



## Overview

- Definition
  - Fungal infection caused by yeast *Cryptococcus* species, most commonly affecting the lungs and central nervous system (CNS)
    - C. neoformans* is most common, predominantly affecting immunosuppressed patients
    - C. gattii* is the second most common, predominantly affecting immunocompetent patients in tropical climates, but there have been clusters of cases in British Columbia, Canada, and in the American Pacific Northwest, as well as sporadic cases in other regions of the United States, Asia, Africa, Mexico, and South America
  - Ubiquitous in soil, decaying wood, and bird droppings; transmitted via inhalation of aerosolized fungus
  - Most common cause of fungal meningitis in immunocompromised hosts
  - Most common ocular fungal infection in HIV/AIDS patients
- Symptoms
  - Blurry vision
  - Floaters
  - Photophobia
  - Pain
  - Diplopia
- Laterality
  - Bilateral
- Course
  - Insidious onset with poor visual prognosis
  - Ocular disease often follows meningitis immediately via hematogenous dissemination or direct extension from leptomeninges

- Age of onset
  - Extremely rare in prepubescent patients
- Gender/race
  - More common in males, even before the AIDS epidemic
  - Worldwide distribution
- Systemic association
  - Pulmonary disease: may be asymptomatic, or presents like pneumonia with shortness of breath, cough, chest pain, and fever
  - Cryptococcal meningitis: intracranial hypertension, headaches, lethargy; altered mental status portends poor prognosis
  - Skin disease: typically reflects systemic infection/disseminated disease, but skin lesions may precede systemic symptoms by 2–8 months; range of skin lesions is broad, including molluscum contagiosum-like umbilicated papules; pustules; soft subcutaneous masses and ulcers
  - Hematogenous dissemination to the heart, liver, prostate, bone, and mucus membranes

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## Exam: Ocular

### Anterior Segment

Occurs if posterior segment infection is not treated promptly

- Conjunctival granulomas and injection
- Keratitis
- Scleral abscess
- Inflammatory iris masses with cells and flare, keratic precipitates, posterior synechiae

### Posterior Segment

- Focal or multifocal chorioretinitis with yellowish to white, elevated, subretinal lesions
- Significant vitritis with fluffy exudates
- Perivascular sheathing
- Subretinal lesions with localized serous retinal detachment

### Neuro-ophthalmological

- Papilledema
- Ocular motor palsies (sixth nerve most common)
- Facial nerve palsy

- Nystagmus
- Ptosis

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### Exam: Systemic

- CNS: fever (though not always present), mental status change, headache, memory loss, personality change, neck rigidity, photophobia, cranial nerve palsies; symptoms can be acute or subacute/chronic
- Skin: painless papules or pustules mostly on head and neck that become ulcerated; can have various appearances resembling acne, molluscum contagiosum, or even basal cell carcinoma
- Pulmonary: cough, tachypnea

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### Laboratory and Radiographic Testing

- Serum cryptococcal antigen
- Chest X-ray/computed tomography (CT)
- CNS imaging (CT or magnetic resonance imaging [MRI]) prior to LP if there is concern for increased intracranial pressure based on history/physical exam
- Lumbar puncture for measurement of opening pressure and cerebrospinal fluid (CSF) analysis; CSF often shows lymphocytosis but absolute numbers of white blood cells (WBCs) are often lower than for other types of meningitis (e.g., <50 cells/microliter), elevated protein, decreased glucose; Immunocompromised patients may have a normal CSF profile. Encapsulated yeasts can be seen on India ink smears in patients with high organism burden. CSF cryptococcal antigen testing yields a titer that informs about the fungal burden and prognosis
- Fungal culture of CSF, sputum, blood, and urine
- Fixed-tissue staining with calcofluor white and Grocott methenamine silver (GMS)

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### Differential Diagnosis

- *Pneumocystis* choroiditis
- Coccidioidomycosis (Valley fever)
- Toxoplasma retinochoroiditis
- Viral retinitis (HSV, VZV, CMV)
- Candidiasis
- Endogenous bacterial endophthalmitis
- Syphilis
- Tuberculosis
- Sarcoidosis
- Intraocular lymphoma

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## Treatment (Dosing Is for Patients with Normal Renal Function)

- Immunocompetent patients
  - Mild–moderate pulmonary or other localized disease without disseminated infection
    - PO fluconazole 400 mg/day for 6–12 months
  - More severe localized disease or meningitis
    - Amphotericin B 0.7–1.0 mg/kg intravenous (IV) qd (or liposomal amphotericin B 3–4 mg/kg IV qd) and PO flucytosine 25 mg/kg q6h for several weeks, then
    - PO fluconazole 400 mg/day
  - Meningitis/ocular disease
    - Amphotericin B 0.7–1.0 mg/kg IV qd (or liposomal amphotericin B 3–4 mg/kg IV qd) and PO flucytosine 25 mg/kg q6h for 2–4 weeks, then
    - PO fluconazole 400 mg/day for 8 weeks, then
    - PO fluconazole 200 mg/day for at least 6–12 months
- Patients with AIDS: all require treatment
  - Mild-to-moderate pulmonary disease
    - PO fluconazole 400 mg/day for 6–12 months
  - Meningitis/severe pulmonary disease/intraocular infection
    - Amphotericin B 0.7–1.0 mg/kg IV qd (or liposomal amphotericin B 3–4 mg/kg IV qd) and PO flucytosine 25 mg/kg q6h >2 weeks, then
    - PO fluconazole 400 mg/day for 10 weeks, then
    - Long-term maintenance therapy with PO fluconazole 200 mg/day for at least 1 year and until CD4 >100, with undetectable viral load on antiviral therapy for at least 3 months but must continue to monitor and restart if CD4 count falls to <100 cells/microliter and/or the serum cryptococcal antigen titers rise
- For severe ocular disease, PPV with intravitreal voriconazole 100 µg/0.1 ml should be performed

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## Referral/Co-management

- Infectious Disease
- Neurology/neurosurgery for patients with increased intracranial pressure, which is typically a very challenging problem that requires frequent LPs or lumbar/ventricular drains