

Practice Guidelines

IDSA Releases Guidelines on Management of Cryptococcal Disease

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Cryptococcosis is an invasive fungal disease associated with high rates of morbidity and mortality in areas with uncontrolled human immunodeficiency virus (HIV) disease and limited access to health care. In medically developed countries, patients with newly diagnosed HIV infection and those receiving high-dose corticosteroids, monoclonal antibodies, or other immunosuppressive agents account for most cases of cryptococcal disease. Despite access to advanced medical care and the availability of highly active antiretroviral therapy, patients with acute cryptococcal meningoencephalitis have a three-month mortality rate of approximately 20 percent.

The Infectious Diseases Society of America (IDSA) recently updated its guidelines on the management of cryptococcal disease. The new guidelines include a discussion of the management of cryptococcal meningoencephalitis in three risk groups: patients who are HIV-positive, organ transplant recipients, and non-HIV-infected and nontransplant hosts. The new guidelines also include specific recommendations for other high-risk groups, such as children, pregnant women, patients in environments with limited health care resources, and those with *Cryptococcus gattii* infection.

Patients Who Are HIV-Positive

INDUCTION AND CONSOLIDATION THERAPY

The preferred regimen for induction and consolidation therapy in patients who are HIV-positive is amphotericin B deoxycholate (0.7 to 1.0 mg per kg per day, intravenously)

plus flucytosine (Ancobon; 100 mg per kg per day, orally, in four divided doses) for at least two weeks, followed by fluconazole (Diflucan; 400 mg [6 mg per kg] per day, orally) for at least eight weeks. Lipid formulations of amphotericin B, including liposomal amphotericin B (3 to 4 mg per kg per day, intravenously) and amphotericin B lipid complex (5 mg per kg per day, intravenously), can be substituted for amphotericin B deoxycholate in patients with or predisposed to renal dysfunction.

Alternative regimens include the following (in order of preference):

- Amphotericin B deoxycholate (0.7 to 1.0 mg per kg per day, intravenously), liposomal amphotericin B (3 to 4 mg per kg per day, intravenously), or amphotericin B lipid complex (5 mg per kg per day, intravenously) for four to six weeks. Liposomal amphotericin B has been administered safely at dosages of 6 mg per kg per day in patients with cryptococcal meningoencephalitis, and could be considered in the event of treatment failure or in patients with high-fungal burden disease.
- Amphotericin B deoxycholate (0.7 mg per kg per day, intravenously) plus fluconazole (800 mg per day, orally) for two weeks, followed by fluconazole (800 mg per day, orally) for at least eight weeks.
- Fluconazole (at least 800 mg per day, orally; 1,200 mg per day is preferred) plus flucytosine (100 mg per kg per day, orally) for six weeks.
- Fluconazole (800 to 2,000 mg per day, orally) for 10 to 12 weeks. A dosage of at least 1,200 mg per day is recommended if fluconazole is used alone.
- Itraconazole (Sporanox; 200 mg twice per day, orally) for 10 to 12 weeks. However, the use of this agent is discouraged.

MAINTENANCE AND PROPHYLACTIC THERAPY

Maintenance therapy should be initiated after the induction and consolidation regimen is complete. Ideally, maintenance therapy is begun when the results of cerebrospinal fluid yeast culture are negative, and it is continued until there is evidence of persistent immune reconstitution with successful highly active antiretroviral therapy.

Regimens include the following:

- Fluconazole (200 mg per day, orally).
- Itraconazole (200 mg twice per day, orally; drug level monitoring is strongly advised).
- Amphotericin B deoxycholate (1 mg per kg per week, intravenously). This is less effective than azoles and is associated with intravenous catheter-related infections.

Highly active antiretroviral therapy should be initiated two to 10 weeks after the initial antifungal treatment is begun. Physicians should consider discontinuing immunosuppressive therapy in patients with a CD4 cell count of greater than 100 cells per mm³ (100×10^9 cells per L) and an undetectable or very low HIV RNA level sustained for at least three months (minimum of 12 months of antifungal therapy). Reinstitution of maintenance therapy should be considered if the CD4 cell count decreases to less than 100 cells per mm³.

A lumbar puncture should be performed and a blood culture obtained in patients with asymptomatic antigenemia. If results are positive, the patient should be treated for symptomatic meningoencephalitis or disseminated disease. If there is no evidence of meningoencephalitis, the patient should receive fluconazole (400 mg per day, orally) until immune reconstitution.

Primary antifungal prophylaxis for cryptococcosis is not routinely recommended in the United States and Europe, but it may be considered in areas with limited availability of highly active antiretroviral therapy, high levels of antiretroviral drug resistance, and a high disease burden.

Organ Transplant Recipients

Cryptococcosis has been documented in an average of 2.8 percent of solid-organ transplant recipients. The median time to disease onset is 21 months after transplantation; 68.5 percent of cases occur more than 12 months after transplantation. Approximately 25 to 54 percent of organ transplant recipients with cryptococcosis have pulmonary infection, and in 6 to 33 percent, the disease is limited to the lungs.

Patients with central nervous system (CNS) disease should be treated with liposomal amphotericin B (3 to 4 mg per kg per day, intravenously) or amphotericin B lipid complex (5 mg per kg per day, intravenously) plus flucytosine (100 mg per kg per day in four divided doses) for at least two weeks, followed by fluconazole (400 to 800 mg [6 to 12 mg per kg] per day, orally) for eight weeks, then a lower dose of fluconazole (200 to 400 mg per day, orally) for six to 12 months. If induction therapy does not include flucytosine, four to six weeks of therapy with liposomal formulations of amphotericin B should be considered. Liposomal

amphotericin B (6 mg per kg per day) may be considered for patients with high-fungal burden disease or relapse.

Fluconazole (400 mg [6 mg per kg] per day) should be given for six to 12 months in patients with mild to moderate non-CNS disease. Those with moderately severe to severe non-CNS disease or disseminated disease without CNS involvement should be treated the same as those with CNS disease.

In the absence of clinical evidence of extrapulmonary or disseminated cryptococcosis, patients with severe pulmonary disease are treated the same as those with CNS disease. Fluconazole (400 mg [6 mg per kg] per day) should be used for six to 12 months in patients with mild to moderate symptoms without diffuse pulmonary infiltrates.

Because of the risk of nephrotoxicity, amphotericin B deoxycholate should be used with caution in transplant recipients and is not recommended as first-line therapy in these patients. If this medication is used, the tolerated dosage is uncertain, but 0.7 mg per kg per day is suggested, with frequent monitoring of renal function.

Non-HIV-Infected, Nontransplant Hosts

Recommendations for immunocompetent hosts are limited because most patients in the two major studies of cryptococcal meningoencephalitis before the HIV epidemic were immunosuppressed. However, patients with less severe or variable host immune defects can still present serious therapeutic challenges.

In immunocompetent hosts, induction therapy is reserved for persons with meningoencephalitis without neurologic complications and negative cerebrospinal fluid yeast cultures after two weeks of treatment. Amphotericin B deoxycholate (0.7 to 1.0 mg per kg per day, intravenously) plus flucytosine (100 mg per kg per day, orally, in four divided doses) is recommended for at least four weeks for induction therapy. Lipid formulations of amphotericin B can be substituted in the second two weeks. Induction therapy may extend to six weeks in patients with neurologic complications, and lipid formulations of amphotericin B may be given for the last four weeks. Consolidation therapy should then be initiated with fluconazole (400 mg per day) for eight weeks.

Liposomal amphotericin B (3 to 4 mg per kg per day, intravenously) or amphotericin B lipid complex (5 mg per kg per day, intravenously) can be used in patients who do not tolerate amphotericin B deoxycholate. If flucytosine is not given or treatment is interrupted, induction therapy with amphotericin B deoxycholate or lipid formulations of amphotericin B can be extended for at least two weeks.

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After induction and consolidation therapy, maintenance therapy should be started with fluconazole (200 mg [3 mg per kg] per day, orally) for six to 12 months.

Special Considerations

CHILDREN

Children with CNS or disseminated disease should receive induction and consolidation therapy with amphotericin B deoxycholate (1 mg per kg per day, intravenously) plus flucytosine (100 mg per kg per day, orally, in four divided doses) for two weeks, followed by eight weeks of fluconazole therapy (10 to 12 mg per kg per day, orally). Children who are not HIV-positive and have not had an organ transplant should follow the treatment length schedule for adults. Those who do not tolerate amphotericin B should be given liposomal amphotericin B (5 mg per kg per day) or amphotericin B lipid complex (5 mg per kg per day).

After induction therapy, fluconazole (6 mg per kg per day) should be given as maintenance therapy. Children with cryptococcal pneumonia should receive fluconazole (6 to 12 mg per kg per day, orally) for six to 12 months. Discontinuation of maintenance therapy in children receiving highly active antiretroviral therapy should be individualized.

PREGNANCY

Pregnant women with CNS or disseminated disease should be treated with amphotericin B deoxycholate or lipid formulations of amphotericin B, with or without flucytosine. Because flucytosine is a U.S. Food and Drug Administration pregnancy category C drug, its potential benefits must be weighed against its risks.

The use of fluconazole (also a pregnancy category C drug) should be avoided in the first trimester and carefully considered in the second and third trimesters, weighing its risks against the need for continuous antifungal drug exposure. Women with limited and stable pulmonary cryptococcosis should be followed closely and given fluconazole after delivery. Immune reconstitution inflammatory syndrome is a risk in the postpartum period, and patients should be monitored for this condition.

ENVIRONMENTS WITH LIMITED HEALTH CARE RESOURCES

When flucytosine is not available, patients with CNS or disseminated disease should receive induction therapy with amphotericin B deoxycholate (1 mg per kg per day, intravenously) for two weeks, or amphotericin B deoxycholate (0.7 mg per kg per day, intravenously) plus fluconazole (800 mg per day) for two weeks. Induction therapy should be followed by consolidation therapy with 800 mg of fluconazole per day for eight

weeks. Maintenance therapy with fluconazole (200 to 400 mg per day, orally) should be given until immune reconstitution.

When other antifungal agents are not available, patients with CNS or disseminated disease should receive induction therapy with fluconazole (at least 800 mg per day; 1,200 mg per day is preferred) for at least 10 weeks or until cerebrospinal fluid culture results are negative. If flucytosine is available, it should be added at a dosage of 100 mg per kg per day, orally, and induction therapy should continue for two to 10 weeks. Induction therapy should be followed by maintenance therapy (200 to 400 mg per day).

When primary fluconazole therapy is used for induction, drug resistance—both primary and secondary—may be an issue, and minimum inhibitory concentration testing is recommended. Patients with azole-resistant strains of cryptococcosis should be given amphotericin B deoxycholate (1 mg per kg per day, intravenously) until cerebrospinal fluid and blood are sterile.

C. GATTII INFECTION

Patients with CNS or disseminated disease from *C. gattii* infection should receive the same induction, consolidation, and suppressive treatment as those with *Cryptococcus neoformans* infection. However, additional diagnostic radiology and follow-up are needed in patients with cryptococcomas and hydrocephalus caused by *C. gattii* infection. Surgery should be considered if there is compression of vital structures or failure to thrive, or if four weeks of therapy does not reduce the size of the cryptococcoma.

Patients with pulmonary cryptococcosis should be treated with the same regimen as those infected with *C. neoformans*. Those with a single, small cryptococcoma should receive fluconazole (400 mg per day). In patients with large or multiple cryptococcomas, four to six weeks of combination therapy with amphotericin B deoxycholate and flucytosine should be considered, followed by fluconazole for six to 18 months, depending on whether surgery was performed. ■

Answers to This Issue's CME Quiz

Q1. A	Q6. A, B, C, D	Q11. A, C, D
Q2. D	Q7. D	Q12. C
Q3. A, B, C	Q8. A, D	Q13. A, B, C
Q4. C	Q9. C	Q14. B
Q5. A, B	Q10. D	Q15. B