Mini-Lecture Series

Updates on Cryptococcal Disease Treatment

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Disclosures

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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

<table>
<thead>
<tr>
<th>Induction (Duration 2 weeks)</th>
<th>Old Recommendation</th>
<th>New Recommendation</th>
</tr>
</thead>
</table>
|                             | 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. | No change |

<table>
<thead>
<tr>
<th><strong>Consolidation</strong> (Duration ≥8 weeks)</th>
<th><strong>Old Recommendation</strong></th>
<th><strong>New Recommendation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole <strong>400 mg</strong> PO once daily</td>
<td>Fluconazole <strong>800 mg</strong> PO once daily (AI)*</td>
<td></td>
</tr>
<tr>
<td>*IF CSF cultures remain negative, then the consolidation fluconazole dose can be reduced to 400 mg once daily</td>
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### Treating Cryptococcal Meningitis – Management of Persistently Positive CSF Cultures after Induction Therapy

<table>
<thead>
<tr>
<th>Consolidation Therapy in Setting of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSITIVE CSF cultures after 2 weeks of Induction Therapy and Clinically stable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Old Recommendation</th>
<th>New Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat induction therapy</td>
<td>Increase fluconazole dose to 1200 mg PO once daily and repeat lumbar puncture 2 weeks later (BIII)</td>
</tr>
<tr>
<td></td>
<td>Duration of consolidation therapy should be 8 weeks from the time the CSF cultures are negative</td>
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STUDIES SUMMARY – Increased Consolidation Dosing

• Clinical trials demonstrated higher rates of breakthrough infection relapses for individuals taking 400 mg compared to 800 mg of fluconazole

• Studies have also shown that antifungal activity of fluconazole in CSF of patients with cryptococcal meningitis increases with higher doses of the drug

Source:
## Treating Cryptococcal Meningitis – Preferred Maintenance Regimen

<table>
<thead>
<tr>
<th>Maintenance (Duration ≥1 year)</th>
<th>Old Recommendation</th>
<th>New Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 200 mg PO once daily</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>

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 ≥1:640

Treatment of non-CNS Cryptococcal Disease

Extrapulmonary or Pulmonary Disease, or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer ≥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 of non-CNS Cryptococcal Disease

**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, then
- Fluconazole 200 mg PO daily for 6 months
  - plus
- Effective combination antiretroviral therapy

• 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 (≥1:640) of cryptococcal antigenemia, manage the same as cryptococcal meningitis
  2. To treat lower titers (≤1:320) of cryptococcal antigenemia, use oral fluconazole (400-800 mg/day)
Acknowledgments

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