

# CRYPTOCOCCAL MENINGITIS

## Introduction

In most cases, cryptococcal meningitis is **caused by the fungus *Cryptococcus neoformans***. It is an encapsulated fungus.

This fungus is found in soil around the world.

*Cryptococcus gattii* and *grubii* can also cause meningitis, but this form can cause disease in patients with a normal immune system as well.

*This type of meningitis is not spread from person to person.*

Usually, it spreads through the bloodstream to the brain from another place in the body that has the infection.

*Cryptococcus neoformans* meningitis most often affects people with a weakened immune system, including people with:

- AIDS
- Cirrhosis (a type of liver disease)
- Diabetes
- Leukaemia
- Lymphoma
- Sarcoidosis
- Organ transplant recipients

Untreated, CM is fatal, especially in people with HIV or AIDS. According to the British Medical Bulletin, 10 to 30 percent of people with HIV-related CM die from the illness.

*The disease is rare in people who have a normal immune system and no long-term health problems are found in them.*

According to the U.S. Centres for Disease Control and Prevention (CDC) infections by *C. neoformans* occur yearly in about 0.4 to 1.3 cases per 100,000 people in the general healthy population.

## **Cryptococcus in those with normal immune function - IRIS**

- The immune reconstitution inflammatory syndrome (IRIS) has been described in those with normal immune function with meningitis caused by *C. gattii* and *C. grubii*.
- Several weeks or even months into appropriate treatment, there can be deterioration with worsening meningitis symptoms and progression or development of new neurological symptoms. IRIS is however much more common in those with poor immune function.
- Magnetic resonance imaging shows increase in the size of brain lesions, and CSF abnormalities (white cell count, protein, glucose) increase.
- Radiographic appearance of cryptococcal IRIS brain lesions can mimic that of toxoplasmosis with ring enhancing lesions on head computed tomography (CT).
- CSF culture is sterile, and there is no increase in CSF cryptococcal antigen titre.
- The increasing inflammation can cause brain injury or be fatal.
- The mechanism behind IRIS in cryptococcal meningitis is primarily immunologic.
- With reversal of immunosuppression, there is paradoxical increased inflammation as the recovering immune system recognises the fungus.
- *In severe IRIS cases, treatment with systemic corticosteroids has been utilized – although evidence-based data are lacking*

## **Symptoms of cryptococcal meningitis include:**

- Onset is often sub acute, progressively worsened over several weeks
- Headache.
- Fever.
- Blurred vision,
- Neck pain.
- Nausea and vomiting.
- Sensitivity to light.
- *Confusion or changes in behaviour.*
- Fatigue
- Dry cough

## **Diagnosis**

**Diagnosis of cryptococcal meningitis requires cerebrospinal fluid (CSF) culture, India ink, or antigen testing.(Crypto-LA)**

1. India ink. It's a common method of the CSF and is a traditional microscopic method of diagnosis, although the sensitivity is poor in early infection, and may miss 15–20% of patients with culture-positive cryptococcal meningitis.
2. CSF culture is considered the gold standard for diagnosis of cryptococcal meningitis

### **Other diagnostic tools.**

- Sputum and urine provides definitive diagnosis.
- Blood cultures may be positive in heavy infections.
- Unusual morphological forms are rarely seen.
- Cryptococcus antigen from cerebrospinal fluid is the best test for diagnosis of cryptococcal meningitis in terms of sensitivity.
- Apart from conventional methods of detection like direct microscopy and culture, rapid diagnostic methods to detect cryptococcal antigen by latex agglutination test, lateral flow immunochromatographic assay (LFA), or enzyme immunoassay (EIA) are being developed.
- A new cryptococcal antigen LFA was FDA approved in July 2011.
- Polymerase chain reaction (PCR) has been used on tissue specimens.

## **Complications**

If left untreated, CM may lead to more serious symptoms, such as:

- Brain damage
- Coma
- Hearing loss
- Hydrocephalus

## **Treatment**

Antifungal drugs are the hallmark of CM.

1] The most common choice is **Amphotericin-B** – daily intravenously (liposomal) - 1 mg/kg/day.

Monitoring closely while on this drug to watch for nephrotoxicity.

In HIV or immune-compromised, additional flucytosine ( 25 mg/kg 4 times per day) another antifungal medication, while amphotericin B, is required.

This combination helps treat the condition quicker.

Spinal fluid testing repeatedly during treatment is required.

If tests come back negative for CM for two weeks, amphotericin B and flucytosine may be stopped.

Then patients should be switched to taking only fluconazole for about eight weeks.

*Lifetime taking this medication helps prevent relapses.*

2] Fluconazole is more rapidly fungicidal when administered singly at a dosage of 1200 mg per day and better than 800 mg per day, in resource-limited settings like African countries where Amphotericin is too costly.

## **Types of Cryptococcal infections**

In humans, *C. neoformans* causes three types of infections

- Wound or cutaneous cryptococcosis
- Pulmonary cryptococcosis
- Cryptococcal meningitis.

## **Primary Cutaneous Cryptococcosis**

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Primary Cutaneous Cryptococcosis (PCC) is a distinct clinical diagnosis separate from the secondary cutaneous cryptococcosis that is spread from systemic infection.

- Males are more likely to develop the infection and a 2020 study showed that the sex bias may be due to a growth hormone, produced by *C. neoformans* called gibberellic acid (GA) that is up regulated by testosterone.
- The upper limbs account for a majority of infections.
- Isolates found in PCC include *Cryptococcus neoformans* (most common), *Cryptococcus gattii*, and *Cryptococcus laurentii*. Prognosis for PCC is generally good outside of disseminated infection
- Morphologic description of the lesions shows *umbilicated papules, nodules, and violaceous plaques that can mimic other cutaneous diseases like molluscum contagiosum and Kaposi's sarcoma.*
- These lesions may be present months before other signs of systemic infection in patients with AIDS.
- *Pigeon breeders (or fanciers) are known to have a high incidence of cryptococcal infections including PCC due to Cryptococcus' association with pigeon droppings.*

### **Pulmonary Cryptococcosis**

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Cryptococcus (both *C. neoformans* and *C. gattii*) plays a common role in pulmonary invasive mycosis seen in adults with HIV and other immune-compromised conditions.

It also affects healthy adults at a much lower frequency and severity as healthy hosts may have no or mild symptoms.

Immune-competent hosts may not seek or require treatment, but careful observation may be important.

Cryptococcal pneumonia has a potential to disseminate to the central nervous system (CNS) especially in immune-compromised individuals.

Pulmonary cryptococcosis has a worldwide distribution and is commonly underdiagnosed due to limitations in diagnostic capabilities.

Since pulmonary nodules are its most common radiological feature, it can clinically and radiologically mimic lung cancer, TB, and other pulmonary mycoses.

The sensitivity of cultures and the Cryptococcal antigen (Cryptola test) with lateral flow device on serum are rarely positive in the absence of disseminated disease.

Moreover, pulmonary cryptococcosis worsens the prognosis of cryptococcal meningitis.

### **Cryptococcal Meningitis**

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Cryptococcal meningitis (infection of the meninges, the tissue covering the brain) is believed to result from dissemination of the fungus from either an observed or unappreciated pulmonary infection.

Often there is also silent dissemination throughout the brain when meningitis is present.

*Cryptococcus gattii* causes infections in immunocompetent people (fully functioning immune system).

People with defects in their immunity, for example, people with AIDS, are especially susceptible to disseminated cryptococcosis.

Though the rate of infection is clearly higher with immunocompromised individuals, some studies suggest a higher mortality rate in patients with non-HIV cryptococcal meningitis secondary to the role of T-cell mediated reaction and injury.

### **Role of CDC**

CDC supports various activities to reduce illness and death from cryptococcal meningitis including:

- Working with health programs to introduce and implement cryptococcal screening and treatment

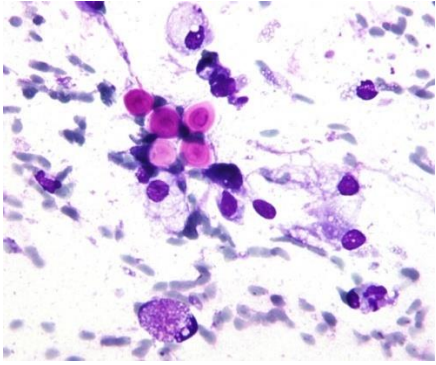
Helping health programs (training materials, help educate physicians, nurses, HIV/AIDS counsellors, pharmacists, and patients) about the diagnosis, management, and prevention of cryptococcal disease.

- assess costs and impact of cryptococcal screening activities
- Supporting training of clinical and laboratory staff on diagnosing, treating, and managing cryptococcal infection and cryptococcal meningitis
- Collaborating with partners to improve access to cryptococcal diagnostics and antifungal drugs

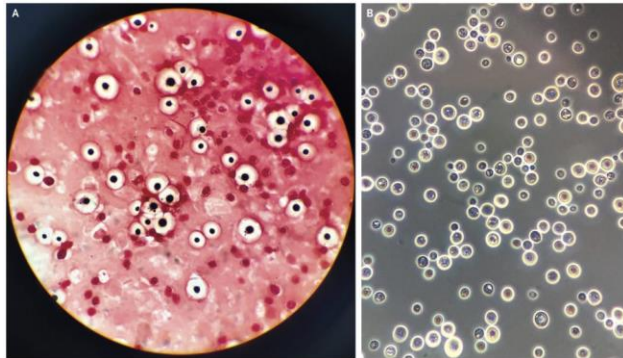
## Summary

Cryptococcal disease is an age old disease ,caused by a fungus, *Cryptococcus neoformans*. However as unlike involvement in immunocompetent individuals, it came into limelight as a important cause of morbidity and mortality after the advent of HIV –AIDS disease era.

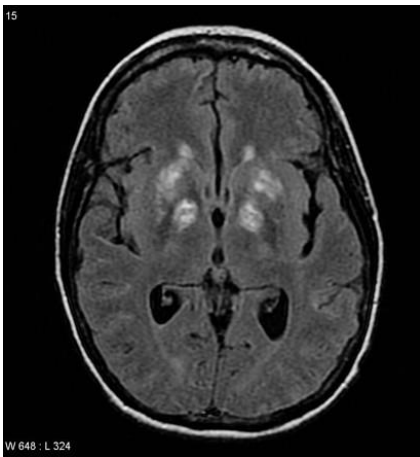
- It's far more common in people with HIV or AIDS patients in Sub-Saharan Africa, where people with this disease have a mortality rate that's estimated to be 50 to 70 percent.
- *Cryptococcus* (both *C. neoformans* and *C. gattii*) is the dominant and leading etiologic agent of meningitis in adults with HIV and is considered an "emerging" disease in healthy adults.
- Although the most common presentation of cryptococcosis is of *C. neoformans* infection in an immunocompromised person (such as persons living with AIDS), the *C. gattii* is being increasingly recognized as a pathogen in what is presumed to be immunocompetent hosts, especially in Canada and Australia.
- This may be due to rare exposure and high pathogenicity, or to unrecognized isolated defects in immunity, specific for this organism.
- Any person who is found to have cryptococcosis at a site outside of the central nervous system (e.g., pulmonary cryptococcosis), a lumbar puncture is indicated to evaluate the cerebrospinal fluid (CSF) for evidence of cryptococcal meningitis, even if they do not have signs or symptoms of CNS disease.
- CD4+ T cells have proven roles in the defense against *Cryptococcus*, but it can also contribute to clinical deterioration due its inflammatory response.
- CDC can also help provide customized resources on training and case studies for cryptococcal screening (discussed above).



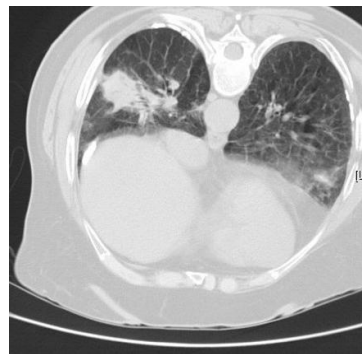
Microscopic picture of Cryptococcus



Microscopic picture of Cryptococcus



MRI in CNS cryptococcosis



CT in pulmonary cryptococcosis



Cutaneous cryptococcosis in HIV




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HIV does not make people dangerous to know, so you can shake their hands and give them a hug: Heaven knows they need it.


*-Princess Diana*

 Healthline



It's not the years in your life that count. It's the life in your years.

-Abe Lincoln

 Healthline