Pulmonary Histoplasmosis

Chadi A. Hage, M.D.,[1,3] L. Joseph Wheat, M.D.,[4] James Loyd, M.D.,[5] Stephen D. Allen, M.D.,[2] Deborah Blue, M.D.,[2] and Kenneth S. Knox, M.D.[1,3]

ABSTRACT

Pulmonary manifestations of histoplasmosis were last reviewed in *Seminars* in 2004. This review highlights the management of the most common clinical syndromes, emphasizing recognition, diagnosis, and treatment. The reader is referred to the earlier review for subjects not fully addressed herein. Knowledge of the utility of serological testing is essential, particularly when antigen tests and cultures are negative. Antigen testing is most useful in patients with more diffuse pulmonary involvement and those with progressive disseminated disease due to the high fungal burden. Detection of antigen in bronchoalveolar lavage fluid may be particularly helpful in certain circumstances. Guidelines for antifungal therapy have been updated and will be discussed for pulmonary syndromes.

KEYWORDS: Histoplasmosis, serology, antigen, diagnosis, treatment

Histoplasmosis is worldwide in distribution but most prevalent in regions of North, Central, and South America, as well as parts of Africa and Asia. The mold grows in soil and infects humans when the soil is disturbed. Microconidia are dispersed into the air and are inhaled, causing pneumonia. The severity of the initial infection depends largely on the amount of the inoculum and immune status of the host. The organism spreads hematogenously to reticuloendothelial tissues during the first few weeks following infection, before the development of cell-mediated immunity to *Histoplasma capsulatum*. With development of cellular immunity, the pulmonary infection and extrapulmonary dissemination resolve spontaneously in more than 99% of cases. In patients who are unable to mount an effective immune response, the infection is usually progressive.

This review focuses on the more common pulmonary manifestations of histoplasmosis, updating a prior review on the subject.[1] Another recent publication is recommended for a more complete up-to-date review of histoplasmosis.[2] The pulmonary manifestations following acute exposure in the nonimmunocompromised host range from asymptomatic pulmonary infection to diffuse pneumonitis, causing respiratory failure and associated with findings of extrapulmonary dissemination. The extent of pulmonary involvement and severity of illness depends on the magnitude of exposure. The pathology shows interstitial inflammation with infiltration of the alveolar spaces with mononuclear cells (Fig. 1). Small budding yeast may be seen by methenamine silver or hematoxylin-eosin stain (Figs. 1C, D). Noncaseating or caseating granuloma is a hallmark of the inflammatory response (Figs. 1E, F). The necrotic nodes may eventually calcify (Fig. 2A) and may cause an exuberant fibrotic reaction resulting in obstruction of mediastinal structures (Fig. 2B). Diagnosis may be established rapidly by demonstration of yeast in tissues or blood in some

[1]Department of Medicine; [2]Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana; [3]Roudebush VA Medical Center, Indianapolis, Indiana; [4]MiraVista Diagnostics and MiraBella Technologies, Indianapolis, Indiana; [5]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

Address for correspondence and reprint requests: L. Joseph Wheat, M.D., MiraVista Diagnostics/MiraBella Technologies, 4444 Decatur Blvd., Ste. 300, Indianapolis, IN 46241 (e-mail: jwheat@miravistalabs.com).

Pulmonary Fungal Infections; Guest Editor, Duane R. Hospenthal, M.D., Ph.D.

Semin Respir Crit Care Med 2008;29:151–165.
DOI 10.1055/s-2008-1063854. ISSN 1069-3424.

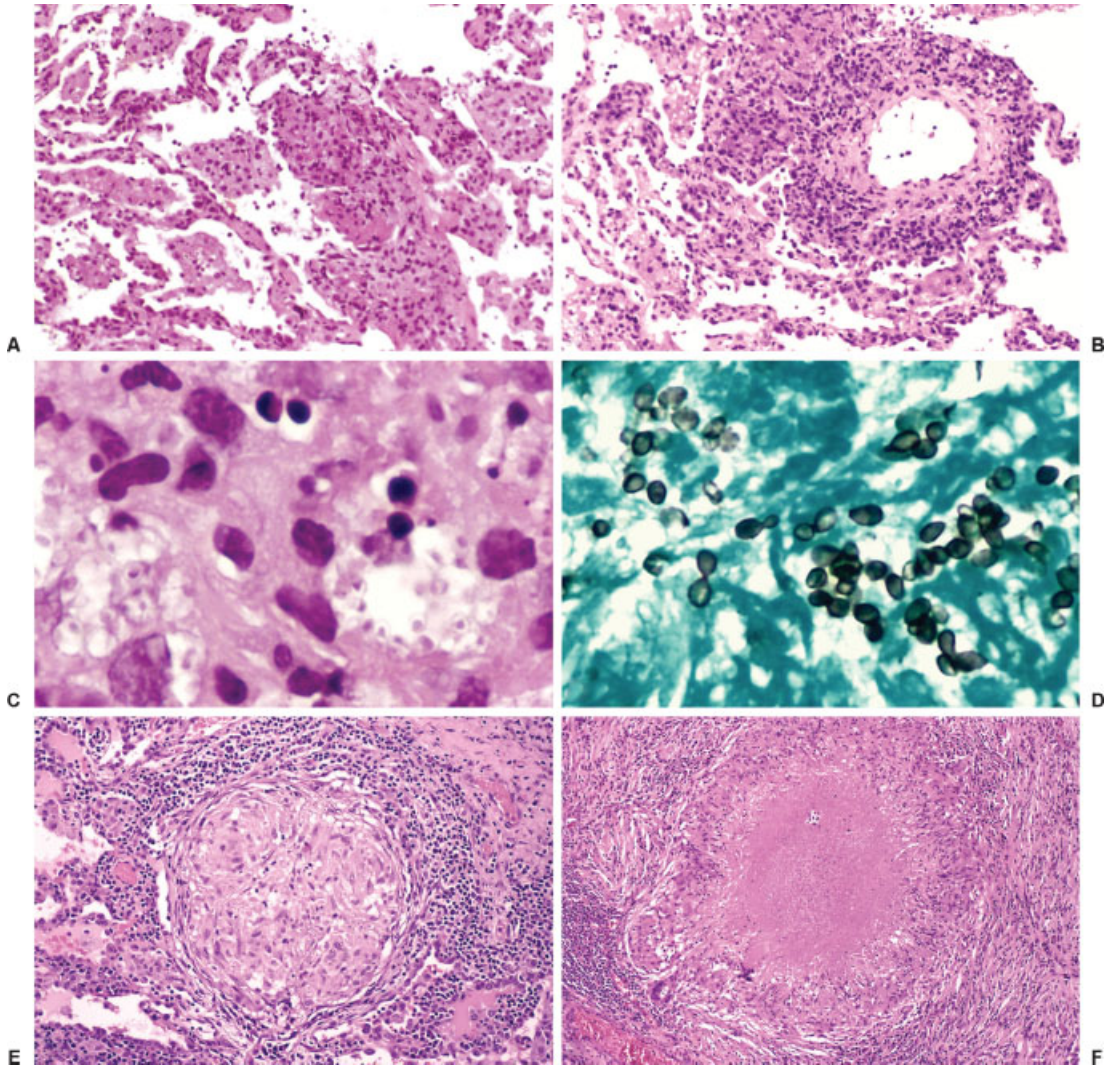

Figure 1 (A–D) Histopathology contrasting acute diffuse pulmonary involvement in a lung segment of a normal host (probable primary infection), and (E,F) with pulmonary granulomas from an immunocompromised patient who had an opportunistic reinfection with *Histoplasma capsulatum*. (A) Diffuse interstitial pneumonitis in an adult (normal host) with recent heavy environmental exposure and subsequent development of progressive pulmonary disease. There is an inflammatory cell infiltrate primarily involving the interalveolar interstitial spaces but present within many alveolar spaces as well. The exudate consists mostly of mononuclear phagocytes, lymphocytes, and occasional plasma cells. Many of the alveolar walls are markedly thickened [hematoxylin and eosin (H&E) × 50]. (B) Another area from the same case as (A) showing focal vasculitis with an infiltrate of lymphocytes and macrophages (H&E × 25). (C) Relatively large alveolar macrophages packed with single and budding yeasts 2 to 4 μm in diameter [same case as shown in (A) and (B)]. The basophilic cytoplasm of these yeasts is retracted from their thin outer cell walls leaving halo-like clear areas that can be confused with capsules (H&E × 500). (D) Intracellular and extracellular yeasts, 2 to 4 μm in diameter, some of which are single, budding, or in short chains [Gomori methenamine silver (GMS) × 500]. (E) Nonnecrotizing (sometimes called epithelioid cell, or noncaseating) granuloma [different patient than shown in (A–D)] from a patient who had recently received chemotherapy for a germ cell tumor). This lesion consists of a focal collection of macrophages (sometimes referred to as histiocytes or epithelioid cells) plus lymphocytes, and occasional plasma cells. A few multinucleated macrophages are present. A thin layer of fibroblasts circumscribes the lesion. Yeasts of *H. capsulatum*, probably present within macrophages of this lesion at an earlier stage, were not identified in this granuloma, or in any of several other nonnecrotizing granulomas within the specimen. Lesions of this type often undergo necrosis to become necrotizing granulomas (H&E × 50). (F) Necrotizing (sometimes referred to as caseating) granuloma from the same lung as in (E). This lesion has a necrotic center surrounded by macrophages, encapsulating fibroblasts, fibrous connective tissue in the periphery, and scattered lymphocytes. A prominent giant cell is present in the lower left of the granuloma (at ~8 o'clock). Microorganisms are usually present only in relatively small numbers in these types of lesions. They are most frequently detected within the most central necrotic material in these granulomas (H&E × 25).

cases (Figs. 2C–D). Cytology and histopathology are invaluable methods for rapid diagnosis but are positive in the minority of cases. Before specific syndromes are discussed, the nonculture or histopathology methods for diagnosis are reviewed.

NONCULTURE OR HISTOPATHOLOGY-BASED DIAGNOSTICS

Histopathology, cytology, and culture are standard diagnostic approaches for endemic mycoses. However, the need for invasive procedures and the inherent delay in culturing the organism often delay diagnosis.[3] This discussion focuses on the use of antigen detection, serology, and polymerase chain reaction (PCR) in the diagnosis of histoplasmosis. Although little new information is available about serological testing, serology is often overlooked or misunderstood and is reviewed in more detail. Antigen detection is also a useful tool for diagnosis of histoplasmosis, and there have been important new improvements, which are reviewed.

Antigen Detection

The *Histoplasma* antigen radioimmunoassay was first reported in 1986[4] and reformatted as an enzyme immunoassay (EIA) 10 years later.[5] Antigen was detected in the urine of ~90% of patients with progressive disseminated histoplasmosis (PDH) and in about one third with other forms of histoplasmosis. Cross-reactions occur in patients with blastomycosis, paracoccidioidomycosis, and penicilliosis marneffei.[6]

In 2003, false-positive results caused by anti-rabbit antibodies were observed in solid organ transplant patients who received rabbit antithymocyte globulin.[7] The assay was extensively modified to prevent false-positivity and improve overall performance. In this second-generation assay, false-positive results caused by anti-rabbit antibodies were reduced by 95% in solid organ transplant recipients.[8] Furthermore, false-positive results were reduced by 75% in all specimens submitted for clinical testing.[9] Cross-reactions with coccidioidomycosis have been observed using the second-generation assay.[10]

Recently, the assay has been further modified to permit quantitation.[11] This modification, which has been incorporated into the third-generation *Histoplasma* antigen assay, eliminates the need to test prior specimens along with current specimens to determine change in antigen level. In the third-generation assay, sensitivity in patients with acquired immunodeficiency syndrome (AIDS) in disseminated histoplasmosis was 98% in urine and over 90% in serum, representing improvements over the original immunoassays (Table 1).[1,4,12–17] Studies are in progress to determine the sensitivity of the assay in patients with PDH and underlying conditions other than AIDS, and in patients with the different pulmonary manifestations. Previous studies revealed reduced sensitivity (~80%) in patients with PDH with immunosuppressive disorders other than AIDS, or no underlying immunosuppression,[12] and in patients with pulmonary histoplasmosis, ranging from ~35% in patients with localized acute pulmonary histoplasmosis to ~75% in those with diffuse involvement.[1]

Experience suggests that detection of antigen in bronchoalveolar lavage (BAL) fluid may improve the sensitivity for diagnosis of pulmonary histoplasmosis. In a preliminary study, antigen was detected in BAL in 84% of patients with pulmonary histoplasmosis.[18] Studies are in progress to compare the sensitivity of antigen detection with that of other diagnostic tests in a larger number of patients.

The antigen test is also useful for monitoring treatment. Antigen levels decline with effective treatment and increase with relapse,[19] providing a useful method for monitoring patients for response to treatment and identifying treatment failure. In the third-generation assay, change in antigen levels based on results from separate assays correlated well with change determined by testing prior and current specimens together.[11]

Serological Tests

Serology provides the basis for diagnosis in most patients with localized pulmonary histoplasmosis. The methods commonly used are complement fixation (CF), immunodiffusion (ID), and enzyme immunoassay (EIA). It is believed that most individuals residing in endemic areas are seropositive, limiting the usefulness of serology. In fact, however, seropositivity in healthy subjects from an endemic area is below 5%.[20]

About 4 to 6 weeks is required to mount an antibody response in histoplasmosis.[13] In evaluation of a common source outbreak, at 3 weeks following exposure, the ID tests were positive in none and the CF test in 5% of cases. By 6 weeks, the positivity rate increased to 50% by ID and 77% by CF. Thus convalescent specimens are recommended if acute histoplasmosis is suspected. The antibody response may be reduced in patients who are immunosuppressed.

The response is proportional to the extent of exposure and severity of illness. In an outbreak the CF test was positive in 18% of asymptomatic, 67% with mild, 86% with moderate, and 100% with severe illnesses, requiring hospitalizaton.[21] The CF titer, however, did not correlate with severity of illness.

Antibodies may persist for several years. In an outbreak in Indiana, titers did not decline until about 2 years after infection.[20] For this reason, other etiologies for the pulmonary illness should be considered before

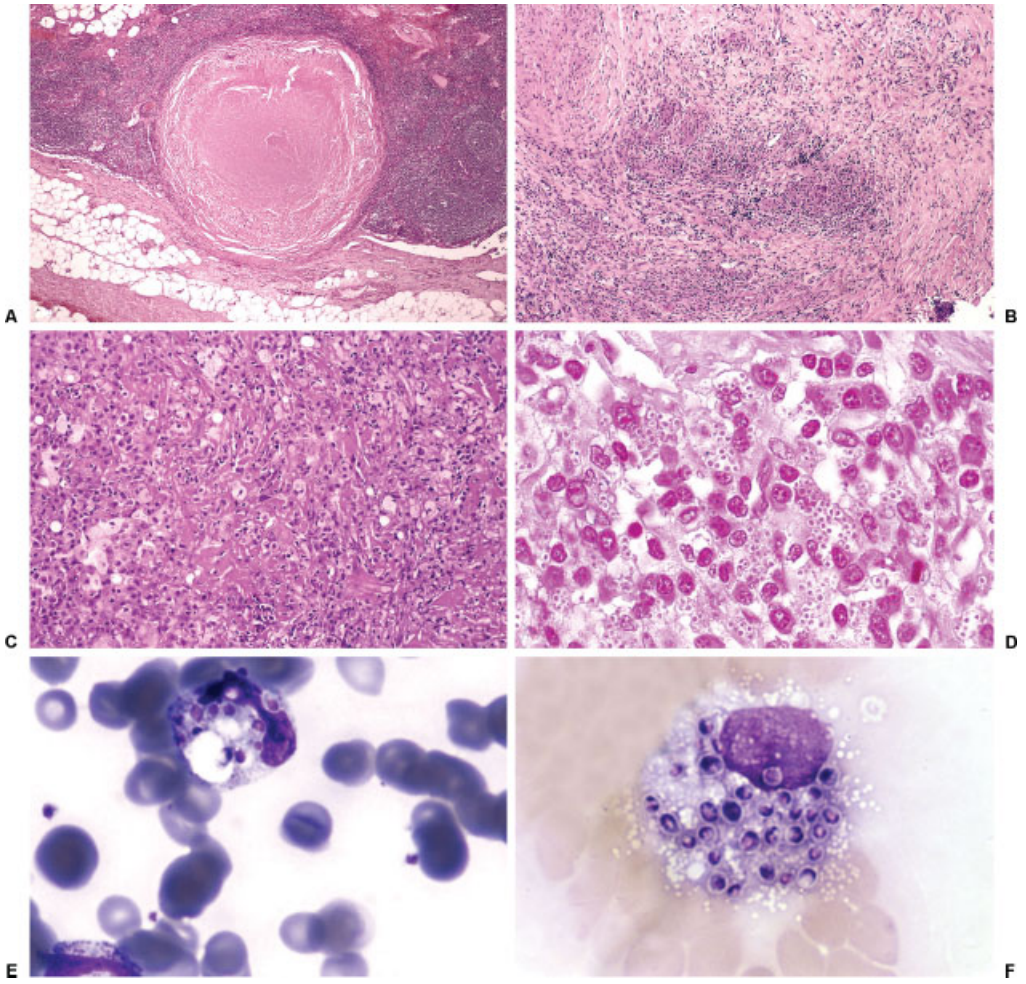

Figure 2 Comparison of mediastinal granuloma, mediastinal fibrosis (or mediastinal sclerosis), and disseminated histoplasmosis. (A) Mediastinal granuloma. This old granuloma in a peribronchial lymph node is encased in a fibrous capsule. A similar, but larger, hyalinized fibrocaseous nodule in another peribronchial node from the same case had undergone more extensive fibrosis and was focally calcified. Yeasts were not identified in Gomori methenamine silver (GMS) stained sections of either lesion. However, these organisms were present in necrotizing granulomas within the lung parenchyma of this patient (not shown). *H. capsulatum* can persist for years in the necrotic material of old mediastinal granulomas, and it is important that all of the available material be examined by the pathologist with this in mind. In endemic areas, granulomas in mediastinal lymph nodes are more often due to *H. capsulatum* but may be a component of tuberculosis or coccidioidomycosis (H&E × 10). (B) Mediastinal fibrosis. Representative section of a mediastinal mass in which extensive perinodal fibrosis was present. The section reveals a mass of fibrous connective tissue with a cellular infiltrate that is prominent within the lower left and central area of the photomicrograph consisting mostly of lymphocytes, macrophages, and scattered fibroblasts. An occasional multinucleated giant cell is present, but well-formed granulomas were difficult to find. Yeasts morphologically consistent with *H. capsulatum* (not shown) were present in small numbers and could easily have been missed without extensive examination of GMS-stained sections (H&E × 25). (C) Disseminated histoplasmosis involving a peripheral lymph node from a patient with acquired immunodeficiency syndrome (AIDS). The lymph node architecture has been replaced by a diffuse infiltrate of macrophages, many of which are packed with yeasts, and extensive necrosis. Neither necrotizing nor nonnecrotizing granulomas were present. Many of the macrophages have lysed with the release of myriads of yeasts from their cytoplasm (H&E × 100). (D) Disseminated histoplasmosis involving lung tissue with myriads of intracellular budding yeasts morphologically consistent with *H. capsulatum*. As was seen in the H&E in (C), the cytoplasm of the yeasts is retracted from their outer cell walls, leaving halo-like clear areas. A mucicarmine stain for polysaccharide can be done, which would stain negatively for *H. capsulatum*, but positively for *Cryptococcus neoformans* [periodic acid–Schiff (PAS) × 250]. (E) Peripheral blood-stained smear (not from a buffy coat) from the above patient with disseminated histoplasmosis. A vacuolated monocyte containing several small yeasts is seen in the upper part of the photo (Giemsa × 500). (F) Bronchoalveolar lavage fluid from a different human immunodeficiency virus–positive individual who had diffuse pulmonary infiltrates. The mononuclear macrophage is packed with a large number of yeasts morphologically consistent with *H. capsulatum* (Diff-Quik × 500).

Table 1 Sensitivity of Diagnostic Studies in Various Histoplasmosis Syndromes

Test	Acute Pulmonary		Chronic Pulmonary	PDH	References
	Diffuse	Localized			
Antigen	75–81%	19–34%	6–14%	91–92%	1,4,12,14,15
Antibody	40–80%	78–89%	93%	63–81%	12,13,15,17
Histopathology	47%	9–38%	$<10\%$	12–43%	4,12,14,16
Culture	40%	9–15%	65–85%	75–85%	4,12,14

PDH, progressive disseminated histoplasmosis.

accepting histoplasmosis as the cause for disease if serology is the basis for diagnosis, especially if the CF titers are low (1:8 to 1:16). Also, cross-reactions may occur in coccidioidomycosis or blastomycosis, which should be considered based upon epidemiological or clinical characteristics, or other laboratory findings.

EIA is also used for measurement of antibodies to *H. capsulatum*. Although EIA is more sensitive than ID or CF, its accuracy remains unsatisfactory.[22,23]

Molecular Diagnostics

Whether PCR is useful for diagnosis of histoplasmosis is uncertain. PCR was not more sensitive than histopathology in one report.[24] PCR was negative in one third of tissues in which yeast was seen by histopathology.[24] PCR was positive in only 8% of urine specimens from patients with histoplasmosis.[25] Furthermore, there are no standardized, validated, and commercially available PCR methods for diagnosis of histoplasmosis. More research is needed before PCR can be recommended.

ASYMPTOMATIC PULMONARY HISTOPLASMOSIS

In most healthy individuals, histoplasmosis is asymptomatic following low-level exposure. Asymptomatic cases are usually identified based upon abnormal radiographs or computed tomographic (CT) scans showing enlarged mediastinal or hilar lymph nodes or pulmonary nodules, which are often calcified. These are usually discovered incidentally during evaluation for other conditions.

Diagnosis

The management of asymptomatic pulmonary nodules can be problematic because they can mimic cancer (Fig. 3). An approach to workup is similar to that for acute pulmonary histoplasmosis, but the sensitivity of antigen detection and serology is lower (Table 2). Biopsy, serial follow-up with CT scans, or surgical resection may be needed, as dictated by the individual clinical scenario. Transthoracic fine-needle biopsy or surgical excision may be appropriate.[26] When a biopsy is performed, caseating or noncaseating granulomas can be found. Histopathology or cytology may show structures resembling *H. capsulatum*, but cultures are rarely positive.[27] When antibodies are detected, they are usually present in low CF titers (1:8 to 1:16). Tests for antigen in the blood or urine are negative because infection is inactive or the fungal burden is low.

Treatment

Treatment for asymptomatic pulmonary nodules or adenopathy is not indicated (Table 3).[28] In some patients symptoms may be present, but these are not usually caused by the nodules or enlarged nodes. Multiple noncalcified nodules or mediastinal adenopathy may represent acute pulmonary histoplasmosis. In the presence of persistent symptoms, accompanied by positive antigen tests, CF titers of 1:32 or higher, histopathology showing yeast resembling *H. capsulatum* or positive cultures,

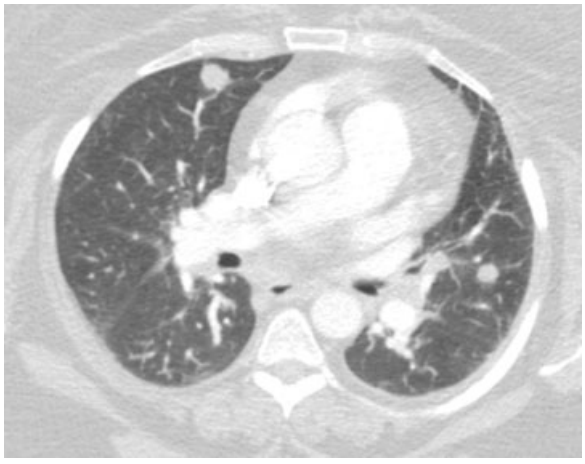

Figure 3 An asymptomatic patient was noted to have pulmonary nodules at the lung bases on an abdominal computed tomographic (CT) scan. A dedicated chest CT was performed and revealed numerous nodules in the lung parenchyma. Two nodules are shown: one nodule in the right anterior lung field and one in the left midlung field. A needle biopsy was attempted and was nondiagnostic. One of the nodules was resected and showed granulomatous inflammation with some necrosis. Fungal stains and cultures were negative. Immunodiffusion showed a positive M band and a yeast complement fixation titer of 1:8. No specific antifungal therapy was instituted.

Table 2 Diagnostic Tests Used in the Detection of Histoplasmosis

Acute pulmonary
Antigen: urine and BAL, most sensitive
Cytology or histopathology: BAL and/or lung biopsy
Serology: ID and CF, may be falsely negative in first 6 weeks after exposure, acute and convalescent, some background positivity in the community
Culture: BAL and/or lung biopsy
Chronic pulmonary
Antigen: usually negative, suggests PDH if positive
Cytology or histopathology: sputum or BAL may be positive
Serology: ID and CF, most sensitive, titers usually $>1:32$
Culture: sputum (at least three specimens) or BAL usually positive
Mediastinal
Antigen: usually negative
Cytology or histopathology: avoid biopsy if suspect fibrosing mediastinitis
Serology: ID and CF, most sensitive but may be false-negative
Culture: Usually negative despite positive histopathology
Progressive disseminated
Antigen: urine and blood; BAL if performed; antigen test is most sensitive
Cytology or histopathology: BAL if infiltrates, other lesions if biopsied, especially bone marrow
Serology: ID and CF, may be falsely negative
Culture: blood culture (at least three specimens) sensitive and noninvasive, BAL and/or lung biopsy if bronchoscopy performed, other lesions

BAL, bronchoalveolar lavage; CF, complement fixation; ID, immunodiffusion; PDH, progressive disseminated histoplasmosis.

Table 3 Indications for Treatment of Histoplasmosis

Definite indication, proven or probable efficacy
Acute diffuse pulmonary, moderately severe or severe symptoms
Chronic cavitary pulmonary
Progressive disseminated
Uncertain indication, unknown efficacy
Acute focal pulmonary, asymptomatic or mild symptoms persistent >1 month
Mediastinal lymphadenitis
Mediastinal granuloma
Inflammatory syndromes (arthritis, erythema nodosum, pericarditis) if treated with corticosteroids
Not recommended, unknown efficacy or ineffective
Mediastinal fibrosis
Pulmonary nodule
Broncholithiasis

Modified from Wheat et al.[28]

itraconazole treatment may be appropriate if no symptomatic improvement occurs after 1 month of observation. Treatment to prevent complications is not generally recommended in the absence of symptoms. Treatment might, however, be appropriate if the patient has chronic obstructive pulmonary disease or is immunocompromised.

ACUTE PULMONARY HISTOPLASMOSIS

Following high inoculum exposures, immunocompetent subjects acutely present within 2 weeks with respiratory symptoms, fever, chills, malaise, dyspnea, cough, chest pain, and diffuse pulmonary involvement. Chest radiographs typically demonstrate bilateral diffuse opacities that initially appear as ill-defined areas of focal airspace disease. Patients frequently exhibit findings of extrapulmonary dissemination, including hepatosplenomegaly, lymphadenopathy, laboratory evidence of bone marrow suppression, and hepatic enzyme elevations. *Histoplasma* may be isolated from extrapulmonary sites in up to one quarter of cases. Dissemination is usually nonprogressive, resolving even without therapy upon the development of cellular immunity to *H. capsulatum*. In severe cases respiratory failure[29,30] and death[30] may ensue if the diagnosis is not established and treatment initiated in a timely fashion, highlighting the importance of early diagnosis of histoplasmosis.

More commonly, following low inoculum exposure, pulmonary illness is subacute and mild, or even asymptomatic. Chest radiographs typically show a single area or several areas of patchy airspace disease. Hilar and mediastinal adenopathy may be present by itself or in association with airspace disease. Although rapid improvement in 2 to 3 weeks is characteristic, the illness may linger in some cases. Often the diagnosis of community-acquired pneumonia is made and antibiotics are prescribed. Because localized acute pulmonary histoplasmosis resolves without therapy in most cases, improvement may be incorrectly attributed to antibiotic therapy, and testing of histoplasmosis is never performed.

Diagnosis

In patients with diffuse pulmonary involvement rapid diagnosis is important because prompt initiation of antifungal therapy may be life saving. Rapid diagnosis may be achieved by direct cytopathological examination of BAL, positive in ~50% of cases. Diagnosis may also be established by detection of *Histoplasma* antigen in urine in up to 75% of such cases. Diagnosis may also be established by detection of antigen in BAL, potentially identifying cases with negative cytopathology or antigenuria.[18] Serology is typically negative during the first month after exposure. If serological tests are negative, follow-up specimens 1 or 2wo months later can detect seroconversion. Although seroconversion may help to

establish the diagnosis of histoplasmosis, the 1- to 2-month delay limits its usefulness in managing the patient. Both ID and CF tests should be performed. Currently available EIA methods are inferior to ID and CF because they are neither as specific nor as sensitive; and they should not be relied upon for screening or confirmatory testing.

Rapid diagnosis is less important in patients with subacute illnesses and more focal pulmonary involvement. Antigenuria is present in about one third of cases because fungal burden is low. Serological tests are usually positive and form the basis for diagnosis in most cases. Bronchoscopy with BAL may be helpful in some cases. Rarely is surgery needed in cases with consistent findings and positive serological tests, especially with CF titers of 1:32 or higher.

Correct interpretation of serological tests in histoplasmosis requires knowledge of their limitations. M precipitins by ID and CF titers of 1:8 and 1:16 may remain positive for several years after infection with *H. capsulatum*, complicating their interpretation. In such cases, if the clinical or radiographic findings are atypical, biopsy may be required. Also, serological tests may cross-react in specimens from patients with blastomycosis and coccidioidomycosis.

Treatment

Most patients with moderate to severe acute histoplasmosis who have diffuse pulmonary infiltrates should be treated (Table 3). Patients should be carefully evaluated for dissemination because a longer duration of therapy would be required. Diffuse infiltrates in the absence of heavy inoculum exposure suggest hematogenous dissemination to the lungs.[31] Similarly, immunosuppressed patients with pulmonary histoplasmosis should be treated as if they have disseminated infection.[32] In those who are hypoxic corticosteroids should be added (Table 4).[33] Liposomal amphotericin B, specifically AmBisome (Astellas Pharma US, Inc., Deerfield, IL), was more effective than the standard deoxycholate formulation in a study of patients with AIDS who had disseminated histoplasmosis,[34] and may be preferred in patients with severe pulmonary disease. Patients with milder manifestations may be treated with itraconazole alone. The optimal duration of therapy is unknown, but a 12-week course is recommended in the patient without underlying disease or evidence of dissemination.

Antifungal therapy is unnecessary in most patients with localized, noncavitary disease. Itraconazole given for 6 to 12 weeks may be helpful in those who remain symptomatic for more than 1 month, however. Treatment is also recommended in immunosuppressed patients with acute histoplasmosis to prevent progressive disseminated disease. Whether treatment in patients with underlying emphysema should be given to prevent chronic pulmonary infection is unknown. If treatment is given to prevent these complications, a 3- to 6-month course is recommended.

MEDIASTINAL LYMPHADENITIS AND GRANULOMA

Mediastinal lymphadenopathy is common in acute histoplasmosis. Mediastinal adenitis is sometimes acutely symptomatic and causes severe chest pain, located centrally and usually worse during inspiration, occasionally causing it to be mistaken for pleuritic pain. In rare cases, the enlarged and inflamed nodes may impinge on airways, the esophagus, or the superior vena cava (SVC). The trachea or major bronchi of children are less rigid and are more susceptible to compression than are adult airways.

Although the mediastinal lymphadenitis resolves and the nodes shrink over time, causing no consequences in most patients, an excessive necrosis or fibrosis can occur in some patients (Fig. 2A). Inflamed and necrotic lymph nodes may coalesce into a mass containing semiliquid material with a thin (1 to 2 mm) fibrotic capsule.[35] The nodal mass may be large (4 to 8 cm) and may impinge on adjacent structures, most often the esophagus. The capsule may attach to adjacent tissues, sometimes leading to fistula formation with drainage of necrotic material into the airways, skin, or esophagus,[35] with concomitant decrease in the size of the mass lesion, and rarely associated with superinfection of the mass by enteric bacteria.[36]

Diagnosis

Diagnosis may be established by serology in most cases. If serology is negative, biopsy may be needed to establish the diagnosis. Granulomatous inflammation is present, and small budding yeast may be seen in cytological preparations or histopathology. Cultures are usually negative, however. Typical radiographic subcapsular or diffuse calcification in some mediastinal granuloma may obviate the need for biopsy, but tuberculosis should be excluded for patients who have probable exposure.

Treatment

Patients with obstructive findings or persistent symptoms lasting more than a month may benefit from therapy. In severe cases adjunctive corticosteroid therapy may be helpful.[37] Nevertheless, the effectiveness of therapy in symptomatic cases is unclear. Although response to treatment has been reported,[37–39] the symptoms may resolve without therapy,[32] complicating assessment of the role of therapy. Accepting the possible

Table 4 Treatment Recommendations for Common Histoplasmosis Syndromes

Syndrome	Recommendations
Acute pulmonary—moderately severe or severe	Lipid AmB* 3.0–5.0 mg/kg/d IV or deoxycholate AmB 0.7–1.0 mg/kg/d IV for 1–2 wk, followed by Itra† 200 mg PO twice daily for a total of 12 wk
	Methylprednisolone, 0.5–1.0 mg/kg/d IV for 1–2 wk
Acute pulmonary—mild to moderate	Symptoms < 4 wk—none
	Symptoms > 4 wk—Itra 200 mg PO once or twice daily for 6–12 wk
Chronic cavitary pulmonary	Itra 200 mg PO once or twice daily for at least 12 months
Mediastinal lymphadenitis	Mild symptoms < 4 wk—none
	Symptoms warranting treatment with prednisone 0.5–1.0 mg/kg/d PO in tapering doses over 1–2 wk—Itra 200 mg PO once or twice daily for 6–12 wk
	Symptoms > 4 wk—Itra 200 mg PO once or twice daily for 6–12 wk
Mediastinal granuloma	Asymptomatic—none
	Symptomatic—Itra 200 mg PO once or twice daily for 6–12 wk
Mediastinal fibrosis	Antifungal treatment not indicated
	Stenting of obstructed vessels can be useful
	Itra 200 mg PO once or twice daily for 6–12 wk‡
Broncholithiasis	Antifungal treatment not indicated
Pulmonary nodule	Antifungal treatment not indicated
Progressive disseminated—moderately severe/severe	Liposomal AmB 3.0 mg/kg/d IV, or AmB lipid complex 5.0 mg/kg/d IV, or deoxycholate AmB 0.7–1.0 mg/kg/d IV for 1–2 wk, then Itra 200 mg PO twice daily for at least 12 months
Progressive disseminated—mild to moderate	Itra 200 mg PO twice daily for at least 12 months§

*Liposomal amphotericin B 3.0 mg/kg/d or amphotericin B lipid complex 5.0 mg/kg/d are recommended for 1–2 weeks, except in meningitis where the dosage of liposomal amphotericin B is 5.0 mg/kg/d for 4–6 weeks. The deoxycholate formulation of amphotericin B 0.7–1.0 mg/kg/d is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity.
†Itraconazole should be given as a loading dose of 200 mg three times daily for the first 3 days followed by 200 mg twice daily thereafter. Itraconazole 200 mg once daily may be sufficient in patients with less severe manifestations of histoplasmosis. If used for prophylaxis, 200 mg daily is recommended. Concentrations of itraconazole in serum should be monitored in patients being treated for chronic pulmonary, disseminated, or central nervous system histoplasmosis; a random serum concentration > 1.0 μg/mL should be sought. Drug monitoring is infrequently needed for patients receiving shorter courses of therapy for acute pulmonary histoplasmosis and its complications.
‡Only if cannot clearly differentiate from mediastinal granuloma.
§Chronic, potentially lifelong, suppressive therapy with itraconazole is required in patients with acquired immunodeficiency syndrome who do not achieve immune reconstitution in response to antiretroviral therapy. Lifelong suppressive therapy may be useful in patients with other immunosuppressive disorders in whom immunosuppression cannot be substantially reduced and in patients who relapse despite appropriate therapy.
Modified from Wheat et al.[28]
AmB, amphotericin B; Lipid AmB, lipid formulation of amphotericin B; Itra, itraconazole; IV, intravenous; PO, by mouth; d, days; wk, weeks; mo, months.

benefit of therapy, a 6- to 12-week trial of itraconazole is reasonable. When significant obstructive symptoms persist, surgical extirpation of the mass in whole or in part, with relief of tension on a band of invasive fibrosis, is often successful, but surgery to prevent fibrosing mediastinitis is not advised.[40]

FIBROSING MEDIASTINITIS

Fibrosing mediastinitis is characterized by excessive dense fibrosis around lymph nodes that invades into vital mediastinal structures (Fig. 2B).[35,41,42] The granulomatous component is less remarkable than in cases of mediastinal granuloma and is surrounded by concentric layers of mature collagen with mononuclear cells and fibroblasts at the periphery. The fibrotic material may reach several centimeters in thickness. A small number of yeast may be seen in the central granuloma, but cultures are negative.

SVC obstruction is most common, but airways, pulmonary arteries or veins, esophagus, and pericardium or even myocardium may be involved. Right hilar node involvement most often causes SVC syndrome or pulmonary artery obstruction, whereas a variety of structures may be damaged by fibrosis of the subcarinal nodes (e.g., arteries, veins, airways, or, rarely, esophagus). Bilateral involvement carries the greatest risk, especially if the pulmonary veins are obstructed, which can lead to progressive right heart failure and a syndrome resembling severe mitral stenosis.[42]

Chest radiographs may be deceptive and show only subtle abnormality, especially when the focus is subcarinal, or may show mediastinal or hilar adenopathy. If the fibrosing mediastinitis has produced airway obstruction, findings of atelectasis may be present. Parenchymal infiltrates caused by infarction or interstitial edema from venous obstruction are commonly misinterpreted as interstitial lung disease and have even led to

unnecessary surgical lung biopsy. Chest CT[43] is the best technique for diagnosis, showing which mediastinal structures are involved (Fig. 4), and the presence and extent of characteristic ectopic calcification. Calcification is present in the vast majority of fibrosing mediastinitis cases in adults. It may be inconspicuous and easily overlooked on plain chest radiographs but is well seen on CT scans, done preferably in the absence of radiographic contrast. Calcification indicates that the initial infection occurred several years before but may develop more rapidly in children. Ventilation–perfusion lung scans are also important, to provide supplemental information about regional distribution of impaired airflow and blood flow. Pulmonary arterial or venous hemodynamic and contrast studies may be required to define the extent and location of pulmonary vascular obstruction.

Diagnosis

The diagnosis is based on the clinical and radiographic findings and supported by positive serological tests in two thirds of cases. Biopsy should be avoided if possible if clinical features are characteristic for fibrosing mediastinitis because of the high risk of serious operative complications.[44] The characteristic features include calcified mediastinal mass at lymph node sites, associated with significant airway or central vascular obstruction, in the absence of systemic symptoms or signs of malignancy or another disease process, in a patient usually less than 40 years old at onset of symptoms. Although silver stain of biopsy specimens shows yeast resembling *H. capsulatum* in two thirds of cases of fibrosing mediastinitis, cultures are positive in less than 10%.[44] Serological tests are positive in two thirds of cases at titers of $\geq$ 1:32.

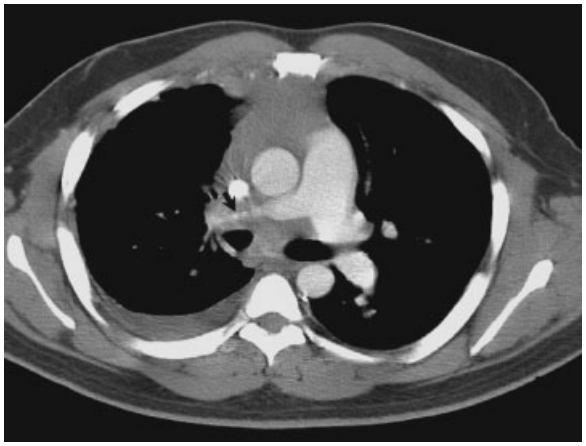

Figure 4 This 34-year-old male had respiratory symptoms prompting a chest x-ray. A small effusion was noted and a chest computed tomographic (CT) scan was obtained. The patient had minimal dyspnea on exertion. The chest CT showed marked narrowing of the right pulmonary artery (*arrow*) with increased mediastinal soft tissue density and some distortion of the right mainstem bronchus. Immunodiffusion showed a positive M band and a yeast complement fixation titer of 1:8. No therapy was instituted and he was diagnosed with fibrosing mediastinitis.

Treatment

The course may be progressive and even fatal, supporting the urgent need to develop effective therapy. Unfortunately pharmacological therapy does not seem to alter the outcome of this complication of histoplasmosis.[41,42] Prospective studies are needed to determine if therapy could prevent progressive fibrosis. Nevertheless, an occasional patient may benefit from therapy, and a trial of itraconazole is reasonable but should be stopped if there is no objective improvement after 3 months. Use of corticosteroids or other anti-inflammatory agents is not recommended. This should not be confused with another rare form of fibrosing mediastinitis not caused by histoplasmosis, which is notable for lack of calcification and responsiveness to corticosteroids.[41]

Placement of intravascular stents may be helpful in selected patients with SVC syndrome or bilateral pulmonary vascular obstruction, although the long-term outcome of such therapy is unknown.[45] Intravascular stent placement has potential for serious complications, including three reports that describe laceration of the aorta after placement of an SVC stent.[46] Placement of stents in the airways has been associated with rapid growth of granulation tissue causing obstruction of the stent, discouraging their use for this indication. Evaluation of all structures (artery, vein, and airway) should be undertaken before placement of any stent because multiple structures may be occluded to the same regions. Embolization of bronchial or other collateral systemic vessels (intercostals, internal mammary) may relieve pulmonary hemorrhage, which usually has its source from exuberant proliferation of systemic arteries into the lung that has occluded pulmonary vessels.

Pulmonary vascular stenting may be useful in some cases. Because involvement of both lungs is life threatening for most patients, and because other therapies are not effective, intervention with pulmonary vascular stenting (artery or vein or both) should be considered for these patients. In contrast, obstruction of major vessels or airways of only one lung is both more common and far less life threatening than bilateral involvement. The autoamputation of one lung may cause chronic pleuritic pain or hemoptysis but is rarely life threatening, so pulmonary vascular stenting is not encouraged in this setting. Pulmonary vascular stenting for unilateral occlusion might be considered in the unusual circumstance to relieve severe symptoms, such as severe exertional dyspnea due to wasted ventilation, or pleural effusion and pain due to infarct in progress.

Surgery is rarely indicated and may have fatal complications. Fewer than 40% of patients benefited and 20% died as a complication of surgery in the largest review of the surgical treatment of fibrosing mediastinitis.[44] Massive hemorrhage is a common surgical complication. This is typically due to venous chest wall collaterals, which develop when the SVC is narrowed, or to hypervascular chest wall systemic arterial development from collaterals that feed into an ipsilateral lung that has pulmonary artery or pulmonary vein occlusion. Others have also reported high operative mortality (~25%) but have advocated earlier surgery.[47] This surgery should only be done by surgeons experienced in operating on patients with fibrosing mediastinitis,[47] and only then with a specific and achievable surgical goal.

Treatment that is intended to prevent fibrosing mediastinitis or the development of symptomatic mediastinal granuloma cannot be justified. Transition from acute histoplasmosis to fibrosing mediastinitis has not been observed.[44] Mediastinal adenopathy is present in most patients with acute histoplasmosis,[35,48] and the enlarged nodes persist for years (Wheat, unpublished observation). Fibrosing mediastinitis, however, is rare, estimated to be < 1 case in 20,000 infections. Treatment to prevent these rare complications is more likely to cause harm than benefit, and whether therapy would prevent them is unknown.

CHRONIC PULMONARY HISTOPLASMOSIS

The presence of structural lung disease, such as emphysema, impairs the pulmonary clearance of *H. capsulatum*. As a result, infection may lead to chronic pulmonary disease with cavity formation and tissue destruction. The course is slowly progressive and can be fatal if untreated, and the management is often challenging. Chronic pulmonary histoplasmosis is often mistaken for reactivation tuberculosis (Fig. 5). Risk factors include the presence of chronic obstructive lung disease, older age, male sex, white race, and immunosuppression.[49] Patients present with chronic cough, dyspnea, chest pain, fatigue, fevers, and sweats. Radiographs typically show changes of emphysema. The disease is almost always in the upper lobes and may be bilateral or unilateral in distribution. Airspace opacities are present and may surround preexisting bullae and produce the appearance of cavitation; this pattern is sometimes referred to as a bullitis. The cavities may enlarge and air–fluid levels may be present.

The inflammatory process progressively destroys lung leading to volume loss and hilar retraction. Pleural thickening adjacent to the lung disease is often present.[49,50] Calcified mediastinal lymph nodes or pulmonary nodules are present in three quarters of cases, suggesting that the process had been present for several years by the time of diagnosis, or that the manifestation resulted from reinfection in patients with calcifications

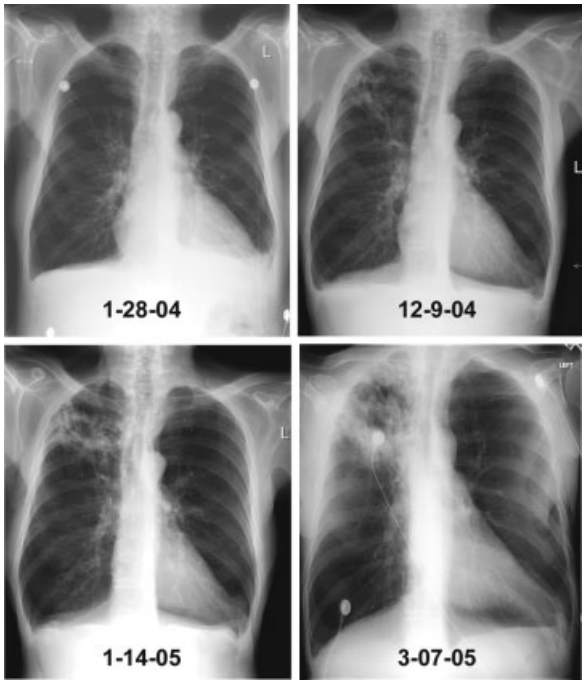

Figure 5 A patient with cough, fever, and dyspnea had progressive right upper lobe infiltrates and was ruled out for tuberculosis multiple times. Because of worsening dyspnea and weight loss, a bronchoscopy was performed to rule out malignancy and other chronic infections. Fungal stain was negative. Fungal culture eventually grew *Histoplasma* from bronchoalveolar lavage. The patient received itraconazole therapy for more than 1 year for chronic pulmonary histoplasmosis.

resulting from prior histoplasmosis.[49] Pathologically, inflammation is disproportionate to the fungal burden, suggesting that hypersensitivity to fungal antigens played a role in the pathogenesis.[50] Vascular compromise, tissue necrosis, and fibrosis are also present.[50] Extensive tissue damage rather than overwhelming infection seems to be the major source of morbidity and mortality in chronic cavitary histoplasmosis.

Diagnosis

The diagnosis can be established by isolation of *H. capsulatum* from the sputum or bronchoscopy specimens in the majority of cases.[49,50] Tests for antigen in urine and blood are usually negative due to the low fungal burden. If bronchoscopy is performed, *Histoplasma* antigen could be detected in bronchial washings or BAL,[18] perhaps reducing the time to diagnosis. Serological tests for anti-*Histoplasma* antibodies are positive in nearly all cases and provide the basis for diagnosis for up to one quarter of cases.

The differential diagnosis of chronic cavitary pulmonary histoplasmosis includes reactivation tuberculosis, nontuberculous mycobacterial infection (*M. avium* complex, *M. kansasii*, and *M. Xenopi),* other

endemic mycosis (blastomycosis, sporotrichosis, and coccidioidomycosis), and sarcoidosis.

Treatment

Treatment is indicated in all patients with chronic pulmonary histoplasmosis. Antifungal therapy halts progression, reduces mortality, eliminates *H. capsulatum* from the sputum, and causes regression of the pulmonary infiltrates in two thirds of cases.[51,52] Itraconazole is recommended for 12 to 24 months and until the chest CT shows no further improvement. Relapse off therapy occurs in 10 to 20% of cases, and justifies follow-up for 1 to 2 years after treatment is stopped.

PROGRESSIVE DISSEMINATED HISTOPLASMOSIS

Most cases of PDH occur in patients with underlying immunosuppression.[32] Common predisposing conditions include hematologic malignancy,[31,53] corticosteroid administration,[31,53] solid-organ transplantation,[54,55] and AIDS.[56,57] Age greater than 65 years[32] and infancy[58,59] have also been recognized as predisposing conditions for decades.[60] With the improvement in antiretroviral therapy, AIDS is a less frequent predisposing condition; and with the advent of treatment with tumor necrosis factor-α (TNF-α) blockers, rheumatologic disease and inflammatory bowel disease have emerged as leading conditions associated with PDH.[61–63] In rare cases, idiopathic CD4 lymphocytopenia[64] and defects in the interleukin-12 or interferon gamma pathways[65] have predisposed to PDH.

Over three quarters of patients with PDH exhibit evidence of pulmonary involvement (Fig. 6). Chest radiographs, abnormal in ~70% of patients, usually show diffuse reticulonodular, interstitial, or miliary infiltrates.[31,56,66] In the absence of a high inoculum exposure, diffuse infiltrates strongly suggests progressive disseminated disease as diffuse infiltrates are rare in patients with subacute pulmonary histoplasmosis.[31]

Diagnosis

Demonstration of extrapulmonary involvement by isolating the organism or visualizing it by fungal stain in extrapulmonary tissue is the strongest evidence of PDH. In recent times, in the presence of compatible clinical findings and a positive *Histoplasma* antigen test, culture and histopathology on extrapulmonary tissue are not commonly performed. An immunocompromised host with pulmonary histoplasmosis usually has concurrent disseminated disease, even though it may not be apparent clinically. We have demonstrated by culture or histopathology that two thirds of immunosuppressed patients had PDH,[32] but the true frequency is probably higher, given the limitations of histopathology and culture, including sparse sampling.

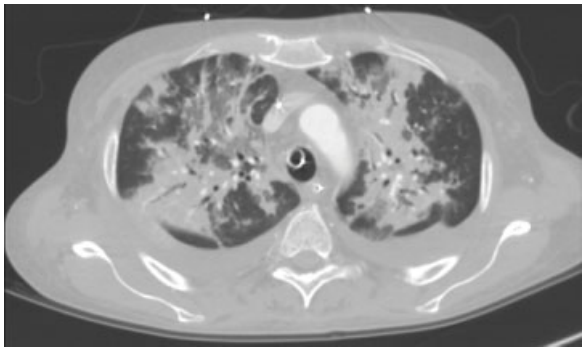

Figure 6 This patient was receiving infliximab for Crohn disease and developed acute shortness of breath requiring intubation for an acute respiratory distress–like syndrome. She had fevers and thrombocytopenia. Computed tomographic scan demonstrated alveolar infiltrates. Bronchoalveolar lavage showed small yeast on silver and Giemsa stains. Bone marrow aspirate also showed yeast. Blood culture eventually grew *Histoplasma*. Yeast complement fixation titer was 1:32. She was treated with amphotericin and later transitioned to oral itraconazole. She has been treated for over 3 months for progressive disseminated histoplasmosis, with itraconazole levels guiding her dosing regimen. Her urine antigen is persistently elevated at 6.4 ng/mL. Infliximab was held and she is to be treated for at least 1 year.

Clinical and laboratory evidence for PDH include progressive weight loss with diffuse pulmonary infiltrates (for more than a month in the absence of a recent high inoculum exposure), hepatosplenomegaly, extrapulmonary lymphadenopathy, mucosal or skin lesions, anemia, leukopenia, thrombocytopenia, hepatic enzyme elevation, or adrenal insufficiency. Lactate dehydrogenase[67] and ferritin[68] elevation may also suggest the diagnosis in patients with AIDS.

The workup for PDH should include three fungal blood cultures, tests for *Histoplasma* antigen in urine and blood, and *Histoplasma* ID and CF. In some instances, Wright-Giemsa stains of peripheral blood may reveal intracellular yeasts within phagocytic mononuclear cells. If bronchoscopy is indicated, BAL and transbronchial biopsy specimens, if feasible, should be cultured for fungus and examined microscopically by a pathologist skilled in recognition of pulmonary pathogens. BAL should also be tested for *Histoplasma* antigen. Other suspicious lesions should be biopsied, and specimens should be processed for histopathologic studies and fungal culture. Thrombocytopenia is common and differentiates disseminated histoplasmosis from other diseases such as sarcoidosis. Bone marrow sampling may be useful in some patients.

Treatment

Infectious Diseases Society of America guidelines[28] should be reviewed for a more thorough discussion of

treatment. Amphotericin B[51,69,70] and itraconazole[71,72] are both highly effective treatments for PDH. In patients with AIDS complicated by PDH, response was 88% to liposomal amphotericin B versus 64% to the deoxycholate formulation, and mortality was lower (2% vs 13%) with liposomal amphotericin B.[70] Most patients with severe or moderately severe disease respond to amphotericin B given for 1 to 2 weeks, followed by itraconazole.[70]

Itraconazole alone is recommended for less ill patients. Response rates to itraconazole are 80 to 100%.[71,72] Itraconazole is administered 200 mg three times daily for 3 days as a loading dose followed by 200 mg twice daily,[71,72] guided by itraconazole blood level testing. Blood levels of itraconazole are somewhat higher using the suspension formulation instead of the capsule, but the suspension is more expensive, less convenient, and causes more nausea than does the capsular formulation, and it is not clearly preferred. The suspension is most useful in patients who are taking medications to reduce gastric acidity or who cannot achieve blood levels > 2 μg/mL with the capsule formulation.

Treatment should be administered for at least 1 year, and sometimes longer in immunosuppressed patients, depending on the status of immunosuppression. In patients who are receiving immunosuppressive medications, immunosuppression should be reduced during the first 2 or 3 months of therapy. Generally TNF-α blockers need to be discontinued. Once the symptoms and clinical findings have resolved or markedly diminished, and the patient continues to receive antifungal therapy, TNF-α blockers may be reinstituted for worsening of the inflammatory condition. Close follow-up is mandatory for those with ongoing immunosuppression.

Lifelong suppressive therapy with itraconazole was the standard of care in patients with AIDS.[73,74] With effective antiretroviral therapy, suppressive therapy is no longer needed in patients who achieve remission of PDH and immune reconstitution with CD4 + T-lymphocyte counts above 150 cells/μL.[75] The need for lifelong antifungal therapy in immunosuppressed conditions other than AIDS is unknown. In organ transplant recipients, lifelong antifungal therapy is not the standard of care but may be needed in some cases. Findings supporting suppressive therapy include persistent clinical evidence of infection, antigenuria > 3 ng/mL, and sustained moderate- to high-level immunosuppression because of chronic or recurrent allograft rejection. Less is known about the standard of care or outcome in patients with chronic inflammatory diseases treated with TNF-α blockers.

Relapsing infection after appropriate therapy may be an indication for lifelong therapy. Ten to 15% of patients relapse.[71,72] Causes for relapse during or following itraconazole therapy include unremitting immunosuppression, inadequate dosing or durations of therapy, poor adherence, use of medications that prevent reduce absorption or increase metabolism, and conditions causing malabsorption of the drug. These factors should be evaluated in choosing the approach to treatment. In some cases repeat treatment with itraconazole may be appropriate, correcting for the deficiencies contributing to the failure. If inadequate drug exposure or drug tolerability could not be corrected, treatment with posaconazole or voriconazole could be considered. In those who failed one or more courses of appropriate therapy, lifelong antifungal suppressive therapy may be needed.

Alternatives to itraconazole are needed in some patients. Posaconazole and voriconazole demonstrate in vitro activity against *H. capsulatum*,[76] and posaconazole has been studied in an animal model.[77,78] Both have been used successfully in small numbers of patients with a variety of different forms of histoplasmosis.[55,79] Prospective studies comparing them to itraconazole or to one another have not been conducted, however. Fluconazole appears to be less effective than itraconazole[80] and may cause development of resistance during therapy.[81] Ketoconazole is rarely used and is thought to be inferior to itraconazole, at least with regard to tolerability. Posaconazole would appear to be the best alternative to itraconazole, followed by voriconazole. Drug exposure may be inadequate with itraconazole,[72,74] posaconazole,[82] and voriconazole,[83] supporting the need for drug-level monitoring. Trough drug levels of 1 μg/mL are recommended but not established as a requirement for response through prospective trials.

REFERENCES

1. Wheat LJ, Conces DJ, Allen S, Blue-Hnidy D, Loyd J. Pulmonary histoplasmosis syndromes: recognition, diagnosis, and management. Semin Respir Crit Care Med 2004;25: 129–144
2. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev 2007;20:115–132
3. Wheat LJ. Improvements in diagnosis of histoplasmosis. Expert Opin Biol Ther 2006;6:1207–1221
4. Wheat LJ, Kohler RB, Tewari RP. Diagnosis of disseminated histoplasmosis by detection of *Histoplasma capsulatum* antigen in serum and urine specimens. N Engl J Med 1986; 314:83–88
5. Durkin MM, Connolly PA, Wheat LJ. Comparison of radioimmunoassay and enzyme-linked immunoassay methods for detection of *Histoplasma capsulatum* var. *capsulatum* antigen. J Clin Microbiol 1997;35:2252–2255
6. Wheat J, Wheat H, Connolly P, et al. Cross-reactivity in *Histoplasma capsulatum* variety *capsulatum* antigen assays of urine samples from patients with endemic mycoses. Clin Infect Dis 1997;24:1169–1171
7. Wheat LJ, Connolly P, Durkin M, et al. False-positive *Histoplasma* antigenemia caused by antithymocyte globulin antibodies. Transpl Infect Dis 2004;6:23–27

8. Wheat LJ, Connolly P, Durkin M, Book BK, Pescovitz MD. Elimination of false-positive *Histoplasma* antigenemia caused by human anti-rabbit antibodies in the second-generation *Histoplasma* antigen assay. Transpl Infect Dis 2006;8:219–221
9. Wheat LJ, Witt J III, Durkin M, Connolly P. Reduction in false antigenemia in the second generation *Histoplasma* antigen assay. Med Mycol 2007;45:169–171
10. Kuberski T, Myers R, Wheat LJ, Kubak BM, Bruckner D, Peuges D. Diagnosis of coccidioidomycosis by antigen detection using cross-reaction with a *Histoplasma* antigen. Clin Infect Dis 2007;44:e50–e54
11. Connolly PA, Durkin MM, Lemonte AM, Hackett EJ, Wheat LJ. Detection of histoplasma antigen by a quantitative enzyme immunoassay. Clin Vaccine Immunol 2007;14:1587–1591
12. Williams B, Fojtasek M, Connolly-Stringfield P, Wheat J. Diagnosis of histoplasmosis by antigen detection during an outbreak in Indianapolis, Ind. Arch Pathol Lab Med 1994; 118:1205–1208
13. Davies SF. Serodiagnosis of histoplasmosis. Semin Respir Infect 1986;1:9–15
14. Wheat LJ. Current diagnosis of histoplasmosis. Trends Microbiol 2003;11:488–494
15. Wheat LJ, Garringer T, Brizendine E, Connolly P. Diagnosis of histoplasmosis by antigen detection based upon experience at the histoplasmosis reference laboratory. Diagn Microbiol Infect Dis 2002;43:29–37
16. Wheat J, French ML, Kohler RB, et al. The diagnostic laboratory tests for histoplasmosis: analysis of experience in a large urban outbreak. Ann Intern Med 1982;97:680–685
17. Sacks JJ, Ajello L, Crockett LK. An outbreak and review of cave-associated histoplasmosis capsulati. J Med Vet Mycol 1986;24:313–327
18. Hage CA, Davis TE, Egan L, et al. Diagnosis of pulmonary histoplasmosis and blastomycosis by detection of antigen in bronchoalveolar lavage fluid using an improved second-generation enzyme-linked immunoassay. Respir Med 2007; 101:43–47
19. Wheat LJ, Connolly-Stringfield P, Blair R, Connolly K, Garringer T, Katz BP. Histoplasmosis relapse in patients with AIDS: detection using *Histoplasma capsulatum* variety *capsulatum* antigen levels. Ann Intern Med 1991;115:936–941
20. Wheat LJ, French MLV. The diagnostic approach in histoplasmosis. Immunol Allergy Pract V 1983;9:19–28
21. Larrabee WF, Ajello L, Kaufman L. An epidemic of histoplasmosis on the isthmus of Panama. Am J Trop Med Hyg 1978;27:281–285
22. Zimmerman SE, French MLV, Kleiman MB, Wheat LJ. Evaluation of an enzyme-linked immunosorbent assay that uses ferrous metal beads for determination of antihistoplasmal immunoglobulins G and M. J Clin Microbiol 1990;28: 59–64
23. Guimaraes AJ, Pizzini CV, Matos Guedes HL, et al. ELISA for early diagnosis of histoplasmosis. J Med Microbiol 2004; 53:509–514
24. Bialek R, Feucht A, Aepinus C, et al. Evaluation of two nested PCR assays for detection of *Histoplasma capsulatum* DNA in human tissue. J Clin Microbiol 2002;40:1644–1647
25. Tang YW, Li H, Durkin MM, et al. Urine polymerase chain reaction is not as sensitive as urine antigen for the diagnosis of disseminated histoplasmosis. Diagn Microbiol Infect Dis 2006;54:283–287
26. Ost D, Fein AM, Feinsilver SH. The solitary pulmonary nodule. N Engl J Med 2003;348:2535–2542
27. Mashburn JD, Dawson DF, Young JM. Pulmonary calcifications and histoplasmosis. Am Rev Respir Dis 1961;84:208–216
28. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007;45:807–825
29. Reynolds RJI, Penn RL, Grafton WD, George RB. Tissue morphology of *Histoplasma capsulatum* in acute histoplasmosis. Am Rev Respir Dis 1984;130:317–320
30. Sollod N. Acute fulminating disseminated histoplasmosis. J S C Med Assoc 1971;67:231–234
31. Sathapatayavongs B, Batteiger BE, Wheat J, Slama TG, Wass JL. Clinical and laboratory features of disseminated histoplasmosis during two large urban outbreaks. Medicine (Baltimore) 1983;62:263–270
32. Wheat LJ, Slama TG, Norton JA, et al. Risk factors for disseminated or fatal histoplasmosis: analysis of a large urban outbreak. Ann Intern Med 1982;96:159–163
33. Wynne JW, Olsen GN. Acute histoplasmosis presenting as the adult respiratory distress syndrome. Chest 1974;66:158–161
34. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 2002;137:105–109
35. Goodwin RA, Loyd JE, des Prez RM. Histoplasmosis in normal hosts. Medicine (Baltimore) 1981;60:231–266
36. Scully RE, Mark EJ, McNeely WF, McNeely BU. Case records of the Massachusetts General Hospital: case 39–1991 presentation of case. N Engl J Med 1991;325:949–956
37. Greenwood MF, Holland P. Tracheal obstruction secondary to *Histoplasma* mediastinal granuloma. Chest 1972;62:642–645
38. Savides TJ, Gress FG, Wheat LJ, Ikenberry S, Hawes RH. Dysphagia due to mediastinal granulomas: diagnosis with endoscopic ultrasonography. Gastroenterology 1995;109: 366–373
39. Jenkins DW, Fisk DE, Byrd RB. Mediastinal histoplasmosis with esophageal abscess. Gastroenterology 1976;70:109–111
40. Dines DE, Payne WS, Bernatz PE, Pairolero PC. Mediastinal granuloma and fibrosing mediastinitis. Chest 1979;75: 320–324
41. Davis AM, Pierson RN, Loyd JE. Mediastinal fibrosis. Semin Respir Infect 2001;16:119–130
42. Goodwin RA, Nickell JA, des Prez RM. Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. Medicine (Baltimore) 1972;51:227–246
43. Weinstein JB, Aronberg DJ, Sagel SS. CT of fibrosing mediastinitis: findings and their utility. AJR Am J Roentgenol 1983;141:247–251
44. Loyd JE, Tillman BF, Atkinson JB, des Prez RM. Mediastinal fibrosis complicating histoplasmosis. Medicine (Baltimore) 1988;67:295–310
45. Doyle TP, Loyd JE, Robbins IM. Percutaneous pulmonary artery and vein stenting: a novel treatment for mediastinal fibrosis. Am J Respir Crit Care Med 2001;164:657–660
46. Recto MR, Bousamra M, Yeh T. Late superior vena cava perforation and aortic laceration after stenting to treat

superior vena cava syndrome secondary to fibrosing mediastinitis. J Invasive Cardiol 2002;14:624–629
47. Mathisen DJ, Grillo HC. Clinical manifestations of mediastinal fibrosis and histoplasmosis. Ann Thorac Surg 1992; 54:1053–1058
48. Wheat LJ, Slama TG, Eitzen HE, Kohler RB, French ML, Biesecker JL. A large urban outbreak of histoplasmosis: clinical features. Ann Intern Med 1981;94:331–337
49. Wheat LJ, Wass J, Norton J, Kohler RB, French ML. Cavitary histoplasmosis occurring during two large urban outbreaks: analysis of clinical, epidemiologic, roentgenographic, and laboratory features. Medicine (Baltimore) 1984;63:201–209
50. Goodwin RA Jr, Owens FT, Snell JD, et al. Chronic pulmonary histoplasmosis. Medicine (Baltimore) 1976;55: 413–452
51. Furcolow ML. Comparison of treated and untreated severe histoplasmosis. JAMA 1963;183:121–127
52. Putnam LR, Sutliff WD, Larkin JC, et al. Histoplasmosis cooperative study: chronic pulmonary histoplasmosis treated with amphotericin B alone and with amphotericin B and triple sulfonamide. Am Rev Respir Dis 1968;97:96–102
53. Adderson EE. Histoplasmosis in a pediatric oncology center. J Pediatr 2004;144:100–106
54. Wheat LJ, Smith EJ, Sathapatayavongs B, et al. Histoplasmosis in renal allograft recipients: two large urban outbreaks. Arch Intern Med 1983;143:703–707
55. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC. Histoplasmosis in solid organ transplant recipients at a large midwestern university transplant center. Transpl Infect Dis 2005;7:109–115
56. Wheat J. Histoplasmosis in the acquired immunodeficiency syndrome. Curr Top Med Mycol 1996;7:7–18
57. Tucker RM, Denning DW, Hanson LH, et al. Interaction of azoles with rifampin, phenytoin, and carbamazepine: in vitro and clinical observations. Clin Infect Dis 1992;14:165–174
58. Odio CM, Navarrete M, Carrillo JM, Mora L, Carranza A. Disseminated histoplasmosis in infants. Pediatr Infect Dis J 1999;18:1065–1068
59. Leggiadro RJ, Barrett FF, Hughes WT. Disseminated histoplasmosis of infancy. Pediatr Infect Dis J 1988;7:799–805
60. Goodwin RA Jr, Shapiro JL, Thurman GH, Thurman SS, des Prez RM. Disseminated histoplasmosis: clinical and pathologic correlations. Medicine (Baltimore) 1980;59:1–33
61. Wood KL, Hage CA, Knox KS, et al. Histoplasmosis after treatment with anti-TNF-α therapy. Am J Respir Crit Care Med 2003;167:1279–1282
62. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum 2002;46:2565–2570
63. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38: 1261–1265
64. Kortsik C, Elmer A, Tamm I. Pleural effusion due to *Histoplasma capsulatum* and idiopathic CD4 lymphocytopenia. Respiration 2003;70:118–122
65. Zerbe CS, Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. Clin Infect Dis 2005;41:e38–e41
66. Conces DJ Jr, Stockberger SM, Tarver RD, Wheat LJ. Disseminated histoplasmosis in AIDS: findings on chest radiographs. AJR Am J Roentgenol 1993;160:15–19
67. Corcoran GR, Al-Abdely H, Flanders CD, Geimer J, Patterson TF. Markedly elevated serum lactate dehydrogenase levels are a clue to the diagnosis of disseminated histoplasmosis in patients with AIDS. Clin Infect Dis 1997;24:942–944
68. Kirn DH, Fredericks D, McCutchan JA, Stites D, Shuman M. Serum ferritin levels correlate with disease activity in patients with AIDS and disseminated histoplasmosis. Clin Infect Dis 1995;21:1048–1049
69. Sarosi GA, Voth DW, Dahl BA, Doto IL, Tosh FE. Disseminated histoplasmosis: results of long-term follow-up: a Center for Disease Control Cooperative Mycoses Study. Ann Intern Med 1971;75:511–516
70. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 2002;137:105–109
71. Dismukes WE, Bradsher RW, Cloud GC, et al. Itraconazole therapy for blastomycosis and histoplasmosis. NIAID Mycoses Study Group. Am J Med 1992;93:489–497
72. Wheat J, Hafner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. Am J Med 1995;98:336–342
73. Wheat J, Hafner R, Wulfsohn M, et al. Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome. The National Institute of Allergy and Infectious Diseases Clinical Trials and Mycoses Study Group Collaborators. Ann Intern Med 1993; 118:610–616
74. Hecht FM, Wheat J, Korzun AH, et al. Itraconazole maintenance treatment for histoplasmosis in AIDS: a prospective, multicenter trial. J Acquir Immune Defic Syndr Hum Retrovirol 1997;16:100–107
75. Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. Clin Infect Dis 2004;38:1485–1489
76. Wheat LJ, Connolly P, Smedema M, et al. Activity of newer triazoles against *Histoplasma capsulatum* from patients with AIDS who failed fluconazole. J Antimicrob Chemother 2006;57:1235–1239
77. Connolly P, Wheat LJ, Schnizlein-Bick C, et al. Comparison of a new triazole, posaconazole, with itraconazole and amphotericin B for treatment of histoplasmosis following pulmonary challenge in immunocompromised mice. Antimicrob Agents Chemother 2000;44:2604–2608
78. Connolly P, Wheat J, Schnizlein-Bick C, et al. Comparison of a new triazole antifungal agent, Schering 56592, with itraconazole and amphotericin B for treatment of histoplasmosis in immunocompetent mice. Antimicrob Agents Chemother 1999;43:322–328
79. Restrepo A, Tobon A, Clark B, et al. Salvage treatment of histoplasmosis with posaconazole. J Infect 2007;54:319–327
80. Wheat J, MaWhinney S, Hafner R, et al. Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. Am J Med 1997;103:223–232

81. Wheat LJ, Connolly P, Smedema M, Brizendine E, Hafner R. Emergence of resistance to fluconazole as a cause of failure during treatment of histoplasmosis in patients with acquired immunodeficiency disease syndrome. Clin Infect Dis 2001;33:1910–1913
82. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007;44: 2–12
83. Freifeld A, Arnold S, Ooi W, et al. Relationship of blood level and susceptibility in voriconazole treatment of histoplasmosis. Antimicrob Agents Chemother 2007;51:2656–2657