# GUIDELINE for Cryptococcosis in Cats

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## Key points

- Cryptococcosis is a non-contagious, rare or sporadic disease, which occurs worldwide and is considered the most common systemic fungal disease in cats.
- It is caused by the *Cryptococcus neoformans-Cryptococcus gattii*species complex, which includes eight genotypes and some subtypes (strains) with different geographical distribution, pathogenicity and antimicrobial susceptibility. However, they are clinically indistinguishable.
- Cats acquire the infection from a contaminated environment.
- Avian guanos, particularly pigeon droppings, offer favourable conditions for the reproduction of *neoformans*, but both *C. neoformans* and *C. gattii*species are associated with decaying vegetation such as Eucalyptus leaves.
- Basidiospores are the infectious propagules of *Cryptococcus* as they penetrate the respiratory system and induce primary infection.
- Asymptomatic colonization of the respiratory tract is more common than clinical disease.
- Cryptococcosis can present in several different clinical forms, including nasal, central nervous system, cutaneous, and systemic forms.
- An easy and reliable test for the diagnosis of cryptococcosis is antigen detection in blood serum, urine and body fluids. Alternatively, biopsy samples can be collected from lesions and submitted for cytology, culture, histopathology and PCR.
- Only isolation and PCR provide identification of the species and the genotype involved.
- Prognosis is favourable in most cases, provided a diagnosis is obtained sufficiently early in the course of disease and treatment compliance in patients and owners is good as a long course treatment (months) and follow-up (years) is required.
- Treatment guidelines have not been established and the choice of the appropriate antifungal drug given depends on many factors, including owner compliance.
- Amphotericin B, ketoconazole, fluconazole and itraconazole have all been used to treat cryptococcosis in cats.
- Surgical excision of any nodules located in the skin, nasal or oral mucosa is a valuable adjunct treatment in cats undergoing medical therapy.
- Cryptococcosis is not a zoonotic disease and cats with the disease are not contagious to humans and other animals. They are considered sentinels of environment contamination.
- The presence of avian guanos, particularly pigeon droppings and some 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.

## Agent properties

Feline cryptococcosis is caused by basidiomycetous yeasts of the genus *Cryptococcus* belonging to the *C. neoformans-C. gattii* complex. A previous classification distinguished five serotypes (A, B, C, D, AD) according to antigenic characteristics of the capsular polysaccharide (Sykes and Malik, 2012). Updated nomenclature, based also on genotyping, differentiates two main species affecting cats: *C. neoformans* – including the varieties *C. n.* var. *grubii* (formerly serotype A) and *C. n.* var. *neoformans* (formerly serotype D) – and *C. gattii* (formerly serotypes B and C). Based on molecular typing and subtyping characterization, isolates from the *C. neoformans-C. gattii* complex includes eight genotypes and some subtypes (strains) with different geographical distribution, pathogenicity and antimicrobial susceptibility (Lester et al., 2011; Trivedi et al., 2011).

The cryptococcus fungus can differentiate into several morphological forms including yeast, chlamydospores, pseudohyphae and hyphae under certain conditions, but it is typically present in the yeast form in mammalian hosts, reproducing by mitosis in animal tissues (Alspaugh et al., 2000; Lin and Heitman, 2006). Other *Cryptococcus* species have been rarely reported in cats: *Cryptococcus albidus* may affect immunocompromised cats and *Cryptococcus magnus* has been isolated in cats with otitis (Kano et al., 2004, 2008).

## Epidemiology

Cryptococcosis affects humans, cats, dogs, ferrets, horses, goats, sheep, cattle, marine mammals, koalas and other marsupials, birds, reptiles, amphibia and fish (Sykes and Malik, 2012; Danesi et al., 2020). It has a worldwide distribution and is observed more commonly in cats than in dogs (McGill et al., 2009). Cats are five to six times more likely to be affected by the disease than dogs, and three times more than horses (McGill et al., 2009).

Unfortunately, *Cryptococcus* is not usually identified to the species and molecular level with routine diagnostic sampling, and data regarding the feline disease in Europe are from single case reports or small case series, since the disease usually occurs sporadically (Castella et al., 2008). Larger retrospective studies are available only from Canada, Australia and California (Craig et al., 2002; O'Brien et al., 2004; Duncan et al., 2005, 2006; McGill et al., 2009; Sykes et al., 2010).

The disease is usually rare or sporadic. However, in 1999, a large-scale outbreak of cryptococcosis caused by *C. gattii* for the first time involved humans, terrestrial (dogs, cats, ferrets, llamas, horses, birds) and marine (porpoises *Phocoenoides dalli*) animals; it occurred on southern Vancouver Island, British Columbia, Canada in a region characterized by wet, mild winters and dry, warm summers. It is now well known that *C. gattii* has a worldwide distribution with a high prevalence along the Pacific coast of North America. In Europe, it has been reported in Austria, Belgium, Denmark, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Sweden and the United Kingdom (Lester et al., 2011; Nunes Rodrigues et al., 2020). Also *C. n.* var. *grubii* has a worldwide distribution and is commonly isolated from affected individuals in various animal species. *Cryptococcus neoformans* is considered a cosmopolitan opportunistic pathogen in human urban populations, whereas *C. gattii* is a true pathogen, more prevalent in rural areas (Sykes and Malik, 2012).

*Cryptococcus neoformans* ecology is usually related to the presence of avian guanos, particularly pigeon droppings, which offer favourable conditions for the mitotic amplification and reproduction of the fungus, but both *Cryptococcus* species have been associated with decaying vegetation such as Eucalyptus leaves (Fortes et al., 2001). Pigeons serve as *C. neoformans* carriers that likely contribute to the worldwide distribution, as they carry *Cryptococcus* on their beaks, feathers, and legs (Pal, 1989). Animals, plants, soils and waterways are sources from which the potential pathogen may be acquired.

### *Prevalence*

Environmental exposure and asymptomatic colonization of the respiratory tract are more common than clinical disease (Malik et al., 1997b; Connolly et al., 1999). Asymptomatic carriage of *C. gattii* has been recognized in 4.3% of cats, 1.1% of dogs and in 2% of wild animals (squirrels) trapped in British Columbia (Bartlett et al., 2003; Duncan et al., 2005).

Retrospective studies of feline cases tend to show a preponderance in males, although this finding was not confirmed in all studies (Malik et al., 1992; Flatland et al., 1996; Jacobs et al., 1997; Gerds-Grogan and Dayrell-Hart, 1997; Lester et al., 2004; McGill et al., 2009; Sykes et al., 2010). Pedigree breeds, such as Ragdoll, Birman, Siamese and Himalayan, were considered more often affected than domestic shorthair or longhair breeds but this finding has not been confirmed in more recent studies (Malik et al., 1992; O'Brien et al., 2004; McGill et al., 2009; Sykes et al., 2010; Trivedi et al., 2011). In contrast with other animal species, where usually young adults contract the infection, cats of any age may be affected (Malik et al., 1992; McGill et al., 2009; Vercelli et al., 2021). No seasonal trend in the diagnosis of infection has been observed (McGill et al., 2009). Additionally, lifestyle does not seem to be a risk factor and the disease has been reported in indoor cats too.

### *Transmission*

Small size infectious propagules, such as basidiospores (<2 µm) and desiccated yeast cells (<3 µm), are easily dispersed by air flow and can penetrate the respiratory system where primary infection takes place. Less frequently, penetrating injuries can directly inoculate infectious particles into the skin. The oral route is probably responsible for unique gastrointestinal lesions that sometimes arise with crypotococcosis (Reis et al., 2021).

## Pathogenesis

*Cryptococcus* is an airborne pathogen, and the nasal cavity is usually the primary site of infection in cats and dogs. In most cases there is only subclinical colonization without invasion of the epithelium (Duncan et al., 2005). When invasion of mucosal tissues occurs, progression to disease occurs locally and/or systemically. In both, people and cats, the infection may follow ingestion of desiccated yeast cells or, more rarely, cutaneous inoculation of fungal forms by penetrating injuries. The incubation period varies from months to years, and the source of infection often remains unknown. The virulence (genotype) and burden of the infecting organisms influence the outcome of infection.

From the upper respiratory tract the infection may spread locally to the central nervous system (CNS) through the ethmoid bone, and rarely also to the lower respiratory tract or systemically (Martins et al., 2011).

There are temperature-sensitive strains which are unable to grow at temperatures $\geq$ 37.0°C and may cause infections only at body sites where the temperature is lower (skin, nose, scrotum) (Bemis et al., 2000; Lin, 2009).

## Immunity

Antibodies produced against capsular antigens are not protective. Persistent infections can occur because the capsule of *Cryptococcus* yeast forms inhibits phagocytosis and other virulence factors, such as melanin production, protects the yeast cells from oxidative damage. *Cryptococcus* is therefore able to survive inside phagocytic cells – such as macrophages and neutrophils – and can be disseminated with these cells (Urban et al., 2006; Lester et al., 2011; Trivedi et al., 2011).

Some studies suggested that cryptococcosis has a higher prevalence or a less favourable outcome in FeLV- or FIV-infected cats (Gerds-Grogan and Dayrell-Hart, 1997; Jacobs et al., 1997), but this conclusion has not been shared by others (Malik et al., 1992; O'Brien et al., 2004, 2006; Norris et al., 2007; Sykes et al., 2010). Cryptococcosis has been reported in cats under chemotherapy or with concurrent opportunistic infections, so a role for poor immunocompetence in the pathogenesis of infection cannot be excluded (Trivedi et al., 2011; Graham et al., 2011).

## Clinical signs

Cryptococcosis caused by *C. neoformans* or *C. gattii* is clinically indistinguishable. The disease can present in several different clinical forms, including the nasal form, CNS form (which can derive from the nasal form or occur independently), the cutaneous form and the systemic form. Geographical differences in the prevalence of some clinical presentations are postulated as a consequence of the distribution of genotypes with differing virulence.

### *Nasal form*

The nasal form is the most common in cats, presenting as a chronic sino-nasal disease, either alone or together with local spread to the skin, subcutis, bones and regional (submandibular) lymph nodes (Malik et al., 1992; O'Brien et al., 2004; McGill et al., 2009). It induces naso-facial swelling followed by deep nonhealing ulceration draining gelatinous exudate, chronic nasal discharge (monolateral or bilateral) with serous, mucopurulent or bloody aspect, stertor and inspiratory dyspnoea, sneezing and snuffling and submandibular lymphadenopathy (Figs. 1-3).

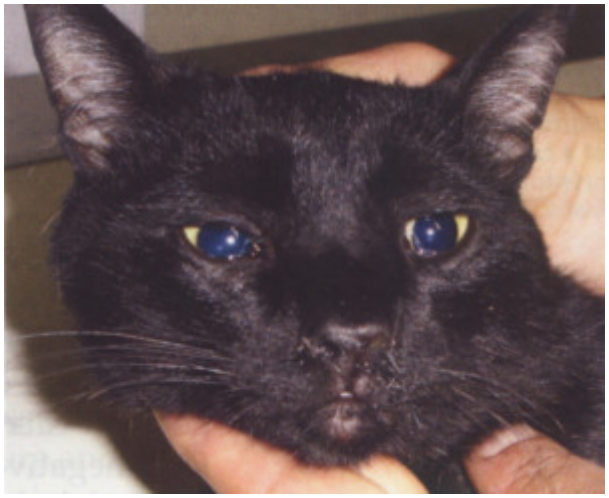

*Fig.1 Nasal cryptococcosis – chronic monolateral nasal discharge and mild nasal deformity. Courtesy of Maria Grazia Pennisi*

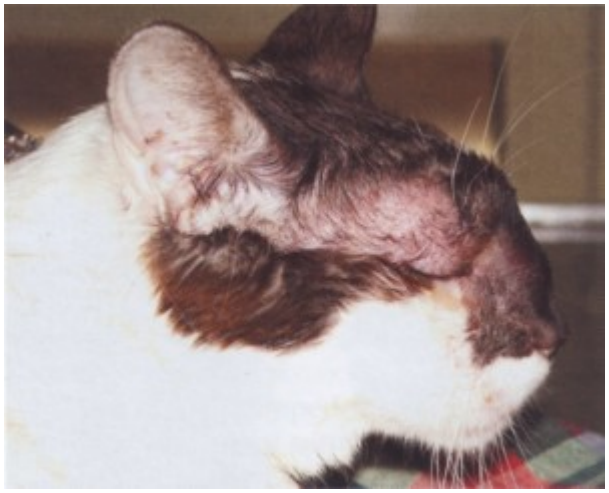

*Fig. 2. Cryptococcal disease – severe naso-facial swelling and deformity. Courtesy of Maria Grazia Pennisi*

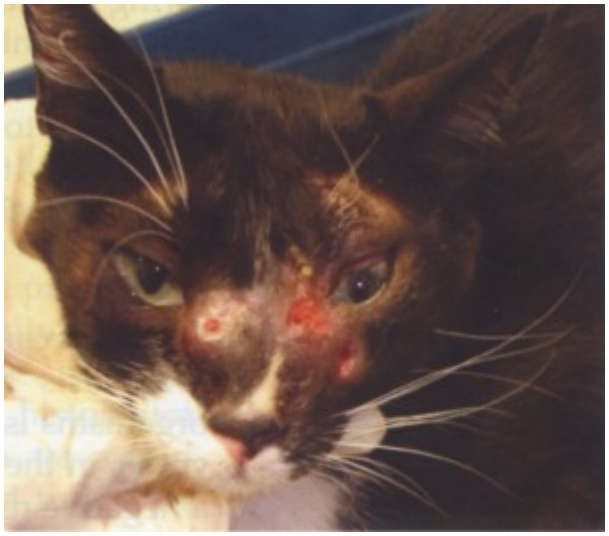

*Fig. 3. Cryptococcal disease – ulcerated skin nodules on the face. Courtesy of Maria Grazia Pennisi*

Anorexia and subsequent weight loss may also be a result of anosmia affecting cats with chronic nasal disease. Cryptococcosis is an important differential in cats with chronic nasal discharge, regardless of whether or not facial swelling and/or skin ulceration is present. In some cases, a protruding fleshy mass from one or both nostrils may occur. Nasopharyngeal granulomas (resembling polyps or cancer) presenting with stertor, inspiratory dyspnoea and open mouth-breathing have also been described (Malik et al., 1997a). Proliferative or ulcerated lesions in the oral cavity or pharynx may also develop (Nunes Rodrigues et al., 2020). Otitis media/interna with vestibular signs may occur (Beatty et al., 2000; Paulin et al., 2013). Lower respiratory tract disease may follow and its manifestation may be evident radiologically as only pulmonary or mediastinal nodules.

## *Central nervous system form*

Central nervous system involvement most likely arises following local dissemination through the cribriform plate; in such cases, sudden blindness due to optical neuritis appears together with seizures or behavioural changes (Vercelli et al., 2021). In other cases it follows systemic dissemination and induces granulomatous encephalomyelitis with solitary or multiple lesions (Belluco et al., 2008; Sykes et al., 2010). Many cats show head or spine pain but other signs of meningeal involvement (hyperesthesia, nuchal rigidity) are not common (Sykes et al., 2010).

## *Cutaneous form*

Cutaneous forms are characterized by solitary or multiple dermal to subcutaneous nodules in the skin: the former are suggestive of direct inoculation, the latter of haematogenous spread from the primary site of infection (Sykes and Malik, 2012). The nodules are usually alopecic, non pruritic and not painful, and commonly accompanied by regional lymphadenopathy.

## *Systemic form*

Systemic forms may occur through haematogenous dissemination and manifest with signs of meningo-encephalomyelitis (see CNS form), uveitis, chorioretinitis, osteomyelitis and polyarthritis, systemic lymphadenitis or multi-organ involvement, including the kidneys (Fig. 4). Cranial venal caval syndrome with severe oedema of the head and neck was reported in a cat presenting a cryptococcal mediastinal mass compressing the vein, but also the oesophagus and trachea (Letendre and Boysen, 2015).

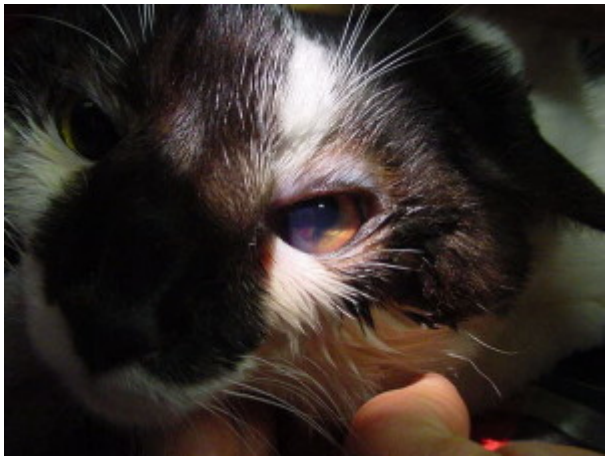

*Fig. 4. Cryptococcal disease – kerato-uveitis and cryptococcoma in the anterior chamber. Courtesy of Maria Grazia Pennisi*

Apathy and cachexia appear in cats with severe dissemination during the prolonged chronic course of the disease. The systemic form, arising from haematogenous dissemination, may or may not follow the classical nasal disease form (Tisdall et al., 2007; Martins et al., 2011).

# Diagnosis

## *Laboratory changes*

Abnormalities in blood tests are non-specific and, if present, show an inflammatory process or they are related to the clinical signs. For instance, in case of seizures elevated creatine kinase concentrations are found (Vercelli et al., 2021).

## *Diagnostic imaging*

Radiology and advanced diagnostic imaging techniques [computed tomography (CT) and magnetic resonance imaging (MRI)] are frequently used in the diagnostic process of chronic nasal and CNS signs. They provide useful information on extension and severity of lesions (particularly the head and lungs). Common abnormal findings are related to the presence of chronic rhinitis, frontal sinusitis and/or intranasal or intracranial focal solitary or multifocal masses or fluid-filled lesions (Sykes et al., 2010). Confirmation of diagnosis is not possible by imaging alone, but resolution of a mass lesion can be followed up by MRI in cats under medical therapy (Karnik et al., 2009; Hammond et al., 2011). MRI findings may also include meningeal enhancement, olfactory lobe, optic nerve and cribriform plate involvement (Sykes et al., 2010; Vercelli et al., 2021).

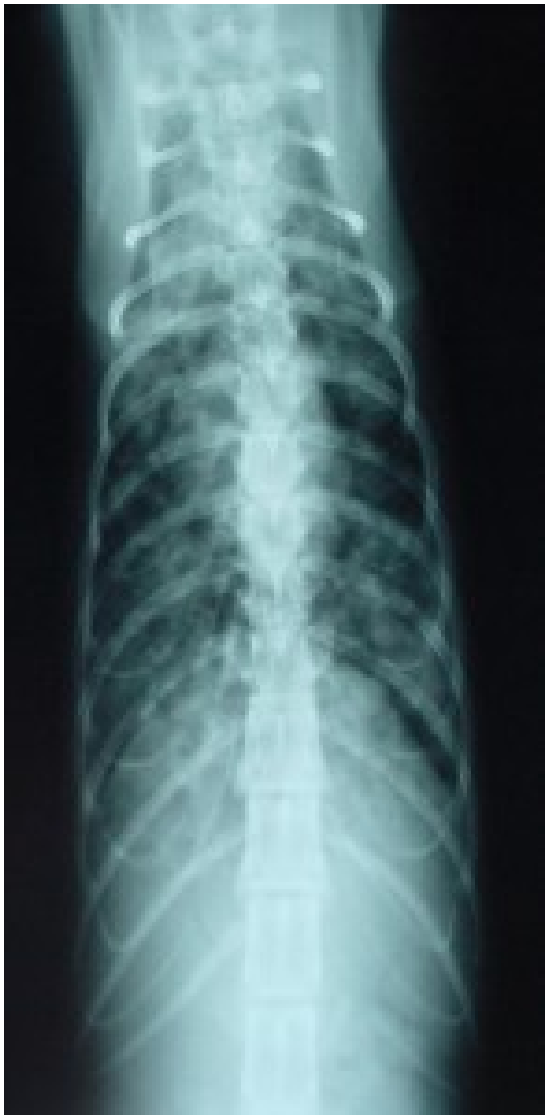

*Fig. 5. Thoracic radiography, ventro-dorsal view: diffuse, multiple, poorly defined nodules with blurred margins in the lung of a cat with systemic cryptococcosis. Courtesy of Maria Grazia Pennisi*

## *Direct detection of the infectious agent*

An easy and reliable test for cryptococcosis diagnosis is antigen detection in body fluids (serum, cerebrospinal fluid (CSF) or urine). Alternatively, samples can be collected from lesions and be submitted for cytology, culture, histopathology and polymerase chain reaction (PCR). Suitable samples include (i) pleural or peritoneal effusions, (ii) CSF, (iii) specimens collected from broncho-alveolar lavage, (iv) fine needle aspirates from nodules or enlarged lymph nodes, (v) biopsies taken from any affected tissues. An increased risk of cerebellar herniation after CSF collection is suspected and this invasive procedure should be considered only when a CNS disease compatible with cryptococcosis has not been confirmed by using other suitable biological samples (Sykes et al., 2010).

Culture and PCR offer the opportunity to identify the infecting species, as well as the genotype involved with PCR.

### Antigen detection

Antigen detection in blood serum is the test of choice if available because it is fast, reliable and minimally invasive. Cryptococcal capsular antigen may be detected by the latex cryptococcal antigen agglutination test (LCAT) on serum, CSF or urine. The sensitivity and specificity of this test is improved by pre-treating samples with heat and a proteinase (pronase, often included in commercial diagnostic kits) and is considered good in cats (Sykes and Malik, 2012). However, in some cases false negative results may occur

(Belluco et al., 2008). A positive LCAT test is indicated by a titre of 1:2 (Trivedi et al., 2011). If the antigen test is negative, and cryptococcosis is still a possibility, tissue samples should be submitted for cytology, histology and culture. On the other hand in case of titres <200, confirmatory cytology, culture or PCR is suggested.

LCAT titres are also an efficient way of monitoring the efficacy of therapy. Treatment is usually continued until a negative LCAT is obtained, but it has been reported that titres continue to decrease after stopping therapy in cats with clinical resolution and continued positive LCAT (O'Brien et al., 2006).

## Cytology

Cytology is an easy tool to diagnose cryptococcosis because the appearance of the organisms is characteristic and the number of yeasts in lesions is usually high, but a negative result does not exclude the diagnosis. Appropriate cytological samples can be obtained through impression smears from ulcerated skin lesions, fine needle aspirates of nodules, impression smears of biopsy samples or broncho-alveolar lavage samples or CSF taps. In the case of renal involvement yeasts may be seen in the urinary sediment (Brandt and Blauvelt, 2010).

Smears stained with Romanowsky-type stain (Wright, Diff-Quick, Giemsa) may show pink to violet, round or budding extracellular yeasts that vary in size (4-15 µm) and shape and are typically surrounded by a clear more or less thick halo corresponding to the unstained capsule (Figs. 6, 7).

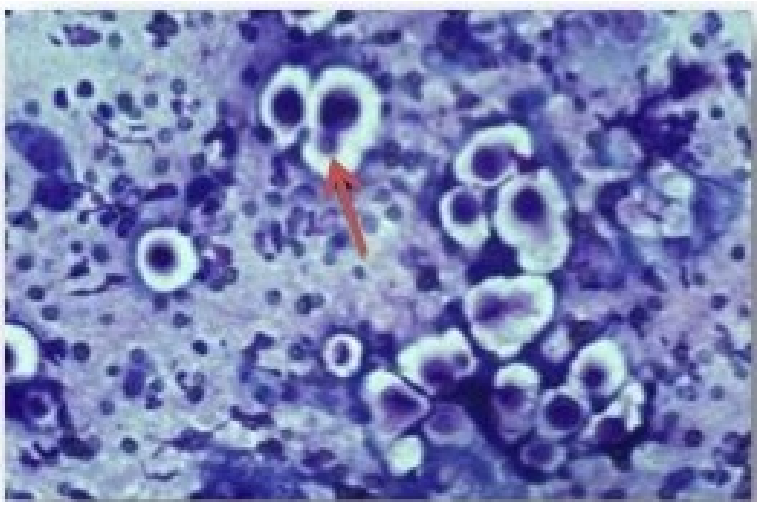

*Fig. 6. Diff Quick stained smear of nasal exudate from a cat with C. neoformans infection. Note the prominent capsule (clear halo) and narrow-necked budding (arrow). Photomicrograph courtesy of Richard Malik.*

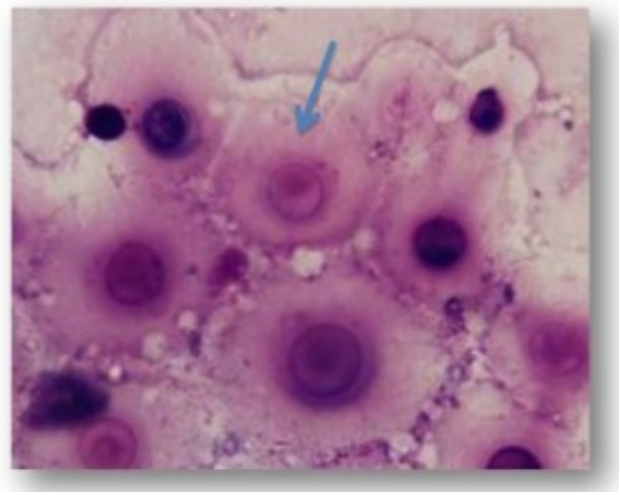

*Fig. 7. Diff Quick stained smear of fine needle aspirate from a cryptococcal lesion. Note the enormous capsule*

*surrounding the yeast cells. Photomicrograph courtesy of Mark Krockenberger*

If a Gram stain is used, the organism appears Gram positive with a Gram negative (pink) capsule. A pyogranulomatous inflammatory pattern on cytology is usually seen. Although filamentous forms are not commonly observed in tissues, these atypical filamentous morphologic forms of *C. neoformans* may be present in cats (Bemis et al., 2000; Lin, 2009).

## Histology

Biopsy samples of the nasal mucosa, lymph nodes or skin nodules may be obtained for histology, but they may also be used to provide impression smears for cytology and material for culture and PCR. Haematoxylin-eosin stained sections show eosinophilic bodies surrounded by a clear halo and a pyogranulomatous reaction (Fig. 8). Mayer's mucicarmine method specifically stains the capsule of *Cryptococcus*. Immunohistochemistry on tissue sections is used for species differentiation, using monoclonal antibodies (Fig. 9) (Krockenberger et al., 2001).

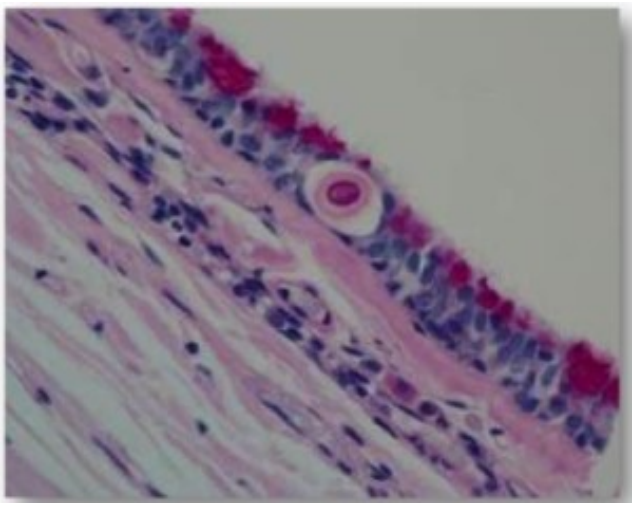

*Fig. 8. Early invasion of Cryptococcus gattii into the respiratory epithelium of a koala. Note the eosinophilic body surrounded by a clear halo. Photomicrograph courtesy of Mark Krockenberger.*

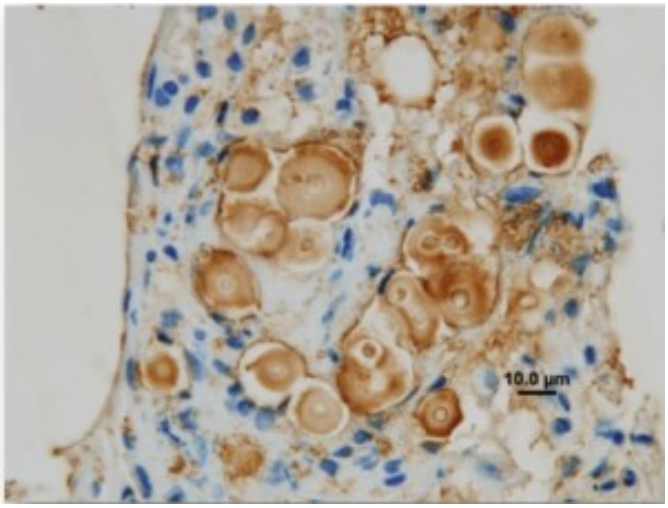


*Fig. 9 Use of immunohistology to demonstrate C. gattii in histological sections using monoclonal antibodies directed against different capsular epitopes. These show up as brown precipitates, highlighting both the yeast cell body and its capsule. Note also the narrow neck budding. Courtesy of Mark*

*Krockenberg*

### Isolation/Culture

Isolation/culture is performed if the LCAT is negative or when titres are low or absent and when PCR is not available. Only samples from nasal biopsies should be submitted for culture, because the presence of *cryptococcus* in nasal discharge cultures is not considered evidence of disease. Positive culture of biopsy samples and histological changes consistent with infection are considered diagnostic and may be used for sensitivity testing of antifungal drugs.

Culture of biopsy samples is more sensitive than cytology in confirming infection. *Cryptococcus* is easily isolated in Sabouraud's dextrose agar after incubation at 25°C and 37°C for 10 days but also on bacterial standard media. It is now possible to differentiate *C. neoformans* from *C. gattii* by culture on a specific agar test (Lester et al., 2011).

When samples are contaminated by bacteria, as often occurs in nasal discharges or secretions, media containing antibiotics are useful to use for *cryptococcus* culture (Sykes and Malik, 2012).

### Polymerase chain reaction (PCR)

Polymerase chain reaction has been developed for genetic identification of *cryptococcus* in CSF, urine, blood and biopsy samples and it is now routinely available in practice (Kano et al., 2001; Meyer et al., 2003; Okabayashi et al., 2006; Vercelli et al., 2021; Reis et al., 2021). This method also allows identification of the pathogen species and genotype.

## *Indirect detection of the infectious agent*

### Antibody detection

Antibody detection is not a diagnostic tool because it cannot distinguish subclinical infection from active disease.

# Treatment

## *Antimicrobial treatment*

No prospective controlled studies exist on the treatment of feline cryptococcosis and all data are based on retrospective studies and case reports. Treatment guidelines have not been established and the choice of the appropriate antifungal drug depends on many factors. Owner compliance is crucial, because of the high costs in terms of both money and the long time required for treatment.

Some retrospective studies on treatment outcomes of feline cryptococcosis have been reported with heterogeneous criteria used for evaluating the success of therapy (Medleau et al., 1995; Davies and Troy, 1996; Jacobs et al., 1997). In the largest retrospective study, performed on 59 cats in 2006, 68% had a successful outcome (O'Brien et al., 2006). Most of them needed one single course of therapy of several months (1 to 24) duration and few cats received a second course of therapy because of clinical recurrence or raised LCAT titre. According to a retrospective study published in 2009, the clinical outcome may be favourable in approximately 2/3 of treated cats (McGill et al., 2009). Most recovered cats presented with sino-nasal or single lesions in the skin, subcutis or intestines, and the ones that did not recover had CNS or disseminated disease.

Amphotericin B (AMB), ketoconazole, fluconazole and itraconazole have all been used to treat cats. Concerning the effect of different therapeutic protocols, there was no significant difference in outcome between cats treated with amphotericin B-containing protocols and those treated with azole monotherapy using fluconazole or itraconazole (O'Brien et al., 2006). Because of renal toxicity of AMB, it was recommended in the past not to exceed a drug total dose of 4-8 mg/kg in the overall course of intravenous treatment (cumulative dose). However, the median cumulative dose of AMB for cats cured at the first attempt was higher (16 mg/kg; range 7-23 mg/kg) when using protocols based on subcutaneous administration compared to the intravenous route (Trivedi et al., 2011). The median duration of treatment for fluconazole-treated cats was significantly shorter (4 months; range 1 to 8 months) than the median for the itraconazole group (9 months; range 3 to 24 months). Liposomal formulations of AMB may be better tolerated but are very expensive and not easily available. Recommendations for treatment based on case studies are that fluconazole or itraconazole are good first choices in mild cases.

In CNS or systemic cases AMB alone or in combination with flucytosine maybe the first choice followed by a long treatment course of fluconazole or itraconazole (O'Brien et al., 2006). Cats with pre-existing renal disease should be treated with itraconazole or fluconazole only (i.e. no AMB). Fluconazole seems to be more effective than itraconazole for infections in the CNS, eye and urinary tract and is also better tolerated (Trivedi et al., 2011; Hammond et al., 2011; Sykes and Malik, 2012). Resistance to fluconazole was reported with some isolates that were susceptible to other azoles (Lester et al., 2011; Kano et al., 2015). A three-month old kitten with seizures caused by cryptococcosis did not respond to fluconazole (10 mg/kg q12h PO) administration. However, clinical recovery and a negative blood PCR result occurred with three administrations of AMB (1 mg/kg q48h IV).

In general, continuation of treatment is recommended until the LCAT is negative. If the LCAT is negative at the time of diagnosis and the disease was confirmed by other methods or if LCAT is not available, treatment should be continued at least until 2 to 4 months after resolution of clinical signs.

### *Symptomatic treatment*

The clinical condition of cats with cerebral cryptococcosis may worsen soon after starting AMB therapy, presumably due to an inflammatory response and increased intracranial pressure. Short-acting corticosteroid (dexamethasone or prednisolone sodium succinate) therapy is reported to be of immediate benefit in such cases and associated with increased survival in the short term (O'Brien et al., 2006; Sykes et al., 2010).

Surgical excision of any nodules located in the skin, nasal or oral mucosa must be considered as a valuable aid in cats under medical therapy (Hunt et al., 2002).

## Treatment of cryptococcosis

| DRUG/THERAPY | DOSE AND DURATION | COMMENTS |
|---|---|---|
| Itraconazole | 50-100mg/cat q24h | good absorption without food. Oral solution better than capsules. Hepatotoxicity possible; monitor liver enzymes periodically / monthly |
| Amphotericin B | 0.25 mg/kg q48h IV to a total dose of 4-16 mg/kg | treatment of choice for CNS infection and/or systemic disease. Significant nephrotoxicity; monitor renal function frequently / weekly |
| Flucytosine | 25-50 mg/kg PO q6h | Synergistic with amphotericin B; do not use as single treatment |
| Fluconazole | 50 mg/cat q12h | Suggested treatment of choice, especially for CNS infection. Good absorption without food. Monitor liver enzymes |
| Terbinafine | 10 mg/kg q24h | Use if resistance to azoles |
| Surgical excision | | Skin, oropharyngeal and nostril granulomas |

IV = INTRAVENOUS, PO = ORAL, CNS = CENTRAL NERVOUS SYSTEM

# Prognosis

Prognosis is favourable in most cases, provided a diagnosis is obtained sufficiently early (before dissemination or before the development of invasive severe lesions) and patient and owner compliance is good to provide a long course treatment (months) and follow-up (years).

Although information on outcomes is quite limited, it seems that cats have a more favourable prognosis than dogs or horses which develop lower respiratory, disseminated and neurological disease more frequently, which are associated with a higher mortality (Duncan et al., 2006; O'Brien et al., 2006; McGill et al., 2009; Sykes et al., 2010).

In one retrospective study, disease severity did not influence outcome, although the presence of CNS involvement had a significantly adverse impact on the outcome of therapy (O'Brien et al., 2006). On the other hand, alteration of the mental status was the only negative prognostic factor in a retrospective study on cats with CNS form, and complete recovery was documented also in cats with a CNS form (Sykes et al., 2010; Hammond et al., 2011; Vercelli et al., 2021).

## Vaccination

Vaccines are not available.

## Prevention

Free-roaming cats in rural areas are potentially more exposed to *Cryptococcus,* even though urban cats can be contaminated through pigeon guano. According to ecology, the presence of avian guanos, particularly pigeon droppings, and some decaying vegetation substrates, such as Eucalyptus leaves, may be considered risk factors (Fortes et al., 2001). Knowledge of local fungal habitats that carry the largest risks of exposure and seasonal variations in the production of infectious propagules would be useful to develop preventive measures for both human and animal infections.

## Zoonotic risk

Feline cryptococcosis , discovered over a century ago, is a non-contagious systemic fungal disease acquired from contaminated environment. For this reason it is not considered a zoonotic disease. Animals may serve as sentinel hosts and the investigation of environmental sources based on feline cases of cryptococcosis is useful for intervention to minimize the risks of human and animal infections (Reis et al., 2021).

### *Acknowledgement*

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