Opportunistic Systemic Mycoses - Cryptococcosis

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Cryptococcosis

Cryptococcosis is a chronic, subacute to acute pulmonary, systemic or meningitic disease, initiated by the inhalation of infectious propagules (basidiospores and/or desiccated yeast cells) from the environment. Primary pulmonary infections have no diagnostic symptoms and are usually subclinical. On dissemination, the fungus usually shows a predilection for the central nervous system, however skin, bones and other visceral organs may also become involved.

Cryptococcus neoformans and *C. gattii* are the principle pathogenic species. *Naganishia albida* (formerly *Cryptococcus albidus*) and *Patiliotrema laurentii* (formely *Cryptococcus laurentii*) have on occasion also been implicated in human infection.

Scientific classification

Kingdom: Fungi

Division: Basidiomycota

Class: Tremellomycetes

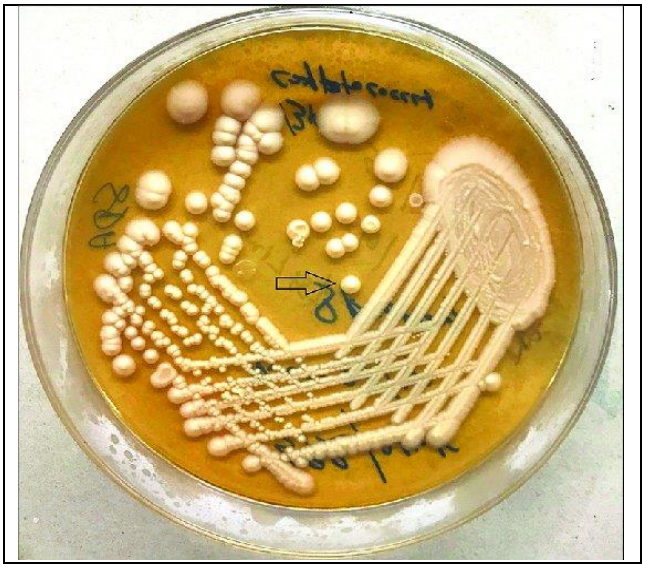
Order: Tremellales

Family: Cryptococcaceae

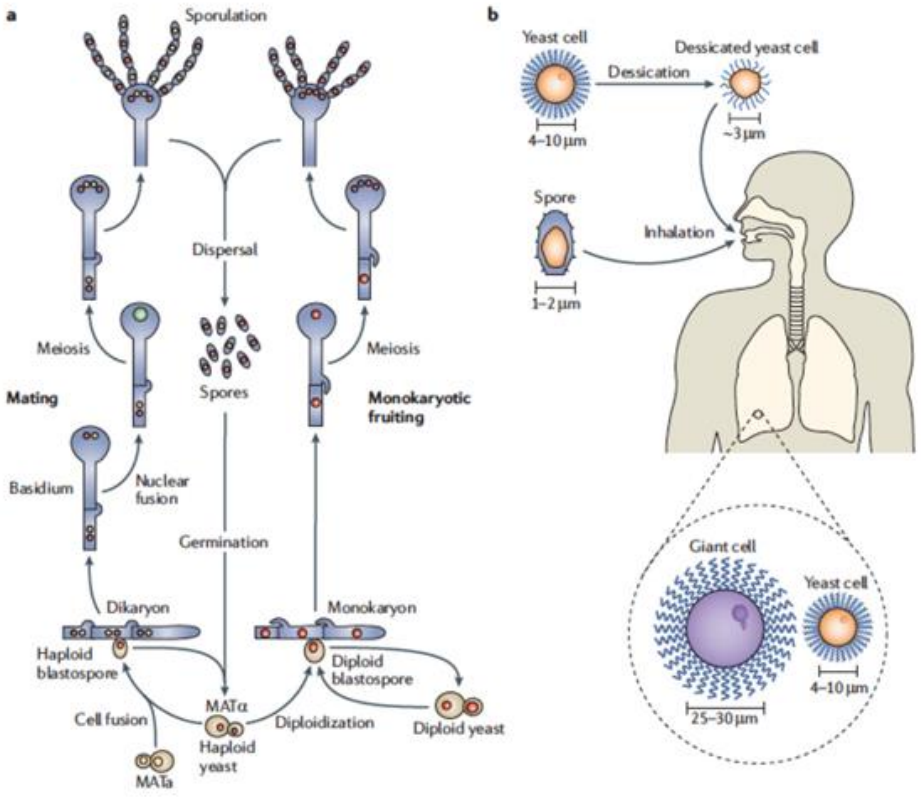
Genus: Cryptococcus (Vuill. 1901).

Species: *Cryptococcus neoformans*,

C. gattii



Lifecycle: Cryptococcus is an environmental fungus found all around the world in soil and is usually associated with bird droppings. While soil contaminated with pigeon droppings is the major environmental source for *C. neoformans*, eucalyptus and other trees and decaying hollows in living trees are the major reservoir for *C. gattii*. Members of the Cryptococcus genus are characterized by elongated, yeast like cells. When two cells of opposite sex mate, they form filaments, which grow and eventually produce tiny basidiospores. Interestingly, this fungus exhibits different forms of sexual, asexual and pseudosexual reproduction cycles.



Lifecycle of Cryptococcus, Spores and dessicated yeast cells initiate infection upon inhalation.

a | Spores result from either mating between cells of opposite mating types (MATa or MATα) and subsequent dikaryon formation (left), or unisexual mating of MATα cells to establish a monokaryotic cell type (right). In both cases, sexual development within the filamentous monokaryon or dikaryon results in meiosis and sporulation. The spores germinate to produce haploid, yeast-like cells that divide by budding. **b** | The yeast cells may become desiccated in the environment such that their small size allows inhalation deep into lung tissue. Germination of spores or vegetative growth of yeast cells in lung tissue results in the proliferation of budding cells and the formation of giant cells in a fraction of the population.

Clinical manifestations:

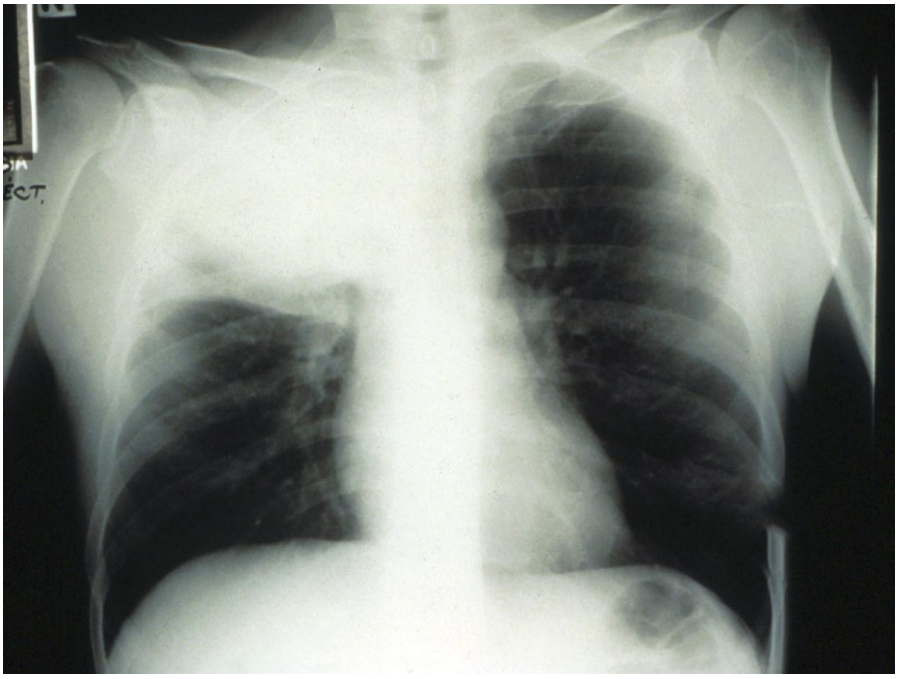
Cryptococcus is an encapsulated basidiomycete yeast-like fungus with a predilection for the respiratory and nervous system of humans and animals. Two species, *C. neoformans* and *C. gattii* are distinguishable biochemically and by molecular techniques. In humans, *C. neoformans* affects immunocompromised hosts predominantly and is the commonest cause of fungal meningitis; worldwide, 7-10% of patients with AIDS are affected. AIDS associated cryptococcosis accounts for 50% of all cryptococcal infections reported annually and usually occurs in HIV patients when their CD4 lymphocyte count is below 200/mm^3. Meningitis is the predominant clinical presentation with fever and headache as the most common symptoms. Secondary cutaneous infections occur in up to 15% of patients with disseminated cryptococcosis and often indicate a poor prognosis. Lesions usually begin as small papules that subsequently ulcerate, but may also present as abscesses, erythematous nodules, or cellulitis. This variety is found worldwide.

In contrast, the distribution of cryptococcosis due to *Cryptococcus gattii* is geographically restricted, non-immunocompromised hosts are usually affected, large mass lesions in lung and/or brain (cryptococcomas) are characteristic and morbidity from neurological disease is high. Human disease is endemic in Australia, Papua New Guinea, parts of Africa, the Mediterranean region, India, south-east Asia, Mexico, Brazil, Paraguay and Southern California.

Pulmonary cryptococcosis:

Asymptomatic carriage of Cryptococcus has been reported from the respiratory tract, especially sputum and from skin in healthy people as a result of normal environmental exposure. In addition, patients with chronic lung disease, such as bronchitis and bronchiectasis, may also have asymptomatic colonization, with Cryptococcus being isolated from their sputum over many years.

Subclinical cryptococcosis may result of environmental exposure, normal individuals may experience a self-limiting pneumonia with accompanying sensitization. Most primary infections of this type have no diagnostic symptoms and are usually discovered only by routine chest x-ray. When present, symptoms include cough, low-grade fever and pleuritic pain.



X-ray showing pulmonary cryptococcal infection [right upper lobe].

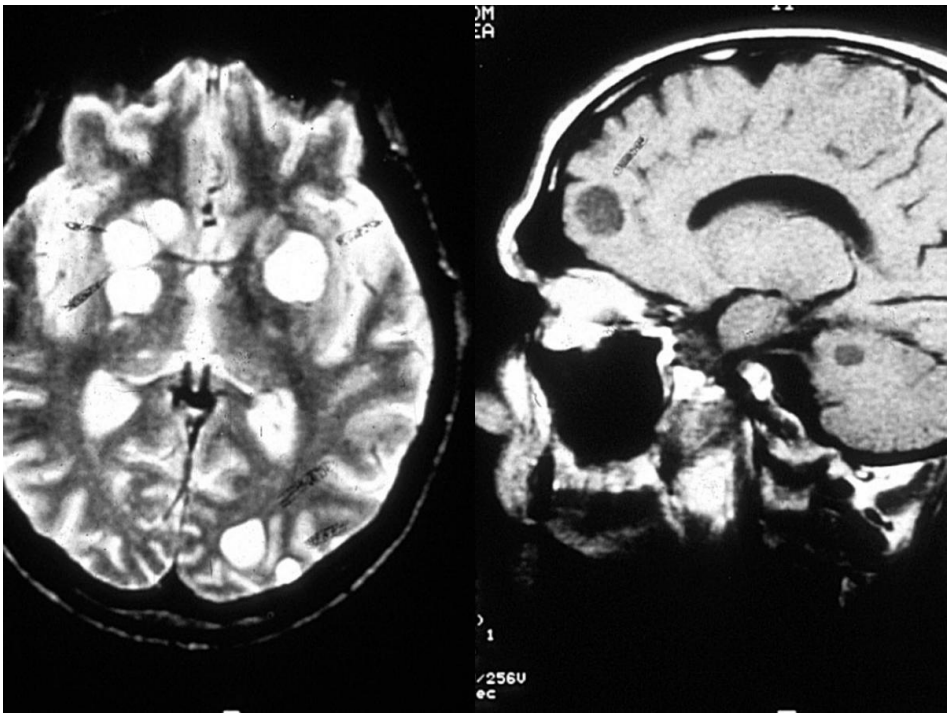
Invasive pulmonary cryptococcosis may occur in some patients when primary infections may not readily resolve in some patients, leading to a more chronic pneumonia progressing slowly over several years. Patients may become pyrexic and have an accompanying cough, however many pulmonary lesions are often asymptomatic, especially when chronic granulomas are formed. Chronic pulmonary cryptococcosis also increases the risk of dissemination to the central nervous system.

Central nervous system:

Dissemination to the brain and meninges is the most common clinical manifestation of cryptococcosis and includes meningitis, meningoencephalitis or expanding cryptococcoma.

Meningitis is the most common clinical form, accounting for up to 85% of the total number of cases, however the clinical signs are rarely dramatic. Symptoms usually develop slowly over several months, and initially include headache, followed by drowsiness, dizziness, irritability, confusion, nausea, vomiting, neck stiffness and focal neurological defects, such as ataxia. Diminishing visual acuity and coma may also occur in later stages of the infection. Acute onset

cases may also occur, especially in patients with widespread disease, and these patients may deteriorate rapidly and die in a matter of weeks.



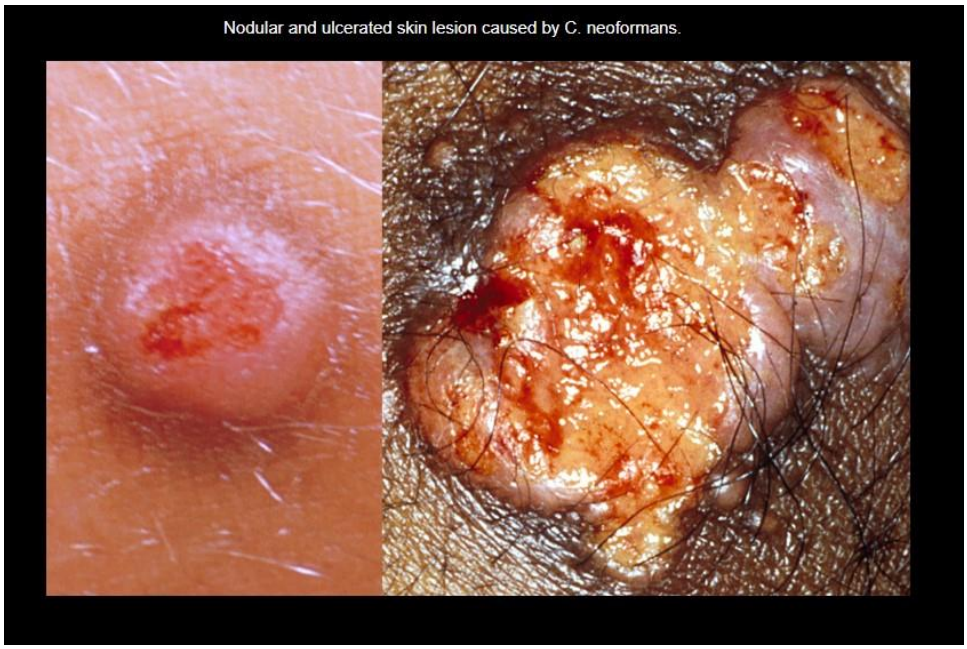
MRI scan showing multiple cryptococcomas [white masses] in the brain.

Cutaneous cryptococcosis:

Primary cutaneous cryptococcosis in the form of ulcerated lesions or cellulitis occasionally occurs, especially in immunosuppressed patients. These lesions may resolve spontaneously or with systemic antifungal treatment. However, all patients with skin lesions should be monitored carefully for possible dissemination to the central nervous system.

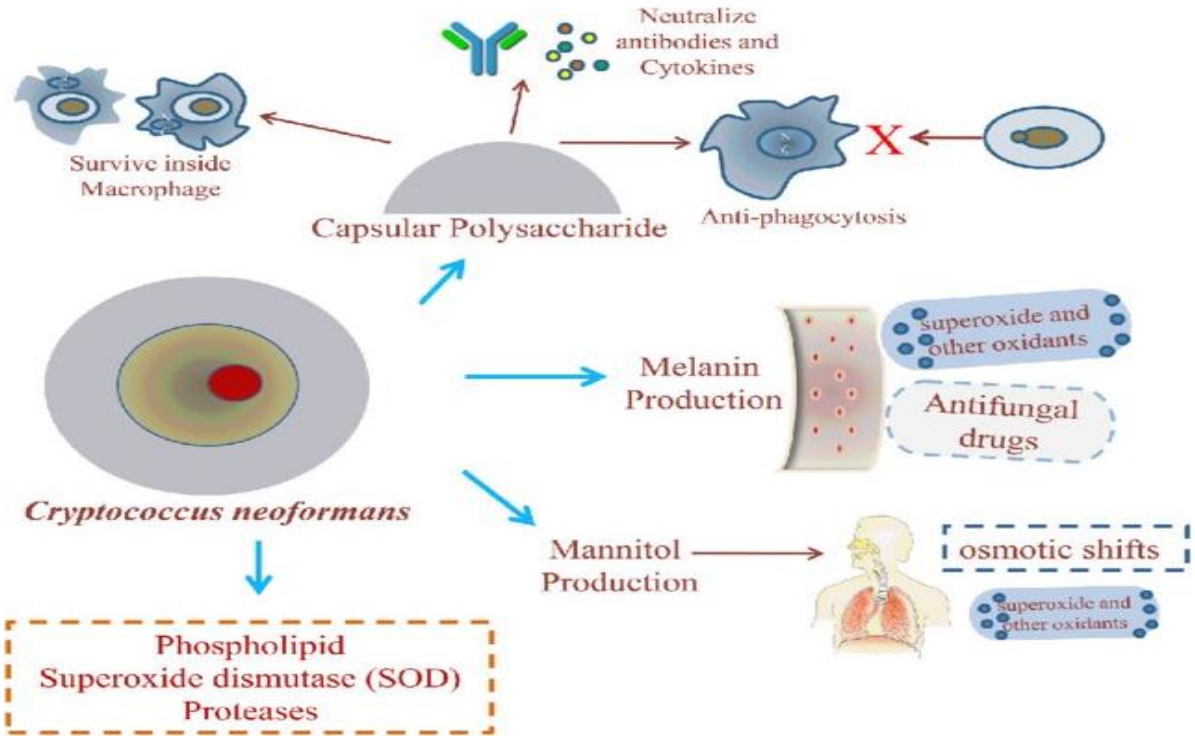
Secondary cutaneous infections occur in up to 15% of patients with disseminated cryptococcosis and often indicate a poor prognosis. Lesions usually begin as small papules that subsequently ulcerate, but may also present as abscesses, erythematous nodules, or cellulitis.

In patients with AIDS, skin manifestations represent the second most common site of disseminated cryptococcosis. Lesions often occur on the head and neck and may present as papules, nodules.



Virulence Factors:

Virulence factors of Cryptococcus: (1) Capsular polysaccharide, (2) melanin pigment production, (3) mannitol production and other virulence factors such as (4) phospholipase B, (5) proteases, and (6) lysophospholipase helps the pathogen to survive inside the host or protect from antifungal drugs.



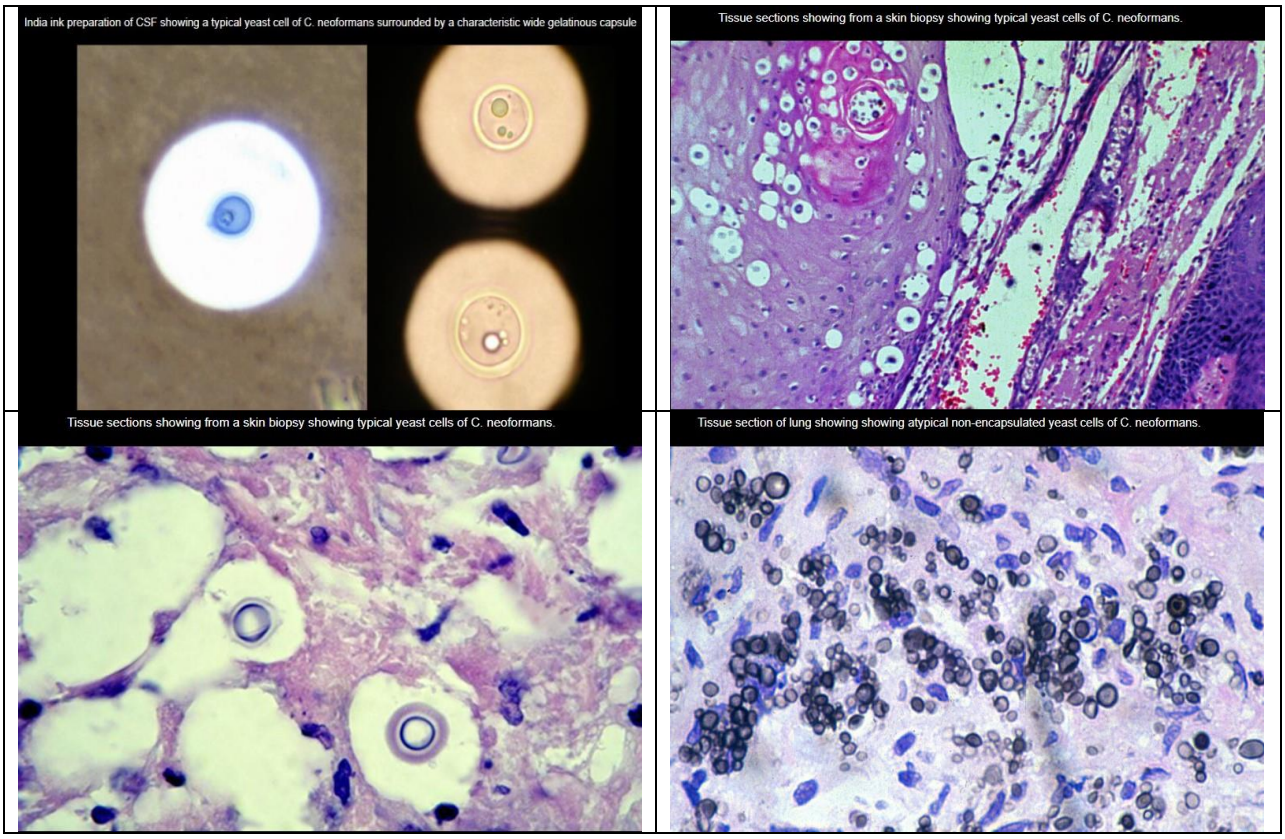
Laboratory diagnosis:

Clinical material:

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

Direct microscopy:

(a) For exudates and body fluids make a thin wet film under a coverslip using India ink to demonstrate encapsulated yeast cells. Sputum and pus may need to be digested with 10% KOH prior to India ink staining. (b) For tissue sections use PAS digest, GMS and H&E, mucicarmine stain is also useful to demonstrate the polysaccharide capsule. Examine for globose to ovoid, budding yeast cells surrounded by wide gelatinous capsules.



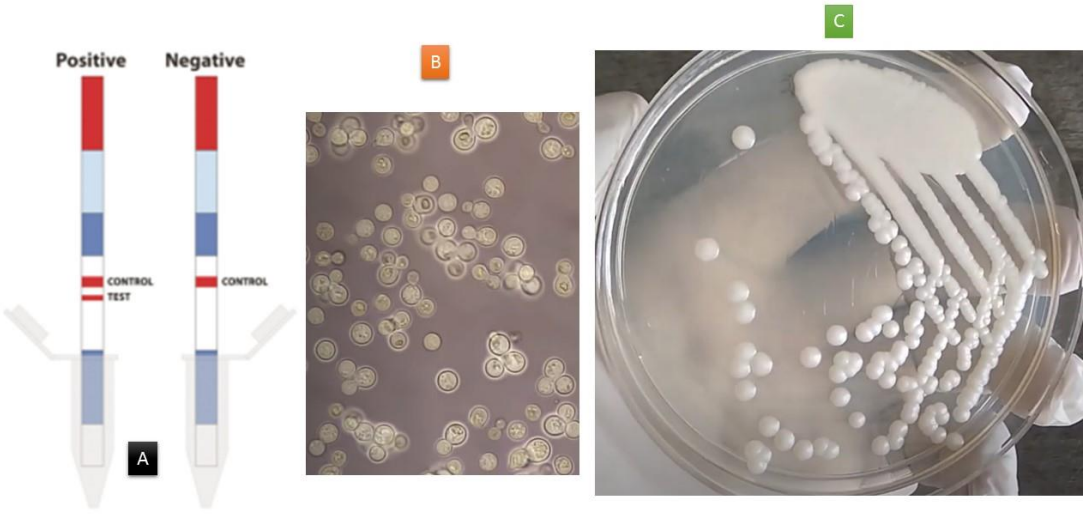
Culture:

Inoculate specimens onto primary isolation media, like Sabouraud's dextrose agar. Look for translucent, smooth gelatinous colonies, later becoming very mucoid and cream in color.

Colonies of Cryptococcus on Sabouraud's dextrose agar

Serology:

It should be noted that the detection of cryptococcal capsular polysaccharide antigen in spinal fluid is now the method of choice for diagnosing patients with cryptococcal meningitis. In AIDS patients, cryptococcal antigen can be detected in the serum in nearly 100% of cases. However, in non-AIDS patients antigen detection in serum is less sensitive with only about 60% of patients with cryptococcosis reported as being positive. Note, serum specimens should be pretreated with pronase to enhance detection of antigen and avoid false negative results.



Figures, A-Cryptococcal Antigen Test ,B-India Ink Staining and C-Cryptococcus growth on SDA

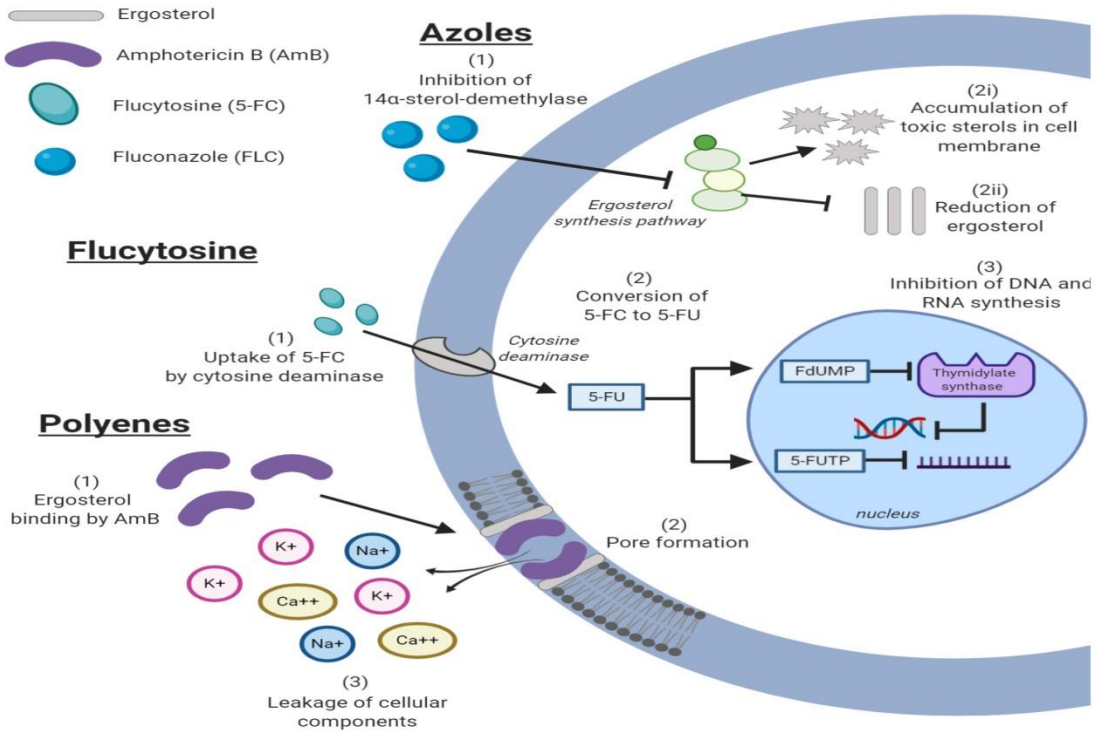
Molecular Test:

Detection of C. neoformans DNA in tissue samples by Nested and Real-Time PCR Assays

Treatment:

Following antifungal drugs are used to treat Cryptococcosis.

1. Amphotericin B.
2. 5- fluorocytosine.
3. Imidazoles (miconazole, keratonazole).
4. Triazoles (itranazole, fluconazol).



Identification:

The genus Cryptococcus is characterized by globose to elongate yeast-like cells or blastoconidia that reproduce by multilateral budding. Pseudohyphae are absent or rudimentary. On solid media the cultures are generally mucoid or slimy in appearance. Red, orange or yellow carotenoid pigments may be produced, but young colonies of most species are usually non-pigmented and are cream in colour. Most strains have encapsulated cells with the extent of capsule formation depending on the medium. Under certain conditions of growth, the capsule may contain starch-like compounds which are released into the medium by many

strains. Within the genus Cryptococcus, fermentation of sugars is negative, assimilation of nitrate is variable, and assimilation of inositol is positive. The genus Cryptococcus is similar to the genus Rhodotorula. The distinctive difference between the two is the assimilation of inositol, which is positive in Cryptococcus.

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