A diagnostics approach to prevention of cryptococcal meningitis in the AIDS patient

Tom Kozel - UNRMed

Disclosure

- UNR has licensed the technology for the CrAg LFA to IMMY
- UNR receives royalty payments from IMMY
- T. Kozel receives a portion of the UNR royalty
**Cryptococcal infection**

- Caused by fungus *Cryptococcus* spp.
  - Found in soil, bird droppings
  - Trees in Pacific Northwest
- Spores are inhaled
- Incubation period unknown, can be dormant for many years
- Reactivation in immunosuppressed (HIV/AIDS) (CD4 <100)
- Meningitis most common form of infection
- No person-to-person transmission

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**Cryptococcal meningitis (CM)**

- Most common cause of meningitis in most of sub-Saharan Africa
- Estimated 15% of all AIDS-related deaths globally
- High mortality (approximately 50% in Africa)
- In developing countries, patients present with advanced disease
Global burden of HIV-related CM

~1 million new cases per year
and ~ 625,000 deaths per year


Causes of death in sub-Saharan Africa
(excluding HIV/AIDS)

How is *Cryptococcus* currently detected?

<table>
<thead>
<tr>
<th>MICROSCOPY¹</th>
<th>CULTURE²</th>
<th>ANTIGEN DETECTION³</th>
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| • India Ink staining  
  • Less sensitive  
  • Increased sensitivity with greater fungal burden | • Less sensitive  
  • Requires days to weeks for final results | • Unique polysaccharide capsule  
  • Present before symptom onset  
  • Highly sensitive and specific |


A new solution for detecting cryptococcal antigen (CrAg)

The new dipstick test (lateral flow assay or LFA) is:

- Simple and quick  
  *Results available in 10 minutes*
- Available  
  *FDA-approved*, *sold commercially*
- Accurate  
  *Highly sensitive and accurate (>95%)*
- Affordable  
  *$2/test*

*FDA-approved in serum. Validation ongoing in urine, whole blood, and plasma.*
CrAg at the Point-of-Care

Antigen is detectable in serum before clinical cryptococcal meningitis occurs

- Antigen tests (such as the LFA) can detect cryptococcal antigen in the blood a median of 22 days (range: 5-234) before symptom onset\(^1\)
- This makes it possible to identify cryptococcal disease early and prevent it from becoming meningitis

\(^1\) French \ et al. AIDS 2002
A new approach: ‘Screen and Treat’

- **Screen** a subset of HIV infected patients with a cryptococcal antigen test (CrAg) and **treat** only those with a positive test.
- Goal is to find people with early cryptococcal disease and **prevent** progression to meningitis through early treatment.

Pfizer’s Diflucan Partnership Program

- Since 2000, present in 63 countries in Africa, Asia, Latin America, & the Caribbean.
- Provides fluconazole free of charge to governments and NGOs.
- Countries with > 1% HIV and AIDS prevalence.
- Indications: cryptococcal meningitis and oesophagheal candidasis.
WHO recommendations for CrAg assay

- The diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children, March, 2018

- Diagnosis of symptomatic patient
  - Settings with access to LP: LP + rapid CSF CrAg assay
  - Settings with no access to LP: Rapid serum or plasma CrAg

- CrAg screening and preemptive treatment
  - CrAg screening prior to ART in patients with CD4 ≤ 100 cells/mm³
  - If positive, initiate preemptive anti-fungal treatment before ART
  - Recommended for all countries globally

- CrAg immunoassay on the first-ever WHO list of essential diagnostics (March, 2018)
Preventing Deaths Due to *Cryptococcus*

**Targeted screening: a cost-effective strategy**

One approach to prevent deaths is known as “targeted screening.” Research suggests that Cryptococcus is able to live in the body undetected, especially when a person’s immune system is weaker than normal. In a targeted screening program, HIV-infected patients are tested for cryptococcal antigen, an indicator of cryptococcal infection, before starting ART. A patient who tests positive for cryptococcal antigen can take oral fluconazole to help the body fight the early stage of the infection. This could prevent the infection from developing into meningitis.

**A simple new test for *Cryptococcus***

A new "dipstick" test for detecting cryptococcal antigen is simple to use on a small sample of serum (a component of blood). The test accurately detects both early and advanced cryptococcal infections more than 95% of the time. In addition, the test is inexpensive, and the results are ready in just 10 minutes. Using this test, targeted screening is a cost-effective approach to prevent deaths from cryptococcal meningitis.

**CDC’s response**

CDC is focusing its efforts on countries in sub-Saharan Africa and Southeast Asia, the areas with the highest number of deaths due to cryptococcal disease. In these regions, CDC is helping build laboratory capacity to reliably diagnose cryptococcal infections and is assisting with the implementation of targeted cryptococcal screening programs. In the future, it is hopeful that diagnostic tests will be available even in remote, rural areas.

CDC’s call to action is to equip half of all HIV clinics in Africa and Asia to perform cryptococcal screening and treatment, which could save 50,000 to 100,000 lives every year. Early identification of cryptococcal-infected patients in resource-limited settings may lead to more timely treatment, reduced mortality due to cryptococcal meningitis, and overall improved quality of life.