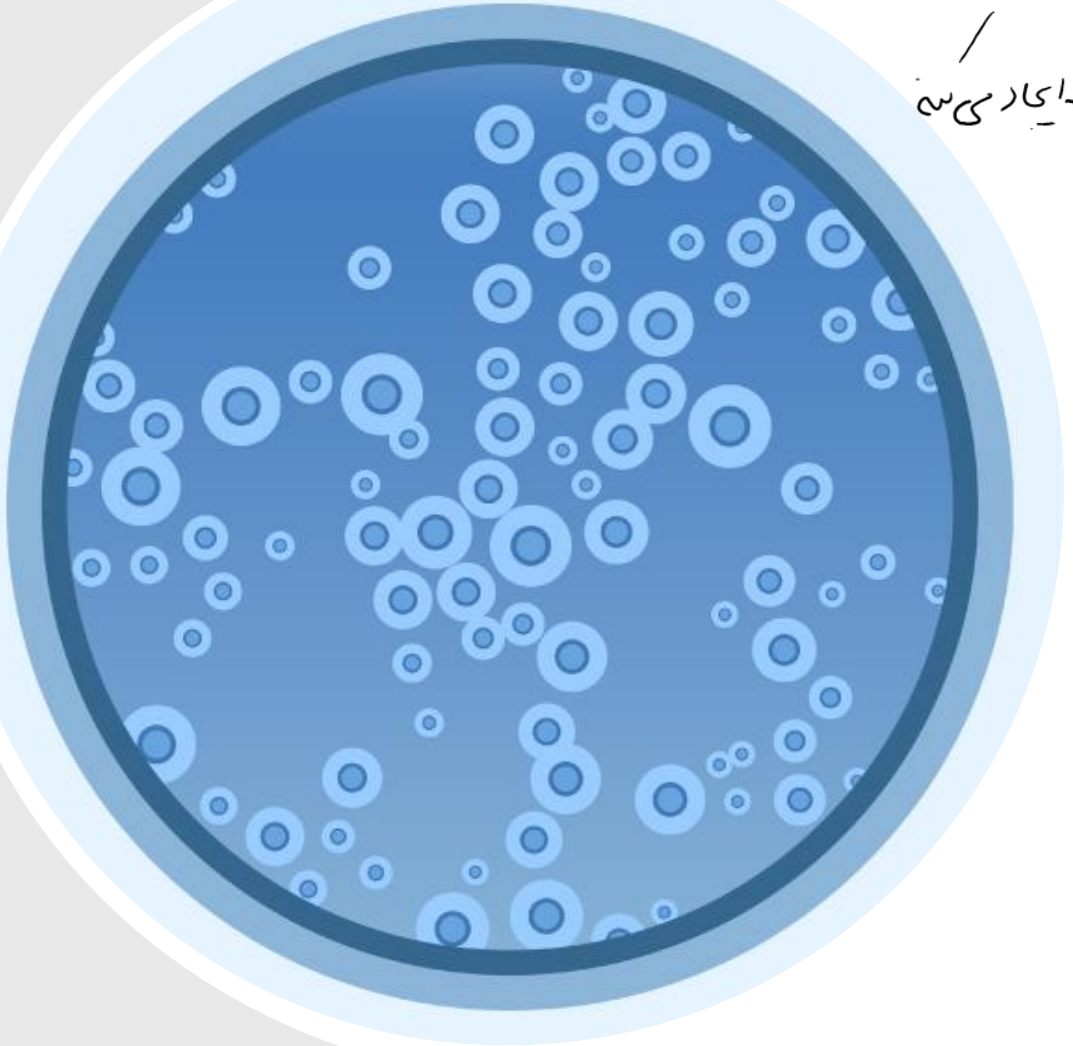


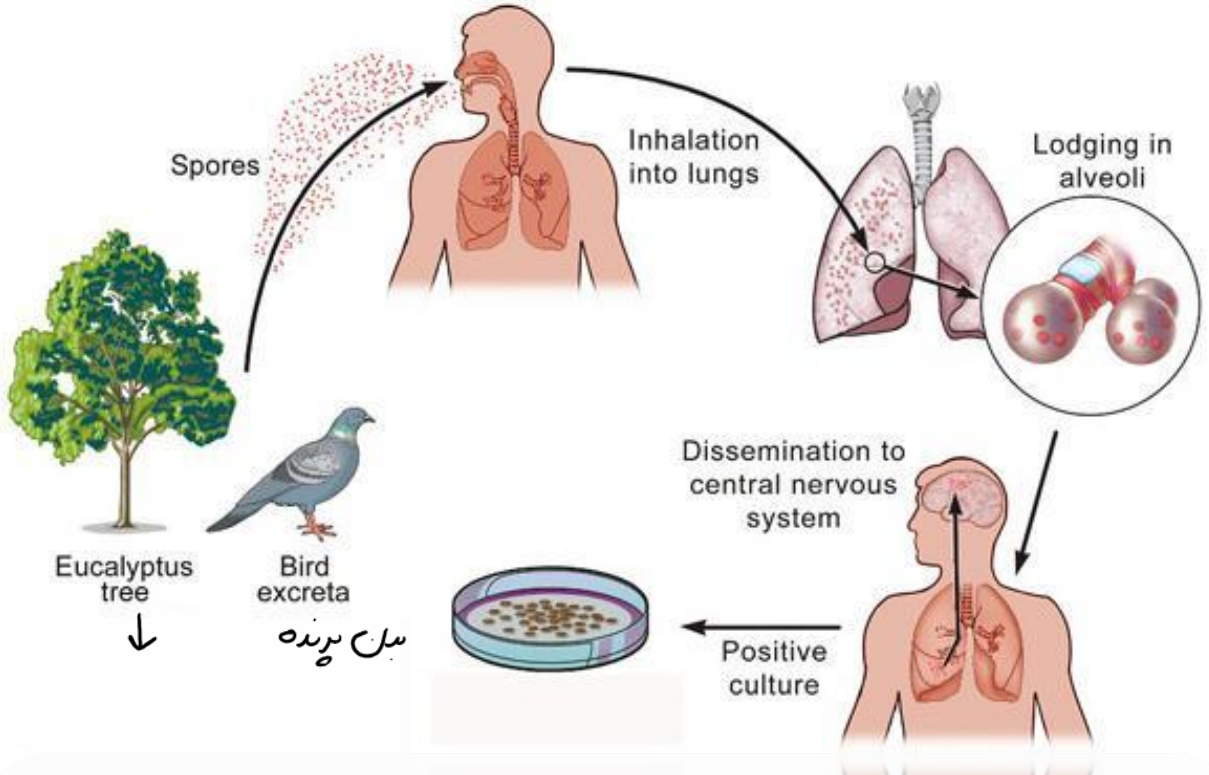
Cryptococcosis

Ali Ahmadi, Ph.D.

Department of Medical Parasitology and Mycology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Introduction

- Cryptococcosis is a systemic mycosis caused by inhalation of basidiospores of the *Cryptococcus* from the environment, found in soil and often associated with pigeon droppings, which develop into the pathogenic form in the body.
- Accounts for significant global morbidity/mortality; WHO lists *C. neoformans* as the top priority pathogen (2022).
- Highest burden in low/middle-income countries; mortality 24-47% at 10 weeks for cryptococcal meningitis (CM).
- Affects lungs, CNS, or any organ; major risk in PLHIV, transplant recipients, and other immunocompromised hosts (CDC 2024).



What fungi cause Cryptococcosis?

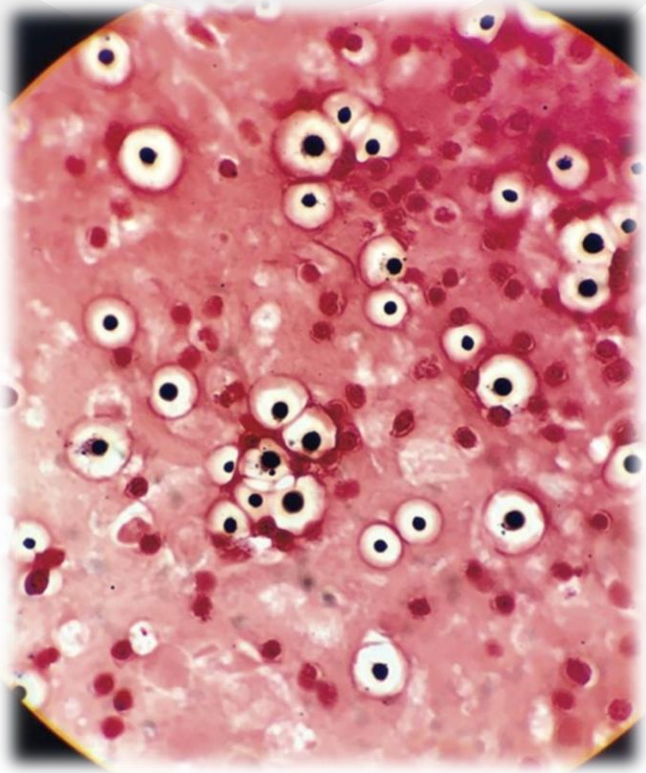
Cryptococcus is a basidiomycetous, encapsulated yeast genus that currently includes more than 70 recognized species, but only a few, grouped into the *C. neoformans* and *C. gattii* species complexes, are pathogenic to humans.

1. *C. neoformans* species complex

C. neoformans (VNI–VNB, serotype A) → سائع زین
C. deneoformans (VNIV, serotype D)
Hybrid (VNIII, serotype AD)

2. *C. gattii* species complex

C. gattii (VGI, serotypes B)
C. deuterogattii (VGIIa,b,c)
C. bacillisporus (VGIII)
C. tetragattii (VGIV, serotypes C)
C. decagattii

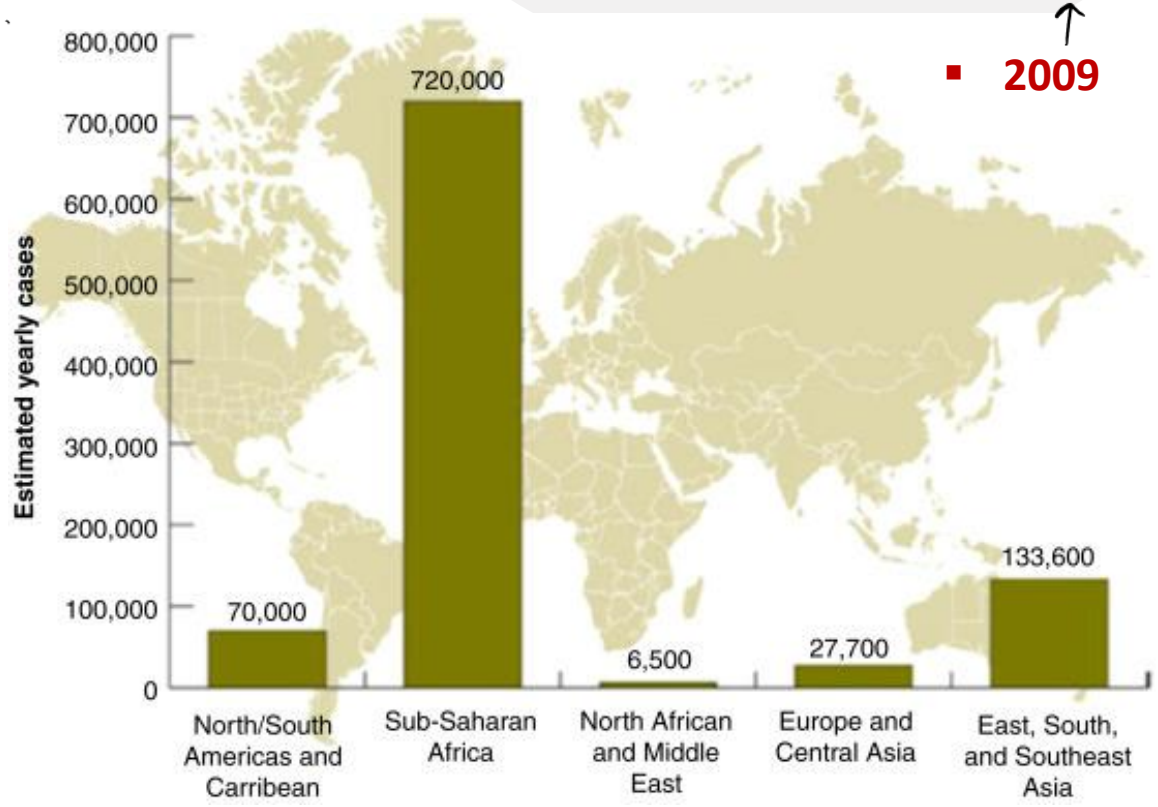


Comparison between *C. neoformans* and *C. gattii* Species Complexes

Feature	*C. neoformans* (Species Complex)	*C. gattii* (Species Complex)
Typical Host	Mainly **immunocompromised patients**, especially those with advanced HIV/AIDS or receiving immunosuppressive therapy.	Often infects **apparently healthy (immunocompetent)** individuals; can also affect immunosuppressed hosts.
Common Clinical Presentation	**Meningitis** is the most frequent form (CM); pulmonary infection may precede CNS disease.	**Pulmonary or CNS cryptococcomas** (mass-like lesions) are frequent; meningitis may occur but tends to be more chronic.
Geographical Distribution	**Worldwide**, with highest burden in Sub-Saharan Africa, India, China, and Brazil. Mostly linked to HIV-associated cases.	Found mainly in **tropical and subtropical** regions—Australia, Canada (Pacific Northwest), Brazil, India, and Africa.
Relative Frequency	**Most common cause** of human cryptococcosis; serotype A (VNI) accounts for ~80–86% of clinical isolates worldwide.	Represents about **11–33%** of cases depending on region (higher in tropical countries and specific outbreaks).
Environmental Sources	Associated with **pigeon droppings**, contaminated **soil**, and **urban environments**; thrives in nitrogen-rich substrates.	Associated with **decaying wood** (eucalyptus, almond, olive trees) and **humid environments**; isolated from soil, air, and trees.

Epidemiology

- Estimated ~152,000 cases of CM annually among PLHIV, causing ~112,000 deaths (majority 75% in sub-Saharan Africa).
- CM remains a leading cause of AIDS-related mortality despite ART expansion; screening and access to diagnostics/therapy are essential.
- Both humans and animals, including domestic dogs and cats, and native Australian animals such as the koala.
- Animal-to-human and human-to-human transmission has been documented rarely.
- The disease is uncommon in children, with a prevalence of 1% in children with AIDS.

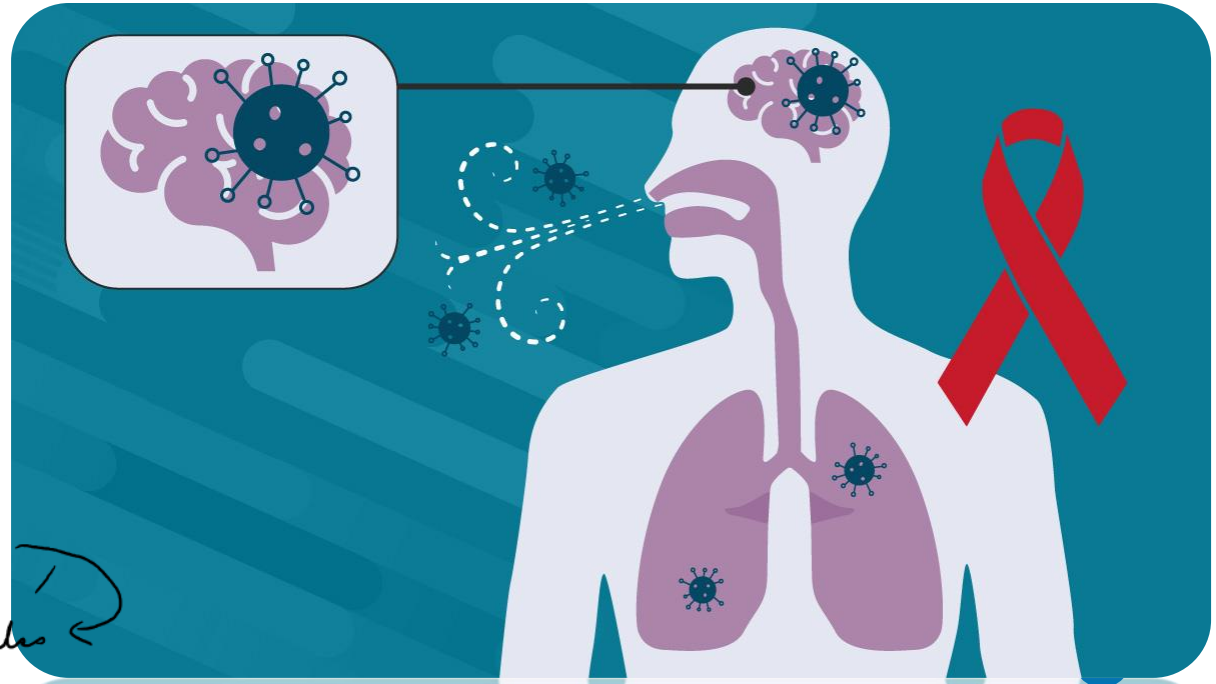


- 2009

+ ۲۰۰ ← HIV+
- ۲۰۰ ← Aids

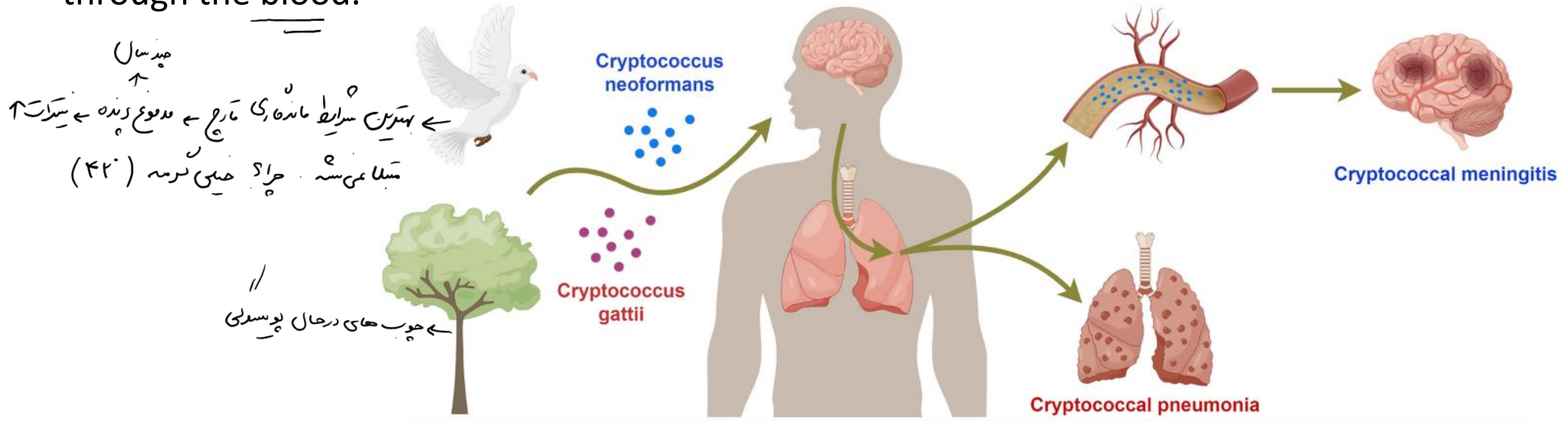
Risk groups

- PLHIV with low CD4 counts (especially <200 cells/µL, and risk increases sharply at <100 and <50).
- Solid-organ transplant recipients and other people receiving significant immunosuppression (steroids, anti-TNF, etc.).
- Occasionally immunocompetent hosts (esp. *C. gattii*).
- No major hereditary predisposition has been identified, but subtle innate immune defects (e.g., low mannose-binding lectin or Fcγ receptor polymorphisms) can influence susceptibility. Enhanced phagocytosis—by host or pathogen variation—may facilitate CNS spread ("Trojan Horse" mechanism).



Pathogenesis

- Infection begins after inhalation of airborne fungal particles (mainly basidiospores or small yeast cells).
- The particles reach the alveoli and are first encountered by alveolar macrophages.
- In healthy people, infection is usually mild or silent (often contained in lung).
- In immunocompromised patients (especially HIV), the fungus multiplies and may spread through the blood.



Pathogenesis

- Body tries to kill the fungus using macrophages and T cells, but the yeast has special defenses:

Virulence Factor	Simple Role
Capsule	Blocks phagocytosis and weakens immune response
Melanin	Protects the fungus from immune attack and oxidative stress
Phospholipase & Urease & Laccase	Help the fungus cross tissues and reach the brain
Ability to grow at 37°C	Allows survival inside the human body

- The yeast can travel through blood and cross the blood–brain barrier, sometimes inside macrophages ("Trojan horse" mechanism).
- In brain → causes meningitis or cryptococcomas (mass-like lesions).
- Severity depends on immune status and strain virulence.

Pathogenesis

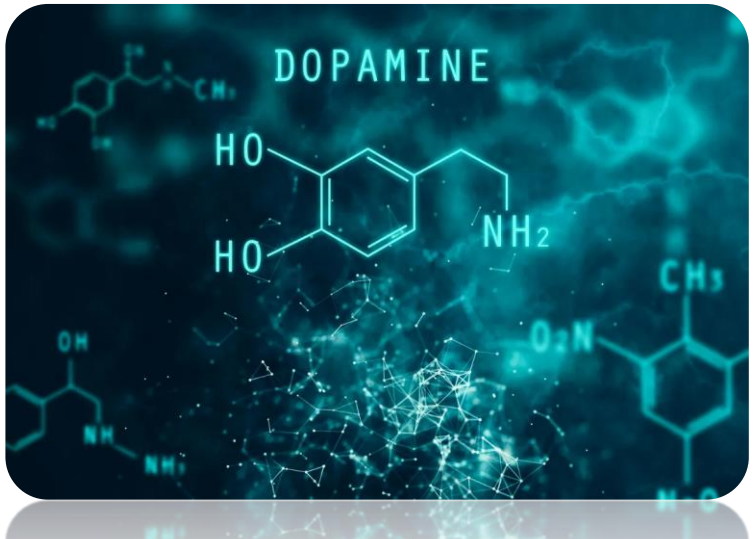
- BBB crossing:

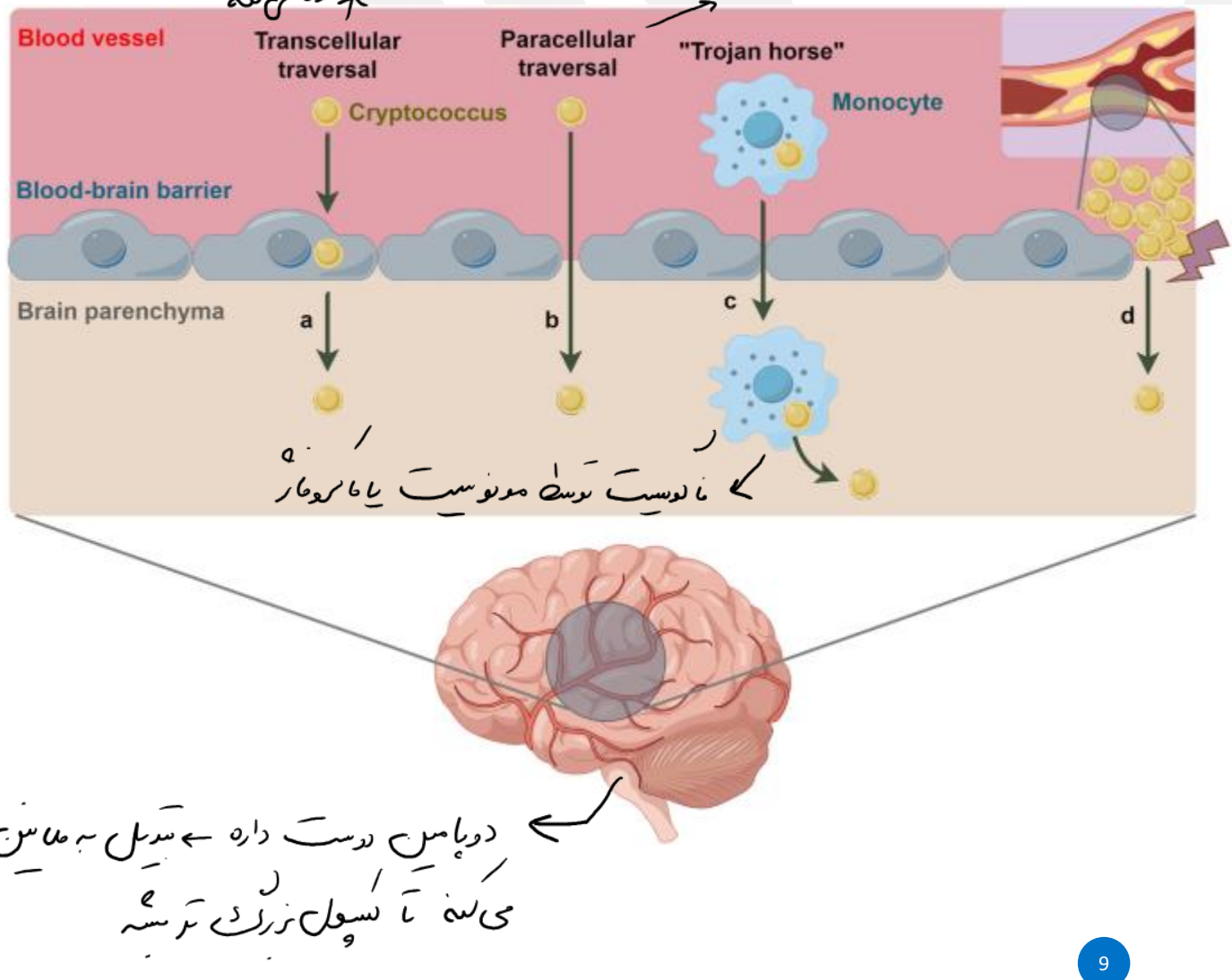
✓ Through endothelial cells (transcellular) – fungus passes through without major damage.

✓ Between cells (paracellular) – loosens cell junctions to pass.

✓ Trojan horse mechanism – monocytes carry the fungus across vessels.

❑ Outcome: Leads to meningitis or cryptococcoma.

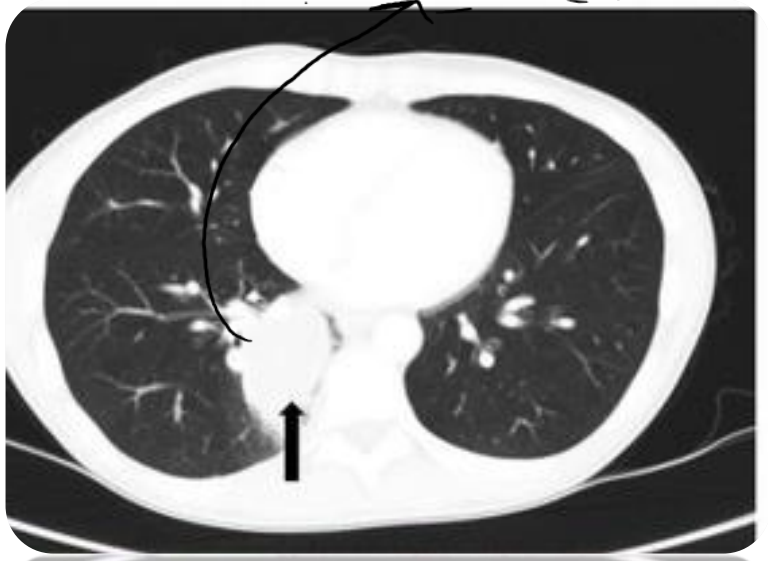




Pulmonary Cryptococcosis

Clinical Manifestations

- Usually, the first site of infection after inhalation.
- Asymptomatic or mild in most immunocompetent individuals.
- In immunocompetent hosts (esp. *C. gattii*):→ Localized nodule or mass (cryptococcoma), may mimic tumor on imaging.
- In immunocompromised hosts (esp. *C. neoformans*):→ Diffuse pneumonia or part of disseminated infection (often with CNS involvement).
- Symptoms: Cough, chest pain, fever, sometimes hemoptysis.
- Radiology: Solitary/multiple nodules, cavitation, or diffuse infiltrates.
- Note: Most pulmonary infections are self-limited, but dissemination risk increases when cell-mediated immunity is impaired.

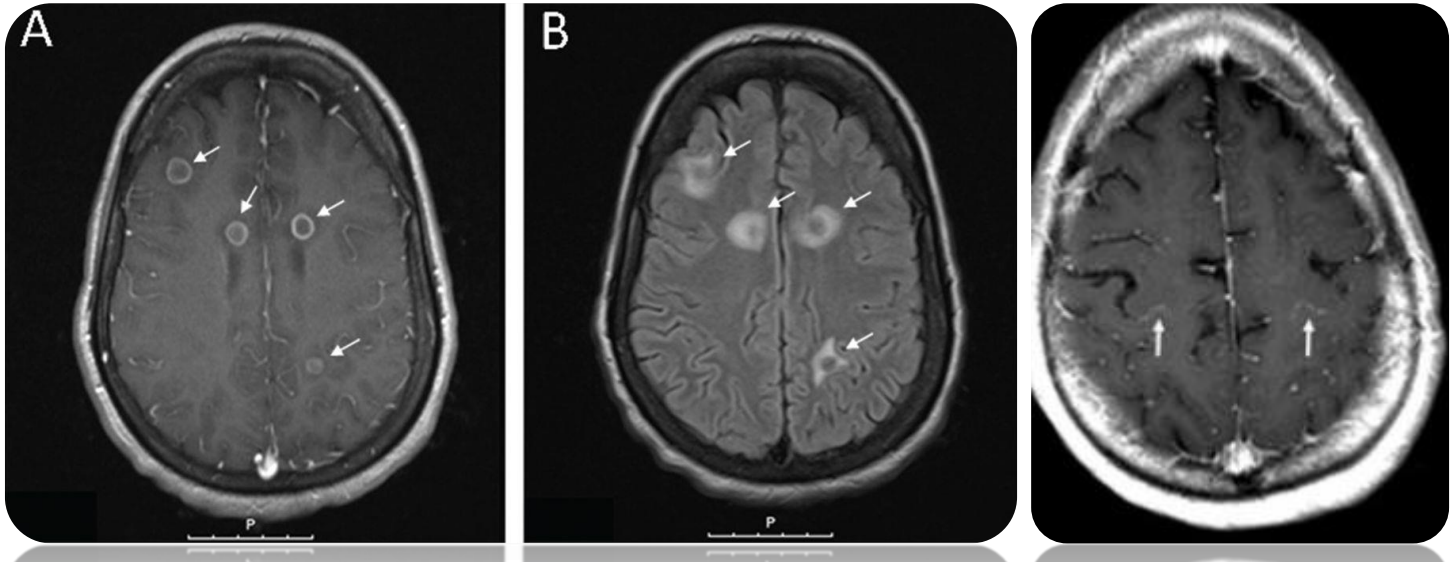


CNS Cryptococcosis

Clinical Manifestations

Form	Typical Host	Clinical Clues	Imaging	Pathology
Cryptococcal Meningitis (CM)	Immunocompromised (*C. neoformans*)	Gradual headache, fever, neck stiffness, confusion, ↑ICP, cranial nerve palsy	MRI: may show meningeal enhancement	Yeast cells in CSF; minimal granulomatous reaction
Cerebral Cryptococcoma	Immunocompetent (*C. gattii)*	Focal brain mass → seizures, focal deficits, visual changes, ↑ICP	MRI: ring-enhancing lesions with surrounding edema	Granulomatous inflammation filled with yeast cells

- In CNS cryptococcosis, *Cryptococcus* primarily causes meningitis.
- In rare cases, especially in severely immunocompromised patients, it can progress to meningoencephalitis.



Disseminated / Cutaneous / Other Sites

- Skin: papules, nodules, umbilicated lesions, violaceous nodular.
- Bone & joints: osteolytic lesions or arthritis (rare).
- Prostate, kidney, liver, spleen: possible reservoirs in disseminated disease.

معمولا
نادي شكل

Diagnosis

1.Clinical material:

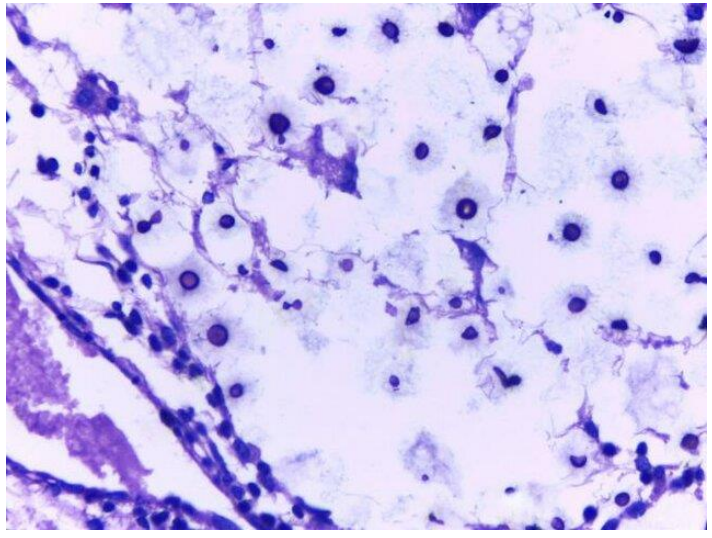
Cerebrospinal fluid (CSF), biopsy tissue, sputum, bronchial washings, BAL, blood, and urine.

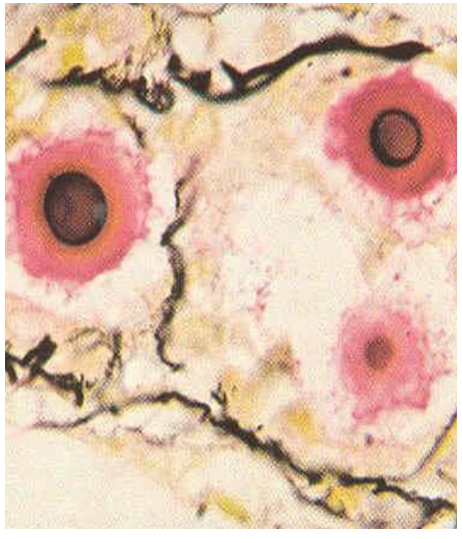
2. Direct Microscopy:

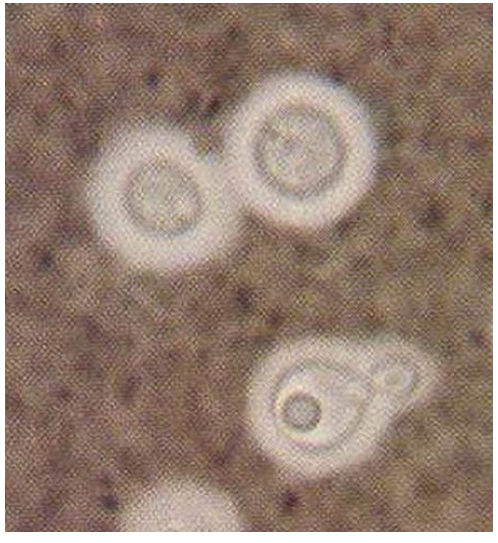
(A) For exudates and body fluids, make a thin wet film under a coverslip using **India ink**.

(B) Within tissue sections, **Mayer's mucicarmine** or Alcian blue stains the capsule of *Cryptococcus* species to distinguish it from other yeasts with similar morphologies.

Examine specimens for **globose to ovoid, budding yeast cells surrounded by wide gelatinous capsules.**

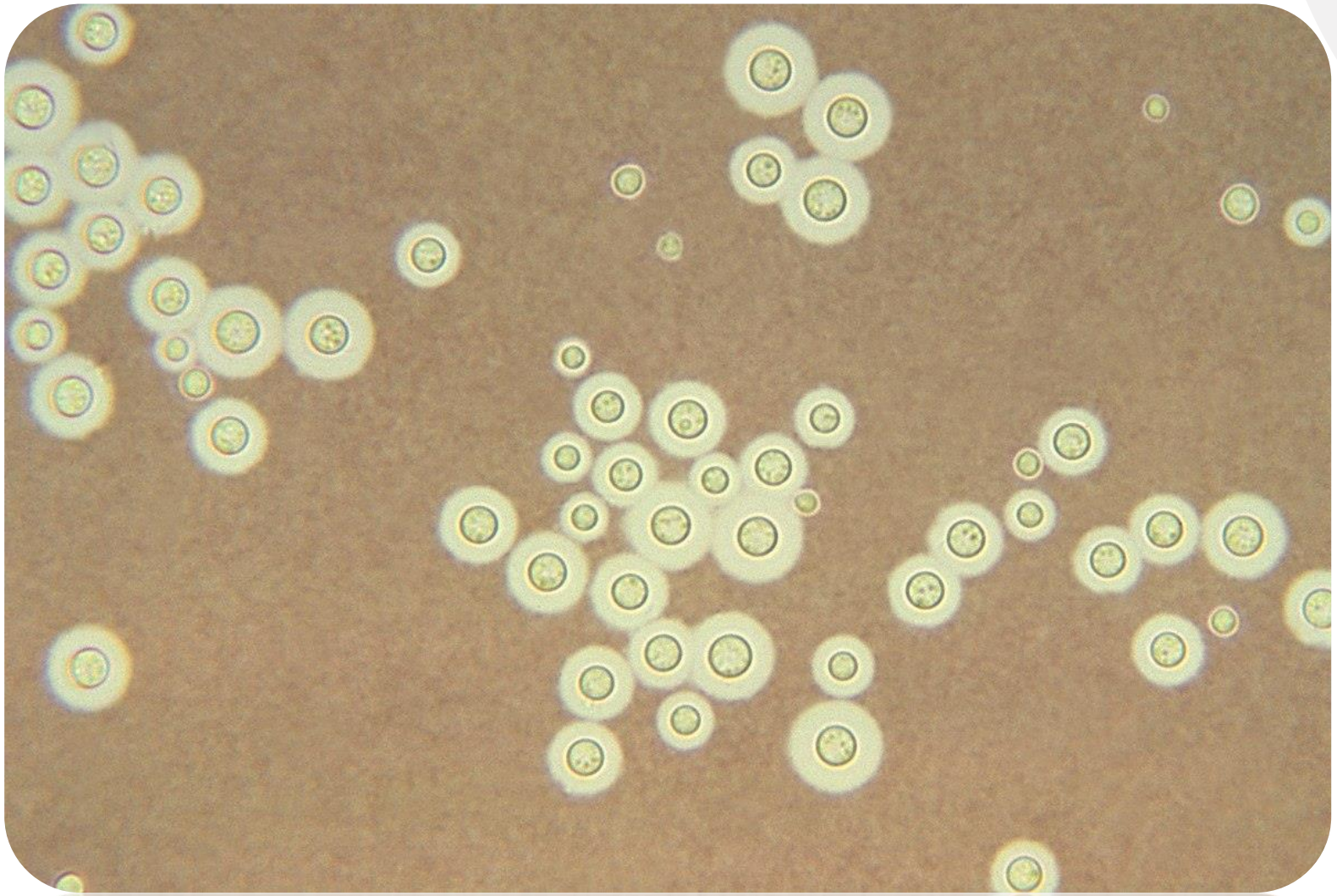






Diagnosis

The demonstration of encapsulated yeast cells in CSF, biopsy tissue, blood or urine should be considered **significant**.



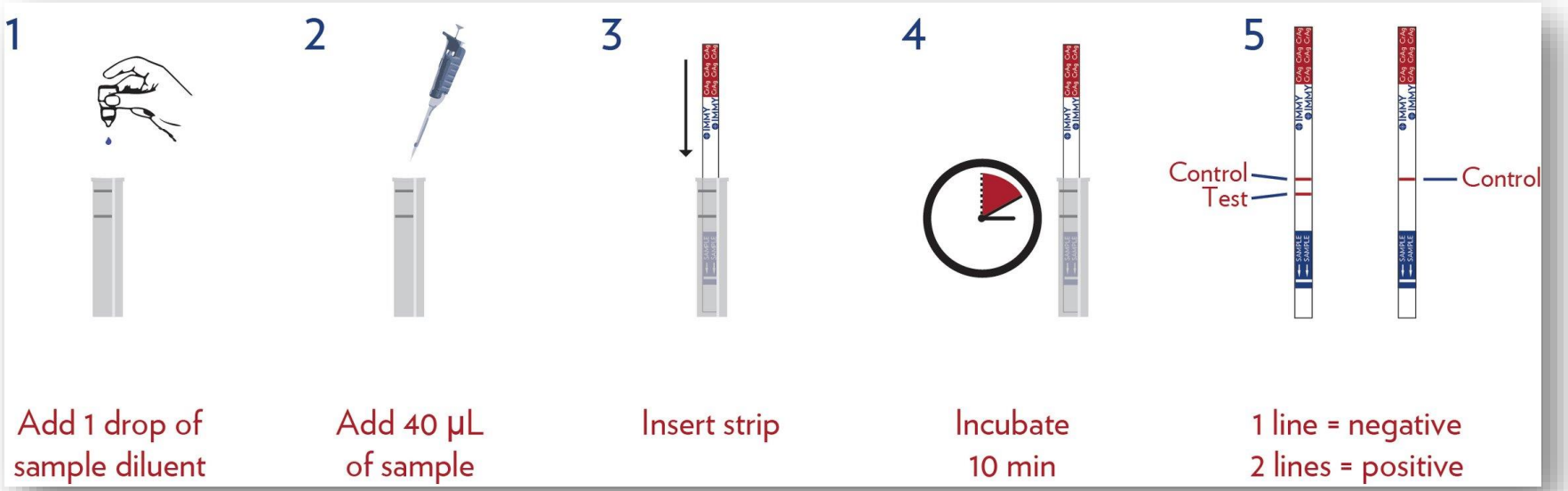
3. Culture (The Gold Standard)

Clinical specimens should be inoculated onto SDA.
Look for white to cream-colored, smooth, mucoid colonies.
The amount of mucoidness of the colonies is related to the thickness of the capsule.
Growth of *Cryptococcus* usually occurs in 36–72 h and is typically slower than that of *Candida* species under the same conditions.
C. neoformans grows at 37°C, whereas nonpathogenic species of *Cryptococcus* do not.
C. neoformans produces melanin, forming smooth brown colonies on birdseed (niger seed) agar.

4. Serology

Cryptococcal antigen (CrAg)

- Lateral flow assay (LFA) is the preferred point-of-care test for serum and CSF (high sensitivity and specificity).
- Serum CrAg positivity may precede symptoms.
- WHO recommends serum CrAg screening for adults and adolescents living with HIV with CD4 <200 cells/µL (priority for <100).
- In AIDS patients, CrAg can be detected in the serum in nearly 100% of cases.
- High CrAg titer associated with worse prognosis.

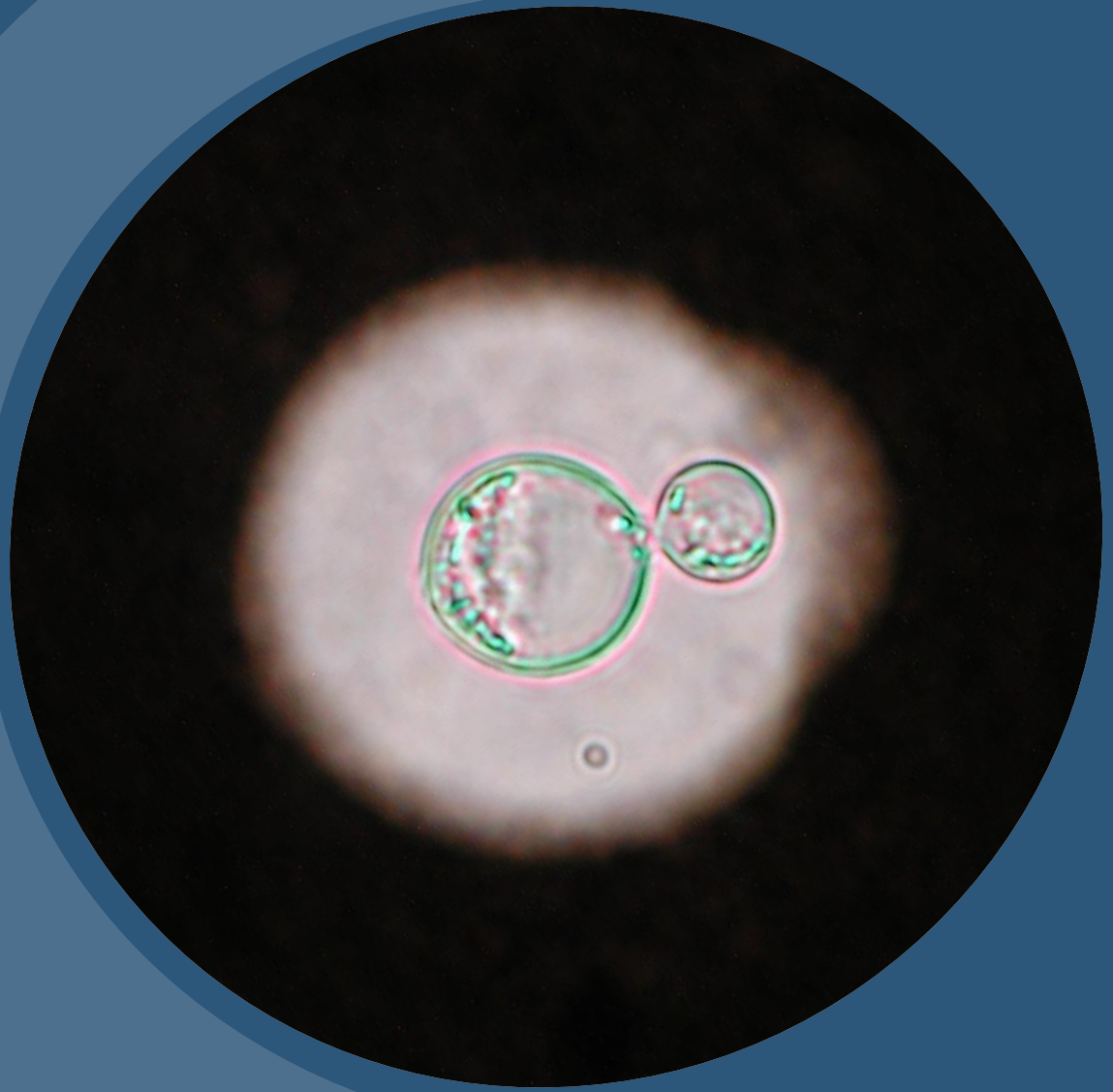


Based on the 2024 Global Guideline (Lancet Infect Dis)

Condition	Regimen, Dose	Duration	Evidence Level
CM - HIV (RRS)	L-AmB 3-4 mg/kg/day + 5-FC 100 mg/kg/day	1-2 weeks	AI
CM - HIV (RLS, AMBITION)	L-AmB 10 mg/kg (single) + 5-FC 100 mg/kg/day + Flu 1200 mg/day	2 weeks	BI
CM - HIV (RLS, limited access)	Amb-D 0.7-1 mg/kg/day + 5-FC 25 mg/kg QID	2 weeks	AI
CM - No 5-FC available	FLU 1200 mg/day	2 weeks	BI (high mortality)
Consolidation (post-induction)	FLU 400 mg/day	8 weeks	AI
Maintenance (relapse prevention)	FLU 200 mg/day	≥1 year (until CD4>200)	AI
Pre-emptive (Asymptomatic CrAg+ in PLHIV, CD4<200)	FLU 1200 mg/day → 800 mg/day → 200 mg/day	2 weeks → 8 weeks → 6 months	AIIu
CM - Non-HIV (e.g., SOT)	L-AmB 3-4 mg/kg/day + 5-FC 100 mg/kg/day	2 weeks	AI

Treatment

- Resistance: All Cryptococcus species are intrinsically resistant to echinocandins.
- Monitoring: Watch for renal/hepatic toxicity (e.g., with Amphotericin B) and Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV patients.
- Do not start ART within the first 2 weeks after CM induction therapy; typically delay ART initiation ~4–6 weeks to reduce risk of cryptococcal-IRIS and mortality.
- Therapeutic LPs (daily or as needed) to reduce pressure are first-line for symptomatic raised ICP (target reduction by ~50% or to <20 cm H_2O).
- *C. gattii* often causes mass lesions (cryptococcomas) requiring longer induction (often 4–6 weeks), sometimes combined medical + surgical management.



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