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Cryptococcosis
Frequently Asked Questions

1. What is cryptococcosis?

Cryptococcosis is a life-threatening fungal disease caused by pathogenic species-complexes within the genus *Cryptococcus*, namely *Cryptococcus neoformans* and *Cryptococcus gattii*. Cryptococcosis is a severe opportunistic infection of individuals with impaired T-cell mediated immunity due to HIV infection or other causes. Rarely, cryptococcosis also occurs among persons with no obvious immune deficiency. The fungus, *Cryptococcus* is found worldwide in decaying organic matter, soil, bird droppings and associated with trees. 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. Cryptococcosis remains a major cause of mortality in HIV-infected individuals worldwide (second only to tuberculosis), despite the now widespread use of antiretroviral therapy (ART).

2. Who can get cryptococcosis?

The largest factor responsible for cryptococcosis is impaired T-cell mediated immunity. HIV infection is the most common reason for impaired T-cell immunity and accounts for 95% of cases in middle and low-income countries. HIV-infected individuals are particularly at risk when their CD4 count drops to below 200 cells/µL. Individuals taking immunosuppressive drugs (including corticosteroids), solid organ transplant recipients and diabetics are also at risk. People with apparently normal immune systems sometimes develop cryptococcosis.

3. Where does cryptococcosis occur in South Africa?

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 diagnosed every year in South Africa. Pulmonary (lung) cryptococcosis is also an important presentation and usually precedes meningitis.

4. How is cryptococcosis acquired?

Disease is acquired by inhalation of microscopic fungal spores from the environment. The incubation period is unknown and fungus may remain dormant in the lungs and other organs for many years. In immunosuppressed persons, particularly HIV-infected persons with CD4 counts under 200 cells/µL, the disease reactivates and spread throughout the body. There is no person-to-person transmission of this disease.

5. 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.

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

Cryptococcus can affect several organs, but most patients will present with meningitis or meningo-encephalitis (with or without neck stiffness). Symptoms and signs are: headache due to raised intracranial pressue, vomiting, confusion, altered level of consciousness, 6th cranial nerve palsies with double vision (diplopia) and visual impairment, swollen optic disk (papilloedema), fever, neck stiffness, memory loss and new-onset psychiatric symptoms, cutaneous lesions (e.g. papules, pustules and nodules), cough, pleuritic chest pain and/or dyspnea progressing to severe pneumonia with respiratory failure. Features on chest X-ray may include cavitation, infiltration and consolidation.

7. How is symptomatic cryptococcosis diagnosed?

Lumbar puncture 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 submitted for chemistry tests, microscopy (cell count, Gram stain, and India ink stain), cryptococcal antigen detection test, bacterial and fungal culture. There are various tests that can be performed to make a diagnosis of cryptococcosis. Using the **India ink stain** on cerebrospinal fluid (CSF) *Cryptococcus* appears as a round yeast form surrounded by a large halo which is the capsule. The India ink test has a relatively poor sensitivity. Therefore, a negative test does not exclude the diagnosis of cryptococcal meningitis. The **Cryptococcal antigen (CrAg) detection tests** detects a component of the fungal capsule and can be performed on CSF and blood using a latex agglutination test (CLAT) or an enzyme immunoassay (EIA) or the newer test - 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 for weeks to months after cryptococcal meningitis has been treated. **Fungal culture** is the gold standard and can be performed on any specimen including CSF, tissue, blood and sputum and provides a definitive diagnosis of cryptococcosis. However, fungal culture may take days to weeks. Culture is the only means to diagnose relapse or recurrent disease. **Histopathology** stains of tissue sections can also be used to identify fungal elements suggestive of *Cryptococcus* species. 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 H2O. 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.

8. How is symptomatic cryptococcal meningitis treated?

Induction phase (In-hospital): Amphotericin B 1 mg/kg/day IVI plus fluconazole 800 mg orally daily for 2 weeks. **Consolidation phase:** Fluconazole 400 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.

Management of patients with a positive screening CrAg test: These patients need to be contacted urgently for follow-up. Signs and symptoms of meningitis need to be excluded. Asymptomatic patients are treated by fluconazole 800 mg orally daily for 2 weeks during the induction phase; fluconazole 400 mg orally daily for 8 weeks during the consolidation phase and fluconazole 200 mg orally daily for at least 12 months during the maintenance phase. ART can be initiated after 2 weeks of antifungal therapy in asymptomatic CrAg-positive patients.

9. Can cryptococcosis be prevented or detected earlier?

Yes. CrAg can be detected in 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. HIV infected adults considered to be at highest risk for cryptococcal meningitis are those with a CD4 count <100 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.

10. Where can I find more information?

Medical/clinical related queries: NICD Hotline +27 82 883 9920 (for use by healthcare professionals only).
Results and laboratory inquiries: NICD Specimen Receiving Laboratory: +27 11 386 6404.
Guidelines and other documents: NICD website at www.nicd.ac.za under the 'Diseases A-Z' tab.