19
Cryptococcus neoformans

1. INTRODUCTION

Cryptococcus neoformans is a yeast-like fungus that is pathogenic to both animals and man. It was first isolated in 1894 by Busse *(1)* from a patient with osteomyelitis of the tibia. The fungus is a saprophitic organism that can be found in soil, on a variety of fruits, as well as in close association with pigeon nests *(2,3)*. There are two varieties of *C. neoformans*: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii*. Each of these varieties, in turn, has two serotypes: A and D for var. *neoformans*, and B and C for var. *gattii*. In addition, there have been reports of human infections caused by two other *Cryptococcus* species: *C. albidus* and *C. laurentii*.

Infection with *C. neoformans* is usually acquired by its inhalation. Although the fungus is common in pigeon feces, the birds are not clinically infected *(4)*. There is no observation of human-to-human transmission of the disease *(5)*.

Cell-mediated immunity seems to provide the major defense against cryptococcal infections, leaving patients with compromised cell-mediated responses (lymphoma, leukemia, sarcoidosis, and those patients receiving corticosteroid therapy) more vulnerable and, therefore, more likely to develop a cryptococcal infection *(6–15)*. The alveolar macrophages represent the initial host's defense against the cryptococcal pathogen and may arrest infection before dissemination occurs. To this end, experiments by Ieong et al. *(16)* have shown that the innate fungicidal activity of primary human alveolar macrophages against *C. neoformans* was impaired after HIV-1 infection in vitro by a mechanism that might have involved a defect of intracellular antimicrobial processing. Also, human neutrophils are known to inhibit and kill *C. neoformans* in vitro and are thought to play an important role in the host's defense against cryptococcosis through both oxidative and nonoxidative mechanisms *(17)*.

Aguirre et al. *(18)* have demonstrated that both interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) were important factors in mediating acquired resistance to cryptococcal meningoencephalitis. To this end, Kawakami et al. *(19)* found that in mice with defective IL-12 production, IL-18 contributed to the hosts's resistance to cryptococcal infection through the induction of IFN-γ production by natural killer (NK) cells, but not through the development of Th1 cells, under the condition in which IL-12 synthesis was deficient.

Cryptococcosis may develop as an acute, subacute or chronic pulmonary, systemic or meningeal mycosis. Although the pulmonary form is usually transitory, mild and often asymptomatic, the involvement of the central nervous system (CNS) is manifested by subacute or chronic meningitis that in immunocompromised hosts could be life-treatening. Cases of patients with idiopathic $CD4^+$ T-lymphocytopenia accosiated with CNS cryptococcosis have also been reported *(20)*.

During dissemination of the disease, skeletal and visceral lesions may occur. Nearly all of the immunocompromised patients are likely to develop disseminated cryptococcosis *(21,22)* with susceptibility to infection being reported for the skin *(23–27)*, bone *(28)*, prostate *(29)*, kidney *(30)*, eyes

From: Opportunistic Infections: Treatment and Prophylaxis
By: Vassil St. Georgiev © Humana Press Inc., Totowa, NJ

(31,32), liver *(33–35)*, spleen *(36)*, adrenals *(36,37)* lymph nodes *(24,35,38,39),* and the gastrointestinal tract *(40)*. Although infrequently, deep cryptococcal infections of the breast have been reported *(41)*. Hypereosinophilia in disseminated disease has also been observed *(42)*.

Larsen et al. *(43)* reported a persistent cryptococcal infection of the prostate in AIDS patients even after an adequate therapy with amphotericin B alone or in combination with flucytosine; this observation suggest the possibility of the prostate serving as a sequestered reservoir of infection from which systemic relapse may occur. To this end, cryptococcal prostatitis in a patient with Behcet's disease was also described *(44)*.

The co-existence of different diseases within the same lesion could be a distinct possibility in patients with HIV infection. In this context, there have been several reports of simultaneous Kaposi's sarcoma and cutaneous cryptococcosis occuring at the same site in a patient with AIDS *(45)*. Limbal nodules and multifocal choroidal lesions due to *C. neoformans* may also occur in AIDS patients *(46)*. Benard et al. *(47)* have presented case reports of two patients with immunodeficiency secondary to paracoccidiodomycosis and opportunistic cryptococcosis. Secondary immunodeficiency likely occured as a consequence of the intestinal loss of proteins and lymphocytes associated with malabsorption syndrome due to obstructed lymphatic drainage; both patients had severe abdominal involvement during the acute paracoccidiodomycosis disease *(47)*.

Molnar-Nadasdy et al. *(48)* have described a unique case of placental cryptococcosis in a pregnant mother with systemic lupus erythematosus (SLE) and steroid treatment. Although there were no clinical or placental signs of transplacental infection, immunohistochemical labeling of villous stromal cells showed a conspicuously increased number of fetal macrophages.

In patients with AIDS, cryptococcal infections are often associated with high relapse rate and poor response to treatment *(49–53)*. Currently, cryptococcosis is considered to be the one of the most life-threatening mycoses in patients with AIDS *(54–60)*. Munoz-Perez et al. *(61)* have described disseminated cryptococcosis presenting as molluscum-like lesions as the first manifestation of AIDS.

Although a common opportunistic mycosis in adults, cryptococcosis complicating pediatric AIDS have also been well-documented *(62)*.

In the majority of patients with normal immunity, cryptococcosis is confined to the lung or the hilar nodes *(21,63–68)* and will hardly require any antifungal therapy *(21,69,70)*. Occasionally, cryptococcal osteomyelitis has also been described in normal hosts *(71)*. Cutaneous cryptococcosis in the nonimmunocompromised host is also a rare entity, and when it does occur, it presents with protean manifestations making clinical diagnosis difficult *(72,73)*. One unusual case of progressive pulmonary disease in an immunocompetent patient presenting as a discrete endobronchial cryptococcoma has been reported by Emmons et al. *(60).* Mahida et al. *(71)* also reported a patient with endobronchial cryptococcal obstruction. Cryptococcal meningitis with severe visual and hearing loss and radiculopathy was described in an immunocompetent patient *(75)*, as well as CNS cryptococcosis with multiple intraventricular cysts *(76)*. The development of adult respiratory distress syndrome (ARDS) caused by pulmonary cryptococcosis in an immunocompetent host has been reported *(77)*.

By far, cryptococcal meningitis is the most dangerous form of the disease. Because some of the patients with cryptococcal meningitis may be asymptomatic *(6,8,78–80)* it is important that the cerebrospinal fluid (CSF) be examined whenever *C. neoformans* is isolated or detected from any site. The onset of cryptococcal meningitis would most likely be insidious, but often it is acute in cases of severely immunocompromised hosts. In the latter case, if untreated, the infection is always fatal *(6,81–84)*.

2. TREATMENT OF CRYPTOCOCCOSIS

The choice of therapy for cryptococcal disease largely dependent on both the anatomic site of infection and the patient's immune status *(88)*.

Presently, there are no clinical trials to evaluate the outcome of therapy for AIDS-related cryptococcal pneumonia. The optimal therapeutic approaches for management of cryptococcal meningitis,

Table 1
Treatment of Cryptococcosis in Immunocompromised Patients

Patients	Site of infection	Drug Regimens
HIV-negative	Pulmonary and non-CNS involvement	Amphotericin B 0.7–1.0 mg/kg, daily + flucytosine 100 mg/kg, daily for 2 wk, then fluconazole 400 mg, daily for at least 10 weeks[a,b,c]
	CNS involvement	Amphotericin B 0.7–1.0 mg/kg, daily for 2 wk, then fluconazole 400-800 mg, daily for 8–10 wk, followed by lower dose fluconazole (200 mg, daily) for 6–12 mo[b,c]
HIV-positive	Pulmonary[d]	Fluconazole 200–400 mg, daily for life; Itraconazole 200–400 mg, daily for life; Fluconazole 400 mg, daily + flucytosine 100–150 mg/kg, daily for 10 wk[a]
	CNS involvement	Amphotericin B 0.7–1.0 mg/kg, daily + flucytosine 100 mg/kg, daily for 2 wk, then fluconazole 400 mg, daily for at least 10 wk[e]

[a]Patients receiving flucytosine for over 2 wk should be monitored for renal toxicity.

[b]For patients with significant renal disease, lipid formulation of amphotericin B may be used. Intrathecal or intraventricular amphotericin B may be used in refractory cases where systemic administration of antifungal therapy had failed.

[c]For patients who cannot tolerate fluconazole, itraconazole (200 mg, b.i.d.) may be taken instead.

[d]Mild-to-moderate symptoms. In patients with more severe disease, amphotericin B should be used initially until symptoms are controlled, and then substituted with an oral azole antimycotic (preferably fluconazole).

[e]Induction/consolidation therapy. In cases where flucytosine is not tolerated, amphotericin B (at the same doses) alone is an acceptable alternative. Lipid amphotericin B may also be used in patients with renal insufficiency.

especially in AIDS patients with underlying T-cell dysfunction, and those with neoplasia or on corticosteroid therapy, are also not completely defined and still subject to discussion (Table 1) *(85–88)*.

Currently, the most recommended therapy for cryptococcosis in HIV-negative immunocompromised patients with pulmonary disease and non-CNS involvement, consists of amphothericin B alone or in combination with flucytosine for the first 2 wk, followed by fluconazole both to complete initial treatment and provide a lifelong maintenance therapy *(88)*.

Although fluconazole and itraconazole have been associated with response rates of 50–60%, amphotericin B is still the drug of choice for inducing a rapid clearance of the fungus, and therefore, a preferable option for initial therapy. Results from a recently completed large clinical trial (MSG 17/ACTG 159) *(85)* have indicated that initial treatment for 2 wk with amphotericin B (0.7 mg/kg once daily), followed by triazole (fluconazole at 400 mg daily, or itraconazole at 400 mg daily) therapy for further 8 wk resulted in mortality rate of less than 8%, which is substantially lower than that of previous studies *(89)*.

Based on the results of a retrospective review of 30 consecutive AIDS patients with cryptococcal infection (median CD4+ count of 0.042×10^9 cells/L) given fluconazole at 400 mg daily, Nightingale *(90)* supported the use fluconazole as initial therapy for AIDS-associated cryptococcosis in these patients. In fact, in the largest comparative study *(91)* there was no difference in the response rates associated with amphotericin B and fluconazole.

Studies by Haubrich et al. *(92)* have also shown that a high-dose (800 mg daily) of fluconazole was well-tolerated by HIV-infected patients and appeared effective primary therapy for cryptococcal disease in AIDS patients.

First-line fluconazole therapy (200–400 mg daily) has also been found effective and well-tolerated in patients with AIDS-associated nonmeningeal cryptococcosis *(93)*.

The standard therapy of disseminated cryptococcosis, particularly of cerebral manifestations, is still amphotericin B-flucytosine combination *(59,86)*. The use of high-dose oral fluconazole for treatment of disseminated cryptococcosis has also been recommended *(94)*.

Disease relapses are frequent in AIDS patients (20–60%) if a long-term maintenance therapy is not applied promptly. In this regard, fluconazole at 200 mg daily has shown to be superior than itraconazole at the same dosage level *(85)*.

Fluconazole has also been used prophylactically *(95–97)*. At 200–400 mg daily, it reduced significantly the incidence of cryptococcosis (and mucosal candidiasis), especially in AIDS patients with $CD4^+$ counts of less than 50 cells/mm^3.

2.1. Amphotericin B

Before the introduction of chemotherapy, 86% of all cases of cryptococcal infections associated with neurological involvement were fatal within one year of onset *(84)*, with death usually resulting from raised intracranial pressure producing cerebral compression. Amphotericin B, which has been in use for treatment of cryptococcosis since the 1950s, is still one of the most frequently applied therapeutic agents against this infection *(98,99)*. Thus, following the introduction of amphotericin B, cure rates as high as 85% have been reported *(100)*.

When given intravenously at daily doses of up to 1.0–1.5 mg/kg (or every other day), amphotericin B accounted for as high as 64% cure rate of patients with cryptococcal meningitis *(5)*. In AIDS patients with cryptococcal meningitis, continuing weekly infusions of amphotericin B after the standard course of therapy has been completed, apparently offered some degree of protection against relapse *(101)*.

A typical primary course of therapy may consist of amphothericin B given daily for at least 4 wk with a total dose ranging from 1.60 to 2.76 g (mean 2.11 g), whereas a maintenance therapy would include treatment with 40–100 mg/wk of amphotericin B ranging from 0.7–1.5 mg/kg body weight *(101)*. It should be emphasized that although a maintenance therapy with this antibiotic will not necessarily provide a total protection against relapse of cryptococcosis in patients with AIDS, the weekly maintenance regimen with amphotericin B is still a recommended current practice that may be carried out indefinitely with AIDS patients who had survived their primary course of antifungal therapy *(102,103)*. However, the continued infusion of amphotericin B is not without a danger and may cause toxicity making it unacceptable to many patients *(101)*.

The total dose of the antibiotic administered during primary therapy may be highly variable; this, in addition to the requirement for maintenance therapy (which may become a life-long treatment) will make the end point of amphothericin B therapy not well defined. Thus, in one study *(103)* involving 48 cases of cryptococcosis complicating AIDS, the cumulative amphotericin B dosage administered to the time of clinical response (defervescence and resolution of symptoms in 48% of the patients) varied between 0.1 and 1.76 g; in the majority of patients, the clinical response was noted early in the treatment when the average cumulative dose was 0.4 g *(103)*.

In a study involving 31 consecutive AIDS patients with cryptococcal disease (28 with meningitis, and 3 with disseminated extrameningeal cryptococcosis), investigators *(104–106)* have examined the efficacy and safety of a short-course primary treatment with relatively high dose of amphotericin B at 1.0 mg/kg daily for 14 d (26 patients also received flucytosine at 100–150 mg/kg daily, given either intravenously or orally), followed by maintenance therapy with fluconazole or itraconazole. Successful therapy was defined as the resolution of symptoms and negative cultures of CSF and/or blood 2 mo after the initial diagnosis. The therapeutic regimen was successful in 29 (93.5%) of all 31 cases, and in 26 (92.8%) of the 28 cases of culture-proven or presumed cryptococcal meningitis; treatment failed in two patients.

A therapy comprising amphotericin B and flucytosine, if maintained over a period of 6 wk, although showing a high rate of success, had also required a permanent relapse prevention *(56)*. With regard to prevention therapy, oral fluconazole could be very effective and is considered by some investigators to be the drug of choice *(56)*.

As reported by Zugar et al. *(49)* and Kovacs et al. *(50)*, in spite of antifungal medication, the mortality rate resulting from cryptococcal meningitis in AIDS patients has ranged from 17–35%, and was 25% in patients having persistently positive cultures *(50)*. By comparison, the relapse rate in non-AIDS patients was between 0% and 35% *(6,10,107)*.

Polsky et al. *(108)* have conducted a retrospective study evaluating the use of intraventricular application of amphotericin B in cases of cryptococcal meningitis in non-AIDS patients. Death during therapy occured in only one of the six patients who had received intraventricular and systemic therapy, and in six of the seven patients on systemic therapy alone. No major adverse effects were reported with the intraventricular administration of the drug. However, the preliminary information in AIDS patients did not provide much encouragment because those patients who received intraventricular amphotericin B did not show any therapeutic benefits *(48,49)*. In addition, the treatment was often complicated by infection of the ventricular shunt and chemical arachnoiditis (consisting of fever, headache, and CSF pleocytosis) forcing the premature discontinuation of the intraventricular therapy *(49,50)*.

An earlier long-term study involving 31 patients with cryptococcal meningitis receiving intravenous amphotericin B (with half of the patients on intrathecal therapy as well) had shown an overall mortality rate of 45% of which 39% was due to cryptococcal meningitis *(8)*. Roberts and Douglas *(109)* reported a successful amphotericin B therapy (with a total dose of 3.0 g) in one case of cryptococcal meningitis accompanied by cryptococcemia. In another study, Sapico *(110)* described the disappearance of focal cryptococcal brain lesion following intravenous infusion of amphotericin B at gradually increasing doses (a total of 3.0 g), whereas Bastin et al. *(111)* applied the drug to cure a case of cryptococcal meningitis associated with polyradiculitis.

Although amphotericin B therapy greatly improved the prognosis of patients with cryptococcal meningitis, overall, there are still important clinical limitations associated with its use, including modest efficacy, nephrotoxicity, and the inconvenience of intravenous application *(112)*.

Ambisome®, an unilamellar liposomal formulation of amphotericin B, was used in the treatment of cryptococcal meningitis in three patients; clinical and mycological remission were observed in two of the patients, with the remaining one showing improvement *(113)*. Coker et al. *(114)* described a successful treatment of cryptococcal meningitis with liposomal amphotericin B after failure of treatment with fluconazole and conventional amphotericin B. Schurmann et al. *(115)* investigated the safety and efficacy of liposomal amphotericin B in treating AIDS-associated disseminated cryptococcosis.

Japanese scientists *(116,117)* have described an unusual therapy of cryptococcal meningitis consisting of small doses of amphotericin B, a large dose of prednisolone, and a continuous removal of CSF.

An individual case of a patient with a solid intracranial cryptococcal granuloma in the motor cortex area was treated initially with intrathecal and intravenous amphotericin B; because no regression of the granuloma was observed, a subsequent gross total surgical excision was successfully performed *(118)*. There are several other reports of combined treatment of intracranial cryptococcal infection with surgery and systemic amphotericin B *(119–122)*.

Intrathecal administration of amphotericin B has been routinely performed by usage of subcutaneous CSF reservoir. The latter comprised a subcutaneous dome of siliconized rubber that can fit into a cranial burr hole with a catheter extending from the dome into a lateral cerebral ventricle *(107,123,124)*. Schonheyder et al. *(125)* observed some complications following intrathecal infusion of amphotericin B using the Rickham reservoir; mainly a persistent infection resulting from the presence of the reservoir.

A renal-transplant recipient who was on immunosuppressive medication (prednisone, azathioprine) and with developed pulmonary cryptococcosis was successfully treated with intravenous amphotericin B *(126)*. In this regard, a Japanese study *(127)* indicated a poor prognosis of antifungal therapies for cryptococcal infections in renal transplant recipients; thus, only one of six patients survived following the graft. Although amphotericin B was found most effective, its nephrotoxicity has always been of prime concern in graft survival.

Shindo *(128)* has found amphotericin B superior to fluconazole, itraconazole, miconazole, and flucytosine (given in various combinations) in the treatment of one patient with cryptococcal meningitis and slight azotemia caused by hypertensive nephrosclerosis.

A diabetic patient with isolated adrenal cryptococcosis (characterized with fungal granuloma and poorly encapsulated pathogen) was treated successfully with surgery and medication with amphotericin B; after a 7-mo follow-up period, there was no evidence of recurrence or dissemination *(129)*.

The use of intravenous amphotericin B in nine cases involving pulmonary cryptococcosis was also reported *(130)*.

Amphotericin B when used at cumulative doses of 189–551 mg, effectively decreased the systemic infections in patients with lymphocytic lymphoma and progranulocytic leukemia *(131)*. Fajardo *(132)* has reported the failure of topical amphotericin B to cure cutaneous cryptococcosis in a patient who previously had Hodgkin's disease in a cervical lymph node; the topical treatment comprised 3% amphotericin B ointment in a polyethylene and mineral oil gel base applied four times daily. In another case report, Kojima et al. *(133)* described a successful treatment by amphotericin B of acute lymphocytic leukemia (ALL) complicated with a generalized cryptococcosis.

Mycotic endocarditis is a rare fungal infection *(134,135)*. Colmers et al. *(2)* described a successful therapy of *C. neoformans*-induced endocarditis manifesting fungemia with intravenous amphotericin B (total dose of 1.58 g).

2.1.1. Toxicity of Amphotericin B

Toxicity studies included a follow-up evaluation of 53 patients treated with amphotericin B. The patients showed an increase in the blood urea nitrogen, acute and permanent nephrotoxicity (age- but not dose-dependent), and a transient reduction of the creatinine clearance during therapy *(136)*. The antibiotic has also been used in cases of pregnancy complicated with cryptococcosis and showing no clinical damage to the fetus *(137,138)*. Li and Lai *(139)* observed acute visual loss in a patient with SLE and cryptococcal meningitis who was receiving a test dose (1.0 mg) of intravenous amphotericin B; caution was recommended in using the anibiotic in cases of cryptococcal meningitis when a desease of the optic nerve is strongly suspected.

2.2. Combinations of Amphotericin B with 5-Fluorocytosine and Other Drugs

Currently, the combination of amphotericin B and 5-fluorocytosine is one of the most frequently used for the treatment of cryptococcosis *(140)*. According to Armstrong *(141)*, therapy of invasive cryptococcosis should include daily doses of amphotericin B (1.0 mg/kg, intravenously) and oral flucytosine (100 mg/kg daily, divided in 4 doses) for a duration (or total dose) depending on the patient's response; maintenance therapy of fluconazole (200 mg daily) is often required and can be administered indefinitely.

Concerning the mechanism of combined amphotericin B/5-FC treatment, it is thought that amphotericin B at low doses would potentiate *(142,143)* the uptake of the flucytosine, thus facilitating a synergistic effect *(144)*.

In 1978, Jimbow et al. *(145)* reported an evaluation of the therapeutic effectiveness of amphotericin B and flucytosine, alone and in combination, in 28 patients with cryptococcal meningitis. The combined regimen (at 0.35 mg/kg amphotericin B daily, i.v., and 150 mg/kg daily of oral flucytosine) was significantly more effective than either drug given alone, both in terms of toxicity and shorter duration of treatment.

Bennett et al. *(146)* conducted a prospective, uncontrolled trial of 15 patients with cryptococcal meningitis to compare a combined therapy of intravenous amphotericin B and oral flucytosine (a 6-wk trial) with amphotericin B given alone (a 10-wk trial). Results showed that as compared to monotherapy with amphotericin B, the combination cured more patients with fewer failures or relapses, more rapid sterilization of CSF ($p < 0.001$), and less nephrotoxicity ($p < 0.05$). The applied regimens were as follows: (1) combination therapy: 0.3 mg/kg of amphotericin B daily, i.v., and 150

mg/kg of 5-FC daily, divided in 6 hourly oral doses; and (2) amphotericin B alone: 0.4 mg/kg daily, i.v. for 42 d, followed by 0.8 mg/kg every other day for 28 d *(146)*.

In order to reduce potential toxicity without compromizing the efficacy, Dismukes et al. *(51)* conducted a multicenter, prospective, randomized clinical trial of 194 patients having cryptococcal meningitis. The trial was designed to compare the efficacy and toxicity of 4- vs 6-wk regimens (identical with those applied by Bennett et al. *[146]*) of combined amphotericin B/5-fluorocytosine therapy. Cure or improvement was observed in 75% of those patients who were treated for 4 wk, and in 85% of those treated for 6 wk, with relapse rates of 27% and 16%, respectively, and a similar incidence of toxicity (44 and 43%, respectively). Based on the results of the trial, the investigators recommended that the 4-wk regimen be applied to patients having no neurological complications, underlying disease or immunosuppressive therapy; patients who do not meet these criteria should be receiving for at least 6 wk the combined amphotericin B/5-fluorocytosine treatment *(51)*. Alternatively, MacGregor *(147)* suggested a modified therapy involving a relatively short course of amphotericin B treatment (3–4 wk) combined with a longer course of 5-fluorocytosine medication. It was assumed that the period necessary for the pathogen to develop a resistance towards 5-FC is early in the treatment when the cryptococcal population is in its peak; therefore, a short initial period of combined therapy (involving the use of amphotericin B) would be sufficient to reduce the cryptococcal population and thereby, the possibility of developing a resistance towards flucytosine. In turn, such therapeutic regimen will allow for a more extended course of single 5-FC therapy and less of amphotericin B-induced toxicity *(147)*.

In an earlier study, Utz et al. *(10)* described the treatment of 15 patients with cryptococcal meningitis with a combination of low-dose intravenous amphotericin B (20 mg daily) and oral flucytosine (150 mg/kg daily); 53% of the patients were reported cured with no relapse. Other reports have indicated that increasing the doses of the antibiotic to conventional levels (0.6–1.0 mg/kg daily) improved the cure rate of patients on a single amphotericin B therapy to 47–58%; repeated courses of amphotericin B treatment increased the cure rate even further (61–67%) *(6,8,9)*.

Schmutzhard and Vejajjiva *(148)* conducted a trial of 24 patients with cryptococcal meningitis using as therapy amphotericin B (1.0 mg/kg daily, i.v.) and oral flucytosine (150 mg/kg daily). None of the patients received corticosteroid therapy. The duration of treatment ranged from 56–104 d. Upon completion, none of the patients died. However, four patients had a relapse within 6 mo; an overall relapse rate of 17% was observed in spite of the higher total dosage of amphotericin B and 5-FC and longer duration of therapy.

In addition to data already discussed, there have been reports from various groups that indicate that, in general, the difference between amphotericin B administered alone, or as part of combined therapy with flucytosine, has not been statistically significant *(49,50,149)*. Furthermore, 5-FC would be difficult to consider for AIDS patients because of its adverse bone marrow-suppressive *(149,150)* and gastrointestinal *(51)* effects, which often are superimposed on symptoms caused by the human immunodeficiency virus (HIV) *(151,152)*. After reviewing the records of 106 patients with cryptococcal infections and AIDS (criteria considered included: efficacy of treatment with amphotericin B alone or in combination with flucytosine, efficacy of suppressive therapy, prognostic clinical characteristics, and the course of nonmeningeal cryptococcosis), Chuck and Sande *(153)* concluded that addition of flucytosine to amphotericin B neither enhanced survival nor prevented relapse, but long-term suppressive therapy appeared to be beneficial. Nevertheless, in a significant number of patients, the flucytosine medication had to be stopped because of cytopenia *(153,154)*.

Cryptococcal infections associated with the CNS can be manifested as focal granulomatous lesions that may contribute to increased mortality (often exceeding 50%). A case report of cerebral cryptococcoma linked to cryptococcal meningitis was treated successfully with a short course of intravenous amphotericin B and oral flucytosine *(155)*. The combined therapy consisted of 20 mg daily of amphotericin B and 150 mg/kg daily of 5-FC for a period of 6 wk, after which the antibiotic was administered alone at a dose of 50 mg given every other day until a total dose of 2.16 g of the

antibiotic had been dispensed. The observed side effects (parasthesia of the hands, edema of the ankles, increased serum creatinine level [168 mol/L], and a lowered serum potassium level [to 3.0 mmol/L]) were transitory *(155)*. One case of cryptococcal meningoencephalitis, which developed after 9 yr of corticosteroid therapy, was resolved successfully with amphotericin B and flucytosine (for 6 wk) and with itraconazole (for another 8 wk) *(156)*.

Systemic treatment with amphotericin B and flucytosine led to resolution of choroidal infiltrates in two AIDS patients with optic edema and cryptococcal choroiditis *(157)*. Picon et al. *(158)* successfully treated with amphotericin B and flucytosine an AIDS patient with cutaneous cryptococcosis manifecting as molluscum contagiosum-like skin lesions.

Tobias et al. *(159)* reported the treatment of two patients with Hodgkin's disease and cryptococcal meningitis with amphotericin B and oral flucytosine; amphotericin B was administered intrathecally as well as by a rapid low-dose intravenous injection.

Watson et al. *(160)* described a long-term study (spanning over 11 yr) that involved treatment of cryptococcal infection in renal-transplant recipients on continued immunosuppressive therapy (prednisolone). The treatment of cryptococcosis, which consisted of combination amphotericin B (0.3–0.5 mg/kg daily, i.v.) and/or oral flucytosine (150 mg/kg daily) led to cure in 10 of 11 patients. In order to preserve graft viability in those patients with stable renal function at the time of diagnosis, maintenance immunosuppressive therapy was continued throughout the antifungal medication *(160)*. Previous reports *(12,161,162)* suggested the need to reduce or even to discontinue the immunosuppressive therapy in order to achieve a cure of cryptococcal infection in cases of renal transplantation. Kong et al. *(163)* treated cryptococcal meningitis in eight cases of renal transplant recipients with SLE. The therapy comprised amphotericin B and flucytosine; at the time of medication all patients were also receiving immunosuppressive therapy (steroids in association with either azathioprine or cyclosporine) *(163)*. Kimura et al. *(164)* described the successful treatment of a case of SLE complicated with cryptococcal meningitis using combination of amphotericin B and 5-FC.

Pulmonary cryptococcosis with an early systemic spread was managed with combination amphotericin B, and flucytosine; following that, a rapid 1-h intravenous infusion of amphotericin B (30 mg) on alternative days was instituted as an outpatient maintenance therapy for a period of approx 6 wk *(165)*.

Cryptococcal osteomyelitis (manifested either as a single bone lesion or a systemic illness in addition to osteomyelitis), has been described on several occasions *(166–169)*. Poliner et al. *(40)* discussed a case of cryptococcal cervical vertebral osteomyelitis that was cured with oral 5-FC (150 mg/kg daily) and amphotericin B (0.3 mg/kg daily, i.v.) for 6 wk with no evidence of systemic toxicity or relapse. In another case *(170)*, a patient who developed osteomyelitis of the skull due to cryptococcosis was successfully treated with amphotericin B and flucytosine.

An AIDS patient who presented with oral lesion of cryptococcosis (gingival ulceration) was successfully cured with amphotericin and flucytosine given over a 4-wk period *(171)*.

Iida et al. *(172)* described the successful treatment of cryptococcal meningitis with combined amphotericin B-ketoconazole therapy.

Echevarria et al. *(173)* reported a case of pulmonary cryptococcosis that was treated successfully with combination of amphotericin B and ketoconazole.

A "fungus ball," which developed in an inactive tuberculosis cavity, was treated with infusion of amphotericin B (total dose of 2.4 g) and sodium iodide (total of 56 g over a 30-d period) directly into the cavity through an indwelling percutaneously inserted endobronchial catheter for a period of 3 mo. A marked improvement was observed without any complications caused by the use of the catheter *(174)*.

2.2.1. Toxicity of Amphotericin B-5-Fluorocytosine Combinations

In view of the existing toxicity of both amphotericin B and flucytosine (especially the negative effect of the latter on the bone marrow), medication of cryptococcal infections with combination of these two drugs should be considered very carefully when severely immunocompromised patients (advanced state of AIDS) are involved. Thus, in a multicenter, prospective randomized trial *(175)*

that lasted for either 4 or 6 wk, the treatment with intravenous amphotericin B (0.3 mg/kg daily) and oral 5-FC (150 mg/kg daily) of 194 patients with cryptococcal meningitis led to the development of one or more adverse side effects in 103 patients. The toxicity included azotemia (51 patients), renal tubular necrosis (2 patients), leukopenia (30 patients), thrombocytopenia (22 patients), diarrhea (26 patients), nausea/vomiting (10 patients), and hepatitis (13 patients). Overall, both the 4- and 6-wk regimens were complicated by toxicity in 44 and 43% of the patients, respectively. In general, the observed side effects appeared during the first 2 wk of therapy in 56%, and during the first 4 wk in 87% of the patients *(175)*.

Shindo et al. *(176)* observed, alongside improvement, the presence of granulocytopenia and thrombocytopenia in one patient given concomitantly amphotericin B and low-dose flucytosine (50 mg/kg daily); it was suggested that both side effects might have been the result of toxic reactions by flucytosine in the azotemic state caused by amphotericin B. In another example, Bryan and McFarland *(177)* reported a fatal bone-marrow applasia in one patient with multiple myeloma and cryptococcal meningitis, following medication of the infection with combined amphotericin B and flucytosine (a total of 151 mg and 30.5 g, respectively). Although amphotericin B is considered beneficial in reducing the flucytosine toxicity on the bone marrow, again, caution should be in order with patients having hematologic malignancies and where a reduced marrow reserve is suspected *(178)*.

2.3. 5-Fluorocytosine (5-FC)

In 1965, flucytosine was first introduced in the therapy of cryptococcosis *(178,179)*. The drug is effective orally and also readily absorbed. Over 90% of it is excreted in the urine within the first 48 h; the observed levels in the CSF were half those present in the plasma *(180,181)*.

Although encouraging, earlier studies on the clinical usefulness of 5-FC against cryptococcal infections were carried out only with a limited number of patients. For example, when 5-FC (100 mg/kg daily, given in 4 oral doses for 20 wk) was applied to one patient following excision of multiple intracerebral supperative cryptococcal granulomas, the drug was well-tolerated and the patient was apparently free of cryptococcal infection 1 yr after the end of medication *(182)*. However, a rapid development of resistance towards 5-FC by *C. neoformans* is commonly observed *(183)*. This has been especially true for patients receiving less than 150 mg/kg daily of the drug at the onset of the infection when the cryptococcal population is at its peak *(183)*.

Consequently, in the therapy of either cryptococcal meningitis or pulmonary cryptococcosis, 5-FC alone was found often inadequate for a successful treatment because of the development of resistance. According to one study *(184)*, only 30% cure rate was observed while relapses and failures resulting from development of drug resistance were common *(185–187)*. For this reason, the use of flucytosine alone limits its use in cryptococcosis. Currently, the combination of amphotericin B and 5-FC is recommended whenever cryptococcal infection (especially with neurological involvement) is diagnosed.

Flucytosine-associated toxicity included liver damage, transient thrombocytopenia, neutropenia, anemia, and eosinophilia *(188)*. In addition, pancytopenia and severe agranulocytosis were also reported *(189–191)*. The damage on bone marrow *(185,192)* (including a fatal marrow aplasia *[192,193]*) is by far the most severe adverse effect of 5-FC and should be addressed properly. Philpot and Lo *(194)* reported the use of flucytosine in the treatment of cryptococcal meningitis in pregnancy without damage to the fetus.

2.4. Azole Derivatives

2.4.1. Miconazole

One general regimen for miconazole therapy of cryptococcal meningitis that has been recommended *(195)*, required an initial intravenous infusion of 30 mg/kg of the drug daily for 3 wk; following that period, if the patient was still unresponsive, miconazole was applied into the CSF space at a dosage of 20 mg twice daily, then going to 20 mg every other day.

In one Japanese study *(196)*, deep-seated mycoses were treated with miconazole at an initial dose of 200 mg (dissolved in at least 200 mL of solvent medium) injected intravenously (by drip-infusion) over a 30–60 min period. If no side effects were observed, 200–400 mg of the drug were administered intravenously over 30 min, 1–3 times daily.

On a negative note, Sung et al. *(197)* reported the failure of miconazole (administered both intravenously and intrathecally) to cure one patient with cryptococcal meningitis and suffering from multiple other complications; a previous combined amphotericin B-flucytosine therapy had also been unsuccessful *(197)*. Deresinsky et al. *(195)* applied miconazole intravenously to two patients with cryptococcosis with inconclusive results and a clinical response that could not be evaluated.

Because of many contradicting reports, the efficacy of miconazole in the therapy of cryptococcal meningitis is still very much in doubt. Since miconazole penetrates poorly into CSF when given systemically, the therapy of most cryptococcal infections associated with CNS involvement will eventually require intrathecal administration of flucytosine *(195,198–200)*. Controlled, randomized trials will be necessary to define unambiguously the usefulness of miconazole in the management of cryptococcal meningitis. In the treatment of pulmonary cryptococcosis, the efficacy of miconazole has also been very much in doubt.

2.4.2. Ketoconazole

Although ketoconazole has shown potent in vitro activity against *C. neoformans*, it is generally ineffective in treating cryptococcal meningitis *(88)*. Perfect et al. *(201)* found ketoconazole ineffective in the treatment of cryptococcal meningitis following therapy with high doses. In a contradicting report *(202)*, a case of cryptococcal meningitis showed improvement after high doses of the drug were applied.

Karaffa et al. *(203)* initiated a ketoconazole therapy in a patient with AIDS and disseminated cryptococcosis; the drug was applied at 400 mg daily but the patient, who continued to do well 5 mo after the diagnosis, still had extremely high serum levels of cryptococcal antigen.

Granier et al. *(204)* reported a successful therapy of localized cutaneous cryptococcosis in a renal allograft recipient receiving ketoconazole in conjunction with systemic steroids and azathioprine; ketoconazole was given orally at 400 mg daily for 6 mo with no relapse or dissemination observed.

2.4.3. Fluconazole

Fluconazole has been extensively studied for its therapeutic efficacy against cryptococcosis *(27,205–210)* especially against cryptococcal meningitis *(211–218)*.

Jones et al. *(219)* conducted a clinical trial using oral fluconazole to treat 32 AIDS patients with cryptococcal meningitis. Of the 11 patients who received a daily primary therapy of 200–400 mg/kg of fluconazole, 67% had a favorable clinical response; in 87% of these cases, the CSF cultures were negative. In addition, fluconazole was used as a secondary therapy in 15 patients who were not responsive to amphotericin B (or amphotericin B-fluconazole combination); positive clinical and mycological responses were obtained in over 60% of the patients. As maintenance therapy, 26 patients received 100–200 mg/kg fluconazole daily; the relapse rate of cryptococcal meningitis was 3.2 cases per 1,000 patient weeks (mean duration of 22 wk of maintenance therapy) *(219)*.

Dupont *(220)* reported a study involving 16 patients with AIDS and cryptococcal meningitis treated with oral fluconazole. The majority of patients received an initial loading dose of 400 mg, followed by 200 mg daily for 2 mo, then maintenance therapy of 100 mg daily. Eleven of 16 patients were clinically cured, concurrent with mycological clearance of all infected sites as well; 4 of 16 patients had clinical improvement but still showed positive CSF cultures; and 1 of 16 patients had clinical deterioration and died with positive CSF culture in spite of being switched to standard treatment *(220)*. This study, however, was not an open one, and the obtained results were not compared to standard therapy with amphotericin B-flucytosine.

Byrne and Wajszczuk *(221)* also described a successful use of 150 mg daily of fluconazole against cryptococcal meningitis in one patient with AIDS who had not responded well to an initial therapy with amphotericin B.

In more extensive clinical trials, the therapeutic efficacy of fluconazole was compared to that of amphotericin B. In a randomized, multicenter study *(92)* lasting for 10 wk, intravenously injected amphotericin B was compared with oral fluconazole (200 mg daily) as primary therapies in AIDS patients with acute cryptococcal meningitis; amphotericin B was given either at a mean daily dose of 0.4 mg/kg, or at 0.5 mg/kg depending on patients' response ($p = 0.34$). The treatment was successful in 25 of 63 patients receiving amphotericin B (40%; 95% confidence interval, 26–53%) and in 44 of the 131 fluconazole recipients (34%; 95% confidence interval, 25–42%) ($p = 0.40$). There was no significant difference in the overall mortality rate between the two groups (amphotericin B vs fluconazole, 14 and 18%, respectively; $p = 0.48$); however, during the first 2 wk of treatment, the mortality in the fluconazole group was higher (15 vs 8%; $p = 0.25$). Treatment was considered successful when the patients had two consecutive negative CSF cultures by the end of the 10-wk trial period. The median length of time to the first negative CSF culture was 42 d (95 confidence interval, 28–71%) for the amphotericin B group, and 64 d (95% confidence interval, 53–67%) for the fluconazole group ($p = 0.25$) *(92)*.

In a recently completed retrospective clinical study, the efficacies of amphotericin B and fluconazole were evaluated in HIV-negative patients (organ-transplant recipients, patients with neoplastic disease) and with meningeal and extrameningeal cryptococcosis *(222)*. Patients with more severe infections (i.e., meningitis, neurological disorders, or higher level of antigen in CSF) were more frequently treated with amphotericin B; a cure rate of less than 70% was achieved regardless of the initial treatment and severity of infection. In general, a Cox regression analysis has shown that in patients older than 60 yr, neoplastic disease, abnormal mental status, disseminated infection at the time of diagnosis, and therapeutic failure were independent predictors of death. Although fluconazole appeared to be equipotent to amphotericin B, only a prospective multicenter study would be sufficient to determine the best treatment regimen for cryptococcal infections in HIV-negative patients *(222)*.

In another randomized clinical trial of AIDS patients with cryptococcal meningitis, Larsen et al. *(223)* compared the therapeutic efficacies of fluconazole with a combination of amphotericin B and flucytosine. The all-male group was randomly assigned to either oral fluconazole (400 mg daily) for 10 wk, or to amphotericin B (0.7 mg/kg daily) for 1 wk, then 3 times weekly for 9 wk combined with flucytosine (150 mg/kg daily, in 4 divided doses). Eight of 14 patients (57%) assigned to fluconazole failed to respond, compared to none of 6 patients assigned to amphotericin B plus flucytosine therapy. The mean duration of positive CSF cultures was 40.6 ± 5.4 d in patients receiving fluconazole, and 15.6 ± 6.6 d in those receiving amphotericin B plus flucytosine. Although such results show that combined amphotericin B-flucytosine medication may be superior to fluconazole in the treatment of cryptococcal meningitis in AIDS patients, the intravenous therapy of amphotericin B has been associated with frequent and often severe side effects compared to oral fluconazole given once daily. Further studies should provide the necessary information to determine the feasibility of the amphotericin B-flucytosine combination and the contribution of flucytosine *(224)*. According to a cost-minimization analysis conducted by Buxton et al. *(225)*, costs associated with the use of fluconazole as primary therapy will likely be significantly lower than those for amphotericin B, but similar (or slightly less) for a maintenance therapy.

A case of cryptococcal meningoencephalitis in a patient with Hodgkin's disease at third-stage B became asymptomatic after 1 wk of therapy with intravenous fluconazole (400 mg daily); 2 mo later, all laboratory tests of CSF and blood specimens were negative *(226)*. Combination of amphotericin B (20 mg daily, i.v.) and flucytosine (2.5 g daily, i.v.) did not lead to any improvement *(226)*. Iacopino et al. *(227)* also used fluconazole to treat disseminated cryptococcosis in a patient with Hodgkin's disease.

Oral fluconazole (once daily at doses of 50–200 mg/kg) was applied to 20 AIDS patients having disseminated cryptococcosis *(228)*. All patients received amphotericin B as primary therapy before entry. Fluconazole medication was successfully maintained in nine patients for a median of 11 mo; seven patients died (five of them did not have evidence of active cryptococcosis at the time of death), and two patients experienced a relapse. Fluconazole had to be discontinued in only one patient when thrombocytopenia developed, and then resolved when the drug was stopped *(228)*.

Bozzette et al. *(229)* also evaluated maintenance therapy with fluconazole in a placebo-controlled, double-blind, clinical trial of AIDS patients with cryptococcal meningitis. The drug was given at 100 mg daily in the first phase of the study, and 200 mg daily in the second phase. Following a clinically successful therapy with flucytosine, 19% of the enrolled patients presented a silent, persistent cryptococcal infection. However, there was no recurrent meningeal infection observed in those patients taking fluconazole (mean duration of follow-up, 164 d; $p = 0.03$), suggesting it as an effective alternative for maintenance therapy against cryptococcal infections *(229)*.

The suppressive efficacy of fluconazole in preventing relapse from cryptococcal meningitis in AIDS patients was corroborated by findings from a larger trial *(230)*. Two suppressive regimens were compared: fluconazole at daily oral doses of 200 mg (11 patients; 59%) vs amphotericin B at 1.0 mg/kg per week (78 patients; 41%). The failure rate of the amphotericin B-treated group was markedly higher (33%; 26 of 78 patients) compared to only 8% of the fluconazole-receiving patients (9 of 11 patients) *(230)*. A successful maintenance therapy of cryptococcosis with fluconazole was also described for 80 AIDS patients from Burundi *(231)*.

In an uncontrolled, open trial with a small number of AIDS patients with cryptococcosis, fluconazole was found to be effective in preventing relapses after the active disease was controlled with amphotericin B *(232)*; however, the drug was found not very effective at conventional doses (50–100 mg daily) usually applied for treatment of active cryptococcosis. Observed side effects of fluconazole included an increase in hepatic function test values in one patient, and seisures in another; in both cases fluconazole had to be discontinued.

C. neoformans-induced pleural empyema secondary to liver cirrhosis due to hepatitis C virus infection responded well to oral fluconazole *(233)*.

Retinitis resulting from disseminated cryptococcosis in a renal allograft recipient showed remarkable improvement following therapy with oral fluconazole *(234)*. Cryptococcal endophthalmitis is a rare disorder, nearly always diagnosed after enucleation or at postmortem examination. Custis et al. *(235)* have described a culture-positive cryptococcal endophthalmitis in a patient with chronic uveitis diagnosed by vitreous biopsy at the time of retinal detachment repair. The fungus, *Cryptococcus laurentii* is a previously unreported non-*neoformans* ocular pathogen. After a 5-mo course of oral fluconazole, the patient was culture-negative; however, the visual declined to hand motions because of hyphema and hypotony.

Although cutaneous cryptococcosis is frequently diagnosed in AIDS patients, it has only seldom been observed in other immunocompromised patients *(27,236–238)*. In one such case, Abraham et al. *(27)* described a renal allograft recipient with necrotic cryptococcal granulomata on the dorsum of the hand but no clinical evidence of systemic infection; the infection was successfully cured after a 6-mo treatment with oral fluconazole (400 mg, daily). Vandersmissen et al. *(236)* described the successful use of a 6-wk course of oral fluconazole in two corticosteroid-treated HIV-negative patients who developed cutaneous cryptococcosis. In a relevant case *(239)*, cryptoccocal whitlow in an HIV-positive patient (unusual clinical presentation of cutaneous cryptococcosis never seen before in this population) was cured with fluconazole at 400 mg daily for 2 mo, and 200 mg daily thereafter. Contrary to AIDS patients who need life-long antifungal maintenance therapy to prevent relapses, suppressive treatment may not be indicated for immunocompromised non-AIDS patients *(236)*.

Other reports describing successful use of oral fluconazole against cryptococcal infections, included laryngeal cryptococcosis *(240)*, neck mass resulting in lytic destruction of portion of the cervical vertebrae *(241)*, and pulmonary cryptococcosis in non-AIDS patients (400 mg daily, for 10–12 wk) *(242)*.

After evaluation of 4,048 patients who received fluconazole for at least 7 d, some of the undesirable side effects included: nausea (3.7%), headache (1.9%), skin rash (1.8%), vomiting (1.7%), abdominal pain (1.7%), and diarrhea (1.5%) *(243)*. Although adverse effects are more likely to occur in HIV-positive patients, their pattern remained essentially the same, with only 1.5% of patients having their medication discontinued because of side effects *(244)*. Fluconazole may also induce multiple hepatic abnormalities usually characterized by asymptomatic and reversible mild hepatic

necrosis. However, Guillaume et al. *(245)* described severe subacute liver damage occuring in an AIDS patient that may be related to prolonged fluconazole maintenance therapy for cryptococcsis; electron microscopic studies revealed the presence of a unusual giant mitochondria with paracrystalline inclusions and enlarged smooth endoplasmic reticulum. All microscopic abnormalities were reversed after discontinuation of fluconazole. Alopecia appeared to be a common adverse effect associated with higher-dose (400 mg daily) of fluconazole given for 2 mo or longer; although sometimes severe, the effect is reversed by discontinuing fluconazole therapy or substantially reducing the daily dose *(246,247)*.

Drug-interaction studies demonstrated that when fluconazole was administered in multiple daily doses of up to 400 mg, it did not produce noticeable effects on testosterone, estrogen, or the ACTH-stimulated cortisol concentrations *(243)*. Furthermore, no drug interaction has been observed when fluconazole was administered (at daily doses of 100 mg or more) concomitantly with cyclosporin A to bone-marrow transplant recipients (but not renal-transplant patients) *(243)*.

Failures of fluconazole in treatment of cryptococcal meningitis *(248)* and prostate cryptococcosis *(249)* have also been reported. For example, a 10-wk regimen of fluconazole, if first given intravenously then orally, resulted in failure in 62% of patients (8 of 13) *(250)*. However, when the drug was administered entirely by oral route, the failure rate was only 10% (5 of 17 patients) *(251)*. To this end, Aller et al. *(252)* have found that MIC valued determined by a modified microdilution method could serve as potential predictors of the clinical response to fluconazole therapy and may help in the identification of patients who will not respond to fluconazole therapy.

Cases of fluconazole-resistant *C. neoformans* have also been reported *(253,254)*.

2.4.4. Itraconazole

Itraconazole, another recently developed triazole-containing antimycotic *(255)*, has been used in the treatment of AIDS patients with meningeal and/or additional neurological cryptococcosis at daily oral doses of 200–400 mg *(220)*. There was no report on the success rate of the treatment, but a maintenance therapy with the drug (200–400 mg daily) was recommended to prevent relapses.

According to Van Cutsem and Cauwenbergh *(256)*, in patients with meningeal or pulmonary cryptococcosis, daily treatment with 200 mg itraconazole for 88 (median) or 139 (median) d produced global responses of 57 and 83% of patients, respectively, and negative mycological response in 51 and 50%, respectively; a similar study involving daily administration of 400 mg of itraconazole to both groups for 160–216 d (median; meningeal) and 160 d (median; pulmonary) resulted in global responses of 86 and 89%, respectively *(256)*.

Data from itraconazole treatment (200 mg daily) of three AIDS patients with disseminated cryptococcosis were reported by Viviani et al. *(257)*. All patients received conventional therapy with amphotericin B prior to itraconazole. Within 1 mo of treatment, suppression of clinical symptoms in two of the patients, and further improvement in the third, were observed. Although cultures became negative, two of the patients still had encapsulated yeast present in the CSF *(381)*. A long-term maintenance therapy with the drug (3.0 mg/kg) has been recommended *(258)*.

The therapeutic efficacy of itraconazole has been examined in 33 patients with various manifestations of cryptococcosis (meningitis, cryptococcemia, cryptococcuria, osteomyelitis, pulmonary cryptococcosis, and soft-tissue cryptococcosis) *(259)*. Thirty-two of the patients were immunocompromised, including 4 transplant recipients and 26 with AIDS. The treatment consisted of 200 mg oral itraconazole, two times daily. Results showed that cryptococcemia was abolished 100%. Furthermore, 65% of the patients with cryptococcal meningitis showed complete response (as manifested by clinical resolution and negative cultures), whereas 25% had partial response, and in 10% the treatment had failed. In 71% of patients with AIDS who had meningitis and were treated with itraconazole as their sole therapy, the response was complete, whereas 21% responded partially, and the therapy failed in 7%. All patients who had pulmonary cryptococcosis, soft-tissue cryptococcosis, or osteomyelitis responded 100% to itraconazole therapy, compared to only 60% of

patients with cryptococcuria. Because itraconazole hardly penetrated the CSF, the results for cryptococcal meningitis suggested that meningeal and parenchymal penetration was important in lowering the therapeutic efficacy *(259)*.

In another report *(260)*, oral itraconazole was successful in 28 patients with cryptococcal meningitis; 18 of them have achieved complete response, including 16 of 24 patients with AIDS.

A clinical trial of five AIDS patients conducted by de Gans et al. *(261)*, demonstrated a promise for itraconazole as maintenance therapy for cryptococcal meningitis. Each patient received initial treatment with amphotericin B (0.3 mg/kg daily, intravenously) and oral 5-FC (150 mg/kg daily, every 6 h) for 6–8 wk. In four of the patients, the titer of cryptococcal antigen in CSF declined. Two of the patients were still alive, respectively, 10 and 12 mo after a maintenance therapy with itraconazole had began with no toxic side effects from the drug *(261)*.

Batungwanayo et al. *(262)* found itraconazole to be highly effective in the prevention of disseminated cryptococcal disease among HIV-positive Rwandan patients with primary pulmonary cryptococcosis.

Oral itraconazole at 100 *(263)*, 200 *(264)*, or 400 mg *(265)* once daily was also used successfully in treatment of localized cutaneous cryptococcosis *(263)*. In another case of cutaneous cryptococcosis in a patient receiving immunosuppressive therapy, medication with itraconazole resulted in lesion improvement after topical treatment proved ineffective *(238)*.

Among the interactions of itraconazole with other drugs, it should be mentioned that its levels were decreased by rifampicin, phenytoin, and phenobarbital, while itraconazole increased the levels of cyclosporin A. Caution should be applied in patients receiving concomitant anticoagulants.

3. PROPHYLAXIS AND MAINTENANCE THERAPY OF CRYPTOCOCCOSIS

Based on results from prospective controlled trials, fluconazole and itraconazole were both able to reduce the frequency of cryptococcosis in patients with advanced HIV disease *(266)*. Although not routinely recommended, the prophylaxis of cryptococcal disease is usually carried out in patients with $CD4^{4+}$ T-lymphocyte counts of less than 50 cells/μL using daily doses of 100–200 mg fluconazole (Table 2) *(266–269)*. After a documented first episode of cryptococcosis, patients should receive lifelong maintenace therapy (secondary prophylaxis) *(266)*.

4. *CRYPTOCOCCUS NEOFORMANS* VAR. *GATTII*

Before the rise of the AIDS epidemic, cryptococcal meningitis in the tropical and subtropical regions usually affected apparently immunocompetent persons, in contrast to those presenting in temperate climates, where infection was most often associated with immunosuppression *(270,271)*. Biotyping of clinical isolates showed that, serotypes B and C characteristic for *C. neoformans* var. *gattii* were commonly identified in patients from the tropical and subtropical areas *(272–276)* whereas serotypes A, D, and A/D of *C. neoformans* var. *neoformans* were found in predominantly temperate regions *(277)*. It seemed that the human disease caused by var. *gattii* had predilection for the respiratory and central nervous systems, and has been endemic for Australia *(278,279)*, Papua New Guinea *(271–275)*, Southern California, and parts of Africa, India, Southeast Asia, and Central and South America (Mexico, Brasil, and Paraguay) *(277)*. Based on results of searches conducted in Australia, the eucalypt species *Eucalyptus camaldulensis* and *E. tereticornis* constituted, although circumstantially, the only known environmental niche of *C. neoformans* var. *gattii (273,280–282)*. Comparison of a single Californian environmental isolate with three environmental isolates from Australia by karyotyping revealed that although genetically different the four isolates were related *(283,284)*.

The course of meningitis caused by the two different varieties of *C. neoformans* may differ *(285,286)*, with mortality rate in the tropics remaining particularly high *(271,275,287)*.

Treatment of *C. neoformans* var. *gattii*-associated meningitis has been most successful with amphotericin B (0.3–1.0 mg/kg daily, parenterally) and flucytosine (150 mg/kg daily, orally) *(275)*.

Table 2
Prophylaxis Against Cryptococcosis

		Prophylactic drug regimens	
Patients	Indication	First line	Alternative line
Adults and adolescents	First episode: CD^{4+} counts of >50 μL	Fluconazole 100–200 mg, p.o., daily	Itraconazole 200 mg, p.o., daily
	Documented disease	Fluconazole 200 mg, p.o., daily	Amphotericin B 0.6–1.0 mg/kg, i.v., 3 times weekly; or Itraconazole 200 mg, p.o., daily
Infants and children[a]	Severe immunosuppression	luconazole 3–6 mg/kg, p.o., daily	Itraconazole 2–5 mg/kg, p.o., every 12–24 h
	Documented disease	Fluconazole 3–6 mg/kg, p.o., daily	Amphotericin B 0.5–1.0 mg/kg, i.v., 1–3 times weekly; or Itraconazole 2–5 mg/kg, p.o., every 12–24 h

[a]Prophylaxis not recommended for most children but only in cases of severe immunosuppression.

Treatment of an AIDS patient with *C. neoformans* var. *gattii*-induced meningitis resulted in poor clinical and mycological response; in vitro sensitivity testing revealed high MIC value suggesting fluconazole resistance *(288)*. Kamei et al. *(289)* have found voriconazole, a new triazole antimycotic, to be more effective than fluconazole when tested in vitro in two different systems.

5. *CRYPTOCOCCUS ALBIDUS*

C. albidus, is commonly isolated yeast from skin of healthy persons, as well as in indoor or outdoor air *(290)*. The organism has also been isolated from blood specimens *(291,292)*. Although rarely, this yeast has been the cause of meningitis *(293–295)*, lung abscess *(291,296)*, and empyema *(297)* in immunocompromised patients. Studying the distribution of yeast isolates from the oral mucosa of HIV-positive patients, Mckee et al. *(298)* found among non-*Candida* yeasts also *C. albidus*.

Loison et al. *(299)* described what appeared to be the first case of septicemia due to *C. albidus* in an HIV-positive patient. The yeast was sensitive in vitro to amphotericin B, fluconazole, miconazole, itraconazole, and 5-FC. Although the infection was resolved initially with a 2-wk treatment with oral fluconazole at 600 mg daily, followed by fluconazole prophylaxis, a relapse did occur prompting change of the antifungal treatment to oral itraconazole (400 mg daily); the patient died shortly thereafter from cardiovascular arrest. In another fatal case, an AIDS patient with *C. albidus* cryptococcemia died on the 14th day of treatment with amphotericin B-flucytosine combination therapy *(300)*.

6. *CRYPTOCOCCUS LAURENTII*

The natural habitat of *C. laurentii* and its prevalence in the environment have not yet been established. There has been no data about its isolation from normal respiratory flora either, although it would appear to be extraordinarily rare *(301,302)*.

Lynch et al. *(301)* reported the first case of pulmonary infection caused by *C. laurentii* manifested as a lung abscess in a patient with dermatomyositis receiving corticosteroid therapy. The isolation of the yeast appeared to be consistent with an opportunistic infection (pulmonary infiltration with cavity formation developed in association with corticosteroid therapy), rather than saprophytic coloniza-

tion. Treatment has been carried out successfully with a 6-wk course of amphotericin B (total dose, 2.0 g). In vitro, the antibiotic showed a MIC value of 0.1 µg/mL against a clinical isolate. The latter was not susceptible to 5-FC (MIC = 500 µg/mL), and there has been no synergism between amphotericin B and 5-FC.

C. laurentii has been diagnosed as the etiologic pathogen in a rare case of cryptococcal endophthalmitis cured successfully with oral fluconazole *(303)*.

Kordossis et al. *(300)* described the first case of *C. laurentii* meningitis in an AIDS patient; the condition was controlled after 2 wk of treatment with amphotericin B and flucytosine and no evidence of infection 20 mo later.

REFERENCES

1. Busse, O. Über Parasitare zelleinschlusse und ihre Zuchtung. *Centralbl. Bakt.*, 16, 175, 1894.
2. Colmers, R. A,, Irniger, W., and Steinberg, D. H. *Cryptococcus neoformans* endocarditis cured by amphotericin. *J. Am. Med. Assoc.*, 199, 762, 1967.
3. Arasteh, K., Staib, F., Grosse, G., Futh, U., and L'Age, M. Cryptococcosis in HIV infection of man: an epidemiological and immunological indicator? *Zentralbl. Bakteriol.*, 284, 153, 1996.
4. Littman, M. C. and Walter, J. E. Cryptococcosis: current status. *Am. J. Med.*, 45, 922, 1968.
5. Sabetta, J. R., and Andriole, V. T. Cryptococcal infection of the central nervous system. *Med. Clin. North Am.*, 69, 333, 1985.
6. Butler, W. T., Alling, D. W., Spickard, A., and Utz, J. P. Diagnostic and prognostic value of clinical and laboratory findings in cryptococcal meningitis. *N. Engl. J. Med.*, 270, 59, 1964.
7. De Wytt, C. N., Dickson, P. L., and Holt, G. W. Cryptococcal meningitis: a review of 32 years' experience. *J. Neurol. Sci.*, 53, 283, 1982.
8. Sarosi, G. A., Parker, J. D., Doto, I. L., and Tosh, F. E. Amphotericin B in cryptococcal meningitis: long-term results of treatment. *Ann. Intern. Med.*, 71, 1079, 1969.
9. Spickard, A., Butler, W. T., Andriole, V., and Utz, J. P. The improved prognosis of cryptococcal meningitis with amphotericin B therapy. *Ann. Intern. Med.*, 58, 66, 1963.
10. Utz, J. P., Garriques, I. L., Sande, M. A., et al. Therapy of cryptococcosis with a combination of flucytosine and amphotericin B. *J. Infect. Dis.*, 132, 368, 1975.
11. Zimmerman, L. E. and Rappaport, H. Occurence of cryptococcosis in patients with malignant disease of the reticuloendothelial system. *Am. J. Clin. Pathol.*, 24, 1050, 1954.
12. Perfect, J. R., Durack, D. T., and Gallis, H. A. Cryptococcemia. *Medicine (Baltimore)*, 62, 98, 1983.
13. Graybill, J. R. and Alford, R. H. Cell-mediated immunity in cryptococcosis. *Cell. Immunol.*, 14, 12, 1974.
14. Schimpff, S. C. and Bennett, J. E. Abnormalities in cell-mediated immunity in patients with *C. neoformans* infections. *J. Allergy Clin. Immunol.*, 55, 430, 1975.
15. Krick, J. A. Familial cryptococcal meningitis. *J. Infect. Dis*, 143, 133, 1981.
16. Ieong, M. H., Reardon, C. C., Levitz, S. M., and Kornfeld, H. Human immunodeficiency virus type 1 infection of alveolar macrophages impairs their innate fungicidal activity. *Am. J. Respir. Crit. Care Med.*, 162(3 Pt. 1), 966–970, 2000.
17. Mambula, S. S., Simons, E. R., Hastey, R. P., and Levitz, S. M. Human neutrophil-mediated nonoxidative antifungal activity against *Cryptococcus neoformans*. *Abstr. 99th Abstr. Gen. Meet. Am. Soc. Microbiol., May 30–June 3*, 303, abstract F-42, 1999.
18. Aguirre, K., Havell, E. A., Gibson, G. W., and Johnson, L. L. Role of tumor necrosis factor and gamma interferon in acquired resistance to *Cryptococcus neoformans* in the central nervous system of mice. *Infect. Immun.*, 63, 1725, 1995.
19. Kawakami, K., Koguchi, Y., Qureshi, M. H., et al. IL-18 contributes to host resistance against infection with *Cryptococcus neoformans* in mice with defective IL-12 synthesis through induction of IFN-gamma production by NK cells. *J. Immunnol.*, 165, 941–947, 2000.
20. Watanabe, H., Inukai, A., Doyu, M., and Sobue, G. CNS cryptococcosis with idiopathic CD4+ T lymphocytopenia. *Rinsho Shinkeigaku*, 40, 249–253, 2000.
21. Kerkering, T. M., Duma, R. J., and Shadomy, S. The evolution of pulmonary cryptococcosis. *Ann. Intern. Med.*, 94, 611, 1981.
22. Reblin, T., Meyer, A., Albrecht, H., and Greten, H. Disseminated cryptococcosis in a patient with AIDS. *Mycoses*, 37, 275, 1994.
23. Sarosi, G. A., Silberfarb, P. M., and Tosh, F. E. Cutaneous cryptococcosis: a sentinel of disseminated disease. *Arch. Dermatol.*, 104, 1, 1971.
24. Srur, E., Misad, C., and Henriquez, A. Extrameningeal cryptococcosis in a patient with AIDS. *Rev. Med. Chil.*, 123, 1009, 1995.
25. Houston, S., Lipp, K., Cobian, L., and Sinnott, J. T. Skin rash in a renal transplant recipients. *Hosp. Pract. (Off. Ed.)*, 30, 89, 1995.
26. Haight, D. O., Esperanza, L. E., Greene, J. N., et al., Case report: cutaneous manifestations of cryptococcosis. *Am. J. Med. Sci.*, 308, 192, 1994.

27. Abraham, K. A., Little, M. A., Casey, R., Smyth, E., and Walshe, J. J. A novel presentation of cryptococcal infection in a renal allograft recipient. *Ir. Med. J.*, 93, 82-84, 2000.
28. Gosling, H. R. and Gilmer, W. S. Skeletal cryptococcosis: report of a case and review of the literature. *J. Bone Joint Surg.*, 38A, 660, 1956.
29. Hinchey, W. W. and Someren, A. Cryptococcal prostatis. *Am. J. Clin. Pathol.*, 75, 257, 1981.
30. Randal, R. E. Jr., Stacy, W. K., Prout, G. R. Jr., et al. Cryptococcal pyelonephritis. *N. Engl. J. Med.*, 279, 60, 1968.
31. Okun, E. and Butler, W. T. Ophthalmologic complications of cryptococcal meningitis. *Arch. Ophthalmol.*, 71, 52, 1964.
32. Weiss, C., Perry, I. H., and Shevky, M. C. Infections of the human eye with *Cryptococcus neoformans* (*Torula histolytica*). *Arch. Ophthalmol.*, 39, 739, 1948.
33. Procknow, J. J., Benfield, J. R., Ripon, J. W., Diener, C. F., and Archer, F. L. Cryptococcal hepatitis presenting as a surgical emergency. *J. Am. Med. Assoc.*, 191, 269, 1965.
34. Sabesin, S. M., Fallon, H. J., and Andriole, V. T. Hepatic failure as a manifestation of cryptococcosis. *Arch. Intern. Med.*, 111, 661, 1963.
35. Goenka, M. K., Mehta, S., Yachha, S., Nagi, B., Chakraborty, A., Malik, A. K. Hepatic involvement culminating in cirrhosis in a child with disseminated cryptococcosis. *J. Clin. Gastroenterol.*, 20, 57, 1995.
36. Baker, R. D. and Haugen, R. K. Tissue damages and tissue diagnosis in cryptococcosis. *Am. J. Clin. Pathol.*, 25, 14, 1955.
37. Bowman, H. E. and Ritchey, J. O. Cryptococcosis (torulosis) involving brain, adrenal, and prostate. *J. Urol.*, 71, 373, 1954.
38. Voyles, G. O. and Beck, E. M. Systemic infection due to *Torula histolytica* (*C. hominis*): report of four cases and review of the literature. *Arch. Intern. Med.*, 77, 504, 1946.
39. Zelman, S., O'Neil, H., and Plaut, A. Disseminated visceral torulosis without nervous system involvement with clinical appearance of granulocytic leukemia. *Am. J. Med.*, 11, 568, 1951.
40. Poliner, J. R., Wilkins, E. B., and Fernald, G. W. Localized osseous cryptococcosis. *J. Pediatr.*, 94, 597, 1979.
41. Goldman, M. and Pottage, J. C. Jr. Cryptococcal infection of the breast. *Clin. Infect. Dis.*, 21, 1166, 1995.
42. Merwaha, R. K., Trehan, A., Jayashree, K., and Vasishta, R. K. Hypereosinophilia in disseminated cryptococcal disease. *Pediatr. Infect. Dis. J.*, 14, 1103, 1995.
43. Larsen, R. A., Bozzette, S., McCutchan, J. A., et al. Persistent *Cryptococcus neoformans* infection of the prostate after successful treatment of meningitis. *Ann. Intern. Med.*, 111, 125, 1989.
44. Fuse, H., Ohkawa, M., Yamaguchi, K., Hirata, A., and Matsubara, F. Cryptococcal prostatitis in a patient with Behcet's disease treated with fluconazole. *Mycopathologia*, 130, 147, 1995.
45. Glassman, S. J. and Hale, M. J. Cutaneous cryptococcosis and Kaposi's sarcoma occuring in the same lesions in a patient with the acquired immunodeficiency syndrome. *Clin. Exp. Dermatol.*, 20, 480, 1995.
46. Muccioli, C., Belfort Junior, R., Neves, R., and Rao, N. Limbal and choroidal *Cryptococcus* infection in the acquired immunodeficiency syndrome. *Am. J. Ophthalmol.*, 120, 539, 1995.
47. Benard, G., Gryschek, R. C., Duarte, A. J., and Shakanai-Yasuda, M. A. Cryptococcosis as an opportunistic infection in immunodeficiency secondary to paracoccidioidomycosis. *Mycopathologia*, 133, 65, 1996.
48. Molnar-Nadasdy, G., Haesly, I., Reed, J., and Altshuler, G. Placental cryptococcosis in a mother with systemic lupus erythematosus. *Arch. Pathol. Lab. Med.*, 118, 757, 1994.
49. Zuger, A., Louie, E., Holzman, R. S., Simberkoff, M. S., and Rahal, J. J. Cryptococcal disease in patients with acquired immunodeficiency syndrome: diagnostic features and outcome of treatment. *Ann. Intern. Med.*, 104, 234, 1986.
50. Kovacs, J. A., Kovacs, A. A., Polis. M., et al. Cryptococcosis in the acquired immunodeficiency syndrome. *Ann. Intern. Med.*, 103, 533, 1985.
51. Dismukes, W. E., Cloud, G., Gallis, H. A., et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. *N. Engl. J. Med.*, 317, 334, 1987.
52. Eng, R. H.K., Bishburg, E., Smith, S. M., and Kapila, R. Cryptococcal infections in patients with acquired immune deficiency syndrome. *Am. J. Med.*, 81, 19, 1986.
53. Theunissen, A. W. J. and Zanen, H. C. Dertig petienten net een "verborgen" ziekte: cryptococcen-meningitis. *Ned. Tijdschr. Geneeskd.*, 131, 1123, 1987.
54. Castro Guardiola, A., Ocana Rivera, I., Gasser Laguna, I., et al. 16 cases of infections by *Cryptococcus neoformans* in patients with AIDS. *Enferm. Infec. Microbiol. Clin.*, 9, 90, 1991.
55. Sugar, A. M. Overview: cryptococcosis in the treatment of AIDS. *Mycopathologia*, 114, 153, 1991.
56. Fur, B. Cryptococcosis in AIDS: therapeutic concepts. *Mycoses*, 33(Suppl.1), 55, 1990.
57. Kirchner, J. T. Opportunistic fungal infections in patients with HIV disease: combating cryptococcosis and histoplasmosis. *Postgrad. Med.*, 99, 209, 1996.
58. Mitchell, T. G. and Perfect, J. R. Cryptococcosis in the era of AIDS: 100 years after the discovery of *Cryptococcus neoformans*. *Clin. Microbiol. Rev.*, 8, 515, 1995.
59. Just-Nübling, G. Therapy of candidiasis and cryptococcosis in AIDS. *Mycoses*, 37(Suppl. 2), 56, 1994.
60. Emmons III, W. W., Luchsinger, S., and Miller, L. Progressive pulmonary cryptococcosis in a patient who is immunocompetent. *South. Med. J.*, 88, 657, 1995.
61. Munoz-Peréz, M. A., Colmenero, M. A., Rodriguez-Pichardo, A., Rodriguez-Pinero, F. J., Rios, J. J., and Camacho, F. Disseminated cryptococcosis presenting as moluscum-like lesions as the first manifestation of AIDS. *Int. J. Dermatol.*, 35, 646, 1996.
62. Gonzalez, C. E., Shetty, D., Lewis, L. L., Mueller, B. U., Pizzo, P. A., and Walsh, T. J. Cryptococcosis in human immunodeficiency virus-infected children. *Pediatr. Infect. Dis. J.*, 15, 796, 1996.

63. Littman, M. L. and Zimmerman, L. E. *Cryptococcosis*. Grune & Stratton, New York, 1956.
64. Haugen, R. K. and Baker, R. D. The pulmonary lesions in cryptococcosis with special reference to subpleural nodules. *Am. J. Clin. Pathol.*, 24, 1381, 1954.
65. Talerman, A., Bradley, J. M., and Woodland, B. Cryptococcal lymphadenitis. *J. Med. Microbiol.*, 3, 633, 1970.
66. Salyer, W. R., Salyer, D. C., and Baker, R. D. Primary complex of *Cryptococcus* and pulmonary lymph nodes. *J. Infect. Dis.*, 130, 74, 1974.
67. Houk, V. N. and Moser, K. M. Pulmonary cryptococcosis: must all receive amphotericin B. *Ann. Intern. Med.*, 63, 583, 1965.
68. Campbell, G. D. Primary pulmonary cryptococcosis. *Am. Rev. Respir. Dis.*, 94, 236, 1966.
69. Duperval, R., Hermans, P. E., Brewer, N. S., and Roberts, G. D. Cryptococcosis with emphasis on the significance of isolation of *C. neoformans* from the respiratory tract. *Chest*, 72, 13, 1977.
70. Hammerman, K. J., Powell, K. E., and Christianson, C. S. Pulmonary cryptococcosis: clinical forms and treatment - CDC cooperative mycoses study. *Am. Rev. Respir. Dis.*, 108, 1116, 1973.
71. Gurevitz, O., Goldschmiedt-Reuven, A., Block, C., Kopolovic, J., Farfel, Z., and Hassin, D. *Cryptococcus neoformans* vertebral osteomyelitis. *J. Med. Vet. Mycol.*, 32, 315, 1994.
72. Anthony, S. A. and Anthony, S. J. Primary cutaneous cryptococcosis in nonimmunocompromised patients. *Cutis*, 56, 96, 1995.
73. Gordon, P. M., Ormerod, A. D., Harvey, G., Atkinson, P., and Best, P. V. Cutaneous cryptococcal infection without immunodeficiency. *Clin. Exp. Dermatol.*, 19, 181, 1994.
74. Mahida, P., Morar, R., Goolam Mohamed, A., Song, E., Tissandie, J. P., and Feldman, C. Cryptococcosis: an unusual cause of endobronchial obstruction. *Eur. Respir. J.*, 9, 837, 1996.
75. Schepelmann, K., Muller, F., and Dichgans, J. Cryptococcal meningitis with severe visual and hearing loss and radiculopathy in a patient without immunodeficiency. *Mycoses*, 36, 429, 1993.
76. Vender, J. R., Miller, D. M., Roth, T., Nair, S., and Reboli, A. C. Intraventricular cryptococcal cysts. *AJNR Am. J. Neuroradiol.*, 17, 110, 1996.
77. Yu, F. C., Perng, W. C., Wu, C. P., Shen, C. Y., and Lee, H. S. Adult respiratory distress syndrome caused by pulmonary cryptococcosis in an immunocompetent host: a case report. *Chung Hua I Hsueh Tsa Chih (Taipei)*, 52, 120, 1993.
78. Hellman, R. N., Hinrichs, J., Sicard, G., Hoover, R., Golden, P., and Hoffsten, P. Cryptococcal pyelonephritis and disseminated cryptococcosis in a renal transplant recipient. *Arch. Intern. Med.*, 141, 128, 1984.
79. Liss, H. P. and Rimland, D. Asymptomatic cryptococcal meningitis. *Am. Rev. Respir. Dis.*, 124, 88, 1981.
80. Tarala, R. A. and Smith, J. D. Cryptococcosis treated by rapid infusion of amphotericin B. *Br. Med. J.*, 281, 28, 1980.
81. Mosberg, W. H. and Arnold, J. G. Torulosis of the central nervous system: review of the literature and report of five cases. *Ann. Intern. Med.*, 32, 1153, 1950.
82. Beeson, P. B. Cryptococcal meningitis of nearly sixteen years' duration. *Arch. Intern. Med.*, 89, 797, 1952.
83. Campbell, G. D., Carrier, R. D., and Busey, J. F. Survival in untreated cryptococcal meningitis. *Neurology*, 31, 1154, 1981.
84. Carton, C. A. and Mount, L. A. Neurosurgical aspects of cryptococcosis. *J. Neurosurg.*, 8, 143, 1951.
85. Powderly, W. G. Recent advances in the management of cryptococcal meningitis in patients with AIDS. *Clin. Infect. Dis.,* 22(suppl. 2), S119, 1996.
86. Dismukes, W. E. Management of cryptococcosis. *Clin. Infect. Dis.*, 17(Suppl. 2), S507, 1993 [see also: *Clin. Infect. Dis.*, 19, 975, 1994].
87. Powderly, W. G. Current approach to the acute management of cryptococcal infections. *J. Infect.*, 41, 18–22, 2000.
88. Saag, M. S., Graybill, R. J., Larsen, R. A., et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin. Infect. Dis.*, 30, 710–718, 2000.
89. Van der Horst, C., Saag, M., Cloud, G., et al. Randomized double blind comparison of amphotericin B (AMB) plus flucytosine to AMB alone (step 1) followed by a comparison of fluconazole to itraconazole (step 2) in the treatment of acute cryptococcal meningitis in patients with AIDS. Part I, *35th Intersci. Conf. Antimicrob. Agents Chemother.*, American Society for Microbiology, Washington, DC, abstract I-216, 1995.
90. Nightingale, S. D. Initial therapy for acquired immunodeficiency syndrome-associated cryptococcosis with fluconazole. *Arch. Intern. Med.*, 13, 538, 1995.
91. Saag, M. S., Powderly, W. G., Cloud, G. A., et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. *N. Engl. J. Med.*, 326, 83, 1992.
92. Haubrich, R. H., Haghighat, D., Bozzette, S. A., Tilles, J., and McCutchan, J. A. High-dose fluconazole for treatment of cryptococcal disease in patients with human immunodeficiency virus infection. *J. Infect. Dis.*, 170, 238, 1994.
93. Meyohas, M. C., Meynard, J. L., Bollens, D., et al. Treatment of non-meningeal cryptococcosis in patients with AIDS. *J. Infect.*, 33, 7, 1996.
94. Sitbon, O., Fourme, T., Bouree, P., Du Pasquier, L., and Salmeron, S. Successful treatment of disseminated *Cryptococcus*is with high-dose oral fluconazole. *AIDS*, 7, 1685, 1993.
95. Ammassari, A., Linzalone, A., Murri, R., Marasca, G., Morace, G., and Antinori, A. Fluconazole for primary prophylaxis of AIDS-associated cryptococcosis: a case controlled study. *Scand. J. Infect. Dis.*, 27, 235, 1995.
96. Nelson, M. R., Fisher, M., Cartledge, J., Rogers, T., and Gazzard, B. G. The role of azoles in the treatment and prophylaxis of cryptococcal disease in HIV infection. *AIDS*, 8, 651, 1994 [see also: *AIDS*, 9, 300, 1995].
97. Manfredi, R., Mastroianni, A., Coronado, O. V., and Chiodo, F. Fluconazole as prophylaxis against fungal infection in patients with advanced HIV infection. *Arch. Intern. Med.*, 157, 64, 1997

98. Georgiev, V. St. Opportunistic/nosocomial infections: treatment and developmental therapeutics. I. Cryptococcosis. *Med. Res. Rev.*, 13, 493–506, 1993.
99. Fernandez-Concepcion, O., Ariosa-Acuna, M. C., Giroud-Benitez, J. L., Pando-Cabrera, A., Garcia-Fidalgo, J. A., and Mestre-Miguelez, R. Cryptococcosis of the central nervous system. A report of five cases. *Rev. Neurol.*, 30, 935–938, 2000.
100. Emmons, C. W., Binford, C. H., and Utz, J. P. *Medical Mycology*, 2nd ed. Lea & Fabiger, Philadelphia, 190, 1970.
101. Zuger, A., Schuster, M., Simberkoff, M. S., Rahal, J. J., and Holzman, R. S. Maintenance amphotericin B for cryptococcal meningitis in the acquired immunodeficiency syndrome (AIDS). *Ann. Intern. Med.*, 109, 592, 1988.
102. Holmberg, K. and Meyer, R. D. Fungal infections in patients with AIDS and AIDS-related complex. *Scand. J. Infect. Dis.*, 18, 179, 1986.
103. Chechani, V. and Kamholz, S. L. Optimal therapy of cryptococcosis in patients with the acquired immunodeficiency syndrome. *NY State J. Med.*, 91, 292, 1991.
104. de Lalla, F., Pellizzer, G., Vaglia, A., et al., Amphotericin B as primary therapy for cryptococcosis in patients with AIDS: reliability of relatively high doses administered over a relatively short period. *Clin. Infect. Dis.*, 20, 263, 1995.
105. Churchill, D. and Coker, R. Amphotericin B as primary therapy for cryptococcosis in patients with AIDS: reliability of relatively high doses over a relatively short period. *Clin. Infect. Dis.*, 21, 1352, 1995.
106. de Lalla, F., Pellizzer, G., Vaglia, A., et al. Amphotericin B as primary therapy for cryptococcosis in patients with AIDS: reliability of relatively high doses over a relatively short period: a reply. *Clin. Infect. Dis.*, 21, 1353, 1995.
107. Diamond, R. D. and Bennett, J. E. A subcutaneous reservoir for intrathecal therapy of fungal meningitis. *N. Engl. J. Med.*, 288, 186, 1973.
108. Polsky, B., Depman, M. R., Gold, J. W. M., Galicich, J. H., and Armstrong, D. Intraventricular therapy of cryptococcal meningitis via a subcutaneous reservoir. *Am. J. Med.*, 81, 24, 1986.
109. Roberts, N. J. and Douglas, R. G. Cryptococcal meningitis: cure despite cryptococcemia. *Arch. Neurol.*, 35, 179, 1978.
110. Sapico, F. L. Disappearance of focal cryptococcal brain lesion on chemotherapy alone. *Lancet*, 1, 560, 1979.
111. Bastin, R., Vildé, J. L., Drouhet, E., and Carbon, C. Primary meningitis due to *Cryptococcus neoformans* associated with polyradiculitis: cure by amphotericin B. *Sem. Hop. Paris.*, 50, 337, 1974.
112. Sugar, A. M., Stern, J. J., and Dupont, B. Overview: treatment of cryptococcal meningitis. *Rev. Infect. Dis.*, 12(Suppl 3), S338, 1990.
113. Hay, R. J. Use of ambisome, liposomal amphotericin B in systemic fungal infections: preliminary findings of a European multicenter study, in *Recent Progress in Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, G. S., and Takeuchi, H., Eds. Marcel Dekker, New York, 323, 1992.
114. Coker, R., Tomlinson, D., and Harris, J. Successful treatment of cryptococcal meningitis with liposomal amphotericin B after failure of treatment with fluconazole and conventional amphotericin B. *AIDS*, 5, 231, 1991.
115. Schurmann, D., de Matos Marques, B., Grunewald, T., Pohle, H. D., Hahn, H., and Ruf, B. Safety and efficacy of liposomal amphotericin B in treating AIDS-associated disseminated cryptococcosis. *J. Infect. Dis.*, 164, 620, 1991.
116. Ikemoto, H., Yashiro, M., Furugori, T., and Kudo, Y. Unusual treatment of cryptococcal meningitis successfully treated with a small amount of amphotericin B, a large amount of prednisolone, and continued removal of cerebrospinal fluid. *J. Antibiot.*, 20, 374, 1967.
117. Yashiro, M., Furugori, T., Kudo, Y., and Ikemoto, H. Cryptococcal meningitis successfully treated with amphotericin B, adrenal corticosteroid, and continuous removal of the cerebrospinal fluid. *Naika*, 20, 1155, 1967.
118. Brisman, R., Reid, R., and Harrington, G. Intracranial cryptococcal granuloma - amphotericin B and surgical excision. *Surg. Neurol.*, 1, 43, 1973.
119. Dillon, M. C. and Sealy, W. C. Surgical aspects of opportunistic fungus infection. *Lab. Invest.*, 11, 1231, 1962.
120. Reeves, D. C. Cryptococcic (*Torula*) granuloma of the scull. *J. Neurol.*, 27, 70, 1967.
121. Rish, B. L. and Meacham, W. F. Intracerebral cystic toruloma. *J. Neurosurg.*, 28, 603, 1968.
122. Vijayan, N., Bhatt, G. P., and Dreyfus, P. M. Intraventricular cryptococcal granuloma. *Neurology*, 21, 728, 1971.
123. Einstein, H. E., Brown, J. F., and Holmes, C. W. Some treatment aspects of coccidioidal meningitis, in *Progress Report of the VA-Armed Forces Coccidioidomycosis Study Group No 7*, Salkin, D. and Huppert, M., Eds. California VA Hospital, San Francisco, 17, 1969.
124. Pappagianis, D. Meningitis in children, in *Progress Report of the VA- Armed Forces Coccidioidomycosis Study Group No 8*, Salkin, D. and Hupper, M., Eds. California VA Hospital, San Francisco, 16, 1969.
125. Schonheyder, H., Thestrup-Pedersen, K., Esmann, V., and Stenderup, A. Cryptococcal meningitis: complications due to intrathecal treatment. *J. Infect. Dis.*, 12, 155, 1980.
126. Swenson, R. S., Kountz, S. L., Blank, N., and Merigan, T. C. Successful renal allograft in a patient with pulmonary cryptococcosis. *Arch. Intern. Med.*, 124, 502, 1969.
127. Oka, S., Sugimoto, H., and Shimada, K. Problems in the treatment of fungal infections after renal transplantation in Japan, in *Recent Progress in Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, G. S., and Takeuchi, H., Eds. Marcel Dekker, New York, 239, 1992.
128. Shindo, K. Treatment of cryptococcal meningitis with five antifungal drugs: the role of amphotericin B. *Drugs Exp. Clin. Res.*, 16, 327, 1991.
129. Liu, Y. C., Cheng, D. L., Liu, C. Y., Yen, M. Y., and Wang, R. S. Isolated cryptococcosis of the adrenal gland. *J. Intern. Med.*, 230, 285, 1991.
130. Perkins, W. Pulmonary cryptococcosis: report on the treatment of nine cases. *Dis. Chest*, 56, 398, 1969.
131. Lopez-Berestein, G., Fainstein, V., Hersh, E. M., et al. Treatment of disseminated fungal infections in mammals with liposome- encapsulated amphotericin B. *U.S. Patent 4,663,167*, 1987.

132. Fajardo, L. F. Failure of topical amphotericin B in cryptococcosis. *Ann. Intern. Med.*, 78, 777, 1973.
133. Kojima, T., Matsuzaki, M., Sano, M., et al. Acute lymphocytic leukemia, complicated with generalized cryptococcosis successfully treated by amphotericin B: a case report. *Rinsho Ketsueki*, 26, 217, 1985.
134. Lerner, P. I. and Weinstein, L. Infective endocarditis in the antibiotic era. *N. Engl. J. Med.*, 274, 388, 1966.
135. Lombardo, T. A., Rabson, A. D., and Dodge, H. T. Mycotic endocarditis: report of a case due to *Cryptococcus neoformans*. *Am. J. Med.*, 22, 664, 1957.
136. Miller, R. P. and Bates, J. H. Amphotericin B toxicity: a follow-up report of 53 patients. *Ann. Intern. Med.*, 71, 1089, 1969.
137. Ellincy, B. R. Amphotericin B usage in pregnancy complicated by cryptococcosis. *Am. J. Obstet. Gynecol.*, 115, 285, 1973.
138. Silberfarb, P. M., Sarosi, G. A., and Tosh, F. E. Cryptococcosis and pregnancy. *Am. J. Obstet. Gynecol.*, 112, 714, 1972.
139. Li, P. K. and Lai, K. N. Amphotericin B induced ocular toxicity in cryptococcal meningitis. *Br. J. Ophthalmol.*, 73, 397, 1989.
140. Kaminaga, Y., Shindo, K., Ito, A., and Iizuma, H. Mycological and clinical study of cryptococcosis in Yokohama City University Hospital during the period from 1965 to 1989. *Kansenshogaku Zasshi*, 65, 374, 1991.
141. Armstrong, D. Treatment of fungal infections in the immunocompromised host, in *Recent Progress in Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, S. G., and Takeuchi, H., Eds. Marcel Dekker, New York, 251, 1992.
142. Hackett, A. J., Sylvester, S. S., Joss, U. R., and Calvin, M. Synergistic effect of rifamycin derivatives and amphotericin B on viral transformation of a murine cell line. *Proc. Natl. Acad. Sci. USA*, 69, 3653, 1972.
143. Kuwano, M., Akiyama, S., Endo, H., and Kohga, M. Potentiation of fusidic acid and lentinan effects upon normal and transformed fibroblastic cells by amphotericin B. *Biochem. Biophys. Res. Commun.*, 49, 1241, 1972.
144. Medoff, G. and Kobayashi, G. S. Amphotericin B and 5-fluorocytosine. *J. Infect. Dis.*, 132, 489, 1975.
145. Jimbow, T., Tejima, Y., and Ikemoto, H. Comparison between 5-fluorocytosine, amphotericin B and the combined administration of these agents in the therapeutic effectiveness for cryptococcal meningitis. *Chemotherapy*, 24, 374, 1978.
146. Bennett, J. E., Dismukes, W. E., Duma, R. J., et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N. Engl. J. Med.*, 301, 127, 1979.
147. MacGregor, R. R. Treatment of cryptococcal meningitis. *N. Engl. J. Med.*, 318, 380, 1988.
148. Schmutzhard, E. and Vejajjiva, A. Treatment of cryptococcal meningitis with high-dose, long-term combination amphotericin B and flucytosine. *Am. J. Med.*, 85, 737, 1988.
149. Sahai, J. Management of cryptococcal meningitis in patients with AIDS. *Clin. Pharmacy*, 7, 528, 1988.
150. Kauffman, C. A. and Frame, P. T. Bone marrow toxicity associated with 5-fluorocytosine therapy. *Antimicrob. Agents Chemother.*, 11, 244, 1977.
151. Donahue, R. E., Johnson, M. M., Zon, L. I., Clark, S. C., and Groopman, J. E. Suppression of in vitro haematopoiesis following human immunodeficiency virus infection. *Nature*, 326, 200, 1987.
152. Kotler, D. P., Gaetz, H. P., Lange, M., Klein, E. B., and Holt, P. R. Enteropathy associated with acquired immunodeficiency syndrome. *Ann. Intern. Med.*, 101, 421, 1984.
153. Chuck, S. L. and Sande, M. A. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. *N. Engl. J. Med.*, 321, 794, 1989.
154. Dismukes, W. E. Treatment of systemic fungal diseases in patients with AIDS, in *Recent Progress in Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, G. S., and Takeuchi, H., Eds. Marcel Dekker, New York, 227, 1992.
155. Bayardelle, P., Giard, N., Maltais, R., Delorme, J., and Brazean, M. Success with amphotericin B and 5-fluorocytosine in treating cerebral cryptococcoma accompanying cryptococcal meningitis. *Can. Med. Assoc. J.*, 127, 732, 1982.
156. Koeleman, J. G., Rustemejer, C., Wijermans, P. W., and MacLaren, D. M. Cryptococcal meningo-encephalitis after prolonged corticosteroid therapy. *Neth. J. Med.*, 36, 242, 1990.
157. Carney, M. D., Combs, J. L., and Waschler, W. Cryptococcal choroiditis. *Retina*, 10, 27, 1990.
158. Picon, L., Vaillant, L., Duong, T., et al. Cutaneous cryptococcosis resembling molluscum contagiosum: a first manifestation of AIDS. *Acta Derm. Venereol. (Stockholm)*, 69, 365, 1989.
159. Tobias, J. S., Wrigley, P. F. M., and Shaw, E. Combination antifungal therapy for cryptococcal meningitis. *Postgrad. Med. J.*, 52, 305, 1976.
160. Watson, A. J., Russell, R. P., Cabreja, R. F., Braverman, R., and Whelton, A. Cure of cryptococcal infection during continued immunosuppressive therapy. *Q. J. Med.*, 55, 169, 1985.
161. Gallis, H. A., Berman, R. A., Cate, T. R., Hamilton, J. D., Gunnels, J.C., and Stickel, D. L. Fungal infection following renal transplantation. *Arch. Intern. Med.*, 135, 1163, 1975.
162. Mills, S. A., Seigler, H. F., and Wolfe, W. G. The incidence and management of pulmonary mycosis in renal allograft patients. *Ann. Surg.*, 182, 617, 1975.
163. Kong, N. C., Sharriah, W., Morad, Z., Suleiman, A. B., and Wong, Y. H. Cryptococcosis in a renal unit. *Aust. N. Z. J. Med.*, 20, 645, 1990.
164. Kimura, K., Hatekayama, M., Miyagi, J., et al. A case of systemic lupus erythematosus with cryptococcal meningitis successfully treated with amphotericin B and 5-FC. *Nipon Naika Gakkai Zasshi*, 75, 406, 1986.
165. Butler, W. P. and Kaufer, G. I. Primary cutaneous cryptococcosis successfully treated with outpatient amphotericin B and 5-fluorocytosine. *Nita*, 8, 295, 1985.
166. Woolfitt, R., Park, H. M., and Greene, M. Localized cryptococcal osteomyelitis. *Radiology*, 120, 290, 1976.

167. Nottebart, H. C., McGehee, R. F., and Utz, J. P. *Cryptococcus neoformans* osteomyelitis: case report of two patients. *Sabouraudia*, 12, 127, 1974.
168. Chand, K. and Lall, K. S. Cryptococcosis of the knee joint. *Acta Orthop. Scand.*, 47, 432, 1976.
169. Nathan, C. F. Cryptococcal osteomyelitis treated with 5-fluorocytosine. *Am. Rev. Respir. Dis.*, 110, 78, 1974.
170. Luhr, H. and Svane, S. Pulmonary pseudomotor caused by *Cryptococcus neoformans*. *Tidsskr. Nor. Laegeforen.*, 111, 3288, 1991.
171. Schmidt-Westhausen, A., Grunewald, T., Reihart, P. A., and Pohle, H. D. Oral cryptococcosis in a patient with AIDS: a case report. *Oral. Dis.*, 1, 77, 1995 [see also: *Oral Dis.*, 1, 61, 1995].
172. Iida, Y., Maehara, K., Okamoto, Y., et al. A case of cryptococcal meningitis treated by ketoconazole and amphotericin B combination therapy. *Kansenshogaku Zasshi*, 60, 189, 1986.
173. Echevarria, A., Pinzon, V., Toro, J., and Diaz Issacs, M. Pulmonary cryptococcosis. *Rev. Med. Panama*, 16, 50, 1991.
174. Aslam, P. A., Larkin, J., Eastridge, C. E., and Hughes, F. A. Endocavitary infusion through percutaneous endobronchial catheter. *Chest*, 57, 94, 1970.
175. Stamm, A. M., Diasio, R. B., Dismukes, W. E., et al. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. *Am. J. Med.*, 83, 236, 1987.
176. Shindo, K., Mizuno, T., Matsumoto, Y., et al. Granulocytopenia and thrombocytopenia associated with combination therapy of amphotericin B and low-dose flucytosine in a patient with cryptococcal meningitis. *DICP*, 23, 672, 1989.
177. Bryan, C. S. and McFarland, J. A. Cryptococcal meningitis: fatal marrow applasia from combined therapy. *J. Am. Med. Assoc.*, 239, 1068, 1978.
178. Tassel, D. and Madoff, M. A., Treatment of *Candida* sepsis and *Cryptococcus* meningitis with 5-fluorocytosine: a new antifungal agent. *J. Am. Med. Assoc.*, 260, 830, 1968.
179. Sanati, H., Messer, S. A., Pfaller, M., et al. Multicenter evaluation of broth microdilution method for susceptibility testing of *Cryptococcus neoformans* against fluconazole. *J. Clin. Microbiol.*, 34, 1280, 1996.
180. Koechlin, B. A., Rubio, S., Palmer, S., Gabriel, T., and Duschinsky, R. The metabolism of 5-fluorocytosine-2[^{14}C] and cytosine[^{14}C] in the rat and the disposition of 5-fluorocytosine- 2[^{14}C] in man. *Biochem. Pharmacol.*, 15, 435, 1966.
181. Shadomy, S. Further in vitro studies with 5-fluorocytosine. *Infect. Immun.*, 2, 484, 1970.
182. Roberts, M., Rinaudo, P. A., Tilton, R. C., and Vilinskas, J. Treatment of multiple intracerebral cryptococcal granulomas with 5-fluorocytosine. *J. Neurosurg.*, 37, 229, 1972.
183. Editorial. Cryptococcosis and 5-fluorocytosine. *Aust. N. Z. J. Med.*, 4, 296, 1974.
184. Sabetta, J. R. and Andriole, V. T. Cryptococcal infections in the central nervous system. *Med. Clin. North Am.*, 69, 334, 1985.
185. Block, E. R. and Bennett, J. E. Clinical and pharmacological studies with 5-fluorocytosine (5-FC). *Clin. Res.*, 20, 525, 1972.
186. Utz, J. P., Shadomy, S., McGehee, R. F., and Tynes, B. S. 5-Fluorocytosine: experience in patients with pulmonary and other forms of cryptococcosis. *Am. Rev. Respir. Dis.*, 99, 975, 1969.
187. Zylstra, W. Cryptococcosis and 5-fluorocytosine: comment. *Aust. N. Z. J. Med.*, 4, 296, 1974.
188. Vandevelle, A. G., Nauceri, A. A., and Johnson III, J. E. 5-Fluorocytosine in the treatment of mycotic infections. *Ann. Intern. Med.*, 77, 43, 1972.
189. Fass, R. J. and Perkins, R. L. 5-Fluorocytosine in the treatment of cryptococcal and *Candida* mycoses. *Ann. Intern. Med.*, 74, 535, 1971.
190. Schlegel, R. J., Bernier, G. M., Bellanti, J. A., et al. Severe candidiasis asociated with thymic displasia, IgA deficiency and plasma antilymphocyte effects. *Pediatrics*, 45, 926, 1970.
191. McDonnell, F. I., Clunie, G. J. A., Petrie, J. J. G., and Rao, A. Experience with 5- fluorocytosine in a dialysis-transplant unit. *Aust. N. Z. J. Med.*, 3, 438, 1973.
192. Kauffman, C. A. and Frame, P. T. Bone marrow toxicity associated with 5-fluorocytosine therapy. *Antimicrob. Agents Chemother.*, 11, 244, 1977.
193. Bryan, C. S. and McFarland, J. A. Cryptococcal meningitis: fatal marrow aplasia from combined therapy. *J. Am. Med. Assoc.*, 239, 1068, 1978.
194. Philpot, C. R. and Lo, D. Cryptococcal meningitis in pregnancy. *Med. J. Aust.*, 2, 1005, 1972.
195. Deresinski, S. C., Lilly, R. B., Levine, H. B., Galgiani, J. N., and Stevens, D. A. Treatment of fungal meningitis with miconazole. *Arch. Intern. Med.*, 137, 1180, 1977.
196. Ito, A., Therapeutic results with miconazole in Japan, in Recent Progress in *Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, G. S., and Takeuchi, H., Eds. Marcel Dekker, New York, 183, 1991.
197. Sung, J. P., Grendale, J. G., and Levine, H. B., Intravenous and intrathecal miconazole therapy for systemic mycosis. *West. J. Med.*, 126, 5, 1977.
198. Weinstein, L. and Jacoby, I., Successful treatment of cerebral cryptococcoma and meningitis with miconazole. *Ann. Intern. Med.*, 93, 569, 1980.
199. Belle, W. E., Treatment of fungal infections of the central nervous system. *Ann. Neurol.*, 9, 417, 1981.
200. Sung, J. P., Campbell, G. D., and Grendahl, J. C., Miconazole therapy for fungal meningitis. *Arch. Neurol.*, 35, 443, 1978.
201. Perfect, J. R., Durack, D. T., Hamilton, J. D., and Gallis, H. A., Failure of ketoconazole in cryptococcal meningitis. *J. Am. Med. Assoc.*, 247, 3349, 1982.
202. Ogushi, F., Tamura, M., Ozaki, T., et al. A case of cryptococcal meningitis improved in the treatment of high dose ketoconazole. *Kansenshogaku Zasshi*, 59, 405, 1985.

203. Karaffa, C. A., Rehm, S. J., and Keys, T. F. The acquired immunodeficiency syndrome and cryptococcosis. *Ann. Intern. Med.,* 104, 891, 1986.
204. Granier, F., Kamitakis, J., Hermier, C., Zhu, Y. Y., and Thivolet, J. Localized cutaneous cryptococcosis successfully treated with ketoconazole. *J. Am. Acad. Dermatol.*, 16, 243, 1987.
205. Bernard, E., Carles, M., Toussaint-Gari, M., Fournier, J. P., and Dellamonica, P. Value of fluconazole in the treatment of systemic yeast infection. *Pathol. Biol. (Paris)*, 37, 690, 1989.
206. Shuttleworth, D., Philpot, C. M., and Knight, A. G. Cutaneous cryptococcosis: treatment with oral fluconazole. *Br. J. Dermatol.*, 120, 683, 1989.
207. Nakashima, M. The clinical study of fluconazole against pulmonary cryptococcosis and aspergillosis, and its pharmacokinetics in patients. *Jpn. J. Antibiot.*, 42, 127, 1989.
208. Mares, M., Sartori, M. T., Carretta, M., Bertaggia, A., and Girolami, A. Rhinophyma-like cryptococcal infection as an early manifestation of AIDS in a hemophilia B patient. *Acta Haematol.*, 84, 101, 1990.
209. Zalcman, G., Lechapt, E., Milleron, B., Denis, M., Mayaud, C., and Akoun, G. Pleuropulmonary cryptococcosis disclosing AIDS. *Rev. Pneumol. Clin.*, 47, 133, 1991.
210. Bozzette, S. A., Larsen, R. A., Chiu, J., et al. Fluconazole treatment of persistent *Cryptococcus neoformans* prostatic infection in AIDS. *Ann. Intern. Med.*, 115, 285, 1991.
211. Sugar, A. M. Overview: cryptococcosis in the treatment of AIDS. *Mycopathologia*, 114, 153, 1991.
212. Levesque, H., Alie-Legrand, M. C., Omnient, Y., et al. *Cryptococcus neoformans* meningitis and cirrhosis: value of fluconazole. *Clin. Biol.*, 13, 942, 1989.
213. Michelone, G., Tacconi, F., Maccabruni, A., Lanzarini, P., Tinelli, M., and Dei Cas, A. Clinical and therapeutic profile of 3 cases of cryptococcal meningitis in patients with AIDS. *G. Ital. Chemoter.*, 36, 95, 1989.
214. Krisch, H. and Sarnow, E. Collection of cases in relation to clinical trials of fluconazole in Germany. *Mycoses*, 33(Suppl. 1), 14S, 1990.
215. Reents, S. B. and Powell, G. Fluconazole success after amphotericin B and flucytosine failure in cryptococcal meningitis. *DICP*, 24, 885, 1990.
216. Lindberg, J. and Edebo, L. Successful treatment of cryptococcal meningitis with fluconazole. *Lakartidningen*, 88, 2245, 1991.
217. Good, C. B. and Leeper, H. F. Profound papilledema due to cryptococcal meningitis in acquired immunodeficiency syndrome: successful treatment with fluconazole. *South. Med. J.*, 84, 394, 1991.
218. Dismukes, W. E. Treatment of systemic fungal diseases in patients with AIDS, in *Recent Progress in Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, G. S., and Takahashi, H., Eds. Marcel Dekker, New York, 227, 1992.
219. Jones, P. D., Marriott, D., and Speed, B. R. Efficacy of fluconazole in cryptoccocal meningitis. *Diagn. Microbiol. Infect. Dis.*, 12(Suppl. 4), 235S, 1989.
220. Dupont, B. Treatment of cryptococcal meningitis, in *Proc. Xth Congr. Int. Soc. Human Animal Mycol., Barcelona*, Torres-Rodriguez, J. M., Ed. J. R. Prous, 197, 1988.
221. Byrne, W. R. and Wajszczuk, C. P. Cryptococcal meningitis in the acquired immunodeficiency syndrome (AIDS): successful treatment with fluconazole after failure of amphotericin B. *Ann. Intern. Med.*, 108, 384, 1988.
222. Dromer, F., Mathoulin, S., Dupont, B., Brugiere, O., and Letenneur, L., Comparison of the efficacy of amphotericin B and fluconazole in the treatment of cryptococcosis in human immunodeficiency virus-negative patients: retrospective analysis of 83 cases. *Clin. Infect. Dis.*, 22(Suppl. 2), S154, 1996.
223. Larsen, R. A., Leal, M. A., and Chan, L. S., Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS: a randomized trial. *Ann. Intern. Med.*, 113, 183, 1990.
224. Wong, R. D. and Goetz, M. B., Treatment of cryptococcal meningitis in AIDS. *J. Infect. Dis.*, 113, 992, 1990.
225. Buxton, M. J., Dubois, D. J., Turner, R. R., Sculpher, M. J., Robinson, P. A., and Searcy, C., Cost implications of alternative treatments for AIDS patients with cryptococcal meningitis: comparison of fluconazole and amphotericin-based therapies. *J. Infect.*, 23, 17, 1991.
226. Bolignano, G., Chindemi, G., and Criseo, G., Cryptococcal meningoencephalitis in a patient with Hodgkin's lymphoma: successful treatment with fluconazole. *Mycoses*, 34, 63, 1991.
227. Iacopino, P., Morabito, F., Martino, B., Bolignano, G., and Nobile, F., Fluconazole for disseminated cryptococcosis in a patient with Hodgkin's disease. *Haematologica*, 76, 260, 1991.
228. Sugar, A. M. and Saunders, C. Oral fluconazole as suppressive therapy of disseminated cryptococcosis in patients with acquired immunodeficiency syndrome. *Am. J. Med.*, 85, 481, 1988.
229. Bozzette, S. A., Larsen, R. A., Chiu, J., et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. *N. Engl. J. Med.*, 324, 580, 1991.
230. Powderly, W., Saag, M., Cloud, G., et al., Fluconazole versus amphotericin B as maintenance therapy for prevention of relapse of AIDS-associated cryptococcal meningitis. *30th Intersci. Conf. Antimicrob. Agents Chemother.* American Society for Microbiology, Washington, DC, abstract 1162, 1990.
231. Laroche, R., Deppner, M., Floch, J. J., et al. Cryptococcosis in Bujumbura, Burundi: apropos of 80 observed cases in 42 months. *Bull. Soc. Pathol. Exot. Fil.*, 83, 159, 1990.
232. Stern, J. J., Hartman, B. J., Sharkey, K., et al. Oral fluconazole therapy for patients with acquired immunodeficiency syndrome and cryptococcosis: experience with 22 patients. *Am. J. Med.*, 85, 477, 1988.
233. Sort, P., Morales, M., Gomez, J., Pares, A., and Rodes, J. Pleural empyema caussed by *Cryptococcus neoformans* in a patient with liver cirrhosis. *Gastroenterol. Hepatol.*, 19, 302, 1996.
234. Agarwal, A., Gupta, A., Sakhuja, V., Talwar, P., Joshi, K., and Chugh, K. S. Retinitis following disseminated

cryptococcosis in a renal allograft recipient: efficacy of oral fluconazole. *Acta Ophthalmol (Copenhagen)*, 69, 402, 1991.
235. Custis, P. H., Haller, J. A., and de Juan, E. Jr. An unusual case of cryptococcal endophthalmitis. *Reina*, 15, 300, 1995.
236. Vandersmissen, G., Meuleman, L., Tits, G., Verhaeghe, A., and Peetermans, W. E. Cutaneous cryptococcosis in corticosteroid-treated patients without AIDS. *Acta Clin. Belg.*, 51, 111, 1996.
237. Halweg, H., Korzeniewska-Kosela, M., Podsiadlo, B., and Krakowka, P. A case of skin cryptococcosis in systemic lupus erythematosus. *Pneumonol. Pol.*, 58, 544, 1990.
238. Pineski, R., Mathurin, S. A., Ruffinengo, O., Alonso, H. O., and Corallini de Bracelenti, B. Cutaneous cryptococcosis in a patient receiving chronic immunosuppressive therapy. *Cutis*, 57, 229, 1996.
239. Verneuil, L., Dompmartin, A., Duhamel, C., et al. Cryptococcal whitlow in a HIV-positive patient. *Ann. Dermatol. Venereol.*, 122, 688, 1995.
240. Kerchner, J. E., Ridley, M. B., and Greene, J. N. Laryngeal *Cryptococcus*: treatment with oral fluconazole. *Arch. Otolaryngol. Head Neck Surg.*, 121, 1193, 1995.
241. Schmidt, D. M., Sercarz, J. A., Kevorkian, K. F., and Canalis, R. F. *Cryptococcus* presenting as a neck mass. *Ann. Otol. Rhinol. Laryngol.*, 104, 711, 1995.
242. Yew, W. W., Wong, P. C., Wong, C. F., Lee, J., and Chau, C. H. Oral fluconazole in the treatment of pulmonary cryptococcosis in non-AIDS patients. *Drugs Exp. Clin. Res.*, 22, 25, 1996.
243. Feczko, J. M. Overview of fluconazole in *Recent Progress in Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, G. S., and Takahashi, H., Eds. Marcel Dekker, New York, 191, 1992.
244. Troke, P. F., Marriott, M. S., Richardson, K., and Tarbit, M. H. In vitro potency and in vivo activity of azoles. *Ann. NY Acad. Sci.*, 544, 284, 1988.
245. Guillaume, M. P., De Prez, C., and Cogan, E. Subacute mitochondroal liver disease in a patient with AIDS: possible relationship to prolonged fluconazole administration. *Am. J. Gastroenterol.*, 91, 165, 1996.
246. Pappas, P. G., Kauffman, C. A., Perfect, J., et al. Alopecia associated with fluconazole therapy. *Ann. Intern. Med.*, 123, 354, 1995 [see comment in *Ann. Intern. Med.*, 125, 153, 1996].
247. Weinroth, S. E., and Tuazon, C. U. Alopecia associated with fluconazole treatment. *Ann. Intern. Med.*, 119, 637, 1993.
248. Coker, R. J. and Harris, J. R. Failure of fluconazole treatment in cryptococcal meningitis despite adequate CSF levels. *J. Infect.*, 123, 101, 1991.
249. Bailly, M. P., Boibieux, A., Biron, F., et al. Persistence of *Cryptococcus neoformans* in prostate: failure of fluconazole despite high doses. *J. Infect. Dis.*, 164, 435, 1991.
250. Pietroski, N., Buckley, R. M., Braffman, M. N., and Stern, J. J. Intravenous and oral fluconazole in treatment of acute cryptococcal meningitis in AIDS. *30th Intersci. Conf. Antimicrob. Agents Chemother.*, American Society for Microbiology, Washington, DC, abstract 576, 1990.
251. Squires, K., Rowland, V., Gassyuk, E., et al. Fluconazole as therapy for acute cryptococcal meningitis. *30th Intersci. Conf. Antimicrob. Agents Chemother.*, American Society for Microbiology, Washington, DC, abstract 573, 1990.
252. Aller, A. I., Martin-Mazuelos, E., Lozano, F., et al. Correlation of fluconazole MICs with clinical outcome in cryptococcal infection. *Antimicrob. Agents Chemother.*, 44, 1544-1548, 2000.
253. Orni-Wasserlauf, R., Siegman-Igra, Y., Izkhakov, E., Bash, E., Polacheck, I., and Giladi, M. Fluconazole-resistant *Cryptococcus neoformans* isolated from an immunocompetent patient without prior exposure to fluconazole. *38th Intersci. Conf. Antimicrob. Agents Chemother.*, American Society of Microbiology, Washington, DC, 458, abstract J-24, 1998.
254. Abi-Hanna, P., Marichal, P., Vandenbossche, H., and Williamson, P. R. Study of fluconazole resistance in *Cryptococcus neoformans* by insertional mutagenesis. *99th Abstr. Gen. Meet. Am. Soc. Microbiol., May 30–June 3*, 6, abstract A-29, 1999.
255. Georgiev, V. St. Opportunistic/nosocomial infections: treatment and developmental therapeutics. II. Cryptococcosis. *Med. Res. Rev.*, 13, 507–527, 1993.
256. Van Cutsem, J. and Cauwenbergh, G. Results of itraconazole treatment in systemic mycoses in animals and man, in *Recent Progress in Antifungal Chemotherapy*, Yamaguchi, H., Kobayashi, G. S., and Takahashi, H., Eds. Marcel Dekker, New York, 203, 1992.
257. Viviani, M. A., Tortorano, A. M., Giani, P. C., et al. Itraconazole for cryptococcal infection in the acquired immunodeficiency syndrome. *Ann. Intern. Med.*, 106, 106,1987.
258. Viviani, M. A., Tortorano, A. M., Langer, M., et al. Experience with itraconazole in cryptococcosis and aspergillosis. *J. Infect.*, 18, 151, 1989.
259. Denning, D. W., Tucker, R. M., Hanson, L. H., Hamilton, J. R., and Stevens, D. A. Itraconazole therapy for cryptococcal meningitis and cryptococcosis. *Arch. Intern. Med.*, 149, 2301, 1989.
260. Denning, D. W., Tucker, R. M., Hanson, L. H., and Stevens, D. A. Itraconazole in opportunistic mycoses: cryptococcosis and aspergillosis. *J. Am. Acad. Dermatol.*, 3, 602, 1990.
261. de Gans, J., Eeftinck Schattenkerk, J. K. M., and van Ketel, R. J. Itraconazole as maintenance treatment for cryptococcal meningitis in the acquired immunodeficiency syndrome. *Br. Med. J.*, 296, 339, 1988.
262. Batungwanayo, J., Taelman, H., Bogaerts, J., et al. Pulmonary cryptococcosis associated with HIV-1 infection in Rwanda: a retrospective study of 37 cases. *AIDS*, 8, 1271, 1994.
263. Sato, T., Koseki, S., Takahashi, S., and Maie, O., Localized cutaneous cryptococcosis successfully treated with itraconazole: review of medication in 18 cases reported in Japan. *Mycoses*, 33, 455, 1990.
264. Goh, C. L., Cutaneous cryptococcosis successfully treated with itraconazole. *Cutis*, 51, 377, 1993.

265. Bettoli, V., Virgili, A., Zampino, M. R., Bedetti, A., and Montanari, P., Cutaneous cryptococcosis in AIDS: successful treatment with itraconazole. *Mycoses*, 36, 433, 1993.
266. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections on persons infected with human immunodeficient virus. *Infect. Dis. Obstetr. Gynecol.*, 8, 5–74, 2000 & *Clin. Infect. Dis.*, 30(Suppl. 1), S29–S65, 2000.
267. Powderly, W. G., Finkelstein, D. M., Feinberg, J., et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. *N. Engl. J. Med.*, 332, 700–705, 1995.
268. Schuman, P., Capps, L., Peng, G., et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.*, 126, 689–696, 1997.
269. Havlir, D. V., Dube, M. P., McCutchan, J. A., et al. Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS. *Clin. Infect. Dis.*, 27, 1369–1375, 1998.
270. Lewis, J. L. and Rabinovich, S. The wide spectrum of cryptococcal infections. *Am. J. Med.*, 53, 315, 1972.
271. Lalloo, D., Fisher, D., Naraqi, S., et al. Cryptococcal meningitis (*C. neoformans* var.*gattii*) leading to blindness in previously healthy Melanesian adults in Papua New Guinea. *Q. J. Med.*, 87, 343, 1994.
272. Currie, B., Vigus, T., Leach, G., and Dwyer, B. *Cryptococcus neoformans* var. *gattii*. *Lancet*, 336, 1442, 1990.
273. Laurenson, I. F., Naraqi, S., Howcroft, N., Burrows, I., and Saulei, S. Cryptococcal meningitis in Papua New Guinea: ecology and the role of eucalypts. *Med. J. Aust.*, 158, 213, 1993.
274. Laurenson, I. F., Naraqi, S., Trevett, A., et al. Cryptococcal investigations in Papua New Guinea. *Proc. 2nd Int. Conf. Cryptococcus & Cryptococcosis*, Milan, 114, 1993.
275. Laurenson, I. F., Trevett, A. J., Lalloo, D. G., et al. Meningitis caused by *Cryptococcus neoformans* var. *gattii* and var. *neoformans* in Papua New Guinea. *Trans. R. Soc. Trop. Med. Hyg.*, 90, 57, 1996.
276. Castanon-Olivares, L. R., Arreguin-Espinosa, R., Ruiz-Palacios y Santos, G., and Lopez- Martinez, R. Frequency of *Cryptococcus* species and varieties in Mexico and their comparison with some Latin American countries. *Rev. Latinoam. Microbiol.*, 42, 35–40, 2000.
277. Kwon-Chung, K. J. and Bennett, J. E. Epidemiologic differences between the two varieties of *Cryptococcus neoformans*. Am. J. Epidemiol., 120, 123, 1984.
278. Ellis, D. H. *Cryptococcus neoformans* var. *gattii* in Australia. *J. Clin. Microbiol.*, 25, 430, 1987.
279. Marriott, D. J., Speed, B. R., Spelman, D., Shaw, D., French, M., and Harkness, J. L. *Cryptococcus neoformans* var. *gattii* infections in Australian HIV-infected patients: a review of seven cases. *8th Annu. Conf. Australs. Soc. HIV Med., Nov. 14–17*, 86, abstract 88, 1996.
280. Sorrell, T. C., Brownlee, A. G., Ruma, P., Malik, R., Pfeiffer, T. J., and Ellis, D. H. Natural environmental sources of *Cryptococcus neoformans* var. *gattii*. *J. Clin. Microbiol.*, 34, 1261, 1996.
281. Pfeiffer, T. J. and Ellis, D. H. Environmental isolation of *Cryptococcus neoformans* var. *gattii* from *Eucalyptus tereticornis*. *J. Med. Vet. Mycol.*, 30, 407, 1992.
282. Sorrell, T. C., Chen, S. C. A., Ruma, P., et al. Concordance of clinical and environmental isolates of *Cryptococcus neoformans* var. *gattii* by random amplification of polymorphic DNA analysis and PCR fingerprinting. *J. Clin. Microbiol.*, 34, 1253, 1996.
283. Kwon-Chung, K. J., Wickes, B. L., Stockman, L., Roberts, G. D., Ellis, D., and Howard, D. H. Virulence, serotype, and molecular characteristics of environmental strains of *Cryptococcus neoformans* var. *gattii*. *Infect. Immun.*, 60, 1869, 1992.
284. Varma, A., Swinne, D., Staib, F., Bennett, J. E., and Kwon-Chung, K. J. Diversity of DNA fingerprints in *Cryptococcus neoformans*. *J. Clin. Microbiol.*, 33, 1807, 1995.
285. Mitchell, D. H., Sorrell, T. C., Allworth, A. M., et al. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. *Clin. Infect. Dis.*, 20, 611, 1995.
286. Speed, R. and Dunt, D. Clinical and host differences between the two varieties of *Cryptococcus neoformans*. *Clin. Infect. Dis.*, 21, 28, 1995.
287. Slobodnik, R. and Naraqi, S. Cryptococcal meningitis, in the Central Province of Papua New Guinea. *Papua New Guinea Med. J.*, 23, 111, 1980.
288. Peetermans, W., Bobbaers, H., Verhaegen, J., and Vandepitte, J. Fluconazole-resistant *Cryptococcus neoformans* var. *gattii* in an AIDS patient. *Acta Clin. Belg.*, 48, 405-409, 1993.
289. Kamei, K., Brummer, E., Nishimura, K., and Miyaji, M. Activity of voriconazole against *Cryptococcus neoformans* var. *gattii* vs. var. *neoformans*: effect of human serum. *Abstr. 98th Gen. Meet. Am. Soc. Microbiol., May 17–21*, 270, abstract F-100, 1998.
290. Gluck, J. L., Myers, J. P., and Pass, L. M. Cryptococcemia due to *Cryptococcus albidus*. *South. Med. J.*, 80, 511, 1987.
291. Gordon, M. A. Pulmonary cryptococcosis: a case due to *Cryptococcus albidus*. *Am. Rev. Respir. Dis.*, 106, 786, 1972.
292. Lin, S. R., Peng, C. E., Yung, S. A., and Yu, H. S. Isolation of *Cryptococcus albidus* var. *albidus* in patient with pemphigus foliaceous. *Kao-Hsiung I Hsueh Ko Hsueh Tsa Chih*, 5, 126, 1989.
293. Weiser, H. G. Zur frage der pathogenität der *Cryptococcus albidus*. *Schweiz. Med. Wochenschr.*, 103, 475, 1973.
294. da Cunha, T. and Lusins, J. *Cryptococcus albidus* meningitis. *South. Med. J.*, 66, 1230, 1973.
295. Mello, J. C., Srinivasan, S., Scott, M. L., and Raff, M. J. *Cryptococcus albidus* meningitis. *J. Infect.*, 2, 79, 1980.
296. Krumholz, R. A. Pulmonary cryptococcosis: a case due to *Cryptococcus albidus*. *Am. Rev. Respir. Dis.*, 105, 421, 1972.
297. Horowitz, I. D., Blumberg, E. A., and Krevolin, L. *Cryptococcus albidus* and mucormycosis empyema in a patient receiving hemodialysis. *South. Med. J.*, 86, 1070, 1993.

298. Mckee, M., Arthington-Skaggs, B. A., Motley, M., et al. Distribution of yeast isolates recovered from the oral mucosa of HIV+ patients: relationship to antifungal drug use. *Abstr. 99th Gen. Meet. Am. Soc. Microbiol., May 30–June 3*, 137, abstract C-161, 1999.
299. Loison, J., Bouchara, J. P., Gueho, E., et al. First report of *Cryptococcus albidus* septicemia in an HIV patient. *J. Infect.*, 33, 139, 1996.
300. Kordossis, T., Avlami, A., Velegraki, A., et al. First report of *Cryptococcus laurentii* meningitis and a fatal case of *Cryptococcus albidus* cryptococcaemia in AIDS patients. *Med. Mycol.*, 36, 335-339, 1998.
301. Lynch III, J. P., Schaberg, D. R., Kissner, D. G., and Kauffman, C. A. *Cryptococcus laurentii* lung abscess. *Am. Rev. Respir. Dis.*, 123, 135, 1981.
302. Chander, J., Sapra, R. K., and Talwar, P. Incidence of cryptococcosis in and around Chandigarch, India during the period 1982–1991. *Mycoses*, 37, 23, 1994.
303. Custis, P. H., Haller, J. A., and de Juan, E. Jr. An unusual case of cryptococcal endophthalmitis. *Reina*, 15, 300, 1995.