

Cryptococcosis



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P Profile

Definition

- Cryptococcosis, the most common systemic mycosis in the domestic cat, is caused by an encapsulated yeast—most commonly *Cryptococcus neoformans* and *C gattii*, both dimorphic, basidiomycetous fungi.

□ *C neoformans*.

- *C neoformans* var *neoformans*.
- *C neoformans* var *grubii*.

- Genotyping via PCR fingerprinting is used to distinguish molecular types and differentiate strains based on geographic location.

- *C neoformans* var *grubii* isolates are molecular types VNI and VNII.
- *C neoformans* var *neoformans* is type VNIV with a hybrid type VNIII.
- *C gattii* isolates are classified as molecular types VGI–VGIV with different genetic subtypes within each VG group representing various strains.

- Reproduction occurs with asexual and sexual phases.
 - Asexual phase is haploid.
 - Sexual phase is by budding.
 - Found within mammalian tissue.
 - Production of basidiospores (ie, infectious component of *Cryptococcus*).

Systems

- Upper respiratory (ie, nasal cavity),

skin, lymph nodes, brain, meninges, and eyes are the most common infection sites.

- Other sites include lungs, mediastinum, gingiva, spleen, myocardium, liver, thyroid gland, tongue, and bone.

Geographic Distribution

- Australia, western Canada, and western United States.
 - Although less prevalent, *Cryptococcus* spp can occur in all parts of the world.

Signalment Species

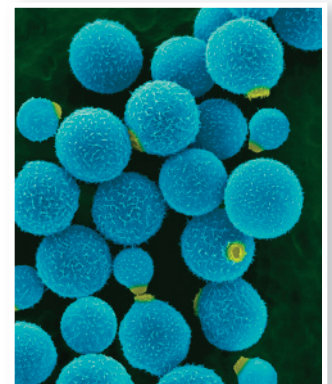
- Most common in cats and dogs; other mammalian species are susceptible.
- All domestic cats are at risk.

Breed

- Siamese, Birman, and Ragdoll cats were overrepresented in a study from Australia.^{1,2}
- No breed predisposition was found in a study in California.^{2,3}

Age

- Cats of all ages are known to become infected.
 - Young adult cats appear at increased risk (2–3 years of age).
 - Median age at infection is 6 years.^{2–4}
 - Exposure can occur years before infection materializes, so older cats may present with signs.
- Predominantly younger, more active dogs are at increased risk.



Cryptococcosis, the most common systemic mycosis in domestic cats, is caused by dimorphic, basidiomycetous fungi.

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Sex

- No known sex predilection.

Causes

- Inhalation of spores from avian guano or affected soils.
- *C neoformans* is also found in decaying plant matter harboring in some tree hollows.
- *C gattii* has been isolated from air, seawater, freshwater, and tree bark.

Risk Factors

- Cats with retroviruses (ie, FeLV, FIV) are not predisposed to infection with *Cryptococcus* spp, but difficulty responding to therapy and relapse of cryptococcosis may be common.^{2,5}
 - These patients may be predisposed to neoplasms (eg, lymphoma, adenocarcinoma, mast cell tumor).
- Opportunistic infections (eg, from *Toxoplasma gondii*) have been reported.

Pathophysiology

- Encapsulated spores (basidiospores) are typically inhaled, initiating infection in the nasal cavities of cats (primarily) and dogs.
- Disease can spread through the cribriform plate, causing meningitis.
 - May involve the optic nerve and eye.
 - May extend into lungs, skin, bones, brain, and other body sites via hematogenous routes.
 - May be detected in the lungs via histopathology without producing clinical signs.
 - Direct contact with open wounds may cause skin lesions.
 - Multiple granulomatous skin lesions are more likely associated with hematogenous spread.

History

- Outdoor cats more susceptible.
- Indoor cats exposed from open windows/doors or indoor plants/soil.
- Transfer from clothing can occur.

Signs:

- Sneezing, head shaking, stertor.
- Inappetence from blocked sinus passages and invasion into the CNS.
- Blindness.

Physical Examination

- Findings in cats (**Figure 1**):
 - Infection with *C gattii* VGI and *C neoformans* var *grubii* may be localized to the nasal cavity.
 - Infection with *C gattii* VGII genotypes can involve multiple organs.
 - Swelling over nasal maxillary of frontal area.
 - Proliferative lesions in the nares.
 - Fungal granulomas in lymph nodes and skin (primarily around head and neck).
 - Mydriasis and optic disc or retinal lesions.
- Findings in dogs:
 - Signs involving multiple organ systems.
 - Neurologic signs, often in conjunction with malaise, are most common:⁶
 - Stumbling.
 - Partial paralysis.
 - Ataxia.
 - Hyperesthesia along dorsum or cervical area.
 - Seizures, sometimes severe.

- Blindness less common than in cats.
- Approximately 50% have upper respiratory signs:⁶
 - Epistaxis.
 - Sneezing.
 - Nasal discharge.
- GI signs.
- Renal involvement.
- Cutaneous lesions.

Dx Diagnosis**Definitive Diagnosis**

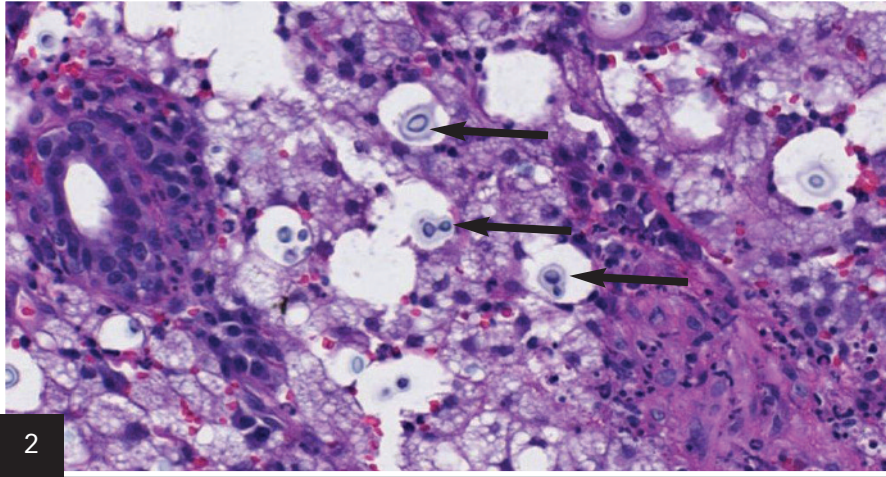
- Cytologic evaluation of tissue samples.
 - Rapid, inexpensive, sensitive test.
 - Does not permit identification of *Cryptococcus* spp.
 - Narrow-based budding yeast capsules evident (**Figure 2**).
- Culture of samples from nasal swab, needle aspiration, cerebrospinal fluid (CSF), lymph nodes, pleural and/or abdominal fluids, urine.
 - Organism grows readily in standard culture media and is not a hazard to laboratory personnel.²
 - *Cryptococcus* spp will not grow on dermatophyte medium containing cycloheximide.
 - Use of selective medium can differentiate *C neoformans* group from

1

(A) Cat presented with classic nasal lesions consistent with cryptococcosis; (B) signs improved after 7 months of treatment with fluconazole. Courtesy of Patricia Ashley, DVM, DACVD

**A****B**

CSF = cerebrospinal fluid



2

Histopathology sample showing *Cryptococcus* organisms (**black arrows**). (Hematoxylin and eosin stain, 100x magnification) Courtesy of Michele Stock, DVM, DACVD

C. gattii.

- ❑ Immunohistochemical staining cannot distinguish various *C. gattii* strains from Pacific Northwest.
- ❑ Can use with titers to evaluate treatment outcome.
- Antigen titers in serum and CSF are highly specific and sensitive.
 - ❑ Aid in diagnosis and determining response to therapy.
 - Initial rise in titers after treatment is expected.
 - Titers should be rechecked 6–8 weeks after initiating therapy.
 - Therapy should be continued until titers are negative; relapse is possible.

Differential Diagnosis

- Infectious rhinitis.
 - ❑ Bacterial.
 - ❑ Viral.
 - ❑ Parasitic.
- Inflammatory rhinitis.
 - ❑ Foreign object.
 - ❑ Lymphoplasmacytic.
 - ❑ Eosinophilic.
 - ❑ Other.
- Neoplasia.
 - ❑ Nasal lymphoma (more common in cats).
 - ❑ Nasal adenocarcinoma (more common in dogs).

Laboratory Findings

- CBC and serum biochemistry findings are nonspecific:
 - ❑ Low-grade nonregenerative anemia.
 - ❑ Lymphopenia.
 - ❑ Monocytosis.
 - ❑ Occasionally elevated globulins (polyclonal gammopathy).
- CSF analysis.
 - ❑ May have encapsulated yeast.
 - ❑ Mild to moderate protein elevations.
 - ❑ Neutrophilic pleocytosis.

Imaging

- Thoracic radiography.
 - ❑ Assess for pulmonary infiltrates, enlarged lymph nodes, mediastinal changes, and effusions from systemic fungal infection.
- Abdominal ultrasonography.
 - ❑ Normal in >80% of cats with cryptococcosis.
 - ❑ Iso-hypoechoic mass lesions in the renal pelvis in cats with renal involvement may be visible.
- MRI.
 - ❑ Helps assess extent of CNS involvement, including mass lesions and optic nerve enlargement.
- CT.
 - ❑ Helps assess destruction of cribriform plate and bony structures of the face.

- ❑ May have contrast-enhancing mass lesions of the nasal planum; soft tissue and fluid opacification are also possible.
- ❑ Also helps assess extent of CNS involvement, including mass lesions and optic nerve enlargement.

Tx Treatment

- Supportive care for anorexic and dehydrated patients should be administered as necessary.
- Surgery:
 - ❑ May be beneficial to cats with large accessible cryptococcomas if medications do not penetrate the lesions.
 - ❑ Is controversial as some cats respond to antifungal therapy (see **Medications**, next page).

Nutritional Aspects

- Feeding tubes (eg, PEG, E-tubes) may be indicated to supply nutritional support until inflammation in the nasal passages subsides with antifungal therapy.

Client Education

- Treatment duration is long and owner compliance with medications and follow-up is imperative.
- Zoonotic transmission of *Cryptococcus* from a pet cockatoo to an immunocompromised person has been reported.⁷
 - ❑ Transmission is via aerosol exposure from bird excreta rather than direct contact with the animal.⁸
 - ❑ Cryptococcosis is the most common opportunistic fungal disease of humans with HIV.⁸
- Other sources indicate no zoonotic potential to immunocompetent individuals.⁶⁻⁹
- Transmission occurs via shared contaminated environments.⁶

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Rx Medications

Azoles

- Fungistatic compounds that alter cell membrane permeability and allow cell contents to leak into the periphery.
- Fluconazole is treatment of choice for maximum penetration into the CNS, eye, and urinary tract with minimal side effects.
 - Standard dose for dogs and cats is 5 mg/kg PO q12h until antigen testing of blood or CSF (if CNS disease is present) is negative (mean duration, 8 months).⁸
 - Some cryptococcal isolates show resistance.
- Itraconazole has been used successfully to treat cryptococcal meningitis.
 - Cats may experience anorexia, vomiting, and hepatocellular damage (all dose-dependent).
 - Oral suspension has greater bioavailability and should be dosed lower than tablet formulation (3 mg/kg PO q24h rather than 10 mg/kg PO q24h).
 - Compounded formulations have been associated with inadequate blood levels.
- For cats with localized disease and resistance to fluconazole, ketoconazole may be preferred by cost-conscious owners.
 - Standard dose of ketoconazole for dogs and cats is 5–10 mg/kg PO q12–24h until antigen testing of blood or CSF (if CNS disease is present) is negative (~6–18 months).⁸
- Other azoles (eg, voriconazole, posaconazole) are effective but expensive.
 - Cats may experience neurologic effects from voriconazole.

Amphotericin B

- Fungicidal compound that also disrupts fungal cell membranes.

- Must be given parenterally.
 - SC protocol may minimize hospitalization and permit outpatient care.
 - 0.5–0.75 mg/kg diluted in large volumes of 0.45% NaCl and 2.5% dextrose 2–3 times/week.
 - Median cumulative dose of 16 mg/kg.
- Newer liposomal and lipid complex preparations are less nephrotoxic than previous formulations.

Flucytosine

- Pyrimidine analog that interferes with fungal nucleic acid synthesis.
- Standard dose (cats only) is 30 mg/kg PO q6h, 50 mg/kg PO q8h, or 75 mg/kg PO q12h, not to exceed 250 mg q6–8h.⁸
- Should not be used as a monotherapy because of risk for resistance.
- May cause bone marrow suppression, GI disturbance, and worsening of pre-existing renal insufficiency.
- Should not be used in conjunction with amphotericin B.
- Use only in cats; dogs tend to develop severe cutaneous drug eruptions.



Follow-up

Complications

- Hepatocellular damage associated with chronic ketoconazole and itraconazole administration is possible and warrants monthly monitoring of liver enzymes.
- Renal toxicity associated with amphotericin B is possible and warrants monthly monitoring of renal values and consideration of using liposome-encapsulated formulations of amphotericin B to reduce risk for renal toxicity.

Future Follow-up

- Serum antigen titers should be monitored monthly for seroconversion during treatment.

- Patients that seroconvert to a negative status should be retested 1 month after therapy.
- Successful treatment occurs when the titer reaches zero.
- Treatment may be indicated for months to years.
- For cats in carrier state, periodic antigen testing is warranted.
 - Antigen titer should decrease by 1 dilution each month during therapy.
 - Failure to achieve this suggests the need for more aggressive therapy (ie, additional medications or change in protocol).⁸



In General

Relative Cost

- Treatment is costly, as it is required for months to years: \$\$\$\$
- Fluconazole and ketoconazole are less expensive than itraconazole.

Cost Key

\$ = up to \$100
 \$\$ = \$101–\$250
 \$\$\$ = \$251–\$500
 \$\$\$\$ = \$501–\$1000
 \$\$\$\$\$ = more than \$1000

Prognosis

- Animals that survive the first 2 weeks of therapy have a reasonable but guarded prognosis.
 - Rapid rate of improvement in the first month can lead to decreased owner compliance, precluding a higher rate of relapse.
- Relapse is possible.
- CNS involvement is the only significant predictor of mortality. ■ **cb**

See Aids & Resources, back page, for references & suggested reading.