Histoplasmosis in Dogs and Cats

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Histoplasma capsulatum is endemic throughout most of the United States with a high prevalence of infections in the Midwest and South. Histoplasmosis is the second most common systemic fungal disease in cats that may be more susceptible than dogs. Infection occurs by inhalation of conidia from the mycelial phase, which subsequently convert to the yeast form. Histoplasma capsulatum is phagocytized and harbored by cells of the mononuclear phagocyte system. Infection may be subclinical or cause clinical pulmonary granulomatous disease or dissemination. Disseminated disease predominantly affects the liver, spleen, gastrointestinal tract, bone and bone marrow, integument, and eyes. Primary gastrointestinal histoplasmosis also occurs. Clinical signs of histoplasmosis often are nonspecific, including chronic wasting, fever, anorexia, respiratory signs, and lameness. Gastrointestinal signs (eg, diarrhea with hematochezia or melena) are common in dogs. The definitive diagnosis is made by identification of the yeast in tissue samples. Itraconazole is the treatment of choice.

KEYWORDS histoplasmosis, dog, cat, fungi, infection etiology, infection epidemiology

The causative agent of histoplasmosis is Histoplasma capsulatum, a dimorphic soil-borne fungus. Soil containing nitrogen-rich organic matter such as excrements in avian and bat habitats favors the growth of the organism by accelerating sporulation.1,2 The organism exists in the environment as a mycelial form and in the host’s body as a yeast. Yeast are 2 to 4 μm in diameter and are surrounded by a 4 μm thick wall.3-6

H. capsulatum has a worldwide distribution in temperate and subtropical climates and is endemic to much of the United States, with the highest prevalence in the Midwestern and Southern states and regions along the Ohio, Missouri, and Mississippi Rivers.7,8 Histoplasmosis also occurs sporadically outside known endemic areas (eg, reported in dogs in Ontario, Canada,6 and Australia10 and in cats in central California11). Based on pathogenicity and morphology, the genus Histoplasma has been thought to consist of three species: H. capsulatum, H. duboisii, and H. farciminosum.12 Recent studies analyzed phylogenetic relationships and identified at least eight clades of Histoplasma from different geographic regions throughout the world suggesting the existence of genetically distinct geographical populations.13 Recently, H. capsulatum isolates from soil, dogs, rats, and humans in Brazil were characterized using a PCR-based random amplified polymorphic DNA (RAPD) assay. Genetic polymorphisms between H. capsulatum strains isolated from animals and soil in the same geographic area were 100% similar, suggesting that an environmental microniche could be acting as a source of infection for animals and humans.14

In a review of 571 cats with deep mycotic infections, histoplasmosis (16.7%) was the second most commonly reported fungal disease after cryptococcosis (46.1%).15 Histoplasmosis affects dogs16,17 and cats15,18 of all ages but is reported predominantly in younger animals: mean age was 3.9 years in 56 cats15 and 4.3 years in 23 dogs.16 Six of 12 dogs17 and 18 of 29 dogs19 in other case series were 1 to 3 years old. Certain sporting and working dogs and more specifically Terriers, Pointers, Weimaraners, and Brittany Spaniels are at increased risk for histoplasmosis.20 Persian cats were slightly overrepresented in a feline case series but there was no gender predisposition.15

Pathogenesis

Infection occurs by inhalation and possibly by ingestion of micro- or macroconidia from the mycelial phase that transform to yeast within the host’s body.3,8,12 The yeast form of the organism is phagocytized by cells of the mononuclear phagocyte system (MPS) and replicates intracellularly. Macrophages are considered the primary hosts for H. capsulatum.9,12 The organism displays mechanisms for resisting host reactive oxygen, nitrogen, and degradative enzymes and for withstanding nutrient starvation conditions.24 Most infections with H. capsulatum are clinically inapparent.3,17 The organism may cause local granulomatous disease of the re-
Clinical Signs

Cats

In cats with histoplasmosis, the duration of illness has ranged from 8 to 11 weeks, although in one study, only 36% of cases had clinical signs for less than 4 weeks. Clinical signs are often chronic and nonspecific despite severe disseminated disease, which was identified in 95% of 54 feline cases that underwent necropsy. A review of 96 cats with histoplasmosis revealed the following distribution of clinical signs: weakness, lethargy, emaciation, and fever (67% of cats), respiratory signs including dyspnea, tachypnea or coughing (39%), cutaneous signs (24%), and skeletal involvement (18% had lameness or swelling of one or more limbs). Clinical signs noted in other reports of single or few cases of feline histoplasmosis included weight loss, anorexia, respiratory signs (dyspnea, tachypnea, coughing, sneezing, wheezing), cutaneous swelling or ulceration, lameness, gagging, and vomiting. Although reported occasionally in the literature, cats with disseminated histoplasmosis and pulmonary involvement seldom cough, even though radiographs show features consistent with pulmonary histoplasmosis. Atypical clinical presentations in cats include disseminated histoplasmosis involving only the skeletal system and primary small and large intestinal histoplasmosis. Intestinal histoplasmosis without concurrent pulmonary involvement may be manifested by clinical signs of chronic wasting, fever, watery diarrhea with hemoschezia and vomiting.

Dogs

In dogs with disseminated histoplasmosis, the duration of clinical signs before presentation has ranged from hours to 1.5 years, although in one study, most (20/24, 83%) dogs were admitted within 14 weeks of the first detection of clinical signs. Chronic diarrhea (often with hemoschezia or melena) and wasting (weight loss, lethargy, weakness, pale mucous membranes) are common clinical signs.

Physical Examination Findings

Cats

Physical examination findings in cats with histoplasmosis include emaciation, fever, pale or icteric mucous membranes, lymphadenopathy, tachypnea, harsh lung sounds, hepatomegaly, or pain on abdominal palpation, joint pain and effusion, and single or multiple cutaneous nodules, ulcerations, or draining tracts. In a review of 8 cats with Histoplasma capsulatum osteomyelitis, none of the cats had obvious physical signs of respiratory tract disease. Ocular disease including choroiditis, chorioretinitis, optic neuritis, anterior uveitis, retinal detachment, panophthalmitis, and glaucoma may also be noted. Ocular signs were seen in as many as 24% of 96 cats with histoplasmosis.

Dogs

Common physical examination findings reported in dogs with histoplasmosis are a thin body condition, fever, pale or icteric mucous membranes, peripheral lymphadenopathy, abnormal lung sounds, and hepatomegaly. Cutaneous nodules, joint swelling and pain, erosions and raised lesions on the tongue, splenomegaly, miosis, anterior uveitis, retinitis, chorioretinitis, optic neuritis, and retinal detachment may also be noted.

Clinicopathologic Abnormalities

Clinicopathologic abnormalities, if present, usually reflect chronic inflammatory disease or bone marrow infiltration by H. capsulatum and are not distinctive for histoplasmosis. In cats, hematologic abnormalities include anemia, neutropenia, thrombocytopenia, or combinations of these changes. Anemia, the most common hematologic abnormality, is usually normocytic, normochromic, and nonregenerative. Leukocytosis (neutrophilia) is less frequently seen. Neutrophils may display...
toxic changes. The complete blood count can be normal even with chronic disease.

Histoplasmosis in dogs causes similar hematologic changes. Normocytic, normochromic, nonregenerative anemia, neutrophilia, leukocytosis, neutropenia, monocytosis, and thrombocytopenia have all been reported. The thrombocytopenia seen in some dogs with systemic histoplasmosis appears to be caused by increased platelet consumption and sequestration, and may contribute to intestinal blood loss and anemia. Eosinophilia and basophilia were reported in one case of disseminated histoplasmosis in a dog with severe fungemia.

Results of serum biochemical analyses often are within reference ranges even with chronic disease. Cats and dogs with histoplasmosis may display hypalbuminemia, hyperglobulinemia, hyperbilirubinemia, and increased activities of serum alanine aminotransferase (ALT), aspartate aminotransferase, and/or alkaline phosphatase. In addition, hypercalcemia of granulomatous disease was reported in a cat with histoplasmosis. Results of urinalyses in cats and dogs are usually within reference ranges; proteinuria may be observed.

**Diagnosis**

The diagnosis of histoplasmosis is made based on clinical signs, radiographic abnormalities (if present), and ultimately, identification of the organism. Residence of the pet within an endemic area or travel history to an endemic area should be considered. As signs may be present for over 1 year before the diagnosis is made, and reactivation of latent infection may occur in the face of immunosuppression, travel history need not be recent.

**Radiography and Endoscopy**

Abnormalities on thoracic radiographs have been noted in as many as 87% of 31 feline patients with histoplasmosis. Radiographic patterns in cats with pulmonary histoplasmosis include fine, diffuse or linear interstitial, or bronchointerstitial infiltrates, diffuse miliary or nodular interstitial infiltrates and alveolar infiltrates. Areas of pulmonary consolidation also may be present. In one cat, there was no clinical or radiographic evidence of pulmonary involvement although the organisms were present in the lungs.

The most common thoracic radiographic abnormalities in dogs with pulmonary histoplasmosis are a bronchointerstitial or interstitial lung pattern and hilar lymphadenopathy. Alveolar or nodular interstitial lung patterns (Fig. 1), pleural effusion and sternal lymphadenopathy are less frequently seen. Less typical radiographic findings reported in canine histoplasmosis have included a focal alveolar opacity in one lung lobe and pleural effusion and a single mass (fungal granuloma) in the thoracic cavity cranial to the heart.

Bone lesions consistent with osteomyelitis were seen in 7 of 7 cats presented with lameness or limb swelling from a total of 96 reviewed cases. These include lytic lesions of one or, more commonly, multiple long bones as well as carpal or tarsal bones. Multifocal lytic metaphyseal lesions are characteristic, suggesting hematogenous fungal invasion. There is a predilection for osseous lesions distal to the elbow and stifle joints in cats. Bone involvement may be associated with soft tissue swelling, peristeal reactions, endosteal new bone formation, or pathologic fractures. Soft tissue swelling, joint effusion, and osteolytic lesions in the long bones, carpus and tarsus also have been reported in the dog. Abdominal radiographs may reveal hepatomegaly or splenomegaly in both dogs and cats as well as peritoneal effusion.

Endoscopic findings in dogs with intestinal histoplasmosis include increased granularity, friability, ulceration, and an increased thickness of the intestinal mucosa; the appearance can be very similar to that of severe colitis. Bronchoscopy in dogs may identify compression of the left and/or right principal bronchi of varying degrees caused by hiliar lymphadenopathy.

**Cytology, Histopathology, Fungal Culture, and PCR**

A definitive diagnosis of histoplasmosis is made by cytologic or histopathologic identification of *H. capsulatum*. Various stains may be used successfully on cytologic preparations, including Diff-Quik, Wright-Giemsa and modified Wright stains. Tissue sections may be stained with special fungal stains like periodic acid-Schiff, Grocott’s methenamine silver or Grocott’s stains. The organisms are usually identified intracellularly within macrophages or, less commonly, free in pyogranulomatous exudates, and are described as oval or round yeast-like cells 2 to 5 μm in diameter with a central, spherical, lightly basophilic body surrounded by a clear halo. Macrophages may also contain rod-shaped organisms indicating a narrow based budding in their cytoplasm.

Occasionally, *H. capsulatum* may be seen within phagocytic cells on peripheral blood smears from dogs and cats. This was noted in 19.6% of 56 feline cases. Infected cells include neutrophils, monocytes and rarely eosinophils, and these may contain anywhere from 0 to 6 organisms. *H. capsulatum* also may be observed on buffy-coat smears. The organism may be identified by cytologic examination of fine-needle aspirates from lymph nodes, lung, liver and spleen, and skin impression smears (Fig. 2). Organisms also can be seen in bone marrow aspirates within phago-
cytes in pleural, peritoneal, joint or cerebrospinal fluid and in rectal scrapings. Cerebrospinal fluid analysis in patients with CNS involvement may reveal a mixed inflammatory cell pleocytosis and increased protein content. Intracellular yeast organisms of *H. capsulatum* also can be detected on cytological preparations from tracheal or bronchoalveolar lavage (BAL) fluid or brushing samples. In contrast to acute pulmonary histoplasmosis in dogs where tracheal or BAL fluid should yield organisms, organisms are less likely to be seen with chronic respiratory infections.

Likewise, *H. capsulatum* may be identified by histopathologic examination of biopsies from intestines, mesenteric lymph nodes, liver, spleen, tongue lesions, bone, conjunctiva and retina among others. Histopathological evidence of *H. capsulatum* in dogs and cats has also been noted in the lung, kidneys, adrenal glands, bone marrow, and brain, usually accompanied by chronic granulomatous inflammation. Gross pathologic lesions may consist of a granular to nodular appearance of the surface of abdominal organs, granulomatous nodules or pinpoint lesions within the visera, thickened intestinal walls with areas of necrosis, mesenteric lymphadenopathy, and peritoneal effusion.

Fungal cultures have yielded *H. capsulatum* from cutaneous lesions, lung, and liver aspirates and pleural and cerebrospinal fluid, but in other reports, culture was not successful from fecal samples in dogs with disseminated histoplasmosis; biopsies from tongue lesions containing the organism, buffy coats, or lymph node aspirates. Growth of the mycelial phase of *H. capsulatum* has zoonotic potential and poses a health hazard as conidia may cause infection of laboratory personnel. Identification of *H. capsulatum* by culture is expensive and incubation periods of 2 to 4 weeks may be required before growth is appreciated.

In several human studies, PCR has been used to detect *H. capsulatum* in tissues. The seminested PCR was highly sensitive and specific and able to detect genomic material corresponding to less than 10 yeast cells without crossreactivity with other bacterial or fungal pathogens. In dogs, *H. capsulatum* var. *farcininosum* infection was detected in a par- 

![Figure 2](image-url) Cytopathology of a cutaneous impression smear from an 18-month-old cat with ulcerative skin lesions. Note the small cluster of fungal organisms within a macrophage and multiple free *Histoplasma* organisms. (Wright-Giemsa stain, 100X, Courtesy Dr. Lynelle Johnson, Davis, CA.)

affin-embedded skin sample using a nested PCR of the internal transcribed spacer region of the fungal rRNA gene.

**Serology**

Several different serologic techniques have been used in the literature to detect antibodies to *H. capsulatum*, but serology is not a reliable diagnostic tool. In humans, standard serologic tests for antibodies to *H. capsulatum* include the immuno-diffusion (ID) and complement fixation (CF) tests. The ID test identifies H and M precipitin bands to *H. capsulatum* and is less sensitive than the CF test. Serum ID tests were positive in few dogs and in 2 of 6 cats with histoplasmosis tested before therapy. In the CF test, culture filtrates of yeast and mycelial phases are used as antigens and serum antibody titers are determined. If antibody titers are low, anticomplementary activity resulting from nonspecific fixation or inactivation of complement may nullify the results. To be valid, the CF titer must be four-fold greater than the anticomplementary antibody titer. Cross-reactivity with other antigens is another potential source of error. In 1 cat, the histoplasma titer by CF was 1:1.256. Serology to detect antibodies against *H. capsulatum* was positive in 4 of 9 feline cases in which serology was performed. Serology for *H. capsulatum* antibodies in 9 cases of canine disseminated histoplasmosis revealed a titer of 1:8 in one case. An antibody gel precipitation test with mycotic antigens revealed a negative serum antibody response despite active infection in a dog. Overall, results of serology are not consistent; false positive results occur because of crossreactivity with other fungi and there are many false negative serologic results in canine and feline histoplasmosis.

Antigen detection tests are now widely used for the diagnosis of histoplasmosis in human medicine. They are usually performed on urine specimens but have not yet been applied to canine or feline patients.

**Therapy**

Itraconazole is the treatment of choice for histoplasmosis in dogs and cats. The recommended dose is 10 mg/kg PO q 12 to 24 hours for a minimum of 4 to 6 months. Treatment should be continued for at least 2 months after resolution of clinical signs. Itraconazole is effective and well tolerated for the treatment of histoplasmosis in cats. It was curative in 6 of 8 cats with disseminated histoplasmosis at a dose of 5 mg/kg PO q 12 hours for 60 to 130 days. In this study, the capsules were opened and the granules mixed with food. Relapses occurred in 2 of 8 cats 6 and 10 months after discontinuation of therapy, respectively, and remission was achieved after reinstituting therapy. Despite the low intraocular concentrations of itraconazole, ocular lesions resolved in cats receiving this dose for 3 to 6 months. Flucinazole (2.5-5 mg/kg PO q 12-24 hours for at least 4-6 months) may be a better choice for ocular and neurologic histoplasmosis because of better penetration compared with itraconazole. With itraconazole, a mild to moderate increase in serum ALT activity after 2 months of therapy is common and usually asymptomatic. Itraconazole at 5 mg/kg PO q 12 hours for 5 months was also effective in cats in another report using capsules or an oral suspension. There appears to be less variability in absorp-
tion of itraconazole if the oral solution rather than capsules are used, allowing the administration at 10 mg/kg PO q 24 hours. Itraconazole is more effective than ketoconazole in cats with histoplasmosis and causes fewer adverse effects, but ketoconazole may be used if expense is a limiting factor. In one study of 16 cats treated with ketoconazole, 11 (68.8%) later died or were euthanized, and 5 (31.3%) cases survived on long-term therapy. Doses of 10 mg/kg q 8 hours, 15 mg/kg q 12 hours or 20 mg/kg q 24 hours were used, with short periods of withholding treatment because of anorexia, lethargy, icterus, and pancytopenia. Ketoconazole at a dose of 20 mg/kg/d for 6 months was curative for cutaneous histoplasmosis lesions in a dog.

In dogs, amphotericin B has been used successfully to treat local and disseminated histoplasmosis, but relapses are common. Amphotericin B in dogs and cats is lethargy, decreased appetite, local cellulitis and phlebitis and azotemia because of nephrotoxicity leading to tubular acidosis. The use of liposomal forms of amphotericin B could be considered in refractory cases, as higher doses can be achieved with less chance of development of nephrotoxicity. In patients with severe disseminated histoplasmosis, combination therapy with amphotericin B (0.25-0.5 mg/kg IV q 48 hours until a cumulative dose of 5-10 mg/kg is reached in dogs and 4-8 mg/kg in cats) and itraconazole or amphotericin B and ketoconazole may provide a more effective control of the infection. It was recently shown that Histoplasma capsulatum produces melanin during mammalian infection and that melanization of H. capsulatum reduces the susceptibility to amphotericin B.

Other, newer antifungal agents that have been evaluated for treatment of histoplasmosis in human patients include the azole drug voriconazole and the echinocandin caspofungin. A combination of voriconazole and amphotericin B was effective in one patient where itraconazole therapy had failed. The use of caspofungin in human patients with histoplasmosis has not been widely evaluated. Caspofungin may have limited efficacy for treatment of histoplasmosis and appears to be more effective when used to treat Aspergillus and Candida infections.

Frequent rechecks are required during and after antifungal therapy to monitor clinical signs and laboratory abnormalities associated with histoplasmosis and adverse effects of the antifungals used. Liver enzymes should be monitored monthly in patients receiving azole therapy and renal parameters monitored before each treatment with amphotericin B. Ancillary therapy of gastrointestinal and respiratory signs in addition to antifungal drugs voriconazole and the echinocandin caspofungin. A combination of voriconazole and amphotericin B was effective in one patient where itraconazole therapy had failed. The use of caspofungin in human patients with histoplasmosis has not been widely evaluated. Caspofungin may have limited efficacy for treatment of histoplasmosis and appears to be more effective when used to treat Aspergillus and Candida infections.

Frequent rechecks are required during and after antifungal therapy to monitor clinical signs and laboratory abnormalities associated with histoplasmosis and adverse effects of the antifungals used. Liver enzymes should be monitored monthly in patients receiving azole therapy and renal parameters monitored before each treatment with amphotericin B. Ancillary therapy of gastrointestinal and respiratory signs in addition to antifungal therapy has been described elsewhere. A retrospective study of 16 dogs with airway obstruction secondary to hilar lymphadenopathy caused by chronic pulmonary histoplasmosis (without dissemination) revealed that clinical signs (eg, coughing) and airway obstruction as assessed by bronchoscopy resolved more rapidly in dogs treated with corticosteroids (prednisone, 2 mg/kg PO q4 hours to 2 mg/kg PO q12 hours for a mean treatment duration of 6-5 weeks) than dogs that did not receive corticosteroids. None of the 10 dogs receiving corticosteroids developed active or disseminated histoplasmosis although the risk of dissemination remains. A BAL or tracheal wash should be performed before treating with corticosteroids, and this treatment should only be considered if organisms cannot be identified as evidence of active infection and if respiratory compromise is very severe.

**Prognosis**

Dogs with pulmonary histoplasmosis have a good prognosis. The prognosis is considered guarded to poor in dogs and cats if dissemination has occurred but depends on the degree of dissemination and the severity of associated clinical signs. Cats that are not severely debilitated have a fair to good prognosis on long-term treatment with itraconazole.

**Public Health Concerns**

Transmission of *H. capsulatum* from pets to humans has not been reported. However, infected pets may be a sentinel for human exposure, and this is especially relevant if the pet resides with immunocompromised human beings. Concurrent infections of owners and pets were reported after exposure to the same environment or source of infective material. A common-source environmental exposure was also suggested by a recent study evaluating the geographical specificity of *H. capsulatum* isolates (see Epidemiology, above). As with other deep fungal infections, bandaging of cutaneous lesions caused by *Histoplasma* is not recommended as it may promote mycelialization of the organism. Fungal cultures of the mycelial form pose a health hazard because of possible exposure of laboratory personnel to infective conidia.

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**References**


