INTRODUCTION — Disseminated *Cryptococcus neoformans* infection is a serious opportunistic infection that occurs in patients with untreated AIDS [1]. Although cryptococcal infection begins in the lungs, meningitis is the most frequently encountered manifestation of cryptococcosis among those with advanced immunosuppression. However, the infection is more properly characterized as "meningoencephalitis" rather than meningitis since the brain parenchyma is almost always involved on histologic examination [2,3].

The clinical manifestations and diagnosis of *C. neoformans* meningoencephalitis in AIDS patients will be reviewed here. Treatment and monitoring of AIDS patients with cryptococcal meningoencephalitis is found elsewhere. The microbiology, clinical manifestations, and treatment of this infection in other patient populations, such as transplant patients, are discussed elsewhere. *C. gattii* infection is also presented separately. (See "Treatment of Cryptococcus neoformans meningoencephalitis in HIV-infected patients" and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis" and "Microbiology and epidemiology of Cryptococcus neoformans infection" and "Clinical manifestations and diagnosis of Cryptococcus neoformans meningoencephalitis in HIV-seronegative patients" and "Treatment of Cryptococcus neoformans meningoencephalitis and disseminated infection in HIV-seronegative patients" and "Cryptococcus neoformans infection outside the central nervous system" and "Cryptococcus gattii infection: Clinical features and diagnosis" and "Cryptococcus gattii infection: Treatment".)

EPIDEMIOLOGY — Globally, it has been estimated that approximately 957,900 cases of cryptococcal meningoencephalitis occur each year, resulting in more than 600,000 deaths [4,5]. The vast majority of cases occur among patients with AIDS and a CD4 count <100 cells/microL. The region with the highest number of estimated cases in 2006 was sub-Saharan Africa (720,000 cases; range, 144,000 to 1.3 million), followed by South and Southeast Asia (120,000 cases; range, 24,000 to 216,000) [4]. Although the incidence of cryptococcal meningoencephalitis has declined in patients who have access to antiretroviral therapy (ART) [6], cryptococcal disease remains a leading cause of mortality in the developing world where access to ART is limited and HIV prevalence remains high [7].

Early diagnosis and treatment may help reduce cryptococcal meningitis-related mortality [8]. One way to diagnose cryptococcal infection early in the course disease is through the detection of serum cryptococcal antigen (CrAg), which can be detected at least three weeks prior to the onset of neurologic symptoms. The prevalence of antigenemia has been found to vary depending upon the geographical area. As an example, in the United States, the prevalence of cryptococcal antigenemia among patients with a CD4 count <100 cells/microL was reported to be approximately 3 percent, whereas in Uganda the prevalence among such patients was 13.5 percent [9,10]. A discussion on the use of screening and early therapy to prevent meningoencephalitis is found elsewhere.
CLINICAL MANIFESTATIONS

Symptoms — Symptoms of cryptococcal meningoencephalitis typically begin indolently over a period of one to two weeks. The most common symptoms are fever, malaise, and headache [2]. Stiff neck, photophobia, and vomiting are seen in one-fourth to one-third of patients. Patients rarely present with coma and fulminant death in days.

Other symptoms suggesting disseminated disease include cough, dyspnea, and skin rash [11]. Visual and hearing loss has also been reported [12,13].

Physical examination — The initial physical examination may be notable for lethargy or confusion in association with fever. In one report, 24 percent of patients had altered mentation on presentation, and 6 percent presented with focal neurologic deficits [2]. Other manifestations of disseminated disease may be evident, including tachypnea and skin lesions resembling molluscum contagiosum (picture 1) [11]. Increased diastolic hypertension may be reflective of increased intracranial pressure.

Laboratories — General laboratory studies are nonspecific. Patients with advanced immunosuppression may have leukopenia, anemia, hypoalbuminemia, and an increased gamma globulin antibody fraction.

DIAGNOSIS — We have a high index of suspicion for cryptococcal meningitis in patients with advanced HIV infection (CD4 cell count <100 cells/microl) who have isolated fever and headache. Initial evaluation includes a careful history, neurologic exam, and serum cryptococcal antigen. Evaluation should also include a lumbar puncture to assess for increased intracranial pressure and culture of cerebrospinal fluid (CSF) to confirm the diagnosis in those with symptoms and/or a positive serum cryptococcal antigen (CrAg).

A more detailed discussion on the diagnosis of cryptococcal meningitis in resource limited settings is found below. (See "Resource limited settings" below.)

Importance of neuroimaging — Prior to a lumbar puncture (LP), patients suspected of having increased intracranial pressure and/or CNS mass lesions must have neuroimaging (eg, computed tomography [CT] scan or magnetic resonance imaging [MRI]). A detailed discussion on when to perform neuroimaging prior to LP is found elsewhere. (See "Lumbar puncture: Technique, indications, contraindications, and complications in adults", section on 'Cerebral herniation'.)

Imaging can detect the presence of mass lesions, increased intracranial pressure, and/or hydrocephalus, all of which impact treatment decisions.

- Imaging may suggest possible increased ICP with or without mass/space occupying lesions in patients with cryptococcal meningitis. While LP and removal of CSF may be beneficial for both diagnostic and therapeutic purposes, the risks and benefits of the procedure must be discussed with the patient and/or health care proxy given the very small, but possible chance of cerebral herniation in the setting of raised intracranial pressure. Consultation with neurology and/or neurosurgery can be obtained to help guide this discussion. A more detailed discussion on the risks of lumbar punctures is found elsewhere. (See "Lumbar puncture: Technique, indications, contraindications, and complications in adults", section on 'Cerebral herniation'.)
- If mass lesions are identified we consider alternative diagnosis (eg toxoplasmosis, lymphoma, tuberculosis) since mass lesions due to *C. neoformans* are rarely seen in patients with HIV
infection [14,15]. The diagnostic approach to HIV-infected patients with mass lesions is discussed elsewhere. (See "Approach to HIV-infected patients with central nervous system lesions").

- If imaging is consistent with cryptococcal-associated hydrocephalus, placement of a ventricular shunt may be required. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring of intracranial pressure').

**Lumbar puncture** — A lumbar puncture is required to obtain CSF for confirmatory testing to make the diagnosis of cryptococcal meningitis. The cerebrospinal fluid (CSF) profile classically demonstrates a low white blood cell count in the CSF (eg, <50 cells/microL) with a mononuclear predominance [16]. The CSF protein may be slightly elevated, while the glucose concentrations are commonly low [13]. Approximately 25 to 30 percent of patients with culture-proven cryptococcal meningoencephalitis have a normal CSF profile [17,18].

A lumbar puncture is also important for determining the patient's intracranial pressure (ICP), which can be associated with significant morbidity and mortality [2,13]. The management of increased ICP is discussed elsewhere. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring of intracranial pressure'.)

**Cryptococcal culture** — CSF should be sent for cryptococcal culture; cream-colored mucoid colonies are seen on agar plates generally within three to seven days.

**India ink staining** — Since the burden of organisms is usually high in AIDS patients, an India ink preparation of the CSF will usually demonstrate typical round encapsulated yeast organisms consistent with cryptococcus in 60 to 80 percent of patients [19]. The advantage of the India ink preparation is that a diagnosis of cryptococcal infection can be made rapidly while confirmatory testing is being performed (eg, CSF culture or antigen). India ink stains should be reviewed by a microbiologist who is familiar with the physical characteristics of the organism.

Regardless of India ink results, a CrAg test should also be performed to confirm the diagnosis. The antigen titer measurement can also provide an estimate of fungal burden and prognosis. (See 'Prognostic factors' below.)

**Cryptococcal antigen (CrAg)** — CrAg can be detected in serum and CSF through immunodiagnostic techniques, such as latex agglutination or sandwich enzyme-linked immunosorbent assay (ELISA). The lateral flow assay (LFA) is an alternative approach to detecting cryptococcal antigen. It is a simple dipstick test that is inexpensive to perform and can be used on urine, blood, serum, CSF, or plasma samples. The LFA compares favorably with the latex agglutination and ELISA, and is used in both resource-limited and resource-available areas [20,21]. In resource-limited settings, the LFA has the potential to improve access to diagnostic testing since centralized laboratory facilities are often unavailable.

**Spinal fluid** — A positive CrAg in the CSF strongly supports the diagnosis of cryptococcal meningitis and is sufficient evidence to initiate treatment in patients with symptoms and/or risk factors that are consistent with infection. Results of the antigen test can be obtained immediately after the lumbar puncture is performed. A positive antigen test can suggest the presence of infection well before the cultures become positive.

The CrAg is very sensitive and specific in the CSF and is commonly detected by latex agglutination. In a study of four latex agglutination assays and one enzyme linked immunoassay, all performed well with sensitivities ranging from 93 to 100 percent and specificities from 93 to 98 percent [22]. With latex
agglutination, diagnostic false positive tests can result from infection due to the fungus *Trichosporon asahii* (formerly *T. beigelii*) or bacteria of the *Stomatococcus* and *Capnocytophaga* genera [23-25]. These positive results are usually present with low titers. False positive CSF cryptococcal antigen results have been reported rarely following exposure of samples to disinfectants or soap, or after samples were placed into an anaerobic transport vial [26-28]. (See "Infections due to Trichosporon species and Blastoschizomyces capitatus".)

The lateral flow assay (LFA) is an alternative approach to detecting cryptococcal antigen, and is easier to use and less expensive compared with latex agglutination. In addition, it appears to perform equally as well as other tests. As an example, in a study of 832 HIV-infected individuals from sub-Saharan Africa, LFA was shown to have >99 percent sensitivity and specificity among persons with suspected meningitis [21]. In this study, LFA had the best test performance when compared with latex agglutination, culture, and India ink microscopy.

**Serum** — In AIDS patients with suspected cryptococcal meningoencephalitis, the sensitivity of serum antigen testing is comparable to CSF testing and is a useful diagnostic modality in patients who cannot undergo lumbar puncture [29].

Screening with serum cryptococcal antigen may also be of high clinical utility in areas where cryptococcal infection is endemic. In Cambodia, for example, cryptococcal antigen screening among 327 HIV-infected patients with advanced immunosuppression demonstrated a prevalence of 18 percent [30]. Of the 59 patients diagnosed with cryptococcal infection, more than one-fourth did not have symptoms suggestive of cryptococcal meningitis. These data suggest that screening may be beneficial in identifying earlier disease in patients with advanced immunosuppression who live in endemic areas.

CrAg titers generally correlate with organism burden and prognosis. However, following titers are not helpful in management of acute disease in HIV-infected patients since changes in titer do not precisely correlate with clinical response [31]. Also, the slope of decline is not helpful in predicting those patients who may relapse [32]. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Laboratory monitoring for fungal infection'.)

**Extraneural cultures** — The diagnosis of cryptococcal disease is occasionally made only after *C. neoformans* is recovered from another body site, such as blood, urine, or sputum. Routine blood cultures may be positive for cryptococci in approximately two-thirds of AIDS-associated cases of meningoencephalitis [2]. If cryptococcemia is suspected, fungal isolator tubes can be ordered for improved sensitivity.

The prostate gland is recognized as an extraneural site from which cryptococci can reside, leading to relapse with systemic dissemination after discontinuation of treatment. Detection of cryptococcus on urine culture can be improved with prostatic massage. Prior to the era of potent antiretroviral therapy (ART), persistent prostatic sequestration of cryptococcus was described in patients who were treated for six weeks with amphotericin with or without flucytosine, with subsequent relapse after treatment discontinuation [33].

**Resource limited settings** — In resource-limited settings, especially in areas where the prevalence of cryptococcal disease is high, the diagnostic approach may be modified. Prompt lumbar puncture with measurement of CSF opening pressure and rapid CSF CrAg assays remains the preferred diagnostic approach. However, obtaining a diagnosis can be challenging in some settings because of limited access to lumbar puncture (LP) and/or neuroimaging. In this setting, the risks and benefits may favor a
lower threshold for performing LP without prior neuroimaging than in resource-available settings where the prevalence of cryptococcal meningitis is also lower.

Patients who have symptoms consistent with cryptococcal meningoencephalitis should be managed in a medical facility that has access to lumbar punctures. If an individual does not have immediate access to LP, or if an LP is clinically contraindicated, the patient should be transferred to a facility where they can undergo further diagnostic evaluation. For these patients, we support the recommendations of the World Health Organization (WHO) that recommend serum or plasma CrAg testing be performed if the results can be delivered in <24 hours [8]. The results of serum/plasma CrAg testing can be used to determine if antifungal treatment should be administered pending further work-up.

- If testing for CrAg is positive, treatment with antifungal therapy should be initiated. (See "Treatment of Cryptococcus neoformans meningoencephalitis in HIV-infected patients", section on 'Approach to antifungal treatment'.)
- If rapid serum or plasma CrAg is negative or not available, empiric therapy should generally not be administered. Instead, the patient should undergo further diagnostic evaluation, in an appropriate setting, as soon as possible.

A strategy involving serum cryptococcal antigen screening and antifungal therapy may reduce the risk of developing cryptococcal meningitis in asymptomatic patients who are at high risk for developing disease. A detailed discussion on the prevention of cryptococcal disease is found elsewhere. (See "Treatment of Cryptococcus neoformans meningoencephalitis in HIV-infected patients", section on 'Screening and treatment of early infection'.)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis in the advanced AIDS patient with fever and headache includes toxoplasmosis, tuberculosis meningitis, lymphoma, syphilis, and progressive multifocal leukoencephalopathy. Patients with toxoplasmosis may also have focal findings, such as specific hand weakness, while patients with cryptococcal meningoencephalitis usually have cranial neuropathies. Patients with tuberculosis meningitis may also have other clues to the diagnosis, such as cough, hemoptysis, and an abnormal chest x-ray. Patients with secondary syphilis with aseptic meningitis usually have normal mentation and a disseminated maculopapular rash. Those with central nervous system (CNS) lymphoma may have focal neurologic deficits with abnormal neuroimaging reflecting an intracranial tumor. (See "Toxoplasmosis in HIV-infected patients" and "Progressive multifocal leukoencephalopathy: Epidemiology, clinical manifestations, and diagnosis" and "Syphilis: Epidemiology, pathophysiology, and clinical manifestations in HIV-uninfected patients", section on 'Clinical manifestations'.)

PROGNOSTIC FACTORS — The prognosis for patients with AIDS-associated central nervous system (CNS) cryptococcosis has improved dramatically with antifungal treatment coupled with potent antiretroviral therapy (ART), which leads to effective viral suppression and immunologic recovery [34,35]. Treatment of cryptococcal meningitis and the timing of ART are discussed elsewhere. (See "Treatment of Cryptococcus neoformans meningoencephalitis in HIV-infected patients" and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis".)

Acute mortality from cryptococcal meningoencephalitis with underlying HIV infection ranges from 6 to 16 percent in resource-available environments [16,34,36-38]. The significant clinical and laboratory predictors of death during the initial few weeks of treatment include [36]:

- Abnormal mental status
- Cerebrospinal fluid (CSF) antigen titer >1:1024
Abnormal mental status on baseline examination or a deterioration of mental status can reflect increased intracranial pressure (ICP). Raised ICP should be considered an urgent medical issue requiring prompt intervention. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring of intracranial pressure'.)

SUMMARY AND RECOMMENDATIONS

- Cryptococcosis is an invasive fungal infection, most commonly caused by Cryptococcus neoformans. Infection begins in the lungs; meningoencephalitis is the most frequently encountered manifestation of cryptococcosis in HIV-infected patients. (See 'Introduction' above.)
- The incidence of cryptococcal meningoencephalitis has declined in patients who have access to antiretroviral therapy (ART). However, cryptococcal disease remains a leading cause of mortality in the developing world. (See 'Epidemiology' above.)
- Symptoms typically begin indolently over a period of one to two weeks. The most common symptoms are fever, malaise, and headache. Other symptoms, suggesting disseminated disease, may be present including cough, dyspnea, and skin rash. (See 'Clinical manifestations' above.)
- The definitive diagnosis of cryptococcal meningoencephalitis is made by culture of the organism from the cerebrospinal fluid (CSF). A positive cryptococcal polysaccharide antigen in the CSF or serum strongly suggests the presence of infection well before the cultures become positive. (See 'Diagnosis' above.)
- Radiographic imaging of the brain must be performed prior to lumbar puncture if there is a concern for increased intracranial pressure (ICP) and/or other space-occupying lesions. (See 'Importance of neuroimaging' above.)
- The significant clinical and laboratory predictors of death during initial therapy include an abnormal mental status, a CSF antigen titer of 1:1024, and a pleocytosis of <20 cells/microL. (See 'Prognostic factors' above.)

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REFERENCES


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GRAPHICS

Disseminated cryptococcosis

Multiple umbilicated papules are present on the face of this patient with cryptococcosis. The lesions resemble molluscum contagiosum.
INTRODUCTION — *Cryptococcus neoformans* meningoencephalitis is one of the leading opportunistic infections seen in patients with untreated AIDS [1]. Management of these severely immunocompromised patients includes antifungal therapy combined with antiretroviral therapy (ART), with careful monitoring for complications related to the invasive fungal infection and the inflammatory syndromes secondary to immune recovery [2].

This topic is devoted to the treatment of the HIV-infected host with *C. neoformans* meningitis. The epidemiology, clinical manifestations, diagnosis, treatment and management of complications of disease are discussed elsewhere. *C. neoformans* infection outside the central nervous system, *C. neoformans* infection in HIV seronegative patients, and *Cryptococcus gattii* infection are also discussed separately. (See "Epidemiology, clinical manifestations, and diagnosis of Cryptococcus neoformans meningoencephalitis in HIV-infected patients" and "Microbiology and epidemiology of Cryptococcus neoformans infection" and "Immune reconstitution inflammatory syndrome" and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis" and "Cryptococcus neoformans infection outside the central nervous system" and "Clinical manifestations and diagnosis of Cryptococcus neoformans meningoencephalitis in HIV-seronegative patients" and "Treatment of Cryptococcus neoformans meningoencephalitis and disseminated infection in HIV seronegative patients" and "Cryptococcus gattii infection: Microbiology, epidemiology, and pathogenesis" and "Cryptococcus gattii infection: Clinical features and diagnosis" and "Cryptococcus gattii infection: Treatment".)

ANTIFUNGAL AGENTS — The primary antifungal agents used for the treatment of cryptococcal meningoencephalitis include intravenous amphotericin B deoxycholate or its lipid formulations, oral *flucytosine*, and oral *fluconazole*. For most patients, liposomal preparations of amphotericin B are preferred to minimize the risk of toxicity and improve the ability to give an uninterrupted induction period of treatment. Echinocandin antifungals do not have significant activity against *C. neoformans* and should not be used to treat this infection [3]. (See "Pharmacology of azoles" and "Pharmacology of amphotericin B".)

Combination therapy with amphotericin B and *flucytosine* is fungicidal (inhibition leads to cell death), while *fluconazole* alone is only fungistatic (ie, inhibits without killing). Importantly, the use of a fungicidal regimen during the initial phase of therapy has been associated with better clinical outcomes [4]. (See 'Induction and consolidation therapy' below.)

GENERAL PRINCIPLES — The HIV-infected patient with advanced immunosuppression (CD4 cell count <50 cells/μL) is at risk for severe cryptococcal meningoencephalitis, which is uniformly fatal within approximately two weeks if untreated [5]. Common presenting symptoms include fever, headache, photophobia, nausea, and vomiting; patients with fulminant disease may present with coma. Predictors of poor outcome include high cerebrospinal fluid (CSF) cryptococcal antigen levels (titer >1:1024), low body weight, poor CSF inflammatory response (<20 cells/μL of CSF), and altered mental status on presentation [6]. (See "Epidemiology, clinical manifestations, and diagnosis of
Clinical trial data demonstrate that the optimal approach to treatment involves three phases: induction therapy for approximately two weeks followed by consolidative therapy for approximately eight weeks [2,7]. Many HIV-infected patients with cryptococcal meningoencephalitis have a high burden of infection in the central nervous system (CNS) with yeast concentrations in the range of a million yeasts/mL of CSF. This high burden of infection requires a combination treatment regimen with fungicidal activity such as amphotericin B with flucytosine to rapidly sterilize the cerebrospinal fluid during induction therapy [4,8]. Long-term maintenance (ie, suppressive) therapy is required to decrease the risk of relapse. (See "Pharmacology of amphotericin B" and "Pharmacology of flucytosine (5-FC)" and "Pharmacology of azoles").

An important component of treatment of cryptococcal meningoencephalitis includes immune reconstitution with potent antiretroviral medications. However, the initiation of antiretroviral therapy (ART) can also lead to complications such as immune reconstitution inflammatory syndrome (IRIS). (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Immune reconstitution inflammatory syndrome'.)

Effective patient management also requires careful evaluation for complications directly related to cryptococcal brain infections, such as increased intracranial pressure, which can lead to blindness, herniation, persistent headaches, and/or neuropathies, if untreated. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring of intracranial pressure'.)

**CLINICAL TRIAL DATA** — The following section illustrates a few of the major trials that have guided the approach to therapeutic management of the HIV-infected patient with cryptococcal meningoencephalitis and form the foundation for the 2010 Infectious Diseases Society of America (IDSA) guidelines [2], as well as recent updates [7].

**Induction and consolidation therapy** — Rapid sterilization of the cerebrospinal fluid (CSF) is linked to better survival rates and decreased rates of relapse among symptomatic patients with cryptococcal meningoencephalitis [4,8-10]. Rapid sterilization also allows conversion from potentially toxic intravenous amphotericin B to better tolerated oral agents. It is critically important to complete this two-week induction fungicidal regimen to optimize clinical outcomes. Thus, lipid formulations of amphotericin B are typically used for initial induction therapy to minimize the risk of toxicity. In addition, adverse events related to amphotericin B or flucytosine should be actively managed, rather than switching to a less potent combination of drugs. (See 'Adverse events' below and 'Approach to antifungal treatment' below and 'Patients who are intolerant of amphotericin B and/or flucytosine' below.)

The period of induction therapy should be extended longer than two weeks if the CSF cultures remain positive after two weeks of treatment and/or the patient has not demonstrated significant clinical improvement. Treatment can also be extended if the CSF cultures are anticipated to remain positive at the end of two weeks of treatment (eg, a severely immunosuppressed patient with a CSF culture that is positive after a week of treatment) [2]. Although persistence of positive cultures may suggest the development of direct drug resistance, this is an extremely uncommon occurrence. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Drug resistance testing'.)

The importance of fungicidal therapy (eg, amphotericin B) versus fungistatic therapy (eg, fluconazole) for induction therapy was illustrated by a trial of 194 patients who were randomly assigned in a 2:1
Two important findings emerged from this trial:

- Mortality was higher within the first two weeks among patients assigned to the fluconazole arm compared with the amphotericin B arm (15 versus 8 percent).
- Compared with fluconazole, treatment with amphotericin B resulted in more rapid CSF sterilization (42 days versus 64 days).

A multicenter, double-blind trial evaluated the effectiveness of two weeks of amphotericin B (dosed higher at 0.7 mg/kg per day), with or without the flucytosine (100 mg/kg per day), as induction therapy in 381 HIV-infected patients with cryptococcal meningocencephalitis [9]. In addition, the investigators compared eight weeks of fluconazole (400 mg daily) or itraconazole (400 mg daily) as consolidation therapy. This trial demonstrated that:

- CSF sterilization at two weeks occurred more frequently among patients receiving combination therapy compared with amphotericin B alone (60 versus 51 percent) without increased toxicity.
- Among the patients who underwent a repeat lumbar puncture at the end of the consolidation phase, the CSF culture was negative in 97 percent of patients on the fluconazole arm (139 of 151) compared with 92 percent in the itraconazole group (93 of 101 patients). However, the data are somewhat limited since a significant percentage of patients assigned to the itraconazole and fluconazole arms did not undergo repeat lumbar puncture (35 and 26 percent, respectively). Clinical outcomes were similar between the two arms.
- Overall mortality was 5.5 percent within the first two weeks and 3.9 percent in the next eight weeks, with no significant difference between groups.
- A multivariate analysis demonstrated that the likelihood of CSF sterilization at the end of 10 weeks was highest among those patients who were assigned combination therapy followed by fluconazole.

In contrast to the trial described above [9], a subsequent randomized open-label trial that compared the efficacy of three different induction therapy regimens showed a mortality benefit with amphotericin B plus flucytosine [8]. In this trial, 299 HIV-positive patients with cryptococcal meningitis in Vietnam were randomly assigned to monotherapy with amphotericin B deoxycholate 1 mg/kg daily for four weeks, combination therapy with amphotericin B deoxycholate 1 mg/kg daily plus flucytosine 100 mg/kg per day in three or four divided doses for two weeks, or amphotericin B deoxycholate 1 mg/kg daily plus fluconazole 400 mg twice daily for two weeks. The following findings were observed:

- Fewer deaths occurred by days 14 and 70 in patients who received amphotericin B plus flucytosine compared with patients who received amphotericin B monotherapy (15 versus 25 deaths by day 14, hazard ratio [HR] 0.57, 95% CI 0.30-1.08; 30 versus 44 deaths by day 70, HR 0.61, 95% CI 0.39-0.97). The mortality reduction was statistically significant at 70 days, but not at 14 days.
- Similar survival rates were observed in patients who received combination therapy with amphotericin B plus fluconazole and amphotericin B monotherapy.
- Combination therapy with amphotericin B plus flucytosine was associated with significantly increased rates of yeast clearance from the CSF (-0.42 log_{10} colony-forming units [CFU]/mL per day compared with -0.31 log_{10} CFU/mL per day with amphotericin B monotherapy and -0.32 log_{10} CFU/mL per day with combination therapy with amphotericin B plus fluconazole).
- Rates of adverse events were similar in all groups, although neutropenia was more common in patients receiving combination therapy with either amphotericin B plus flucytosine (34 percent) or...
amphotericin B plus fluconazole (32 percent) compared with amphotericin B monotherapy (19 percent).

The superiority of combination therapy with amphotericin B plus flucytosine observed in this trial with respect to both mortality and rates of yeast clearance from the CSF strongly supports the recommendation to use this regimen for induction therapy of cryptococcal meningitis [12]. (See 'Induction and consolidation' below.)

Other trials have confirmed faster rates of CSF sterilization and lower rates of relapse with amphotericin B plus flucytosine than amphotericin B alone [13-16], and it is the combination of choice for the induction phase of therapy for cryptococcal meningitis. However since flucytosine is not available in some resource-limited settings, an important question is whether combination therapy with amphotericin B plus an azole results in comparable outcomes as amphotericin B plus flucytosine. This was addressed in a trial of 80 HIV-positive antiretroviral therapy (ART)-naïve patients in South Africa who presented with cryptococcal meningitis [17]. Patients were randomly assigned to four treatment arms for a two-week period of induction therapy: amphotericin B deoxycholate (0.7 to 1 mg/kg/day) plus flucytosine (25 mg/kg orally four times daily), amphotericin B deoxycholate (0.7 to 1 mg/kg IV daily) plus fluconazole (800 mg orally daily), amphotericin B deoxycholate (0.7 to 1 mg/kg/day) plus fluconazole (600 mg orally daily), or amphotericin B deoxycholate (0.7 to 1 mg/kg/day) plus voriconazole (300 mg orally twice daily). There were no statistically significant differences in the rate of clearance of cryptococcal CFU in CSF samples among the four treatment groups. Overall mortality was 12 percent at 2 weeks and 29 percent at 10 weeks, with no statistically significant differences among the groups.

In an open-label study, 143 HIV-infected individuals in the United States or Thailand diagnosed with cryptococcal meningitis were randomly assigned to induction therapy with amphotericin B deoxycholate (0.7 mg/kg/day) alone or amphotericin B deoxycholate (0.7 mg/kg/day) plus fluconazole (400 mg/day) or amphotericin B deoxycholate (0.7 mg/kg/day) plus fluconazole (800 mg/day) [18]. Following the induction phase of therapy, patients who initially received amphotericin B monotherapy were switched to fluconazole (400 mg/day) for eight weeks, whereas those who initially received amphotericin B plus fluconazole were switched to consolidation therapy with fluconazole at the same dose to which they were randomly assigned (400 or 800 mg per day) for eight weeks. Although this study was not powered to demonstrate statistically significant differences in efficacy among the treatment arms, the arm that received high-dose fluconazole (800 mg per day) showed a trend towards better outcomes and the regimen was well tolerated.

Trials examined whether there may be a role for triple combination therapy with amphotericin B/flucytosine/fluconazole compared with dual therapy. No additional benefit was observed in one study [14], but triple combination therapy appeared to have a more favorable outcome in another study [19].

The optimal induction dose of amphotericin B is imprecise since 0.5 mg/kg/day was not directly compared with 0.7 mg/kg/day in the above mentioned clinical trial [9]. However, comparison of 0.7 mg/kg/day with 1 mg/kg/day amphotericin B demonstrated no difference in mortality at 10 weeks in a small trial among 64 HIV-infected patients with cryptococcal meningoencephalitis [20].

Fluconazole is generally preferred over itraconazole since the bioavailability of itraconazole varies significantly from person to person and drug monitoring is generally needed to assure appropriate serum levels have been achieved. In addition, itraconazole is associated with significant gastrointestinal symptoms, and its penetration into the CSF compartment is substantially less than fluconazole. (See "Pharmacology of azoles").
Maintenance therapy — Early in the AIDS epidemic, primary therapy for cryptococcal meningoencephalitis was followed by frequent relapse after treatment discontinuation [21]. In 1991, 84 AIDS patients with a history of cryptococcal meningoencephalitis who were randomly assigned to 200 mg of daily fluconazole (after primary induction and consolidative therapy) had a much lower incidence of relapse than those who were assigned to placebo (none versus 15 percent) [21].

Subsequent trials comparing fluconazole with either weekly intravenous amphotericin B or oral itraconazole for cryptococcal meningoencephalitis demonstrated that fluconazole was the most efficacious antifungal agent for maintenance therapy [7,13,22]. For example, in one clinical trial of 108 HIV-infected patients, the relapse rate among those treated with itraconazole was 23 percent compared with 4 percent of those taking fluconazole [13].

APPROACH TO ANTFUNGAL TREATMENT

Induction and consolidation

● The initial preferred approach to the patient with cryptococcal meningoencephalitis includes combination antifungal therapy for the induction phase of therapy followed by consolidation therapy with fluconazole alone [2,7]. Dosing for patients with renal insufficiency is discussed below. (See 'Patients with established renal insufficiency' below.)

● For most patients, we recommend induction therapy with liposomal amphotericin B (3 to 4 mg/kg intravenously [IV] daily) plus flucytosine (100 mg/kg per day orally in four divided doses) for a minimum of two weeks, followed by consolidation therapy with fluconazole at a dose of 400 mg orally once daily for a minimum of eight weeks. However, amphotericin B deoxycholate (0.7 mg/kg IV daily) can be used if liposomal amphotericin is not available (eg, because of cost) and/or the patient is not at risk for developing nephrotoxicity. (See 'Patients without risk of nephrotoxicity' below.)

● If flucytosine is not available, we recommend liposomal amphotericin B (3 to 4 mg/kg IV daily) or amphotericin B deoxycholate (0.7 mg/kg IV daily) plus fluconazole (800 mg daily orally) for a minimum of two weeks, followed by consolidation therapy with fluconazole at a dose of 800 mg orally daily for a minimum of eight weeks.

Induction therapy should be continued if clinical improvement is not yet observed or if cerebrospinal fluid (CSF) sterilization has not yet been achieved at two weeks [2]. The regimen and the length of re-induction will be guided by the clinical and microbiological response. Use of intrathecal or intraventricular amphotericin B is not advised since systemic administration demonstrates good efficacy and these other direct routes can be associated with arachnoiditis [23]. Such patients should be managed in consultation with an Infectious Disease physician who has experience in treating cryptococcal disease.

A discussion on how to manage patients who cannot tolerate amphotericin B and/or flucytosine is found below. (See 'Patients who are intolerant of amphotericin B and/or flucytosine' below.)

There is no role for empiric glucocorticoids during induction therapy. This is in contrast to other conditions (eg, tuberculous meningitis) where they are routinely administered as part of initial therapy. The use of glucocorticoids for patients with cryptococcal meningitis was evaluated in a randomized trial that included 451 patients from Asia and Africa [24]. Patients received amphotericin plus fluconazole with or without dexamethasone (starting at 0.3 mg/kg per day and then tapered over six weeks). The trial was stopped early after an interim analysis found no difference in mortality or the rate of immune reconstitution inflammatory syndromes (IRIS) between the two groups at 10 weeks; in addition, patients who received adjunctive glucocorticosteroids were less likely to have a good
neurologic outcome (13 versus 25 percent; odds ratio 0.42, 95 CI 0.25 to 0.69). Patients who received dexamethasone also had significantly slower rates of fungal clearance after approximately two weeks, and were significantly more likely to develop an adverse event (eg, infection, renal or cardiac event) by six months (667 versus 494 events). The use of glucocorticoids for the management of patients who develop IRIS is discussed elsewhere. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis").

Maintenance — At the completion of eight weeks, maintenance therapy with lower-dose fluconazole (200 mg daily) should be continued for long-term suppression (minimum of one year). Maintenance therapy can be discontinued if the patient has achieved sufficient immunologic recovery (ie, CD4 count >100 cells/microL) with effective antiretroviral therapy (ART). (See 'Discontinuation of maintenance therapy' below.)

SPECIAL TREATMENT CONSIDERATIONS

Patients without risk of nephrotoxicity — Amphotericin B deoxycholate and liposomal amphotericin B are both effective for the treatment of cryptococcal meningitis [25]. We suggest induction therapy with liposomal amphotericin B rather than the deoxycholate formulation for patients with baseline normal renal function and without risk factors for renal failure (eg, diabetes, uncontrolled hypertension, HIV nephropathy, and/or being administered other nephrotoxic drugs). The use of liposomal amphotericin is associated with less toxicity (eg, nephrotoxicity, infusion reactions, anemia) [25,26]. Thus, it is more likely that induction therapy will be uninterrupted with the use of the lipid formulation, which is an important factor for the successful management of cryptococcal meningoencephalitis [27]. Amphotericin B deoxycholate (0.7mg/kg IV daily) can be used for patients with normal renal function who are without risk of nephrotoxicity if liposomal amphotericin is not available.

However, guidelines differ with regard to the preferred type of amphotericin B preparation that they recommend for patients at low risk of nephrotoxicity:

- The guidelines from the Infectious Disease Society of America recommend the use of amphotericin B deoxycholate as the preferred preparation for most individuals with cryptococcal meningoencephalitis [2]. The rationale for this choice is that there is extensive clinical experience with this preparation, and that dosages of 0.7mg/kg per day administered with adjunctive saline infusions are generally well tolerated for a period of two weeks.

- The guidelines from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America recommend the liposomal amphotericin B preparation for all individuals [7]. This view is based on the growing body of evidence that lipid formulations are effective in patients with disseminated disease and are associated with a decreased risk of nephrotoxicity. However, there are no comparative studies with the combination of lipid formulations of amphotericin B and fluconazole together for cryptococcal meningoencephalitis.

- Guidelines from the World Health Organization consider liposomal amphotericin B (3 mg/kg/day) as an alternative strategy to amphotericin B deoxycholate since both formulations are effective and the liposomal formulations are much more costly [28].

Patients at risk of renal insufficiency — During the induction phase, we recommend lipid formulations of amphotericin B for patients at risk for renal failure (eg, those with diabetes or uncontrolled hypertension, patients taking other nephrotoxic drugs, or patients with suspected HIV nephropathy) [2,7]. All formulations of amphotericin B can cause renal functional impairment, including decreases in the glomerular filtration rate. However, compared with standard amphotericin B deoxycholate, lipid formulations of amphotericin B are associated with comparable efficacy and a lower
incidence of acute kidney injury and renal tubular dysfunction, although at increased drug acquisition cost [25,29,30]. (See “Amphotericin B nephrotoxicity”.)

We agree with the guidelines that recommend 3 to 4 mg/kg IV daily of liposomal amphotericin B for HIV-infected patients with cryptococcal meningoencephalitis [2,7], based upon clinical trials demonstrating clinical equivalence between this regimen and 0.7 mg/kg/day of standard amphotericin B deoxycholate [25,30]. Amphotericin B lipid complex (5 mg/kg IV daily) or Ambisome (6 mg/kg IV daily) are acceptable alternatives [2].

The efficacy of conventional amphotericin B (0.7 mg/kg/day) was compared with two dosing regimens of liposomal amphotericin B (3 mg/kg/day in the second arm; 6 mg/kg/day in a third arm) among 267 HIV-infected patients with cryptococcal meningoencephalitis [25]. The mean serum creatinine amongst the trial participants was approximately 1.1 mg/dL; those with a serum creatinine greater than twice the normal range were excluded. Efficacy was similar in all arms, although there was less nephrotoxicity among patients in the 3 mg/kg/day liposomal amphotericin B arm. Infusion reactions were less frequent in both liposomal treatment groups compared with the standard amphotericin B group.

**Patients with established renal insufficiency** — We strongly recommend lipid formulations of amphotericin B for patients with renal dysfunction to reduce the risk of nephrotoxicity. (See 'Patients at risk of renal insufficiency' above.)

Although difficult to use in patients with renal impairment, the dose of amphotericin B for treatment does not need to be adjusted for renal dysfunction. However, the dose of flucytosine should be adjusted in patients with reduced kidney function. Dose modifications are discussed in the Lexicomp drug information topic within UpToDate and within the individual topic review. (See "Pharmacology of flucytosine (5-FC)", section on 'Dose modification'.)

A discussion on the management of patients who develop renal insufficiency while receiving amphotericin B is found elsewhere. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Amphotericin B'.)

**ADVERSE EVENTS** — Amphotericin B deoxycholate is frequently associated with electrolyte disturbances, anemia, renal insufficiency, and infusion site reactions, such as drug fever and rigors. These adverse events are reduced when liposomal preparations are used [25]. The symptoms of an infusion reaction can be minimized or prevented by premedication with acetaminophen (usual adult dose, 650 to 1000 mg orally) and/or diphenhydramine (usual adult dose, 25 to 50 mg orally or intravenously). The risk of renal dysfunction associated with amphotericin B may be reduced with infusion of normal saline before and during therapy. (See "Pharmacology of amphotericin B", section on 'Infusion-related reactions' and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring for drug toxicity' and "Amphotericin B nephrotoxicity".)

Flucytosine is mainly associated with gastrointestinal intolerance. Laboratory abnormalities include elevations in aminotransferases, anemia, leukopenia, and thrombocytopenia. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring for drug toxicity'.)

Fluconazole is generally well tolerated [18]; patients occasionally may develop rash or abnormal aminotransferases. Itraconazole is associated with significant gastrointestinal intolerance and pedal edema and requires drug monitoring due to significant differences in bioavailability from person to person. (See "Pharmacology of flucytosine (5-FC)" and "Pharmacology of azoles".)
PATIENTS WHO ARE INTOLERANT OF AMPHOTERICIN B AND/OR FLUCYTOSINE — Some patients have difficulty tolerating amphotericin B and/or flucytosine. Alternative regimens are available; however, they appear suboptimal for cerebrospinal fluid (CSF) sterilization [2,18,31,32] (see 'Induction and consolidation' above and 'Adverse events' above). As examples:

- In an open-label study of high-dose fluconazole (400 to 800 mg daily) combined with flucytosine for induction/consolidative therapy, 25 percent of patients still had positive cultures after 10 weeks of treatment and 13 percent died [31,32]. In another small clinical trial, there were a lower number of deaths in the combination therapy arm compared with fluconazole alone (200 mg daily), but overall mortality rates were high (16 versus 40 percent) [32].
- When measuring rates of CSF sterilization, the combination of amphotericin B plus fluconazole (400 mg daily) was found to be inferior to amphotericin B plus flucytosine for induction/consolidation, but more effective than amphotericin B monotherapy [14].

Thus, before changing a patient’s regimen, it is important to see if any of the individual’s adverse reactions can be managed without a change in therapy.

- The use of lipid amphotericin may reduce the risk of adverse events related to amphotericin B deoxycholate. Discussions on the management of infusion reactions and nephrotoxicity are found elsewhere. (See 'Adverse events' above and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring for drug toxicity' and "Pharmacology of amphotericin B", section on 'Infusion-related reactions' and "Amphotericin B nephrotoxicity", section on ‘Salt loading’.)
- For those with an adverse reaction to flucytosine, serum levels may be helpful to assess if a dose adjustment is required. Additional discussions of the management of adverse reactions related to flucytosine are found elsewhere. (See 'Adverse events' above and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring for drug toxicity' and "Pharmacology of flucytosine (5-FQ)", section on 'Management of toxicities'.)

If the patient is still unable to tolerate amphotericin B plus flucytosine, the regimen can be modified.

- For those who are unable to tolerate flucytosine, amphotericin B plus fluconazole (800 mg per day) is the preferred polyene-azole combination [18]. The adverse events associated with amphotericin B plus fluconazole are mainly related to those expected with amphotericin B administration.
- For those unable to tolerate amphotericin B, we administer fluconazole 800 mg daily with flucytosine (100 mg/kg daily in four divided doses orally). On rare occasion when neither amphotericin nor flucytosine can be tolerated, fluconazole alone (1200 mg daily) can be used [7].

Since these modified regimens appear to be less effective, it is important that patients are monitored closely for evidence of treatment failure. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Sterilization of cerebrospinal fluid' and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Clinical monitoring during treatment'.)
WHEN TO INITIATE ANTIRETROVIRAL THERAPY — Immune recovery is an important part of the successful treatment of cryptococcal meningitis. However, initiation of ART can be associated with an immune reconstitution inflammatory syndrome (IRIS). The timing of when to initiate ART to minimize the risks of IRIS is discussed elsewhere. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Timing of antiretroviral therapy'.)

DRUG INTERACTIONS — Before starting antiretroviral therapy, drug-drug interactions must be checked and considered, particularly with the azoles. (See "Pharmacology of azoles".

THERAPEUTIC COMPLICATIONS — Multiple complications can occur during antifungal therapy related to adverse drug-related events. In addition, patients with severe cryptococcal meningoencephalitis may develop increased intracranial pressure, which can lead to significant morbidity and mortality. Furthermore, some patients who initiate antiretroviral therapy (ART) can develop an inflammatory cerebrospinal fluid (CSF) profile with symptomatic increased intracranial pressure that is related to immune recovery. A full discussion of the symptoms, signs, and management of these IRIS complications are found elsewhere. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis".)

DISCONTINUATION OF MAINTENANCE THERAPY — We agree with guidelines that recommend discontinuing maintenance therapy for individuals on antiretroviral therapy (ART) who have a CD4 cell count greater than 100 cells/microL, who have an undetectable viral load on ART for greater than three months, and have received a minimum of one year of azole maintenance therapy [2,7].

Small trials and observational studies suggest that maintenance therapy for C. neoformans can be safely discontinued in the majority of patients who have a CD4 cell count >100 cells/microL on effective ART [33,34]. CD4 cell counts are usually monitored every three to four months. (See "Patient monitoring during HIV antiretroviral therapy", section on 'Frequency of immunologic and virologic monitoring'.)

● In a prospective trial, 42 AIDS patients in Thailand were randomly assigned to continue or discontinue maintenance therapy when the CD4 cell count had risen to >100 cells/microL along with HIV viral suppression for three months [33]. There were no relapses in either arm after 48 weeks of observation.

● In an observational study, 4 of 100 patients who discontinued maintenance therapy had a clinical relapse of cryptococcal infection [34].

● In an observational cohort of 358 patients who discontinued prophylaxis for various opportunistic infections, 39 had a history of cryptococcal meningitis [35]. The absolute CD4 cell count was 100 to 199 in 8 patients and >200 cells/microL in 28 patients at the time of discontinuation of maintenance therapy; none of the patients relapsed.

With discontinuation of azole maintenance therapy, the clinician must continue to follow patients closely, and reinitiation of maintenance therapy is indicated if the patient’s CD4 cell count declines to less than 100 cells/microL and/or there is a significant rise in serum cryptococcal antigen titer. (See "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on 'Monitoring of serum cryptococcal antigen'.)

PREVENTING SYMPTOMATIC DISEASE

Primary prevention — The best way to prevent cryptococcal disease in HIV-infected individuals is through early initiation of antiretroviral therapy (ART). Antiretroviral therapy reduces mortality as well
as serious AIDS- and non-AIDS-related complications, and should be initiated regardless of the CD4 count. (See "When to initiate antiretroviral therapy in HIV-infected patients".)

We suggest not using routine antifungal prophylaxis for primary prevention of cryptococcal infection. This is supported by major guideline panels because of the lack of overall survival benefit, drug interactions, adverse effects, potential antifungal drug resistance, and cost [2,7,28]. A Cochrane systematic review identified five randomized controlled trials using antifungal interventions for the primary prevention of cryptococcal disease in a total of 1316 HIV-infected patients [36]. The incidence of cryptococcal disease decreased significantly in patients taking either fluconazole or itraconazole; however, there was no significant effect on mortality. Similar findings regarding lack of survival benefit have been observed in resource-limited settings [37].

**Screening and treatment of early infection** — In addition to starting ART, a strategy involving serum cryptococcal antigen (CrAg) screening and antifungal therapy may reduce the risk of developing cryptococcal meningitis in patients who are at high risk for developing disease [7,28,38-41]. Cryptococcal antigen is detectable in serum at least three weeks prior to the onset of neurologic symptoms.

We suggest serum CrAg screening for asymptomatic patients not receiving ART with a CD4 count <100 cells/microL if they are from resource-limited settings where the prevalence of cryptococcal antigenemia is >3 percent. Although evidence is limited, this approach to screening is in agreement with recommendations from the World Health Organization [28]. For patients in the United States, guidelines state that screening should be considered in patients with a CD4 count <100 cells/microL (especially those with a CD4 count <50 cells/microL) if the prevalence of cryptococcal antigenemia is approximately 3 percent, which has been reported within some United States cohorts [7,42,43]. (See "Epidemiology, clinical manifestations, and diagnosis of Cryptococcus neoformans meningoencephalitis in HIV-infected patients".)

Patients who test negative for serum CrAg should initiate ART. Patients who test positive for serum CrAg should undergo a careful history and exam to elicit signs and symptoms of cryptococcal meningitis, as well as a lumbar puncture (regardless of signs and symptoms) to evaluate for the presence of CSF CrAg or positive CSF cryptococcal cultures. Antiretroviral therapy should be held pending return of the cerebrospinal fluid (CSF) studies, but antifungal therapy with fluconazole 400 mg daily should be started.

- If the LP is negative (ie, negative CSF CrAg and culture), antifungal therapy with fluconazole (400 mg daily) should be continued and ART can be started concurrently. We discontinue pre-emptive fluconazole therapy in those patients receiving ART if they achieve a CD4 cell count >100 cells/microL for at least three months.
- If there is evidence of CNS involvement (ie, positive CSF CrAg or culture) patients should be treated for cryptococcal meningoencephalitis, and ART should be initiated 2 to 10 weeks after induction treatment. (See ‘Approach to antifungal treatment’ above and "Clinical management and monitoring during antifungal therapy of the HIV-infected patient with cryptococcal meningoencephalitis", section on ‘Timing of antiretroviral therapy’.)

In certain resource-limited settings, it may not be possible to perform a lumbar puncture on all asymptomatic patients, and then the decision to initiate fluconazole must be based upon the absence of clinical disease. For such patients, we initiate ART two to four weeks after pre-emptive therapy with fluconazole has been started.
Small studies in resource-limited settings have suggested a clinical benefit of using screening and a pre-emptive therapeutic strategy to prevent development of cryptococcal meningitis [7,28,38-41]; however, there are no high quality data to demonstrate the efficacy of this approach. As examples:

- In a study of 295 antiretroviral (ART)-naïve patients in Uganda starting HIV therapy, 26 patients with a CD4 cell count ≤100 cells/microl had a positive serum CrAg. All of the patients with a positive serum CrAg were started on ART [38]. In addition, 21 were treated with fluconazole (200 to 400 mg/day) for two to four weeks, whereas five were treated with ART alone. Clinical cryptococcal meningitis developed in three of the fluconazole-treated persons, and the 30-month survival was 71 percent (95% CI 48% to 89%). In the five CRAG-positive persons who were not treated with fluconazole, all died within two months of ART initiation.

- In another study that evaluated approximately 2000 patients in Tanzania and Zambia with a CD4 count <200 cells/microl, an intervention that included ART, community support, and CrAg testing with pre-emptive fluconazole was compared with standard of care (ART plus clinic based-visits) [41]. Patients who received the intervention had a significant reduction in mortality at 12 months compared with those who received standard of care (13 versus 18 percent). However, it is unclear if the mortality benefit was from screening and pre-emptive therapy for cryptococcal disease or from enhanced community support.

- In a prospective study of 645 ART-naïve patients with a CD4 count ≤100 cells/microl from South Africa, 28 patients tested positive for serum CrAg using the lateral flow assay (LFA) and 21 received antifungal therapy [40]. Ten patients agreed to LP and four tested positive for CrAg in the CSF and received amphotericin. Of the remaining 17, all received fluconazole and none developed cryptococcal meningitis. These findings were compared with a historical control where 7 of 25 serum CrAg-positive patients (28 percent) who did not receive pre-emptive antifungal therapy went on to develop cryptococcal meningoencephalitis [44].

Studies evaluating cost-effectiveness have suggested that this screen and treat strategy can be cost-effective in resource-limited areas where the prevalence of cryptococcal antigenemia is >3 percent [38,39,45,46]. These findings were based upon reductions in mortality found in some of the studies above [38,39]. However, the low quality of the evidence results in substantial uncertainty as to the true effect of this approach on mortality. As such, the cost-effectiveness results are similarly uncertain.

SUMMARY AND RECOMMENDATIONS

- Cryptococcal meningoencephalitis occurs mainly in HIV-infected patients with advanced immunosuppression related to untreated AIDS. (See ‘Introduction’ above.)

- The main antifungal agents used for the treatment of cryptococcal meningitis include intravenous amphotericin B deoxycholate and its lipid formulations, oral flucytosine, and oral fluconazole. Amphotericin B and flucytosine are fungicidal (inhibition leads to cell death), while fluconazole is only fungistatic (ie, inhibits without killing). Lipid formulations of amphotericin B are preferred for patients with renal dysfunction and at risk for renal failure and in all patients where induction therapy might be at risk for interruption. (See ‘Antifungal agents’ above.)

- Cryptococcal meningoencephalitis is uniformly fatal if untreated. The therapeutic approach includes three phases: induction and consolidation for a total of 10 weeks to decrease early mortality and to rapidly sterilize the cerebrospinal fluid (CSF), followed by maintenance therapy to prevent relapse of infection. (See ‘General principles’ above.)

- For patients with cryptococcal meningoencephalitis, we recommend intravenous (IV) amphotericin B with oral flucytosine during the two-week induction phase of therapy (Grade 1A). The dose of flucytosine is 100 mg/kg per day in four divided doses, adjusted for renal function. If flucytosine is not available, or if it is not tolerated, we recommend fluconazole (800 mg daily.
orally) in addition to amphotericin B during the two-week induction phase of therapy (Grade 1B). It is important that induction therapy not be interrupted. (See 'Induction and consolidation' above.)

- For patients with normal renal function, we suggest liposomal amphotericin B (3 to 4 mg/kg IV daily) rather than amphotericin B deoxycholate (Grade 2B). However, amphotericin B deoxycholate (0.7 mg/kg IV daily) is a suitable alternative for such patients if liposomal amphotericin is not available. (See 'Patients without risk of nephrotoxicity' above.)
- For patients with baseline renal dysfunction and for those at risk for renal failure (e.g., those with diabetes or uncontrolled hypertension or patients taking other nephrotoxic drugs), we recommend liposomal amphotericin B (3 to 4 mg/kg IV daily) rather than amphotericin B deoxycholate (Grade 1B). The incidence and severity of decreased renal function is reduced with liposomal amphotericin B compared with amphotericin deoxycholate, particularly among patients at increased risk of nephrotoxicity. (See 'Patients at risk of renal insufficiency' above and 'Patients with established renal insufficiency' above.)

- If there is clinical improvement during the two-week induction therapy period, amphotericin B and flucytosine can be discontinued and oral azole therapy initiated for the eight-week consolidation phase of treatment. For patients who received amphotericin B plus flucytosine during the induction phase of therapy, we recommend fluconazole (400 mg per day orally) rather than itraconazole during the consolidation phase (Grade 1B). For patients who received amphotericin B plus fluconazole during the induction phase of therapy, we suggest fluconazole at a dose of 800 mg orally daily rather than itraconazole or fluconazole at a lower dose (Grade 2C). (See 'Induction and consolidation' above.)

- After the completion of induction/consolidation phases of therapy, we recommend fluconazole (200 mg daily) for maintenance treatment compared with no therapy (Grade 1A). Long-term chronic suppression should be continued for a minimum of one year. (See 'Maintenance therapy' above.)

- We discontinue maintenance fluconazole therapy in asymptomatic patients who have CD4 cell counts >100 cells/microL, who have an undetectable viral load on antiretroviral therapy (ART) for greater than three months and who have received a minimum of one year of azole maintenance therapy. Close follow-up is advised, and fluconazole should be reinitiated if the CD4 cell count declines to <100 cells/microL. (See 'Discontinuation of maintenance therapy' above.)

- We suggest not routinely administering antifungal prophylaxis for primary prevention of cryptococcal disease (Grade 2B). However, for asymptomatic patients with a CD4 count <100 cells/microL not receiving ART, who are from resource-limited settings where the prevalence of cryptococcal antigenemia is >3 percent, we suggest a strategy involving serum cryptococcal antigen screening prior to initiation of ART (Grade 2C). The management of patients who screen positive for cryptococcal antigen is discussed above. (See 'Preventing symptomatic disease' above.)

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REFERENCES


