



What is cryptococcosis?

- Cryptococcosis is a rare non-contagious fungal (yeast) disease, acquired from a contaminated environment.
- It is caused by the *C. neoformans*-*C. gattii* species complex which can also infect humans, domestic and wild mammals and birds.
- Various genotypes with different epidemiology and virulence exist, but they are not commonly identified in practice.
- Despite being rare, cryptococcosis is the most common systemic fungal disease in cats worldwide.

Pathogenesis

- Cryptococcus is an airborne pathogen but skin inoculation of fungal basidiospores that develop in the environment can also occur.
- Primary site of infection is the upper respiratory tract followed by local invasion and dissemination in any tissues.
- The yeast cell survives inside phagocytic cells such as macrophages, dendritic cells, and neutrophils, replicating both extracellularly and intracellularly.
- Host cells are also infected through host cell-to-cell transfer.

Clinical signs

- Disease caused by different genotypes or species are indistinguishable clinically.
- Most common manifestations include:
 - Chronic nasal (serous, mucopurulent or haemorrhagic) discharge that can be monolateral or bilateral;
 - Naso-facial swelling followed by deep non-healing ulcerations draining gelatinous exudate;
 - Nasopharyngeal granulomas presenting with stertor, inspiratory dyspnoea and open mouth-breathing;
 - Otitis media/interna with vestibular signs and proliferative or ulcerated lesions in the oral cavity or pharynx.
- Atypical forms are characterized by one or more skin nodules that are not painful but may be firm or fluctuant.

- Solitary nodules are suggestive of direct inoculation.
- Multiple nodules are suggestive of haematogenous spread from the primary site of infection.
- Haematogenous dissemination may lead to meningoencephalomyelitis, uveitis, chorioretinitis, osteomyelitis, polyarthritis, systemic lymphadenitis and multi-organ involvement.
- Disease of the central nervous system (CNS) occurring after local invasion through the cribriform plate manifests with sudden blindness, seizure and/or behavioural changes.
- In case of haematogenous dissemination various progressive monofocal or multifocal signs are seen.
- Apathy and cachexia appear in chronic cases with systemic dissemination.

Diagnosis

- **Cytology:** samples stained with Romanowsky-type stains demonstrate pink to violet, round or budding yeasts that vary in size (4-15 microns) and shape. They are typically surrounded by a clear, quite thick halo corresponding to the unstained capsule.
- **Culture** is generally more sensitive than cytology for confirming infection. It should be performed from biopsied samples because mucous surfaces may be contaminated by *Cryptococcus*, leading to false positive results.
- **Histology and immunohistochemistry** can be used to confirm the invasion of tissues by *Cryptococcus* as well as for species differentiation.
- **PCR** has been developed for genetic identification in tissue and body fluids.
- **Antigen detection** is a first line, easy and reliable test for cryptococcosis. Quantitative detection of capsular antigen can be rapidly obtained by latex cryptococcal antigen agglutination tests (LCAT) on serum, urine, and other fluids.

Prognosis

- Early diagnosis (before dissemination) is essential for a favourable prognosis.
- Owner compliance is crucial, because of the high costs and length of treatment.



Disease management and prevention

- Treatment guidelines have not been established and the choice of the appropriate antifungal drug depends on many factors, including owner compliance.
- Amphotericin B, fluconazole and itraconazole are most commonly used to treat cats.
- Surgical excision of any nodules and masses must be considered in affected tissues as a valuable aid in cats under medical therapy.
- In general, long-term treatment is recommended until the LCAT serum antigen test is negative. Renal (amphotericin B) and liver (fluconazole, itraconazole) toxicity have to be monitored.
- The presence of bird droppings, particularly pigeon droppings, and decaying vegetation substrates such as Eucalyptus leaves, may be considered a risk factor but efficient preventative measures have not been demonstrated.
- Vaccines are not available.

Common antimicrobial treatments for cryptococcosis in cats

Drug	Dose and administration	Notes
Amphotericin B (50 mg vial; stock solution 5 mg/ml)	0.25 mg/kg q48h IV (cumulative dose: 4-8 mg/kg) 0.5 mg/kg q48h SC in 350 ml/cat of hypotonic solution* (cumulative dose: 7-23 mg/kg)	First choice in CNS, eye and systemic disease in combination with flucytosine (if available) or fluconazole. Nephrotoxic drug: monitor renal function and avoid if renal disease present.
Flucytosine (250-500 mg oral formulations)	25-50 mg/kg q8h PO	Always in combination with amphotericin B (synergistic activity). Lower dose in cases of renal disease. Gastrointestinal adverse signs.
Fluconazole (50 mg capsule or 10 mg/ml oral suspension)	50 mg/cat (or 10 mg/kg) q12-24h PO	Teratogenic drug. Gastrointestinal adverse signs. First choice monotherapy in localized forms of disease.
Itraconazole (10 mg/ml oral solution)	5 mg/kg q24h PO	Teratogenic and hepatotoxic drug.
Terbinafine (250 mg tablet)	30-40 mg/kg q24h PO	In combination with azole drugs or as monotherapy in azole-refractory cases. Gastrointestinal adverse effects.

* 0.45% NaCl + 2.5% dextrose (obtained by combining 0.9% NaCl and 5% dextrose 1:1)



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- Cryptococcal disease: severe nasofacial swelling and deformity.



- Cryptococcal disease: ulcerated skin nodules on the face.