MiraVista
VETERINARY DIAGNOSTICS

Review of Histoplasmosis in Animals

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DIAGNOSTIC TEST	TEST CODE	SPECIMEN TYPE
MVista® *Histoplasma* Antigen Quantitative EIA	310	Urine, Serum, BAL, CSF & other pipetteable fluid
Histoplasma Antibody by Immunodiffusion	321	Serum
MVista® *Histoplasma* Canine Antibody IgG EIA	327	Serum, CSF
MVista® *Histoplasma* Feline Antibody IgG EIA	328	Serum, CSF

1. Introduction

Histoplasmosis is a common endemic mycosis in the United States. In a 1981 study, the case rates per 100,000 patient-years-at-risk at 14 colleges of veterinary medicine for histoplasmosis was 2.5 times higher than blastomycosis and 3.5 times higher than coccidioidomycosis (1). *Histoplasma capsulatum* was isolated from 22% of healthy appearing dogs from Cincinnati, Ohio while *Blastomyces dermatitidis* was isolated from only 2% (2). In Lexington Kentucky, *H. capsulatum* was isolated from 40% of healthy dogs while *B. dermatitidis* was isolated from only 1% (3). In Africa histoplasmosis may be caused by *H. capsulatum* variety *duboisii* (4) and in Ethiopia and the Middle East by *H. capsulatum* variety *farciminosi* (5-7).

While histoplasmosis is not transmissible from animal to human, concurrent infection is not uncommon because of shared exposure (8). Histoplasmosis usually causes pulmonary and/or disseminated disease. Familiarity with the clinical manifestations may alert a veterinarian to consider the diagnosis. Antigen detection in urine and serum may provide a rapid diagnosis, precluding the need for invasive procedures to obtain specimens for organism identification in many patients. Antibody testing may be useful in cases with negative results by antigen testing. Itraconazole is the treatment of choice, and therapy may be monitored by antigen testing. Itraconazole absorption and metabolism vary considerably, at times causing undetectable or toxic blood levels, and blood level measurement is encouraged to assure adequate drug exposure.

2. Epidemiology

Histoplasmosis caused by *Histoplasma capsulatum* variety *capsulatum* is endemic in certain parts of North and South America. In the U.S., the fungus is most frequently found in the Ohio and Mississippi river valleys (Fig. 1). In some endemic areas, histoplasmosis is the most common systemic mycosis in animals. Between 1964 and 1976, 14 schools of veterinary medicine in the United States and Canada participated in a study of systemic mycoses and noted rates per hundred thousand patient years of 62 for histoplasmosis, 25 for blastomycosis and 17 for coccidioidomycosis (1).

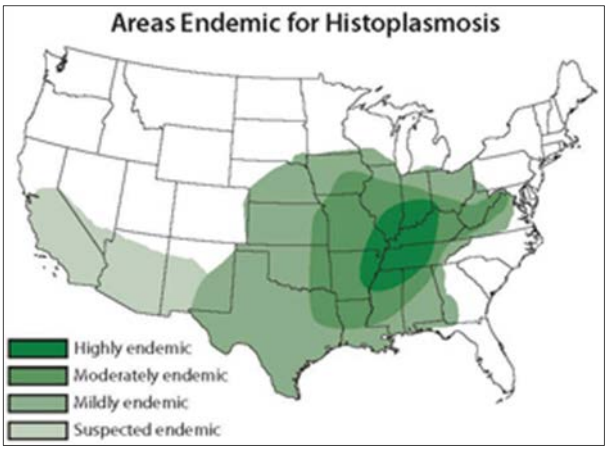

Figure 1. Endemic range for histoplasmosis in the U.S. (Centers for Disease Control; cdc.gov, 10/12/16)

In Kentucky, 47% of dogs (9) and 50% of Thoroughbred horses exhibited *Histoplasma* skin test reactivity, while only 7.3% of horses demonstrated *Blastomyces* skin test reactivity (10). Histoplasmosis was twice as frequent in animals from rural than from urban areas (3). Histoplasmosis also occurs outside of the traditional endemic area (11;12).

Several dog breeds have been shown to have an increased risk of histoplasmosis, including the Pointer, Weimeraner and Brittany spaniel (2). Mean age at diagnosis from one large study was 3.6 years (2). This older (1981) epidemiologic study indicated that cats had a similar incidence of histoplasmosis as that seen in dogs. Recent observations suggest that feline histoplasmosis is far more common than canine histoplasmosis, especially in the south central U.S. (Oklahoma, Texas and surrounding states; unpublished observations). Persian cats are slightly over-represented in older studies, while Siamese cats are marginally under-represented (55). Interestingly, indoor-only cats remain at risk for histoplasmosis (49, 88). Cases also occur in horses (13-24), llamas (25), sea mammals (26-28) and wild animals (12;29-40).

3. Pathogenesis

Histoplasmosis is caused by inhalation of microconidia or hyphal fragments. Although intestinal lesions are prominent in dogs with disseminated histoplasmosis, experimental infection by gastric inoculation failed to induce disease in dogs (41). All mammals are susceptible to histoplasmosis, but cases have been reported most often in dogs, cats, and horses. Birds, because of their higher body temperature, are not susceptible to natural infection (42) but may be infected experimentally, causing infection localized to their feathers (43).

Cellular immunity is critical in defense against *H. capsulatum*, based on analysis of risk factors for severe disease. The microconidia are inhaled and in the lungs they attract dendritic cells, neutrophils and macrophages, which phagocytose the organism, which transform into yeasts and multiply unchecked in the non-immune subject. During the first two weeks, the infection progresses and disseminates hematogenously throughout the reticuloendothelial system. By day 14 of infection, specific T cell immunity develops, halting proliferation of the yeast and progression of the infection. Evidence for self-limited dissemination includes demonstration of calcified granulomas in the spleen and liver in healthy individuals in endemic areas for histoplasmosis, which contain non-viable organisms and occasional isolation of *H. capsulatum* from extrapulmonary specimens in patients with acute pulmonary histoplasmosis.

Cytokines that are most important in immunity to *H. capsulatum* include IL-12, IL-18, TNF-α and interferon-γ. A successful T cell response requires dendritic cells, CD4 and CD8 T lymphocytes and activated macrophages. T cells produce interferon-□ and tumor necrosis factor-□, which activate macrophages to kill *Histoplasma* yeast. The importance of TNF-α in humans is highlighted by the emerging recognition of histoplasmosis as a major opportunistic infection in patients treated with TNF inhibitors.

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While histoplasmosis is self-limited in over 95% of healthy humans, chronic and/or progressive disease may occur more often in animals. Thirty one to 44% of euthanized dogs and cats in endemic areas had evidence for histoplasmosis (2;44;45). Chronic infection also is common in bats (46;47). Interestingly the tissue reaction in bats was minimal or absent, possibly explaining their inability to eradicate the organism (46-49). The infection rate varied markedly in different genera of bats, suggesting genetic differences in susceptibility (50). *Histoplasma* was not isolated from wild-caught mice, suggesting that their immune response was able to kill the organism (42).

4. Clinical Presentation

The severity of clinical manifestations corre¬lates with the intensity of exposure and the underlying health of the exposed individual. Cole described rapidly progressive fatal course over two to four weeks in 10% of dogs with histoplasmosis, and chronic progressive course over two to 20 months in 90% (51). Demonstration of positive cultures of pulmonary and extrapulmonary tissues of apparently healthy dogs and cats from endemic areas suggest that the clinical findings may be overlooked in many cases (2;3;44). In one study 44% of 100 consecutive adult dogs and cats submitted to a for voluntary euthanasia, only two of which appeared to be obviously ill, that underwent complete necropsy with pathology and culture of pulmonary and extrapulmonary tissues exhibited evidence for active histoplasmosis (44).

Table 1. Clinical findings in dogs (55) and cats (54;56)

Finding	Dogs (%)	Cats (%)
Fever	25	58
Weight Loss	42	83
Respiratory Symptoms	50	39-42
Chest Radiograph Abnormal	NS*	87-88
Lethargy/Depression	58	66
Intestinal-Diarrhea, Bleeding	83	NS
Hepatomegaly	NS	33
Splenomegaly	NS	17
Lymphadenopathy	33	33
Eye Lesions or Discharge	NS	24-42
Bone Lesions	NS	18
Skin Lesions	NS	8
Anemia	58	100
Hepatic Enzyme ↑	50	40

*NS = not stated

Noteworthy was that only five dogs were known to have histoplasmosis during the previous seven years. Syndromes most commonly identified include pneumonia, mediastinal lymphadenitis, and progressive disseminated histoplasmosis.

Pulmonary

Pneumonia is the most common manifestation of histoplasmosis. Dogs usually present with signs of fever, dyspnea, cough and lethargy. Radiographic findings characteristically include diffuse nodules, referred to as "cotton tuft" lesions (52) (Figure 3) or diffuse interstitial infiltrates, often accompanied by hilar lymphadenopathy (53). Alveolar infiltrates are rarely seen (53).

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Mediastinal Lymphadenitis

Enlarged hilar or mediastinal lymph nodes may impinge upon the airways and cause cough and respiratory distress (54;55). Radiographs show tracheobronchial lymphadenopathy usually accompanied by interstitial pneumonia. The outcome has ranged from spontaneous resolution to progressive obstruction of the airways and death. Concurrent dissemination may occur (55).

Progressive Disseminated Histoplasmosis

Fever, weight loss, reduced activity, anemia, and interstitial lung disease are the most common manifestations in cats (56), while diarrhea, intestinal blood loss, anemia and reduced activity predominate in dogs (51;57) (Table 1). Bone lesions are common in cats (56). Central nervous system and ocular lesions may be found in all animal species. Endocarditis also has been reported, noted in seven of 17 (41%) necropsy cases in dogs (58). Other tissues commonly involved at necropsy include liver, spleen, abdominal lymph nodes, and less frequently involved are adrenal glands, kidneys, pancreas (51).

Pulmonary involvement occurs in most cases and is usually manifested as labored breathing (56;57). Radiographs typically show diffuse interstitial, miliary or nodular infiltrates (56).

Abnormal physical findings include hepatomegaly, splenomegaly, eye lesions or discharge, subcutaneous nodules, and skin lesions (56;57). The common laboratory abnormalities are anemia, leukopenia, thrombocytopenia, hypoalbuminemia, increased liver enzyme activity, creatinine elevation, and hypercalcemia (59). The untreated course ranges from subclinical chronic infection to a rapidly fatal illness.

Equine Abortion

Infections in the fetus or neonatal foal may occur, causing the mare to abort or the foal to die soon after birth (22;24;60). Pulmonary and disseminated involvement usually are present in the fetus or newborn (24). In most cases the mare appears healthy but the placenta is involved.

5. Diagnosis

Prompt diagnosis offers the greatest chance for recovery from histoplasmosis, made possible by early therapy (61). Today most cases are diagnosed by detection of *Histoplasma* antigen in the urine and/or serum or demonstration of yeast in the body fluids or tissues. Antibody detection may be useful in cases in which antigen tests and/or pathology are negative or specimens are not available for pathology.

Pathology

As most reports required demonstration of *Histoplasma* yeasts in tissues or body fluids or positive culture for diagnosis (56;57), the sensitivity of pathology is uncertain. In humans the detection of antigen in the urine or serum is more sensitive than pathology or culture (62). Other limitations of pathology are the requirements to perform invasive procedures to obtain specimens for evaluation and that the pathologists are experienced with recognition of fungal organisms.

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Antigen Detection

A galactomannan antigen in the cell wall of proliferating *Histoplasma* yeasts is released into the tissues and blood, and excreted in the urine. Antigen was detected in the urine of 94% of cats (82) and 90% of dogs (90) with histoplasmosis. The highest sensitivity is achieved by testing both urine and serum. Antigen also may be detected in the respiratory secretions in humans with pulmonary histoplasmosis and cerebrospinal fluid of those with meningitis. Based on the experience in blastomycosis (63), antigen levels decline during treatment and increase with relapse (63), providing a tool for monitoring therapy.

The antigen found in histoplasmosis cross reacts with that found in blastomycosis (64). Furthermore, the clinical findings and endemic distribution overlap. Thus, differentiation of the two mycoses may be difficult, but treatment is the same, reducing the need to distinguish histoplasmosis and blastomycosis. Antibody testing may distinguish these two mycoses (65).

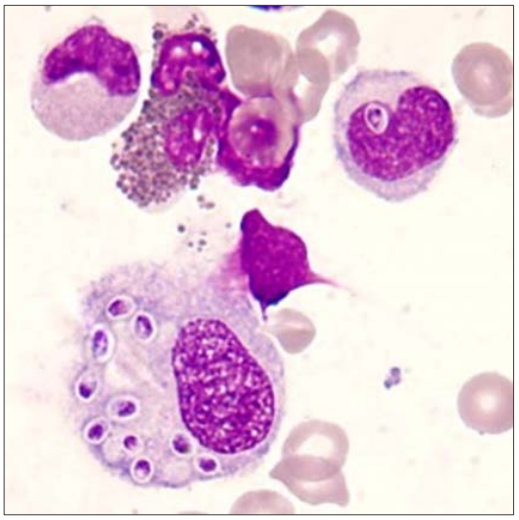

Figure 1. Cytologic appearance of *H. capsulatum* yeasts inside macrophages. 1000X, Wright-Giemsa stain

Culture

Culture is rarely performed, but usually is positive in disseminated cases (2). The major limitation is the slow growth rate and small risk to laboratory personnel from exposure to the mycelial form of the fungus.

Antibody Detection

Antibody detection has been infrequently used in veterinary medicine to aid in the diagnosis of histoplasmosis. Historically, only complement fixation (CF) and agar gel immunodiffusion (AGID) methods have been available. The sensitivity of CF was reported to be about 90% (66) in one report and 11% in another (58). The CF test is often uninterpretable in dogs because their serum is anti-complementary, and CF is not offered commercially at veterinary reference laboratories. Agar gel immunodiffusion (AGID) is offered commercially, but the sensitivity was only 25% in one report (3). Positive results have been reported in cats (52) and horses with histoplasmosis (24).

Sensitivity may be improved using an enzyme immunoassay, which has also been described in dogs with blastomycosis (91). IgG antibodies were detected by the MVista® *Histoplasma* antibody EIA in 88% of human patients with acute pulmonary histoplasmosis, and the specificity was 95% (67). Combining antigen and antibody detection, the sensitivity was 96%. The MVista antibody EIA contains a standard curve, permitting quantification of antibody levels and comparison of results in specimens tested in different assays. Ongoing studies in dogs and cats with histoplasmosis suggest that the sensitivity and specificity of the antibody EIA is similar to that seen for humans with acute pulmonary histoplasmosis (unpublished data). In addition, positive results have been observed in the antibody EIA test for dogs and cats with localized ocular or gastrointestinal disease (in which antigen results are more likely to be false negative).

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Molecular Techniques

PCR has been reported to be positive in the tissues in dogs with histoplasmosis (68-72) and in other species (26;27;33;68;69;73) . Most reports describe results in single cases. No studies have reported the sensitivity and specificity and none have reported results on body fluids, or compared PCR to other diagnostic methods. Additional studies are needed to assess the role of PCR for diagnosis of histoplasmosis.

6. Treatment

Guidelines for treatment are provided, but textbooks and other reviews should be used for more thorough instruction on antifungal treatment in animals. Relapse has occurred after stopping therapy in 40% of successfully treated cases (74). Readers are referred to a comprehensive review on antifungal treatment of small animals for more information about the agents most commonly used in veterinary medicine (75).

Table 2. Treatment Recommendations
Itraconazole 5-10 mg/kg/day or fluconazole 10 mg/mg/day for 4-6 months[1] Consider amphotericin B[2] in severe cases, including respiratory insufficiency[3] Monitor antigen every 3 months and if suspect relapse Itraconazole blood level[4]
[1]Some cases may require more than 6 months of treatment; [2]lipid formulation better tolerated [3]may benefit from adjunctive corticosteroid therapy; [4]day 14 (dogs) to 21 (cats) of therapy to ensure levels between 3.0 and 10 µg/mL by bioassay and 1.0 and 5 µg/mL by HPLC or LC/MS and if suspect relapse or itraconazole toxicity.

Amphotericin B

Amphotericin B is the treatment of choice in severe cases in humans and induces a clinical response more rapidly than itraconazole (76) or fluconazole. Reasons for amphotericin B's superiority include its fungicidal mode of action and intravenous route of administration, rapidly providing therapeutic blood concentrations. Administration of amphotericin B for the first 3 to 7 days of therapy may improve early survival, after which treatment could be changed to itraconazole or fluconazole. Lipid forms of amphotericin B are better tolerated but more expensive than the deoxycholate formulation. Renal function and serum electrolytes should be monitored during treatment.

Itraconazole

The usual dosage is 5 (77) to 10 mg/kg (78;79) given once or twice daily. At least 4-6 months of therapy is typically administered. A study in cats found itraconazole to be effective in six of 13 cases, while 3 were euthanized or died, four required a change in therapy to fluconazole because of lack of response or toxicity (74). Four of the 13 cats experienced a relapse. Treatment should be continued until at least 1-2 months after resolution of clinical signs and probably until antigen is no longer detected in urine, based on experience in blastomycosis (63). Antigen concentration should be monitored at 3 and 6 months after discontinuation of therapy, and upon recurrence of clinical findings suggestive for relapse. In another report of five cases treated

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with itraconazole for 3 to 8 months, all responded to therapy and remained well with follow-up from 24 to 70 months (80).

Brand-name itraconazole (Sporanox®, Janssen Pharmaceuticals) or generic itraconazole should be used, as compounded powder formulations have poor bioavailability (81) (23). Blood levels should be measured 14 (dogs) to 21 (cats) days after beginning therapy, and the preferred range is 3.0 to 10.0 µg/mL as measured by bioassay, and at least 1.0 µg/mL (itraconazole component only) by HPLC or LC-MS. In a prospective human trial, the 2 patients who failed therapy because of progressive histoplasmosis with positive blood culture had levels by bioassay that were undetectable or 1.8 µg/mL (82). Blood levels above 10.0 µg/mL by bioassay (about 5 µg/mL by HPLC may cause more toxicity and are unnecessary. Inability to achieve therapeutic concentration and intolerable side effects are reasons to switch to another triazole. Itraconazole is eliminated by hepatic metabolism through cytochrome P450, and blood levels may be affected by medications that interact with that enzyme.

Itraconazole may cause a variety of adverse effects, most commonly loss of appetite, anorexia, vomiting, or diarrhea, which may be related to high blood levels (83). Bilirubin and hepatic enzymes also may be elevated, in association with clinical evidence for hepatitis in some cases; and should be monitored during therapy. Serum alanine aminotransferase (ALT) greater than 200 U/L may warrant discontinuation of itraconazole (84). Itraconazole may be restarted at half of the former dose. Ulcerative dermatitis was also observed in 7.5% of dogs receiving itraconazole at 10 mg/kg/d (85).

Fluconazole

Response to fluconazole was similar to that with itraconazole in cats (74). Of 17 cats treated with fluconazole, 3 died or were euthanized, 9 completed therapy, one switched to itraconazole because of poor response, and 4 relapsed. Some veterinarians prefer fluconazole for treatment of cases involving the CNS, eye, or prostate because, as a consequence of its smaller molecular size and lipophilicity, it achieves better penetration into these tissues. Other reasons for choosing fluconazole include lower cost and better tolerability. Doses of at least 10 mg/kg/day are recommended.

Other Azoles

Ketoconazole is infrequently used because, based on studies in blastomycosis (86), it is less effective and causes more adverse effects than itraconazole. One of five cats with histoplasmosis responded to ketoconazole (52). Posaconazole and voriconazole are more active than fluconazole and have been used successfully in humans with histoplasmosis, but have not been evaluated in animals. *Histoplasma* also is susceptible to isavuconazole, a newly approved antifungal azole, but clinical studies for treatment of histoplasmosis have not been reported. The newer azoles are more expensive than itraconazole or fluconazole.

Terbinafine

In vitro activity has been demonstrated with MICs below 0.39 µg/ml in 90% of strains (87). In vivo efficacy has been reported in animal models (88) and in patients with African histoplasmosis (89).

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Adjunctive Therapy

Schulman noted rapid clinical improvement in ten dogs with mediastinal lymphadenitis causing airway obstruction, five of which also received antifungal treatment (54). Corticosteroids also may be helpful in cases of diffuse pulmonary histoplasmosis complicated by respiratory insufficiency. Concurrent antifungal therapy is recommended to reduce the risk for progressive dissemination caused by corticosteroid-induced immunosuppression.

Monitoring Therapy

The antigen test often is used in deciding when to stop therapy and to diagnose relapse. In 27 dogs with blastomycosis, antigen levels in urine were negative in 70% at the time of treatment discontinuation (63). (http://onlinelibrary.wiley.com/doi/10.1111/jvim.12306/abstract) Relapse occurred in 7 dogs (26%), 2 of which had a positive urine antigen at treatment discontinuation, and was associated with a rise in antigenuria in 5. The authors recommended continuing therapy until the clinical findings, including eye exam, resolved, thoracic radiographs were normal or stable and urinary antigen was negative. A reasonable approach would be to test for antigenuria every 3 months during therapy, at 3 and 6 months after stopping therapy, and if relapse is suspected.

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