

Journal of Feline Medicine and Surgery

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Journal of Feline Medicine and Surgery 2013 15: 624
DOI: 10.1177/1098612X13489226

The online version of this article can be found at:

<http://jfm.sagepub.com/content/15/7/624>

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What is This?

RARE SYSTEMIC MYCOSES IN CATS: BLASTOMYCOSIS, HISTOPLASMOSIS AND COCCIDIOIDOMYCOSIS

ABCD guidelines on prevention and management



Albert Lloret, Katrin Hartmann, Maria Grazia Pennisi, Lluís Ferrer*, Diane Addie, Sándor Belák, Corine Boucraut-Baralon, Herman Egberink, Tadeusz Frymus, Tim Gruffydd-Jones, Margaret J Hosie, Hans Lutz, Fulvio Marsilio, Karin Möstl, Alan D Radford, Etienne Thiry, Uwe Truyen and Marian C Horzinek

Overview: Rare fungal infections, including those hitherto not reported in Europe, may occur sporadically in non-endemic areas, or imported cases may be seen.

Infections: Blastomycosis is mainly seen in North America; no cases have been reported in Europe. Histoplasmosis, which is endemic in the eastern US, Central and South America, has been diagnosed in Japan and Europe. Coccidioidomycosis is endemic in the southwestern US, Central and South America; only one imported case has been reported in Europe. The primary mode of transmission is inhalation of conidia or spores from the environment.

Disease signs: Most feline cases present with a combination of clinical signs (mainly respiratory, along with skin, eye, central nervous system and bone). Lymphadenopathy and systemic signs may be present.

Diagnosis: Diagnosis is based on fungal detection by cytology and/or histology. Commercial laboratories do not routinely perform fungal culture. Diagnosis of coccidioidomycosis, which is more difficult, may be supported by antibody detection.

Treatment: Treatment consists of prolonged systemic antifungal therapy, with itraconazole as the first-choice agent for histoplasmosis and blastomycosis. The prognosis is good if owner compliance is adequate and adverse drug effects do not occur.

Prevention: Cat owners travelling to endemic areas should be warned about these diseases. There is no zoonotic risk.

Fungal properties and epidemiology

Rare systemic fungal infections in Europe are blastomycosis (caused by *Blastomyces dermatitidis*), histoplasmosis (caused by *Histoplasma capsulatum*) and coccidioidomycosis (caused by *Coccidioides immitis*). In endemic areas, these infections are more frequent in dogs; scientific data for cats are scarce and mainly based on a few retrospective case series or reports.

These diseases are endemic in some areas of the Americas, but in recent years more cases have been reported from non-endemic areas.^{1–5} At risk are mainly outdoor, free-roaming cats with access to fungal organisms in the soil.¹ However, an outbreak of blastomycosis has been reported in an urban non-endemic area (Chicago, Illinois), in five indoor cats; unusual drought was suggested as the most likely cause.²

Histoplasmosis has also been diagnosed in indoor cats, associated with exposure to contaminated soil linked to construction work, potted plants and unfinished basements.^{6,7} The first reported cases of histoplasmosis in Europe and Japan have been published in recent years. In both cases diagnosis was confirmed by post-mortem examination, involving histology, special stains and immunohistochemistry.^{3,5} Italy, Germany and Turkey should be considered endemic areas for histoplasmosis, as suggested by the European Confederation of Medical Mycology Working Group.⁸

Few case reports and one case series of coccidioidomycosis have been published so far, and only in endemic areas. One case in a cat imported from the USA has been diagnosed in Portugal.⁴

European Advisory Board on Cat Diseases

The European Advisory Board on Cat Diseases (ABCD) is a body of experts in immunology, vaccinology and clinical feline medicine that issues guidelines on prevention and management of feline infectious diseases in Europe, for the benefit of the health and welfare of cats. The guidelines are based on current scientific knowledge of the diseases and available vaccines concerned.

The latest version of the rare systemic mycoses in cats guidelines is available at www.abcd-vets.org

*The ABCD is grateful to Professor Lluís Ferrer, of the Foster Hospital for Small Animals, Cummings School of Veterinary Medicine, Tufts University, USA, who, though not a member of the Board, contributed to this article.

Pathogenesis

Fungal systemic mycoses are not contagious among cats, with infection occurring after the organism is contracted from the environment. Inhalation of aerosolised conidia or spores establishes a primary infection site in the lungs; thereafter, yeast dissemination to the lymphatic, skeletal and central nervous (CNS) systems occurs, as well as to the eyes and skin, with pyogranulomatous inflammation.⁹

Clinical presentation

Systemic mycoses generally produce a combination of clinical signs related to the target sites of infection, including the respiratory tract (which is usually the primary focus), bone, CNS, eyes, lymph nodes and skin.^{1,9}

✦ **Blastomycosis** Cats usually show pneumonia (dyspnoea, tachypnoea, coughing) and skin disease (non-ulcerated dermal masses or large abscesses) and non-specific signs like fever, lethargy, anorexia and weight loss.^{10,11} Chorioretinitis and common CNS signs may also be present in cats with disseminated disease.¹¹ CNS infection rarely occurs without evidence of systemic disease.¹² Lymph node involvement is not a common feature.^{10,13} Abnormal blood values are non-specific, indicative of an inflammatory process. In one cat with pulmonary and cutaneous blastomycosis, hypercalcaemia and increased levels of calcitriol were found, which returned to normal after treatment.¹⁴ Thoracic radiographs mainly demonstrate nodular interstitial to alveolar patterns and areas of consolidation. Diffuse bronchial patterns are also observed.^{10,14} Immunosuppression and retroviral infection have not usually been present in the cases reported.^{9,10}

✦ **Histoplasmosis** Cats usually show pneumonia, gastrointestinal disease and sometimes progressive disseminated disease.^{15,16} Cases have also been reported of disseminated infections without respiratory signs.^{16,17} Intestinal involvement may occur, with pyogranulomatous lesions in the small bowel and mesenteric lymph node enlargement.⁵ In disseminated disease, the liver, lymph nodes, eyes and bone marrow are affected. One case of disseminated histoplasmosis presenting as an acquired skin fragility syndrome has been reported.¹⁸

✦ **Coccidioidomycosis** Cats usually show skin, respiratory, musculoskeletal, neurological and ocular signs.^{19,20} Ocular disease (anterior uveitis, granulomatous chorioretinitis, blindness) has been diagnosed in cats without systemic signs.²¹

These systemic mycoses are endemic in some areas of the Americas, but in recent years more cases have been reported from non-endemic areas.



Diagnosis

Diagnosis is usually based on the demonstration of yeast cells in affected tissues by cytology and/or histology.^{1,9,15}

Cytology

The characteristic morphology of the yeast cells (*B dermatitidis* – thick-walled, 8–12 µm cells without a capsule; *H capsulatum* – round to oval intracellular yeast cells with a basophilic centre surrounded by a light halo) is in most cases sufficient to confirm the diagnosis. Respiratory tract (by lung fine needle aspiration or bronchoalveolar lavage), skin, lymph node (not in blastomycosis) and bone marrow (histoplasmosis) samples are most suitable for diagnosis.^{9,15}

Cytology is less reliable for the diagnosis of coccidioidomycosis.^{19,21,22}

Histopathology

Histology is needed for diagnosis when cytology fails, especially in coccidioidomycosis.²² Pyogranulomatous inflammatory responses and the presence of yeasts with the typical morphology in each case are diagnostic. Special staining for fungal organisms (periodic acid-Schiff, Gridley's or Gomori methenamine silver) may improve the sensitivity.^{9,15,22}

Culture

Culture is the gold standard for diagnosis, but is not frequently performed in practice. Concerns about the potential risks to laboratory personnel handling the samples should govern the procedures.

Other tests

Tests have been developed for the detection of blastomycosis antigen in blood and urine of dogs and humans.²³ The highest sensitivity is achieved by testing both blood and urine. Cross-reactions occur with histoplasmosis, as the antigen is identical for both organisms; the test may therefore be seen as an assay to screen for both mycoses.²⁴ Antigen detection tests have also been used to monitor response (including duration of response) to treatment.^{23,25} Antigen testing has not been critically evaluated in cats, and recommendations about its use cannot be given.

Assays to detect antibodies against these fungal organisms have been developed, but they are of low sensitivity and specificity for blastomycosis and histoplasmosis, not discriminating between current disease and previous exposure.^{1,9}

In contrast, serology using an agar gel immunodiffusion test is the basis for the diagnosis of feline coccidioidomycosis. High

Table 1 Treatment of rare systemic mycoses

Disease	Drug	Dose and frequency	Comments
Blastomycosis	Itraconazole	10 mg/kg PO q24h	Long-term treatment, commonly >3 months
	Amphotericin B	0.25 mg/kg q48h IV to a total dose of 4–16 mg/kg	Often combined with azoles in severely affected animals, including those with hypoxaemia or CNS signs. Risk of significant nephrotoxicity; monitor BUN and creatinine
	Fluconazole	2.5–10 mg/kg PO q12h	Preferred if CNS involvement. Good absorption without food. Monitor liver enzymes
Histoplasmosis	Itraconazole	10 mg/kg PO q24h	Duration 2–4 months. 100% efficacy in one small case series
	Amphotericin B	0.25 mg/kg q48h IV to a total dose of 4–16 mg/kg	Combine with itraconazole in severe cases
Coccidioidomycosis	Ketoconazole	10 mg/kg PO q12h	Administer with food for good absorption. Hepatotoxicity possible; monitor liver enzymes. Duration 3–6 months required
	Fluconazole	10 mg/kg PO q12h	

BUN = blood urea nitrogen, CNS = central nervous system

sensitivity (83%) has been established in cats by a retrospective study [EBM grade III].¹⁹ False-negative results may be expected in the first 2 months of acute infection. Coccidioidomycosis is usually diagnosed by a combination of serology, cytology and/or histopathology.^{19,21,22}

Treatment

No prospective studies exist on the treatment of feline systemic mycoses. Available data on treatment are based on retrospective studies and case reports.

Itraconazole is currently the treatment of choice for blastomycosis and histoplasmosis [EBM grade III].^{1,16,26} Amphotericin B and fluconazole may be used as well, especially in severe cases or those with CNS signs [EBM grade III].^{1,16} In a study of eight cats with histoplasmosis, long-term itraconazole treatment was well tolerated and cured all the patients [EBM grade III].¹⁵

EBM grades

The ranking system for grading the level of evidence of various statements within this article is described on page 533 of this Special Issue.

Ketoconazole or fluconazole have been used most frequently in feline coccidioidomycosis [EBM grade III].^{1,19} In a recent report of cats with ocular coccidioidomycosis, fluconazole was effective, although long term treatment was necessary in one case [EBM grade IV].²¹

Table 1 lists the treatment options for these infections.

There are no vaccines available.

Funding

The authors received no specific grant from any funding agency in the public, commercial or not-for-profit sectors for the preparation of this article. The ABCD is supported by Merial, but is a scientifically independent body.

Conflict of interest

The authors do not have any potential conflicts of interest to declare.

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Disease in humans

Systemic mycoses are not considered zoonotic, as they are not contagious among cats nor generally transmitted by cat-to-human contacts. Infection occurs by contact with spores or conidia from the environment where they reside as soil saprophytes. Concerns are justified about the potential danger for laboratory personnel manipulating samples for culture.

Exceptionally, the first case of cat-to-human transmission of coccidioidomycosis has recently been reported; the infection was transmitted to a veterinary assistant through a bite from an infected cat.²⁷

Zoonotic risk
Systemic mycoses are not considered zoonotic.



KEY POINTS

- ❖ Cat owners travelling to endemic areas should be warned about these rare systemic mycoses. Practitioners in Europe should consider these infections in cats coming from endemic areas.
- ❖ Italy, Germany and Turkey should be considered endemic areas for histoplasmosis, based on recommendations made by the European Confederation of Medical Mycology Working Group. So far only one cat with histoplasmosis has been reported from Italy.
- ❖ Respiratory involvement is common and frequently the primary site of infection. Dissemination may occur to skin, gastrointestinal system, lymph nodes, liver, CNS, eye and bone.
- ❖ Fine-needle aspirates and cytology are of high sensitivity in the diagnosis of blastomycosis and histoplasmosis.
- ❖ Itraconazole, administered over several months, is the first-line treatment for blastomycosis and histoplasmosis, and fluconazole for coccidioidomycosis.



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