

Fungal Infection in HIV-infected Persons

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Infection with the human immunodeficiency virus (HIV) results in progressive deterioration in host immunity. Although HIV infection most consistently alters T-helper cell function, in reality the aberrations in immunity are potentially more global. Thus, defects in B-lymphocyte, neutrophil, and **monocyte/macrophage** function as well as in the modulation of immune function by various cytokines are now well-recognized as being associated with HIV infection and as contributing to the profound immunodeficiency seen in many infected persons (1-4).

Fungi are widely distributed throughout the environment. The lungs are the common portal of entry for **most** fungi into the human host. Multiple components of the normal host defense mechanism usually control **fungal** infections, thereby preventing local progression or dissemination. Experimental challenge to the lungs of laboratory animals with pathogenic fungi typi-

cally results in an acute neutrophil response followed by an influx of mononuclear cells (5). It appears that both cell types can kill fungi by oxidative and nonoxidative mechanisms, although certain fungi are more susceptible than others to killing by **neutrophils** (6). Acquired resistance to fungi probably reflects a complex **interaction** involving sensitized T lymphocytes acting as inducers of macrophages (7-9). In addition, antibody-dependent killing mediated by lymphocytes, monocytes, or neutrophils may be a particularly important factor in limiting the growth of some fungi (10). **Given** the role of these defense mechanisms, the abundance of fungi in our environment, and the spectrum of immune defects resulting from HIV infection, **fungal** disease would be expected to complicate HIV infection. Although pulmonary involvement with fungi accounted for a relatively small proportion of all pulmonary complications occurring over an **18-mo** period among HIV-infected persons at all stages of infection in one study (11), **fungal** disease at **all** anatomic sites accounted for over 20% of the AIDS-defining diseases reported to the Centers for Disease Control (CDC) between 1987 and 1988 (12). Moreover, that figure is an underestimate of the actual incidence of **fungal** disease among HIV-infected persons because those data only included initial AIDS-defining illnesses. Because most pulmonary **fungal** disease, for example, has not been considered AIDS defining, such disease is not reflected in the **CDC's** statistics.

Pneumocystis carinii, previously thought of as a parasite, is not considered a fungus by many authorities. Since treatment of this infection has been addressed by previous **ATS** statements, treatment of this organism will not be included in this statement.

CANDIDA INFECTIONS IN AIDS AND HIV INFECTION

Epidemiology

Infections with *Candida albicans* are extremely common in patients with AIDS and HIV infection. Oral candidiasis (thrush) is seen in virtually all patients at some time during the natural history of HIV infection (13, 14). The presence of oral **candidiasis** is a predictor for progression to AIDS (15). Esophageal **candidiasis** is the AIDS-defining illness in at least 14% of **HIV**-infected persons (16, 17). Esophageal candidiasis has also been reported rarely as a manifestation of acute HIV infection, a setting in which it has not generally been considered diagnostic of full-blown AIDS (18). Chronic, refractory vaginal candidiasis is common in women with HIV infection.

Clinical Manifestations

Oral candidiasis may involve the tongue, uvula, palate, and buccal mucosa. It takes two forms: early during the HIV infection there are white, exudative lesions, while further into the course of the disease, lesions may be erythematous and atrophic. Esophageal candidiasis is usually associated with odynophagia or **dysphagia** but may be asymptomatic and is usually accompanied by oral candidiasis (19). Endoscopy usually reveals typical white plaques on a friable erythematous mucosa and, on occasion, esophageal ulceration. Other opportunistic infections, such as **cytomegalovirus** or herpes virus, may give rise to identical symptoms. Moreover, a single patient may have multiple infections simultaneously.

In contrast to the high incidence of oral and esophageal candidiasis in HIV infection, the occurrence of disseminated candidiasis with candidemia or other organ involvement is rare. When candidemia is seen in HIV-infected patients, it usually occurs in patients receiving multiple antibiotics by indwelling catheters. Similarly, candidemia is seen in patients receiving bone marrow toxic agents for intercurrent infections or neoplasms complicating HIV infection. Although candidiasis of the trachea, bronchi, or lungs is considered diagnostic of AIDS, respiratory tract disease with invasive *Candida* organisms is unusual. Other sites of involvement, documented only as case reports, include the brain, meninges, eye, and gall bladder (20-23). The low frequency of disseminated *Candida* disease is in marked contrast to the high frequency of other fungal diseases in AIDS patients, such as cryptococcosis, histoplasmosis, and coccidioidomycosis.

The immunopathogenic explanation for this marked discrepancy in the site of *Candida* infections in patients with AIDS is not clear. The defect in cellular immunity characteristic of HIV infection predisposes to mucocutaneous *Candida* infections but is apparently less important for immune protection against dissemination of the *Candida* species, unlike other fungal pathogens. The role of the polymorphonuclear leukocyte in defense against infection with *Candida* is of the greatest importance, as indicated by the relatively common occurrence of disseminated candidiasis in neutropenic patients without defects in cellular immunity (24). Lastly, humoral immunity may have a specific role in preventing dissemination of *Candida* organisms in HIV infection. Antibody specifically directed against a 47-kD antigen of *C. albicans* is more common in HIV-infected patients than in other *Candida*-associated conditions, and the hypothesis is that this antibody, produced as a result of polyclonal B-cell activation, may limit the dissemination of *Candida* organisms in this setting (25).

Diagnosis

Diagnosis of oropharyngeal candidiasis usually presents no problems. The fungus is readily seen and cultured from scrapings of oropharyngeal lesions. Esophageal candidiasis is most often diagnosed presumptively, i.e., odynophagia and/or dysphagia in the presence of oral candidiasis. Barium esophagram usually reveals the typical "cobblestone" appearance. Discrete masses and ulcers may also be seen. The definite diagnosis is established by endoscopy with visualization of the characteristic raised plaque lesions and friable mucosa. Biopsy shows pseudohyphae. Care must be taken to examine the specimen for other pathogens besides *Candida*, such as herpes virus or cytomegalovirus, since multiple pathogen-induced lesions are common.

Treatment

Oropharyngeal candidiasis may be treated either locally with clotrimazole troches or with oral azole therapy. Occasionally, intravenous amphotericin B may be required to treat refractory infections. Although many experts favor oral azole therapy over local therapy, comparative studies have not shown superiority of oral azoles. In addition, local therapy may be associated with fewer side effects (26). Oral azole therapy may be ketoconazole or fluconazole, 100-200 mg daily. Ketoconazole's uncertain absorption in advanced HIV infection and the greater frequency of gastrointestinal side effects makes its use problematic. Recent reports have documented emerging resistance in *Candida* isolates from patients who have been treated with fluconazole for extended periods (27).

Esophageal candidiasis requires systemic therapy. In this setting, fluconazole is more effective than ketoconazole (28). Occasionally, patients will not improve with fluconazole therapy and intravenous amphotericin B is needed.

CRYPTOCOCCOSIS IN AIDS

Epidemiology

Cryptococcosis is the most common systemic fungal disease in HIV-infected persons. Studies indicate that 6-10% of this patient population with altered T-cell host defenses will develop cryptococcal disease (29). The central nervous system (CNS) is the most commonly involved organ in cryptococcosis, and meningitis is the most common clinical manifestation (29-31). Other involved organs are the lungs, eyes, skin, prostate gland, and skeletal system.

Clinical Manifestations and Diagnosis

Cryptococcal meningitis should always be considered in any HIV-infected person whose symptoms include acute or chronic headache and fever. In up to 30% of cases, headache or other CNS symptoms may be absent; in these patients, persistent, unexplained fever and malaise may be the only symptoms. Seizures, focal neurologic abnormalities, and obtundation or coma are noted in about one third of patients (29-31). Extraneural cryptococcal disease, including cryptococemia, pneumonia, and ulcerative skin lesions or umbilicated papules mimicking molluscum contagiosum, is present in 25-50% of cases (29-31).

The diagnosis of cryptococcal meningitis is based on a positive culture of cerebrospinal fluid (CSF) for *C. neoformans* and/or a positive latex agglutination test for cryptococcal antigen in CSF and serum (32). Serum antigen titers are often strikingly high (e.g., >1:10,000). The India ink preparation is positive in about 75% of cases. Importantly, the CSF formula may be unimpressive; that is, no or very few white blood cells, a normal protein, and a normal glucose, in contrast to the usual finding of an abnormal CSF formula with lymphocytic pleocytosis in non-AIDS patients with cryptococcal meningitis. As a result, in AIDS patients with meningitis, a common scenario is a normal CSF formula, accompanied by a positive culture, positive cryptococcal antigen test, and positive India ink (32).

Pulmonary cryptococcosis is highly variable in its manifestations. Roentgenographic findings of patchy segmental or interstitial pneumonitis, single or multiple nodules, or tumor-like masses mimicking carcinoma are most common (31, 33). Lymphadenopathy, cavitation, and pleural effusions are more common in HIV-infected patients than in non-HIV-infected individuals. Since cultures and wet preparations of expectorated sputum are positive for *C. neoformans* in less than 25% of cases, bronchoscopy with biopsy for both culture and histopathology is usually necessary for diagnosis. In some patients *P. carinii* may be a co-pathogen, contributing to the pulmonary disease. While tests of serum for cryptococcal antigen are often negative in non-HIV-infected patients, serum cryptococcal antigen tests are almost always positive in high titers in HIV-infected patients with cryptococcal lung disease. In every patient with proven pulmonary cryptococcosis, a lumbar puncture should be performed, whether evidence of CNS disease is apparent.

In patients with suspected cutaneous or osseous cryptococcosis, biopsy is the most definitive diagnostic test. Because the prostate gland may be a silent reservoir of cryptococcal infection in as many as 30% of HIV-infected patients and cryptococcosis, prostatic massage followed by collection of a midstream urine sample for fungal culture should be considered, especially in patients who relapse during or after therapy (34).

Therapy

Cryptococcal meningitis in AIDS patients is associated with significant morbidity and mortality. Even among patients receiving antifungal therapy, the mortality rate during the first 6 wk after diagnosis ranges from 10-20%. Moreover, the relapse rate if therapy is discontinued approaches 50-60% (29-31). Accord-

ingly, aggressive antifungal therapy is necessary and should consist of intensive primary or induction treatment to gain control of infection, followed by life-long maintenance or suppressive therapy in an attempt to prevent relapse.

For primary therapy in the majority of patients, **amphotericin B (AMB)** in a dose of **0.5–1.0 mg/kg** per day is the drug of choice. Although combination therapy with AMB and **flucytosine** is the preferred treatment regimen for cryptococcal meningitis in non-HIV-infected persons, there is controversy about the use of combination therapy in AIDS patients (29, 35, 36). In this population, flucytosine appears to be associated with a high incidence of drug-induced cytopenias, often superimposed upon preexisting bone-marrow suppression secondary to zidovudine, cytotoxic chemotherapy, and opportunistic infectious diseases. If flucytosine is administered, the dose should be approximately **100 mg/kg** per day; dosage adjustments should be based on weekly measurements of serum concentrations of flucytosine, plus results of renal function tests and complete blood counts. When serum flucytosine concentration assays are not readily available, many authorities caution against the use of this agent. The goal of primary therapy is to sterilize the CSF (i.e., conversion of cultures from positive to negative). While there are no data to provide guidelines about absolute minimum or maximum total doses of AMB as primary therapy, sterilization of the CSF in most patients is achieved by total doses ranging from **500–2,000 mg**.

Fluconazole, an antifungal triazole, offers an alternative to AMB as primary therapy (30). The recommended dose of fluconazole is **400 mg/d**. The advantages of fluconazole are: (1) good penetration into CSF (although there is no clear evidence that this is of any clinical benefit), (2) availability in both oral and intravenous formulations; and (3) lack of significant adverse effects. The major disadvantage of fluconazole is less rapid sterilization of CSF when compared with AMB. The efficacy of fluconazole in all prospective randomized clinical trials has been under 50%. Consequently, AMB should be preferentially administered to AIDS patients at high risk for death, such as those who present in an obtunded or comatose state, with a high baseline CSF cryptococcal antigen titer, and/or a low CSF white blood cell count ($<20/\text{mm}^3$) (30). Other therapeutic regimens for primary therapy of AIDS-associated cryptococcal meningitis have been advocated, including high dose fluconazole (**800 mg/d**) (37) itraconazole (38), and the combination of two oral drugs, fluconazole and flucytosine (39). Controlled trials of these various agents and combinations are currently under way.

Increased intracranial pressure is a major contributor to the mortality and morbidity of cryptococcal meningitis. The infection damages the subarachnoid villi responsible for reabsorbing CSF. Opening pressure should be measured in any lumbar puncture when cryptococcal meningitis is suspected. CSF may safely be removed to keep CSF pressure below 20 cm water. Some patients may require repeated LP to maintain CSF pressure levels below 20 cm water even as the infection is responding to therapy. Some patients will require a shunting procedure to stabilize CSF pressures.

Once primary therapy has halted progression of disease and sterilized the CSF, **all** AIDS patients with cryptococcal meningitis require chronic maintenance therapy (40). Two approaches have been used, namely, AMB, **1.0 mg/kg** given weekly, or oral fluconazole, **200 mg** given daily. Results of a joint NIAID AIDS Clinical Trials Group and NIAID Mycoses Study Group prospective multicenter comparative study indicate that oral fluconazole is associated with fewer relapses than AMB (2% versus **14%**, $p < 0.001$) (41). In addition, fluconazole is less toxic and better tolerated, resulting in better patient compliance. Accordingly, fluconazole is the recommended drug of choice for maintenance therapy, which must be continued for life (40, 41).

HISTOPLASMOSIS

Epidemiology

Progressive disseminated histoplasmosis (PDH) is a rare complication of infection with *Histoplasma capsulatum* in normal hosts. Immunocompromised persons living in the endemic areas for *H. capsulatum* are at increased risk for developing PDH (42, 43). The first report of PDH complicating the course of HIV infection was not published until 1983, after most of the other opportunistic infections associated with HIV infection had been described. Subsequent cases of PDH were described from the endemic areas for *H. capsulatum* followed by small series of patients from areas outside the endemic area for *H. capsulatum* among individuals who had lived in endemic zones previously (44–46).

The overall incidence of PDH in HIV-infected persons is variable from place to place. In Houston and Dallas, Texas, on the fringes of the endemic area for histoplasmosis, it is approximately 5% (46, 47). On the other hand, in Indianapolis, Indiana, in the heart of the endemic area, almost 27% of HIV-infected patients developed PDH (48). This is higher than the incidence of 6–10% of HIV-infected persons who develop cryptococcal meningitis in the United States (29).

Pathophysiology

PDH in HIV-infected individuals is either the result of reactivation of previous infection or progression to disseminated disease shortly after the initial infection. In patients from areas where histoplasmosis is not endemic but who had lived in endemic areas years before, PDH occurs as reactivation disease (49). The chest roentgenogram is normal in approximately a quarter of these patients, and findings compatible with a recent pulmonary infection, indicating primary disease, are not present (50). On the other hand, Wheat and colleagues (48) found an extremely high frequency of PDH among HIV-infected individuals from Indianapolis after a recent city-wide epidemic of histoplasmosis, suggesting progression of the primary infection. Thus, data support both pathogenic mechanisms.

Clinical Manifestations

The clinical presentation of PDH is similar to many other pulmonary and systemic infections occurring in HIV-infected individuals. In a recent clinical review of PDH complicating HIV infection, fever and weight loss were the most common symptoms, occurring in 75% and 50% of patients, respectively. Splenomegaly and lymphadenopathy occurred in 30% of patients, and hepatomegaly occurred in 26%. Routine laboratory examination showed anemia in 30%, leukopenia in 24%, and thrombocytopenia in 20%, all conditions frequently seen in HIV infection and in patients on zidovudine treatment. The chest roentgenogram demonstrated diffuse interstitial infiltrates in up to 70% of patients (49). These patients are more likely to have respiratory symptoms of cough or dyspnea than those with normal chest roentgenograms. Atypical presentations of PDH in patients with HIV include intestinal ulcers, with or without bleeding (51), intracerebral histoplasmosis (52), meningitis (52), skin lesions, and disseminated intravascular coagulation complicating an overwhelming infection (50). Some of these manifestations have a poor prognosis.

Diagnosis

Diagnosis depends on the rapid identification of the fungus from biologic material. The simplest and most readily available test is the examination of the peripheral blood smear. In a recent series, the test was positive in 12 of 26 patients (46%) and in 10 of the 12 positive, this test provided the initial diagnosis of PDH (47). The fungus is readily recovered from blood culture using

the lysis centrifugation technique, which should always be used. In the Indiana series, the blood culture from Indiana University Hospital was positive in 91% of the patients tested (50). Examination of the bone marrow is also helpful—the organisms are readily seen in periodic acid Schiff stained specimens, and culture is also frequently positive (49). In addition, examination of respiratory secretions or biopsy of skin lesions should be performed when indicated.

Standard serologic tests are also frequently positive. The combination of the immunodiffusion and complement fixation tests will be positive in about 80% of the patients (50). Unfortunately, these tests are time consuming and the results may not be readily available. Wheat and coworkers (53) reported the results of a radio-immunoassay for *H. capsulatum* polysaccharide antigen. The test was positive in the urine of 70 of 72 HIV-infected patients with PDH (53). The same test has also been used to follow patients and to detect relapses (54).

Treatment

Treatment of PDH in HIV-infected patients is difficult and a "cure" should not be expected. Relapse is common in the absence of continued antifungal therapy. Early series where continued antifungal suppression was not given showed rates of relapse of over 50% (49).

In the early days of the outbreak, the mainstay of treatment was AMB. One gram of AMB was administered rapidly, followed by continuous weekly infusions of 150 mg until a total dose of 2 g was reached. Following completion of primary therapy, weekly or biweekly infusions of 50-80 mg of AMB were effective in reducing the frequency of relapse (55). Ketoconazole is ineffective as initial therapy, and relapses have been reported when it has been used in doses of 200 mg/d for suppression (56).

Based on recently published information, 200 mg of itraconazole twice daily is a reasonable choice for primary therapy of mild to moderately severe cases, effective in 85% of such instances (57, 58). In more severely ill patients, an initial course of 500 mg of AMB is likely to produce more rapid stabilization of the patient, before switching to itraconazole. Chronic treatment with 200 mg of itraconazole twice daily is highly effective suppressive therapy, maintaining remission in 95% of cases (59). Fluconazole in doses of 200-400 mg daily is less effective than itraconazole as chronic maintenance therapy (60).

COCCIDIOIDOMYCOSIS

Epidemiology

Coccidioidomycosis, a fungal infection due to *Coccidioides immitis*, is endemic to large portions of the southwestern United States (61, 62). Life-threatening coccidioidal infection has been noted in patients infected with HIV, as has occurred in other persons with defects in cellular immunity (63-65). In Arizona, for example, coccidioidomycosis is the third most commonly reported opportunistic infection among HIV-infected individuals.

Clinical Manifestations

With clinically apparent coccidioidal infections in HIV-infected patients, CD, lymphocyte counts are typically below 250/mm³ (65). A chest radiograph revealing bilateral diffuse reticulonodular pulmonary infiltrates in association with fever and dyspnea is a common presentation of coccidioidomycosis during HIV infection. Survival from this form of infection has been poor (65, 66). Other patients may develop focal lesions beyond the chest, including skin, lymph nodes, liver, and meninges. In still others, however, coccidioidal infection may product nodules, patchy infiltrates, or cavities that may be indistinguishable from those which normally occur in immunocompetent persons (65). Milder

infections have usually occurred in patients with relatively higher CD, counts and before the occurrence of other AIDS-defining opportunistic diseases (65). Even so, accurate prediction of the course of coccidioidal infections in specific instances is difficult.

A prospective study (66) of the incidence of coccidioidomycosis conducted among 170 HIV-infected subjects living in the coccidioidal endemic area has provided the following observations: (1) active coccidioidomycosis is common among this group of patients; by 3.5 yr of follow-up, nearly 25% of the cohort had developed active disease; (2) the risk of developing active coccidioidomycosis was significantly associated with a CD, lymphocyte count < 250 and a diagnosis of AIDS; and (3) factors associated with prior infection with *C. immitis*, such as living in the endemic area for > 2 yr, a positive spherulin skin test, or a history of prior coccidioidomycosis, were not associated with the development of active infection. These data suggest that coccidioidomycosis among HIV-infected individuals living in the coccidioidal endemic area is a major opportunistic infection. Development of active disease is most closely associated with immunosuppression. While some cases represent reactivation of prior infection, others are clearly due to recently acquired infection. Identification of patients with prior coccidioidal infection will not necessarily assist in predicting which patients will develop active coccidioidomycosis.

Diagnosis

Diagnosis requires either recovery of the fungus in culture or visualization of the organism in biologic material or **histopathologic** sections. Identification of *C. immitis* by KOH stain or Papanicolaou stain of expectorated sputum is rarely positive. Cytologic identification of spherules either through Papanicolaou stain or Gomori methanamine silver stain of bronchoalveolar lavage fluid has been found to occur only in approximately 40% of cases of proven pulmonary coccidioidomycosis in HIV-infected patients. Culture of the same fluid is usually positive but requires 3-5 d of incubation before there is visible growth of the fungus. In cases where rapid diagnosis is required, such as in patients with diffuse, reticulonodular disease, transbronchial biopsy with cytologic examination of the tissue may be required (67). Standard serologic tests should be obtained on all patients in whom coccidioidomycosis is suspected. The test will frequently be positive in patients with active infection, and it is worthwhile to follow titers to monitor success of therapy.

Treatment

Therapy should be started on all HIV-infected patients with active coccidioidomycosis, and some form of maintenance therapy should continue for life.

Patients with diffuse pulmonary infiltrates should be treated with AMB. Although therapy with oral triazoles such as fluconazole or itraconazole may be efficacious (68, 69), experience is limited. Ketoconazole has been tried as initial therapy in some patients and often has proved unsatisfactory (65).

Patients with focal lesions beyond the chest, such as lymphadenopathy, skin lesions, osteomyelitis, or meningitis, vary in the degree of acuity of the infection and, therefore, in some patients alternatives to AMB may be more attractive. If lesions are progressing rapidly, AMB remains the most appropriate treatment. On the other hand, if the lesions are more indolent, fluconazole, itraconazole, or ketoconazole may be considered. Neither fluconazole nor itraconazole is approved by the FDA for treatment of coccidioidomycosis. In a recent study fluconazole therapy of coccidioidal meningitis demonstrated an overall response rate of 79%. Nine of these patients were HIV-infected and as a group their rate of response was similar. Other studies using oral azole therapy have also been encouraging (58, 70, 71).

Treatment of focal pulmonary lesions is less certain. Containment of the infection to a focal area may indicate that the patient's immune response is relatively intact. A recent prospective study from the endemic area showed no early deaths in the group with focal disease (66). It is therefore possible that therapy is less critical than in those with more widespread infection. Nevertheless, since the long-term prognosis is not certain, all patients, regardless of CD count, should be treated. Oral **fluconazole** is often recommended in such cases, primarily because of its predictable absorption and more favorable pharmacologic profile than other commercially available azole antifungal agents.

As epidemiologic studies have demonstrated, it is possible to have skin test evidence of prior coccidioidal infection and remain free of active coccidioidal disease (66). Thus, in the absence of symptoms, such patients need not be treated. Similarly, prophylactic use of antifungals based on either epidemiologic or immunologic data is of unknown value, expensive, and probably should not be instituted until additional data support this approach.

BLASTOMYCOSIS

Epidemiology

Blastomycosis is an uncommon disease complicating HIV infection. In addition to a few isolated case reports, only a single series of 15 patients with this combination has been reported (72). The spectrum of illness is wide, ranging from relatively indolent pulmonary infection to widely disseminated and fulminant disease with rapid death. While most recognized cases were reported from the endemic area of the fungus, several individuals have been described who developed clinical blastomycosis in areas outside the endemic area. While all these patients have resided in known endemic areas in the past, they were away from the potential sources of infection for several years. Thus, it appears that late reactivation of dormant foci of blastomycosis may occur when host immunity is diminished due to progressive HIV infection. Similar to the pattern seen in other endemic **mycoses**, blastomycosis was a late complication of HIV infection. The vast majority of patients had CD counts under 200 (72).

Clinical Manifestations

Although the clinical presentation of the reported patients has been variable, the lungs were involved in the majority. The radiographic pattern varied from segmental or **lobar** infiltrate to multiple nodules; widespread miliary pattern was the most common finding on chest radiographs. Similar to histoplasmosis and coccidioidomycosis complicating HIV infection, fulminant, diffuse interstitial or miliary disease, occasionally leading to adult respiratory distress syndrome, has a grave prognosis. In addition, CNS involvement was frequent (72).

Diagnosis

Diagnosis requires either recovery of the fungus in culture or visualization of the organism in biologic material or **histopathologic** sections. The most rapid test is visualization of the characteristic single budding yeast with doubly **refractile** wall from respiratory secretions or other material after 10% potassium hydroxide (KOH) **digestion** (73). Alternatively, respiratory secretions may be stained with the Papanicolaou method (74). Recovery of the organism from culture is not difficult but is time consuming. Standard serologic tests are not considered reliable. A negative test does not rule out blastomycosis, and a positive test does not establish the diagnosis either. However, when a serologic test is positive, every effort should be made to confirm the diagnosis by more invasive tests.

Treatment

Primary treatment of the infection should be with AMB. Since many of the patients are critically ill and the frequency of CNS involvement is high, primary therapy with azoles is suboptimal. Although the optimal dose of AMB is not established, a total dose of 1-2 g should be adequate to bring the infection under control (73). After an induction course of AMB therapy, chronic maintenance therapy with itraconazole is indicated. A definite regimen for chronic suppressive therapy of CNS blastomycosis has not been established. AMB or itraconazole may be tried. The role of fluconazole is uncertain in blastomycosis.

SPOROTRICHOSIS

Sporothrix schenckii, a tissue dimorphic fungus, causes frequent lymphocutaneous disease after percutaneous inoculation. The organism may also cause pulmonary, disseminated, and CNS disease on rare occasions. To date only a handful of *S. schenckii* infections have been reported as complications of HIV infection. Most of the patients had extensively disseminated disease, including the skin, joints, lungs, and bone marrow (75). Most patients received AMB as primary therapy, but in only one patient was this treatment apparently successful. While the new triazole, itraconazole, appears to be reasonably effective in **immunocompetent** patients (76, 77), its use in HIV-infected individuals has been limited (78). Treatment with AMB should be used for patients with life-threatening disease or CNS infection.

ASPERGILLOSIS

Epidemiology and Pathophysiology

The relationship between infections with *Aspergillus* species and HIV-infected patients is difficult to define. In the initial definition of AIDS published by the CDC in 1983, *Aspergillus* species infection was included as an AIDS-defining condition. Subsequent revisions of AIDS-defining guidelines by CDC (17), however, deleted *Aspergillus* species infections, since the number of infected and reported patients were small. Moreover, the accepted pathogenesis of invasive aspergillosis does not involve **cell-mediated** immunity but rather is associated with depletion of neutrophils and monocyte/macrophages (79).

Recent reports, however, again focused on *Aspergillus* species infection among HIV-infected patients (80-84). This association appears especially common among individuals who have previously noted risk factors for *Aspergillus* species infections: granulocytopenia or administration of glucocorticoids or broad spectrum antimicrobial agents (81-83). While the majority of HIV-infected patients with aspergillosis fall into these risk groups, a growing number of patients are reported without any recognizable clearly defined risk factors (80, 81).

Clinical Manifestations and Diagnosis

The clinical manifestations of *Aspergillus* species infections depends upon the extent of the disease and the organs involved. The lung is involved in the majority of patients, either **as** the sole organ or as part of the disseminated infection. CNS, heart, kidney, paranasal sinuses, and the skin may be involved alone or in combination (81). Recently, endobronchial-obstructing aspergillosis with mucoid impaction was described; in certain patients an ***Aspergillus*-containing** pseudomembrane is also seen within the bronchial lumen. Tissue invasion may follow with the formation of ulcerative or plaque-like lesions (85).

The diagnosis of aspergillosis requires the documentation of tissue invasion of biopsy specimens or recovery of the fungus from otherwise sterile sites. Recovery of *Aspergillus* species from respiratory secretions is common in HIV-infected patients, and

most such patients do not appear to have recognizable *Aspergillus* infection (82). Nevertheless, recovery of *Aspergillus* species in HIV-infected patients with a compatible pulmonary illness and no other recognizable infectious cause should raise the possibility of *Aspergillus* infection.

Treatment

It is difficult to make any authoritative statements about the treatment of *Aspergillus* species infection in HIV-infected patients. While the majority of patients were treated with **AMB**, the results of treatment were poor (8-82). Itraconazole, the most promising of the antifungal azoles against *Aspergillus* species, has been used with some success (86). At the present time, it appears that early diagnosis and prompt treatment with **AMB** represents the best approach. The role of itraconazole will require further delineation.

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