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CLINICAL REVIEW

Histoplasmosis in Veterinary Medicine 2020

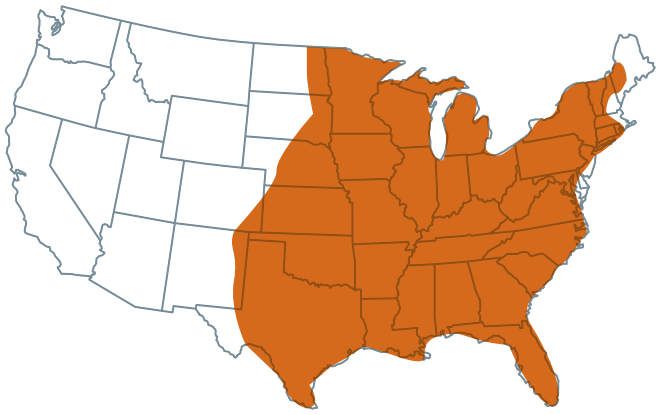
INTRODUCTION

Histoplasmosis is a common enzootic mycosis in the United States. In a 1981 study, the case rates per 100,000 dog-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]. An older study showed that *Histoplasma capsulatum* was isolated from 22% of healthy appearing dogs from Cincinnati, Ohio while *Blastomyces dermatitidis* was isolated from only 2%.[2] A second study showed that in Lexington, Kentucky, *H. capsulatum* was isolated from 40% of healthy dogs while *B. dermatitidis* was isolated from only 1% [3]. Inexplicably, more recent clinical experience would suggest that isolation of H. capsulatum from dogs or cat without histoplasmosis is very uncommon. In Africa, histoplasmosis may be caused by *H. capsulatum* variety *duboisii* [4] and in Ethiopia and the Middle East by *H. capsulatum* variety *farciminosum* [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 or disseminated disease. Although likely a result of dissemination, disease apparently localized to a single body system including the skin, eye, bone/joints, and GI tract has also been reported [9-12]. Familiarity with these clinical manifestations may alert a veterinarian to consider the diagnosis. Antigen detection in urine and serum often provides a rapid diagnosis, precluding the need for invasive procedures to obtain specimens for organism identification or culture. Antibody testing may be useful in cases with negative antigen testing results. Itraconazole is the treatment of choice, and therapy should be monitored by antigen testing. Itraconazole absorption and metabolism vary considerably, at times causing undetectable or toxic blood levels, and blood level measurement (therapeutic drug monitoring) is encouraged to assure adequate drug exposure [13].

EPIDEMIOLOGY

Histoplasmosis caused by *Histoplasma capsulatum* variety *capsulatum* is enzootic 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 (**Figure**). In some enzootic 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 in dogs and noted rates per hundred thousand patient years of 62 for histoplasmosis, 25 for blastomycosis and 17 for coccidioidomycosis [1]. However, cases have been reported from non-enzootic areas, including in cats and raccoons from California [14,15]. In Kentucky, 47% of dogs and 50% of thoroughbred horses exhibited *Histoplasma* skin test reactivity, while only 7.3% of horses demonstrated *Blastomyces* skin test reactivity [16, 17]. Histoplasmosis was twice as frequent in animals from rural than from urban areas [3].



CDC map of estimated areas with histoplasmosis

Several dog breeds have been shown to have an increased risk of histoplasmosis, including the Pointer, Weimaraner and Brittany [1]. Mean age at diagnosis from one large study was 3.6 years [1]. This older study indicated that cats had a

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similar incidence of histoplasmosis as that seen in dogs, but in certain areas, cats are at least 4 times as likely to have histoplasmosis (personal communication) [1]. Persian cats are slightly over-represented in older studies, while Siamese cats are marginally under-represented [18]. Interestingly, indoor-only cats remain at risk for histoplasmosis [19,20]. Cases also occur in horses [21-32], llamas [33], sea mammals [34-36], exotic pets and wild animals [15,37-48].

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 [49]. 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 but may be infected experimentally, causing infection localized to feather tips [50,51].

Cellular immunity is critical in defense against *H. capsulatum*, based on analysis of risk factors for severe disease [52]. The microconidia are inhaled and attract dendritic cells, neutrophils and macrophages, which phagocytose the organism that then 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-γ and TNF-α, 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 [53,54].

While histoplasmosis is self-limited in over 95% of healthy humans, chronic and/or progressive disease may occur more common in animals. However, 31% to 44% of euthanized dogs and cats in enzootic areas had culture evidence for chronic histoplasmosis, suggesting sub-clinical infections do occur [2,55,56].

A study of newborn mongrel puppies experimentally infected with *Blastomyces dermatitidis* provides insight into immunity to blastomycosis and histoplasmosis [57]. Thirty-three puppies were obtained from a non-enzootic area (Cheyenne, Wyoming) and exposed to soil inoculated with *B. dermatitidis*. The puppies were exposed to the soil in a wooden shed for 2 days and then were housed in cages near the shed for 8 weeks. Six dogs died, three of which had positive cultures for *Blastomyces*, including one with positive cultures for *Histoplasma*. The survivors (N=27) remained healthy. One third of the dogs were autopsied at the 119th week following infection and used as controls and 18 dogs were immunosuppressed with azathioprine and prednisone. The immunosuppressed dogs were autopsied at the 130th week following exposure and tissues were cultured for fungus. *Histoplasma* was isolated from the tissues in 14/18 dogs (78%) and *Blastomyces* was isolated from none. The study was conducted in central Kentucky, a highly enzootic area for histoplasmosis, and enzootic exposure was the mode of infection. These findings show that the immune response in dogs was adequate to prevent chronic blastomycosis but not histoplasmosis. This also differs from immunity in humans, where prior exposure induces long-lasting protection against reinfection, reactivation or relapse [54].

Like dogs, chronic histoplasmosis also is common in bats. [58,59] Interestingly the tissue reaction in bats is minimal or absent, possibly explaining their inability to eradicate

the organism [58-61]. The infection rate varies markedly in different genera of bats, suggesting genetic differences in susceptibility [62]. In one study, *Histoplasma* was not isolated from wild-caught mice, suggesting that their immune response is able to eliminate the organism [51].

CLINICAL PRESENTATION

The severity of clinical manifestations correlates with the intensity of exposure (size of inoculum) 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% [63]. Demonstration of positive cultures of pulmonary and extrapulmonary tissues of apparently healthy dogs and cats from enzootic areas suggest that the clinical findings may be overlooked in many cases [2,3,64]. In one study, 44% of 100 consecutive adult dogs and cats that underwent voluntary euthanasia and complete necropsy with pathology and culture of pulmonary and extrapulmonary tissues, exhibited evidence for active histoplasmosis [55]. Noteworthy was that fact that only five dogs were known to have had histoplasmosis during the previous seven years.

Pulmonary. Pneumonia, as part of progressive disseminated disease, is one of the most common manifestation of histoplasmosis, described in 72% of dogs in which thoracic radiographs were performed obtained [9]. Dogs often present with dyspnea, cough, fever, and lethargy. Radiographs showed interstitial disease in 44%, alveolar disease in 12%, bronchial disease in 10%, and a mixed pattern in 16%. Interstitial disease was most often characterized as diffuse (68%) and “miliary” or structured interstitial in 14%, respectively [9].

Pneumonia is the most common manifestation in cats occurring in 39-44% of cases [65-67]. Symptoms include dyspnea, tachypnea and less commonly cough [19,67]. Diffuse interstitial infiltrates or lung nodules were described in 40-67% cases, miliary infiltrates in 6-17%, and alveolar infiltrates in 13-17% [19,67]. Nasal discharge also was described [67]. Sneezing occurs in some cases (personal communications).

Mediastinal lymphadenitis. Less commonly, no lung abnormalities were noted but sternal (12%), tracheobronchial (6%), or cranial mediastinal lymphadenopathy (2%) or pleural effusions (8%) were noted [18]. These may impinge upon the airways and cause cough and respiratory distress [18,68]. Radiographs showed tracheobronchial lymphadenopathy usually accompanied by interstitial pneumonia. The outcome has ranged from spontaneous resolution, resolution with corticosteroid treatment alone or combined with antifungal therapy, and progressive obstruction of the airways and death [68]. Concurrent dissemination may occur [18].

Progressive disseminated histoplasmosis. Much of the information is derived from reports in cats. Fever, weight loss, reduced activity, anemia, and interstitial lung disease are the most common manifestations in cats, (Table 1) [12,19,65]. Pulmonary involvement occurs in many cases and is usually manifested as tachypnea and dyspnea. Radiographs typically show diffuse interstitial or miliary or nodular infiltrates. Bone and joint involvement are more common as compared with dogs [11,20]. In addition, bone marrow involvement, causing cytopenia of one or multiple cell lines, is also relatively more common in cats as compared with dogs. Abnormal physical findings include hepatomegaly, splenomegaly, lymphadenopathy, eye lesions or discharge, nasal discharge, subcutaneous nodules, and skin lesions. The untreated course ranges from subclinical, chronic infection to a rapidly fatal illness.

In dogs, diarrhea, intestinal blood loss, anemia and reduced activity predominate [9,63,69]. It is common for clinical manifestations to be limited to GI disease. Tissues commonly involved at necropsy include liver, spleen, abdominal lymph nodes, large intestine, and less frequently CNS, ocular, bone/joints, bone marrow, adrenal glands, kidneys, and pancreas [63,69,70].

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CLINICAL REVIEW

Equine abortion. Infections in the fetus or neonatal foal may occur, causing abortion or early foal death [9,20,30,32,71,72]. Pulmonary and disseminated involvement usually are present in the fetus or newborn [32]. In most cases, the mare appears healthy, but the placenta is involved.

LABORATORY FINDINGS

Common laboratory abnormalities include anemia, leukopenia, leukocytosis, thrombocytopenia, hypoalbuminemia, hyperglobulinemia, increased liver enzymes and bilirubin, creatinine elevation, hypokalemia, and hypercalcemia (Table 2) [9,12,19,20,65,67,69,72]. Hypocalcemia usually correlates with hypoalbuminemia. Hypercalcemia is caused by dysregulated production of 1,25-(OH2)D3 (calcitriol) by macrophages in alveoli and other areas of granulomatous inflammation and may be accompanied by angiotensin-converting enzyme elevation, leading to a misdiagnosis of sarcoidosis and inappropriate treatment with corticosteroids in humans [9,73].

DIAGNOSIS

Prompt diagnosis offers the greatest chance for recovery from histoplasmosis, made possible by early therapy [74]. Today most cases are diagnosed by detection of *Histoplasma* antigen in the urine and/or serum or demonstration of yeast in the bodily fluids or tissues [9,12,75-77]. Antibody detection may be useful in cases in which antigen tests and/or pathology are negative or specimens are not available for pathology. Currently comparative studies evaluating pathology, culture, antigen and antibody detection are unavailable.

Cytopathology or Histopathology. Biopsy or fine-needle aspiration of readily accessible lesions for cytopathology or histopathology may provide the quickest and most accurate basis for diagnosis and may be positive in cases with negative antigen results. Cytology of rectal scrapings may be positive in cases with intestinal involvement [9].

Culture. Fungal culture may be positive in those with negative pathology. Its major limitation is the slow growth rate requiring 4-6 weeks for culture results in many cases. And there may be a small risk of human exposure by sharp injuries while handling the tissue in the clinic or pathology laboratory.

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 and 92% of dogs (unpublished data) with histoplasmosis [75-77]. The highest sensitivity is achieved by testing both urine and serum: Antigen may be positive in the serum but negative in the urine [78]. Antigen also may be detected in the respiratory secretions in humans with pulmonary histoplasmosis and cerebrospinal fluid of those with meningitis. Antigen levels decline during treatment and increase with relapse, providing a tool for monitoring therapy [12].

Commercially available *Histoplasma* antigen agent specific reagents (IMMY, *HISTOPLASMA* GM EIA) have been studied in cats [77]. Using a 1.1 ng/mL diagnostic cut off, sensitivity was 77% and specificity was 97%. Using a 0.25 ng/mL cut off, sensitivity was 89% and specificity 80%. By comparison, sensitivity of the MiraVista *Histoplasma* antigen EIA was 94% and specificity 96%. The MiraVista assay has been validated for quantification and used for treatment monitoring. The agent specific reagents have not been validated for treatment monitoring.

The antigen found in histoplasmosis cross reacts with that found in blastomycosis [79]. Furthermore, the clinical findings and enzootic distribution overlap. Thus, differentiation of the two mycoses may be difficult, but treatment is similar, in many cases reducing the need to distinguish the two organisms. Antibody testing using *Histoplasma* IgG and *Blastomyces* IgG antibody enzyme-immunoassays (EIA) may distinguish these two mycoses [80].

Antibody detection. Antibody detection has been infrequently used for diagnosis in veterinary medicine. Historically, only complement fixation (CF) and agar gel

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immunodiffusion (AGID) methods have been available. The sensitivity of CF was 90% in one report and 11% in another [57,81]. 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 studies have not been conducted to establish sensitivity and specificity.

Sensitivity may be improved using an IgG anti-*Histoplasma* antibody EIA developed at MiraVista Diagnostics. The sensitivity in dogs and cats was 78% and the specificity was 97% in dogs and 84% in cats (data on file, MiraVista Diagnostics).

Clinical situations to consider antibody testing:

1. When histoplasmosis is suspected but antigen testing is negative or low positive (<1 ng/mL)
2. When differentiation between histoplasmosis and blastomycosis or other (cross-reacting) organism is clinically indicated
3. To determine exposure to *Histoplasma* for point-source outbreaks or other environmental investigations

Molecular techniques. PCR has been reported to be positive in the tissues in dogs with histoplasmosis and in other species [34,35,41,82-87]. Most reports describe results in single cases and no studies have reported the sensitivity and specificity or results in bodily fluids. No studies have compared PCR to other antigen detection. Additional studies are needed to assess the role of molecular diagnostics for histoplasmosis.

TREATMENT

Guidelines for treatment are presented here and in Infectious Diseases of Dogs and Cats [88].

Amphotericin B. Amphotericin B is the treatment of choice in severe cases in humans and induces a clinical response more rapidly than itraconazole [89]. Reasons that amphotericin B is effective includes its fungicidal mode of action and intravenous route of administration, rapidly providing therapeutic blood concentrations. Administration of amphotericin B initially may improve early survival, after which treatment could be transitioned to itraconazole. Lipid/liposomal forms of amphotericin B are better tolerated but are more expensive than the deoxycholate formulation. Renal function and serum electrolytes should be monitored during treatment.

Anti-inflammatory treatment with low doses of corticosteroids may be helpful in reducing systemic side effects of amphotericin B [90]. Some veterinarians recommend use of corticosteroids to prevent clinical worsening after initiation of treatment attributed to an inflammatory reaction to antigens released from “dying” *Histoplasma* organisms (personal communications) [9,20].

Itraconazole. The usual dosage in dogs is approximately 5 mg/kg/day after a 3 day loading phase at 10 mg/kg/day [91]. The usual dosage with cats is 10 mg/kg/day with capsule and 7.5 mg/kg/day with solution [92]. At least 6 months of therapy is recommended [88]. A retrospective study in dogs reported that 71% (17/24) responded to itraconazole and 17% relapsed [9]. Combining data from 3 retrospective studies in cats, 68/79 (86%) of those treated with itraconazole survived to hospital discharge [19,20,72]. Since histoplasmosis is often chronic and requires long term treatment, longer term survival is arguably more important, and in one study, 6-month survival with itraconazole was 35/53 (66%) [20]. Relapse rates were reported in 3 studies and occurred in 8/36 (22%) of cats receiving itraconazole [12,19,72]. Retrospective design, small sample size and inclusion of cases spanning over many years were limitations of some of these studies. A prospective study in humans with AIDS reported an 85% (50/59) response rate and no relapses: Only 2 of the failures were attributed to progressive histoplasmosis and itraconazole blood levels were below 2.0 µg/mL in both [93].

Generic FDA approved itraconazole capsules are preferred as it achieves similar blood levels to the brand-name Sporanox® (Janssen Pharmaceuticals) and is considerably

less expensive [94]. An itraconazole solution (Itrafungol®) is labeled for the treatment of dermatophytosis in cats and is essentially identical to Sporanox® solution. Compounded powder formulations (capsule or solution) have poor bioavailability [13,95] and are not recommended in either species [13,88,95]. If needed for smaller animals, FDA approved capsules can be opened, weighed and separated, and placed in smaller capsules. Alternatively, a 100 mg capsule every other day might be appropriate for cats [95]. Blood levels should be measured 14 (dogs) to 21 (cats) days after beginning therapy, and the preferred range is 2-7 µg/mL as measured by bioassay, and at least 1.0-2.0 µg/mL by HPLC or LC-MS. Bioassay levels above 7.0 µg/mL cause more toxicity and are unnecessary. Oral bioavailability of the capsule is increased by a recent meal and decreased by concurrent administration of an antacid. Inability to achieve therapeutic concentration, intolerable side effects, drug-to-drug interactions, and lack of clinical improvement during treatment are reasons to switch to another triazole.

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 [96]. 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 [97]. Itraconazole may be restarted at half of the former dose, based on trough itraconazole blood levels. Ulcerative dermatitis was observed in 7.5% of dogs receiving itraconazole at 10 mg/kg/day [97].

Fluconazole. Studies in cats and dogs were retrospective and small, preventing accurate assessment of the effectiveness of fluconazole therapy [9,19,20]. Relapse rates were 22% and 17% for cats and dogs, respectively [9,19]. Fluconazole and itraconazole susceptibility were assessed in *Histoplasma* isolates from humans who failed fluconazole: Resistance developed to fluconazole in 59% of failure isolates and cross resistance was observed to voriconazole [98,99]. Given the inherent relative low sensitivity, and potential for acquired resistance, it is considered a second-line choice for oral antifungal treatment of histoplasmosis in dogs and cats. In the clinical scenario where itraconazole is not well tolerated, or the cost of itraconazole precludes its use, fluconazole should be considered. To help decrease the chance of acquired resistance, an appropriate dose (20 mg/kg/day in dogs or 100 mg/day in cats) and duration (at least 6 months) of FDA approved drug should be used. Unlike itraconazole, oral bioavailability is not affected by recent meal or concurrent antacid administration.

Other azoles. Ketoconazole is infrequently used as it is not effective. One of 5 cats with histoplasmosis, in one study, responded to ketoconazole [100]. In small studies, posaconazole, voriconazole and isavuconazole have been used successfully in humans [101-103]. The voriconazole study evaluated patients who discontinued other treatments because of intolerance or toxicity (8 patients) and increasing urinary antigen (1 patient): 3 patients improved and 6 remained stable [102]. Resistance to voriconazole has been observed in isolates from AIDS patients with histoplasmosis that failed treatment with fluconazole [98,104]. The newer azoles are more expensive than itraconazole. Posaconazole and voriconazole have been used with success as salvage therapy for dogs and cats with histoplasmosis that have failed itraconazole and fluconazole therapy (unpublished data). Although early reports of neurotoxicity with voriconazole in cats has limited its use clinically, lower doses (12.5mg total every 72 hours) might be effective, while minimizing adverse effects [105].

Terbinafine. *Histoplasma* is susceptible to this allylamine antifungal agent [43]. Moreover a pharmacokinetic study in dogs showed adequate oral bioavailability [106]. Studies to evaluate its effectiveness in histoplasmosis are lacking, but some veterinarians use it in combination with other antifungals, as salvage therapy, in patients failing other treatments (personal communications).

Duration of treatment. The optimal duration of therapy is unclear as prospective studies have not been conducted. The duration of treatment in humans with disseminated or chronic pulmonary histoplasmosis is at least 12 months [107]. Treatment for at least 6 months is recommended in dogs and cats [88].

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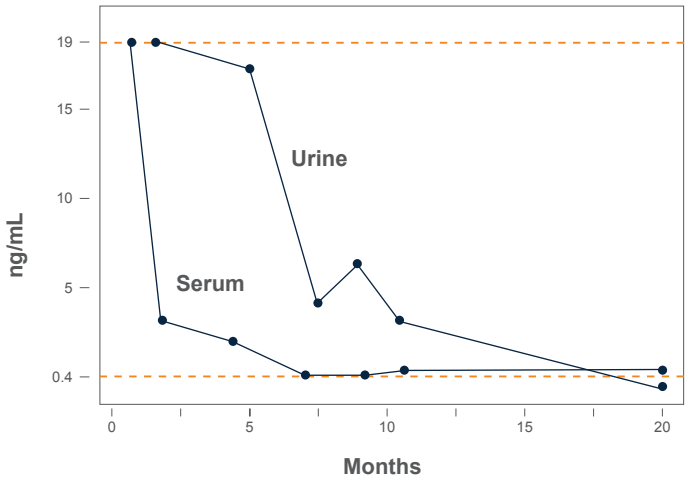
CLINICAL REVIEW

Adjunctive therapy. Schulman noted rapid clinical improvement in 10 dogs with mediastinal lymphadenitis causing airway obstruction that received corticosteroids, five of which also received antifungal treatment [68]. Corticosteroids also may be helpful in cases of diffuse pulmonary histoplasmosis complicated by respiratory insufficiency and in cases of inflammatory CNS or ocular disease. Concurrent antifungal therapy is recommended to reduce the risk for progressive dissemination caused by corticosteroid-induced immunosuppression.

Antigen monitoring. Antigen should be tested in urine at least every 3 months during treatment, at 6 and 12 months after stopping treatment, and any time the clinical findings suggest recurrence. And if the urine antigen is "Above Limit of Quantification, ALQ" serum should be used for monitoring instead. When the serum antigen is negative, resume monitoring urine antigen until negative. Consultation should be obtained for questions about discontinuation of treatment and if antigen remains positive more than 12 months.

Failure of the antigen concentration to decline also raises concern about the effectiveness of treatment, which may be caused by inadequate itraconazole blood levels or development of resistance to fluconazole [12]. If itraconazole blood levels are subtherapeutic, the dosage should be increased, and blood levels should be rechecked 14-21 days later. An increase in antigen concentration after stopping treatment suggests recurrence. An example of antigen clearance in urine and serum is presented in the **Figure**.



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CLINICAL REVIEW

Table 1. Clinical Findings in Dogs and Cats with Histoplasmosis

Finding	Dog (%)	Cat (%)
General/systemic		
Fever	20-60	25-50
Inappetence	20-60	40-50
Lethargy/Depression	60-70	35-70
Weight Loss	40-80	50-85
Respiratory		
Coughing	10-20	10-20
Dyspnea	10-40	45-60
Tachypnea	30-40	35-50
Epistaxis	<10	<10
Nasal discharge	10-20	10-20
Gastrointestinal		
Diarrhea	20-80	10-15
Hematochezia	20-30	<10
Hepatomegaly*	10-20	20-40
Splenomegaly*	10-40	20-40
Icterus	10-20	15-30
Abdominal Lymphadenopathy	20-50	30-40
Miscellaneous		
Mouth	<10	<10
Ocular	5-40	5-25
Neurologic	5-10	<5
Bone/joint	10-30	15-30
Peripheral Lymphadenopathy	20-60	30-60
Skin	10-20	10-20

NR-not reported
*Hepatomegaly and splenomegaly often reported as abdominal organomegaly

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CLINICAL REVIEW

Table 2. Laboratory Abnormalities in Dogs and Cats with Histoplasmosis

Laboratory	Dog (%)	Cat (%)
Anemia	30-100	35-55
Thrombocytopenia*	10-30	40-50
Decreased WBC	5-40	10-25
Increased WBC	5-40	5-20
Increased ALT	10-60	5-35
Increased ALP	10-50	<10
Increased Bilirubin	20-30	20-30
Decreased Albumin	80-100	30-40
Increased Globulin	25-50	10-20
Increased Creatinine	5-10	5-15
Decreased Calcium	30-40	10-45
Increased Calcium	5-25	5-25

*Platelet count often not reported due to platelet clumping in cats

Table 3. Sensitivity and Specificity of *Histoplasma* Antigen and Antibody Testing at MiraVista Diagnostics

Test	Specimen	Sensitivity	Specificity	Reference
Histoplasma antigen	Urine (dog) Urine (cat)	92% 94%	99% 100%	76, MVD 75
Histoplasma IgG Antibody EIA	Serum (dog) Serum (cat)	78% 78%	97% 84%	MVD MVD

Table 4. What Test(s) to Order for Histoplasmosis in Dogs and Cats

Endemic	Primary	Secondary
Histoplasmosis	*Histoplasma* urine antigen (code 310)	*Histoplasma* IgG antibody (code 327-canine) *Histoplasma* IgG antibody (code 328-feline) *Histoplasma* FID antibody (code 321) *Histoplasma* serum antigen (code 310)

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Table 5. Treatment Recommendations for Histoplasmosis in Dogs and Cats

Category	Daily dose	Duration
Dogs	Itraconazole 5 mg/kg BID for 3 days then SID	6-12 months
Cats	Itraconazole 5 mg/kg BID or 10 mg/kg SID^	6-12 months
Severe disease*	Lipid or Liposome encapsulated Amphotericin B 1.0 mg/kg (dog) or 0.5 mg/kg (cat) IV 3 times a week or EOD	Up to 24 mg/kg (dog) and 12 mg/kg (cat) cumulative
	Itraconazole as above	6-12 months

^A lower starting dose of itraconazole solution is recommended (7.5 mg/kg/day)
*Administration of anti-inflammatory doses of corticosteroids may reduce amphotericin B toxicity and inflammatory response to antigens released from *Histoplasma* yeast

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CLINICAL REVIEW

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