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Endemic Mycoses in AIDS: a Clinical Review

JOSEPH WHEAT*

Departments of Medicine and Pathology, Roudebush Department of Veterans Affairs Hospital, Indiana University School of Medicine, Indianapolis, Indiana

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INTRODUCTION

Certain mycoses are common and major causes of morbidity in patients with AIDS who have lived in the areas where these mycoses are endemic. The incidence and severity of these mycoses increase with progression of human immunodeficiency virus (HIV) infection and reduction in CD4 counts, as shown in Fig. 1. Histoplasmosis caused by *Histoplasma capsulatum* var. *capsulatum* is the most commonly diagnosed endemic mycosis in patients with AIDS. Infection with *H. capsulatum* var. *duboisii* has been reported in patients with AIDS from Africa. Histoplasmosis mostly afflicts patients residing in the Mississippi and Ohio River Valleys of the United States and in Latin America. Coccidioidomycosis is less common than histoplasmosis but may be seen in patients with AIDS who reside in or have visited the southwestern United States and parts of Latin America. Blastomycosis is the least common opportunistic endemic mycosis in patients with AIDS. Diagnosis of these systemic mycoses requires knowledge of their clinical syndromes, a high index of suspicion, and knowledge of the accuracy and limitations of tests used for diagnosis of fungal infections. Antifungal treatment induces remission of clinical illness but does not eradicate the infection in patients with AIDS who have disseminated mycoses. Suppressive therapy must be continued to prevent relapse. Strategies to prevent these common and serious complications of HIV infection are being studied.

* Mailing address: Wishard Memorial Hospital, Room WOP 430, 1001 West Tenth St., Indianapolis, IN 46202-2879. Phone: (317) 630-6262. Fax: (317) 630-7522.

HISTOPLASMOSIS

Mycology

H. capsulatum var. *capsulatum* is an ascomycete of the family *Arthrodermataceae*. Its teleomorphic state is *Ajellomyces capsulatus. H. capsulatum* var. *capsulatum* grows as a mold in the soil and on appropriate culture media at temperatures of less than 35°C. Hyphae bear tuberculate macroconidia that are 8 to 14 μm in diameter and smaller microconidia (2 to 5 μm) which are the infectious form of the organism (Fig. 2). *H. capsulatum* is found primarily in microfoci containing large amounts of rotted guano where starlings, pigeons, and grackles have roosted or bats have inhabited. At temperatures above 35°C and in mammalian tissues, *H. capsulatum* grows as a yeast measuring 2 to 4 μm in diameter. Growth on fungal media is relatively slow, requiring incubation for 4 to 5 days to several weeks. Definitive identification requires conversion of the mold to the yeast, demonstration of specific reactivity with anti-*H. capsulatum* antisera (exoantigen tests), or reactivity with nucleic acid probes.

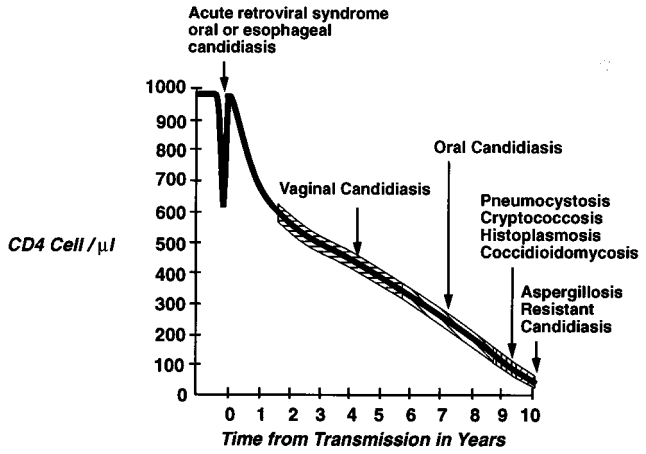

FIG. 1. Occurrence of fungal infections during the course of progressive HIV infection. Reprinted from reference 66a with permission of the publisher.

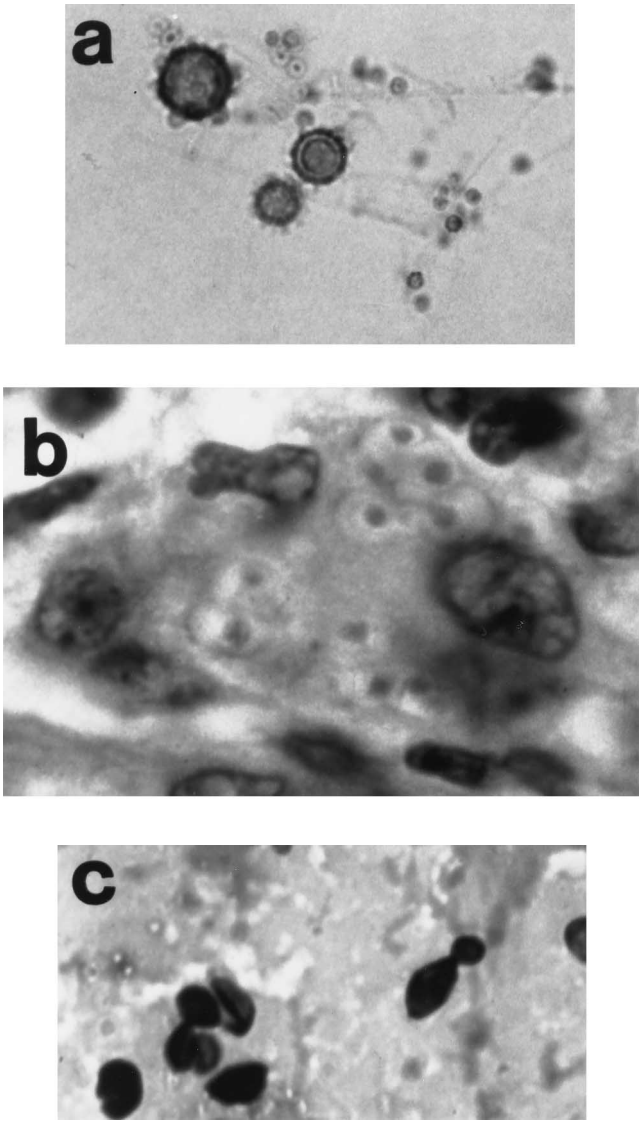

FIG. 2. Fungal stains of *H. capsulatum* showing mold by lactol phenol cotton blue stain (a), yeast by hematoxylin-eosin stain (b), and yeast by methenamine-silver stain (c).

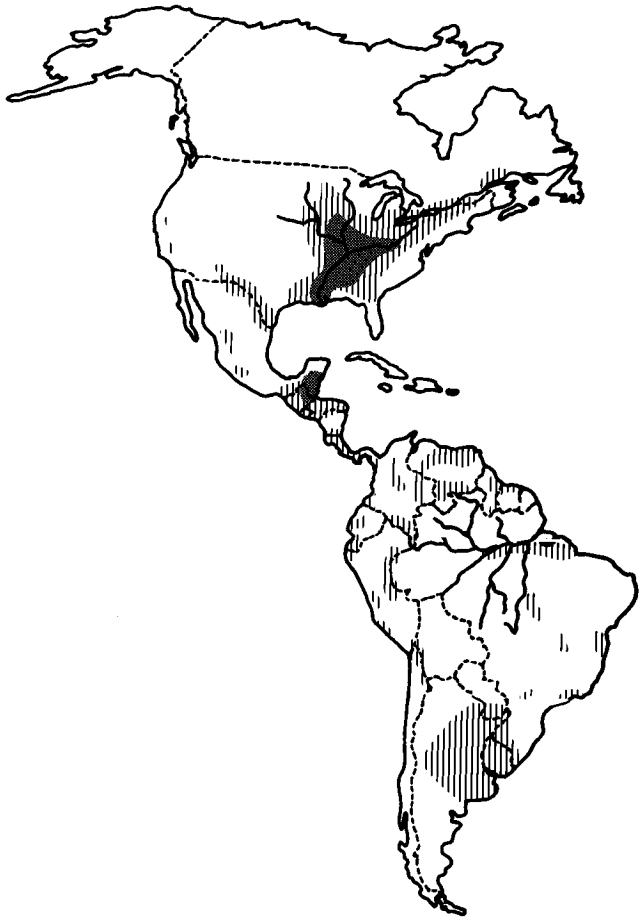

FIG. 3. Distribution of histoplasmosis endemicity in the Americas. The highest incidences are in the finely stippled areas of North and Central America. Reprinted from reference 54a with permission of the publisher.

Epidemiology

Histoplasmosis represents the first manifestation of AIDS in 50 to 75% of patients. Histoplasmosis occurs in 2 to 5% of patients with AIDS from areas of endemicity (Fig. 3) and in up to 25% of those from selected cities (42, 68). The high incidence in Indianapolis, Ind.; Kansas City, Kans.; Memphis, Tenn.; and Nashville, Tenn., probably is explained by patients exposed during outbreaks of histoplasmosis in these cities. Cases also have been reported in Europe, Africa, and Southeast Asia (6, 11, 14, 29, 35, 54, 55, 57).

Whether infections in patients in the region of endemicity are caused by exogenous exposure or reactivation of old infection is unknown. Calcified mediastinal lymph nodes seen on chest radiograms consistent with prior histoplasmosis occurred in 36% of the cases in Indianapolis (15), supporting either reactivation or reinfection as the mode of acquisition. The clustering of cases during an outbreak, however, favors reinfection rather than reactivation of disease (Fig. 4).

Histoplasmosis occurs in less than 1% of patients from areas of nonendemicity, where reactivation of latent infection is more likely than exogenous infection (68). Strains of *H. capsulatum* from five Puerto Rican immigrants to New York City had a mitochondrial DNA pattern characteristic of that found in strains from Panama, supporting the hypothesis that reactivation is a common mode of acquisition in areas where histoplasmosis is not endemic (36). However, exposure to

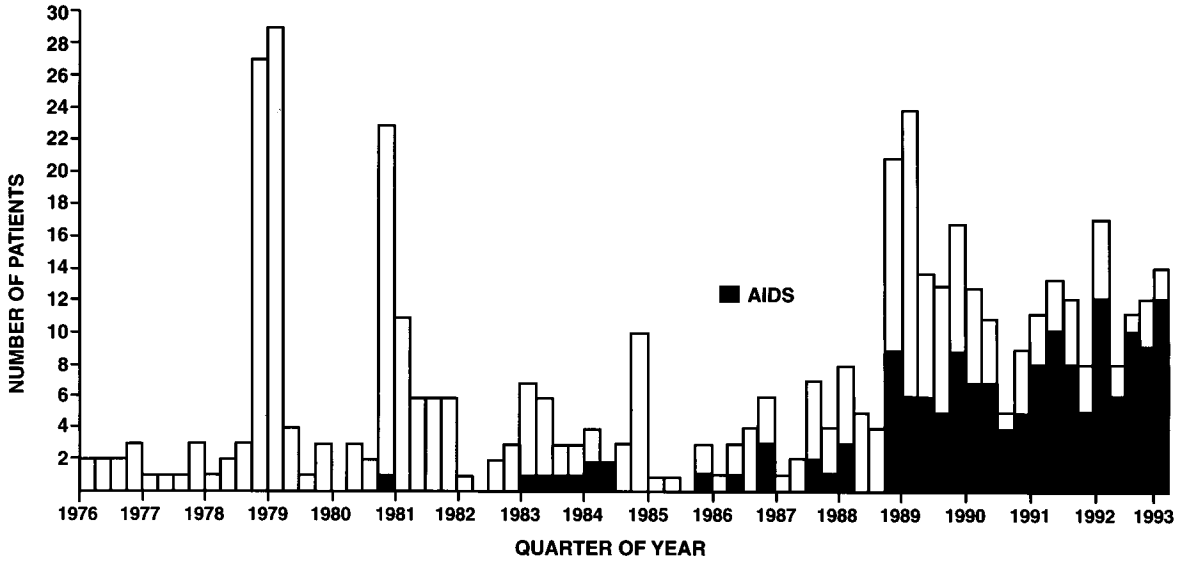

FIG. 4. Occurrence of culture-proven cases of histoplasmosis at six Indianapolis hospitals since 1976. Cases designated by solid columns occurred in patients with AIDS. The first case of histoplasmosis in a patient with AIDS occurred in a patient who acquired AIDS in New York City and moved in 1980 to Indianapolis, where she died of histoplasmosis 6 months later.

microfoci of fungi in old buildings contaminated with bird or bat guano may occur outside the areas of endemicity (34). Careful studies using molecular typing will be needed to determine the mode of acquisition of infection in patients with AIDS.

Pathogenesis

Infection with *H. capsulatum* develops when microconidia or hyphal elements are inhaled and convert into yeasts in the lungs or when organisms in old foci of infection reactivate during immunosuppression. *H. capsulatum* parasitizes macrophages, which may assist in dissemination throughout the mononuclear phagocyte system. Cellular immunity plays an essential role in defense against *H. capsulatum* (16). With development of specific cellular immunity, cytokines arm macrophages and other cellular defense mechanisms come into play to kill the fungus and halt progression of the disease (75). Patients with AIDS are at high risk for progressive infections with *H. capsulatum* because cellular immunity is severely impaired.

Clinical Findings

H. capsulatum causes disseminated disease in 95% of cases in patients with AIDS (68). Ninety percent of cases have occurred in patients with CD4 counts below 200/μl. Most patients present with fever, fatigue, and weight loss of 1 to 2 months in duration. Although the illness may be rapidly fatal, a subacute presentation over 1 to 3 months is characteristic. Respiratory complaints of cough or dyspnea occur in half of the patients. Other common findings include hepatosplenomegaly and lymphadenopathy in about 25% of patients. Less commonly, 10 to 20% of patients present with a sepsis syndrome, meningitis, or gastrointestinal involvement (67, 68). Localized pulmonary infection may occur in patients who are not yet severely immunosuppressed and who have CD4 lymphocyte counts above 300/μl.

Chest radiograms show diffuse infiltrates, usually in a miliary reticulonodular pattern (Fig. 5) (15, 53, 56). Focal infiltrates or nodules are seen in about 10% of cases. Small numbers of nodules up to 5 cm in diameter may be seen in a minority of patients. Mediastinal adenopathy is uncommon, occurring in 6 to 20% of cases (15, 53). Less common radiographic abnor-

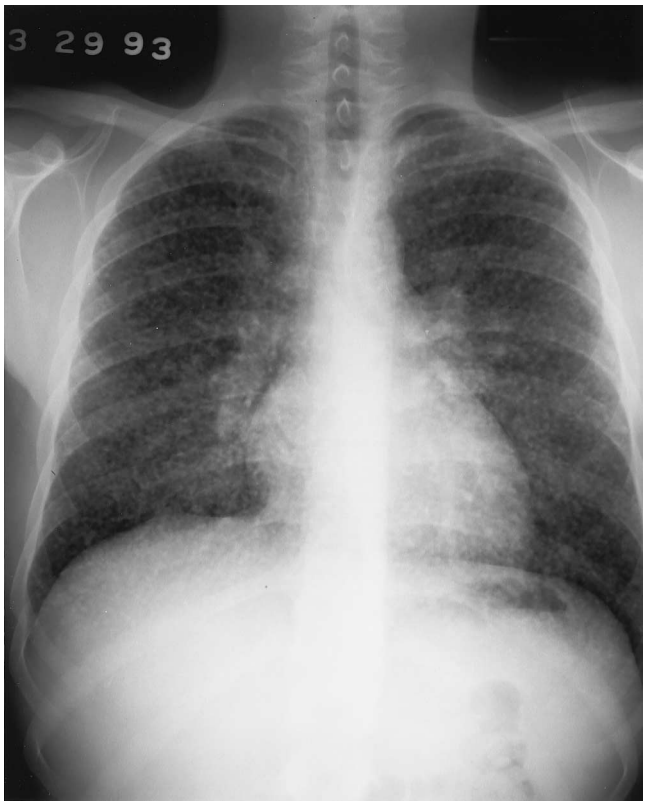

FIG. 5. Chest radiogram showing miliary reticulonodular pattern characteristic of histoplasmosis in patients with AIDS. The nodularity is suggestive of histoplasmosis and *P. carinii* pneumonia.

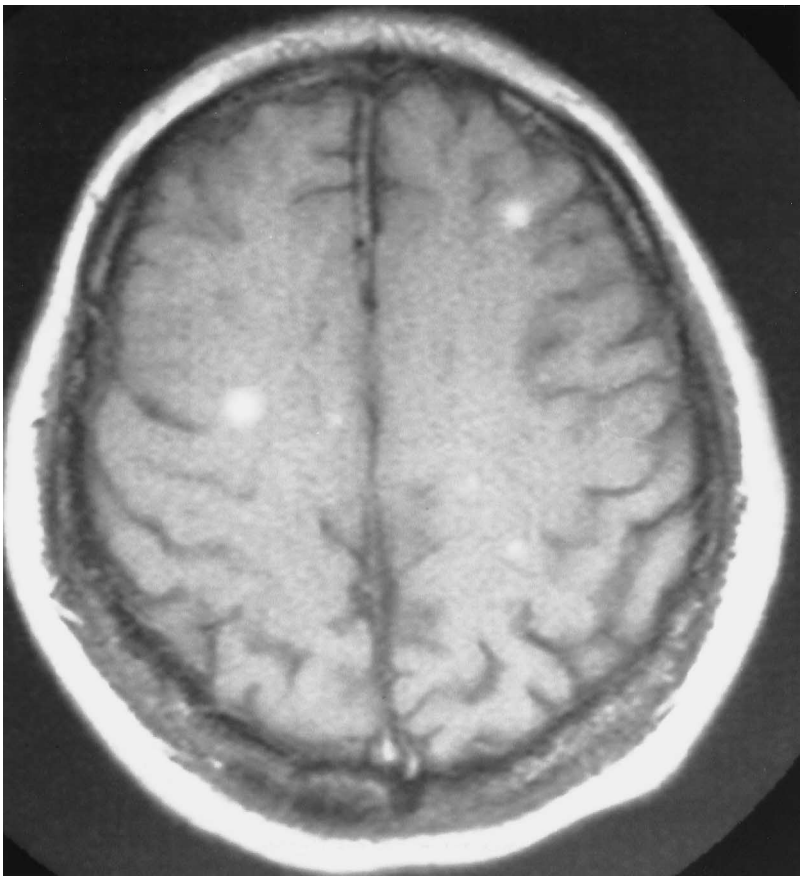

FIG. 6. Multiple enhancing cerebral lesions in a patient with disseminated histoplasmosis.

malities include the presence of cavities and pleural effusions. Radiographic findings often resemble those seen in patients with *Pneumocystis carinii* pneumonia, emphasizing the need to do bronchoscopy to establish the correct diagnosis so that appropriate treatment may be given. Concurrent infection with *P. carinii* may occur in up to 25% of cases.

Ten to 20% of patients present with a syndrome resembling septicemia, with shock, respiratory insufficiency, hepatic and renal failure, and rhabdomyolysis (68). This syndrome appears to represent a late manifestation of histoplasmosis in cases where the diagnosis is delayed because the patient did not seek medical care or the physician did not consider the diagnosis of histoplasmosis. This late syndrome is recognized more often in patients with AIDS than in those who are not coinfected with HIV. Mortality is high in patients who present with a sepsislike illness. Pathophysiologic mechanisms causing this syndrome have not been described.

Central nervous system involvement complicates 10 to 20% of cases and may be manifested as lymphocytic meningitis, focal brain lesions, or diffuse encephalitis (4, 68). Patients complain of fever and headache and often are confused or demonstrate mental status changes. Seizures or focal neurological deficits occur in 10 to 30% of cases. In patients with meningitis, cerebrospinal fluid abnormalities include lymphocytic pleocytosis, protein elevation, and hypoglycorraghia. Single or multiple enhancing brain lesions may be seen by computerized tomography scan or magnetic resonance imaging in one-third of cases (Fig. 6). The prognosis is poor in patients with such neurological findings (68).

About 10% of patients have gastrointestinal manifestations of disease, including diarrhea, abdominal pain, intestinal obstruction or perforation, bleeding, or peritonitis (1, 12). Lesions may occur anywhere along the gastrointestinal tract from the mouth (Fig. 7) to the anus but are more common in the small intestine and right colon (Fig. 8) (21, 30, 33, 39). Patchy erythema, plaques, ulcerations, pseudopolyps, small (3- to 8-mm) nodules, thickened intestinal folds, luminal masses, and strictures may be seen at endoscopy; occasionally, these resemble cancer or inflammatory bowel disease (12, 24, 30). Omental and mesenteric nodules that cause peritonitis and ascites have been reported (1). Abdominal computerized tomography scans commonly show hepatomegaly, splenomegaly, enlarged lymph nodes, splenic lucencies, and adrenal enlargement (53). Biopsy specimens from intestinal lesions show necrotizing granulomas containing *H. capsulatum* organisms.

A variety of skin lesions occur in about 10% of cases (20). These include erythematous or hyperpigmented papules, diffuse maculopapules, pustules, folliculitis, plaques with ulcerations, papules or nodules with keratinic plugging, eczematous changes, eosinophilic pustular folliculitis, erythema multiforme, and rosacea-like rashes (6, 13, 20, 22, 62). Diagnosis frequently has been made by biopsy examination of skin lesions that show *H. capsulatum* organisms.

Rare clinical manifestations include adrenal insufficiency (53), pericarditis, pleuritis (42), pancreatitis, prostatitis (41), and retinitis (40, 58).

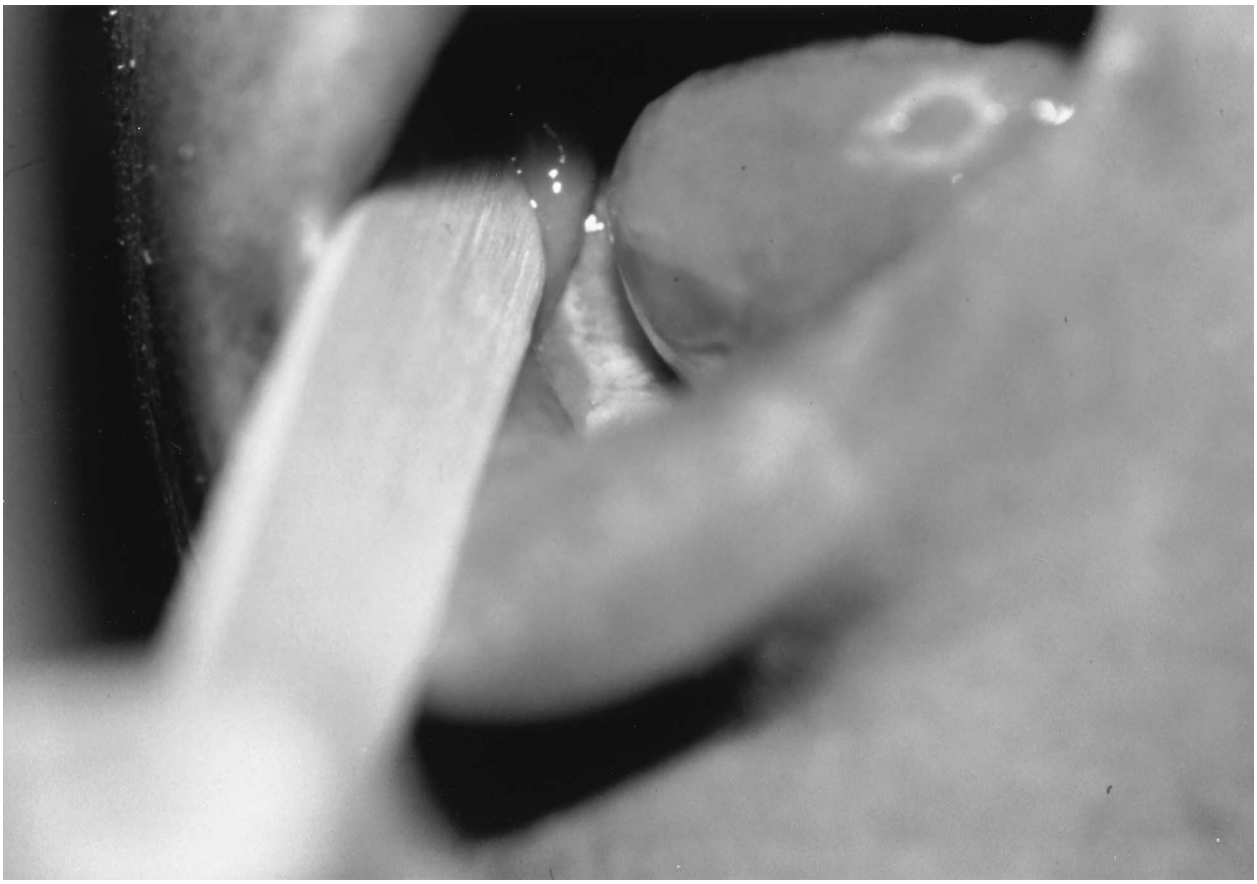

FIG. 7. Tongue and lower gingiva ulcers caused by histoplasmosis.

Diagnosis

The diagnosis of disseminated histoplasmosis requires a high index of clinical suspicion and awareness of the uses and limitations of the tests commonly used to identify fungal diseases. *H. capsulatum* has been isolated in culture from blood, bone marrow, respiratory secretions, or localized skin lesions in >85% of cases (Fig. 9) (44, 46, 68, 76). Cultures of bone marrow have been positive with the greatest frequency (70 to 90%). Cultures of respiratory specimens obtained at bronchoscopy are positive less often (50 to 75% of the time). *H. capsulatum* has been isolated from bronchoalveolar lavage fluid from patients with respiratory complaints or hypoxia despite negative chest radiograms. Isolation of *H. capsulatum* may occur within 1 week in a minority of patients but usually takes several weeks. Delay in diagnosis while awaiting results of fungal cultures may lead to a fatal outcome in more severe cases. The mean times required to isolate *H. capsulatum* from blood cultures were 8 to 13 days with the lysis-centrifugation technique and 19 to 24 days with biphasic techniques (5, 7, 51). Improved recognition of positive cultures through immunologic or molecular diagnostic techniques is needed. Advancements in early diagnosis made possible by antigen detection have improved the outlook for patients with histoplasmosis.

Detection of antigen in body fluids permits rapid diagnosis of disseminated histoplasmosis in patients with AIDS (68). Antigen testing is performed by radioimmunoassay or enzyme immunoassay, using polyclonal antibodies to *H. capsulatum*. In these sandwich assays, antibody is coated onto wells of microtiter plates. Antigen present in body fluid specimens binds to

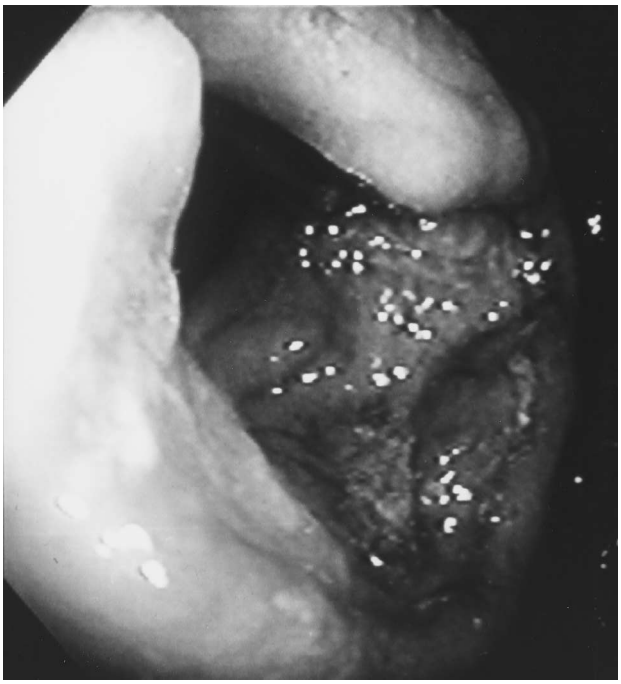

FIG. 8. Intestinal lesion of histoplasmosis in a patient with AIDS. (Provided by Douglas Dieterich, New York University School of Medicine, New York).

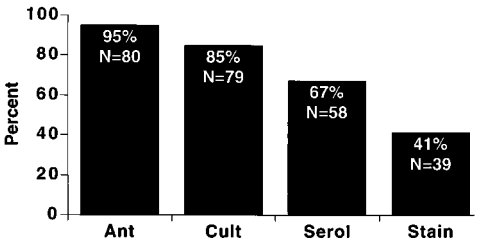

FIG. 9. Comparison of the sensitivities of different diagnostic tests for disseminated histoplasmosis in patients with AIDS. Ant, antigen detection; cult, culture; serol, serology; stain, fungal stain of tissues.

this capture antibody and is detected with labeled detector antibody. The tests can be performed in 1 workday and permit accurate diagnosis of disseminated or extensive pulmonary histoplasmosis. Antigen detection is the most sensitive method for diagnosis of disseminated histoplasmosis in patients with AIDS (~95%) and has been used as the basis for treatment in 80% of cases that have occurred in Indianapolis during the last 5 years (see Fig. 4 for statistics). Antigen was detected in the urine of 95% and the serum of 86% of cases (Fig. 10). Less commonly (~70%), antigen may be detected in bronchoalveolar lavage fluid (71) or cerebrospinal fluid (74) of patients with pulmonary or meningeal involvement (Fig. 10). Tests for antigen may be negative in 5 to 10% of cases, mostly in those with mild clinical manifestations or localized sites of dissemination (27, 28).

The specificity of antigen detection has been greater than 98% (71, 73). Cross-reactions have occurred in patients with coccidioidomycosis, paracoccidioidomycosis, and blastomycosis, but studies to determine the rate of cross-reactivity have not been conducted. These organisms share similar antigens, thus explaining the cross-reactivity. However, cross-reactions are of limited clinical importance since specific diagnosis usually can be made on the basis of epidemiologic features or positive cultures. Also, indications for treatment and specific therapies are similar for these endemic mycoses. Cross-reactions with *Aspergillus*, *Candida*, or *Cryptococcus* spp. do not occur. Of hundreds of specimens from patients with these infections tested, positive results have been identified only in those from patients concurrently infected with *H. capsulatum.*

Tests for antigen should be performed on urine and serum from all patients with suspected disseminated histoplasmosis. Cases will be missed if only serum, cerebrospinal fluid, or

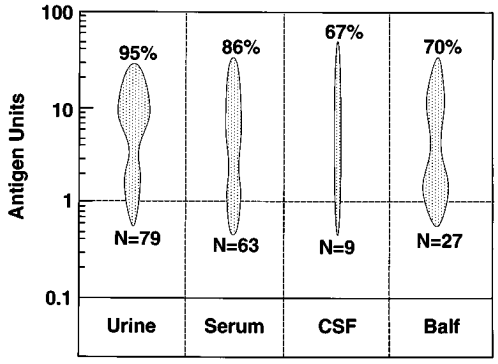

FIG. 10. Diagnosis of histoplasmosis by antigen detection in different body fluids from patients with AIDS. The percentages refer to the proportions of specimens with positive tests for antigen. N, number of patients tested; CSF, cerebrospinal fluid; Balf, bronchoalveolar lavage fluid.

TABLE 1. Outcome of treatment of histoplasmosis in patients with AIDS

Agent	No. of patients treated (% with positive response)		Reference(s)
	Induction phase	Maintenance phase	
Amphotericin B	69 (77)	21 (81)	68
Ketoconazole	11 (9)	20 (50)	68
Itraconazole	59 (85)	42 (93)	64, 72
Fluconazole	49 (74)	36 (61)	65

alveolar lavage fluid is tested. Testing is available by sending specimens to the Histoplasmosis Reference Laboratory in Indianapolis, and results are available within 1 to 2 days.

Microscopic examination of tissue sections or peripheral blood smears stained with fungal stains also permits rapid diagnosis, but with a lower sensitivity than antigen detection. Fungal stains of tissues were positive in 41% of cases studied in Indianapolis. The sensitivity of microscopic examination may be low if pathologists are not experienced in recognition of *H. capsulatum*. The highest yield of positive diagnosis is from bone marrow smears, which are positive in 50 to 75% of patients (37, 68, 76). Morphologic findings in biopsies of bone specimens include granulomas, lymphohistocytic aggregates, and diffuse macrophage infiltrates, and rarely, no pathologic changes are seen (37).

Examination of biopsy specimens of mouth, skin, or gastrointestinal nodules or ulcers and enlarged lymph nodes is another safe and rapid method for diagnosis but is positive in fewer than 25% of cases. Biopsy may be helpful if tests for antigen detection cannot be performed expeditiously (within 48 h) or are negative. Care must be taken in interpretation of fungal stains, however, as other fungal organisms, especially *Candida glabrata*, *P. carinii*, and artifacts that stain, may be misidentified as *H. capsulatum*. Improvements in direct detection procedures are needed to increase the sensitivity and specificity of these tests. Immunostaining or molecular diagnostic approaches may overcome these deficiencies.

Serologic tests are less sensitive than cultures or antigen detection tests in patients with AIDS and are positive in 50 to 70% of cases (68). The serologic response is reduced because of the B-lymphocyte impairment that occurs in HIV infection. Both immunodiffusion and complement fixation tests must be performed to achieve maximum sensitivity, and complement fixation tests must be done only at laboratories with skilled personnel. The role of the newer serologic tests that use enzyme immunoassay is unknown. Rarely, however, do serologic tests provide the sole basis for diagnosis of histoplasmosis in patients with AIDS. Rather, positive serologic tests support the need for additional workup, including biopsies, and assist in assessment of positive tests for antigen in patients with negative cultures.

Treatment

Untreated disseminated histoplasmosis is a progressively fatal infection in patients with AIDS. Treatment includes an induction phase to produce a clinical remission and a suppressive maintenance phase to prevent relapse. Amphotericin B is highly effective, inducing remission in 80% of patients, usually within the first week of therapy (Table 1) (46, 68). Most failures occur in patients who are severely ill or who have central nervous system histoplasmosis. Less commonly, failures have occurred in patients who cannot tolerate at least 25 mg of

TABLE 2. Recommendations for treatment of histoplasmosis in patients with AIDS

Phase	Disease severity	Drug	Dose (mg/day)	Duration of treatment
Induction	Mild	Itraconazole	400	3 mo
	Moderate or severe	Amphotericin then	50	3 days–2 wk
		Itraconazole	400	10 wk
Maintenance		Itraconazole[a] or	200[b]	Life
		Itraconazole	400	Life

[a] Fluconazole is an alternative drug in patients who cannot take itraconazole. The fluconazole dosage should be 800 mg/day for induction and 400 mg/day for maintenance.
[b] If itraconazole plasma concentrations are more than 4 μg/ml on the 400-mg/day induction dose, the dosage may be reduced to 200 mg/day.

TABLE 3. Situations contraindicating treatment with itraconazole

Situation	Absolute contraindication	Relative contraindication
Medications	Rifampin (Rifadin)	Antacids
	Terfenadine (Seldane)[a]	H-2 blockers (cimetidine, ranitidine, others)
	Astemizole (Hismanal)[a]	Rifabutin (Mycobutin)
	Omeprazole (Prilosec)[b]	
Conditions	Itraconazole allergy	Malabsorption
	Inability to take oral medications	Severe diarrhea
		Severe hepatic insufficiency
		Histoplasma meningitis[c]

[a] Potential to induce ventricular tachycardia and sudden death.
[b] More potent inhibitor of gastric acid production than H-2 blockers.
[c] Efficacy in meningitis is unknown. Itraconazole may be an alternative if the patient cannot take amphotericin B or is failing amphotericin B therapy.

amphotericin B daily. Amphotericin B is the treatment of choice in patients with moderately severe or severe manifestations of histoplasmosis. Clinical findings of severe histoplasmosis can include hypotension with systolic blood pressure of less than 90 mm Hg, hypoxia with pO_2 of <60 torr, mental status changes, evidence of rhabdomyolysis with creatine kinase levels that are >10 times normal, or coagulopathy. Findings suggestive of moderately severe histoplasmosis include fever of >39.5°C, a Karnofsky score of <60, serum albumin of <3 g/dl, hepatic enzyme elevation of more than five times normal, neutropenia of <500 cells per μl or thrombocytopenia with a platelet count of <50,000/μl, and a creatinine level of more than five times normal. Amphotericin B in doses of 50 mg daily, or 1 mg/kg in individuals weighing less than 50 kg, should be given for 3 to 14 days, and this should be followed by treatment with itraconazole (Table 2).

Ketoconazole is not an acceptable treatment for histoplasmosis in patients with AIDS because the response has been <20% (56, 68). The reasons for ketoconazole's low effectiveness may include poor absorption caused by the reduced gastric acid output in patients with AIDS (38) or poor compliance caused by nausea. Clinical data indicate that triazole antifungal agents are superior agents for treatment of histoplasmosis.

Itraconazole given in doses of 200 mg three times daily for 3 days and then twice daily for 12 weeks is highly effective for patients with mild histoplasmosis, inducing remission in 85% of cases, as seen in Table 1 (72). However, treatment failures occurred in patients with moderately severe disease. The response to itraconazole was slower than that to amphotericin B, supporting the regimen of initial treatment with amphotericin B for patients with moderately severe or severe clinical manifestations (Table 2).

Itraconazole's role in the treatment of central nervous system histoplasmosis is unknown. Itraconazole does not achieve detectable concentrations in cerebrospinal fluid, causing concern about its role in the treatment of meningitis. However, itraconazole has been used successfully for treatment of cryptococcal meningitis despite this theoretical limitation (17, 18). Furthermore, there is no published clinical experience using itraconazole in the treatment of meningitis caused by *H. capsulatum*. Thus, patients receiving itraconazole for this indication must be monitored carefully.

Because of itraconazole's variable absorption, concentrations of the drug in blood should be measured 2 to 4 h after administration of a dose during the second week of therapy. Concentrations of at least 2 μg/ml by bioassay and 0.5 μg/ml by high-pressure liquid-phase chromatography should be considered therapeutic during induction therapy. Unfortunately, itraconazole is insoluble in water and is not available for intravenous administration, preventing its use in patients who cannot take oral medications. Also, therapeutic concentrations may not be achieved in patients with diarrhea. Testing for the concentration of drug in blood is available at several reference laboratories.

Interactions with drugs that reduce the absorption of itraconazole (H-2 antagonists and omeprazole) or accelerate its metabolism (rifampin, ribabutin, phenytoin, carbamazepine, and barbiturates) must be recognized before this treatment option is selected. While antacids and H-2 antagonists may affect blood levels in only a small percentage of patients (~20%), rifampin prevents achievement of detectable itraconazole levels in most patients (60) and must not be administered concurrently (Table 3). Omeprazole reduces gastric acid production more completely than do H-2 antagonists and may have a more profound effect on absorption. The effects of other cytochrome P450 inducers and the more potent gastric acid inhibitor Prilosec on itraconazole concentrations are less well understood. Other enzyme inducers should be avoided if possible, but if they are used concurrently, itraconazole blood concentrations must be monitored.

Fluconazole's role in induction therapy is under investigation in a prospective trial with an 800-mg daily dose. Fluconazole has several advantages over itraconazole, including more predictable absorption, better penetration into the cerebrospinal fluid, fewer drug interactions, and availability of an intravenous formulation. However, failures caused by fluconazole-resistant strains have been observed (65). Its role in histoplasmosis awaits completion of this trial.

Of note, itraconazole and fluconazole increase blood concentrations of the antihistamine drugs terfenadine (Seldane) and astemizole (Hismanal), potentially causing serious ventricular arrhythmias and even death (52). Combinations of these drugs should be strictly avoided. Increased blood concentrations and toxicities of phenytoin, coumadin, oral hypoglycemics, digitalis, and cyclosporine, when given in combination with itraconazole and fluconazole, also must be recognized so that these treatments can be monitored appropriately.

Corticosteroid treatment has been given to a few patients with histoplasmosis who had concurrent *P. carinii* pneumonia with respiratory insufficiency. The histoplasmosis responded to amphotericin B or itraconazole despite the immunosuppressive effects of corticosteroids in these cases (63a). Whether

corticosteroids would improve the course of disease in patients with respiratory compromise caused by histoplasmosis is unknown, but at least one patient appears to have responded to such therapy (63a).

Relapse is common unless suppressive maintenance therapy is given (68). Relapse has occurred in 35 (56) to 80% (68) of patients who did not continue chronic maintenance therapy following completion of amphotericin B. Amphotericin B given weekly (68) or biweekly (43) was more effective in 81 to 95% of patients than was ketoconazole (50%) for prevention of recurrence (Table 1), but amphotericin B is inconvenient to administer and is toxic. Itraconazole in doses of 200 mg twice daily was well tolerated and highly effective (93%) as maintenance therapy in patients who completed a course of 15 mg of amphotericin B per kg (64) or itraconazole (63a) as induction therapy. Fluconazole (400 mg) daily for maintenance therapy is under investigation in patients who received 800 mg daily for induction therapy for 12 weeks. In a retrospective study, it was moderately effective for patients who received induction treatment with amphotericin B (47). Relapse occurred in 9 of 76 patients (12%), primarily patients taking 100 mg daily, suggesting that patients should receive at least 200 mg daily.

Itraconazole, 200 mg twice daily, is the maintenance treatment of choice, but fluconazole, 200 to 400 mg daily, is an alternative for patients who cannot take or do not absorb itraconazole. The itraconazole dose could be reduced to 200 or 300 mg daily in patients with documented levels of at least 4 μg/ml, striving to keep concentrations above 1 μg/ml during maintenance therapy.

The optimal maintenance therapy for patients with central nervous system involvement is unknown. Amphotericin B given weekly or biweekly is not ideally suited for this purpose because it fails to achieve detectable levels in the cerebrospinal fluid. Treatment failures of infection localized to the brain or meninges have been reported in patients receiving amphotericin B for induction (63) or maintenance (68) therapy. Itraconazole and fluconazole have been used successfully in such patients (63a), even though itraconazole also fails to reach detectable levels in the cerebrospinal fluid. Careful clinical follow-up with repeat lumbar puncture is needed to assure sustained remission.

Measurement of antigen in blood and urine is useful for monitoring the response to therapy. Antigen levels fall with successful therapy (68, 70, 72) and increase with relapse (Fig. 11) (69). Increases in antigen levels of more than 2 units suggest recurrence and support further laboratory evaluation and consideration of the patient for resumption of induction therapy. Use of antigen detection methods to diagnose relapse requires measurement of antigen levels at 3- to 4-month intervals and direct comparison in the same assay of the current specimen with the last previous specimen (10).

Prevention

Antifungal prophylaxis to prevent histoplasmosis would warrant consideration if prophylaxis were known to be effective and safe. Its use might be indicated in cities such as Indianapolis, Kansas City, Memphis, and Nashville where prevalence rates of histoplasmosis in patients with AIDS are high (>15%). A trial of itraconazole versus placebo is in progress in these cities. In a retrospective study from Dallas, Tex., however, fluconazole was not found to reduce the occurrence of histoplasmosis in patients with AIDS (45). A recommendation for prophylaxis cannot be supported until prophylaxis is proven to be useful in a prospective trial. In areas where the prevalence of histoplasmosis is low, the inconvenience and side effects of triazole therapy and the high cost of prophylaxis may cancel any potential benefit.

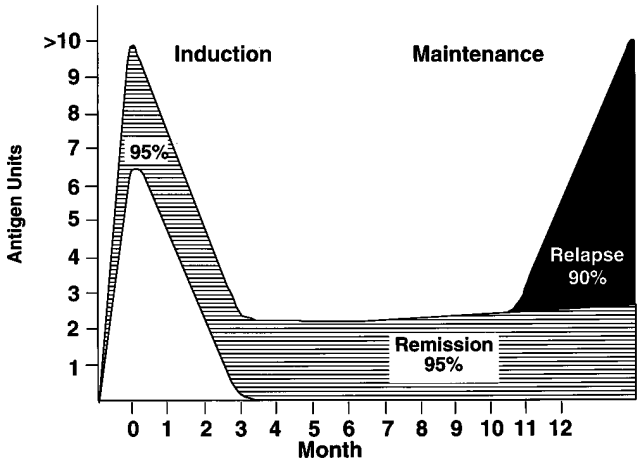

FIG. 11. Diagnosis of relapse of histoplasmosis by antigen detection in patients with AIDS. The graph depicts antigen levels measured during therapy. During the induction phase, 95% of patients had levels (units) of antigen between 6.5 and 10. Antigen units remained below 3 during remission but rose again up to 10 U for the 90% of patients who relapsed.

Vaccination might be another strategy to prevent histoplasmosis in areas of high prevalence. Research is needed to develop safe and effective vaccines and to explore this preventive approach in HIV-infected individuals living in areas where histoplasmosis is endemic.

COCCIDIOIDOMYCOSIS

Mycology

Coccidioidomycosis is caused by the pathogenic fungus *Coccidioides immitis. C. immitis* is the most virulent of the fungi affecting humans, causing infection upon exposure to only a few conidia and severe disease with larger inocula. It is a dimorphic fungus that grows as a mold with septate hyphae in the soil and on culture media and as an endosporulating spherule in the tissues of patients. Its barrel-shaped arthroconidia are 2.5 to 4 by 3 to 6 μm in size and are the infectious particles found in soil.

C. immitis converts to an endosporulating spherule at 37 to 40°C. Spherules measure 30 to 60 μm in diameter and contain endospores that are 2 to 5 μm in diameter (Fig. 12). Growth on fungal media occurs by the fourth day after inoculation of the specimen, at which time identification with nucleic acid probes is possible.

Epidemiology

C. immitis is found in microfoci in a spotty distribution in the hot, semiarid southwestern United States, northern Mexico, and Central America (Fig. 13). Growth is enhanced by bat and rodent droppings. Exposure is heaviest in the late summer and fall when dusty conditions exist, especially following rainy winters. Cases in patients with AIDS have been reported in Texas, Arizona, and southern California. In Tucson, Ariz., coccidioidomycosis was the third most frequently reported opportunistic infection in patients with AIDS, occurring in one-fourth of patients (3, 9). In other cities within the region of endemicity, however, coccidioidomycosis is much less common (<2%). Reasons for the higher prevalence in Tucson are

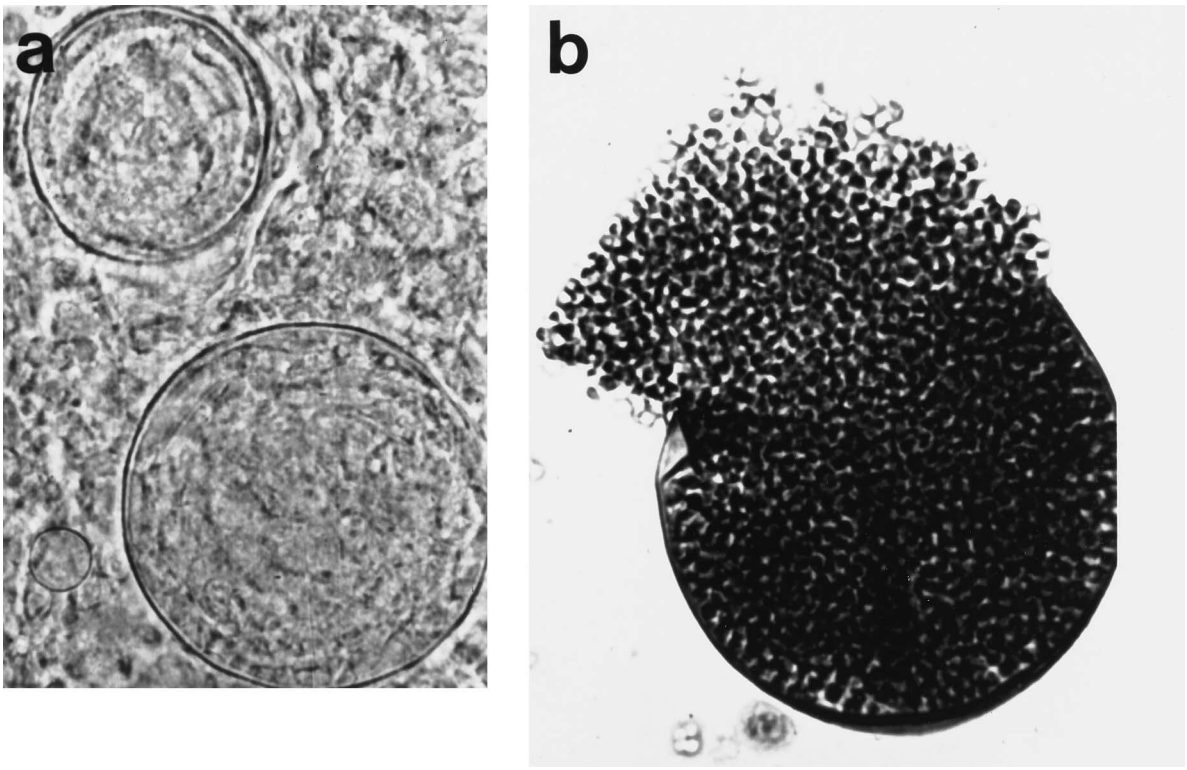

FIG. 12. Fungal stains showing *C. immitis* spherules in tissues (a). Release of endospores leads to spread of the infection (b). Panel b was reprinted from reference 54a with permission of the publisher.

unknown. Unlike *H. capsulatum*, which may be found in urban areas and in a variety of environmental niches, *C. immitis* is more restricted in distribution, a factor contributing to its lower incidence within the zone of endemicity. In large windborne outbreaks, however, individuals have been affected without having been directly exposed to these environmental niches.

Pathogenesis

Infection occurs following inhalation of arthroconidia of the mycelial form of the fungus or reactivation of latent infection. In the host the arthroconidia swell and form spherules with a thick wall (Fig. 12). The spherules enlarge and develop endospores. These mature spherules rupture, releasing endospores that spread locally and disseminate to extrapulmonary sites. Although neutrophils participate in the early inflammatory response to *C. immitis*, the predominant tissue reaction is granulomatous. Cellular immunity is the key defense mechanism in coccidioidomycosis, serving to arm macrophages to halt progression of the infection. Because they lack cellular immunity, patients with AIDS experience severe progressive forms of coccidioidomycosis.

Reactivation of latent disease remains to be proven as the mode of acquisition of coccidioidomycosis in patients with AIDS (3, 25). Only 2 of 13 patients who developed coccidioidomycosis during a prospective study in an area of endemicity demonstrated positive spherulin skin tests as evidence of prior coccidioidomycosis (3).

Clinical Findings

While *C. immitis* causes asymptomatic or mild respiratory illness in most healthy individuals, severe, often fatal disease

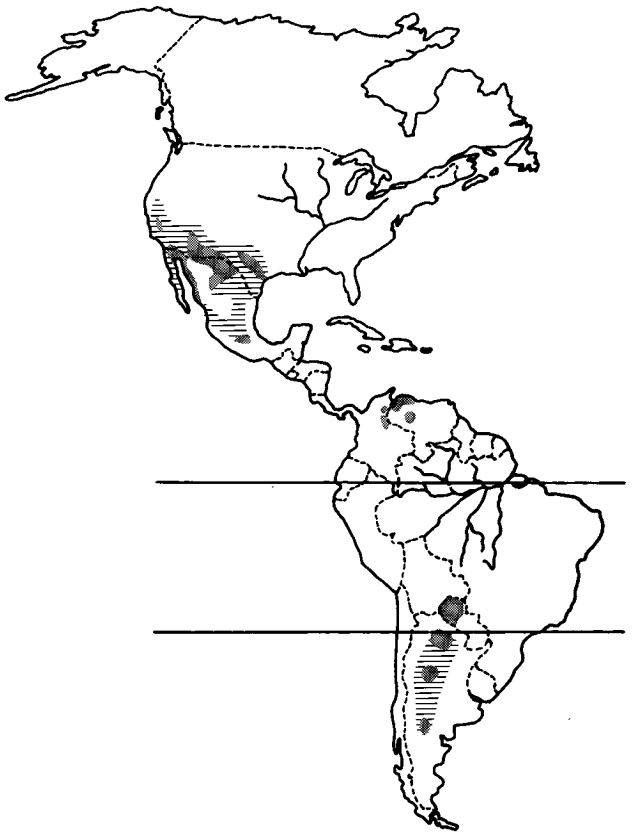

FIG. 13. Distribution of coccidioidomycosis endemicity in North, Central, and South America showing the high incidence in the southwestern United States. Reprinted from reference 54a with permission of the publisher.

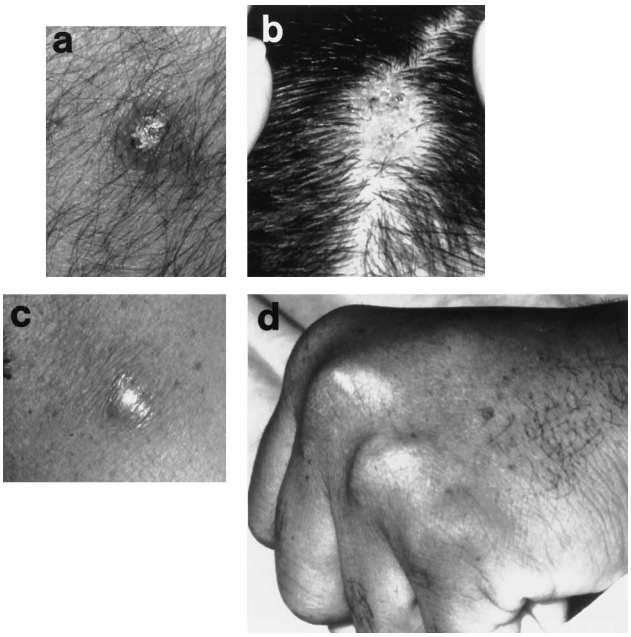

FIG. 14. Skin manifestations of coccidioidomycosis. (a and b) Crusted lesions; (c and d) nodular lesions.

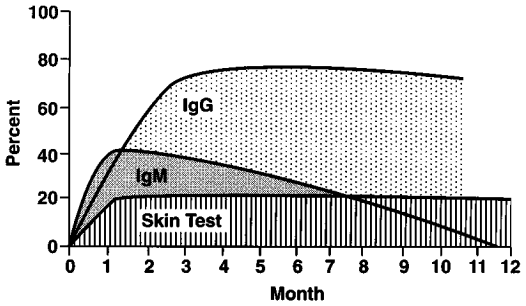

FIG. 15. Time course of skin test and serologic response to coccidioidomycosis in patients with AIDS. IgG and IgM, immunoglobulins G and M.

occurs in patients with AIDS (9). CD4 counts were <150/μl in most patients. The majority of patients (80%) presented with diffuse or focal pulmonary disease and 15% presented with extrapulmonary illnesses, although dissemination can be demonstrated at autopsy in most cases (9, 23). Common sites of extrapulmonary dissemination include lymph nodes, liver, skin, peritoneum, kidneys, thyroid, adrenal, heart, pituitary, esophagus, and pancreas.

Common complaints include fatigue, fever, weight loss, night sweats, chest pain, cough, and dyspnea. Most patients present with subacute illnesses lasting over a few weeks to several months. A variety of skin manifestations occur in about 5% of cases, as shown in Fig. 14 (23). These include papules, pustules, plaques, nodules, ulcers, abscesses, and proliferative lesions. Organisms are readily demonstrated in these cutaneous lesions. Bone and joint lesions are common and usually are unifocal. Patients with meningitis manifest headache, nausea, vomiting, and confusion. Their cerebrospinal fluid shows lymphocytic pleocytosis, as in other patients with coccidioidal meningitis (23).

Chest radiograms show diffuse reticulonodular infiltrates in 45% of cases and focal infiltrates in 35%. Nodules, cavities, adenopathy, and pleural effusions also may be seen (23). Diffuse infiltrates appear to be more common in patients with AIDS than in other patient groups (9), and this group of patients presents with respiratory failure and has a poor prognosis, with about 70% mortality.

Diagnosis

Diagnosis is made by fungal stain and culture of clinical material. Examination of sputum or bronchoalveolar lavage fluid is appropriate in patients with pulmonary manifestations (2). Spherules may be seen in respiratory secretions or tissues. Cultures are usually positive from the above sites, with growth apparent in 3 to 5 days in most instances. Blood cultures are positive infrequently (23). Organisms isolated from cultures can be rapidly identified as *C. immitis* by using nucleic acid probe technology.

Serologic tests, which are positive in >80% of cases, may give a clue to the diagnosis (Fig. 15) (23). Demonstration of elevated levels of antibodies to *C. immitis* has been the sole basis for diagnosis in a small proportion of cases in patients with AIDS (23, 25). First the immunoglobulin M antibody response to coccidioidin is detected by tube precipitation. The immunoglobulin G response, measured by complement fixation, follows the immunoglobulin M response and persists longer (48). Immunodiffusion is also widely used to detect antibodies to *C. immitis*. Immunodiffusion is simpler to perform than tube precipitation or complement fixation, making it a popular alternative to those tests (66). While newer tests for antibodies that use enzyme or radioimmunoassay techniques show promise as replacements for the older technologies, their accuracy remains uncertain. Tests for antigen detection have not yet proven useful diagnostically and are not available for clinical use (61).

Treatment

Response to treatment has been disappointing in patients with AIDS and diffuse pulmonary coccidioidomycosis. In one report, fewer than half of patients with diffuse pulmonary involvement responded to amphotericin B (9). In a retrospective review, five AIDS patients with coccidioidomycosis improved during treatment with fluconazole, suggesting that it may be useful in some patients (25). Amphotericin B has been recommended for patients with diffuse interstitial infiltrates (2), but fluconazole, 400 to 800 mg daily, is an alternative in those with mild illnesses (2). Itraconazole also has been used for treatment of coccidioidomycosis, inducing a response in 60% of patients without AIDS (31), but its activity in patients with AIDS has not been studied.

Fluconazole and itraconazole have been used to treat coccidioidal meningitis and may be alternatives to amphotericin B. Eighty percent of patients with coccidioidal meningitis responded to fluconazole treatment, often after failing to respond to amphotericin B (26). In another study, itraconazole was found to induce a positive clinical response in four of five patients (59).

Chronic maintenance treatment is needed to prevent relapse, an approach supported by recurrence or demonstration of active infection at autopsy following treatment (9, 23). Fluconazole, 200 to 400 mg daily, or amphotericin B administered weekly is recommended (2). Itraconazole also may be effective.

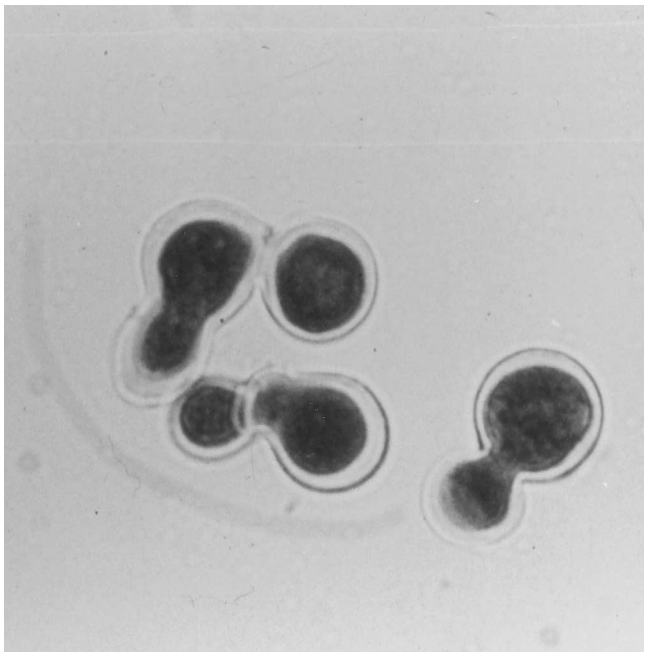

FIG. 16. Fungal stain showing typical *B. dermatitidis* yeast cells with thick refractile wall.

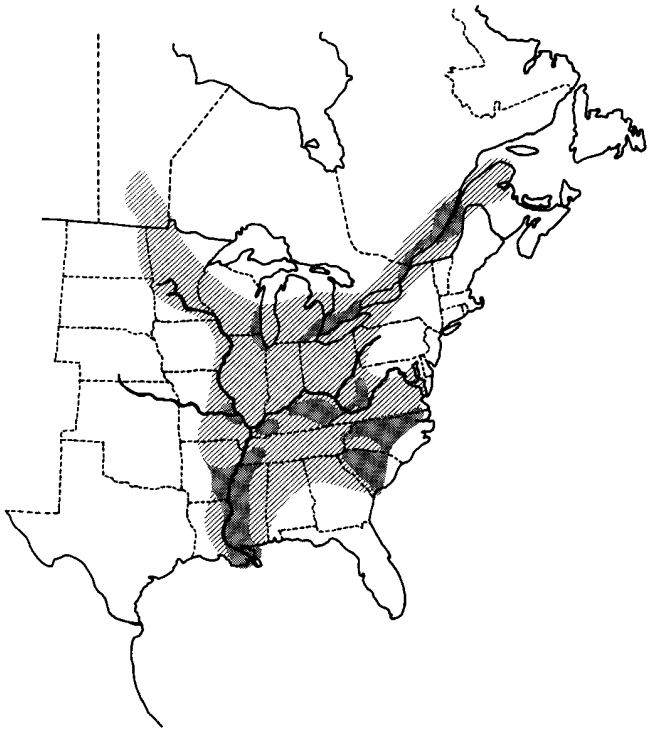

FIG. 17. Distribution of blastomycosis endemicity in North America. Reprinted from reference 54a with permission of the publisher.

Prevention

Studies using 200 mg of fluconazole daily prophylactically to prevent coccidioidomycosis in patients living in areas of high incidence are in progress. Until such studies have been completed, prophylaxis cannot be recommended (25). Travel to areas where coccidioidomycosis is endemic places patients at some risk. Patients should be advised to avoid these areas during periods of active outbreaks, for example, as reported in parts of southern California during the past several years. Patients should avoid the desert during the late summer and fall during windy periods when dusty conditions prevail and arthrospores are more likely to be airborne.

BLASTOMYCOSIS

Mycology

Blastomyces dermatitidis is a thermally dimorphic fungus producing mycelia with 2- to 10-μm, round to oval or pear-shaped conidia at 25°C and broad-based budding yeasts with thick refractile walls varying in size from 8 to 15 μm up to 30 μm in diameter at 37°C (Fig. 16). Like *H. capsulatum*, *B. dermatitidis* is an ascomycete and has a teleomorphic form, *Ajellomyces dermatitidis*. Growth of *B. dermatitidis* is favored by soil containing organic matter, acid pH, and moisture. Although not recognized as an opportunistic pathogen, cases have been described in patients with AIDS (49). Recent studies show that the incidence of blastomycosis in patients with impaired cellular immunity has increased during the past 15 years (32, 50).

Epidemiology

The organism may be found in microfoci enriched with animal excreta. Rare isolations from soil have occurred in samples from areas inhabited by farm animals and from beaver lodges or dams. The presence of decaying organic material appears to be required to support the sustained growth of *B. dermatitidis* in soil. Its geographic distribution overlaps that of *H. capsulatum* (Fig. 17). Cases have been reported in patients with AIDS in the midwestern and southeastern United States and in parts of New York and Canada which border the St. Lawrence River.

Pathogenesis

Disease is acquired by inhaling conidia, which cause local pulmonary infection often accompanied by extrapulmonary dissemination. As with other endemic mycoses, cellular immunity is important for defense against *B. dermatitidis* infection. Neutrophils are recruited first to sites of infection but lymphocytes arrive later, leading to pyogranuloma formation. Cellular immune responses, as measured by in vitro reactivity of circulating lymphocytes to *B. dermatitidis* antigens, may be demonstrated in immunocompetent patients. The importance of cellular immunity also has been established in animal models, which demonstrate that suppression of cellular immunity leads to progressive infection (8).

Clinical Findings

Most cases of blastomycosis in patients with AIDS have occurred in patients with CD4 counts below 200/μl. Clinical findings are more severe in patients with AIDS than in non-immunocompromised individuals. Patients present with localized pulmonary involvement or with disseminated disease, each occurring in about half of patients. Presenting symptoms in patients with pulmonary blastomycosis include fever, cough, dyspnea, chest pain, and weight loss. Patients with pulmonary blastomycosis had focal or diffuse infiltrates on chest radiograms. Bilateral nodules, cavities, and pleural effusions also may be seen.

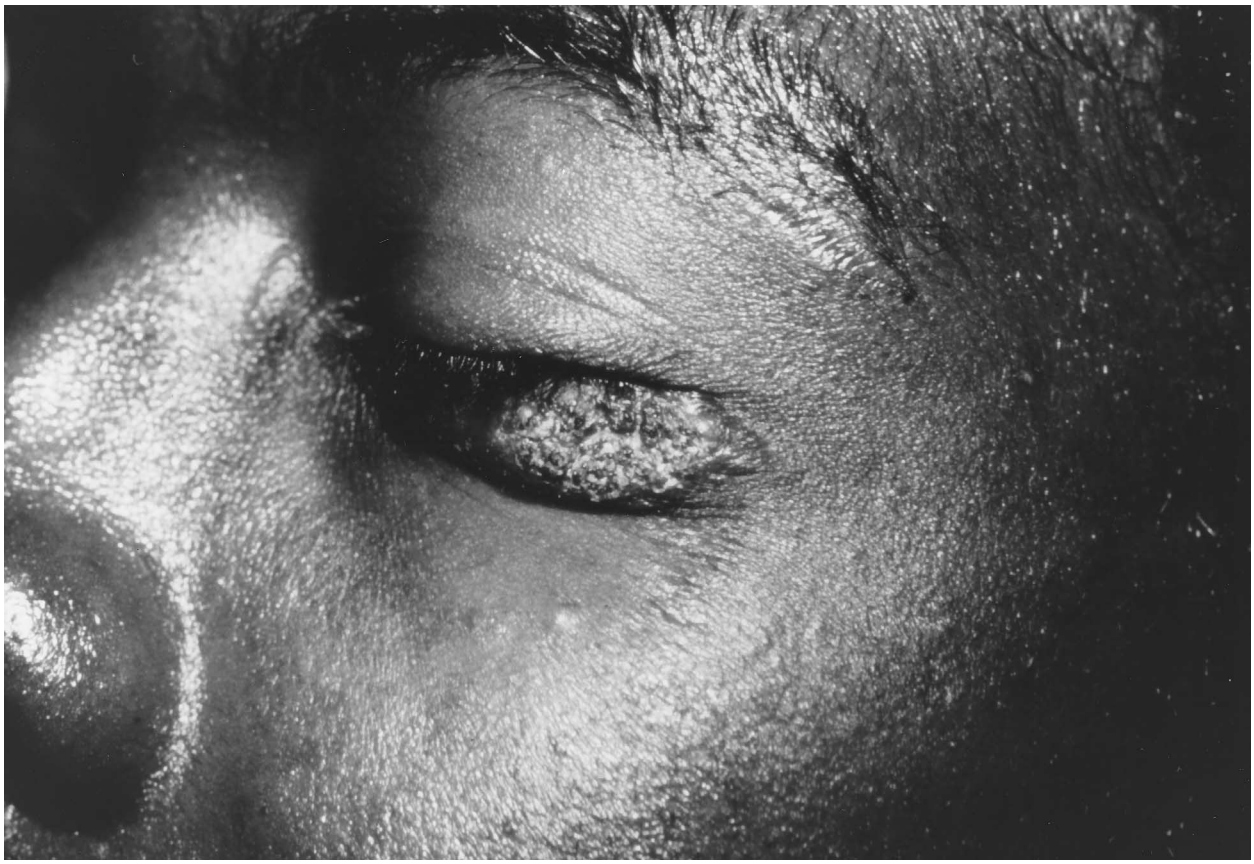

FIG. 18. Skin lesion in disseminated blastomycosis.

Widespread disseminated disease typically involves multiple organs. Patients have presented with clinical findings of septicemia, as seen with histoplasmosis. Cutaneous lesions (Fig. 18) are less common in patients with AIDS than in normal hosts, reported in 2 of 15 patients in a recent review (49). Central nervous system involvement manifested as meningitis or brain lesions is common (~40%). Other sites of dissemination include the spleen, liver, kidneys, bone marrow, lymph nodes, and thyroid in 10 to 25% of cases (49).

Diagnosis

Diagnosis is based on demonstration of organisms by culture or examination of clinical material, usually bronchoalveolar lavage fluid or lung biopsy material stained with fungal stains. Cultures are positive in over 90% of patients (49). *B. dermatitidis* was isolated most frequently from bronchoscopy specimens, cerebrospinal fluid or brain, skin, and blood. Of note is that fungal stains have been positive in most cases, thus providing a more rapid diagnosis than culture. Serologic tests for antibodies are typically negative and not useful for diagnosis of blastomycosis (49). Tests for antigen are not yet available, but a cross-reacting antigen may be detected in the *H. capsulatum* antigen assay. However, sufficient numbers of specimens from patients with disseminated blastomycosis have not been tested to determine the test sensitivity. Specimens of urine, blood, or other body fluids may be submitted for testing to the Histoplasmosis Reference Laboratory in Indianapolis.

Treatment

Amphotericin B is effective treatment for blastomycosis in patients with AIDS. Nine of 11 patients (82%) responded to such treatment (49). Ketoconazole, although usually effective in the immunocompetent host, is unsatisfactory treatment in patients with AIDS. Itraconazole is highly effective treatment of blastomycosis in the normal host (19) and should be useful in patients with AIDS.

These findings support the use of amphotericin B for induction treatment in patients with moderately severe or severe clinical manifestations. Itraconazole is a reasonable alternative for patients with mild disease. Relapse is common, supporting the need for chronic maintenance treatment to prevent recurrence. Itraconazole is a good choice for maintenance therapy (200 to 400 mg daily).

Prevention

The prevalence of blastomycosis in patients with AIDS is too low to justify prophylaxis. However, the pattern of endemicity of blastomycosis overlaps that of histoplasmosis. If antifungal prophylaxis or vaccination proves to be useful for prevention of histoplasmosis, blastomycosis also will be prevented because vaccines effective for prevention of histoplasmosis also may provide cross-protection against blastomycosis.

SUMMARY

Histoplasmosis and coccidioidomycosis are serious opportunistic infections in patients with AIDS who reside in areas of endemicity in the United States and Central and South America. Histoplasmosis occurs in 2 to 5% of individuals from areas of endemicity and in up to 25% of patients with AIDS in certain cities. Most cases of coccidioidomycosis have been reported from Tucson. Blastomycosis, although less common, also must be recognized as an opportunistic infection in patients with AIDS. Prompt diagnosis requires knowledge of the clinical syndromes and diagnostic tests as well as a high index of suspicion.

Diagnosis usually has been made by fungal stains or cultures. Serologic tests for antibodies are useful for diagnosis of histoplasmosis and coccidioidomycosis. Tests for antigen are helpful in establishing a rapid diagnosis in histoplasmosis. Histoplasmosis and blastomycosis respond well to antifungal treatment, but relapse is common without chronic suppressive therapy. Amphotericin B is highly effective and remains the treatment of choice for patients with severe clinical manifestations. Itraconazole is the preferred treatment for patients with mild clinical findings. Drug interactions are common with itraconazole and must be considered to avoid treatment failure because of inadequate absorption or rapid elimination of itraconazole and to avoid toxicities with other medications which are eliminated by hepatic metabolism using cytochrome P450 enzymes. Improvements in treatment are needed in coccidioidomycosis. Mortality remains high despite treatment with amphotericin B. Fluconazole or itraconazole could be used for mild cases and for chronic suppressive therapy. Research is needed to identify preventive strategies in patients at risk. These strategies may include use of prophylactic antifungal therapy or vaccination. Prophylactic studies evaluating fluconazole and itraconazole have been conducted and should provide information soon.

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