurs less frequently[16]. The fibrotic mass of tissue gradually invades the adjacent anatomic structures (tracheobronchial tree, esophagus and superior vena cava, the pulmonary arteries, and the pulmonary veins) severely compromising their function[14,16].
   c. Bronchial compromise- is best defined by computerized tomography [CT][14]

Table 1
Fouteen cases of Histoplasmosis form Brazil

Region	Age/sex*	Clinical presentation	Symptoms	Underlying disease/contamination	Evolution**	Observations
South	8/m	APH	Fever, cough, mild dyspnoea, nocturnal sweating, weight loss	No	Self resolution	
South	12/m	APH	Prolonged fever. Abdominal pain, cough, weight loss	Daily exposure to birds	Cured	
South	6/m	APH	Cough fever	Daily exposure to bats	Not available	
Southwest	14/f	CPH	asymptomatic	Chemotherapy for bone cancer	Not available	
Southwest	15/f	CPH	Progressive dyspnoea, productive cough, fever	Cystic fibrosis	Death	
South	10/m	Histoplasmoma	dyspnoea,cough, weakness, weight loss	Mediastinal tumour, chemotherapy	NA	
South	3/m	CNS				
no pulmonary	Hemiparesis	No	Death	Post mortem diagnosis		
South	8/f	CNS	Fever, headache, confusion, anorexia	No	Death	
South	15/m	CNS	Neck stiffness	Hydrocephaly, SNC valve	NA	
South	1/m	Disseminated	Diarrhea, fever, seizures	No	Death	Post mortem diagnosis
South	13/m	Disseminated	Dysphonic, fever, weight loss	No	NA	
South	13/f	Disseminated plus laryngeal involvement	Dysphonic	Lymphoma, exposure to chicken droppings	Cure	
South	4/f	Disseminated	Fever	No	NA	
Center West	13/m	Disseminated	Cough, dyspnoea, fever	Immunosupression kidney transplant	Cure	

As it can be seen in the Table 6 out of 14 patients have no recognizable underlying condition and three presented with the acute form of pulmonary histoplasmosis.
APH: Acute pulmonary histoplasmosis, CPH: chronic pulmonary histoplasmosis, CNS: central nervous system
* m = male f = female.
** NA not available.

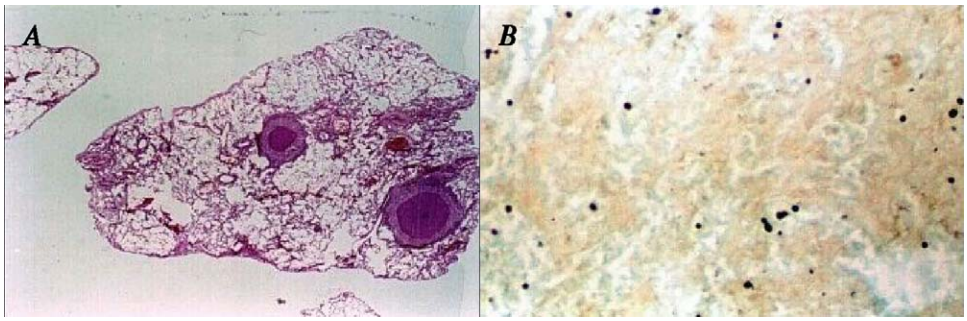

Figure 2. Lung biopsy of an 8 year old child with acute pulmonary histoplasmosis: A) Two granulomas with caseous necrosis. (H&E 10X); B) Small oval fungi elements with unipolar buddingGMS 40X).

d. Vascular compromise – Superior vena cava, the pulmonary arteries, and the pulmonary veins can be compromised by the fibrotic process[16]
e. Esophageal compromise may occur.
2. Peripheral airway disease
3. Bronchial or vascular compression
4. Pericarditis- can be appreciated by an enlarged cardiac silhouette. Pericardial effusion is rare, but is commonly seen when histoplasma pericarditis is present[14]. It is commonly accompanied by pericardial effusion, pneumonia, and adenopathy. Pericardial effusion must be confirmed by echocardiography.
5. Calcification

In HIV, adult patients present with a normal chest radiograph in up to 50% of patients with disseminated disease but these patients will progress to demonstrate diffuse opacities concurrent with the development of respiratory symptoms. High-resolution CT findings may include miliary nodules associated with disseminated disease, lymphadenopathy, and less commonly diffuse parenchymal consolidation[14,16].

Skin test

As in tuberculin tests, a positive skin test for histoplasmosis is only indicative of exposure and 80% to 90% of people have positive results without evidence of active disease in endemic areas, quite the opposite appears to be true in the paediatric group. Conversely, up to 50% of immunocompromised patients with disseminated disease have negative skin test results. In addition, administration of the histoplasmin skin test can falsely elevate antibody titers in 15% to 25% of patients. False-positive skin tests have been seen in patients with blastomycosis and coccidioidomycosis[17,18].

Laboratory diagnostic

The diagnosis of histoplasmosis is problematic due to the small size of the yeast which is frequently missed without careful examination. Cytologic examination of bronchoalveolar lavage fluid or sputum generally does not show the tiny yeasts of *H capsulatum*[5]. Isolation of *H. capsulatum* in culture is the most definitive method for diagnosis[18].

Direct examination

Rounded to oval yeast cells measuring 2-4 μm in diameter, suggestive *of H. capsulatum*, may be seen by fungal staining of biopsy specimens from pulmonary, mediastinal or extrapulmonary tissues. Less commonly, organisms may be observed by fungal staining of sputum, sterile body fluids or peripheral blood smears. In disseminated histoplasmosis the highest yield is from bone marrow[19].

The yeast forms (micronidia) are found inside and outside macrophages[2]. The organism is not encapsulated although in tissue it is surrounded by a clear zone which was first mistakenly described as a capsule by Darling[1,2].

Histopathology

The tissue response in histoplasmosis follows the general course of histopathological reactions described as granulomas. The early lesions in the lung are areas of pneumonia containing a large number of macrophages and lymphocytes with occasional epithelioid cells and multinucleated giant cells.

Histologic examination of the nodes involved show varying degrees of central caseation, and calcification will occasionally occur.

Grocott-Gomori methenamine-silver nitrate and periodic acid-Schiff [PAS] stains are the most useful for visualizing *Histoplasma* organisms in tissues. Areas of caseous necrosis with a surrounding fibrous capsule which prevents the spread of the organism are characteristic. *H. capsulatum* may also be seen in tissues inside macrophages[18] (Fig. 2).

Culture

Cultures are most useful in patients with disseminated or chronic pulmonary histoplasmosis, being positive in 50-85% of cases[17]. In disseminated disease, the highest culture yield is from bone marrow or blood, being positive in over 75% of cases[9].

Since *H. capsulatum* in mycelial form is resistant to cycloheximide and grows slowly, the greatest media culture for its primary isolation is Mycosel®. In this agar, other filamentous fungi contaminants are inhibited permitting only *H. capsulatum* growth.

H. capsulatum is a dimorphic fungus which exists in mycelial form in the environment at 25 °C and in yeast form in tissues at 37 °C. The organism is slow growing, requiring 2 to 4 weeks for colonies to appear. However, isolates have been identified in less than 7 days when a large number of infecting cells have been present[11]. At the filamentous stage colonies are white to brown with cottony texture and reverse white, sometimes orange tan. Microscopically septate hyphae [1 to 2 μm in diameter], microconidia and characteristic macroconidia are seen. The tuberculate macroconidia are spherical with spike-like projections and measure 8 to 14 μm in diameter. The conversion from the mycelial form to the yeast phase is necessary to confirm the diagnosis. To obtain the yeast phase, which is sensitive to cycloheximide, the agar culture recommended is brain heart infusion (BHI) medium in which isolates show moist white colonies, characterized microscopically by small, round or oval budding cells and occasional abortive hyphae.

Cultures of sputum are positive in only two thirds of patients with cavitary disease and in less than one third of patients with chronic or non-cavitary disease[9].

Lysis-centrifugation system (Isolator®, Wampole Laboratories)

Blood cultures, especially those using the lysis–centrifugation system (Isolator tube), frequently yield the organism in patients who have disseminated histoplasmosis.

Isolator tubes contain EDTA as an anticoagulant, saponin as a lysing agent, and a fluorcarbon compound that acts as a cushion during centrifugation. The sediment of lysed cells is inoculated onto solid media, which enable the intracellular *H. capsulatum* to grow and be identified by microscopy and colony morphology.

Serologic tests

Serologic tests are positive in 90% of patients with symptomatic disease.

There are two main types of assays which measure antibodies anti-*H. capsulatum*: Immunodiffusion test (ID) and Complement fixation test (CFT). The sensitivity of the ID and CFT assays is approximately 80%, and performing both assays increases the possibility of making a diagnosis[5]. However, CFT is done only in reference diagnostic centers, while ID is a simple and rapid test routinely used in Mycology Laboratories. Although CFT is more sensitive than ID, especially early in the disease, the D test remains positive longer and is more specific than CFT[21].

ID measures antibody response to H. capsulatum, showing two precipitation bands (M and H). Patients who have acute pneumonia may show an M band. The test becomes positive after 4-6 weeks and peaks at 2-3 months after infection.

Patients who have chronic cavitary pulmonary histoplasmosis and chronic progressive disseminated histoplasmosis almost always show positive results with both assays. However, in patients who are immunosuppressed and who cannot mount an antibody response, serology is rarely useful and should not be relied on to help make the diagnosis of histoplasmosis[5,22].

False-positive results occur in patients with other diseases, such as blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and tuberculosis.

H. capsulatum antigen assay provides a rapid and sensitive diagnostic tool for patients who have disseminated infection. It's rarely detected in patients who have chronic pulmonary histoplasmosis or granulomatous mediastinitis, but is positive in approximately 80% of those who have acute pulmonary histoplasmosis[5].

Antigen appears 2 to 3 weeks after exposure, - 4-u1.0-B0-8016-7406-9.50049-3–bib35 and haemagglutinin can be found in the urine or blood of 50% to 80% of patients with disseminated histoplasmosis and in the bronchoalveolar lavage fluid of 70% of AIDS patients with pulmonary histoplasmosis[10]. False-positive results have been reported in patients with blastomycosis, paracoccidioidomycosis, and coccidioidomycosis.

Testing for antigen is more sensitive in urine than in serum. It is usually not positive in localized pulmonary disease, but is in primary disseminated disease in children or in immunossupressed patients. Haemagglutinin levels decline in response to treatment therefore it is a useful parameter to check while considering response and duration of therapy.

Differential Diagnosis

Occasionally, the yeast forms of *H. capsulatum* have dark foci when stained which is a staining pattern similar to that of *Pneumocystis jiroveci*ii. However, the presence of budding yeast forms as well as the lack of an intra-alveolar location and foamy exudate help diagnose histoplasmosis. The intracellular forms of *Blastomyces dermatitides* can measure 2 to 4 μm, similar to the yeast forms of H. capsulatum. However, the presence of larger sized (8 to 15 μm) yeast forms with broad based buds and thick, double-contoured walls aid in the diagnosis of blastomycosis. Capsule-deficient *Cryptococcus* usually shows a weakly positive reaction with mucicarmine and the size of the organisms is more variable, ranging from 2 to 20 μm. *Candida glabrata* may resemble *H. capsulatum* due to the similar size and propensity for growth within histiocytes. However, C. glabrata stains well with haematoxylin and eosin (H&E) stain, lacks the halo effect seen in *H. capsulatum*, and is usually larger and more variable in size with a broader-based bud than H. capsulatum. Rarely, *Candida* sp. is mistaken for *H. capsulatum*, but the presence of pseudohyphae aids in the separation[23].

Molecular Biology

Polymerase chain reaction (PCR)- can confirm diagnosis in the mycelial phase. DNA probes on clinical isolates are also being used by many centers to confirm the diagnosis.

TREATMENT

Guidelines for the treatment of histoplasmosis were published in 2007[8]. Indications for antifungal therapy are listed in Table 2. The antifungal agents that have proven to be effective and are preferred for treatment of histoplasmosis include amphotericin B, liposomal amphotericin B, amphotericin B lipid complex, and itraconazole. In children, a one month course of amphotericin B deoxycholate is usually curative[8,20,24,25].

Acute Pulmonary Histoplasmosis

Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate (1.0 mg/kg daily) is usually well tolerated, and is preferred to the lipid preparations[8,20]. Antifungal treatment has been recommended in patients whose symptoms do not improve within 1 month.

Progressive Disseminated Histoplasmosis

Amphotericin B deoxycholate (1.0 mg/kg daily for 4-6 weeks) is recommended. Amphotericin B deoxycholate (1.0 mg/kg daily for 2-4 weeks) followed by itraconazole (5.0-10.0 mg/kg daily in 2 doses) to complete 3 months of therapy is an alternative.

Table 2
Indications for antifungal therapy*

Indications for antifungal therapy.
Definite indication, proven or probable efficacy
Acute diffuse pulmonary infection, moderately severe symptoms, or severe symptoms
Chronic cavitary pulmonary infection
Progressive disseminated infection
CNS infection
Uncertain indication, unknown efficacy
Acute focal pulmonary infection, asymptomatic case, or mild symptoms that persist for >1 month
Mediastinal lymphadenitis
Mediastinal granuloma
Inflammatory syndromes, treated with corticosteroids
Not recommended, unknown efficacy or ineffective
Mediastinal fibrosis
Pulmonary nodule
Broncholithiasis
Presumed ocular histoplasmosis syndrome

*Adapted from Wheat et al. [2007]ref [8].

Longer therapy may be needed for patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. Lifelong suppressive therapy with itraconazole (5.0 mg/kg daily, up to 200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who experience relapse despite having appropriate therapy. Blood levels of itraconazole should be obtained to ensure adequate drug exposure[8,20].

Antigen levels should be monitored during therapy and for 12 months after therapy is ended to monitor for relapse.

Persistent low-level antigenuria may not be a reason to prolong treatment in patients who have completed appropriate therapy and have no evidence of active infection.

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