Cryptococcosis

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Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the cause. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of patients with HIV in high-income countries had disseminated cryptococcosis.[1] In a surveillance study in the late 1990s, people with HIV who developed cryptococcosis were severely immunosuppressed and had limited access to routine HIV medical care.[2] Current estimates indicate that every year, approximately 280,000 cases of cryptococcal infection in people with AIDS occur worldwide, and the disease accounts for 15% of AIDS-related deaths.[3] Overall, 90% of cryptococcal cases in people with HIV[4] are observed in those who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3. The incidence of the disease has declined substantially among people treated with ART.[4]

Clinical Manifestations

In people with HIV, cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache slowly developing over many weeks, with a median onset of 2 weeks after infection.[1] Classic meningeal symptoms and signs—such as neck stiffness and photophobia—occur in only one-quarter to one-third of patients. Some patients experience encephalopathic symptoms—such as lethargy, altered mentation, personality changes, and memory loss—that are usually a result of increased intracranial pressure (ICP). Among people presenting with cryptococcal meningitis shortly after initiating ART, the symptom onset can be more acute, likely related to unmasking immune reconstitution inflammatory syndrome (IRIS).[5]

Cryptococcosis usually is disseminated when diagnosed in a patient with HIV. In spite of widespread disseminated disease, patients with HIV may manifest few symptoms suggesting a disseminated infection. Any organ can be involved, and skin lesions may show different manifestations, including umbilicated skin lesions that mimic those seen with molluscum contagiosum. Isolated pulmonary infection is also possible; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although nodular infiltrates have been reported. Pulmonary cryptococcosis may present as acute respiratory distress syndrome and even mimic *Pneumocystis* pneumonia.

Diagnosis

Analysis of cerebrospinal fluid (CSF) generally demonstrates mildly elevated protein levels, low-to-normal glucose concentrations, and a variable presence of pleocytosis consisting mostly of lymphocytes. Some patients with HIV have very few CSF inflammatory cells. A Gram stain or an India ink preparation, if available, may demonstrate numerous yeast forms. In patients with HIV and cryptococcal meningitis, the opening pressure in the CSF may be elevated, with pressures ≥25 cm H_2O occurring in 60% to 80% of patients.[6,7]

Cryptococcal disease can be diagnosed by culture, CSF microscopy, cryptococcal antigen (CrAg) detection, or CSF polymerase chain reaction (PCR). In patients with HIV-related cryptococcal meningitis, approximately 50% of blood cultures will be positive, and approximately 80% of CSF cultures will be positive. Visible *Cryptococcus* colonies on a Sabouraud dextrose agar plate generally can be detected within 7 days. *Cryptococcus* may be identified occasionally on a routine Gram stain preparation of CSF as poorly staining Gram-positive yeasts. India ink staining of CSF demonstrates encapsulated yeasts in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. India ink is relatively insensitive early in disease when <1,000 *Cryptococcus* colony-forming units (CFU)/mL are present.[8]

CSF CrAg is usually positive in patients with cryptococcal meningoencephalitis; however, early meningitis can present with negative CSF studies and positive CrAg in blood only.[9] Thus, serum CrAg testing always should be performed in an immunocompromised individual with an unknown central nervous system (CNS) disorder.[9] Serum CrAg is positive in both meningeal and non-meningeal cryptococcal infections and may be present weeks to months before symptom onset.[10]

Three methods exist for antigen detection: latex agglutination, enzyme immunoassay (EIA), and lateral flow assay (LFA). The IMMY CrAg LFA (IMMY, Norman, Oklahoma) is the only LFA test for CrAg approved by the Food and Drug Administration (FDA). It is a useful initial screening tool to diagnose cryptococcosis in patients with HIV when applied to serum or plasma,[8,11] and it also can be used with whole blood or CSF. CrAg testing of serum or plasma may be particularly useful when a lumbar puncture is delayed or refused. In a patient with HIV, when serum CrAg LFA titers are $\geq$1:160, disseminated disease becomes increasingly more likely, and when CrAg LFA titers are $\geq$1:640, disseminated and/or CNS involvement should be assumed, regardless of CSF test results.[12,13] Antigen titers by the LFA are approximately fourfold higher than those with latex agglutination or EIA testing, thus a titer of 1:640 by LFA is approximately equal to a titer of 1:160 by EIA or latex agglutination.

In 2016, the BioFire FilmArray Meningitis/Encephalitis Panel PCR assay (Biofire Diagnostics, Salt Lake City, UT) was approved by the FDA. This multiplex PCR tests for 14 targets, including *C. neoformans* and *C. gattii*, and performs well in infections with a moderate to high fungal burden.[14-16] False negative results have been noted to occur when there is a low burden of organisms; in one study, when there were <100 CFU/mL, the sensitivity of the PCR test fell to 50%.[14] In one well-described case, a woman who had two negative results with this PCR assay later had a positive result on a CrAg test done by IMMY LFA.[17] Thus, a negative CSF PCR does not completely exclude cryptococcal meningitis, and CrAg testing of CSF and blood should always be performed simultaneously. The PCR assay appears to have diagnostic utility when a second episode of cryptococcal meningitis is suspected; the test has been noted to differentiate a relapse (PCR positive) from IRIS (PCR negative).[14]

Preventing Exposure

Cryptococcus is ubiquitous in the environment. People with HIV cannot completely avoid exposure to *C. neoformans* or *C. gattii*. Limited epidemiological evidence suggests that exposure to dried bird droppings, including those from chickens and pet birds, may increase the risk of infection.

Preventing Disease

The incidence of cryptococcal disease is low among people with HIV in the United States. However, one report indicates that among study participants with HIV in the United States with peripheral blood CD4 counts ≤100 cells/mm^3, the prevalence of cryptococcal antigenemia—a harbinger of disease—was 2.9%, and for those with CD4 counts ≤50 cells/ mm^3, the prevalence was 4.3%.[18] Routine surveillance testing for serum CrAg in people with newly diagnosed HIV who have no overt clinical signs of meningitis is recommended for patients whose CD4 counts are ≤100 cells/mm^3 and particularly in those with CD4 counts ≤50 cells/mm^3 **(AII).** A positive test generally should prompt CSF evaluation for CNS infection **(BIII),** particularly when the serum LFA titer is ≥1:160 **(AII).**[13]

Prospective, controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in patients with HIV[19,20] who have CD4 counts <100 cells/mm^3.[19,21] However, in the United States, primary prophylaxis in the absence of a positive serum CrAg test is not recommended because of the relative infrequency of cryptococcal disease, lack of survival benefit associated with prophylaxis, possibility of drug‑drug interactions, potential development of antifungal drug resistance, and costs **(BII).**

Treating Disease

Treatment consists of three phases: induction, consolidation, and maintenance.

Induction Treatment

For induction treatment of cryptococcal meningitis and other forms of extrapulmonary cryptococcosis, an amphotericin B formulation given intravenously, in combination with oral flucytosine, is recommended **(AI).** Historically, amphotericin B deoxycholate at a dose of 0.7 to 1.0 mg/kg daily has been the preferred formulation of the drug. However, evidence that lipid formulations of amphotericin B are effective for cryptococcosis is growing, particularly in patients who experience clinically significant kidney dysfunction during therapy or who are likely to develop acute kidney injury. A study that compared amphotericin B deoxycholate (0.7 mg/kg daily) and liposomal amphotericin B (AmBisome®) at two doses (3 mg/kg daily and 6 mg/kg daily) showed similar efficacy for all three regimens; however, less nephrotoxicity was observed among those receiving the 3 mg/kg daily liposomal amphotericin B regimen.[20] Additional data from animal models and a phase 2 trial in humans, show that single-dose liposomal amphotericin B at a dose of 10 mg/kg has similar rates of CSF yeast clearance and less toxicity than 14 days of amphotericin B deoxycholate.[22]

The preferred regimen for primary induction therapy for patients with normal renal function is 2 weeks of an amphotericin B formulation once daily plus flucytosine 25 mg/kg four times daily **(AI).**[23,24] Based on available clinical trial data and clinical experience, liposomal amphotericin B, at a dose of 3 to 4 mg/kg daily, is the favored formulation **(AI).**

Amphotericin B deoxycholate at a dose of 0.7 to 1.0 mg/kg daily is equally effective and can be used if the costs of lipid formulations are prohibitive and/or interruption of induction therapy because of kidney damage is unlikely **(AI).**

The noncomparative CLEAR study demonstrated a 58% response rate in patients with HIV who were treated with amphotericin B lipid complex at a mean dose of 4.4 mg/kg daily.[25] Thus,

amphotericin B lipid complex at a dose of 5 mg/kg daily can be used as an alternative amphotericin B formulation although fewer data are available to support its use **(BII).**

When using flucytosine, therapeutic drug monitoring should be performed, if available, particularly in patients who have renal impairment. Serum peak concentrations of flucytosine, should be obtained 2 hours postdose after three to five doses have been administered. Peak serum concentrations should be between 25 mg/L and 100 mg/L.[16] Renal function should be monitored closely and the flucytosine dose adjusted accordingly for patients with renal impairment. The dose of flucytosine should be reduced by 50% for every 50% decline in creatinine clearance. The addition of flucytosine to the amphotericin B regimen during acute treatment is associated with more rapid sterilization of CSF and survival benefit.[23,26-28] A randomized clinical trial also showed that the combination of amphotericin B deoxycholate at a dose of 1 mg/kg daily plus flucytosine was associated with improved survival compared to the same dose of amphotericin B without adjunctive flucytosine.[29] Adjunctive fluconazole 800 to 1,200 mg per day plus amphotericin B has been used in the absence of flucytosine, but adjunctive flucytosine has a survival advantage over adjunctive fluconazole and is preferred **(AI).**[24] Amphotericin B deoxycholate alone or with fluconazole at a dose of 800 to 1,200 mg daily **(BI)** or lipid-formulation amphotericin B alone **(BI)** or with fluconazole at a dose of 800 to 1,200 mg daily **(BIII)** may be viable options in some circumstances, but they are less preferable alternatives than lipid-formulation amphotericin B plus flucytosine.[24]

Fluconazole (1,200 mg daily) plus flucytosine is also a potential alternative to amphotericin B regimens **(BII).** Some experts would use 800 mg fluconazole daily with flucytosine **(BIII).**[24,30] Fluconazole alone, based on studies assessing early fungicidal activity, is inferior to amphotericin B for induction therapy[31,32] and is recommended only for patients who cannot tolerate or who do not respond to standard treatment. If fluconazole alone is used for primary induction therapy, the starting daily dose should be 1,200 mg **(CI).**[33]

The duration of induction therapy historically has been 2 weeks. In a multicenter clinical trial that evaluated 10-week outcomes of treatment of cryptococcal meningitis in 721 African adults with HIV, 1 week of amphotericin B deoxycholate therapy was shown to be noninferior to 2 weeks,[24] and at 1 year, follow-up of 236 patients from this treatment trial showed continued noninferiority of the 1-week regimen compared with the 2-week regimen.[34] Thus, in resource-limited settings, 1 week of amphotericin B deoxycholate with flucytosine followed by high-dose fluconazole is now preferred (**BIII).**[35] However, in high-resource settings where the less toxic liposomal or other lipid amphotericin B formulations is used and a greater capacity to provide supportive care to mitigate amphotericin B toxicities exists, 2 weeks of induction amphotericin B combination therapy is recommended **(AI).**

Consolidation Treatment

A lumbar puncture and repeat CSF culture should be performed after 2 weeks of induction therapy. At that point, clinically stable patients may be switched to consolidation therapy while awaiting CSF culture results. Successful induction therapy is defined as substantial clinical improvement and a negative CSF culture from the end-of-induction lumbar puncture. India ink and CSF CrAg frequently remain positive at Week 2 of therapy and are not indicative of failure. Monitoring serum or CSF CrAg titers is of no value in determining initial response to therapy and **is not recommended (AII).**[36,37] If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of lumbar opening pressure and CSF culture, should be performed.

Consolidation therapy should be initiated with fluconazole 800 mg daily **(AI).** The recommendation to use 800 mg rather than 400 mg fluconazole for consolidation therapy is based on several findings. Early clinical trials that used 400 mg fluconazole for consolidation noted breakthrough infection during consolidation.[23] Fluconazole 400 mg per day provides concentrations in the CSF that are only fungistatic, and other studies showed that the early antifungal activity of fluconazole in CSF of patients with cryptococcal meningitis increases linearly with increasing doses of the drug.[29,31] A phase 2 trial of treatment with either 400 mg or 800 mg fluconazole found that relapses were more frequent in patients receiving 400 mg fluconazole.[38] In clinically stable patients, the dose of fluconazole for consolidation therapy should be 800 mg per day until CSF cultures are known to be sterile and ART is initiated, at which point the dose can be decreased to 400 mg per day **(AII).**[39]

For patients who have completed 2 weeks of induction therapy, but have not improved clinically or remain clinically unstable, continuation of amphotericin B plus flucytosine is recommended until the CSF cultures are confirmed to be negative **(BIII).** For patients who have improved clinically, but whose CSF remains culture positive after 2 weeks of induction therapy, the fluconazole dose should be increased to 1,200 mg per day and another lumbar puncture should be performed 2 weeks later **(BIII).** For all patients with CSF cultures positive at Week 2, the duration of consolidation therapy should be 8 weeks from the time the CSF cultures are negative **(AI).**[23,26,40]

An alternative approach for outpatients who are not ill enough to be hospitalized but still have positive CSF cultures after completing 2 weeks of induction therapy is to continue flucytosine for an additional 2 weeks together with fluconazole at a dose of 1,200 mg per day before starting single-drug consolidation therapy.

Itraconazole can be used as an alternative therapy for consolidation **(CI),** but it is clearly inferior to fluconazole.[40] Limited data are available for use of the newer triazoles—voriconazole, posaconazole, and isavuconazole—for either consolidation or maintenance therapy for patients with cryptococcosis. Most of the reported data have been on use of these extended-spectrum triazole antifungals for treatment of refractory cases, with success rates of approximately 50%.[41-43] Currently, the role of posaconazole, voriconazole, and isavuconazole in the initial management of cryptococcosis has not been established in randomized clinical trials, and these agents are **not recommended** for consolidation or maintenance therapy **(AIII).** Echinocandins have no activity against *Cryptococcus* spp. and **are not recommended** for clinical management of cryptococcosis **(AII).**

Maintenance Treatment

Fluconazole 200 mg per day is used for maintenance treatment and continue until at least one year from initiation of antifungal therapy **(AI)** (see the Preventing Recurrence section below).[44]

Treatment of Non-CNS Cryptococcosis and Asymptomatic Antigenemia

Non-CNS, extrapulmonary cryptococcosis and diffuse pulmonary disease should be treated the same as CNS disease **(BIII).** For those with mild to moderate symptoms and only focal pulmonary infiltrates, treatment with fluconazole 400 to 800 mg per day for 10 weeks followed by 200 mg daily for a total of 6 months combined with effective ART is recommended **(BIII).**[26]

Patients with isolated or asymptomatic cryptococcal antigenemia without meningitis and low serum CrAg titers (i.e., $\leq$1:320 using LFA) can be treated in a similar fashion as patients with mild to moderate symptoms and only focal pulmonary cryptococcosis with fluconazole 400 to 800 mg per

day **(BIII).** If the serum CrAg titer by LFA is ≥1:640 (or ≥1:160 by EIA or latex agglutination), even in the absence of meningitis, the risk for mortality and/or progression to meningitis increases with fluconazole monotherapy alone, and patients should be treated the same as patients with cryptococcal meningitis **(BIII).**[13] All patients with asymptomatic cryptococcal antigenemia should have their CSF sampled to rule out CNS disease. If serum CrAg titers are ≥1:640 with the LFA test and a CSF sample is not available, CNS involvement should be assumed regardless of CSF culture results or clinical signs or symptoms, and the patient should be treated as detailed above for CNS disease **(AII).**[12,13,45]

Special Considerations with Regard to Starting ART

Unlike with other opportunistic infections, ART initiation generally is deferred for 4 to 6 weeks after antifungal agents are started **(AI).** A randomized clinical trial conducted at three sites in Africa compared patients with cryptococcal meningitis who started ART within 1 to 2 weeks (median 8 days) after the diagnosis of meningitis with patients for whom ART was delayed for 4 to 6 weeks (median 35 days) after diagnosis.[46] This clinical trial used amphotericin B deoxycholate 0.7 to 1.0 mg/kg once daily plus fluconazole 800 mg once daily during the induction phase of antifungal treatment. A significantly greater increase in 6-month mortality occurred in the early ART group than in the delayed ART group (45% versus 30%, $P = 0.03$). This increase was most pronounced during the first 8 to 30 days of study ($P = 0.007$). The difference in mortality between the early ART group and the delayed ART group was even greater among individuals with CSF white cell count <5 cells/μL ($P = 0.008$). The excess of deaths in the early ART group was likely attributable to paradoxical IRIS.[47]

Most experts aim to start ART after 4 to 6 weeks of antifungal therapy; however, individual patient factors may alter this timing. In general, ensuring that the patient's CSF cultures are sterile before starting ART will reduce the risk of IRIS.[48] If ART must be started sooner, the patient should be monitored closely for paradoxical IRIS with a low threshold to intervene (see "Monitoring of Response to Therapy and Adverse Events," below). For non-CNS cryptococcosis, for which the risk of IRIS appears to be lower, the optimal time to begin ART and antifungal therapy is less clear. However, in patients with non-CNS cryptococcosis, it is prudent to delay initiation of ART for 2 weeks after starting antifungal therapy **(BIII).**

All of the triazole antifungals have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents. These interactions and recommendations for dosage adjustments, where feasible, are listed in the drug–drug interaction tables in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.

Monitoring of Response to Therapy and Adverse Events

Elevation of ICP can cause clinical deterioration despite a microbiologic response; complications are more likely to occur if the CSF lumbar opening pressure is ≥25 cm H_2O in the lateral decubitus position.[6,23] In a large clinical trial in patients with AIDS and cryptococcal meningitis, increased ICP was associated with 93% of deaths during the first 2 weeks of antifungal therapy and 40% of deaths during weeks 3 to 10.[6] In another clinical trial, patients with HIV-associated cryptococcal meningitis who received at least one therapeutic lumbar puncture within 7 days after diagnosis (median time of 3 days) had a 69% relative reduction in the risk of death through 11 days, regardless of initial opening pressure.[49] Although it is uncertain which patients with high lumbar opening pressures will

experience clinical deterioration, those with symptoms and signs of increased ICP require immediate clinical intervention to reduce ICP.

Control of elevated ICP is critical to reducing acute mortality. Lumbar opening pressure should be measured in all patients with cryptococcal meningitis at the time of diagnosis. However, in routine practice, CSF opening pressure frequently is not measured. Among patients in whom CSF opening pressure was not measured initially, a repeat lumbar puncture should be performed with measurement of opening pressure. For patients with ongoing headaches, a repeat lumbar puncture should be performed with urgency, and among those without headaches, a repeat lumber puncture should be considered strongly within 48 hours of the initial procedure.[49] Measures to decrease ICP should be used for all patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs indicative of increased ICP. Drainage of CSF via lumbar puncture is recommended for initial management **(AII).** One approach is to remove a volume of CSF that at least halves the opening pressure or normalizes the pressure to <20 cm H_2O.[49,50] In the absence of a manometer, removal of 20 to 25 mL of CSF is recommended **(AIII).** Among patients with ongoing symptoms, therapeutic lumbar punctures should be repeated daily until symptoms and signs consistently improve and opening pressure normalizes to <20 cm H_2O **(AII).** Because a survival benefit is associated with therapeutic lumbar puncture regardless of baseline CSF opening pressure, strong consideration should be given to repeating a therapeutic lumbar puncture within 72 hours of the initial procedure in those patients who are relatively asymptomatic or who had a baseline CSF opening pressure of <20 cm H_2O, **(BII).**[49] This second lumbar puncture can be especially useful if the initial opening pressure was not measured **(AII).** ICP can be a dynamic process that changes over time.

CSF shunting through a lumbar drain or ventriculostomy should be considered for patients who cannot tolerate repeated lumbar punctures or for those in whom signs and symptoms of increased ICP persist after multiple lumbar punctures **(BIII).** Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended (AIII).** Acetazolamide **should not be used** as therapy for increased ICP management because it may exacerbate hyperchloremic acidosis from amphotericin B and does not result in a decrease in ICP **(AI).**[51] A randomized study that compared a 6-week course of a tapering dose of dexamethasone with placebo among 451 Asian and African patients with cryptococcal meningitis found that dexamethasone did not improve survival through 10 weeks, was noted to decrease killing of *Cryptococcus*, and was associated with more adverse events.[52] These data support the recommendation that corticosteroids **should not be used** during induction therapy for ICP control for HIV-associated cryptococcal meningitis unless they are being used for treatment of IRIS **(AI).**

Patients treated with amphotericin B formulations should be monitored for nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 1,000 mL of normal saline reduces the risk of nephrotoxicity during amphotericin B treatment. For people with severe infusion-related adverse reactions, acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered 30 minutes before the infusion to reduce the severity of amphotericin infusion reactions **(CIII),** but scant data exist to support these practices. Meperidine (25–50 mg titrated during infusion) is effective for preventing and treating amphotericin B–associated rigors **(BII).** Routine use of potassium chloride, 40 mEq per day and magnesium 8 mEq per day, supplementation should be considered because the risk of hypokalemia and hypomagnesemia becomes near universal after 1 week of therapy, regardless of amphotericin B formulation **(AII).**[53]

In patients receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and can be guided by flucytosine levels. Peak serum flucytosine levels should be obtained 2 hours after an oral dose; the therapeutic range is between 25 and 100 mg/L. If therapeutic drug monitoring is not possible or kidney dysfunction is not present, frequent complete blood counts with differential (i.e., at least biweekly) can be used to detect cytopenias **(BII).**[24] Flucytosine is associated with concentration-dependent bone marrow toxicity. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities.

Common side effects of higher dose fluconazole therapy can include dry skin (17% of patients) and alopecia (16% of patients).[54] Increased liver transaminases or alkaline phosphatase are relatively rare with fluconazole 400 to 800 mg use, with only 1 to 2% having values >5 times the upper limit of normal.[46] For people who have difficulty tolerating higher fluconazole doses, it appears safe to reduce the consolidation therapy fluconazole dose to 400 mg per day after initiation of ART **(BII).**[39]

Immune Reconstitution Inflammatory Syndrome

An estimated 10 to 30% of people with HIV who have cryptococcal meningitis experience IRIS after initiation or re-initiation of effective ART.[55,56] Patients with HIV who have cryptococcal IRIS are more likely to be ART naive and have less CSF inflammation on initial presentation.[57] The risk of IRIS can be minimized by achieving CSF culture sterility before starting ART, using fluconazole 800 mg per day as consolidation therapy, and deferring ART initiation for 4 to 6 weeks from the start of antifungal therapy **(AII).**[46,58] Distinguishing paradoxical IRIS from treatment failure with culture-positive relapse is difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite microbiological evidence of effective antifungal therapy with sterile CSF cultures,[57,59] whereas treatment failure is associated with continued positive cultures. The primary microbiological criterion for treatment failure is a CSF culture that yields *Cryptococcus*; the culture may take days to weeks to become positive. A negative PCR test (e.g., Biofire FilmArray Meningitis/Encephalitis Panel) has a high predictive value for predicting sterile CSF cultures and can be diagnostically useful to distinguish paradoxical IRIS with a negative CSF PCR from culture-positive relapse with a positive CSF PCR.[14]

The appropriate management strategy for IRIS is to continue both ART and antifungal therapy and reduce elevated ICP if present **(AII).** While diagnostic tests are pending, escalating antifungal therapy is appropriate, such as restarting amphotericin B therapy or increasing the fluconazole dose to 1,200 mg per day **(BIII).** In patients with severe symptoms of IRIS, some experts recommend a brief course of tapering doses of corticosteroids. Dosages have varied, but commonly start at 1.0 mg/kg per day of prednisone **(BIII);** precise data-driven management strategies have not been developed. Serum C–reactive protein (CRP) is generally elevated at the time IRIS develops;[60] CRP will decrease with corticosteroid therapy if IRIS is present and can be used to monitor IRIS resolution. At hospital discharge, restarting fluconazole therapy at consolidation therapy doses to be continued for 8 weeks is recommended **(BIII).**

The risk of IRIS appears to be much lower and the syndrome seems to be less severe with other forms of cryptococcosis—such as lymphadenitis, cutaneous abscesses, and bony lesions—than with cryptococcal meningitis.[61] Management of IRIS with other forms of cryptococcosis is similar to that for IRIS associated with cryptococcal meningitis, including continuing ART, initiating or continuing antifungal therapy **(AIII),** and considering the use of corticosteroids if clinical symptoms are severe **(CIII).**

Managing Treatment Failure

Treatment failure is defined as: (1) a lack of clinical improvement and continued positive cultures after 2 weeks of appropriate therapy that has included management of increased ICP, or (2) relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥4 weeks of treatment. Primary fluconazole resistance in *Cryptococcus* isolates has been reported in the United States but is uncommon.[62] Therefore, susceptibility testing is not recommended routinely for initial management of cryptococcosis. However, if treatment failure or relapse occurs, *Cryptococcus* isolates should undergo antifungal susceptibility testing. Robust clinical data are lacking, but strains of *Cryptococcus* with fluconazole minimum inhibitory concentrations (MIC) ≥16 µg/mL are considered not fully susceptible.[63,64]

Optimal therapy for patients with treatment failure has not been established. Patients who do not respond to induction with fluconazole monotherapy should be switched to amphotericin B, with or without flucytosine. Those initially treated with an amphotericin B formulation should remain on this agent until clinical response occurs. In this setting, liposomal amphotericin B (4–6 mg/kg daily) or amphotericin B lipid complex (5 mg/kg daily) is better tolerated and has greater efficacy than the deoxycholate formulation[20,65,66] and should be considered when initial treatment with other regimens fails **(AII).**

In the setting of treatment failure or relapse, verifying CSF culture sterility at the completion of re-induction therapy is critical **(AIII).** After CSF sterility is achieved, outpatient consolidation therapy should consist of fluconazole at a higher dose of 1,200 mg per day and optimization of ART. For *Cryptococcus* with decreased azole-susceptibility (i.e., ≥16 µg/mL MIC for fluconazole) some experts would recommend adjunctive weekly amphotericin B administration during consolidation therapy **(BIII).**[64] Higher doses of fluconazole (i.e., 1,200 mg per day) in combination with flucytosine 25 mg/kg 4 times per day also may be considered **(BI).** The newer triazoles—posaconazole, voriconazole, and isavuconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy, but they offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates high-level fluconazole resistance. Most clinical failures are not due to antifungal drug resistance, but rather result from inadequate induction therapy, nonadherence, drug interactions that decrease the serum concentrations of fluconazole (e.g., with rifampin), or the development of paradoxical IRIS.

Preventing Recurrence

When to Start Maintenance Therapy

Patients who have completed 10 weeks of induction and consolidation therapy for cryptococcal meningitis or disseminated cryptococcosis should be treated with chronic maintenance or suppressive therapy with fluconazole 200 mg per day for at least 1 year **(AI).** Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease **(CI).**[40] One study demonstrated that only 70% of patients receiving fluconazole 200 mg per day achieved therapeutic concentrations of fluconazole in plasma when the fluconazole MIC was ≥8 µg/mL, and only 30% when the MIC was 16 µg/mL.[64] For patients in whom susceptibility studies have been performed and the fluconazole MIC is ≥8 µg/mL, some experts recommend that the fluconazole dose be increased to 400 mg per day **(BIII).** Failure to administer secondary prophylaxis for an entire year is the most common reason for subsequent relapse of cryptococcal disease.[67]

When to Stop Maintenance Therapy

Only a few patients have been evaluated for relapse after successful antifungal therapy for cryptococcosis and discontinuation of maintenance therapy while on ART. In a European study, recurrences of cryptococcosis were not found among 39 participants on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 count was 297 cells/mm^3, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[68] A prospective, randomized study of 60 patients in Thailand documented no recurrences of cryptococcosis during 48 weeks of follow-up among 22 patients whose antifungal therapy was discontinued after reaching a CD4 count >100 cells/mm^3 with a sustained undetectable HIV RNA level for 3 months on potent ART.[69] Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated opportunistic infections, it is reasonable to discontinue maintenance therapy after at least 1 year from initiation of antifungal therapy, in patients whose CD4 counts are >100 cells/mm^3 with undetectable viral loads on ART **(BII).**[70] Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/mm^3 **(AIII).**

Special Considerations During Pregnancy

The diagnosis of cryptococcal infections in individuals who are pregnant is similar to that in individuals who are not pregnant. Treatment should be initiated promptly after a diagnosis is confirmed. It should be emphasized that initiating antifungal therapy during the postpartum period is associated with an increased risk of IRIS.[71]

Lipid formulations of amphotericin B are preferred for the initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis in patients who are pregnant. Extensive clinical experience with amphotericin B has not documented teratogenicity. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

In animal studies, flucytosine is teratogenic; experience in humans is limited to case reports and small series. Therefore, flucytosine use should be considered only when the benefits outweigh the risks to the fetus and only in the third trimester **(AIII).**

Fluconazole is teratogenic in the first trimester. Congenital malformations similar to those observed in animals exposed to the drug—including craniofacial and limb abnormalities—have been reported in infants born to mothers who received fluconazole at doses of ≥400 mg per day through or beyond the first trimester of pregnancy.[72] A recent systematic review and meta-analysis of cohort or case-control studies reporting fetal outcomes after exposure to fluconazole in the first trimester of pregnancy analyzed more than 16,000 exposures and found an association with increased risk of heart defects and spontaneous abortion; exposure to a fluconazole dose ≥150 mg was associated with an increase in overall congenital malformations.[73] One registry-based cohort study included in the systematic review[74] and a more recent large population-based case-control study[75] specifically noted an increase in conotruncal heart defects. The latter study also suggested an increase in cleft lip with cleft palate.

A nationwide cohort study in Denmark also found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies or those with topical azole exposure only.[76] A cohort study using Swedish and

Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use during pregnancy and risk of stillbirth or neonatal death.[77] Most of the studies regarding effects of fluconazole during pregnancy have involved low doses of the drug and short-term exposure.

On the basis of reported birth defects, the FDA classified fluconazole as pregnancy category D for any use other than a single dose of fluconazole 150 mg to treat vaginal candidiasis. Use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh the risks. For pregnant women, amphotericin B should be continued throughout the first trimester. After induction therapy, weekly amphotericin B has been used for consolidation therapy for women who are pregnant throughout the first trimester.[71] After the first trimester, switching to oral fluconazole 200 mg per day may be considered if appropriate clinically.

In a case series of 12 pregnant Ugandan women with cryptococcal meningitis who received amphotericin B deoxycholate 0.7 to 1 mg/kg induction therapy, maternal mortality was 25%.[71] Stillbirths and miscarriages were common during the initial maternal hospitalization with only 33% (4 live births out of 12 pregnancies) fetal survival.[71] Consolidation therapy comprised weekly amphotericin during the first trimester and fluconazole thereafter. With life-threatening cryptococcal disease, fetal demise is common even without fluconazole exposure.[71]

Although case reports of birth defects in infants exposed to itraconazole exist, prospective cohort studies of >300 women with first-trimester exposure did not show an increased risk of fetal malformation.[78,79] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII).** Voriconazole (at doses lower than recommended human doses), posaconazole, and isavuconazole are teratogenic and embryotoxic in animals; no adequately controlled studies have assessed their teratogenicity and embryotoxicity in humans. Voriconazole, posaconazole, and isavuconazole **are not recommended** for use during pregnancy, especially in the first trimester **(AIII).**

Recommendations for Treating Cryptococcosis

Treating Cryptococcal Meningitis

Treatment consists of three phases: induction, consolidation, and maintenance therapy.

Induction Therapy (Duration of Therapy: 2 Weeks, Followed by Consolidation Therapy)

Preferred Regimens

- Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day (AI), *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day (AI)—if cost is an issue and the risk of renal dysfunction is low.

Note: Flucytosine dose should be adjusted in renal impairment (see Table 6).

Alternative Regimens

- Amphotericin B lipid complex 5 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day (BII); *or*
- Liposomal amphotericin B 3–4 mg/kg IV once daily plus fluconazole 800–1,200 mg PO or IV once daily (BIII); *or*
- Fluconazole 1,200 mg PO or IV once daily plus flucytosine 25 mg/kg PO four times a day (BII); *or*
- Fluconazole 800 mg PO or IV once daily plus flucytosine 25 mg/kg PO four times a day (BIII); *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus fluconazole 800–1,200 mg PO or IV once daily (BI); *or*
- Liposomal amphotericin B 3–4 mg/kg IV once daily alone (BI); *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily alone (BI); *or*
- Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day for 1 week followed by fluconazole 1,200 mg PO once daily (BIII); *or*
- Fluconazole 1,200 mg PO or IV once daily alone (CI)

If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative (BIII).

Consolidation Therapy (**Duration of Therapy:** ≥8 Weeks, Followed by Maintenance Therapy)

Preferred Regimen

- Fluconazole 800 mg PO once daily (AI)
- For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg PO once daily (AII)
- If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, increase fluconazole dose to 1,200mg and perform LP 2 weeks later (BIII); duration of consolidation therapy should be 8 weeks from the time of negative CSF culture (AI).

Maintenance Therapy

Preferred Regimen

- Fluconazole 200 mg PO once daily for ≥1 year from initiation of antifungal therapy (AI)—see below for recommendation on when to stop maintenance therapy

Stopping Maintenance Therapy

If the Following Criteria Are Fulfilled (BII)

- At least 1 year from initiation of antifungal therapy, *and*
- Patient remains asymptomatic from cryptococcal infection, *and*
- CD4 count ≥100 cells/mm^3 and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy

- If CD4 count declines to ≤100 cells/mm^3 (AIII)

Treating Non-CNS Extrapulmonary, Diffuse Pulmonary Disease, or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer ≥1:640)

- Same treatment as for CNS disease (BIII)

Treating Non-CNS Focal Pulmonary Disease or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer ≤1:320)

- Fluconazole 400 to 800 mg PO daily for 10 weeks followed by fluconazole 200 mg daily for a total of 6 months (BIII)

Other Considerations

- Addition of flucytosine to an amphotericin B-based regimen has been associated with more rapid sterilization of CSF, decreased risk for subsequent relapse, and improved survival.
- When flucytosine is used, serum concentrations (if TDM available) should be monitored 2 hours postdose, after 3–5 doses have been administered, and drug concentration should be between 25 and 100 mg/L. Alternatively, if flucytosine levels cannot be measured, at least twice weekly complete blood counts may be used to monitor for cytopenias.
- CSF opening pressure should always be measured when an LP is performed. Repeated therapeutic LPs are essential to manage symptomatic increased ICP and have a survival benefit (AII).
- Typical duration of induction therapy is 2 weeks. In the setting of severe amphotericin B–induced toxicity, at least 1 week of amphotericin B deoxycholate was noninferior to 2 weeks of amphotericin B deoxycholate (BIII).[24]
- Corticosteroids should not be used routinely during induction therapy unless used for management of IRIS (AI).
- Corticosteroids and mannitol are ineffective in reducing ICP and are not recommended (AIII).
- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 4 lists these interactions and recommends dosage adjustments where feasible.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LFA = lateral flow assay; LP = lumbar puncture; PO = orally; TDM = therapeutic drug monitoring

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