Fungal Infections of the Lung
Anke V. Jacobs, M.D., and Howard L. Leaf, M.D.

Introduction
The incidence of the endemic dimorphic fungal infections of the lung (histoplasmosis, coccidioidomycosis, and blastomycosis) has seemingly increased over the past several decades in the United States [1], although concrete epidemiologic data supporting this perception had been lacking. Some data addressing this issue have recently been published. For example, a report from the Centers for Disease Control and Prevention [2] summarizes trends in incidence rates of coccidioidomycosis in Arizona, and another article sheds some light on the epidemiology of blastomycosis in northeast Tennessee [3].

Of the opportunistic mycoses that may affect the lung, cryptococcosis has been seen at a higher incidence, largely owing to the epidemic of HIV infection. The greater incidence of aspergillosis is due largely to the increasingly prolonged maintenance of critical ill patients, to chemotherapy and radiation therapy for malignancy, to other immunosuppressive drugs, and to the widespread use of antibiotics [4••].

Each of these most common mycoses is reviewed. Many newer drugs are currently under investigation and are discussed with the individual fungi they affect.

Histoplasmosis
Approximately 90% of persons infected with Histoplasma capsulatum are asymptomatic or have an illness so mild that they do not seek medical attention. Depending on the inoculum size and whether infection results from primary exposure or reexposure in a previously immune host, the incubation period ranges from 3 to 21 days. A heavy inoculum of H. capsulatum can cause acute pulmonary infection in an otherwise healthy host [5]. The risk of high-inoculum exposure was demonstrated in an immunocompetent patient in Kentucky who was exposed to such an inoculum and developed a severe pulmonary infection [6]. Data from a Mexican study indicate that there may be a genetic risk factor (HLA-22) for pulmonary histoplasmosis [7].

A definitive diagnosis of histoplasmosis requires isolation and identification of the organism by cultures, histologic examination, and antibody and antigen detection. The organism is readily seen in macrophages with the use of either a silver or a periodic acid–Schiff stain. Histoplasma may be isolated from blood, bone marrow, respiratory tract secretions and other sites, although it may take up to 4 weeks to obtain positive cultures. The best single serologic test is measurement of the Histoplasma polysaccharide antigen (HPA) level [8••]. This test has a high sensitivity (95%) and specificity (98%). Both urine and serum should be tested [9], the better performing diagnostic test is the urinary antigen [10].

Itraconazole has been used successfully in pulmonary, non–life-threatening histoplasmosis, including chronic cavitary pulmonary disease and disseminated non-meningeal histoplasmosis, and for prevention of relapse in patients with AIDS with disseminated histoplasmosis (Table 1) [11]. The recommendation is for 200 mg in a daily oral dose for 9 months. Fluconazole has been compared to itraconazole in recent trials and found to be only moderately effective in the treatment of histoplasmosis and should be reserved for patients who cannot tolerate itraconazole, given its intrinsically poorer activity [12]. Patients with life-threatening histoplasmosis (ie, impending respiratory failure) need to be started on amphotericin B. They may benefit from a short course of amphotericin B (total dose, 500–1000 mg) [13], at doses of 0.5 to 1.0 mg/kg/day IV for 1 week, followed by 0.8 mg/kg/day every other day [13]. Some advocate concomitant corticosteroid therapy.

In chronic (cavitary) pulmonary histoplasmosis some success has been achieved with itraconazole 200 mg orally twice a day for 6 to 12 months. In progressive disseminated disease in the immunocompetent host, itraconazole at 400 mg orally twice a day for 6 to 12 months may be considered as first line therapy, if life-threatening disease is not present. Progressive disseminated histoplasmosis is the most common form of the disease among HIV-infected patients. In HIV-infected patients, treatment is not curative and suppressive therapy is needed as relapses are common.

Fungi, both endemic and opportunistic, continue to be recognized as increasingly frequent pulmonary pathogens. Better appreciation of their epidemiology and clinical course, as well as clarification of the roles of the newer triazoles and lipid formulations of amphotericin B in treatment, have occurred within the past few years. Both endemic and opportunistic fungal pulmonary pathogens are reviewed, with emphasis on recent therapeutic advances.
with the cessation of treatment. If, in such patients, disseminated disease is mild, the patient may be treated initially with itraconazole 300 mg orally twice a day for 3 days, followed by 200 mg orally twice a day for 12 weeks [14]. A recent study has also shown fluconazole at doses of 800 mg orally daily over 12 weeks to give a reasonable response [15•]. In moderate to severe disseminated histoplasmosis, amphotericin B should remain the first line of treatment with a total dose of 35 mg/kg followed by itraconazole 200 mg twice daily indefinitely. With itraconazole

**Table 1. Therapeutic guidelines for selected pulmonary mycoses**

| Pathogen                | Therapy                                                                                                                                 |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| **Histoplasma capsulatum** |                                                                                                                                                             |
| Mild to moderate disease | Itraconazole 200 mg qd†                                                                                                                         |
| Severe disease           | Amphotericin B 0.5–1.0 mg/kg/d                                                                                                                     |
| Chronic disease          | Itraconazole 200 mg bid or Ketoconazole 400–800 mg qd                                                                                          |
|                         | Amphotericin B to a total dose of 35 mg/kg                                                                                                      |
| In HIV—mild disease      | Itraconazole 300 mg tid x 3 days, then 200 mg bid                                                                                               |
| In HIV—moderate to severe disease | Amphotericin B to a total dose of 35 mg/kg, followed by itraconazole 200 mg qd for life                                                   |
| Prophylaxis in endemic areas | Itraconazole 200 mg qd                                                                                                                          |
| Blastomyces dermatitidis |                                                                                                                                                             |
| Mild to moderate disease  | Itraconazole 200–400 mg qd or Ketoconazole 400–800 mg qd                                                                                       |
| Severe disease           | Amphotericin B 0.5 mg/kg qd                                                                                                                        |
| High relapse rate in HIV, chronic suppressive therapy | Itraconazole 200 mg bid                                                                                                                     |
| Coccioides immitis       |                                                                                                                                                             |
| Mild to moderate disease  | Fluconazole 400–800 mg qd or Itraconazole 200 mg bid or Amphotericin B 0.6–1.0 mg/kg qd (total dose 2.5 g)                                       |
| HIV prophylaxis in endemic areas if CD4 <50 | Fluconazole 200 mg qd                                                                                                                           |
| Cryptococcus neoformans  |                                                                                                                                                             |
| Moderate to severe disease | Amphotericin B 0.5–0.8 mg/kg/d +/- flucytosine; when clinical response seen, complete course with fluconazole or Amphotericin B alone to total dose of 2–3 g |
| In HIV                  | Fluconazole 400 mg daily (for mild disease) or Liposomal amphotericin, or amphotericin B plus flucytosine, or amphotericin B alone to total dose of 2.5 g or Fluconazole 400 mg qd (for mild disease) |
| Life-long suppression therapy, where indicated | Fluconazole 200 mg qd or Amphotericin B IV weekly or Amphotericin B 1.0–1.5 mg/kg qd (total dose 2.5 g) or Itraconazole loading dose 300 mg po bid x 3 days, then 200 mg po bid for 1 year or Lipid formulation amphotericin B (ABLC, ABCD, liposomal amphotericin B) |
| Aspergillus species      |                                                                                                                                                             |
|                         | Amphotericin B 1.0–1.5 mg/kg qd (total dose 2.5 g) or Itraconazole loading dose 300 mg po bid x 3 days, then 200 mg po bid for 1 year or Lipid formulation amphotericin B (ABLC, ABCD, liposomal amphotericin B) |

*See text for details (recommendations are for nonmeningeal localized pulmonary disease).
†No therapy is indicated for mild disease.
ABCD—amphotericin B colloidal dispersion; ABLC—amphotericin B lipid complex; bid—twice a day; po—orally; qd—every day; tid—three times a day.
suppressive therapy 200 mg daily fewer than 5% of patients experience a relapse after an average of 87 weeks of therapy [16•].

MK-991 (L-743,872) has been used in mice to treat for histoplasmosis and was shown to be protective in immunocompetent mice. This suggests that MK-991 may be appropriate for clinical development in histoplasmosis (Table 2) [17].

The patients response to therapy may be followed by declining serum and urine *H. capsulatum* var. *capsulatum* polysaccharide antigen (HPA), which can also be useful in assessing relapse.

The immunocompromised host would greatly benefit from a vaccine. Studies focusing on vaccination with recombinant heat shock protein 60 from *H. capsulatum* have shown it to protect mice against pulmonary histoplasmosis [18].

**Table 2. Newer antifungal agents**

| Antifungal agents                  | Recent reports of activity demonstrated against                                      |
|-----------------------------------|----------------------------------------------------------------------------------------|
| Azole derivatives                 | Aspergillus species                                                                    |
| Sertaconazole                     | Aspergillus species, Coccidioides immitis                                               |
| Bifonazole                        | C. immitis                                                                              |
| Voriconazole (UK-109-496)         | Aspergillus species, Cryptococcus neoformans                                           |
| SCH 56,592                        | Aspergillus species                                                                     |
| UR-9,751, UR-9,746                 | Aspergillus species, Candida species                                                    |
| U9R,825                            | Aspergillus species, Histoplasma capsulatum, Candida species, not C. neoformans         |
| ER-30346                           | Blastomyces dermatitidis                                                                |
| SCH 39,304                         | *H. capsulatum*                                                                         |
| SCH 42,427                         | Aspergillus species, C. neoformans, Candida species                                     |
| TAK-182                            | Aspergillus species                                                                     |
| Echinocandins                      |                                                                                         |
| MK-0991 (L-743,872)               | Aspergillus species                                                                     |
| LY 303366                          | Aspergillus species, Candida species                                                    |
| Pneumocandins                      | Aspergillus species, Histoplasma capsulatum, Candida species, not C. neoformans         |
| L-743,873                          |                                                                                         |
| Nihokomycins                       | Blastomyces dermatitidis                                                                |
| Nihokomycin Z (SP-920704)          | *H. capsulatum*                                                                         |
| Pradimicin-benaminocinns           | Aspergillus species, C. neoformans, Candida species                                     |
| Compounds in early development     |                                                                                         |
| Allylamines                        | Aspergillus species                                                                     |
| Terbinafine (Lamisil-SF86-327)     |                                                                                         |
| N afilin                           |                                                                                         |
| Thiocarbamates                     |                                                                                         |
| Tolnaftate                         |                                                                                         |

Blastomycosis

Blastomycosis is a relatively uncommon disease, even in the endemic regions in the United States, such as the upper midwestern, south central, and southeastern areas. The disease is caused by inhalation of airborne spores from *Blastomyces dermatitidis*, a dimorphic fungus found in soil. The prevalence of the disease is not precisely known because of the lack of an accurate screening test, such as a skin test antigen. A previous study from Wisconsin [19] and a recent study from northeast Tennessee [3] indicate that there has been a significant increase in cases of blastomycosis. In Tennessee the increase in incidence, quadrupling from 1988 to 1995, was found to be coincident with major new construction in the area that disrupted the top soil layer and allowed for aerosolization of spores. Another recent report, however, indicated that in a highly endemic area in Wisconsin, the mean annual incidence of human blastomycosis appears to have remained stable over the past 13 years [20].

The clinical course and symptoms are quite variable [21] and range from asymptomatic, to acute, subacute, or chronic pulmonary disease, as well as acute lung injury [22], which rarely occurs, but produces an illness with serious morbidity and an estimated 50% mortality. Acute lung injury, and occasional adult respiratory distress syndrome (ARDS), may occur even in the immunocompetent host [23].

Although blastomycosis occasionally infects patients with underlying immunosuppression, this is much less frequently seen than in the other endemic mycoses. Nevertheless, it has become an increasingly recognized serious infection in the immunocompromised host in recent years. It has been reported in patients with abnormalities of T-cell function such as those with AIDS, transplant recipients, and patients with long-term glucocorticoid use, hematologic malignancy, pregnancy, and other conditions. Clinically, the disease in the immunocompromised patient is potentially much more severe and is characterized by dissemination, frequently affecting the central nervous sys-
ARDS and mycotic pulmonary involvement are common complications encountered in the immunocompromised host, and mortality exceeds 30% [24]. In patients with AIDS, it has been reported in those with CD4 counts less than 200 cells/mm³. Frequently, AIDS patients experience relapses posttreatment.

Because blastomycosis is relatively uncommon and has such diverse presentations, it is often not considered in the differential diagnosis. A positive culture is considered the gold standard for diagnosis [25]. The organisms may not grow for up to 30 days, however. Occasionally, B. dermatitidis can be identified by direct microscopic examination of the characteristic broad-based budding yeast forms of wet, unstained clinical specimens such as sputum and secretions, or by special histopathologic stains. B. dermatitidis can also be identified early using DNA probes [25]. At present, no serologic or antigen detection method with adequate sensitivity and specificity or skin test is available.

Prior to the development of the azoles, amphotericin B was the drug of choice in severe disease. A study comparing in vitro susceptibilities of B. dermatitidis to ketoconazole, itraconazole, and fluconazole clearly showed that itraconazole was the most active of this group against B. dermatitidis, whereas fluconazole was least active [26]. In acute disease, the patient may be observed if clinical improvement is noted, if not, treatment with itraconazole 200 mg po bid for 6 months may be begun. If itraconazole cannot be tolerated, ketoconazole at doses of 400 to 800 mg orally every day may be substituted. Ketoconazole has been used successfully in non-life-threatening disease, but because of superior efficacy and fewer side effects, itraconazole has largely supplanted ketoconazole for this indication. In acute disease with respiratory failure, amphotericin B should be the first line of treatment. A daily dose of 0.5 mg/kg/day to a total dose of greater than 1.5 is recommended [10]. Trials with fluconazole have shown that daily doses of 400 mg to 800 mg for at least 6 months is effective therapy for non-life-threatening blastomycosis [27]. In the normal host, chronic blastomycosis may be initially treated with itraconazole 200 mg orally twice a day for 6 months or, alternatively, ketoconazole 400 to 800 mg orally every day.

In the immunosuppressed patient, treatment may begin with amphotericin B and be changed to itraconazole 200 mg orally twice a day for 6 to 12 months after clinical improvement is noted. In HIV-infected patients, owing to the high relapse rate, especially in those with AIDS, it seems reasonable to administer chronic suppressive therapy with itraconazole 200 mg orally twice a day to prevent relapse [24].

With regard to investigational drugs, the efficacy of nikkomycin Z against experimental pulmonary blastomycosis has been reported. In vitro, nikkomycin Z showed good activity against B. dermatitidis. The efficacies of various treatment durations and doses of nikkomycin Z were compared with those of itraconazole and amphotericin B. The result showed that 100% survival was achieved with all nikkomycin Z doses. In addition, nikkomycin Z and amphotericin B, but not itraconazole, reduced infection as compared with controls. Nikkomycin Z given orally appeared to be well tolerated and could result in biologic cure [28•].

Besides new antifungal agents, vaccines are being explored. It has been observed that humans infected with B. dermatitidis develop strong immune responses to the yeast surface adhesin WI-1. A study has looked at the immunogenicity of WI-1 and the ability of anti–WI-1 immune responses to protect against lethal pulmonary infections in mice [29]. The results suggest that administering WI-1 increases antibody and cell-mediated immune responses, which enhances resistance against pulmonary infections with B. dermatitidis in mice. Further investigation of mechanisms of vaccine-induced resistance is indicated.

Coccidioidomycosis

The incidence of coccidioidomycosis in the southwestern United States has risen sharply over the past decade, mainly because of environmental and demographic changes [30]. A widely reported example of an environmental exposure occurred following the Northridge, California earthquake in 1994, which resulted in a significantly increased risk for developing acute coccidioidomycosis in proximate areas following the event [31••]. In Arizona between 1990 and 1995, the number of reported cases of coccidioidomycosis increased by 144%. Moreover, persons over the age of 65 years and persons with HIV infection were disproportionately affected. Possible explanations included weather patterns and increasing immigration to the region of a more susceptible older population not previously exposed to coccidioidomycosis and with underlying medical conditions [2].

Cases of coccidioidomycosis have also been reported with increasing frequency from atypical locales, as in a report from Japan, where the patient had worked as a cotton mill worker [32] or as in an imported case in Hungary [33]. Cases of coccidioidomycosis complicating AIDS are being described more frequently in the endemic areas of the United States. It is the third most commonly reported opportunistic infection in AIDS. In a recent report, one group examined genotypes of Coccidioides immitis and discovered significant differences in the allele frequency between three populations of C. immitis studied in California, Arizona, and Texas. This would indicate that the increase seen in coccidioidomycosis in certain areas is due to the particular C. immitis in that region and not to a novel introduced strain [34].

Extrapulmonary complications are uncommon. However, coccidioidomycosis may disseminate and cause disease in skin, bone, and meninges among other sites [35]. Reports of C. immitis causing septic shock have also been reported [36•]. The risk for disseminated coccidioidomycosis is higher among men, within certain ethnic groups, in
pregnancy, and in the immunocompromised host. The differences in ethnic groups may be attributed to a gene or genes that increase the susceptibility to infection [35]. Studies in inbred strains of mice have shown that interleukin-10 is consistently associated with susceptibility to infection with C. immitis [37].

Coccidioidomycosis has been observed to be particularly severe in patients with AIDS or organ transplants. A study from UCLA [38] quantified the morbidity and mortality of coccidioidomycosis in liver transplant patients. The median time of onset for infection after transplantation was 8 weeks, and 50% of patients died. Maintenance therapy is required in the survivors. In a group of HIV-infected patients, overall mortality was 60% [39].

As most patients with progressive disease have a productive cough with mucopurulent sputum, a rapid direct diagnosis of coccidioidomycosis can often be made by visualization of the organisms in sputum. C. immitis grows relatively quickly on appropriate culture media and can be quickly identified by DNA hybridization testing or exoantigen testing. If cultural recovery of the organisms is not successful, bronchoscopy, transbronchial biopsy, thoracoscopic biopsy, or open-lung biopsy may be needed to make the diagnosis. Cultures of core needle biopsies are, however, insensitive in the detection of specific microorganisms [40]. Serologic testing is extremely valuable in establishing the diagnosis. An IgM antibody to coccidioidin is measured by tube precipitin, immunodiffusion-tube precipitin, IgM enzyme-linked immunosorbent assays (ELISAs), or latex agglutination. These tests show positive results early in the course of the illness. IgG is measured by complement-fixation (CF), IgG ELISAs, or immunodiffusion CF. The complement-fixing antibody is quantified and appears only in low titer, if at all, in early disease, but in high titer in most patients with disseminated disease.

The majority of patients with acute primary infection recover without therapy. Patients with severe primary disease should receive therapy, however. Amphotericin B has been the cornerstone of treatment of coccidioidomycosis and is still considered first-line treatment in severe progressive pulmonary disease, as well as in disseminated and severe meningeal disease. The azoles, in particular fluconazole and itraconazole, have offered alternatives to the frequently poorly tolerated amphotericin B [35]. A recent report of a Chinese man with disseminated coccidioidomycosis treated with amphotericin B lipid complex (ABLC) represents one clinical success [41]. Further evaluation of therapy with ABLC is needed. Fluconazole at doses of 400 to 800 mg orally every day for a duration of 12 to 18 months can be used to treat acute pulmonary disease as well as extrapulmonary disease and mild-to-moderate meningeal disease. A problem encountered with treatment of coccidioidomycosis is the relatively high relapse rate after apparently successful treatment [42]. All HIV-infected patients with coccidioidomycosis should have treatment continued for life, preferably with fluconazole or, alternatively, itraconazole. Primary prophylaxis in HIV patients living in endemic areas with a positive skin test result is not recommended unless the CD4 count is less than 50 cells/mm³. These patients should receive either fluconazole 200 mg orally every day or itraconazole 200 mg orally every day [43].

Two new azole derivatives, UR-9746 and UR-9751, have been shown to reduce C. immitis infection in the spleens, lungs, and livers of treated mice. Neither compound demonstrated any notable toxicity and, on a milligram-per-kilogram of body weight basis, both were at least 10-fold superior to fluconazole in prolonging survival and clearing C. immitis infection [44]. The triazole SCH56592 has been shown in trials against disseminated murine coccidioidomycosis to be superior, at high doses, to fluconazole and itraconazole in reducing colony-forming units in the spleen, liver, and lung, and in cures of surviving mice. Neither fluconazole or itraconazole was able to effect cure in survivors. Apparently, SCH56592 has potent in vivo activity against C. immitis [45].

Vaccines in animal models are being investigated. A whole-spherule vaccine, which is protective against the lethal challenge of laboratory animals with C. immitis, was fractioned and yielded a soluble, subcellular fraction termed the 27K vaccine. This vaccine, in one report, was able to protect mice against lethal intranasal and intravenous challenge with C. immitis [46]. Another vaccine under investigation is the recombinant protein, proline-rich antigen (PRA) of C. immitis. Immunized mice challenged intraperitoneally with virulent C. immitis had greatly reduced fungal burden in lung and spleen compared with control animals [47].

**Aspergillosis**

Aspergillus species are responsible for four types of pulmonary disease, namely allergic bronchopulmonary aspergillosis (ABPA), aspergillosis, chronic necrotizing pulmonary aspergillosis (CNPA), and invasive aspergillosis (Fig. 1) [48]. There has been a substantial increase in the number of cases of invasive aspergillosis found at autopsies. In Frankfurt, Germany, a 14-fold increase in the number of cases between 1978 and 1992 was documented. The reasons for this increase were the advent of AIDS, new intensive chemotherapy for solid tumors and hematologic malignancies, an increase in the number of solid tumor recipients, and immunosuppressive regimens for autoimmune diseases [49••]. Patients with HIV infection have an increased frequency of invasive aspergillosis and their prognosis, despite aggressive antifungal treatment, remains dismal [50]. Cases of invasive aspergillosis in patients with only chronic obstructive pulmonary disease as their underlying defect have been described [51].

The lack of sensitivity of diagnostic procedures delays the time of diagnosis of invasive aspergillosis. Early diagnostic tests are needed, and presumptive antifungal therapy among high-risk patients is mandatory [52].
Demonstration of Aspergillus by both culture and microscopic examination in tissue provides a clear diagnosis. Although repeated isolation of the organism in culture may support the diagnosis, confirmation requires histologic demonstration of tissue invasion by typical septate acute-angle-branching hyphae. Serology is of limited value, but recent work to demonstrate antigens appears promising. A recent study compared the latex agglutination test to a new sandwich ELISA in patients with histologically proven invasive aspergillosis and found that on average the antigen ELISA gave positive results faster and was positive in all patients, as opposed to the latex test, which gave positive results in five of six patients [53].

In the correct clinical setting, CT findings frequently suggest a specific diagnosis [54]. Since 1991, thoracic CT scans at one center were systematically performed in febrile neutropenic patients with pulmonary infiltrates. This approach allowed the recognition of a suggestive CT halo sign in 92% of patients, compared with 13% before this date, and the mean time to diagnosis of invasive pulmonary aspergillosis was reduced from 7 days to 1.9 days [55].

Although corticosteroids are the mainstay of therapy in ABPA, itraconazole has been used both as monotherapy and as an adjunct to therapy. A recent report described one successful use of itraconazole. Although the patient suffered two relapses, the symptoms subsided without corticosteroid therapy [56].

Medical management of invasive pulmonary aspergillosis is often inadequate in the immunocompromised host. In one series it was shown that surgical resection of invasive pulmonary aspergillosis was able to clear Aspergillus infection in 69% of the patients and is an effective form of therapy in a properly selected patient population [57]. Intravenous amphotericin B remains the drug of choice for invasive aspergillosis. However, the response remains poor in severely immunocompromised patients. Recommended doses of 1 to 1.5 mg/kg/day are indicated, to a total dose of 2.5 g. A study from the National Institutes of Allergy and Infectious Disease Mycoses Study Group looked at the use of itraconazole for treatment of invasive aspergillosis and concluded that it is effective in many patients with aspergillosis. A treatment period of several months was required in those patients who responded to obtain an objective improvement [58].

Newer agents are gaining increasing attention. A report of invasive pulmonary Aspergillus nidulans infection in a 5-year-old boy with chronic granulomatous disease treated successfully with voriconazole was reported from the Netherlands [59]. A new class of antifungal drugs, the echinocandins and pneumocandins [60], are lipopeptide antifungal agents that inhibit the synthesis of 1,3-β-D-glucan, a cell wall component found in many pathogenic fungi. LY303366 is an echinocandin with excellent in vitro activity against Aspergillus species. In a neutropenic murine model of invasive aspergillosis, in vivo resistance of Aspergillus fumigatus to amphotericin B was demonstrated, and LY303366 appeared to be effective against amphotericin B–susceptible and –resistant A. fumigatus infections [61]. Comparisons of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic fungi and yeasts have been reported [62]. The results suggest that these new agents have a broad spectrum of activity in vitro. In vivo effectiveness remains to be determined. UR-9,825, a new triazole derivative, has been shown to display good in vitro activity against A. fumigatus. It showed good activity in rat systemic infections with Aspergillus after a dose of 1 mg/kg orally twice a day, but somewhat less than that of amphotericin B [63]. ABLC has been evaluated for its efficacy for invasive fungal infections, including aspergillosis, and results were favorable in patients who cannot tolerate amphotericin B [64]. Two dosages of liposomal amphotericin B for treatment of invasive aspergillosis were compared in a European Organization for Research and Treatment of Cancer multinational randomized trial [65••]. The patients were either neutropenic with malignancy or undergoing bone marrow transplantation. The results indicated that the lower dose of 1 mg/kg/day was just as effective as the 4 mg/kg/day dose, and no advantages using the higher dose were observed [65••].

Although Aspergillus is infrequently isolated in HIV-infected patients, the associated high mortality rate in documented infection necessitates serious consideration of its clinical significance in those with advanced disease [66]. The treatment of choice is amphotericin B but the mortality rate is greater than 80% [67]. A study performed at Bellevue Hospital compared pulmonary aspergillosis in the HIV-negative and -positive patient in a retrospective study. It was found that although tuberculosis and sarcoidosis are the most common predisposing disease, Pneumocystis carinii pneumonia in the HIV-infected patient is a risk factor for pulmonary aspergillosis, and that HIV patients with a CD4 count below 100 cells/mm³ are more likely to have disease progression. It was also seen that the
Cryptococcosis

Life-threatening infections caused by Cryptococcus neoformans have been increasing over the past 10 years as a result of the AIDS epidemic and the expanded use of immune-suppressive drugs [69••]. Clinically, the most commonly recognized form of cryptococcosis is meningitis, although a few postmortem studies have indicated that lung and central nervous system disease is seen with equal frequency. AIDS is the predisposing factor in more than 80% of cryptococcal infections. Primary pulmonary infection may remain mild and asymptomatic even while the fungus is spreading to other organs. Primary pulmonary infections in the normal host are frequently asymptomatic but may regress or progress spontaneously, presenting as a severe pneumonia, or may remain stable for many years. Symptomatic pneumonia is characterized by cough with scant sputum production, sometimes blood-streaked sputum. In HIV patients, fever, cough (at times productive) dyspnea, chest pain, and occasional hemoptysis are typical findings and ARDS may also ensue [70]. On chest radiographs in HIV patients pneumonia frequently presents as diffuse interstitial, alveolar, or nodular pulmonary infiltrates that can be associated with hilar adenopathy and occasional pleural effusions [71]. Focal alveolar consolidation are also seen, and, in rare instances, cavernous destruction of the lung (cryptococcoma) may be seen [72]. Cryptococcal pneumonia should be considered in the differential diagnosis of P. carinii pneumonia, myilar tuberculosis, or bacterial pneumonia in the HIV patient. Synchronous pulmonary cryptococcosis and histoplasmosis have also been encountered in the immunosuppressed host [73•].

Detection of the organism by culture is required for definite diagnosis. Cryptococcal capsular antigens are shed in body fluids and their detection by the latex cryptococcal agglutinin test in the serum or cerebrospinal fluid is a valuable diagnostic tool [74]. It is less sensitive, however, in nonmeningeal than in meningeal cryptococcosis. Rapid diagnosis by examination of smears with India ink may give support to a presumptive diagnosis. Special histopathologic stains with Mayer’s mucicarmine or methenamine silver may reveal the encapsulated single budding yeast. There are also atypical cytomorphic appearances of C. neoformans [75], however, which may be confused for other fungal species. DNA-probes for the detection of C. neoformans have been studied and may provide means for early diagnosis [76•].

Pulmonary cryptococcosis in the healthy host may be treated, if treatment is warranted, with fluconazole 200 to 400 mg orally daily, or alternatively with fluconazole plus flucytosine [77]. In immunosuppressed patients, pulmonary cryptococcosis should be treated initially with amphotericin B with or without flucytosine until stable and then continued on fluconazole 200 mg orally every day for another year. Variations on this basic strategy have been reported [78••]. Another approach to the primary treatment of cryptococcosis in patients with AIDS would be a relatively high dose of amphotericin B over a short period [79].

The role of lipid preparations is under investigation. Liposomal amphotericin B at 4 mg/kg resulted in a significantly earlier cerebrospinal fluid culture conversion in meningitis compared with amphotericin B at 0.7 mg/kg, was less nephrotoxic, and had equal clinical efficacy when used for the treatment of primary episode of AIDS-associated cryptococcal meningitis [80]. Lifetime suppression therapy is usually with fluconazole 200 mg orally every day, although amphotericin B once weekly 0.5 to 1.0 mg/kg IV may be used. Itraconazole may be a suitable alternative for patients unable to take fluconazole [78••].

Intricate host-organism interactions make the full understanding of the pathogenicity and virulence of C. neoformans difficult [69••]. Studies seem to indicate that C. neoformans is capable of inducing progression of HIV disease. A study from the Netherlands suggests that C. neoformans may actually accelerate the course of HIV disease by stimulating the HIV replication through major histocompatibility complex class II–mediated antigen presentation, and that cryptococcal mannanprotein may be one of the responsible components [81]. Another investigation indicated that C. neoformans, as well as Candida albicans, enhance HIV expression in monocytic cells through a tumor necrosis factor–α and NF-κB–dependent mechanism which may further impair host immunity and accelerate the course of HIV disease [82]. In one study it was found that C. neoformans is able to induce interleukin-6 production, which in turn can stimulate replication of HIV in monocytic cells [83]. C. neoformans may be involved in the regulating of B7-1(CD80) and B7-2(CD86) costimulatory molecules that may suggest a potential mechanism for the poor inflammatory response observed in C. neoformans infections [84]. Another study looked at the role of exogenous interleukin-10 in the development of immune response against C. neoformans. IL-10 is abundantly produced during the progression of AIDS and it was found that the presence of IL-10 in HIV patients may contribute to augment the pathogenic effect of C. neoformans [85].

Many agents have been tested for in vitro activity against C. neoformans. In one study of such agents, it was found that sertaconazole was statistically more active than bifonazole and terbinafine against C. neoformans strains [86]. In another study, the in vitro comparative efficacy of voriconazole and itraconazole against fluconazole-resistant and -sensitive C. neoformans were investigated. Voriconazole was more potent than itraconazole for fluconazole-susceptible isolates and as potent as itraconazole for fluconazole-resistant dose-dependent isolates and for fluconazole-resistant isolates [87]. A study from the United Kingdom investigated the stereoselective inter-
action of the azole SCH39304 with the cytochrome P-450
monooxygenase system isolated from C. neoformans and
found that the SS enantiomer was able to bind to the P-450
system [88]. A difference in drug susceptibility depending
on the serotype of C. neoformans has also been seen. Serotype
A was less susceptible to fluconazole than serotype D,
and both serotypes were highly susceptible to itraconazole
[89]. In another study, the effect of chloroquine on the
anticytococcal activity of mononuclear phagocytes was
investigated. It was found that chloroquine enhances the
activity of mononuclear phagocytes against C. neoformans
and is therapeutic in murine models of cryptococcosis. Thus,
chboroquine might have clinical utility for the prophylaxis
and treatment of human cryptococcosis [90].

Immune-based therapies have been actively investi-
gated as well. The effect of murine IgG1 monoclonal anti-
body (mAB) 2H1, which binds to C. neoformans glucuronoxylomannan on pulmonary infection in immu-
nocompetent mice was examined. mAB administration
prior to infection prolonged survival without reducing the
number of yeast in the body. This study may indicate that
antibody administration can produce quantitative as well as
qualitative changes in the inflammatory response to C. neo-
formans [91]. A murine mAB 1887 to C. neoformans polysac-
charide is under investigation as a candidate for human
therapeutic trials. Administration of this antibody in mice
led to a rapid clearance of serum cryptococcal antigen [92].
Granulocyte colony-stimulating factor given to HIV-
infected subjects improved anticytococcal activity in neutrophils [93].

Conclusions
Fungi, both endemic and opportunistic, are increasingly
 Important lung pathogens. Triazole antifungal agents have
revolutionized therapy in many cases, although for most
severe infections amphotericin B as the deoxycholate or as
one of the available lipid preparations remains the stan-
dard of care. Vaccines or other immune-based therapies
are largely in early stages of preclinical development.

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