

Updates on Cryptococcal Disease Treatment

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Updates in Opportunistic Infections Guidelines

Management of Cryptococcal Disease

- Treatment of cryptococcal meningitis
- Treatment of non-central nervous system (CNS) cryptococcosis
- Treatment for individuals with asymptomatic cryptococcal antigenemia
- Summary

How do you treat Cryptococcal Meningitis?

Phases of Treatment for Cryptococcal Meningitis

INDUCTION

≥2 weeks *plus* clinical improvement *plus* negative CSF culture



CONSOLIDATION

≥8 weeks *plus* negative CSF culture



MAINTENANCE

≥1 year

Treating Cryptococcal Meningitis – Preferred Induction Regimen

	Old Recommendation	New Recommendation
Induction (Duration 2 weeks)	Liposomal amphotericin B 3–4 mg/kg IV once daily <i>plus</i> flucytosine 25 mg/kg PO four times a day (AI) <i>or</i> Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily <i>plus</i> flucytosine 25 mg/kg PO four times a day (AI)—if cost is an issue and the risk of renal dysfunction is low.	No change

Treating Cryptococcal Meningitis – Preferred Consolidation Regimen

	Old Recommendation	New Recommendation
Consolidation (Duration ≥8 weeks)	Fluconazole 400 mg PO once daily	Fluconazole 800 mg PO once daily (AI)* *IF CSF cultures remain negative, then the consolidation fluconazole dose can be reduced to 400 mg once daily

Treating Cryptococcal Meningitis – *Management of Persistently Positive CSF Cultures after Induction Therapy*

	Old Recommendation	New Recommendation
Consolidation Therapy in Setting of: POSITIVE CSF cultures after 2 weeks of Induction Therapy <i>and</i> Clinically stable	Repeat induction therapy	Increase fluconazole dose to 1200 mg PO once daily and repeat lumbar puncture 2 weeks later (BIII) Duration of consolidation therapy should be 8 weeks from the time the CSF cultures are negative

STUDIES SUMMARY – Increased Consolidation Dosing

- 1,2 Clinical trials demonstrated higher rates of breakthrough infection relapses for individuals taking 400 mg compared to 800 mg of fluconazole
- 3,4 Studies have also shown that antifungal activity of fluconazole in CSF of patients with cryptococcal meningitis increases with higher doses of the drug

Source:

1. van der Horst CM, et al. *N Engl J Med*. 1997;337(1):15-21
2. Pappas PG, et al. *Clin Infect Dis*. 2009;48(12):1775-1783
3. Day JN, et al. *N Engl J Med*. 2013;368(14):1291-1302
4. Bicanic T, et al. *Clin Infect Dis*. 2007;45(1):76-80

Treating Cryptococcal Meningitis – *Preferred Maintenance Regimen*

	Old Recommendation	New Recommendation
Maintenance (Duration \geq 1 year)	Fluconazole 200 mg PO once daily	No change

Preferred Therapy for Cryptococcal Meningitis in Persons with HIV

- **Induction**

- Amphotericin B (liposomal or deoxycholate) IV once daily plus flucytosine PO 4 times a day for ≥ 2 weeks

- **Consolidation**

- Fluconazole 800 mg PO once daily
- If CSF culture is negative, the fluconazole dose can be reduced to 400 mg PO once daily
- If CSF culture remains positive (but patient is clinically stable) after induction therapy, increase fluconazole dose to 1,200 mg and repeat lumbar puncture 2 weeks later
- Continue consolidation for 8 weeks from negative CSF culture

- **Maintenance**

- Fluconazole 200 mg PO once daily for ≥ 1 year

How do you treat Non-CNS Cryptococcal Disease?

Treatment for Non-CNS Cryptococcal Disease: Serum LFA Titer $\geq 1:640$

Treatment of non-CNS Cryptococcal Disease

Extrapulmonary or Pulmonary Disease, or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer $\geq 1:640$):

Treat the same as cryptococcal meningitis: Induction + Consolidation + Maintenance

- High titers of cryptococcal antigen are associated with higher mortality and risk of progression to meningitis with fluconazole monotherapy

Treatment for Non-CNS Cryptococcal Disease: Serum LFA Titer $\leq 1:320$

Treatment of non-CNS Cryptococcal Disease

Focal Pulmonary Disease or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer $\leq 1:320$):

Fluconazole 400 to 800 mg PO daily for 10 weeks, then

Fluconazole 200 mg PO daily for 6 months

plus

Effective combination antiretroviral therapy

Cryptococcosis July 2022 Guideline Update Summary

- **Treatment of Cryptococcal Meningitis**

1. For consolidation treatment, the recommended dose of oral fluconazole has been increased from 400 to 800 mg/day
2. If CSF cultures positive after 2 weeks of induction therapy, increase oral fluconazole dose to 1200 mg/day and repeat lumbar puncture 2 weeks later

- **Treatment of Non-CNS Cryptococcal Disease**

1. To treat high titers ($\geq 1:640$) of cryptococcal antigenemia, manage the same as cryptococcal meningitis
2. To treat lower titers ($\leq 1:320$) of cryptococcal antigenemia, use oral fluconazole (400-800 mg/day)

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