

Cryptococcosis

*Torulosis,
European blastomycosis,
Busse-Buschke's disease*

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Etiology

Cryptococcosis is nearly always caused by *Cryptococcus neoformans*, an encapsulated yeast (Division Basidiomycota). Unlike most pathogenic fungi, this organism occurs in the yeast form both in the host and in the environment. The perfect (mycelial) stage of this fungus is called *Filobasidiella neoformans* or *Filobasidiella bacillisporus*. This stage has never been isolated from patients or found in nature; it is only found in the laboratory under certain conditions.

C. neoformans is surrounded by a large capsule within its hosts and on some culture media. This capsule is important in its resistance to phagocytosis and in the identification of the organism. Strains differ in their virulence for animals and possibly humans, but the immune status of the host seems to be more important than the virulence of the strain. There are four serotypes - A, B, C and D - based on capsular antigens. There are three varieties:

Cryptococcus neoformans var. *neoformans* comprises serotypes A and D. This organism is ubiquitous and causes most cases of cryptococcosis. In humans, it is an opportunistic pathogen that mainly affects immunocompromised hosts.

In 1999, it was proposed that serotype A be called *C. neoformans* var *grubii* and serotype D be called *C. neoformans* var *neoformans*. Because the older literature does not make this distinction, both serotypes A and D are referred to as *C. neoformans* var *neoformans* in this outline.

Cryptococcus neoformans var. *gattii* comprises serotypes B and C. This variety is less common in the environment than *C. neoformans* var *neoformans*. In humans, it is mainly found in immunocompetent hosts. It has also been isolated from some cases of cryptococcosis in animals including cats, dogs, porpoises and llamas.

There are two perfect states of *C. neoformans*: *Filobasidiella neoformans* var *neoformans* is the result of mating between *C. neoformans* var *neoformans* serotypes A and D. *Filobasidiella bacillisporus* is the result of mating between *C. neoformans* var *gattii* serotypes B and C.

Some strains of serotypes A and D can mate with strains of serotypes B and C. *Cryptococcus* species other than *C. neoformans* are, with rare exceptions, considered to be saprophytic and nonpathogenic. *Cryptococcus laurentii* has been associated with 15 cases of human disease. These cases mainly occurred in hosts with diseases or conditions that predisposed them to fungal infections.

Geographic Distribution

C. neoformans var. *neoformans* is found worldwide in the soil. Serotype A is the most common serotype in the U.S. *C. neoformans* var. *gattii* has been found around eucalyptus trees in tropical and sub-tropical areas including Australia, California and parts of South and Central America. It was also isolated from Vancouver Island, British Columbia during an outbreak of cryptococcosis.

Transmission

C. neoformans grows naturally in the environment. *C. neoformans* var *neoformans* is ubiquitous in the soil, where it grows as a saprophyte. It is common in old pigeon nests and around pigeon droppings; the bird droppings appear to create a favorable environment for its growth. It can also be isolated from numerous environmental sources including vegetables and fruit, house dust, air conditioners, air and sawdust. It can survive for months to years outside the host.

C. neoformans var *gattii* is found in bark and plant debris under eucalyptus trees (the river red gum tree *Eucalyptus camaldulensis* and the forest red gum tree, *E. tereticornis*). It is also found in the air around these trees, particularly when they bloom in late spring. It is not associated with pigeon droppings. Recently, *C. neoformans* var *gattii* was isolated from trees and soil on Vancouver Island in British Columbia.

Transmission seems to be mainly by inhalation, but *C. neoformans* can also enter the body through the skin. Infections seem to be acquired mainly from the environment. Cryptococcosis can also result from the reactivation of a latent infection.



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Cryptococcal mastitis in cattle is usually associated with the treatment of the mammary gland for another condition. The organism may be introduced into the teat in contaminated syringes, cannulas or antibiotic preparations. It can also enter the mammary gland if the teat ends are not adequately cleaned before treatment.

Cryptococcosis does not seem to be very contagious. There are no reports of transmission from mammalian animals to other animals or to humans. However, in one recent case, an immunosuppressed human probably acquired *C. neoformans* from the feces of an asymptomatic pet bird. Human-to-human transmission is extremely rare and has mainly occurred under unusual circumstances. Vertical transmission was recently described, when a HIV-positive mother with peripartum cryptococcal meningitis infected her newborn.

Disinfection

C. neoformans is susceptible to 1% sodium hypochlorite, iodine, phenolic disinfectants, glutaraldehyde and formaldehyde. Its susceptibility to 70% ethanol is questionable. This organism can also be killed by moist heat of 121°C for a minimum of 15 minutes.

Infections in Humans

Incubation Period

The incubation period in humans is unknown. Pulmonary infections may precede CNS disease by months or years.

Clinical Signs

In humans, the spectrum of disease varies from asymptomatic colonization of the airways to meningitis and other serious diseases. *C. neoformans* var *neoformans* is an opportunist that mainly causes disease in immunosuppressed patients. In these patients, there may be little inflammation and the symptoms can be mild even with extensive disease. Patients infected with *C. neoformans* var *gattii* are usually immunocompetent.

The initial infection usually occurs in the lungs. Pulmonary cryptococcosis can be accompanied by respiratory disease or radiological abnormalities, but most infections (in both immunocompetent and immunosuppressed hosts) are asymptomatic.

In immunocompetent patients, *C. neoformans* can cause coughing and pleuritic chest pain. A low-grade fever, dyspnea, weight loss and malaise may also be seen. Most symptomatic infections are self-limited, but chronic infections and rare cases of fatal cryptococcal pneumonia have been reported. In most healthy people, the infection remains confined to the lungs.

In immunosuppressed patients, the symptoms of pulmonary cryptococcosis may include fever, malaise, coughing,

pleuritic pain, dyspnea, headache, weight loss and rarely, hemoptysis. Pneumonia or acute respiratory distress syndrome can occur. Pulmonary disease is more likely to be progressive in immunosuppressed patients.

After the initial pulmonary infection, *C. neoformans* may spread to other organ systems, particularly in immunosuppressed patients. The organism can disseminate even if the pulmonary infection was asymptomatic. In many patients, the first sign of cryptococcosis is disseminated disease.

The most common form of disseminated cryptococcosis is CNS disease, particularly subacute or chronic meningitis and meningoencephalitis. The symptoms may include a headache, nausea, vomiting and changes in mental status such as personality changes, lethargy or confusion. A fever and stiff neck are less common signs. Seizures, ataxia, aphasia, hearing defects, blurred vision, photophobia, other motor or sensory deficits and coma may also be seen. Elevated CSF pressure can lead to hydrocephalus and dementia. Untreated CNS infections are fatal in days to months.

Either meningitis/ meningoencephalitis or focal mass lesions (cryptococcomas) can occur in immunocompetent patients. Cryptococcomas are often associated with focal neurologic signs.

In AIDS patients, the presentation is typically subacute. In the initial stages, these patients may have few symptoms or only nonspecific signs. Common symptoms are a headache and fever and, less often, altered mental status. Focal CNS disease is uncommon in AIDS patients.

C. neoformans can cause ocular lesions including optic neuritis, chorioretinitis and endophthalmitis.

C. neoformans can cause a wide variety of skin lesions including papules, vesicles, bullae, ulcers, purpura, subcutaneous tumor-like masses and abscesses. The lesions can mimic other diseases including acne, lipomas, syphilis, tuberculosis and basal cell carcinoma. AIDS patients may have umbilicated papules that resemble molluscum contagiosum. Cellulitis is common in organ transplant recipients. Skin disease can occur alone in healthy people, but in immunosuppressed patients it suggests disseminated disease.

Less frequent syndromes include osteomyelitis, septic arthritis, myocarditis, hepatitis, peritonitis, renal abscesses, prostatitis, myositis and gastroenteritis. In AIDS patients, invasion of the adrenal glands can cause adrenal insufficiency.

Cryptococcus laurentii infections

Only 15 cases of human *C. laurentii* infection have been documented in the literature. The symptoms included fever, hypotension and a wide variety of other clinical signs, depending on the organs affected.

Communicability

Person-to-person transmission is very rare and has occurred mainly in unusual circumstances. One case was acquired in a corneal transplant from an infected donor. A

health care worker developed localized skin disease after accidental self-inoculation with contaminated blood. A case of mother-to-child transmission was also reported recently in a HIV-positive woman with peripartum cryptococcal meningitis. There are no reports of infection by casual contact.

Diagnostic Tests

Cryptococcosis is usually diagnosed by detection of the organism in tissues or fluids. In CNS disease, *C. neoformans* may be found in the CSF.

C. neoformans can sometimes be found in clinical samples by direct observation. This organism is an encapsulated 4 to 6 µm, round to oval yeast. It is surrounded by a halo-like capsule that stains strongly with Mayer's mucicarmine. In an India ink preparation, yeast cells surrounded by a clear halo (the capsule) may be seen; unless budding is observed, the organisms can be confused with fat droplets or other artifacts. Other useful stains include Alcian blue, Gomori methenamine silver, periodic acid-Schiff (PAS), and Masson-Fontan silver stain. *C. neoformans* can be identified in the tissues by immunofluorescence.

A definitive diagnosis can be obtained by culturing the blood, CSF, sputum, bronchoalveolar lavage washings or urine. Although *C. neoformans* grows on most media, growth is best on fungal media such as Sabaraud's dextrose agar without cycloheximide. Colonies usually appear within 2 to 5 days but growth may be delayed in samples with few organisms. The organism is identified by its appearance, its ability to grow at 37°C and biochemical tests.

A latex agglutination test or ELISA can detect *C. neoformans* capsular antigens in blood, CSF or urine. This test may not be positive if the disease is localized (e.g. in the lungs). False positive reactions can be seen with other microorganisms such as *Trichosporon beigelii* or if rheumatoid factor is present.

Other diagnostic tests include CT and MRI in patients with CNS disease, and x-rays in patients with pulmonary disease. Serology is not considered to be useful in humans, as antibodies are often found in healthy people.

Treatment

Cryptococcosis can be treated with amphotericin b, 5-fluorocytosine, fluconazole, itraconazole and ketoconazole. After the initial therapy, long term or lifelong treatment may be required in AIDS patients. Immunocompetent patients may or may not be treated if the infection is confined to the lungs, as these infections are usually self-limiting. *C. neoformans* var *gattii* infections often respond slowly to treatment.

There is no standard treatment for *C. laurentii*, but some cases were treated successfully with amphotericin B.

Prevention

Prevention of environmental exposure is difficult, as *C. neoformans* is ubiquitous in the environment. Avoidance and/or environmental control of pigeon droppings may be beneficial in preventing disease due to *C. neoformans* var *neoformans*. Removal of pigeon droppings should be preceded by chemical decontamination or wetting with water or oil to decrease aerosolization. Pigeon droppings can remain infectious for up to 2 years.

C. neoformans var *gattii* infections are mainly associated with exposure to eucalyptus trees, particularly during the period when they bloom (November to February). Avoidance of these trees may reduce the risk of exposure but other sources of *C. neoformans* var *gattii* also seem to exist.

Pet birds can carry *C. neoformans* var *neoformans* asymptomatically in the intestinal tract. The organisms are found mainly in the feces and can be aerosolized by sweeping, cleaning the cage and similar activities.

Animals that may be sources of *C. neoformans* should be treated with caution, particularly by people who are immunosuppressed. Although no cases of mammal-to-human transmission have been reported, people handling animals with cryptococcosis should also use appropriate precautions and wear protective clothing such as gloves and a mask. Cages and litter boxes should also be decontaminated regularly. Fluconazole has been used for prophylaxis in AIDS patients.

Morbidity and Mortality

Most cases of cryptococcosis are caused by *C. neoformans* var *neoformans* and occur in people with depressed cell-mediated immunity. AIDS patients and organ transplant recipients are particularly susceptible. Early in the AIDS epidemic, 5-8% of HIV-infected persons developed cryptococcosis; with more effective retroviral therapy, the incidence has decreased. The annual incidence of disease is currently 0.4-1.3 cases per 100,000 persons in the general population, 2 to 7 cases per 1,000 AIDS patients, and 0.3 to 5.3 cases per 100 transplant patients. Some forms of cancer, sarcoidosis and prolonged treatment with corticosteroids also increase the risk of serious disease. Cases of cryptococcosis usually occur sporadically; however, an unusual outbreak caused by *C. neoformans* var *gattii* was reported in British Columbia in 2001/2002. In this outbreak, 45 confirmed cases were reported in animals and 50 cases in humans.

The outcome of a *C. neoformans* infection depends on the health of the host, the form of the disease and the treatment. Healthy people seem to be exposed frequently without becoming ill. Serologic surveys suggest that many children encounter *C. neoformans* in early childhood, and pulmonary granulomas containing this organism have been reported as an incidental finding in people with no history of cryptococcosis. Symptomatic pulmonary infections are uncommon in

healthy people, and usually resolve without treatment. There is little information on the incidence of disseminated disease: although most sources state that infections in healthy people usually remain confined to the lungs, two studies found CNS disease in 17% or 69% of immunocompetent hosts with untreated pulmonary cryptococcosis.

CNS disease and disseminated infections are fatal without treatment. In healthy people, most cases can be treated successfully if the disease is caught early, but the case fatality rate is higher if the person is immunosuppressed. Permanent neurologic damage including loss of vision, decreased mental function, hydrocephalus and cranial nerve palsies can be seen in survivors. *C. neoformans* can also persist in the prostate gland after treatment; these bacteria can cause relapses in HIV-infected men. Approximately 20-60% of AIDS patients relapse unless they receive long-term or life-long maintenance therapy. The overall mortality rate for cryptococcosis is 12-28%. In organ transplant patients, mortality rates from 20-100% have been reported.

Species other than *C. neoformans* are very rarely pathogenic. Fifteen symptomatic *C. laurentii* infections have been documented in the literature, mainly in people with other diseases or factors that predisposed them to fungal infections. All but one patient, who died due to the underlying disease, recovered after treatment.

Infections in Animals

Species Affected

Clinical cryptococcosis is most often found in cats. Outbreaks of cryptococcal mastitis and pneumonia have been described in cattle. Clinical cases have also been reported in dogs, ferrets, guinea pigs, horses, sheep, goats, pigs, llamas, foxes, mink, cheetahs, gazelles, koalas, wallabies, porpoises, non-human primates and other animals. *C. neoformans* can be isolated from asymptomatic mammals.

C. neoformans can be found in the feces of birds including canaries, budgerigars, psittacine birds, chickens, sparrows, starlings, skylarks, pigeons and turtledoves. The presence of this organism in the feces can be due to a transient asymptomatic intestinal infection, or to the inoculation of the feces with organisms carried on the beaks or feet. Clinical infections in birds are very rare.

Incubation Period

The incubation period for cryptococcosis is unknown.

Clinical Signs

Cats

In cats, disease may be seen in a single organ system or many. Fever occurs in some but not all cases. The symptoms may gradually become more severe over weeks or months.

Upper respiratory disease (unilateral or bilateral chronic rhinitis or sinusitis) is the most common form of cryptococcosis in cats. The symptoms may include sneezing, snoring or snorting, dyspnea, or a mucopurulent or serosanguineous nasal discharge. Polyp-like masses may protrude from one or both nostrils. The cervical lymph nodes can be enlarged and ulcerative or proliferative lesions are occasionally seen on the tongue, gingiva or palate. Pulmonary symptoms are uncommon.

C. neoformans can cause skin lesions, particularly on the face. Typically, there are one or more firm, nodular, cutaneous or subcutaneous swellings on the head, particularly the bridge of the nose, side of the face, upper lip or nostril. Some lesions may ulcerate. There is little or no pruritus. Fluctuant or firm papules and nodules may also occur on other parts of the body; generalized skin disease suggests disseminated cryptococcosis.

Central nervous system (CNS) disease, due either to a focal mass lesion or diffuse neurologic disease, is also common. Neurologic signs may be mild or severe, and can include a change in temperament, depression, disorientation, ataxia, paresis or paralysis, seizures, circling, abnormal pupillary responses, anisocoria and blindness. Deficits of cranial nerves 5 to 12 are often found. In one case, the only symptom was unusual sleepiness.

Ocular lesions may include chorioretinitis, optic neuritis, panophthalmitis and iridocyclitis. There may be small transparent focal retinal detachments with a minimal inflammatory response. Ocular lesions often accompany other syndromes but may be seen alone.

C. neoformans can also invade other organs and less common presentations, including osteomyelitis, may be seen.

Dogs

Most dogs have severe disseminated disease. Neurologic disease is the most common form in dogs and resembles the disease in cats. Ocular lesions are also common and may include granulomatous chorioretinitis and optic neuritis. Disease can also occur in other organs, but cryptococcosis rarely affects the nasal cavity in dogs.

Cattle

Outbreaks of cryptococcal mastitis occur in cows. The symptoms may include anorexia, decreased milk production, and enlargement of the supramammary lymph nodes. The affected quarters are usually swollen and firm. The milk may be viscid, mucoid and grayish-white, or it may be watery with flakes.

Sheep and goats

Pulmonary disease and mastitis have been described in sheep and goats. In one goat, *C. neoformans* was associated with an alopecic, exudative skin lesion on the head.

Horses

Syndromes that have been reported in horses include meningoencephalitis, pulmonary disease, upper respiratory disease affecting the frontal sinuses and para-orbital area, and abortions. Obstructive growths in the nasal cavities are the most common presentation.

Birds

Cryptococcosis is very rare in birds; mycotic rhinitis and sinusitis have been described. However, the organism can be found in their feces especially in pigeons.

Communicability

C. neoformans is thought to be acquired mainly from the environment rather than from infected animals. There are no reports of transmission from mammals to other mammals or to humans. However, in one recent case, a person appears to have acquired cryptococcosis from the feces of a pet bird. This pet bird was asymptomatic as is the usual case in birds. It is possible that other cases of avian-to-human transmission exist, but they have not been well documented.

Diagnostic Tests

Cryptococcosis is usually diagnosed by detecting *C. neoformans* in biopsies, impression smears, aspirates, or swabs of nasal secretions or skin exudates. In cases of CNS disease, *C. neoformans* may be found in the cerebrospinal fluid (CSF).

C. neoformans can sometimes be found in clinical samples by direct observation. This organism is an encapsulated 4 to 6 µm, round to oval yeast. It is surrounded by a halo-like capsule that stains strongly with Mayer's mucicarmine. In an India ink preparation, yeast cells surrounded by a clear halo (the capsule) may be seen; unless budding is observed, the organisms can be confused with fat droplets or other artifacts. Other useful stains include Alcian blue, Gomori methenamine silver, periodic acid-Schiff (PAS), Masson-Fontan silver stain, Gram's stain, new methylene blue and Wright's stain. *C. neoformans* can be identified in the tissues by immunofluorescence.

A definitive diagnosis can be obtained by culture. Although *C. neoformans* grows on most media, growth is best on fungal media such as Sabaraud's dextrose agar without cycloheximide. Colonies usually appear within 2-5 days but growth may be delayed in samples with few organisms. The organism is identified by its appearance, its ability to grow at 37°C and biochemical tests.

A latex agglutination test or ELISA can detect *C. neoformans* capsular antigens in blood, CSF or urine.

Serology may be useful in some cases; however, large amounts of capsular antigen in the circulation appear to tie up antibodies. Cats with clinical disease seldom have positive titers. Serologic tests used in cats include complement

fixation, immunodiffusion, indirect immunofluorescence and tube agglutination.

Treatment

Cryptococcosis can be treated with amphotericin B, flucytosine, itraconazole and fluconazole. Amphotericin B and flucytosine are often used in combination. A combination of ketoconazole and itraconazole has been effective in some experimentally infected cats, including animals with neurologic disease.

Prevention

In most cases, there is no practical means of prevention other than to avoid exposure to the soil, particularly soil contaminated with abundant bird droppings, and the environment around eucalyptus trees.

Cryptococcal mastitis in cattle is usually associated with the treatment of the mammary gland for another condition. Care should be taken not to contaminate syringes, cannulas or antibiotic preparations with *C. neoformans* from soil or other sources. The teat ends should also be adequately prepared before treatment.

Morbidity and Mortality

Cases of cryptococcosis usually occur sporadically; however, an unusual outbreak, with at least 45 confirmed cases in animals and 50 cases in humans, was reported on Vancouver Island, British Columbia in 2001/2002. Most of the cases occurred in immunocompetent animals and were due to *C. neoformans* var *gattii*.

Clinical cryptococcosis is reported most often in cats. It is particularly common in cats that are immunosuppressed by feline leukemia virus or feline immunodeficiency virus infections. Cryptococcosis may also be more common in immunosuppressed dogs. The prognosis is guarded, especially in cases with CNS disease. Untreated infections are fatal.

Cryptococcal mastitis in cattle is usually associated with treatment of the mammary gland for another condition. Fungal mastitis is usually mild, but some infections can cause the death of the cow. Cattle rarely recover spontaneously from cryptococcal mastitis.

Clinical cryptococcosis is very rare in birds, but the organism can be carried transiently in the intestinal tract. *C. neoformans* has been isolated from the feces of 26% of canaries, 18% of carrier pigeons, 2% of budgerigars and 1% of psittacine birds.

Post-Mortem Lesions [Click to view images](#)

The gross lesions may appear either as granulomas or as gelatinous masses with minimal inflammation. In cats, lesions can occur in any organ system. Often, there is a viscous exudate in the nasal passages and sinuses, and/or small gelatinous nodules scattered on the viscera of the abdominal and thoracic cavities. In cases with CNS involvement, the

meninges may be congested and thickened. They sometimes have a cloudy, gelatinous appearance, and they may be covered by a scant mucoid exudate. Abscesses may be found in the brain or spinal cord. Ocular lesions including chorioretinitis or panophthalmitis can also be seen. CNS disease in cats may be associated with only minimal inflammation.

Most dogs have disseminated disease, with granulomas throughout the body. Pulmonary involvement is common, even in dogs with no symptoms of respiratory disease. Lesions may also be found on other organs including the kidneys, lymph nodes, spleen and liver. The CNS lesions resemble those in cats, with meningoencephalitis and abscesses in the brain and spinal cord; however, in dogs the lesions are often accompanied by granulomatous inflammation.

In an affected goat, there was fluid in the pleural and peritoneal cavities, atelectasis in the lungs, and dark red plaques in the trachea.

Internet Resources

- Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/ncidod/dbmd/diseaseinfo/cryptococcosis_t.htm
- eMedicine.com - Cryptococcosis
<http://www.emedicine.com/med/topic482.htm>
- eMedicine.com - Cryptococcosis, CNS
<http://www.emedicine.com/radio/topic200.htm>
- International Veterinary Information Service (IVIS)
<http://www.ivis.org>
- Material Safety Data Sheets –Canadian Laboratory Center for Disease Control
<http://www.hc-sc.gc.ca/pphb-dgsp/msds-ftss/index.html#menu>
- Medical Microbiology
<http://www.gsbs.utmb.edu/microbook>
- The Merck Manual
<http://www.merck.com/pubs/mmanual/>
- The Merck Veterinary Manual
<http://www.merckvetmanual.com/mvm/index.jsp>

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