

## Practice Guidelines for the Management of Cryptococcal Disease

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### Executive Summary

An 8-person subcommittee of the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group evaluated available data on the treatment of cryptococcal disease. Opinion regarding optimal treatment was based on personal experience and information in the literature. The relative strength of each recommendation was graded according to the type and degree of evidence available to support the recommendation, in keeping with previously published guidelines by the Infectious Diseases Society of America (IDSA). The panel conferred in person (on 2 occasions), by conference call, and through written reviews of each draft of the manuscript.

The choice of treatment for disease caused by *Cryptococcus neoformans* depends on both the anatomic sites of involvement and the host's immune status. For immunocompetent hosts with isolated pulmonary disease, careful observation may be warranted; in the case of symptomatic infection, indicated treatment is fluconazole, 200–400 mg/day for 3–6 months. For those individuals with non-CNS-isolated cryptococemia, a positive serum cryptococcal antigen titer >1 : 8, or urinary tract or cutaneous disease, recommended treatment is oral azole therapy (fluconazole) for 3–6 months. In each case, careful assessment of the CNS is required to rule out occult meningitis. For those individuals who are unable to tolerate fluconazole, itraconazole (200–400 mg/day for 6–12 months) is an acceptable alternative. For patients with more severe disease, treatment with amphotericin B (0.5–1 mg/kg/d) may be necessary for 6–10 weeks. For otherwise healthy hosts with CNS disease, standard therapy consists of amphotericin B, 0.7–1 mg/kg/d, plus flucytosine, 100 mg/kg/d, for 6–10 weeks. An alternative to this regimen is amphotericin B (0.7–1 mg/kg/d) plus 5-flucytosine (100 mg/kg/d) for 2 weeks, followed by fluconazole (400 mg/day) for a minimum of 10 weeks. Fluconazole “consolidation” therapy may be continued for as long as 6–12 months, depending on the clinical status of the patient. HIV-negative, immunocomprom-

ised hosts should be treated in the same fashion as those with CNS disease, regardless of the site of involvement.

Cryptococcal disease that develops in patients with HIV infection always warrants therapy. For those patients with HIV who present with isolated pulmonary or urinary tract disease, fluconazole at 200–400 mg/d is indicated. Although the ultimate impact from highly active antiretroviral therapy (HAART) is currently unclear, it is recommended that all HIV-infected individuals continue maintenance therapy for life. Among those individuals who are unable to tolerate fluconazole, itraconazole (200–400 mg/d) is an acceptable alternative. For patients with more severe disease, a combination of fluconazole (400 mg/d) plus flucytosine (100–150 mg/d) may be used for 10 weeks, followed by fluconazole maintenance therapy. Among patients with HIV infection and cryptococcal meningitis, induction therapy with amphotericin B (0.7–1 mg/kg/d) plus flucytosine (100 mg/kg/d for 2 weeks) followed by fluconazole (400 mg/d) for a minimum of 10 weeks is the treatment of choice. After 10 weeks of therapy, the fluconazole dosage may be reduced to 200 mg/d, depending on the patient's clinical status. Fluconazole should be continued for life. An alternative regimen for AIDS-associated cryptococcal meningitis is amphotericin B (0.7–1 mg/kg/d) plus 5-flucytosine (100 mg/kg/d) for 6–10 weeks, followed by fluconazole maintenance therapy. Induction therapy beginning with an azole alone is generally discouraged. Lipid formulations of amphotericin B can be substituted for amphotericin B for patients whose renal function is impaired. Fluconazole (400–800 mg/d) plus flucytosine (100–150 mg/kg/d) for 6 weeks is an alternative to the use of amphotericin B, although toxicity with this regimen is high. In all cases of cryptococcal meningitis, careful attention to the management of intracranial pressure is imperative to assure optimal clinical outcome.

### Introduction

As is true for other systemic mycoses, treatment of disease due to *C. neoformans* have improved dramatically over the last 2 decades. Before 1950, disseminated cryptococcal disease was uniformly fatal. With the advent of polyene antifungal agents, particularly amphotericin B, successful outcomes were achieved in as much as 60%–70% of patients with cryptococcal meningitis, depending on the status of the host at the time of presentation [1]. During the early 1970s, flucytosine was estab-

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lished as an orally bioavailable agent with potent activity against *C. neoformans*; however, this activity was lost rapidly because of the development of resistance when the drug was used as monotherapy [2]. When flucytosine was added to amphotericin B as combination therapy, overall outcome of therapy was improved and the duration of treatment could be reduced from 10 weeks to 4–6 weeks, depending on the status of the host [1, 3]. Beginning in the 1980s, orally bioavailable azole antifungal agents with activity against *C. neoformans* were introduced, in particular, itraconazole and fluconazole. At approximately the same time, the incidence of cryptococcal infections rose dramatically, due in large part to the explosion of the AIDS epidemic around the world and the use of more potent immunosuppressive agents by increasing numbers of solid organ transplant recipients [4].

As the overall incidence of cryptococcal disease has increased so has the number of treatment options available to treat the disease. At the present time, in addition to amphotericin B and flucytosine, other drugs, namely fluconazole, itraconazole, and lipid formulations of amphotericin B, are available to treat cryptococcal infections. These agents can be used alone or in combination with other agents with varying degrees of success. Some of the treatment regimens currently in use have not been studied in randomized clinical trials, but rather are used on the basis of anecdotal reports or open-label phase II studies. As a result, most clinicians are uncertain about which agents to use for which underlying disease state, in what combination, and for what duration. It is notable that, despite the relatively short time AIDS has been in existence, more data now exist on the treatment of AIDS-associated cryptococcal meningitis than on the treatment of any other form of cryptococcal infection.

## Guidelines for the Treatment of Cryptococcosis in Patients without HIV Infection

### Pulmonary and Non-CNS Disease

The presentation of pulmonary cryptococcosis can range from asymptomatic nodular disease to severe acute respiratory distress syndrome (ARDS). Classic symptoms of pneumonitis, including cough, fever, and sputum production, may be present, or pleural symptoms may predominate. The lung is the principal route of entry for infection. The presence of a positive serum cryptococcal antigen titer implies deep tissue invasion and a high likelihood of disseminated disease. The organism has a strong predilection for infecting the CNS; however, infection has been reported in virtually every organ in the body.

**Objectives.** The goal of treatment is cure of the infection and prevention of dissemination of disease to the CNS.

**Options.** Few studies have been conducted that specifically evaluate outcomes among HIV-negative patients with pulmonary or non-CNS disease. Therefore, the specific treatment of choice and the optimal duration of treatment have not been fully elucidated for HIV-negative patients. It is clear that all

immunocompromised patients require treatment, since they are at high risk for development of disseminated infection. Patients with symptoms need treatment. Although all asymptomatic patients with positive cultures should be considered for treatment, many immunocompetent patients with positive sputum cultures have done well without therapy [5]. However, patients with nonpulmonary, extraneural (e.g., bone or skin) disease require specific antifungal therapy. Surgery should be performed for patients with persistent or refractory pulmonary or bone disease, but it is rarely needed.

**Outcomes.** The desired outcome is resolution of symptoms such as cough, shortness of breath, sputum production, chest pain, fever, and resolution or stabilization of abnormalities (infiltrates, nodules, or masses) on chest radiograph. In cases of extrapulmonary, non-CNS disease, resolution of symptoms and signs, as well as other markers of disease (e.g., radiographic abnormalities), is the desired outcome.

**Recommendations.** Specific recommendations for the treatment of non-HIV-associated cryptococcal pulmonary disease are summarized in table 1. Regardless of the treatment chosen, it is imperative that all patients with pulmonary and extrapulmonary cryptococcal disease have a lumbar puncture performed to rule out concomitant CNS infection. Immunocompetent patients who are asymptomatic and who have a culture of the lung that is positive for *C. neoformans* may be observed carefully or treated with fluconazole, 200–400 mg/d for 3–6 months [3, 4, 6, 7] (AIII; see article by Sobel [8] for definitions of categories reflecting the strength of each recommendation for or against its use and grades reflecting the quality of evidence on which recommendations are based). Immunocompetent patients who present with mild-to-moderate symptoms should be treated with fluconazole, 200–400 mg/d for 6–12 months [3, 4] (AIII). In cases where fluconazole is not an option, an acceptable alternative regimen is itraconazole, 200–400 mg/d, for 6–12 months [9] (BIII). The toxicity of amphotericin B limits its utility as a desired agent in the treatment of mild-to-moderate pulmonary disease among immunocompetent hosts. However, if oral azole therapy cannot be given, or the pulmonary disease is severe or progressive, amphotericin B is recommended, 0.4–0.7 mg/kg/d for a total dose of 1000–2000 mg (BIII). Ketoconazole has in vitro activity against *C. neoformans*, but is generally ineffective in the treatment of cryptococcal meningitis and should be used rarely, if at all, in this setting [10] (CIII). Some reports describe the successful use of flucytosine (100 mg/kg/d for 6–12 months) as therapy for pulmonary cryptococcal disease; however, concern about the development of resistance to flucytosine when used alone limits its use in this setting [2, 5] (DII). Immunocompromised patients with non-CNS pulmonary and extrapulmonary disease should be treated in the same fashion as patients with CNS disease [4, 6] (AIII).

Some patients present with isolated cryptococemia, a positive serum cryptococcal antigen titer (>1 : 8) without evidence

**Table 1.** Preferred treatment options for cryptococcal disease in HIV-negative patients.

Cryptococcal disease, treatment regimen	Reference	Class
<b>Pulmonary</b>		
Mild-to-moderate symptoms or culture-positive specimen from this site <sup>a</sup>		
Fluconazole, 200–400 mg/d for 6–12 mo <sup>b</sup>	[4, 7]	AIII
Itraconazole, 200–400 mg/d for 6–12 mo <sup>c</sup>	[9]	BIII
Amphotericin B, 0.5–1 mg/kg/d (total, 1000–2000 mg)		BIII
Severe symptoms and immunocompromised hosts		
Treat like CNS disease	[4–6]	
<b>CNS</b>		
Induction/consolidation <sup>d</sup> : amphotericin B, 0.7–1 mg/kg/d plus flucytosine, 100 mg/kg/d for 2 w, then fluconazole, 400 mg/d for minimum 10 w <sup>e</sup>	[7, 11]	AI
Amphotericin B, 0.7–1 mg/kg/d plus flucytosine, 100 mg/kg/d for 6–10 w <sup>f</sup>	[1, 3, 29]	AI
Amphotericin B, 0.7–1 mg/kg/d for 6–10 w	[1]	CI
Lipid formulation of amphotericin B, 3–6 mg/kg/d for 6–10 w <sup>e,f</sup>	[12, 19, 20]	CIII

<sup>a</sup> The clinician must determine whether to follow lung therapeutic regimen or CNS (disseminated) regimen for treatment of infection in other body sites (e.g., skin). When other disseminated sites of infection are noted or the patient is at risk for disseminated infection, it is important to rule out CNS disease.

<sup>b</sup> Duration of therapy is based on resolution of disease.

<sup>c</sup> Not formally approved by the US Food and Drug Administration for use in cryptococcal disease.

<sup>d</sup> It is important to note that this preferred regimen has not been specifically studied in patients without HIV infection but has many features that are attractive for successful management of this infection.

<sup>e</sup> Among patients receiving prolonged (>2 w) of flucytosine, renal function should be monitored frequently and dose adjustment should be made via use of a nomogram, or preferably, through monitoring of serum flucytosine levels. Serum flucytosine levels should be measured 2 h after dose, with optimal levels between 30 and 80 µg/mL.

<sup>f</sup> Experience with lipid preparations of amphotericin B is limited in the treatment of cryptococcal meningitis without HIV infection, but with present experience, AmBisome 4 mg/kg would be the best substitute for amphotericin B in this infection.

of clinical disease, or a positive urine culture or prostatic disease. Although no retrospective or prospective studies have been conducted to investigate treatment options for such patients, they should probably be treated with antifungal therapy (AIII).

**Benefits and harms.** Early, appropriate treatment of non-CNS pulmonary and extrapulmonary cryptococcosis reduces morbidity and prevents progression to potentially life-threatening CNS disease. Among patients with solid organ transplants, aggressive treatment of early cryptococcal disease may prevent loss of the transplanted organ. Drug-related toxicities and development of adverse drug-drug interactions are the principal potential harms of therapeutic intervention.

**Costs.** Drug acquisition costs are high for antifungal therapies administered for 6–12 months. Additional costs are accrued for monthly monitoring and supervision of therapies associated with most of the recommended regimens.

### CNS Disease

CNS disease usually presents as meningitis and on rare occasions as single or multiple focal mass lesions (cryptococcomas). The CNS disease may be associated with concurrent pneumonia or with other evidence of disseminated disease, such as focal skin lesions, but most commonly presents as solitary CNS infection without other manifestations of disease. Whether the CNS disease is associated with involvement of other body sites, treatment remains the same.

**Objectives.** The goal of treatment is cure of the infection (CSF sterilization) and prevention of long-term CNS system sequelae, such as cranial nerve palsies, hearing loss, and blindness.

**Options.** In contrast to non-CNS disease, several studies have been performed that specifically evaluate outcomes among HIV-negative patients with cryptococcal meningitis. Studies evaluating the effectiveness of amphotericin B, with or without flucytosine, have elucidated the optimal length of therapy for HIV-negative, immunocompromised and immunocompetent hosts. However, no randomized studies in these population groups have been completed in the era of triazole therapy.

**Outcomes.** The desired outcome is resolution of abnormalities, such as fever, headache, altered mental status, meningeal signs, elevated intracranial pressure, and cranial nerve abnormalities. In cases of CNS mass lesions (cryptococcomas), radiographic resolution of lesions is the desired outcome.

**Recommendations.** Specific recommendations for the treatment of non-HIV-associated cryptococcal meningitis are summarized in table 1. Combination therapy of amphotericin B and flucytosine will sterilize CSF within 2 weeks of treatment in 60%–90% of patients [1, 3]. Most immunocompetent patients will be treated successfully with 6 weeks of combination therapy [1, 3] (AI); however, owing to the requirement of iv therapy for an extended period of time and the relative toxicity of the regimen, alternatives to this approach have been advocated. Despite the absence of controlled clinical trial data from HIV-

negative populations of patients, a frequently used alternative treatment for cryptococcal meningitis in immunocompetent patients is an induction course of amphotericin B (0.5–1 mg/kg/d) with flucytosine (100 mg/kg/d) for 2 weeks, followed by consolidation therapy with fluconazole (400 mg/d) for an additional 8–10 weeks [7] (BIII). This recommendation is extrapolated from the treatment experience of patients with HIV-associated cryptococcal meningitis [11, 13]. Pilot studies that have investigated fluconazole with flucytosine as initial therapy yielded unsatisfactory outcomes [7]. Therefore, initial therapy with fluconazole, even among “low risk” patients, is discouraged (DIII). A lumbar puncture is recommended after 2 weeks of treatment to assess the status of CSF sterilization. Patients with a positive culture at 2 weeks may require a longer course of induction therapy. Also, it is optional to continue fluconazole (200 mg/d) for 6–12 months (BIII).

Immunosuppressed patients, such as solid organ transplant recipients, require more prolonged therapy [3]. On the basis of experience of treating cryptococcal meningitis in HIV disease, it is reasonable to follow a similar induction, consolidation, and suppression strategy, since previous strategies reported failure rates of 15%–20% with 6 weeks of treatment with combination amphotericin B/5-flucytosine [3]. Therapy with amphotericin B (0.7–1 mg/kg/d) for 2 weeks, followed by 8–10 weeks of fluconazole (400–800 mg/d), is followed with 6–12 months of suppressive therapy with a lower dose of fluconazole (200 mg/d) (BIII). For those patients receiving long-term prednisone therapy, reduction of the prednisone dosage (or its equivalent) to 10 mg/d, if possible, may result in improved outcome to antifungal therapy.

For both immunocompetent and immunocompromised patients with significant renal disease, lipid formulations of amphotericin B may be substituted for amphotericin B during the induction phase [12] (CIII). For patients who are unable to tolerate fluconazole, itraconazole (200 mg twice daily) may be substituted (CIII). Most parenchymal lesions will respond to antifungal treatment; large (>3 cm) accessible CNS lesions may require surgery. All patients should be monitored closely for evidence of elevated intracranial pressure and managed in a fashion similar to HIV-positive patients (see below). Treatment decisions should not be based routinely or exclusively on cryptococcal polysaccharide antigen titers in either the serum or CSF [31, 34] (AI). Because the goal is cure following cessation of therapy, patients requiring suppressive therapy for >1–2 years should be considered failures.

Intrathecal or intraventricular amphotericin B may be used in refractory cases where systemic administration of antifungal therapy has failed. Owing to its inherent toxicity and difficulty of administration, this therapy is recommended only in this salvage setting [14] (CII).

**Benefits and harms.** Early, appropriate treatment of cryptococcal meningitis reduces both morbidity and mortality. Drug-related toxicities and development of adverse drug-drug

interactions are the principal harms of therapeutic intervention. Toxic side effects of amphotericin B are common and include nausea, vomiting, chills, fever, and rigors, which can occur with each dose. The most troublesome toxic side effect is renal injury, including elevation of the serum creatinine, hypokalemia, hypomagnesemia, and renal tubular acidosis. In addition, anemia occurs frequently and thrombocytopenia occurs occasionally (possibly as a result of exposure to heparin). It is necessary to carefully monitor serum electrolytes, renal function, and bone marrow function. Nevertheless, amphotericin B can be employed safely and effectively; only 3% of patients will have toxic side effects of a magnitude that requires it to be discontinued within the first 2 weeks of therapy [11].

**Costs.** Drug acquisition costs are high for antifungal therapies administered for 6–12 months. Additional costs are accrued for daily, weekly, and monthly monitoring of therapies associated with most of the recommended regimens.

## Guidelines for the Treatment of Pulmonary and CNS Cryptococcosis in Patients with HIV Infection

### Therapy for AIDS-Related Cryptococcal Pneumonia

Pneumonia is thought to herald the onset of disseminated disease. Cryptococcal pneumonia is usually characterized by fever and cough that produces scant sputum. There is little to distinguish cryptococcal pneumonia from other causes of atypical pneumonia in HIV-infected patients. With the exception of the typical skin lesions (which mimic molluscum contagiosum) associated with disseminated cryptococcosis, history, physical examination, or routine laboratory testing cannot elicit features suggestive of cryptococcal disease. Yet, because of the potentially grave consequences of overlooking this illness, it is imperative to assess AIDS patients with pneumonia for possible fungal infection. Sputum fungal culture, blood fungal culture, and a serum cryptococcal antigen test are appropriate laboratory studies in any HIV-infected patient with pneumonia and a CD4<sup>+</sup> T lymphocyte count <200 cells/mL. If any test is positive for *C. neoformans*, then a CSF examination is recommended to exclude cryptococcal meningitis.

**Objectives.** The goal of treatment is control of the infection and prevention of dissemination of disease to the CNS.

**Options.** There are no controlled clinical trials describing the outcome of therapy for AIDS-related cryptococcal pneumonia (table 2). Indeed, few studies have been conducted that specifically evaluate outcomes among HIV-infected patients with pulmonary or non-CNS disease. Therefore, the specific treatment of choice has not been fully elucidated. It is clear that all HIV-infected patients require treatment, since they are at high risk for disseminated infection. Surgery should be considered for patients with persistent or refractory pulmonary or bone lesions. Some HIV-infected patients present with isolated cryptococemia or a positive serum cryptococcal antigen titer (>1 : 8) without evidence of clinical disease. Although no spe-

**Table 2.** Treatment options for cryptococcal disease in HIV-infected patients.

Cryptococcal disease, treatment regimen	Reference	Class
<b>Pulmonary</b>		
Mild-to-moderate symptoms or culture-positive specimen from this site <sup>a</sup>		
Fluconazole, 200–400 mg/d, lifelong	[15]	AII
Itraconazole, 200–400 mg/d, lifelong <sup>b</sup>	[9]	CII
Fluconazole, 400 mg/d plus flucytosine 100–150 mg/kg/d for 10 w	[15]	CII
<b>CNS</b>		
Induction/consolidation: amphotericin B, 0.7–1 mg/kg/d plus flucytosine, 100 mg/kg/d for 2 w, then fluconazole, 400 mg/d for a minimum of 10 w <sup>c</sup>		
Amphotericin B, 0.7–1 mg/kg/d plus 5 flucytosine 100 mg/kg/d for 6–10 w	[11, 32]	AI
Amphotericin B, 0.7–1 mg/kg/d for 6–10 w	[13, 18, 29]	BI
Amphotericin B, 0.7–1 mg/kg/d for 6–10 w	[13]	CI
Fluconazole, 400–800 mg/d for 10–12 w	[13, 18, 36, 37]	CI
Itraconazole, 400 mg/d for 10–12 w <sup>b</sup>	[9, 33]	CII
Fluconazole, 400–800 mg/d plus flucytosine, 100–150 mg/kg/d for 6 w	[16, 28]	CII
Lipid formulation of amphotericin B, 3–6 mg/kg/d for 6–10 w <sup>d,b</sup>	[12, 19, 20]	CII
<b>Maintenance:</b>		
Fluconazole, 200–400 mg po q.d., lifelong <sup>c</sup>	[17, 23, 24]	AI
Itraconazole, 200 mg po bid, lifelong <sup>c</sup>	[9, 17]	BI
Amphotericin B, 1 mg/kg iv 1–3 times/w, lifelong <sup>c</sup>	[24]	CI

NOTE. Among patients receiving prolonged (>2 w) or flucytosine therapy, renal function should be monitored frequently and dose adjustment should be made via use of a nomogram, or preferably, through monitoring of serum flucytosine levels. Serum flucytosine levels should be measured 2 h after dose with optimal levels between 30 and 80  $\mu\text{g/mL}$ .

<sup>a</sup> The clinician must determine whether to follow lung therapeutic regimen or CNS (disseminated) regimen for treatment of infection in other body sites. When other disseminated sites of infection are noted or patient is at risk for disseminated infection, it is important to rule out CNS disease.

<sup>d</sup> Experience with lipid preparations of amphotericin B are limited in treatment of cryptococcal meningitis with HIV infection, but with present experience, AmBisome 4 mg/kg would be the choice for amphotericin B substitution in this infection.

<sup>c</sup> Unclear whether secondary prophylaxis may be discontinued in patients with prolonged success with highly active antiretroviral therapy.

<sup>b</sup> Not formally approved by the US Food and Drug Administration for use in cryptococcal disease.

cific studies have been designed to investigate treatment options for such patients, they should be treated.

**Outcomes.** The desired outcome is resolution of symptoms, such as cough, shortness of breath, sputum production, chest pain, fever, and resolution or stabilization of abnormalities (infiltrates, nodules, masses, etc.) on chest radiograph. In cases of extrapulmonary, non-CNS disease, resolution of lesions is the desired outcome.

**Recommendations.** Specific recommendations for the treatment of HIV-associated cryptococcal pulmonary disease are summarized in table 2. Patients who present with mild-to-moderate symptoms or who are asymptomatic with a positive culture for *C. neoformans* from the lung should be treated with fluconazole, 200–400 mg/d for life [3, 4, 15] (AII); however, long-term follow-up studies on the duration of treatment in the era of HAART are needed. In cases where fluconazole is not an option, an acceptable alternative is itraconazole, 400 mg/d for life [9] (CII). A potential treatment option is combination therapy with fluconazole, 400 mg/d, plus flucytosine, 150 mg/kg/d, for 10 weeks; however, the toxicity associated with this regimen limits its utility [15] (CII). In patients with more severe disease, amphotericin B should be used until symptoms are controlled, then an oral azole agent, preferably fluconazole, can be substituted (BIII). Ketoconazole is generally ineffective in the treatment of cryptococcosis in HIV-infected patients and should probably be avoided [10, 30] (DII).

**Benefits and harms.** Early, appropriate treatment of non-

CNS pulmonary and extrapulmonary cryptococcosis in HIV-infected patients reduces morbidity and prevents progression to potentially life-threatening CNS disease. The prevention of progression to cryptococcal meningitis is the principal goal of therapy in this population. Uniform success cannot be anticipated with existing therapy; however, since the mortality associated with cryptococcal meningitis can be up to 25% among persons with AIDS, the use of therapies that result in even modest levels of success are worthy. Adverse effects from fluconazole monotherapy at 400 mg daily are uncommon. However, there are considerable side effects from flucytosine (150 mg/kg/d) when given in combination with fluconazole for 10 weeks in patients with HIV-associated cryptococcal meningitis [16]. Dose-limiting adverse effects (predominantly gastrointestinal in nature) that resulted in the discontinuation of flucytosine were reported in 28% of patients; and another 32% described significant side effects that did not result in the discontinuation of therapy.

**Costs.** Drug acquisition costs are high for antifungal therapies administered for life. Additional costs are accrued for monthly monitoring of therapies associated with most of the recommended regimens.

#### Therapy for AIDS-Related Cryptococcal Meningitis

**Induction therapy.** Recognition of cryptococcal meningitis in HIV-infected patients requires a high index of suspicion.

Patients typically present with fever and/or headache of gradual onset, which becomes progressively more debilitating. However, it is also important to exclude cryptococcal meningitis in patients with seizures, bizarre behavior, confusion, progressive dementia, or unexplained fever. Classic signs of meningeal irritation commonly are absent on physical examination, and routine laboratory assessment is rarely revealing. Because of the potential for mass lesions within the brain among patients with AIDS, imaging of the CNS should be performed before CSF sampling. While awaiting the results of imaging studies, the serum should be tested for the presence of cryptococcal polysaccharide antigen. The serum cryptococcal antigen is positive in >99% of subjects with cryptococcal meningitis, usually at titers >1 : 2048 [11, 13].

Defining the presence of meningitis and its severity is essential; there is no adequate substitute for examination of the CSF. Routine studies should include the following: measurement of CSF opening pressure (with the patient in the lateral recumbent position); collection of sufficient CSF for fungal culture (3 mL); and the measurement of CSF cryptococcal antigen titer, glucose level, protein level, and cell count with differential (5 mL total).

**Objectives.** The objective of treatment is eradication of the infection and control of elevated intracranial pressure. However, failing eradication, which is common in HIV disease, long-term control of infection and resolution of clinical evidence of disease are the principal goals.

**Options.** Three antifungal drugs are of benefit in the treatment of cryptococcal meningitis in patients with AIDS: amphotericin B, fluconazole, and flucytosine. Itraconazole appears less active than fluconazole [17, 33]. Because of the relatively rapid emergence of drug resistance, flucytosine is not employed as a single agent and is, therefore, only used in combination with amphotericin B or fluconazole. Two clinical trials found that therapy with a combination of amphotericin B plus flucytosine was superior to amphotericin B alone or fluconazole monotherapy [11, 18]. Similarly, therapy with a combination of fluconazole plus flucytosine seems to be superior to fluconazole alone [16, 28], although this regimen is more toxic than fluconazole monotherapy. Recently, lipid formulations of amphotericin B have been tested in cryptococcal meningitis and may have some toxicity profile advantages over the conventional amphotericin B formulation when used alone or possibly with flucytosine [12, 29].

**Outcomes.** The desired outcome is resolution of abnormalities, such as fever, headache, altered mental status, ocular signs, and elevated intracranial pressure. In cases of CNS masses (cryptococcoma), resolution of lesions is the desired outcome.

**Recommendations.** A summary of treatment recommendations for AIDS-associated cryptococcal meningitis is provided in table 2. Amphotericin B (0.7–1 mg/kg given iv daily for  $\geq 2$  weeks) combined with flucytosine, 100 mg/kg given orally in 4 divided doses per day, is the initial treatment of choice [11, 13, 18, 29] (AI). In cases where flucytosine cannot

be administered, amphotericin B alone (administered at the same doses listed above) is an acceptable alternative [13] (BI). After the 2-week period of successful induction therapy, consolidation therapy should be initiated with fluconazole (400 mg orally once daily) administered for 8 weeks or until CSF cultures are sterile [11] (AI). In cases where fluconazole cannot be given, itraconazole is an acceptable, albeit less effective, alternative [9, 33] (B, I). Lipid formulations of amphotericin B appear beneficial and may be useful for patients with cryptococcal meningitis and renal insufficiency [12, 18–21] (CII). The optimal dose of lipid formulations of amphotericin B has not been determined, but AmBisome has been effective at doses of 4 mg/kg/d [12]. Combination therapy with fluconazole (400–800 mg/d) and flucytosine (100 mg/kg/d in 4 divided doses) has been shown to be effective in the treatment of AIDS-associated cryptococcal meningitis [16, 29]. However, owing to the toxicity of this regimen, it is recommended only as an alternative option for therapy [16] (CII). Intrathecal or intraventricular amphotericin B may be used in refractory cases where systemic administration of antifungal therapy has failed [14]. Owing to its inherent toxicity and difficulty of administration, it is recommended only in a salvage setting [14] (CII).

In selected cases, susceptibility testing of the *C. neoformans* isolate may be beneficial to patient management, particularly if a comparison can be determined between baseline and sequential isolates. Such testing is generally best used in cases of relapse or in cases of refractory disease. At this time, susceptibility testing of isolates is not recommended for routine patient care (CIII).

**Benefits and harms.** Early, appropriate treatment of HIV-associated cryptococcal meningitis significantly reduces both the morbidity and mortality associated with this disorder. In the most recent large comparative study of this disease, the overall mortality was 6%; in contrast, previous treatment studies experienced mortality rates of 14%–25% [11, 13]. Toxic side effects from amphotericin B are common. Flucytosine dosage must be adjusted on the basis of hematologic toxicities or, preferably, based on measurement of flucytosine levels. Toxicity associated with use of fluconazole/flucytosine combination therapy is substantial [15].

**Costs.** Drug acquisition costs are high for antifungal therapies administered for life. Additional costs are accrued for the biweekly monitoring of therapies during acute induction therapy and every-other-week monitoring during consolidation therapy.

**Maintenance therapy.** Among patients with AIDS-associated cryptococcal meningitis who are treated successfully, there is a high risk of relapse in the absence of maintenance therapy. This was demonstrated in a placebo-controlled, double-blind, randomized trial evaluating the effectiveness of fluconazole for maintenance therapy after successful primary treatment with either amphotericin B alone or in combination with flucytosine in patients with AIDS [23]. Three percent of fluconazole patients and 37% of placebo patients relapsed at

any site. Fifteen percent of patients in the placebo arm developed CNS relapse compared with no relapses in the fluconazole group.

**Objectives.** The primary objective of maintenance therapy is the prevention of relapse of cryptococcal meningitis.

**Options.** There are 2 key elements in preventing relapse of cryptococcal meningitis: (1) control of HIV replication by means of potent HAART and (2) the use of chronic antifungal therapy to prevent microbial relapse. Prospective clinical trials and carefully conducted observational studies show that potent antiretroviral therapy reduces the incidence of opportunistic infections [25–27]. The prevalence of cryptococcosis in these studies was too low to provide direct evidence or confirm that antiretroviral therapy affects cryptococcal disease, but there is no biological basis to suspect that control of cryptococcosis in AIDS patients would not be improved by the use of HAART. Three potential options exist for antifungal maintenance therapy: fluconazole, itraconazole, and weekly or biweekly amphotericin B.

**Outcomes.** The desired outcome is continued absence of symptoms associated with cryptococcal meningitis and resolution or stabilization of cranial nerve abnormalities. No laboratory or clinical test, such as serial serum or CSF cryptococcal antigen testing, is useful for monitoring for microbial relapse during the maintenance phase of treatment [31, 34].

**Recommendations.** Aggressive antiretroviral therapy should be administered in accordance with standards of care in the community [35]. In conjunction with antiretroviral therapy, long-term maintenance antifungal therapy should be administered. Oral fluconazole, 200 mg/d, is the most effective maintenance therapy for AIDS-associated cryptococcal meningitis [17, 24] (AI). A randomized comparative trial demonstrated the superiority of fluconazole (200 mg/d) over amphotericin B (1 mg/kg/w) as maintenance therapy [24]. Patients in the amphotericin B group had significantly more relapses, more drug-related adverse events, and more bacterial infections, including bacteremia [24]. Relapse rates were 2% for fluconazole and 17% for amphotericin B. Therefore, owing to its toxicity and difficulty with administration, amphotericin B maintenance therapy should be reserved for those patients who have had multiple relapses while receiving azole therapy or who are intolerant of the azole agents (CI).

In another randomized comparative trial, fluconazole was demonstrated to be superior to itraconazole as maintenance therapy for cryptococcal disease [17]. This trial was terminated by an independent data safety monitoring board after preliminary results revealed a CSF culture relapse rate of 4% among patients receiving fluconazole (200 mg/d), compared with 24% relapse among itraconazole (200 mg/d) recipients [17]. Thus, itraconazole should be used in cases where the patient is intolerant of fluconazole or has failed fluconazole therapy (BI). It may be prudent to use doses of 200 mg of itraconazole twice daily (BIII). Ketoconazole is not effective as maintenance ther-

apy [30] (DII). Although some preliminary evidence suggests lower relapse rates of opportunistic infections when patients have been successfully treated with potent antiretroviral therapy, until proven otherwise, maintenance therapy for cryptococcal meningitis should be administered for life (AI). For selected patients who have responded very well to HAART, consideration might be given to discontinuing secondary antifungal prophylaxis after 12–18 months of successful suppression of HIV viral replication (CIII).

**Benefits and harms.** Preventing relapse of cryptococcosis reduces mortality and morbidity and slows the progression of HIV disease. Fluconazole is well-tolerated; nausea, abdominal pain, and skin rash are the most common adverse effects.

**Costs.** Drug acquisition costs are high for antifungal therapies administered for life. Additional costs are accrued for the monthly monitoring of therapies during maintenance therapy.

### Management of Elevated Intracranial Pressure

In both HIV-negative and HIV-positive patients with cryptococcal meningitis, elevated intracranial pressure occurs in excess of 50% of patients [22]. Elevated intracranial pressure is an important contributor to morbidity and mortality of cryptococcal meningitis. Elevated intracranial pressure is defined as opening pressure >200 mm H<sub>2</sub>O, measured with the patient in a reclining (lateral decubitus) position. By this definition, almost three-fourths of 221 HIV-infected patients in a recent NIAID-sponsored Mycoses Study Group trial had elevated intracranial pressure at baseline. One-fourth of the patients had opening pressures >350 mm H<sub>2</sub>O [22]. Aggressive management of elevated intracranial pressure has not been employed consistently in HIV-negative patients with cryptococcal meningitis, and its impact on outcome is unclear. Among HIV-infected patients with elevated CSF pressures, a poorer clinical response was noted among patients whose pressure increased between baseline and week 2 of treatment; benefit from management of intracranial pressure is inferred from reduced mortality in this population [22].

Similarly, HIV-negative patients may have elevated CSF pressure associated with meningeal inflammation, cryptococcomas, and either communicating or, very rarely, obstructive hydrocephalus. Focal neurological signs may reflect mass lesions. HIV-infected patients with elevated intracranial pressure do not differ clinically from those with normal opening pressure, except that neurological manifestations of disease are more severe among those with higher pressures [21, 22]. Common manifestations in this setting include papilledema, hearing loss, loss of visual acuity, pathological reflexes, severe headache, and abnormal mentation.

In HIV-infected patients, evaluation of the CSF reveals minimal inflammation (frequently, few leukocytes; and normal levels of glucose and protein) but uncontrolled fungal growth in the CSF. CSF antigen titers are higher and the India ink smear

**Table 3.** Management of elevated intracranial pressure in HIV-infected patients with cryptococcal disease.

Assessment	Management	Class
Before treatment		
Focal neurological signs, obtunded	Radiographic imaging before lumbar puncture to identify mass lesions that may contraindicate lumbar puncture	BII
Normal opening pressure	Initiate medical therapy, with follow-up lumbar puncture at 2 w	AI
Opening pressure >250 mm H <sub>2</sub> O	Lumbar drainage sufficient to achieve closing pressure ≤200 mm H <sub>2</sub> O or 50% of initial opening pressure	AII
Follow-up for elevated pressure		
If elevated pressure persists:	Repeated drainage daily until opening pressure is stable	AII
	Lumbar drain	BII
	Ventriculoperitoneal shunt	BII
	Corticosteroids: not recommended for HIV-infected patients, and evidence of benefit for HIV-negative patients is not established	CIII

is more frequently positive among patients with elevated opening pressure than among patients with normal opening pressure. The elevated intracranial pressure in this setting is thought to be due, in part, to interference with CSF reabsorption in the arachnoid villi, caused by high levels of fungal polysaccharide antigen or excessive growth of the organism per se.

**Objectives.** The primary objective of effective intracranial pressure management is the reduction of morbidity and mortality associated with cryptococcal meningitis in both HIV and HIV-negative patients.

**Options.** Several treatment options exist for managing elevated intracranial pressure (table 3) including intermittent CSF drainage by means of sequential lumbar punctures, insertion of a lumbar drain, or placement of a ventriculoperitoneal shunt. Medical approaches, including the use of corticosteroids, acetazolamide, or mannitol, have not been shown to be effective in the setting of cryptococcal meningitis.

**Recommendations.** The principal intervention for reducing elevated intracranial pressure is percutaneous lumbar drainage [21, 22] (AII). Radiographic imaging of the brain is recommended prior to performance of the initial lumbar puncture to rule out the presence of a space-occupying lesion [21] (BII). Among patients with normal baseline opening pressure (<200 mm H<sub>2</sub>O), a repeat lumbar puncture should be performed 2 weeks after initiation of therapy to exclude elevated pressure and to evaluate culture status. For patients with elevated baseline opening pressure, lumbar drainage should remove enough CSF to reduce the opening pressure by 50%. Patients should initially undergo daily lumbar punctures to maintain CSF opening pressure in the normal range. When the CSF pressure is normal for several days, the procedure can be suspended. Occasionally patients who present with extremely high opening pressures (>400 mm H<sub>2</sub>O) may require a lumbar drain, especially when frequent lumbar punctures are required to or fail to control symptoms of elevated intracranial pressure. In cases where repeated lumbar punctures or use of a lumbar drain fail to control elevated pressure symptoms, or when persistent or progressive neurological deficits are present, a ventriculoperitoneal shunt is indicated [21, 22] (BII).

Treatment with steroids has yielded mixed results in both HIV-infected and HIV-negative patients, and its impact on out-

come is unclear. Owing to the intense fungal burden and large amount of replication in patients with HIV disease, adjunctive steroid therapy is not recommended for HIV-infected patients (DIII). Among HIV-negative patients, the benefit of steroid therapy is not well-established and should not be used (DIII). Acetazolamide and mannitol have not been shown to provide any clear benefit in the management of elevated intracranial pressure resulting from cryptococcal meningitis (DIII).

**Benefits and harms.** Aggressive management of elevated intracranial pressure is perhaps the most important factor in reducing mortality and minimizing morbidity of acute cryptococcal meningitis. The main risk of lumbar drainage occurs in the setting of a coexistent mass lesion and obstructive hydrocephalus, which is a relatively rare complication of cryptococcal disease. Prolonged external lumbar drainage places patients at major risk for bacterial infection. Ventriculoperitoneal shunts may become secondarily infected with bacteria; however, this is an uncommon complication. Secondary infection of the shunt with *C. neoformans* generally does not occur if antifungal therapy has been instituted.

**Costs.** Lumbar punctures are relatively inexpensive. Lumbar drains are typically used in intensive care unit settings, which are associated with higher costs. Placement of a ventriculoperitoneal shunt requires neurosurgical intervention with general anesthesia, which is an expensive, but potentially life-saving, procedure.

#### References

- Bennett JE, Dismukes W, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med* 1979;301:126–31.
- Utz JP, Tynes JS, Shadomy HJ, et al. 5-fluorocytosine in human cryptococcosis. *Antimicrob Agents Chemother* 1968;8:344–6.
- Dismukes WE, Cloud G, Gallis HA, et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. *N Engl J Med* 1987;317:334–41.
- Dromer F, Mathoulin S, Dupont B, et al. 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* 1996;22:S154–60.
- Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryp-

- tococcosis: clinical implications from a study of 41 patients with and without compromising host factors. *Ann Intern Med* **1981**;94:611-6.
6. Yamaguchi H, Ikemoto H, Watanabe K, et al. Fluconazole monotherapy for cryptococcosis in non-AIDS patients. *Eur J Clin Microbiol Infect Dis* **1996**;15:787-92.
  7. Pappas PG, Perfect J, Larsen RA, et al. Cryptococcosis in HIV-negative patients: analysis of 306 cases [abstract 101]. In: 36th annual meeting of the Infectious Diseases Society of America (Denver, CO). Alexandria, VA: Infectious Diseases Society of America, **1998**.
  8. Sobel JD. Practice guidelines for the treatment of fungal infections. *Clin Infect Dis* **2000**;30:652 (in this issue).
  9. Denning DW, Tucker RM, Hanson LH, et al. Itraconazole therapy for cryptococcal meningitis and cryptococcosis. *Arch Intern Med* **1989**;149:2301-8.
  10. Dismukes WE, Stamm AM, Graybill JR, et al. Treatment of systemic mycoses with ketoconazole: emphasis on toxicity and clinical response in 52 patients. National Institute of Allergy and Infectious Diseases Collaborative Antifungal Study. *Ann Intern Med* **1983**;98:13-20.
  11. van der Horst C, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med* **1997**;337:15-21.
  12. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS* **1997**;11:1463-71.
  13. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. *N Engl J Med* **1992**;326:83-9.
  14. Polsky B, Depman MR, Gold JW, et al. Intraventricular therapy of cryptococcal meningitis via a subcutaneous reservoir. *Am J Med* **1986**;81:24-8.
  15. Jones B, Larsen RA, Forthal D, Haghhighat D, Bozzette S. Treatment of nonmeningeal cryptococcal disease in HIV-infected persons [abstract F4]. In: Proceedings of the 91st annual meeting of the American Society for Microbiology (Dallas, TX). Washington, DC: American Society for Microbiology, **1991**.
  16. Larsen RA, Bozzette SA, Jones B, et al. Fluconazole combined with flucytosine for cryptococcal meningitis in persons with AIDS. *Clin Infect Dis* **1994**;19:741-5.
  17. Saag MS, Cloud GC, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. *Clin Infect Dis* **1999**;28:291-6.
  18. Larsen RA, Leal MAE, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for the treatment of cryptococcal meningitis in AIDS: a randomized trial. *Ann Intern Med* **1990**;113:183-7.
  19. Coker RJ, Viviani M, Gazzard BG, et al. Treatment of cryptococcosis with liposomal amphotericin B (AmBisome) in 23 patients with AIDS. *AIDS* **1993**;7:829-34.
  20. Diamond DM, Bauer M, Daniel BE, et al. Amphotericin B colloidal dispersion combined with flucytosine with or without fluconazole for treatment of murine cryptococcal meningitis. *Antimicrob Agents Chemother* **1998**;42:528-33.
  21. Denning DW, Armstrong RW, Lewis BH, Stevens DA. Elevated cerebrospinal fluid pressures in patients with cryptococcal meningitis and acquired immunodeficiency syndrome. *Am J Med* **1991**;91:267-72.
  22. Graybill JR, Sobel J, Saag M, et al. Cerebrospinal fluid hypertension patients with AIDS and cryptococcal meningitis [abstract I-153]. In: Program and abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (Toronto, ON, Canada). Washington, DC: American Society for Microbiology, **1997**.
  23. Bozzette SA, Larsen RA, 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* **1991**;324:580-4.
  24. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med* **1992**;326:793-8.
  25. CAESAR Coordinating Committee. Randomized trial of addition of lamivudine or lamivudine plus zidovudine to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial. *Lancet* **1997**;349:1413-21.
  26. Hammer S, Squires K, Hughes MD, et al. A controlled trial of two nucleoside analogues plus zidovudine in persons with human immunodeficiency virus infection and CD4 cell counts of 200 cells per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med* **1997**;337:725-33.
  27. Palella FJ, Delaney K, Moorman A, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* **1998**;338:853-60.
  28. Mayanja-Kizza H, Oishi K, Mitarai S, et al. Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS. *Clin Infect Dis* **1998**;26:1362-8.
  29. White M, Cirrioni C, Blevins A, Armstrong D. Cryptococcal meningitis: outcome in patients with AIDS and patients with neoplastic disease. *J Infect Dis* **1992**;165:960-3.
  30. Chuck SL, Sande MA. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. *N Engl J Med* **1989**;321:794-9.
  31. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. *Clin Infect Dis* **1994**;18:789-92.
  32. Powderly WG. Cryptococcal meningitis and AIDS. *Clin Infect Dis* **1993**;17:837-42.
  33. de Gans J, Portegies P, Tiessens G, et al. Itraconazole compared with amphotericin B plus flucytosine in AIDS patients with cryptococcal meningitis. *AIDS* **1992**;6:185-90.
  34. Tuazon CU, Powderly WG, Cloud CA, et al. Utility of serum and CSF cryptococcal antigen in the management of cryptococcal meningitis in AIDS patients [abstract 334]. In: 34th Annual Meeting of the Infectious Diseases Society of America (Denver). Alexandria, VA: Infectious Diseases Society of America, **1998**.
  35. Carpenter C, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society—USA Panel. *JAMA* **1998**;280:78-86.
  36. Berry AJ, Rinaldi MG, Graybill JR. Use of high-dose fluconazole as salvage therapy for cryptococcal meningitis in patients with AIDS. *Antimicrob Agents Chemother* **1992**;36:690-2.
  37. Menichetti F, Fiorio M, Tosti A, et al. High-dose fluconazole therapy for cryptococcal meningitis in patients with AIDS. *Clin Infect Dis* **1996**;22:838-40.