Challenges in Management of Cryptococcal Meningitis

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Overview

- Epidemiology
- Pathogenesis
- Clinical presentation
- Diagnosis
- Prognostic factors
- Antifungal Treatment
- HIVCS guidelines
- Pressure Management
- Conclusion
**C. neoformans - Leading Cause of meningitis in SSA**

- SSA 15%-30% of AIDS $\Rightarrow$ cryptococcal Dx
- HAART decreases incidence significantly

![Table 1. Diagnostic categories and HIV seropositivity in 406 suspected cases of meningitis.](image)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
<th>HIV tests carried out (n)</th>
<th>HIV seropositive [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcal</td>
<td>89 (45)</td>
<td>80</td>
<td>80 (100)</td>
</tr>
<tr>
<td>Mononuclear</td>
<td>54 (27)</td>
<td>51</td>
<td>43 (83)</td>
</tr>
<tr>
<td>Pyogenic</td>
<td>31 (16)</td>
<td>31</td>
<td>25 (81)</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>24 (12)</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Undefined</td>
<td>2 (1)</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>200 (100)</td>
<td>188</td>
<td>170 (90)</td>
</tr>
</tbody>
</table>

Non-meningitis
Incidence rates of *Cryptococcus spp.* in South Africa (2005-07)

<table>
<thead>
<tr>
<th>Province</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Cases / 100 000</td>
<td>n</td>
</tr>
<tr>
<td>Eastern Cape</td>
<td>447</td>
<td>7</td>
<td>1357</td>
</tr>
<tr>
<td>Free State</td>
<td>227</td>
<td>9</td>
<td>287</td>
</tr>
<tr>
<td>Gauteng</td>
<td>1571</td>
<td>16</td>
<td>1856</td>
</tr>
<tr>
<td>Kw aZulu-Natal</td>
<td>882</td>
<td>9</td>
<td>1348</td>
</tr>
<tr>
<td>Limpopo</td>
<td>123</td>
<td>2</td>
<td>215</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>348</td>
<td>11</td>
<td>439</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>50</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>North West</td>
<td>206</td>
<td>6</td>
<td>378</td>
</tr>
<tr>
<td>Western Cape</td>
<td>332</td>
<td>7</td>
<td>353</td>
</tr>
<tr>
<td><strong>South Africa</strong></td>
<td><strong>4186</strong></td>
<td><strong>9</strong></td>
<td><strong>6296</strong></td>
</tr>
</tbody>
</table>
Pathogenesis of Cryptococcal Disease

Ubiquitous in soil

acquired in childhood

Immune defect

Eucalyptus tree
Bird excreta

Positive culture

Dissemination to central nervous system

Lodging in alveoli
Neurologic Manifestations

Meningoencephalitis, Cryptococcomas

- Headache - 90%
- Confusion - 26%
- Seizures - 22%
- Focal neurological signs
  - 6th nerve palsies, hearing loss, loss of vision, papilledema
- Fever and neck rigidity mild or absent
Cryptococcoma

cerebellum. (b) On an axial T2-weighted image, the mass is heterogeneous in signal intensity but predominantly hyperintense, with a surrounding rim of T2 hyperintensity, a finding consistent with edema. (c) Axial postcontrast T1-weighted image reveals peripheral nodular enhancement of the lesion.
Cerebrospinal Fluid

- CSF Characteristics Unimpressive
- No to low cell counts - lymphocytic
- CSF protein normal to modestly elevated
- CSF glucose typically normal
Diagnosis

**India Ink:** Sn 60% - 80%

**CLAT:** Serum: Sn 97%, Sp 95%, CSF: Sn 100% Sp 96%

*Fig. 3. India ink microscopy stain demonstrating encapsulated cryptococcal yeasts, some of them budding.*
Clinical Presentation

Occurs in about 10-15% of patients
Pulmonary cryptococcosis
Prognostic Factors
Baseline Mental State

Altered mental status

Survival probability

No
Yes

No. of weeks follow-up
Baseline Fungal Load

Survival probability

Baseline CFU count

EFA: Rate of Clearance of Fungus
Rate of Clearance of Cryptococcal CFU's from CSF

- Correlates with 2 week survival independent of other prognostic markers (M/S, baseline load)
- Associated less with survival at 10/52
- Emerging as suitable marker of response
- Clear fungus rapidly in the first 2/52 might improve clinical outcome
- Early CSF sterilization ⇒ important goal?

Management of CM

- Primary prophylaxis
- Preemptive Treatment
- Treating the fungus
- Managing pressure
- Secondary Prophylaxis
- Managing the HIV
Currently Recommended Antifungal Treatment

Table 2. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus–Infected Individuals

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)(^a)</td>
<td>2 weeks</td>
<td>A-I</td>
</tr>
</tbody>
</table>

Alternatives for induction therapy\(^b\)

<table>
<thead>
<tr>
<th>Alternatives for induction therapy (^b)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AmBd plus fluconazole</td>
<td>...</td>
<td>B-I</td>
</tr>
<tr>
<td>Fluconazole plus flucytosine</td>
<td>...</td>
<td>B-II</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>...</td>
<td>B-II</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>...</td>
<td>C-II</td>
</tr>
</tbody>
</table>

Consolidation therapy: fluconazole (400 mg per day)            |

| Maintenance therapy: fluconazole (200 mg per day)\(^a\)        | \(\geq 1\) year\(^c\) | A-I      |

Alternatives for maintenance therapy\(^b\)

<table>
<thead>
<tr>
<th>Alternatives for maintenance therapy (^b)</th>
<th>(\geq 1) year(^c)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole (400 mg per day)(^d)</td>
<td>(\geq 1) year(^c)</td>
<td>C-I</td>
</tr>
<tr>
<td>AmBd (1 mg/kg per week)(^d)</td>
<td>(\geq 1) year(^c)</td>
<td>C-I</td>
</tr>
</tbody>
</table>
AmB, AmB+5FU, AmB + FLZ, AmB+FLZ+5FU

Figure 3: Fall in CSF CFU over time by treatment group

Brouwer et al, Lancet 2004; 363: 1764
[AmB 1mg/kg vs AmB 0.7mg/kg] + 5FC

- Rapidly fungicidal
- No difference in survival
- No difference in toxicity

Not powered

AIDS: 23 (6), 701
AmB 1mg/kg vs. FLZ 400mg

Prospective observational study 54 pts

EFA AmB 1mg/kg/day significantly better than FLZ 400 mg/day.

CID: 2007; 45:76–80
RCT open-label Safety & Efficacy AMB vs. AMB+FLZ (143 pts)

- **Intensive phase of treatment (14 days):**
  - AMB 0.7 mg/kg (Standard therapy)
  - AMB 0.7 mg/kg + FLZ 400 mg (low-dose combo)
  - AMB 0.7 mg/kg + FLZ 800 mg (hi dose combo)

- **Consolidation phase (8/52):**
  - FLZ 400/d
  - FLZ 800/d

- **Primary end point:**
  - Severe toxicities
  - Composite - survival, neuro stability, neg CSF cultures at day 14/7

CID 2009; 48:1775-83
Mortality at 14 days
Std Arm 22.2%, n=46
AmB + FLZ 400: 17%, n=48
AmB + FLZ 800: 18.4%, n=41

AmB + FLZ 800 mg numerically better outcome at each point

Phase II study: safety and efficacy study

CID 2009; 48:1775-83

Figure 3. Kaplan Meier estimates of overall survival for the modified intention-to-treat population.
AmB vs. AmB + FLZ
Safety and Efficacy

- Phase II RCT
- No differences in treatment toxicities - mostly AMB toxicity
- AmB + FLZ 800 mg x 2/52 followed by FLZ 800 mg daily for 8/52 is well-tolerated and efficacious in treatment of CNS crypto

CID 2009; 48:1775-83
FLZ 800mg vs. 1200mg

- Consolidation 400mg FLZ
- Significantly greater EFA
- Well tolerated no LFT disturbance
- Mortality was no different between the 2 doses

CID: 2008;47:1556-1561

![Graphs showing bacterial load reduction over time for groups 1 and 2 with different doses of FLZ.](image-url)
FLZ Combination with 5FC

- Consolidation 800mg FLZ

- FLZ 1200mg
- EFA 0.11log

- 5FC + FLZ (1200mg)
- EFA 0.28log

n=17

N=20

CID: 2010;50:338-344
Combo: ↓ deaths 2/52 (10% vs 37%) 10/52 (43% vs 58%), ↑ neutropenia (5 vs 1) but no ↑ infections
Summary of Treatment Options

- AmB + 5FC likely most effective
- AmB at 1mg/kg
- AmB + FLZ - minimum dose 800mg
- FLZ ≥ 1200mg/d +5FC (oral)
- FLZ ≥ 1200mg/d (oral)
Managing Intracranial Pressure

Control of ICP is critical - influences outcome

~ 50% have increased baseline ICP

Associated with high fungal burden

↑CSF pressure associated with morbidity & mortality

Should be managed aggressively by repeated lumbar punctures, temporary lumbar drain, or CSF diversion
RECOMMENDATION 2: INITIAL TREATMENT OF CRYPTOCOCCOSIS

1. **Antifungal treatment of a first episode of CC**

   **Induction phase:** Amphotericin B 1 mg/kg/dose ivi for 2 weeks (minimum 1 week).

   **Consolidation phase:** Fluconazole 400 mg po daily for 8 weeks.

   **Secondary prophylaxis:** Fluconazole 200 mg po daily for life or until CD4 >200 cells/µl for more than 6 months on ART (at least 12 months’ fluconazole in total).

2. **Antifungal treatment of a subsequent episode** of CC that is thought to be due to fluconazole ‘resistance’:

   **Induction phase:** Amphotericin B 1 mg/kg/dose ivi for 2-4 weeks or until CSF is sterile.

   **Consolidation phase:** Fluconazole 800 mg po daily for 8 weeks with or without weekly amphotericin B 1 mg/kg.

   **Secondary prophylaxis:** Fluconazole 400 mg po daily for life (at least 12 months’ fluconazole in total) OR Weekly amphotericin B 1 mg/kg/dose OR weekly amphotericin B 1 mg/kg/dose plus daily fluconazole 400 mg.

   Secondary prophylaxis can be discontinued if CD4 count is >200/µl for 6 months on ART.
Conclusion

- CM leading causes of AIDS mortality in SSA
- Require high index of suspicion
- Optimal treatment AmB plus 5FC
- Alternatives FLZ + 5FC, high dose FLZ
- Control of increased ICP is critical for a positive outcome.
Questions
Cryptococcal Optimal ART Timing (COAT) Study

• HIV+ ART-naïve pts with CrM

• Randomized to:
  • Early ART at 1-2 wks vs
  • “Std” ART at 5-6 wks

• AmB 0.7-1.0 mg/kg/d + Fluc 800 mg/d x 14 d