NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

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CENTRE FOR HEALTHCARE-ASSOCIATED INFECTIONS, AMR AND MYCOSES

Cryptococcosis
Frequently Asked Questions

1. What is cryptococcosis?

Cryptococcosis is a life-threatening fungal disease caused by pathogenic (disease-causing) species-complexes within the genus *Cryptococcus*, namely *Cryptococcus neoformans* and *Cryptococcus gattii*. Cryptococcosis is usually a severe opportunistic infection of individuals with defective T-cell mediated immunity although this disease can also occur among persons with no obvious immune deficiency. *Cryptococcus neoformans* is the most common cause of HIV-related adult meningoencephalitis in central and southern Africa, accounting for more than 60% of laboratory-confirmed cases. Thousands of cases are still diagnosed every year in South Africa. Pulmonary cryptococcosis is also an important disease manifestation (usually preceding meningitis) with one study reporting 7% prevalence in a group of South African miners (HIV prevalence of 24%). The pathogenic *Cryptococcus* species are abundant in the environment, e.g. in soil contaminated by pigeon droppings. Latent (dormant) infection occurs in almost all people who are exposed to *Cryptococcus*. However, with immune suppression, the fungus reactivates ("wakes up") and spreads to the brain, and sometimes other organs via the bloodstream. Following reactivation, meningitis is the most common manifestation of cryptococcal disease. Cryptococcosis remains a major cause of mortality in individuals living with HIV worldwide (second only to tuberculosis), despite the now widespread use of antiretroviral therapy (ART).

2. Who can get cryptococcosis?

The largest driver of cryptococcosis is defective T-cell mediated immunity, with HIV infection being a major risk factor, accounting for 95% of cases in middle and low-income countries. Individuals living with HIV are particularly at risk when their CD4 count drops to below 200 cells/µL, either because they have not started ART yet or have interrupted their ART. Individuals taking immunosuppressive drugs (including corticosteroids), solid organ transplant recipients, pregnant women and diabetics are also at risk of cryptococcal disease. People with apparently normal immune systems sometimes develop cryptococcosis.

3. How is cryptococcosis acquired?

The disease-causing fungi in the genus *Cryptococcus* are found worldwide in decaying organic matter, soil, bird droppings and associated with trees. Infection is acquired by inhalation of microscopic fungal "spores" from the environment. The incubation period is unknown and fungi may remain dormant in the lungs and other organs for many years. In immunosuppressed persons, particularly people with HIV and CD4 counts under 200, the fungus reactivates and spread throughout the body. There is no person-to-person transmission of this disease.

4. Does cryptococcosis affect animals?

Yes. Cryptococcosis is most common in cats but also is seen in dogs, cattle, horses, sheep, goats, birds, and wild animals, including marine mammals.

5. What are the signs and symptoms of cryptococcosis in humans?

Cryptococcus can affect several organs, but most patients seek healthcare with meningitis or brain involvement. Clinical presentation of patients with cryptococcosis may include:

- Symptoms and signs related to raised pressure inside the skull: headache, vomiting, confusion, altered level of consciousness, double vision (diplopia) and visual impairment
- Fever
- Signs associated with inflammation/ irritation of the lining of the brain: neck stiffness
- Symptoms of brain inflammation including memory loss and new-onset psychiatric symptoms
- Skin papules, pustules and nodules
- Lung involvement with no symptoms, or cough and sharp chest pain, shortness of breath progressing to severe pneumonia. Features on chest X-ray may include cavitation, infiltration and consolidation.

6. How is symptomatic cryptococcosis diagnosed?

There are various tests that can be performed to make a diagnosis of cryptococcosis.

- **India ink stain** of cerebrospinal fluid (CSF): A special stain called an India ink stain can be performed on CSF. Under the microscope, *Cryptococcus* appears as a round yeast surrounded by a large halo which is the capsule. The India ink test has a relatively poor sensitivity compared to culture. Therefore, a negative test does not exclude the diagnosis of cryptococcal meningitis.
- **Cryptococcal antigen (CrAg) detection tests**: CrAg, a component of the fungal capsule and a marker of active disease, is produced by *Cryptococcus.* Tests to detect CrAg can be performed on CSF and blood. Traditional older tests to detect CrAg include a latex agglutination test (CLAT) and an enzyme immunoassay (EIA). An improved test format is a lateral flow assay (LFA). This is a dipstick test with accuracy greater than 95%. It is also affordable and quick. Results are available within 10 minutes. CrAg tests (LFA, CLAT and EIA) remain positive in CSF or blood for weeks to months after cryptococcal meningitis has been treated.
- **Fungal culture** can be performed on any specimen including CSF, tissue, blood and sputum. Culture is the gold standard, i.e. provides a definitive diagnosis of cryptococcosis. However, fungal culture may take days to weeks for a result. Culture is the only means to diagnose relapse or recurrent disease.
- **Histopathology**: Tissue sections (of skin, lung, brain, etc.) can also be stained to identify fungal elements suggestive of *Cryptococcus* species

Lumbar puncture: A lumbar puncture (LP) is essential in order to confirm the diagnosis of cryptococcal meningitis (CM). A medical practitioner needs to ensure that there are no focal neurological signs before performing a LP. If there are focal neurological signs, a CT scan will be performed first to rule out a space-occupying lesion. CSF is usually sent to a lab for chemistry tests, microscopy (cell count, Gram stain, India Ink stain), cryptococcal antigen detection test, bacterial and fungal culture. Patients with CM often have raised intracranial pressure (ICP), which can lead to death if left untreated. Therefore, the opening CSF pressure needs to be recorded at the time of performing the LP. Normal CSF pressure is <20 cm H_2O. Patients with CM, who have raised ICP, require therapeutic lumbar

punctures to remove sufficient CSF to normalise the pressure. This leads to an improvement in symptoms related to raised ICP, including headache, confusion and vomiting.

7. How is symptomatic cryptococcal meningitis treated in HIV?

Induction phase	Preferred – Liposomal amphotericin B 10 mg/kg as a single IV infusion, then flucytosine 100 mg/kg in 4 divided doses orally plus fluconazole 1200 mg orally for 2 weeks Alternative - Amphotericin B deoxycholate 1 mg/kg/day IVI plus flucytosine 100 mg/kg in 4 divided doses orally for 1 week, then fluconazole 1200 mg orally for 1 week
Consolidation phase	Fluconazole 800 mg orally daily for 8 weeks
Maintenance phase	Fluconazole 200 mg orally daily , for at least 12 months

Management of raised ICP by therapeutic LPs

Alleviate pressure initially by draining CSF to decrease opening pressure at initial LP. Thereafter the need for pressure relief should be dictated by recurrence of symptoms of raised ICP. Some patients may require daily therapeutic lumbar punctures until the pressure normalises.

Pain and symptom management

Reduction of intracranial pressure alleviates headache and confusion. Residual pain may be managed with paracetamol and mild opiates. Non-steroidal anti-inflammatory agents should be avoided in patients receiving amphotericin B because concomitant administration may increase potential for kidney damage.

Initiation of ART in patients with cryptococcal meningitis

Patients who are diagnosed with CM receive at least 4 to 6 weeks of antifungal treatment, prior to the initiation of ART. If ART is initiated earlier, clinical worsening of cryptococcal disease can occur. This is referred to as the immune reconstitution inflammatory syndrome (IRIS), and can be life-threatening.

8. Can cryptococcosis be prevented or detected earlier?

Yes. CrAg can be detected in the blood weeks to months before symptoms of meningitis develop. The presence of CrAg in the blood is referred to as cryptococcal antigenaemia and is highly predictive of who will develop meningitis. Screening for CrAg in the blood, in patients at highest risk for cryptococcal meningitis, provides a window of opportunity to identify cryptococcal disease early and treat in order to prevent progression to meningitis. Adults with HIV considered to be at highest risk for cryptococcal meningitis are those with a CD4 count <200 cells/µl. Reflex CrAg laboratory screening is now performed at all NHLS CD4 laboratories across South Africa. This means that any CD4 count sample with a result of < 100 cells/µl will automatically have a CrAg LFA performed on the remaining blood sample. In some SA provinces, reflex screening is performed if the CD4 count is 100-200 cells/µl.

Management of patients with a positive screening CrAg test: These patients need to be contacted urgently for follow-up and a lumbar puncture to exclude meningitis. Asymptomatic patients are treated as indicated below. ART can be initiated after 2 weeks of antifungal therapy in asymptomatic CrAg-positive patients.

Induction phase	Fluconazole 1200 mg orally daily for 2 weeks
Consolidation phase	Fluconazole 800 mg orally daily for 8 weeks
Maintenance phase	Fluconazole 200 mg orally daily for at least 12 months

9. Where can I find more information?

Active surveillance for cryptococcosis is performed by NICD's GERMS-SA surveillance network. All cases (India ink or CrAg or culture positive cases) are detected by NICD using electronic laboratory information systems. NICD also actively monitors the national CrAg screening programme.

Additional information on cryptococcosis is available on the following website references:

For the public:

www.preventcrypto.org

www.life-worldwide.org/

For healthcare workers:

www.sahivsoc.org/

www.cdc.gov

www.who.int

https://www.idsociety.org/

www.gaffi.org/

www.preventcrypto.org

www.life-worldwide.org/

Contact the NICD hotline (+27 82 883 9920) after hours and in emergency situations (for healthcare professionals only)