Blastomycosis in Veterinary Medicine

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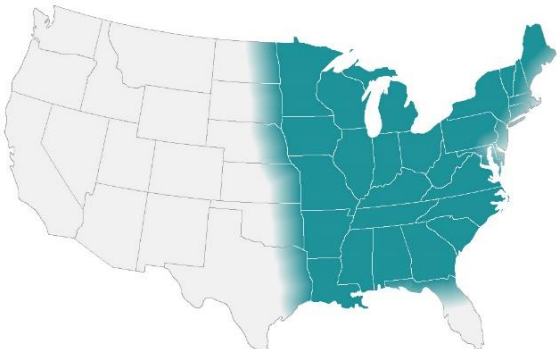
Introduction

Blastomycosis is acquired by inhaling fungal spores and causes respiratory or disseminated infection. If the inoculum is small, and the animal is immunocompetent, the infection might be limited to the respiratory tract and may cause few or no clinical signs. Alternatively, severe respiratory or disseminated disease can be fatal, if not diagnosed early. Many cases can be diagnosed by identification of the yeast in cytologic or histologic samples. Early diagnosis may also be aided by detection of *Blastomyces* antigen in urine or serum or anti-fungal antibodies in serum. This document will review the clinical features of blastomycosis in dogs and cats and discuss the current diagnostic and treatment recommendations.

Epidemiology



CDC map of estimated blastomycosis

While blastomycosis can occur in a wide variety of animals, most diagnosed cases are in dogs. Enzootic areas for blastomycosis include the Mississippi, Ohio, and Missouri river valleys, the Eastern Seaboard, Southern Canada, and areas adjacent to the Great Lakes and St. Lawrence River system (**Figure**). The states with highest incidence are Wisconsin, Minnesota, Missouri, Illinois, Michigan, Kentucky, West Virginia, Arkansas, Tennessee, Louisiana, and Mississippi. Other endemic states include Indiana, Iowa, Ohio, Virginia, Georgia, Alabama, N. Carolina, S. Carolina, and Vermont.

Cases, however, can occur outside the enzootic area.[1] The annual incidence is approximately 1420 cases per 100,000 dogs in a highly enzootic area.[2] Proximity to waterways and exposure to excavation are significant risk factors, but it's unclear if age, sex, and activities such as hunting or swimming increase risk. While most cases occur in dogs with extensive outdoor exposure, indoor only animals can also be infected.[1] Cases occur most often in the fall but can occur any time of the year.[3,4]

Blastomycosis occurs in young dogs with the highest rates in Coonhounds, Pointers and Weimaraners.[3,4] Doberman Pinschers and Retrievers might also be at increased risk for blastomycosis, but any breed is susceptible if exposed to the organism. In some reports, the prevalence was higher in males than females.[4,5] Higher rates in sexually intact male dogs was thought to be caused by roaming behavior or selective use in hunting.[4] The incidence blastomycosis in cats is much lower as compared with dogs, with one retrospective study over 11 years at a Canadian veterinary school showing 151 total blastomycosis cases, of which only 6 were feline (4%).[6] A 5-year survey of the Veterinary Medical Data Program found only 3 infected cats compared to 324 dogs.[7]

Clinical Findings

The most common clinical findings are nonspecific and include loss of appetite, lethargy, weight loss, and fever (Table 1). Respiratory signs also are common, and radiographs show nodular or interstitial infiltrates, often referred to as a "snowstorm pattern".[3] Less frequently thoracic radiographs show an alveolar or lobar pattern, tracheobronchial lymphadenopathy, large solitary mass-like lesions, or cavitary lesions.[3] Nodular and/or ulcerative skin lesions with draining tracts and lymphadenopathy are commonly present. Among fatal cases, the organs most often involved are the lungs and CNS.[4] Ocular lesions occur in about one third of cases.[8] Many other organ systems can be involved including bone, abdominal viscera, and the genitourinary tract.[3]

Early detection of ocular disease is important for salvaging vision. In a review of cases with ocular involvement, endophthalmitis was most common, followed by posterior segment disease, and anterior segment disease.[8] Lens rupture is a potential complication.[9] In an earlier report, the most common ocular lesion was anterior uveitis, and other manifestations including retinal detachment, panophthalmitis, and glaucoma. The most common ocular exam findings include photophobia, conjunctival hyperemia, miosis, blepharospasm, and aqueous flare. Most dogs also had disease in other body systems. The presence of ocular or periocular disease in animals from enzootic areas should prompt careful evaluation for blastomycosis.

Large surveys are not available to define the most common clinical manifestations in cats, but these are similar to dogs. Respiratory signs and dermal lesions were the most common findings in a study of 8 cats.[10] Chorioretinitis and CNS signs have also been reported in cats with disseminated blastomycosis.[11] Affected cats commonly have negative retroviral status, and immunosuppression is not typically associated with development of blastomycosis.[10,12]

Diagnosis

Ninety-five percent of diagnoses are based on compatible clinical findings confirmed by positive laboratory tests.[4] Most are based on antigen detection or pathology. The diagnostic performance of antigen and antibody detection tests offered at MiraVista Diagnostics are depicted in Table 2 and recommendations for what biomarker test to order is in Table 3.

Pathology and culture. Cytopathology and/or histopathology is a common method for diagnosis. *Blastomyces* organisms appear in cytologic preparations stained with Romanowsky-type stains as 8-20 µm, blue, spherical, thick-walled yeasts. Broad-based budding is commonly observed. Cytology was positive in 71% of cases in one report, including mostly skin and lymph node samples, and occasionally transtracheal washes.[3] In some cases, cytology of subretinal aspirates have been positive.[13] Fungal culture could potentially be positive in samples that are pathology negative but the long turn around time (4-6 weeks) for culture limits it's usefulness clinically.

Antigen detection. *Blastomyces* surface antigens can be detected by an enzyme immunoassay (EIA) in body fluids including urine, serum, bronchoalveolar lavage fluid, cerebrospinal fluid, etc.[14] In 2006, Spector et al. demonstrated that the antigen test is also useful in dogs, showing 94% sensitivity (urine) and 87% sensitivity (serum) in dogs with pathology-proven blastomycosis (Table 2).[15] Antigen concentration correlates with the severity of the infection, and results are essentially always positive in moderate-severe or severe blastomycosis. Antigen tests might initially be negative in mild or localized cases and those presenting with peracute or acute disease (1-2 weeks);

therefore, a negative result does not exclude the diagnosis. In addition, high cross-reactivity occurs between *Blastomyces* and *Histoplasma* antigens and current antigen detection tests cannot reliably differentiate the two systemic fungal infections. In general, there is no need to order testing for both antigens.

Antibody detection. Tests for antibody to *Blastomyces* using immunodiffusion (ID) methods have limited clinical utility. Enzyme immunoassay (EIA) methods for IgG antibody detection reportedly have higher sensitivity compared to ID, 95% and 65%, respectively [16] (Table 2). *Blastomyces* canine IgG is available at MiraVista Diagnostics (MVista® *Blastomyces* Canine IgG antibody EIA). The specificity of the IgG antibody EIA is high (95% in healthy control dogs from an enzootic area, 100% in dogs with nonfungal pulmonary disease), although some cross-reactivity is observed in dogs with histoplasmosis.[16] Antibody testing may be useful for diagnosis of cases with suspected false negative antigen results, or in cases with weekly positive antigen results in which the clinical findings are equivocal. There is no commercially available feline antibody EIA, but the *Blastomyces* ID can be used in cats.

DNA detection. Polymerase chain reaction (PCR) assays were demonstrated to detect *Blastomyces* DNA in 8/13 paraffin-embedded canine tissue samples in which yeast cells were seen microscopically, as well as in soil samples from a dog kennel housing dogs with blastomycosis.[17,18] Real-time PCR assays are available from several diagnostic laboratories. There is no published data regarding the diagnostic performance of RT-PCR for the diagnosis of blastomycosis in veterinary species. Until that data is available, PCR testing on blood or urine is not recommended and blastomycosis cannot be ruled out by negative PCR on any sample type.

Treatment

Amphotericin B. In severe, life-threatening cases, lipid or liposomal encapsulated (Abelcet® or Ambisome®) amphotericin B is recommended at a starting dosage of 1.0 mg/kg (dog) or 0.5 mg/kg (cat), three times weekly (or every other day) by intravenous infusion, over 4-6 hours, up to a cumulative dose of 24 mg/kg (dog) or 12 mg/kg

(cat)(Table 4).[21] Higher doses (2-3 mg/kg/dose) might be tolerated, especially in dogs. Renal function, electrolytes, and potassium levels should be monitored during treatment. Respiratory failure is the cause of death in most cases and supplemental oxygen is appropriate. Reasons that amphotericin B is more effective than itraconazole include immediate achievement of therapeutic blood levels and its fungicidal mode of action: Itraconazole requires up to a week to reach therapeutic levels and is fungistatic. Anti-inflammatory treatment with low doses of corticosteroids may be helpful in reducing systemic side effects of amphotericin B and clinical worsening attributed to inflammatory reaction to antigens released from "dying" *Blastomyces* organisms.

Itraconazole. In non-life-threatening cases, FDA approved itraconazole is recommended.[22] Generic FDA approved itraconazole capsules are less expensive than Sporanox capsules and achieves similar concentrations in the blood.[23] FDA approved itraconazole capsules should be administered with food to achieve maximum blood levels. Compounded itraconazole should not be used, as blood levels are undetectable or very low.[22,23]

The dosage to achieve therapeutic blood concentration is 5 mg/kg/day in dogs and 10 mg/kg/day capsule in cats (5 mg/kg/day solution in cats), although therapeutic drug monitoring is highly recommended to attain the optimum dosage.
Itraconazole is eliminated by hepatic metabolism through cytochrome P450 enzymes, and blood levels may be affected by medications that interact these.[24] Itraconazole blood level measurement is recommended at steady state for all patients (day 14 of treatment for dogs and day 21 for cats) and any time treatment failure or drug toxicity is suspected.

Itraconazole blood level testing is performed by bioassay at MiraVista Diagnostics. The bioassay determines itraconazole concentration by inhibition fungal growth. The bioassay is simple and inexpensive. Blood levels between 2-7 µg/ml are recommended to maximize efficacy and minimize toxicity. The primary limitation of the bioassay is that other antifungal agents will inhibit fungal growth and overestimate itraconazole concentration. Even when only itraconazole is administered, bioassay concentrations are

higher as compared with HPLC, in part because the bioassay measures antifungal activity of itraconazole and all active metabolites (hydroxy-itraconazole, etc.).

Blood level testing using high performance liquid chromatography (HPLC) or mass spectroscopy (MS) are offered at several commercial laboratories. Trough blood levels of at least 1-2 µg/ml are recommended but specific recommendations are unavailable for the upper range.[24] Combined itraconazole and hydroxy-itraconazole concentrations above 5 µg/ml may be unnecessary and are more likely cause toxicity (personal communications). Some laboratories do not report the hydroxy-itraconazole metabolite, and it is important to have both concentrations to assess risk for toxicity.

Itraconazole can cause a variety of adverse effects, most commonly loss of appetite, anorexia, vomiting, or diarrhea, which is often related to toxic blood levels.[25] Hepatoxicity and ulcerative skin lesions are also related to toxicity. Serum liver enzymes should be monitored during therapy. Activity of serum alanine aminotransferase (ALT) greater than 200 U/L in the presence of signs of toxicity might warrant discontinuation of itraconazole until appetite returns and ALT activity returns to <100 U/L.[26] 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/day and is associated with elevated itraconazole blood levels. Skin lesions usually resolve rapidly with dose reduction or discontinuation followed by resumption at a lower dose after lesions have resolved.[23]

Fluconazole. Fluconazole is used for treatment of blastomycosis because of its lower cost, and in some cases because of its ocular or cerebrospinal fluid penetration. Response to itraconazole and fluconazole was compared in a retrospective study.[27] Of note is that severity of respiratory disease was greater in dogs treated with itraconazole, while neurologic disease was more common in the fluconazole group. Ninety percent of dogs treated with itraconazole at an average dose of 5 mg/kg/day, for a median time of 4 months, achieved clinical remission, but 18% relapsed. Seventy-five percent of dogs treated with fluconazole at 10 mg/kg/day, for six months, responded to therapy, but 22% relapsed. There was a 10% and 25% mortality rate with itraconazole and fluconazole, respectively. While the differences in survival and relapse rates were not statistically

significant, they suggest that itraconazole is more effective than fluconazole, which is the case in humans.[28] The primary indication for fluconazole is where itraconazole cannot be tolerated. Traditionally, fluconazole blood level monitoring has been considered unnecessary because levels were thought to be predictable but based recent findings of a population based pharmacokinetic study in dogs and cats, this dogma should be revisited.[29]

A potential limitation of fluconazole use is the development of resistance in isolates from patients who have relapsed while receiving fluconazole, which has been documented in humans and animals with histoplasmosis.[30,31] Whether development of resistance was the cause of failure in veterinary patients with blastomycosis has not been studied but should be considered. Fungal isolates that are resistant to fluconazole may also become resistant to voriconazole (unpublished studies at MiraVista Diagnostics).[32]

Other azoles. Other treatment options include newer azoles such as posaconazole and voriconazole. They are active *in vitro* [30] and effective in animal models of blastomycosis.[33-35] However, neither has been studied for treatment of blastomycosis in dogs or cats. There are case reports of patients with CNS blastomycosis treated successfully with voriconazole.[36-38] These newer azoles are more expensive than itraconazole and might require therapeutic drug monitoring to assure adequate blood levels. Ketoconazole is less effective than other azoles and is not recommended.[39]

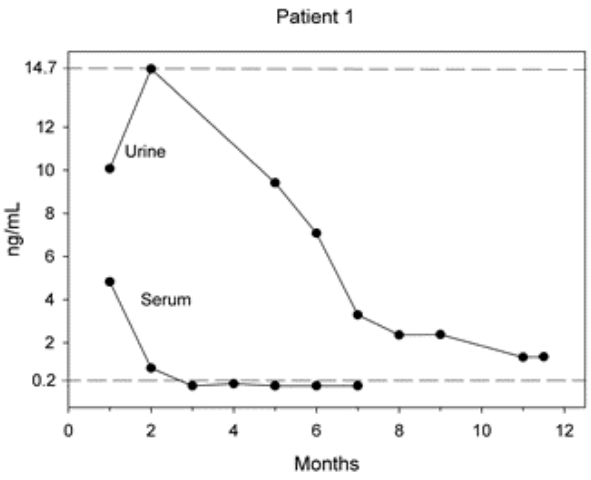
Terbinafine. *Blastomyces* is susceptible to this allylamine antifungal agent.[40] Moreover, a pharmacokinetic study in dogs showed that a 30-35 mg/kg dose provided blood concentration above the reported MIC for *Blastomyces* for approximately 18 hours. Studies to evaluate its effectiveness in blastomycosis are lacking but some veterinarians use it as salvage therapy in animals failing other treatments.

Adjunctive therapy. In one study, lung infiltrates worsened in the initial week of therapy, attributed to an inflammatory response to antigens released from dying organisms.[42] Up to 50% of dogs with severe lung disease die during the first week of therapy.

Dexamethasone (0.25-0.5 mg/kg IV for 2-3 days) may be given to dogs that develop life-threatening respiratory signs.[7]

Duration of treatment. The optimal duration of therapy is unclear as prospective studies have not been conducted. Treatment should be continued for at least 6 months and likely longer in most animals. Multiple clinical markers such as signs, physical exam abnormalities, imaging, and antigen concentrations should be used (Table 5).

Antigen monitoring. A prospective study assessed antigen clearance during treatment with fluconazole.[42] The antigen concentration decreased during treatment but there was no correlation between residual antigen concentration at discontinuation of treatment and the occurrence of relapse. Table 5 shows criteria for stopping treatment. Consultation should be sought if antigen levels are not declining after 3 months of treatment or if treatment must be extended beyond 18 months based on the above criteria.



Antigen should be tested in urine in at least 3-month intervals during treatment and at 6 months and yearly after stopping treatment, and any time the clinical findings suggest relapse. If urine antigen is “Above Limit of Quantification, ALQ” serum can be used for treatment monitoring instead. When the serum antigen is negative, resume monitoring urine antigen until negative.

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. If itraconazole levels are subtherapeutic, the dosage should be increased, and blood levels should be rechecked 14-21 days later. Increase in antigen concentration after stopping treatment suggests relapse.

Table 1. Organ systems involved in dogs with blastomycosis.

Finding	Frequency (%)
Respiratory	89
Lymph node	57
Ocular	49
Skin	41
Bone/joint	11
Neurologic	4
Abdominal viscera	2

Table 2. Diagnostic performance of antigen and antibody testing for blastomycosis in dogs and cats.

Test	Specimen	Sensitivity (%)	Specificity (%)	Reference
Blastomyces Antigen EIA	Urine (dog) Serum (cat)	100 >95	95 >95	[16]
Blastomyces Antibody EIA Blastomyces Antibody ID	Serum (dog) Serum (dog	95 18-6	95 100	[16] [15, 16]

Table 3. What test to order for diagnosis of blastomycosis in dogs and cats.

Endemic	Primary	Secondary
Blastomycosis	*Blastomyces* antigen urine (code 316)	*Blastomyces* IgG antibody (code 330; canine no feline assay available)* *Blastomyces* FID antibody (code 322; feline)

Secondary tests should be considered if the primary test is negative.
*Most important if the cost for all secondary tests is prohibitive

Table 4. Treatment recommendations for dogs and cats with blastomycosis.

Category	Dose	Duration
Dogs	Itraconazole 5 mg/kg/day	>6 months
Cats	Itraconazole 10 mg/kg/day (capsule) or 5 mg/kg/day (solution)	>6 months
Severe disease*	Amphotericin B 1.0 mg/kg (dog)^ or 0.5 mg/kg (cat) IV 3 times/week (or EOD)	Up to 12 mg/kg (cat) or 24 mg/kg (dog) cumulative dose
	Itraconazole as above	>6 months

*Administration of anti-inflammatory doses of corticosteroids may reduce amphotericin B related inflammation and response to antigens released dying fungal organisms.
^ This is a starting dose and dogs might tolerate higher doses (2-3 mg/kg/dose)

Table 5. Meet all of the following criteria before stopping antifungal treatment for blastomycosis.

Monitoring Tool	Criteria	Notes
Treatment Duration	Minimum of 6 months	▪ Required duration is often much longer.
History	≥1-month past resolution of clinical signs	▪ Mild exercise intolerance might persist, most notable in working or performance animals. ▪ Persistent tracheobronchial lymphadenopathy can cause cough, requiring concurrent corticosteroid treatment.
Physical Examination	≥1-month past resolution of physical exam abnormalities	▪ Differentiating active ocular disease from permanent inactive change is important.
Imaging Studies	≥1-month past resolution of imaging abnormalities	▪ Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease. ▪ Radiographic bone lesions should improve but might never return to normal.
MVista® Histo Antigen eia (urine)	≥1-month past no detectable antigen OR Antigen ≤0.4 ng/ml on 2 consecutive rechecks at least 3 months apart	▪ Most dogs, and essentially all cats, have no detectable antigen at the time of remission. ▪ Submit antigen test at diagnosis, every 3 months during treatment, and at 6 months then every 12 months after treatment.

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