

# Blastomycosis in Dogs

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Blastomycosis can be rapidly fatal if not suspected and diagnosed early. In addition to histopathology, antigen detection can aid in early diagnosis. A fungal polysaccharide antigen is shed into the blood and urine, yielding a positive result in over 90% of cases. Itraconazole is the treatment of choice, yet about half of the cases are fatal or recur when treatment is stopped. Causes for failure include severe disease at the time the diagnosis is made, inadequate itraconazole blood levels, and persistent infection when treatment is discontinued. Amphotericin B alone or combined with itraconazole for the first week may improve outcome in severe cases, and itraconazole treatment for four to six months, and until the antigen test in the urine is negative may reduce the relapse rate. Itraconazole blood level monitoring may improve outcome by assuring adequate dosing and adherence. Posaconazole and voriconazole also are potential treatments for blastomycosis, but are more expensive and unlikely to be more effective than itraconazole.

## Epidemiology

While blastomycosis may occur in a wide variety of animals, most diagnosed cases are in dogs. Endemic areas for blastomycosis include the Mississippi, Ohio, and Missouri river valleys, the Eastern Seaboard, Southern Canada, and areas adjacent to the Great Lakes.



Figure 1. Endemic areas

The states with areas of highest endemnicity are Wisconsin, Minnesota, Missouri, Illinois, Michigan, Kentucky, West Virginia, Arkansas, Tennessee, North Carolina, South Carolina, Louisiana, and Mississippi. Other endemic states include Indiana, Iowa, Ohio, Virginia, Georgia, and Alabama. However, cases may occur outside the endemic area [1].

The annual incidence was 1420 cases per 100,000 dogs in a highly-endemic area [2]. Proximity to waterways and exposure to excavation were significant risk factors but age, sex, hunting, swimming and exposure to beavers were not. While most cases occur in dogs with extensive outdoor exposure, cases also may be seen in indoor pets [1].

Cases occur most often in the fall [3,4], but may occur any time of the year.

Blastomycosis occurs mainly in young, large-breed dogs [3], with the highest rates in Coonhounds, Pointers, and Weimaraners [4]. Doberman Pinschers and Retrievers also may 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].

## Clinical findings

Blastomycosis is acquired by inhaling fungal spores, and causes a respiratory and/or disseminated infection. If the inoculum is small and the animal is not immunocompromised, the infection may be limited to the respiratory tract and may have few or no clinical signs. The most common clinical findings are nonspecific and include loss of appetite, weight loss, and fever, Table 1.

Table 1. Clinical findings

Fever	62%
Respiratory	49%
Skin lesions	49%
Depression	48%
Anorexia	44%
Ocular	43%
Weight-loss	37%
CNS	6%

Respiratory abnormalities also are common, and radiographs show nodular or interstitial infiltrates, often referred to as a “snowstorm pattern”. [3]. Less frequently thoracic radiographs show tracheal bronchial lymphadenopathy, masses, or cavitory lesions [3]. Draining skin tracts and lymphadenopathy are commonly present. Among fatal cases, the organs most often involved are the lungs, eyes and skin [4]. Ocular lesions occur in nearly half of cases [6]. Other less common sites of dissemination include the central nervous system and genitourinary tract [3].

Early detection of the ocular lesions is important for saving vision and for diagnosing the systemic nature of the disease. In a review of cases with ocular involvement, endophthalmitis was most common, followed by posterior segment disease, and anterior segment disease [6]. Lens rupture is a potential complication [7]. In an earlier report, the most common ocular lesion was uveitis and other manifestations included retinal detachment, panophthalmitis, and glaucoma [8]. The most common ocular findings included photophobia, conjunctival hyperemia, miosis, blepharospasm, and aqueous flare. Most of the patients also exhibited pneumonia and many had skin lesions or enlarged lymph nodes. The presence of ocular disease in patients from areas endemic for blastomycosis should prompt careful evaluation for the condition.

### Diagnosis

In a review of the Veterinary Medical Database, in over 90% of cases the diagnosis was validated by laboratory tests, while in <5% the diagnosis was based solely on clinical findings [4]. Cytologic examination of infected tissues or fluids has been the most common basis for diagnosis, figure 2 [3].

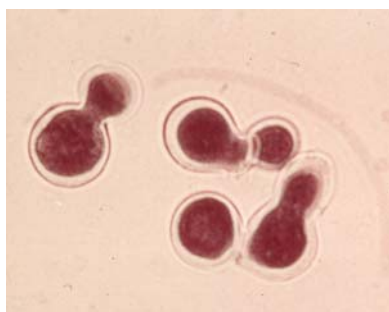


Fig 2. KOH wet mount

Cytology was positive in 71% of cases in one report [3]. Pathology is characterized by a purulent or pyogranulomatous inflammatory process [9]. In that report cytology was most frequently positive in specimens from skin and lymph nodes, and transtracheal washes were positive in a few cases.

Rapid diagnosis also may be established by detection of *B. dermatitidis* antigen in body fluids, Table 2 [10].

Table 2. Sensitivity of diagnostic tests

Test	Sensitivity	Reference
Cytology	71-94%	[3,9]
Antigen detection	Urine -94% Serum -87%	[10,11]
Culture	12%	[3]
Serology-ID	41-83%	[3,12]

A polysaccharide antigen is produced by the proliferating yeast and released into the tissues and body fluids. This antigen may be detected by an enzyme immunoassay using antibodies to *B. dermatitidis* [10]. Antigen was detected in the urine of 93% cases of blastomycosis in humans, and in a similar proportion of dogs, Figure 3[11].

Antigen also may be detected in bronchial aspirates, cerebrospinal fluid, and other sites of infection. Production of the antigen declines with effective therapy and increases with relapse. Cross-reactions occur with histoplasmosis.

Eye involvement may be difficult to diagnose. Aspirates of aqueous humor show inflammatory changes but are usually negative by cytology and culture because of the paucity of organisms. In some cases cytology or culture from subretinal aspirates have been positive [8]. Diagnosis also may be made by detection of antigen (unpublished observation) or DNA [13] materials aspirated from the eye.

Serologic tests using immunodiffusion (ID) may be used for diagnosis of blastomycosis. Sensitivity has ranged from 41% [12] to 83% [3]. However, Arceneaux noted that the diagnosis was based on ID results in only 6% of dogs, even though tests were positive in 83% [3], implying that the results were not available early in the course of the illness

Serology using more sensitive methods may be more useful than ID. A commercially available enzyme immunoassay (EIA) for detection of antibodies to the *Blastomyces* A-antigen has been studied in humans [14]. The EIA was more sensitive (83%) than ID

(21%) but was cross reactive with histoplasmosis. Others reported sensitivity of 92% in canine cases using a radioimmunoassay for antibodies to a specific *B. dermatitidis* WI-1 (also called Bad-1) antigen, compared to 41% by ID [12]. That assay has not been produced for clinical testing, however. We have detected elevated IgG antibody levels in 67% of canine cases by EIA using a commercially-available antigen [11]. Those specimens were not tested by ID to compare the sensitivity of the two methods, however.

### ***Treatment***

Although effective therapy is available, one quarter of dogs died, usually during the first week of treatment, and most often due to respiratory failure [15]. There was a strong correlation between the extent of lung involvement and survival time. Outcome is especially poor in cases with brain or spinal cord involvement. Added to the 25% mortality rate, another 25% relapsed, yielding an overall failure rate of about 50%. Treatment recommendations are summarized in Table 3.

Table 3. Treatment recommendations

Severe cases: Amphotericin B & itraconazole 4-7 days followed by itraconazole 4-6 months
Mild cases: Itraconazole 4-6 months

The 50% failure rate indicates that improvements in treatment are needed. First, veterinarians must maintain a high level of suspicion in dogs from endemic areas with consistent clinical findings, particularly if there is no improvement with antibiotic therapy.

Several treatment regimens have been evaluated in dogs with blastomycosis (Appendix). Amphotericin B was more effective than ketoconazole. The response to ketoconazole 10 mg/kg daily for 60 days was 33% compared to 65% for amphotericin B 1 mg/kg/d for a total course of 8-9 mg/kg [16]. Initial treatment with amphotericin B 1 mg/kg/d for four doses followed by ketoconazole was successful in 61% of cases, and had less nephrotoxicity than 8-9 mg/kg courses of amphotericin B. Others reported similar findings in dogs treated with a combination of amphotericin B and ketoconazole [3].

Itraconazole also is effective and has become the treatment of choice in most cases. Response to a 60-

day course of itraconazole 10 mg/kg/d was 74%, while a lower dose of 5 mg/kg/d given with food was nearly as effective [15]. However the itraconazole dose was increased to 10 mg/kg/d in about 20% of the dogs receiving the 5 mg/kg dose, and in some, treatment was continued beyond 60 days. Itraconazole absorption is variable, and blood levels may be inadequate in some cases. Drug level monitoring should be considered.

Ketoconazole is an alternative if itraconazole is too expensive. Although ketoconazole was not very effective as initial therapy, response was similar to that of itraconazole in dogs that first received four doses of amphotericin B [16].

With amphotericin B or itraconazole, one quarter of cases are fatal. To improve outcome in severe cases, some recommend combined therapy with amphotericin B and itraconazole [1].

Other options include posaconazole and voriconazole. Both are active in vitro [17] and effective in animal models of blastomycosis [18,19]. Neither has been studied in humans or dogs, however. There are case reports of patients with CNS blastomycosis treated successfully with voriconazole [20,21]. These newer azoles are more expensive than itraconazole. Fluconazole appears to be less effective than itraconazole, and must be used at relatively high doses, based on experience in humans [22].

Although about 75% of dogs respond to treatment, relapse is common, occurring in about 25% of responders (Appendix). Relapse usually occurs within the first year following therapy [3,15], but may occur two or three years later. In one report only one-third of the relapses responded to a second course of itraconazole [15] and in another report four of five dogs responded [3]. Some recommend at least four to six months of itraconazole [1], to reduce the likelihood of relapse. In some cases that relapse despite four to six months of itraconazole, itraconazole suppressive therapy given two or three times weekly may prevent recurrence. The antigen test may be useful for diagnosing relapse, indicated by the two spikes in (Figure 3).

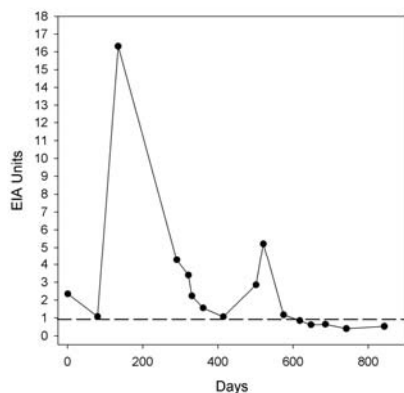


Figure 3. Antigenuria with relapse

Combination treatment with topical anti-inflammatory and systemic antifungal therapy is recommended in cases with ocular involvement [1]. Treatment was more effective in milder cases (two-thirds responded) than severe cases (none responded) [6]. In another report over half of patients were euthanized or died, while some responded to amphotericin B [8].

### Conclusion

Blastomycosis should be considered as a differential diagnosis for large-breed dogs that live close to a body of water in areas in which the disease is endemic or in dogs with a history of being transported to endemic areas that subsequently develop signs of pulmonary, ocular, lymphatic, or cutaneous disease. A high index of suspicion and early diagnosis are essential to a favorable outcome of therapy. Itraconazole 5 mg/kg/d with food should be given for at least two months, and one month after resolution of clinical findings [23]. Patients should be observed for relapse for at least one year, and therapy may be extended in such cases. The optimal regimen and effectiveness of therapy is unclear in cases with severe disease, however amphotericin B 0.5-1 mg/kg given daily or three times weekly to achieve a cumulative dose of 4 mg/kg followed by itraconazole 5 mg/kg/d for 2 to 3 months is suggested. Antigen testing may assist in deciding when to stop treatment.

## Appendix. Summary of treatment studies

<u>Drug</u>	<u>Cure</u>	<u>Death</u>	<u>Relapse</u>	<u>Reference</u>
Keto 10 mg/kg/d for 60 days (N=9)	3 (33%)	3 (33%)	3 (33%)	Legendre 1984 [16]
AmB 1 mg/kg/dose for 8-9 mg/kg (N=35)	20 (57%)	8 (23%)	5 (20%)	Legendre 1984[16]
AmB 1 mg/kg/d for 4 doses then Keto 10 mg/kg/d for 60 days N=18	11 (61%)	4 (22%)	3 (17%)	Legendre 1984[16]
AmB and Keto 10 mg/kg/d for 60 days N=19	12 (63%)	7 (37%)	Not stated	Arceneaux 1998 [3]
Itra)10 mg/kg/d for 60 days (N=56)	30 (54%)	14 (25%)	12 (21%)	Legendre 1996 [15]
Itra 5 mg/kg/d with food for 60 days (N=35)	19 (54%)	9 (26%)	7 (20%)	Legendre 1996 [15]
Itra 10 mg/kg/d for 60-90 days (N=31)	16 (52%)	10 (32%)	5 (16%)	Arceneaux 1998 [3]
Overall with AmB, AmB + Keto, or Itra N=195	108 (55%)	52 (27%)	35 (18%)	[3,15,16]

Keto=ketoconazole, AmB=amphotericin B, itra=itraconazole.

## Reference List

1. Bromel C and Sykes JE. Epidemiology, diagnosis, and treatment of blastomycosis in dogs and cats. *Clin Tech Small Anim Pract* 2005; 20:233-9.
2. Baumgardner DJ, Paretsky DP, and Yopp AC. The epidemiology of blastomycosis in dogs: north central Wisconsin, USA. *J Med Vet Mycol* 1995; 33:171-6.
3. Arceneaux KA, Taboada J, and Hosgood G. Blastomycosis in dogs: 115 cases (1980-1995). *J Am Vet Med Assoc* 1998; 213:658-64.
4. Rudmann DG, Coolman BR, Perez CM, and Glickman LT. Evaluation of risk factors for blastomycosis in dogs: 857 cases (1980-1990). *J Am Vet Med Assoc* 1992; 201:1754-9.
5. Selby LA, Becker SV, and Hayes HW, Jr. Epidemiologic risk factors associated with canine systemic mycoses. *Am J Epidemiol* 1981; 113:133-9.
6. Bloom JD, Hamor RE, and Gerding PA, Jr. Ocular blastomycosis in dogs: 73 cases, 108 eyes (1985-1993). *J Am Vet Med Assoc* 1996; 209:1271-4.

7. Hendrix DV, Rohrbach BW, Bochsler PN, and English RV. Comparison of histologic lesions of endophthalmitis induced by *Blastomyces dermatitidis* in untreated and treated dogs: 36 cases (1986-2001). *J Am Vet Med Assoc* 2004; 224:1317-22.
8. Buyukmihci N. Ocular lesions of blastomycosis in the dog. *J Am Vet Med Assoc* 1982; 180:426-31.
9. Garma-Avina A. Cytologic findings in 43 cases of blastomycosis diagnosed ante-mortem in naturally-infected dogs. *Mycopathologia* 1995; 131:87-91.
10. Durkin M, Witt J, LeMonte A, Wheat B, and Connolly P. Antigen Assay with the Potential To Aid in Diagnosis of Blastomycosis. *J Clin Microbiol* 2004; 42:4873-5.
11. Deborah Spector, Joseph Wheat, David Beamis, Bart Rohrbach, Joseph Taboada, and Alfred M. Legendre. Antigen Testing for the Diagnosis of Blastomycosis. *J Vet Intern Med* 2006; 20:711-2.
12. Klein BS, Squires RA, Lloyd JK, Ruge DR, and Legendre AM. Canine antibody response to *Blastomyces dermatitidis* WI-1 antigen. *Am J Vet Res* 2000; 61:554-8.
13. Bialek R, Feucht A, Aepinus C et al. Evaluation of two nested PCR assays for detection of *Histoplasma capsulatum* DNA in human tissue. *J Clin Microbiol* 2002; 40:1644-7.
14. Bradsher RW and Pappas PG. Detection of specific antibodies in human blastomycosis by enzyme immunoassay. *South Med J* 1995; 88:1256-9.
15. Legendre AM, Rohrbach BW, Toal RL, Rinaldi MG, Grace LL, and Jones JB. Treatment of blastomycosis with itraconazole in 112 dogs. *J Vet Intern Med* 1996; 10:365-71.
16. Legendre AM, Selcer BA, Edwards DF, and Stevens R. Treatment of canine blastomycosis with amphotericin B and ketoconazole. *J Am Vet Med Assoc* 1984; 184:1249-54.
17. Gonzalez GM, Fothergill AW, Sutton DA, Rinaldi MG, and Loebenberg D. In vitro activities of new and established triazoles against opportunistic filamentous and dimorphic fungi. *Med Mycol* 2005; 43:281-4.
18. Sugar AM and Liu XP. In vitro and in vivo activities of SCH 56592 against *Blastomyces dermatitidis*. *Antimicrob Agents Chemother* 1996; 40:1314-6.
19. Sugar AM and Liu XP. Efficacy of Voriconazole in Treatment of Murine Pulmonary Blastomycosis. *Antimicrob Agents Chemother* 2001; 45:601-4.
20. Bakleh M, Aksamit AJ, Tleyjeh IM, and Marshall WF. Successful treatment of cerebral blastomycosis with voriconazole. *Clin Infect Dis* 2005; 40:e69-e71.
21. Borgia SM, Fuller JD, Sarabia A, and El Helou P. Cerebral blastomycosis: a case series incorporating voriconazole in the treatment regimen. *Med Mycol* 2006; 44:659-64.

22. Pappas PG, Bradsher RW, Kauffman CA et al. Treatment of blastomycosis with higher doses of fluconazole. *Clin Infect Dis* 1997; 25:200-5.
23. Krohne SG. Canine systemic fungal infections. *Vet Clin North Am Small Anim Pract* 2000; 30:1063-90.