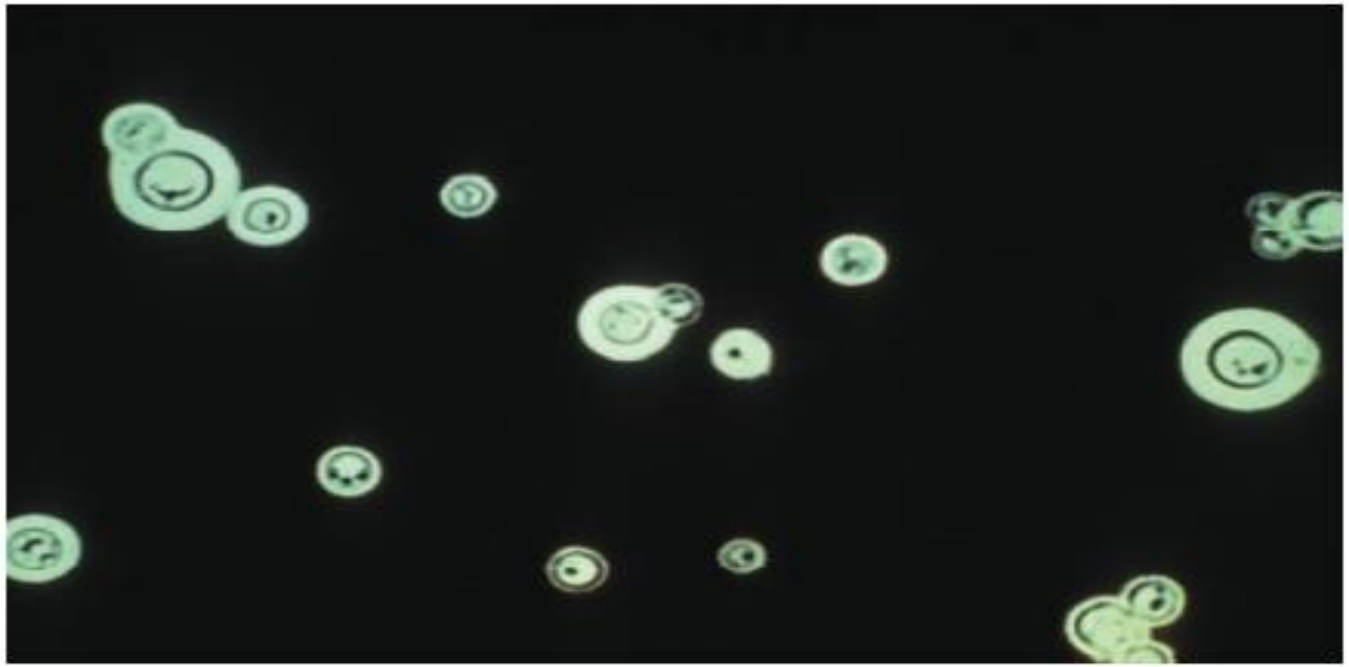
Cryptococcosis

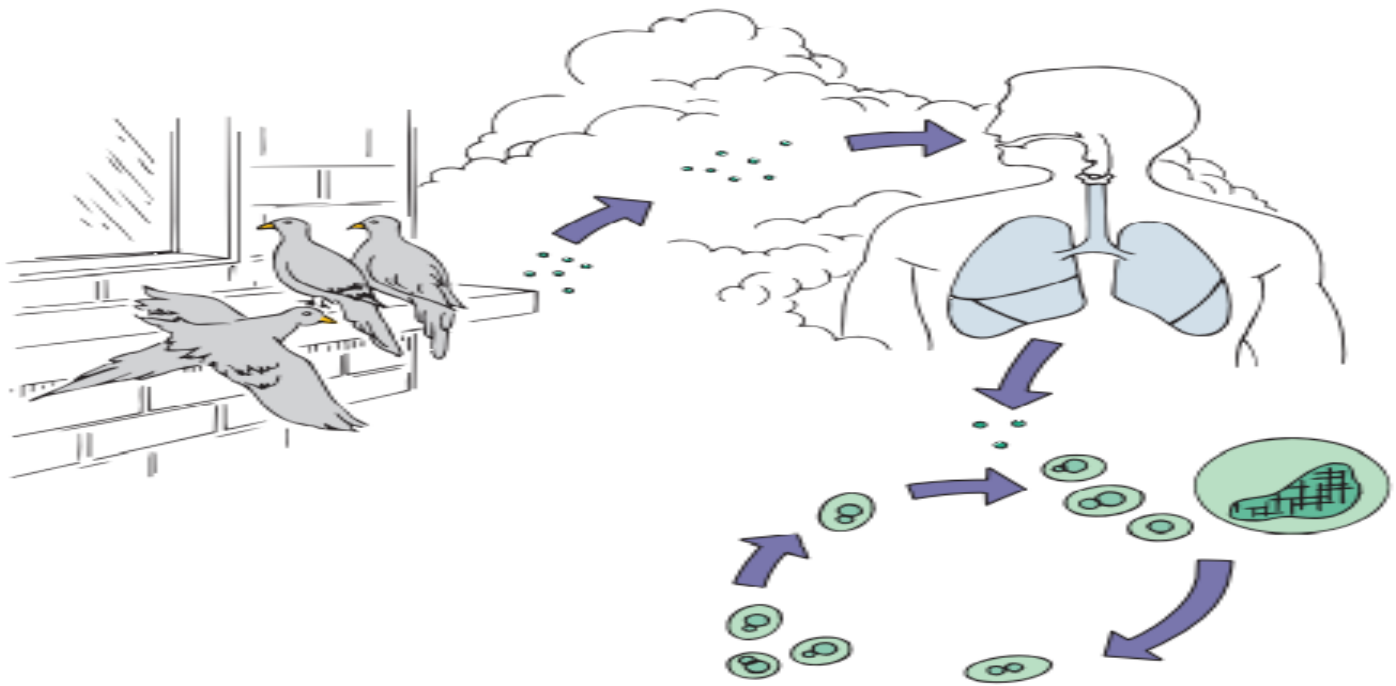
- Cryptococcosis is a systemic mycosis caused by the encapsulated, basidiomycetous, yeast like fungi *C. neoformans* and *C. gattii.*
- *C. neoformans* is worldwide in distribution and found as a ubiquitous saprophyte of soil, especially soil enriched with pigeon droppings.
- C. neoformans includes capsular serotypes A, D, and AD, and *C. gattii* includes serotypes B and C.
- *C. neoformans* is further divided into two varieties, var. grubii (serotype A) and var. neoformans (serotype D)

Morphology

- Microscopically, *C. neoformans and C. gattii* are spherical to oval, encapsulated, yeastlike organisms, 2 to 20 µm in diameter.
- Replication is by budding from a relatively narrow base. Single buds are usually formed, but multiple buds and chains of budding cells are sometimes present .
- Germ tubes, hyphae, and pseudohyphae are usually absent in clinical material.
- In tissue and upon staining with India ink, the cells are variable in size, spherical, oval, or elliptic, and are surrounded by optically clear, smoothly contoured, spherical zones or “halos” that represent the extracellular polysaccharide capsule The capsule is a distinctive marker that may have a diameter of up to five times that of the fungal cell.
- The cell wall of C. neoformans contains melanin, which may be demonstrated by staining with the Fontana-Masson stain.

Cryptococcus neoformans





Epidemiology

- *Cryptococcosis* is usually acquired by inhaling aerosolized cells of *C. neoformans and C. gattii* from the environment .
- Subsequent dissemination from the lungs, usually to the CNS, produces clinical disease in susceptible individuals.
- Although both *C. neoformans* and *C. gattii* are pathogenic for immunocompetent individuals, *C. neoformans* is most often encountered as an opportunistic pathogen. It is the most common cause of fungal meningitis and tends to occur in patients with defective cellular immunity.
- Whereas *C. neoformans* var. neoformans and var. grubii are found worldwide in association with soil contaminated with avian excreta, C. gattii is generally found in tropical and subtropical climates in association with eucalyptus trees.
- *C. neoformans* is a major opportunistic pathogen of patients with AIDS. Individuals with CD4+ lymphocyte counts of less than 200/mm^3 are at high risk for CNS and disseminated cryptococcosis.

Clinical Syndromes

- Cryptococcosis may present as a pneumonic process or more commonly as a CNS infection secondary to hematogenous and lymphatic spread from a primary pulmonary focus. Less often, a more widely disseminated infection may be seen with cutaneous, mucocutaneous, osseous, and visceral forms of the disease.
- Pulmonary cryptococcosis is variable in presentation, from an asymptomatic process to a more fulminant bilateral pneumonia. Nodular infiltrates may be either unilateral or bilateral, becoming more diffuse in severe infections.

- C. neoformans and C. gattii are highly neurotropic, and the most common form of disease is cerebromeningeal. The course of disease is variable and may be quite chronic; however, it is inevitably fatal if untreated.
- Both meninges and the underlying brain tissue are involved, and the clinical presentation is that of fever, headache, meningismus, visual disturbances, abnormal mental status, and seizures.
- The clinical picture is highly dependent upon the patient’s immune status and tends to be dramatically severe in AIDS patients and other severely compromised patients treated with steroids or other immunosuppressive agents.

- Parenchymal lesions (cryptococcomas) are uncommon in infections caused by C. neoformans but are the most common presentation of CNS cryptococcosis in immunocompetent hosts infected with *C. gattii*. Other manifestations of disseminated cryptococcosis include skin lesions, which occur in 10% to 15% of patients ; ocular infections, including chorioretinitis, vitritis, and ocular nerve invasion; osseous lesions involving the vertebrae and bony prominences; and prostatic involvement, which may be an asymptomatic reservoir of infection.

Laboratory Diagnosis

- The diagnosis of infection caused by *C. neoformans* and *C. gattii* may be made by culture of blood, cerebrospinal fluid (CSF), or other clinical material .
- Microscopic examination of CSF may reveal the characteristic encapsulated budding yeast cells.
- The cells of C. neoformans, when present in CSF or other clinical material, may be visualized with Gram stain , India ink , or other stains .
- Culture of clinical material on routine mycologic media will produce mucoid colonies composed of round, encapsulated, budding yeast cells that are urease positive within 3 to 5 days.
- Species identification may be accomplished by carbohydrate assimilation testing, by growth on niger seed agar (C. neoformans colonies become brown to black in color), or by directly testing for phenoloxidase activity (positive)

- Most commonly, however, the diagnosis of cryptococcal meningitis is made by direct detection of the capsular polysaccharide antigen in serum or CSF .
- Detection of cryptococcal antigen is accomplished by using one of several commercially available latex agglutination or enzyme immunoassay kits.
- polymerase chain reaction (PCR)

Treatment

- Cryptococcal meningitis (and other disseminated forms of cryptococcosis) is universally fatal if left untreated.
- In addition to prompt administration of appropriate antifungal therapy, effective management of CNS pressure and immune reconstitution inflammatory syndrome (IRIS) are crucial to successful treatment of cryptococcal meningitis.
- All patients should receive amphotericin B plus flucytosine acutely for 2 weeks (induction therapy), followed by 8-week consolidation with either oral fluconazole (preferred) or itraconazole. AIDS patients generally require lifelong maintenance therapy with either fluconazole or itraconazole. In non-AIDS patients, treatment may be discontinued after the consolidation therapy; however, relapse may be seen in up to 26% of these patients within 3 to 6 months after discontinuation of therapy. Thus a prolonged consolidation treatment with an azole for up to 1 year may be advisable even with patients without AIDS.