



Diagnosing HIV-associated cryptococcal meningitis

Which clinical features to look for?

Training module structure



- ▶ This training module is organised into 7 sections which can be accessed individually.
- ▶ This is section 4: **Diagnosing HIV-associated cryptococcal meningitis**
- ▶ It is recommended to complete all sections and access them sequentially from 1 to 7.
- ▶ All references and acknowledgments can be found in the notes section of each slide as well as more information and external links to resources.



Differential diagnoses

- ▶ TB meningitis is the most common – see TBM module
- ▶ Cerebral Malaria
- ▶ Meningoencephalitis caused by other organisms (mycobacterial, viral, bacterial, *Toxoplasma gondii*, neurosyphilis etc.) – See other modules for details.
- ▶ Space-occupying lesions (lymphoma, *T. gondii*, abscess, etc.)
- ▶ HIV encephalopathy
- ▶ Other conditions (toxic, metabolic, autoimmune, intracranial bleed, etc.)



CSF parameters

Please see lumbar puncture (LP) workshop for symptoms and signs and initial routine laboratory test results for HIV-associated meningo-encephalitis.

CSF samples for PLHIV presenting with meningo-encephalitis need a basic CSF analysis with WCC and differential, CSF protein and glucose.

- ▶ CSF opening pressure not useful to distinguish meningitis cause but often elevated in CM patients (can be normal).
- ▶ Total CSF white cell count is of limited use for immunocompromised (HIV+) patients – it may be below 10 cells/ μ L or 10-500 cells/ μ L.
- ▶ CSF glucose levels may be normal or low.
- ▶ CSF protein levels may be normal or slightly elevated.

Diagnostic methods



CrAg LFA

- ▷ Cryptococcal antigen Lateral Flow Assay
- ▷ High specificity (99%) and sensitivity (99%)
- ▷ Rapid (10 mins)
- ▷ Easy to perform
- ▷ Assays include: FDA-approved IMMY & semi-quantitative CE marked Biosynex CryptoPS

India Ink stain (microscopy)

- ▷ Performed on CSF
- ▷ High specificity
- ▷ Low Sensitivity (60-80%)

Culture - Gold standard

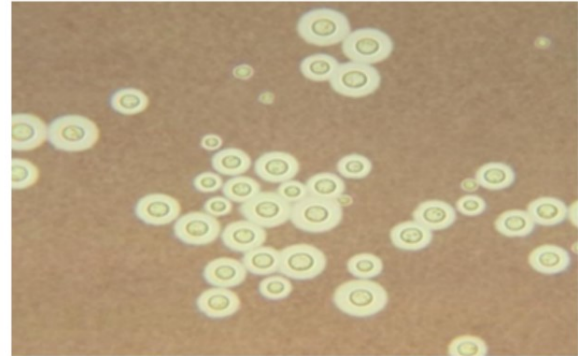
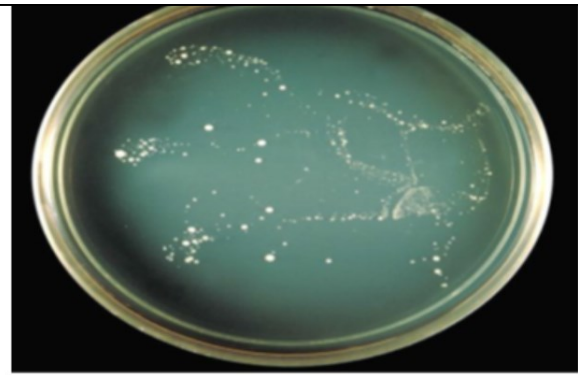
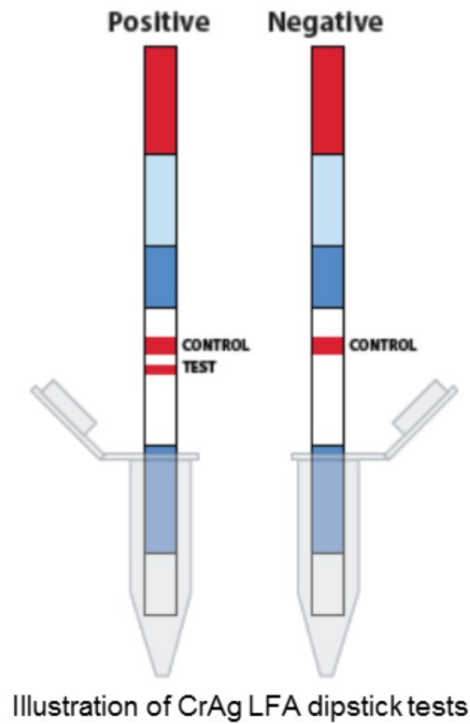
- ▷ Can only grow if you have live organism
- ▷ Positive within 72 hours
- ▷ CSF should be cultured for fungi using Sabouraud medium, for:
 - 5 days at 30°C to 35°C in aerobic conditions (for 1st episode)
 - 14-21 days if relapse episode.

CrAg LFA may also pick up dead yeast. Can be used to test blood and cerebrospinal fluid (CSF). The CrAg LFA result may remain positive up to a year following the initial diagnosis of cryptococcal meningitis.

India Ink performed is performed by a laboratory technician. The background is stained (negative stain) and the yeasts with the recognisable large capsules become visible. But it is technician dependant and you can get false positives if you confuse it with candida (more oval) or artifacts (bubbles). Centrifuging the CSF specimen can improve the sensitivity. Dead yeast cells after appropriate antifungal treatment can remain in the CSF and cause false-positive results despite a negative culture.

Fungal culture should ideally be performed at baseline (to confirm the diagnosis) and at any relapse (to ascertain if culture positive and- if available- test for resistance. Consider performing fungal culture at the end of the induction period of treatment to determine culture negativity.

CrAg LFA,
Culture, and
India Ink



CrAg image courtesy of IMMY 2701 Corporate Centre Dr Norman, OK 73069 USA

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A positive
CrAg LFA test



DREAMM project training, Malawi, November 2017. Image courtesy of EDCTP.

Biosynex
semi –
quantitative
CrAg LFA



DREAMM project training, Malawi, November 2017. Image courtesy of EDCTP

CE marked Biosynex CryptoPS (Biosynex, Strasbourg, France) allows detection of high or low CrAg titres by T1 or T2 bands on test cassette.

Culture media
preparation
and India Ink
staining



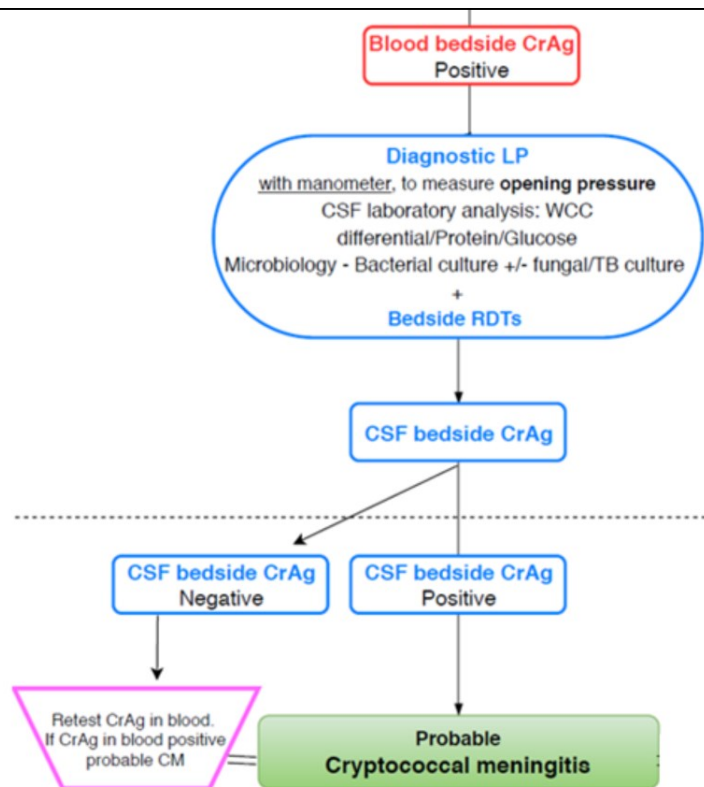
DREAMM project training, Dar Es Salaam, August 2017. Fungal culture media preparation and India ink staining. Images courtesy of Robert Harris, St George's University of London,



Diagnosis of CCM using the DREAMM algorithm

- ▶ The blood and CSF of all DREAMM patients will be tested for cryptococcal antigen (CrAg) using the CrAg LFA.
- ▶ Patients with a positive CrAg LFA result will have the CSF opening pressure routinely measured using a manometer in order to identify and manage raised intracranial pressure, a common complication of cryptococcal meningitis (refer to appropriate slides on raised intracranial pressure).
- ▶ Raised intracranial pressure needs to be managed aggressively with repeated therapeutic LPs.
- ▶ Fungal culture will be performed on all DREAMM patients as this is the gold standard for diagnosis.

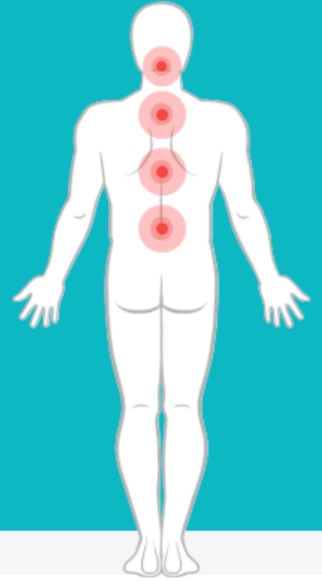
LP: Lumbar puncture CSF: Cerebrospinal fluid



A portion of the DREAMM Diagnostic and Management Algorithm is shown highlighting the diagnostic process for CCM when a patient presents with signs and symptoms compatible with HIV-associated meningo-encephalitis.

DREAMM Clinical Training

HIV-associated cryptococcal meningitis





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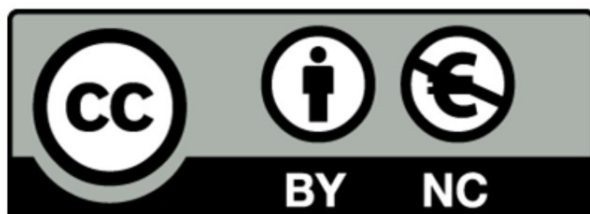
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Education programme topics

- ▷ General meningo-encephalitis patient management
- ▷ **Cryptococcal meningitis - CCM**
- ▷ Tuberculous meningitis – TBM
- ▷ Bacterial meningitis – BM
- ▷ Toxoplasmic encephalitis - Toxo
- ▷ Neurosyphilis – NS