Are there opportunities to manage cryptococcal meningitis better?

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Opportunities for improvement

1. Earlier detection
2. First-line antifungal treatment
3. Adjunctive treatment

Cryptococcal meningitis can be prevented

Screen for cryptococcal antigen in blood of ART-naive HIV+ patients with CD4 <100

Screen positive → antifungals
Start ART at a safe interval & continue antifungals
Screen negative → start ART immediately

Screen & treat saves lives
28% ↓ in all-cause mortality

CrAg screening approaches

Reflex laboratory

Visit 1 Blood draw for baseline CD4
Lab Blood tested for CrAg if CD4 <100
Visit 2 Return for CD4 and CrAg result

Provider laboratory

Visit 1 Blood draw for baseline CD4
Lab Return for CD4
Visit 2 Return for CD4
Lab Blood draw for CrAg
Visit 3 Return for CrAg result
CrAg screening approaches

Point-of-care CrAg with laboratory CD4

Visit 1
Blood draw for CD4 count

Lab

Visit 2
Return for CD4 result and test for CrAg

Point-of-care CD4 and CrAg

Visit 1
POC test for CD4 count → POC CrAg test if CD4 <100

Rapid adoption of intervention in SA

WHO recommended
Teamwork

Burden and mortality
Seed funding

Lab infrastructure

Provider laboratory screening

9192 patients with CD4 count <100

2872 with CD4 done at a hospital

899 with CD4 done at a Cape Town clinic

1356 with prior CM or prevalent CM

1795 already on ART

4395 eligible patients

Only 27% screened 2.1% CLAT-positive

Reflex laboratory screening

53 241 patients with CD4 count <100

>95% screened 3.7% CrAg LFA-positive

Higher screening costs  Lower treatment costs  Saves more lives

Lower screening costs  Higher treatment costs  Saves fewer lives

Reflex vs. provider lab screening?
Cryptococcal antigen screening when CD4+ T-lymphocyte count <100 cells/µl

- Initiate ART
- No fluconazole

A lumbar puncture may be considered if available.

Special situations include:

- Prior cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

Symptomatic for meningitis if either of the following is present:

1. Headache
2. Confusion

Start fluconazole 1200 mg daily and refer immediately for lumbar puncture

Lumbar puncture (+) POSITIVE

- Contact patient for urgent follow-up
- Screen for symptoms of meningitis
- Check for special situations

Lumbar puncture (-)

Operational barriers to screen & treat

Continuum of HIV care

AmB plus SFC is the most rapidly fungicidal regimen

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1. Earlier detection
2. First-line antifungal treatment
3. Adjunctive treatment
**AmB plus 5FC: ~40% ↓ mortality**


**Confirmed superior rate of fungal clearance**


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### Antifungal regimens

<table>
<thead>
<tr>
<th>Agents available</th>
<th>Toxicity prevention package</th>
<th>Induction (2 weeks)</th>
<th>Consolidation (8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B combination</td>
<td>Available</td>
<td>Ampho B + flucytosine [Strong/High]</td>
<td>Fluconazole 400-800 mg [Strong/Low]</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Not available</td>
<td>Ampho B + fluconazole [Short course] [Conditional/Low]</td>
<td>Fluconazole 800 mg</td>
</tr>
<tr>
<td>No amphotericin B</td>
<td>Not available</td>
<td>Fluconazole ± flucytosine [1200 mg] [Conditional/Low]</td>
<td>Fluconazole 800 mg</td>
</tr>
</tbody>
</table>

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### Advancing Cryptococcal meningitis Treatment for Africa (ACTA)

A phase III, randomised, controlled trial for the treatment of HIV-associated cryptococcal meningitis:

1. Fluconazole plus flucytosine for 2 weeks
2. Amphotericin B plus EITHER fluconazole OR flucytosine for 7 days
3. Amphotericin B plus EITHER fluconazole OR flucytosine for 14 days

Malawi, Zambia, Cameroon and Tanzania
target: 680 patients

ISRCTN45035509; DOI 10.1186/ISRCTN45035509

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### Manage amphotericin B deoxycholate toxicities

30% nephrotoxicity
~40% hypokalaemia

Meiring ST, et al. Submitted

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### ...and facilitate access to lipid formulations of amphotericin B

Near future: Second-line agent for those with renal dysfunction
Future: Short-course induction treatment (Jarvis JN. Ambition-CM trial)
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Raised pressure must be managed

- If opening pressure is >25 cm H₂O, remove 10-30 ml CSF to reduce pressure by at least 50% or to <20 cm H₂O
- Repeat LP whenever there are symptoms or signs of RICP
- Daily therapeutic LPs may be required

...one drop of CSF at a time?

Adjunctive dexamethasone is harmful

Adjunctive interferon-γ is promising

Adjunctive sertraline is also promising

Jarvis JN, et al. AIDS 2012
Summary

• Cryptococcal meningitis is a devastating opportunistic infection which is still an issue in 2016

• We have new strategies to detect cryptococcal disease earlier and manage meningitis more aggressively

• Renewed hope to improve patient outcomes if properly implemented

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